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Habilitationsschrift

Die Fontan-assoziierte Lebererkrankung

als Langzeitkomplikation

einer univentrikulären Palliation

Zur Erlangung der Lehrbefähigung

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1. Abkürzungsverzeichnis

AVSD	Atrioventrikulärer Septumdefekt
FALD	*Fontan-associated liver disease;*
	Fontan-assoziierte Lebererkrankung
γGT	γ-Glutamyltransferase
HABR	*Hepatic arterial buffer response*
LAVRI	*Left atrioventricular valve reduction index*
LiMAx test	*Maximal liver function capacity test*
mAVVI	*Modified atrioventricular valve index*
RV/LV inflow angle	*Right ventricular/ left ventricular inflow angle*
TE	Transiente Elastographie
UVH	Univentrikuläre Herzfehler
VCR	*Ventricular cavity ratio*
VO_{2max}	Maximale Sauerstoffaufnahmekapazität

2. Einleitung

2.1 Indikationsstellung für eine univentrikuläre Palliation bei Patientinnen und Patienten mit ventrikulärer Imbalance

Mit einer Prävalenz von 0,8 % aller Lebendgeborenen gehören angeborene Herzfehler zu den häufigsten kongenitalen Fehlbildungen.[1] Der Fehlbildungskomplex der univentrikulären Herzfehler (UVH) umfasst ein heterogenes Spektrum von kardialen Malformationen mit einer anatomischen oder funktionellen singulären Herzkammer; die Prävalenz beträgt 5 %.[2] Eine einheitliche Klassifikation der UVH ist aufgrund der Vielfalt der anatomischen Varianten schwierig zu etablieren. Generell kann zwischen Herzfehlern mit Atresie einer Atrioventrikularklappe (Mitral- oder Trikuspidalatresie), Mündung beider Atrioventrikularklappen in einen singulären Ventrikel (Doppelter Einlass des linken Ventrikels), Auslass der beiden großen Arterien aus einer Herzkammer (Doppelter Auslass des rechten Ventrikels), einer gemeinsamen Atrioventrikularklappe in Kombination mit Ventrikelimbalance (unbalancierter atrioventrikulärer Septumdefekt, AVSD), einer Hypoplasie des links – oder rechtsseitigen Ein- und Ausflusstraktes (Hypoplastisches Links- oder Rechtsherzsyndrom) oder komplexen Herzfehlern in Kombination mit einem Heterotaxie-Syndrom unterschieden werden.[3] Trotz ausgeprägter anatomischer Heterogenität ist die Pathophysiologie der UVH durch eine Parallelschaltung des pulmonalen und systemischen Kreislaufes mit konsekutiver zentraler Zyanose und Volumenüberladung des singulären Ventrikels charakterisiert. Ohne chirurgische Intervention ist die Überlebensprognose von Patientinnen und Patienten mit einem UVH mit einer Mortalität von 70 % bis zum 14. Lebensjahr äußerst limitiert.[4] Das Therapiekonzept der UVH basiert auf einer anatomischen Trennung der pulmonalen und systemischen Zirkulation und geht auf die im Jahr 1968 von François M. Fontan eingeführte Fontan-Operation zur chirurgischen Palliation der Trikuspidalatresie zurück.[5] Die ursprünglich eingeführte Operationstechnik beinhaltete eine Anastomose der rechten Pulmonalarterie an die obere Hohlvene, während die linke Pulmonalarterie durch die Implantation einer klappentragenden humanen Gefäßprothese (*Homograft)* mit dem rechten Vorhofohr verbunden wurde.[5] In den letzten Jahrzehnten wurde diese Operationsmethode weiterentwickelt und optimiert: Nach Implementierung einer direkten Verbindung zwischen dem rechten Vorhofohr und den Pulmonalarterien, der atriopulmonalen Konnektion, hat sich die Anlage einer totalen cavopulmonalen Anastomose in Form eines lateralen Tunnels oder eines extrakardialen *Conduits* als Modifikation der Wahl durchgesetzt.[6,7] Heutzutage stellen die Fontan-Operation und ihre Modifikationen den letzten Schritt eines mehrstufigen chirurgischen Konzeptes zur definitiven Palliation aller univentrikulären Malformationen mit zufriedenstellenden Langzeitergebnissen dar.[8,9]

Während die Indikationsstellung zur Fontan-Operation bei Herzfehlern mit einer ausgeprägt hypoplastischen Herzkammer, wie dem Hypoplastischen Linksherzsyndrom, eindeutig ist[10], existieren für komplexe Herzfehler mit einer biventrikulären Imbalance, wie dem unbalancierten AVSD, weder definierten Leitlinien noch ein therapieorientierter Konsens. Obwohl heutzutage die Mehrzahl der Patientinnen und Patienten nach einer Fontan-Operation das Erwachsenenalter erreicht,[8,9] sind die Morbidität und Mortalität durch hämodynamische Langzeitkomplikationen, welche eine progrediente Herzinsuffizienz, Herzrhythmusstörungen oder Thromboembolien umfassen, sowie Sekundärorganerkrankungen, limitiert.[11-14] Die Indikation zur univentrikulären Palliation bei Patientinnen und Patienten, welche möglicherweise einer biventrikulären Korrektur zugänglich sind, sollte daher kritisch gestellt werden. Umgekehrt ist die

Durchführung einer operativen Korrektur bei hierfür ungeeigneten Personen mit einem unbalancierten AVSD mit einer erhöhten Mortalität, einem protrahierten postoperativen Verlauf sowie multiplen Reoperationen und Reinterventionen assoziiert.[15] Die Definition von anatomischen Voraussetzungen und präoperativ erfassbaren diagnostischen Kriterien zur Selektion von potentiellen Kandidatinnen und Kandidaten für eine biventrikuläre Korrektur nimmt daher einen hohen Stellenwert in der aktuellen wissenschaftlichen Debatte ein. Insbesondere echokardiographisch messbare Parameter, welche die Dimensionen der unbalancierten Ventrikel sowie das Verteilungsverhältnis der Anteile der gemeinsamen Atrioventrikularklappe erfassen, scheinen zuverlässig die Durchführbarkeit einer biventrikulären Korrektur und das postoperative Überleben bei Personen mit einem unbalancierten AVSD voraussagen zu können.[16,17] Die Anwendbarkeit von operativen Therapiestrategien zur schrittweisen Rekrutierung eines grenzwertig hypoplastischen linken Ventrikels und Durchführung einer biventrikulären Konversion von initial univentrikulär palliierten Patientinnen und Patienten stellen einen weiteren Forschungsschwerpunkt in der Therapie von kardialen Anomalien mit einer ventrikulären Imbalance dar[18,19].

2.2 Pathophysiologie und Versagen der Fontan-Zirkulation

Bei der Fontan-Operation wird das systemvenöse Blut der oberen und unteren Hohlvene unter Umgehung eines subpulmonalen Ventrikels in die Pulmonalarterien umgeleitet. Hierdurch sind die Vorlast und konsekutiv das Herzzeitvolumen des Systemventrikels von einem passiven pulmonalen Blutfluss abhängig, welcher einen niedrigen pulmonalvaskulären Gefäßwiderstand und eine optimale systolische und diastolische Ventrikelfunktion voraussetzt.[20,21] Die negativen Effekte eines non-pulsatilen pulmonalen Blutflusses auf das pulmonalvaskuläre Gefäßbett konnten in unterschiedlichen Studien nachgewiesen werden: Eine Dysfunktion des Gefäßendothels und Apoptose von glatten Muskelzellen induzieren ein adverses pulmonalvaskuläres *Remodelling,* welches durch proliferative fibrotische Umbauprozesse der *Tunica intima* und eine Atrophie der *Tunica media* charakterisiert ist.[22-24] Adverses pulmonalvaskuläres *Remodelling* beeinträchtigt die endothel-abhängige Vasodilatation und führt zu einer Erhöhung des pulmonalvaskulären Widerstandes, welcher durch einen verminderten pulmonalvaskulären Rückfluss die Vorlast des Systemventrikels reduziert und konsekutiv in einer Abnahme des Herzzeitvolumens resultiert.[22-24] Weiterhin entwickelt die Mehrheit der Fontan-Patientinnen und -Patienten eine progrediente Einschränkung der systolischen und diastolischen Funktion des singulären Ventrikels im Langzeitverlauf. Als Hauptursache für die ventrikuläre Funktionseinschränkung wird ein adverses ventrikuläres *Remodelling* mit fortschreitender Myokardfibrose angenommen.[25] Eine eingeschränkte Ventrikelfunktion führt zu einer Erhöhung der intrakardialen Füllungsdrücke und einer vermehrten pulmonalvaskulären Kongestion, welche die Druckerhöhung im pulmonalarteriellen Gefäßbett aggraviert.[21] Diese hämodynamischen Charakteristika der unphysiologischen Kreislaufverhältnisse nach einer Fontan-Operation- eine chronische system- und pulmonalvenöse Kongestion, ein erhöhter pulmonalvaskulärer Widerstand sowie ein vermindertes Herzzeitvolumen - führen langfristig und unumgänglich zu einem Versagen der Fontan-Zirkulation.[11]

Das Fontan-Versagen ist deskriptiv und uneinheitlich definiert als eine chronisch-progressive Form der Herzinsuffizienz, welche durch unterschiedliche klinische und hämodynamische Phänotypen gekennzeichnet ist.[21,26] Neben dem Vorliegen einer erhaltenen oder reduzierten ventrikulären Ejektionsfraktion, kann das Versagen der Fontan-Zirkulation mit dem Auftreten von kardialen Komorbiditäten wie

Herzrhythmusstörungen, einer eingeschränkten kardiopulmonalen Belastbarkeit, einer progredienten Zyanose und thromboembolischen Komplikationen assoziiert sein.[9,12,27] Weitere Manifestationsformen des Fontan-Versagens umfassen Sekundärorganerkrankungen, wie Gebrechlichkeit, Proteinverlustenteropathie, plastische Bronchitis, Funktionsstörungen des Lymphgefäßsystems sowie eine chronische Niereninsuffizienz.[13,28-30] Die multifaktorielle Genese, die Heterogenität der Ausprägung und die langjährige Adaptation der Patientinnen und Patienten an ihre schleichend eintretende klinische Verschlechterung erschweren die Diagnosestellung des Fontan-Versagens und verzögern die Initiierung einer adäquaten Therapie, welche eine weitere Herausforderung bei dieser Patientenkohorte darstellt.[31,32] Eine medikamentöse antikongestive Therapie führt bei Personen mit einer Fontan-Zirkulation in der Regel nur passager zu einer Verbesserung der klinischen Symptomatik.[31,32] Eine profunde Datenlage zur Verbesserung der Überlebensprognose oder Reduktion der Anzahl der durch eine kardialen Dekompensation verursachten Hospitalisationen durch Initiierung einer leitliniengerechten antikongestiven Therapie ist für Patientinnen und Patienten mit einer Fontan-Zirkulation im Gegensatz zu herzinsuffizienten Personen mit einer biventrikulären Anatomie nicht existent. Die Ergebnisse von Studien zur Wirksamkeit einer lungengefäßwiderstandssenkenden Therapie sind kontrovers, so dass keine klaren Therapieempfehlungen für eine generelle Initiierung dieser abgeleitet werden können.[33,34] Die Möglichkeiten einer mechanischen Kreislaufunterstützung sind durch die anatomischen Besonderheiten von Fontan-Patientinnen und -Patienten ebenfalls limitiert. Bisher existiert kein für den Fontan-Kreislauf speziell entwickeltes mechanisches Herzunterstützungssystem, welches den subpulmonalen Ventrikel adäquat ersetzt. Der Einsatz von Herzunterstützungssystemen, welche für Patientinnen und Patienten mit einer biventrikulären Anatomie entwickelt worden sind, konnte in einigen Einzelfällen erfolgreich durchgeführt werden.[35,36] Aufgrund der hohen perioperativen Komplikationsrate und der fehlenden langfristigen Regredienz sowohl der Herzinsuffizienzsymtomatik als auch der Endorganschäden konnten diese Einzellfallergebnisse jedoch bisher nicht zu einer standardisierten Etablierung der mechanischen Kreislaufunterstützung als *bridge to transplant* oder *destination therapy* führen.[35,36] Bei Fontan-Patientinnen und -Patienten mit erhaltener systolischer Ventrikelfunktion würde die Implantation eines für ein linksventrikuläres Pumpversagen entwickelten Herzunterstützungssystems nicht in einer Erhöhung des verminderten Herzzeitvolumens, sondern in einer Zunahme der system- und pulmonalvenösen Kongestion resultieren und die klinischen Symptome und Endorganschädigung der versagenden Fontan-Zirkulation verstärken. Die Entwicklung und Implementierung eines cavopulmonalen Unterstützungssystems, welches den fehlenden subpulmonalen Ventrikel suffizient ersetzt, ist Gegenstand der aktuellen Forschung.[37] Aufgrund der begrenzten Wirksamkeit einer medikamentösen antikongestiven Therapie und der limitierten Möglichkeiten einer mechanischen Kreislaufunterstützung stellt die Herztransplantation die *ultima ratio* zur Therapie des Versagens der Fontan-Zirkulation dar. Während eine Herztransplantation bei pädiatrischen Patientinnen und Patienten mit einer Fontan-Zirkulation heutzutage zufriedenstellende Ergebnisse hinsichtlich der Rate an perioperativen Komplikationen und dem Langzeitüberleben aufweist,[38] ist diese bei Adulten weiterhin mit einer erhöhten Mortalität und Morbidität assoziiert.[39,40] Die aktuelle 1-Jahresüberlebensrate nach Herztransplantation erwachsender Fontan-Patientinnen und -Patienten wird mit 65 % angegeben und liegt deutlich unterhalb der Überlebensprognose von transplantierten Personen mit biventrikulärer Anatomie.[39] Zu den Ursachen einer erhöhten postoperativen Sterblichkeitsrate zählen chirurgisch-technischen Herausforderungen, wie multiple Voroperationen und damit einhergehende intrathorakale Verwachsungen, ein erhöhtes Blutungsrisiko sowie die Notwendigkeit der Korrektur von möglichen Fontan-Obstruktionen, welche die Operations- und Organischämiezeit zusätzlich verlängern. Der früh-postoperative Verlauf wird häufig durch die Notwendigkeit einer mechanischen Kreislaufunterstützung oder Nierenersatztherapie verkompliziert. Eine vermehrte Sensibilisierung mit Antikörpern gegen humane Leukozytenantigene durch multiple Vortransfusionen geht ebenfalls mit einem erhöhten Risiko für ein vorzeitiges Transplantatversagen einher.[38] Zusätzlich wurden eine präoperativ eingeschränkte Leber- und/ oder Nierenfunktion als weitere Risikofaktoren für eine erhöhte postoperative Morbidität und Mortalität identifiziert.[39,40]

Im Gegensatz zu Personen mit einer biventrikulären Anatomie fehlen für Fontan-Patientinnen und –Patienten Leitlinien und konsensbasierte Kriterien zur Listung für eine Herztransplantation, so dass die Indikationsstellung häufig verzögert im Stadium eines manifesten Fontan-Versagens mit fortgeschrittenen Sekundärorganerkrankungen erfolgt und die Prognose für eine erfolgreiche Herztransplantation beeinträchtigt.

Die Etablierung eines Risikoscores zur Einschätzung der Langzeitmortalität von Personen mit einer Fontan-Zirkulation könnte die rechtzeitige Detektion eines Fontan-Versagens vereinfachen.[41,42] Zur Erstellung eines Risikoscores eignen sich anatomische, hämodynamische und laborchemische Parameter, welche mit einer niedrigeren Überlebensrate assoziiert sind. Als anatomische Risikofaktoren konnten das Vorliegen einer Heterotaxie, eines rechten Systemventrikels, das Alter bei Fontan-Operation oder die Art der Fontan-Modifikation identifiziert werden.[43] Zu den hämodynamischen Parametern, welche mit einer erhöhten Langzeitmortalität einhergehen, zählen eine reduzierte kardiopulmonale Belastbarkeit, ein erhöhter pulmonalarterieller Mitteldruck, ein erhöhter end-diastolischer Druck im

Systemventrikel, das Vorliegen einer Zyanose oder das Auftreten von brady- oder tachykarden Herzrhythmusstörungen.[42] Weitere Risikofaktoren für eine erhöhte Sterblichkeitsrate stellen das Vorliegen einer schweren Insuffizienz der systemischen Atrioventrikularklappe, einer deutlich eingeschränkten systolischen oder diastolischen Ventrikelfunktion, einer Proteinverlustenteropathie, einer plastischen Bronchitis oder einer hepatischen und renalen Dysfunktion dar.[40,42]

Die Etablierung eines simplifizierten, multimodalen Risikoscores, welcher klinische, laborchemische und hämodynamische Parameter berücksichtigt, könnte durch die frühzeitige Detektion eines Fontan-Versagens und konsekutiv eine zeitgerechte Listung für eine Herztransplantation die Prognose dieser Patientinnen und Patienten erheblich verbessern.

2.3 Fontan-assoziierte Lebererkrankung

Mit einer Inzidenzrate von bis zu 86 % ist die Fontan-assoziierte Lebererkrankung (*Fontan-associated liver disease*, FALD) eine der häufigsten Sekundärorganerkrankungen bei Fontan-Patientinnen und -Patienten.[44,45] Unter FALD werden alle strukturellen, laborchemischen und funktionellen hepatischen Abnormalitäten zusammengefasst, welche auf die unphysiologische Fontan-Zirkulation zurückzuführen sind.[46,47] Die exakten Ursachen für die Entstehung der FALD sind unklar. Im Konsens wird von einer multifaktoriellen Pathogenese basierend auf den hämodynamischen Charakteristika des Fontan-Kreislaufes und den hieraus resultierenden Veränderungen der hepatischen Zirkulation ausgegangen.[48,49] Die chronische systemvenöse und lymphatische Kongestion resultieren in einer Dilatation der Lebersinusoide und konsekutiv in einer Aktivierung der hepatozellulären Mechanotransduktion, welche den fibrotischen Umbauprozess der Leber fördert:

Aktivierte perivaskuläre Sternzellen transformieren zu Myofibroblasen und produzieren abnormale extrazelluläre Matrix, welche überwiegend aus Kollagen Typ I und III besteht und sowohl perisinusoidal als auch periportal abgelagert wird.[49,50] Zusätzlich führt ein erhöhter zentralvenöser Druck zu einer Umverteilung der hepatischen Perfusion zu Gunsten des arteriellen Zuflusses, setzt die Effektivität des hepatischen Autoregulationsmechanismus (*hepatic arterial buffer response*, HABR) herab und erhöht die Vulnerabilität des Organs für akute Ischämieschäden.[51] Als weitere Ursachen werden ein dauerhaft reduziertes Herzminutenvolumen mit daraus resultierender hepatischer Minderperfusion, eine zentrale Zyanose mit hepatozellulärer Hypoxie und Nekrose, eine chronische systemische Inflammation oder intrahepatische Mikrothromben, welche durch den generalisierten prothrombotischen Status der Fontan-Zirkulation entstehen, angenommen.[49,50] Histopathologisch ist FALD durch eine ausgeprägte sinusoidale Dilatation, die Kombination einer zentrolobulären und perisinusoidalen Fibrose sowie das Fehlen einer inflammatorischen Reaktion charakterisiert. [52,53] Ein weiteres FALD-spezifisches histologisches Merkmal ist das Auftreten von hypervaskularisierten Knötchen, welche ähnlich einer fokalen nodulären Hyperplasie durch die Ausbildung einer zentralen sternförmigen Narbe mit einer darin verlaufenden Arterie mit radspeichenartigen Gefäßausläufern gekennzeichnet sind.[54] Diese arterialisierten Knötchen scheinen gehäuft bei Patientinnen und Patienten mit erhöhten Mitteldrücken im Fontankreislauf aufzutreten und könnten als Reaktion auf eine hepatovenöse Kongestion und damit verbundene Zunahme des arteriellen und Deprivation des portalvenösen Zuflusses im Sinne des HABR entstehen.[54]

Das Spektrum der FALD ist vielseitig und erstreckt sich von leicht erhöhten Leberenzymwerten, sonographischen Zeichen einer Leberfibrose bis hin zu einer weit fortgeschrittenen Leberzirrhose und dem hepatozellulären Karzinom (HCC).[55.56] Zu den häufigen laborchemischen Veränderungen gehören eine Erhöhung der Aspartat-Aminotransferase, der Alanin-Aminotransferase, des Bilirubins oder der γ-Glutamyltransferase (γGT).[55] Als typische sonographisch detektierbare morphologische Leberveränderungen wurden ein heterogenes Leberparenchym, eine segmentale Hypertrophie und/oder Atrophie, das Auftreten von hyperechogenen Läsionen sowie einer Splenomegalie oder Aszites beschrieben.[58]

Der Progress der FALD ist schleichend, die Erkrankung bleibt über einen langen Zeitraum latent und manifestiert sich erst im Spätstadium durch klinische Zeichen einer Leberzirrhose oder des HCC.[56] Die Detektion der FALD ist multimodal, zur Diagnosestellung werden laborchemische Analysen, Lebersonographie, transiente Elastographie und Schichtbildgebungsverfahren wie Magnetresonanz- oder Computertomographie herangezogen.[57-60] Histologische Untersuchungen belegten, dass eine Leberfibrose in unterschiedlichem Ausmaß bei nahezu allen Fontan-Patientinnen und -Patienten trotz unauffälliger Ergebnisse der nicht-invasiven Diagnostik nachweisbar ist.[57]

Die Interpretation dieser Untersuchungsergebnisse, ihre Einordnung in den klinischen Kontext und Einbeziehung in die therapeutische Entscheidungsfindung sind weiterhin Gegenstand der aktuellen Forschung. Eine weitere zentrale Fragestellung bleibt die Rolle der FALD in der Detektion und Therapie des Fontan-Versagens und die Indikationsstellung zur einer isolierten Herz- oder kombinierten Herzlebertransplantation bei Patientinnen und –Patienten mit hämodynamischer Kompromittierung und klinisch manifester FALD.

2.3 Effekte eines körperlichen Ausdauertrainings auf die Hämodynamik der Fontan-Zirkulation

Die hämodynamischen Charakteristika der Fontan-Zirkulation - eine chronische venöse Kongestion, das Fehlen einer pulmonalarteriellen Pulsatilität, ein erhöhter pulmonalvaskulärer Widerstand sowie eine reduzierte Vorlast des Univentrikels- resultieren in einem dauerhaft verminderten Herzzeitvolumen und einer im Vergleich zur gleichaltrigen Normalbevölkerung deutlichen Einschränkung der kardiopulmonalen Belastbarkeit.[61] Die bestehende Prädisposition für eine progrediente Beeinträchtigung der systolischen und diastolischen Funktion des singulären Systemventrikels trägt zusätzlich zu einer stetigen Reduktion der kardiopulmonalen Belastbarkeit bei, welche bei Fontan-Patientinnen und -Patienten bereits in der frühen Adoleszenz beginnt.[62] Aufgrund des Fehlens eines subpulmonalen Ventrikels kann das Herzzeitvolumen von Personen mit einem Fontan-Kreislauf nicht über eine erhöhte Vorlast, sondern überwiegend durch eine Steigerung der Herzfrequenz reguliert werden. Ein adäquater Anstieg der Herzfrequenz unter Belastung wird bei einer hohen Anzahl der Fontan-Patientinnen und -Patienten durch das Vorliegen einer Sinusknotendysfunktion oder einer medikamentös induzierten chronotropen Inkompetenz verhindert. Neben den kardialen Limitationen tragen respiratorische Beeinträchtigungen wie eine restriktive Lungenfunktion, eine verminderte pulmonale Diffusionskapazität und maximale Sauerstoffaufnahme sowie eine reduzierte inspiratorische Muskelkraft zur Belastungsintoleranz von Fontan-Patientinnen und -Patienten bei.[63]

In vielen auf kardiovaskuläre Erkrankungen spezialisierten Zentren stellt körperliches Training einen wichtigen Bestandteil der nicht-pharmakologischen Therapie von Personen mit kardiopulmonalen Erkrankungen dar, da es die Überlebensrate und die subjektive Lebensqualität signifikant verbessert.[64,65] Die positiven Effekte eines regelmäßigen Ausdauertrainings auf die Überlebensprognose und Lebensqualität von Patientinnen und Patienten mit einer Fontan-Zirkulation sind nur unzureichend untersucht. Eine Abnahme der maximalen Sauerstoffaufnahmekapazität (VO_{2max}) ist jedoch nachweislich mit einem erhöhten Risiko für Mortalität und durch kardiale Dekompensation bedingte Hospitalisationen assoziiert.[66,67] Die Studienlage zur Steigerung der VO_{2max} durch regelmäßiges körperliches Ausdauertraining ist limitiert und weist diskrepante Ergebnisse auf. Während einige Autoren von einer signifikanten Verbesserung der kardiopulmonalen Belastbarkeit und Lebensqualität durch die Teilnahme an einem standardisierten mehrmonatigen Ausdauertrainingsprogramm berichten,[68,69] konnten diese positiven Effekte in einer prospektiven, randomisierten Studie nicht bestätigt werden.[70]

Die Inkongruenz der Studienergebnisse könnte auf der niedrigen Anzahl der eingeschlossenen Patientinnen und Patienten, dem unterschiedlichen Alter der Studienteilnehmer:innen sowie der Verwendung von verschiedenen Trainingsprotokollen mit unterschiedlicher Art, Intensität und Dauer der Trainingseinheiten basieren. Der Trainingseffekt könne zusätzlich durch die Verfügbarkeit einer externen Supervision des Ausdauertrainings im Vergleich zu ausschließlich auf intrinsischer Motivation aufbauenden heimbasierten Trainingsprogrammen beeinflusst werden. Die Mehrheit der bisher veröffentlichten Studienergebnisse bezieht sich auf einen Studienzeitraum von maximal 12 Wochen. Die Erfassung eines langfristigen Benefits durch regelmäßiges körperliches Training bedarf klinischer Studien mit einem längeren Beobachtungszeitraum.

Neben kardiopulmonalem Ausdauertraining stellen die Einführung von Atemtrainingsmethoden, respiratorischem Muskeltraining sowie Beinmuskeltraining weitere Möglichkeiten der Verbesserung der kardiopulmonalen Belastbarkeit von

Fontan-Patientinnen und – Patienten dar.[71-73] Das Hauptziel dieser Trainingsmethoden ist eine Steigerung der Vorlast und konsekutiv des Herzzeitvolumens des singulären Systemventrikels durch eine Erhöhung des pulmonalen Blutflusses. Randomisierte klinischen Studien mit einer hohen Patientenanzahl zur Belegung einer Effektivität der verschiedenen Trainingsmethoden liegen zum aktuellen Zeitpunkt jedoch nicht vor.

Der positive Einfluss von körperlichem Training auf den Progress von Sekundärorganerkrankungen konnte bisher nicht nachgewiesen werden. Einerseits existieren Hinweise, dass eine kontrollierte regelmäßige körperliche Betätigung die Ausprägung von Sekundärorganerkrankungen, insbesondere im Bereich der Leber, positiv beeinflussen könnte.[74] Umgekehrt, führt körperliches Training nachweislich zu einem signifikanten Anstieg des peripher- und zentralvenösen Druckes während der Belastung und könnte die bereits vorliegenden und durch die venöse Kongestion ausgelösten Endorganschäden aggravieren.[75]

Die Auswirkungen eines über einen längeren Zeitraum durchgeführten und individualisierten kardiopulmonalen Ausdauertrainings und respiratorischen Muskeltrainings auf die Überlebensprognose, die Morbidität und Lebensqualität von Patientinnen und Patienten mit einem Fontan-Kreislauf sind nur unzureichend untersucht. Insbesondere die Durchführbarkeit und Effizienz eines individualisierten heim-basierten Trainings bei pädiatrischen und adulten Fontan-Patientinnen und – Patienten bedarf weiterer klinischen Studien.

3. Fragestellung und Zielsetzung

Das Ziel der in der Habilitationsschrift vorgelegten klinischen Arbeiten war die Beantwortung folgender Fragen:

1. Kann die operative Strategie von Patientinnen und Patienten mit ventrikulärer Imbalance durch eine dezidierte präoperativ durchgeführte Echokardiographie festgelegt werden?
2. Wie sind die Inzidenz und das klinische Krankheitsspektrum der FALD?
3. Welche Einfluss– und Risikofaktoren können für die Entstehung und Ausprägung von FALD identifiziert werden?
4. Kann eine Graduierung der FALD zur Detektion eines Versagens der Fontan-Zirkulation genutzt werden?
5. Welcher zeitliche Zusammenhang besteht zwischen dem Auftreten von FALD-spezifischen morphologischen Veränderungen und der Einschränkung der enzymatischen Leberfunktion?
6. Welchen Einfluss hat die Hämodynamik der Fontan-Zirkulation auf die enzymatische Leberfunktion?
7. Können die kardiopulmonale Belastbarkeit und die respiratorische Funktion von Fontan-Patientinnen und Patienten durch ein individualisiertes heim-basiertes Ausdauertraining gesteigert werden?

4. Eigene Arbeiten

4.1 Anwendung einer dezidierten präoperativen Echokardiographie zur Statuierung der operativen Strategie bei Patientinnen und Patienten mit ventrikulärer Imbalance

Die Arbeit

Schleiger, A., Kramer P., Schafstedde, M., Yigitbasi, M., Danne, F., Murin, P., Cho, M.Y., Photiadis, J., Berger, F., Ovroutski, S. Can Left Atrioventricular Valve Reduction Index (LAVRI) predict the surgical strategy for repair of atrioventricular septal defect? Pediatric Cardiology, 02/2021, 898-905, 42.

untersuchte, ob die operative Therapiestrategie bei Patientinnen und Patienten mit einem kompletten AVSD durch eine dezidierte präoperativ durchgeführte Echokardiographie festgelegt werden kann. Die retrospektive Auswertung echokardiographischer Daten von 352 Patientinnen und Patienten umfasste die Messung von Parametern wie der *ventricular cavity ratio* (VCR), dem *modified atrioventricular valve index* (mAVVI) sowie dem *right ventricular/left ventricular (RV/LV) inflow angle.* Zusätzlich wurde der *left atrioventricular valve reduction index* (LAVRI) eingeführt, welcher die linksventrikuläre Atrioventrikularklappenfläche nach chirurgischem Nahtverschluss des Klappensegelspaltes (*Cleft*) errechnet, und auf seine Validität und Anwendbarkeit überprüft. Die Ergebnisse der Arbeit zeigten, dass die echokardiographischen Parameter VCR, mAVVI, RV/LV *inflow angle* sowie der eingeführte LAVRI signifikant mit der operativen Therapiestrategie korrelierten. Insbesondere der neu eingeführte LAVRI kann valide zur Entscheidungsfindung zwischen einer biventrikulären Korrektur und einer univentrikulären Palliation herangezogen werden.

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ORIGINAL ARTICLE

Can Left Atrioventricular Valve Reduction Index (LAVRI) Predict the Surgical Strategy for Repair of Atrioventricular Septal Defect?

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Abstract

Despite improved survival, surgical treatment of atrioventricular septal defect (AVSD) remains challenging. The optimal technique for primary left atrioventricular valve (LAVV) repair and prediction of suitability for biventricular approach in unbalanced AVSD are still controversial. We evaluated the ability of our recently developed echocardiographic left atrioventricular valve reduction index (LAVRI) in predicting LAVV reoperation rate and surgical strategy for unbalanced AVSD. Retrospective echocardiographic analysis was available in 352 of 790 patients with AVSD treated in our institution and included modified atrioventricular valve index (mAVVI), ventricular cavity ratio (VCR), and right ventricle/left ventricle (RV/LV) inflow angle. LAVRI estimates LAVV area after complete cleft closure and was analyzed with regard to surgical strategy in primary LAVV repair and unbalanced AVSD. Of the entire cohort, 284/352 (80.68%) patients underwent biventricular repair and 68/352 (19.31%) patients underwent univentricular palliation. LAVV reoperation was performed in 25/284 (8.80%) patients after surgical correction of AVSD. LAVRI was significantly lower in patients requiring LAVV reoperation (1.92 cm^2/m^2 [IQR 1.31] vs. 2.89 cm^2/m^2 [IQR 1.37], $p = 0.002$) and significantly differed between patients receiving complete and no/partial cleft closure (2.89 cm^2/m^2 [IQR 1.35] vs. 2.07 cm^2/m^2 [IQR 1.69]; $p = 0.002$). Of 82 patients diagnosed with unbalanced AVSD, 14 were suitable for biventricular repair (17.07%). mAVVI, LAVRI, VCR, and RV/LV inflow angle accurately distinguished between balanced and unbalanced AVSD and predicted surgical strategy (all $p < 0.001$). LAVRI may predict surgical strategy in primary LAVV repair, LAVV reoperation risk, and suitability for biventricular approach in unbalanced AVSD anatomy.

Keywords Atrioventricular septal defect · Echocardiographic analysis · Preoperative decision-making · Left atrioventricular valve repair · Unbalanced atrioventricular septal defect

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Abbreviations

AVSD	Atrioventricular septal defect
(L)AVV	(Left) atrioventricular valve
BVR	Biventricular repair
UVP	Univentricular palliation
LAVRI	Left atrioventricular valve reduction index
VSD	Ventricular septal defect
mAVVI	Modified atrioventricular valve index
VCR	Ventricular cavity ratio
RV/LV	Right ventricle/ left ventricle
IQR	Interquartile range
ROC	Receiver operating characteristic
Vs.	Versus
AUC	Area under the curve
CI	Confidence interval
ICU	Intensive care unit
h	Hours

Introduction

Due to advances in surgical techniques, postoperative management, and pre- and intraoperative echocardiographic imaging, survival rates after surgical correction of atrioventricular septal defect (AVSD) significantly increased over the past decades [1–3]. Nevertheless, regurgitation of the left atrioventricular valve (LAVV) represents the major cause for reoperation, long-term morbidity, and mortality [3–5]. Associated cardiovascular anomalies, malformations of the LAVV, infeasible primary complete cleft closure and normal karyotype have been described as risk factors for reoperation [3–6]. Additionally, the degree of LAVV regurgitation after AVSD repair strongly correlates with the indication for subsequent LAVV reconstruction or replacement [3, 4]. Therefore, the preoperative evaluation of atrioventricular valve anatomy seems indispensable for devising the optimal surgical strategy of primary LAVV repair and predicting the risk for LAVV reoperation.

Another challenge concerning AVSD repair is the surgical management of unbalanced AVSD due to uncertainties in decision-making between biventricular repair (BVR) and univentricular palliation (UVP) in borderline AVSD anatomy. Unbalanced AVSD is commonly defined by ventricular hypoplasia, malalignment of the atrioventricular junction and atrioventricular valve dysplasia [7]. Compared to patients with balanced AVSD, in patients with unbalanced anatomy, BVR is associated with a higher mortality rate and a more complicated postoperative course including numerous re-interventions [7–11]. Although various echocardiographic indices have been introduced to facilitate decision-making, so far no universal recommendations exist to unequivocally select the optimal therapeutic approach in case of ventricular imbalance.

In this study we introduce our recently developed left atrioventricular valve reduction index (LAVRI) for preoperative echocardiographic assessment in patients with AVSD. We evaluated the ability of LAVRI in devising surgical strategy in primary LAVV repair and predicting the LAVV reoperation risk. Additionally, we performed a detailed retrospective echocardiographic analysis measuring ventricular septal defect (VSD) size, modified atrioventricular valve index (mAVVI), ventricular cavity ratio (VCR), right ventricular/ left ventricular (RV/LV) inflow angle, and LAVRI to analyze and compare the usability of LAVRI in predicting and defining surgical strategy in unbalanced AVSD anatomy.

Patients and Methods

Study Design and Patient Cohort

We retrospectively identified 790 patients diagnosed with AVSD in our institution. All patients who underwent surgical correction of AVSD or palliation before January 2006 were excluded due to the unavailability of digitally archived echocardiograms for retrospective analysis ($n = 419$). Fourteen patients, who did not receive corrective surgery in our institution, but were referred from other centers for reoperation, were excluded from further analysis. Additional five patients were excluded, since surgical correction was not performed until conclusion of data acquisition. Echocardiograms and medical records of 352 patients were reviewed for this study. Median follow-up after AVSD repair was 6.21 years [IQR 7.34]. Unbalanced AVSD was defined as the presence of hypoplastic or non-apex forming ventricles and/or an atrioventricular valve override of > 60% over either ventricle [11]. Parameters extracted from postoperative course included total hospital stay, ICU stay, and ventilation time. The study was approved by the institutional review board and ethics committee (decision number: EA2/127/16). Informed consent was not considered mandatory due to the retrospective character of this study.

Echocardiograpic Evaluation

Echocardiographic analysis was performed retrospectively on digitally archived routine pre- and postoperative echocardiograms. Parameters assessed included mAVVI, VCR, RV/LV inflow angle, and our developed LAVRI. mAVVI was obtained by visualizing the orifice of the common AV valve in the left anterior oblique view at end-diastole and bisecting the common AV valve along a connecting line from muscular to infundibular ventricular septum [5]. The mAVVI was calculated by dividing the left AVV area by the total AVV area [5]. VCR was calculated as the ratio between the left ventricular length multiplied with the left ventricular width and the right ventricular length multiplied with the right ventricular width [8]. Ventricular length and width were measured in apical four-chamber view from the AV valve to the apex and from ventricular septum to the lateral wall of each ventricle [8]. RV/LV angle was measured in the apical four-chamber view from the crest of the ventricular septum as the apex to each atrioventricular valve hingepoint [12]. LAVRI was developed by our study group to predict resulting LAVV area after complete cleft closure using a modified formula for the calculation of an ellipse area: A = πab; A = area, a = major LAVV radius, b = minor LAVV radius minus cleft size. Major and minor LAVV radius were measured in the left anterior oblique view of the common AV valve at end-diastole after bisecting the common AV valve along the line from muscular to infundibular ventricular septum into left and right AVV area (Fig. 1). Cleft size was measured from the coaptation zone of the left mural, superior, and inferior bringing leaflet to a line corresponding to the plane of the interventricular septum in the left anterior oblique view (Fig. 1). LAVRI was obtained by indexing predicted resulting LAVV area after complete cleft closure to body surface area calculated from the Du Bois formula (Fig. 2). Postoperative AV valve regurgitation was classified as absent/ mild, moderate and severe by visual assessment of the regurgitation jet dimensions in color Doppler sonography. Additionally, mean inflow pressure gradient was determined from Doppler velocity flow curve of the left and right AV valve. Echocardiograms were evaluated by one echocardiographer (AS) and measurements were verified by a second echocardiographer (SO). Both echocardiographers were blinded to the surgical approach. All measurements were obtained in three cardiac cycles and values averaged for final analysis. Echocardiography was performed using two echocardiographic devices (Vivid 7 and E 9, GE Healthcare, Solingen, Germany). Xcelera V (Philips Healthcare, Eindhoven, The Netherlands) was used for retrospective echocardiographic measurements.

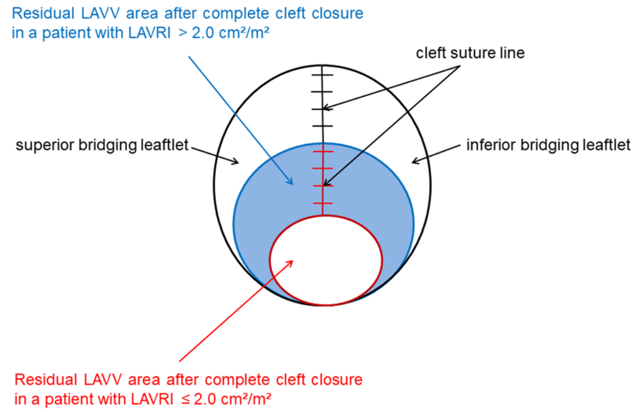
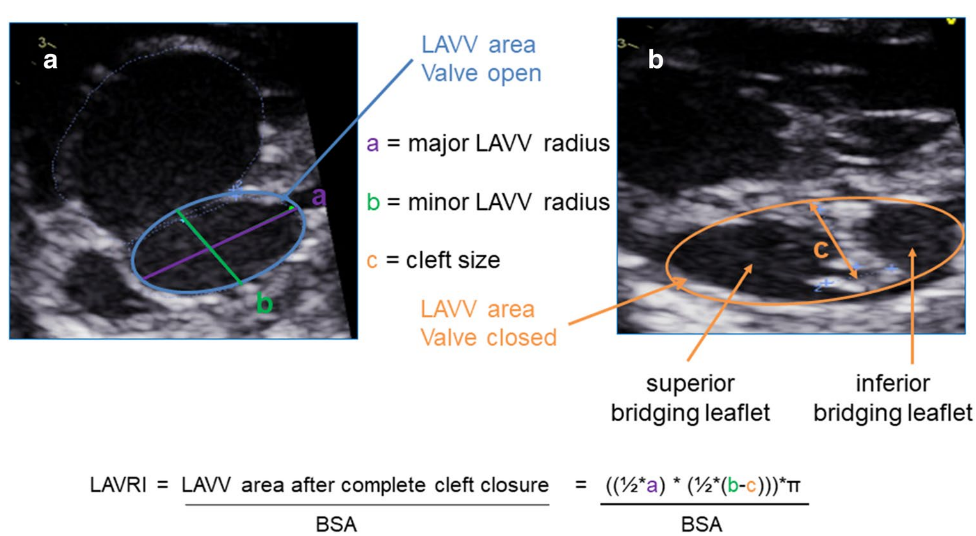


Fig. 2 Schematic drawing of the residual LAVV orifice after complete cleft closure in patients with a LAVRI ≤ 2.0 cm^2/m^2 (red) and > 2.0 cm^2/m^2 (blue). *LAVV* left atrioventricular valve area, *LAVRI* left atrioventricular valve reduction index

Surgical Technique of AVSD Repair

Our institutional technique of AVSD repair has previously been described in detail [3]. Briefly, all patients were placed on cardiopulmonary bypass with aortic and bicaval cannulation in moderate hypothermia (32 °C rectal temperature). Cardioplegic arrest was achieved using Kirsch/ hydroxyethyl starch or Bretschneider cardioplegic solution. Based on AVSD anatomy, corrective surgery was performed using two-patch technique in 177 patients, single-patch technique in 18 patients, patch closure of the atrial septum and direct closure of the ventricular septum (or vice versa) in 54 patients and sole patch closure of the atrial septum in 35 patients. Two-hundred forty-seven patients underwent complete and 37 patients no/ partial cleft closure.

Fig. 1 Measurement and calculation of LAVRI. Left anterior oblique view of the common AV valve at end-diastole (**a**) and systole (**b**) in a patient with right-dominant unbalanced AVSD. Measurements required for LAVRI calculation: a = major LAVV radius, b = minor LAVV radius, and c = cleft size. *LAVV* left atrioventricular valve area, *LAVRI* left atrioventricular valve reduction index



Statistical Analysis

Data were obtained from medical records of the German Heart Centre Berlin. Patients characteristics are expressed as median and interquartile range [IQR] calculated as 75th minus 25th percentile. Patients` characteristics and echocardiographic indices were compared using chi-square test for categorical variables and Mann–Whitney *U* test for continuous variables. Predictability for surgical strategy of echocardiographic indices was analyzed using receiver operating characteristic (ROC) curves. Statistical analysis was performed using SPSS statistical software program (version 23, IBM Corp., NY, USA). A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

Patient characteristics of the entire cohort are listed in Table 1. Of 352 consecutive patients operated in the past 14 years, 284 underwent surgical repair of AVSD and 68 received univentricular palliation, respectively. In the BVR subgroup 244 patients were diagnosed with complete, 35 patients with intermediate, and 5 patients with partial AVSD. Trisomy 21 was present in 168 patients. Median patient age at corrective surgery was 5.20 months [IQR 3.91] and median patient weight 5.44 kg [IQR 2.40]. Forty-eight patients presented with complex AVSD including the following associated cardiac malformations: right ventricular outflow tract obstruction/ pulmonary atresia ($n = 16$), coarctation of the aorta/interrupted aortic arch ($n = 23$), total or partial anomalous pulmonary venous connection ($n = 9$), double outlet right ventricle ($n = 4$), heterotaxy ($n = 6$) or malposition of the great arteries ($n = 2$).

Surgical Strategy in Balanced AVSD

Of 284 patients who received BVR, primary LAVV repair was performed with complete cleft closure in 247 patients and partial cleft closure in 28 patients. In 9 patients, cleft closure was not feasible due to abnormal LAVV anatomy or unfavorably small LAVV size to avoid postoperative stenosis.

Preoperative LAVRI measurement was retrospectively available in 171 of 284 patients (60.21%). LAVRI was

Table 1 Patient characteristics

Characteristic, *n* (%)/[IQR]	Entire cohort	BVR	UVP	*p*-value
Number of patients	352	284	68	
Male	147 (41.76)	116 (40.84)	31 (45.59)	0.496
Trisomy 21	168 (47.73)	168 (59.15)	0 (0.0)	**< 0.001**
Patient weight (kg)[a]	5.40 [2.68]	5.44 [2.40]	5.23 [5.15]	0.177
BSA (m^2)	0.30 [0.09]	0.30 [0.07]	0.29 [0.19]	0.245
Patient age (months)[a]	5.64 [07.69]	5.16 [3.96]	31.7 [38.07]	**< 0.001**
AVSD type				
Complete	312 (88.64)	244 (85.92)	68 (100.0)	**< 0.001**
Intermediate	35 (9.94)	35 (12.32)	0 (0.0)	**0.001**
Partial	5 (1.42)	5 (1.76)	0 (0.0)	0.588
Complex AVSD	110 (31.25)	48 (16.90)	62 (91.18)	**< 0.001**
RVOTO/PA	51 (14.49)	16 (5.63)	35 (51.47)	**< 0.001**
CoA/AAH	37 (10.51)	23 (8.10)	14 (20.59)	**0.007**
TAPVD/PAPVD	37 (10.51)	9 (3.17)	28 (41.18)	**< 0.001**
DORV	23 (6.53)	4 (1.41)	19 (27.94)	**< 0.001**
Heterotaxy	39 (11.08)	6 (2.11)	33 (48.53)	**< 0.001**
TGA	39 (11.08)	2 (0.70)	37 (54.41)	**< 0.001**

Statistically significant results are given in bold letters

Data are presented as median [IQR] or frequencies (%)

AAH hypoplastic aortic arch, *AVSD* atrioventricular septal defect, *BSA* body surface area, *BVR* biventricular repair, *CoA* aortic coarctation, *DORV* double outlet right ventricle, *PAPVD* partial abnormal pulmonary venous drainage, *RVOTO/PA* right ventricular outflow tract obstruction/pulmonary atresia, *TAPVD* total abnormal pulmonary venous drainage, *TGA* transposition of the great arteries, *UVP* univentricular palliation

[a]Patient age and weight refer to the date of echocardiographic examination, which was used for retrospective analysis and measurement of indices

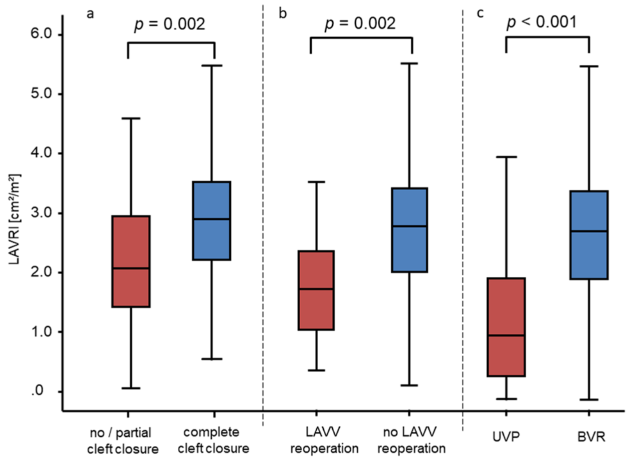


Fig. 3 **a** LAVRI according to strategy for primary LAVV repair. Patients are divided into two groups based on surgical strategy: Group 1: No/ partial cleft closure ($n=29$), group 2: complete cleft closure ($n=142$). **b** LAVRI according to requirement of LAVV reoperation. Patients are divided into patients with ($n=16$) and patients without reoperation ($n=155$). **c** LAVRI according to surgical strategy. Patients are divided into two groups: Group 1 UVP ($n=46$), Group 2 BVR ($n=171$). *LAVRI* left atrioventricular valve reduction index

significantly lower in patients receiving primary LAVV repair with no/partial cleft closure compared to patients receiving complete cleft closure (2.07 cm^2/m^2 [IQR 1.69] vs. 2.89 cm^2/m^2 [IQR 1.35]; $p=0.002$, Fig. 3a). Patients with no/ partial cleft closure required LAVV reoperation significantly more frequent than patients with complete cleft closure ($n_1=8/36$ (22.22%) vs. $n_2=17/248$ (6.85%); $p=0.007$). Twenty-five patients required a reoperation addressing the LAVV. Of these, 21 patients underwent secondary LAVV repair and 4 patients LAVV replacement. After initial re-repair of the LAVV, 4 patients required subsequent valve replacement after a median follow-up of 10.22 months [IQR 2.01]. According to intraoperative findings, major causes of moderate or severe LAVV regurgitation were dehiscence of the cleft suture ($n=8$), partial cleft closure ($n=12$), infeasible primary repair of double orifice ($n=6$) or leaflet prolapse ($n=1$). Most common reoperation techniques were redo cleft closure ($n=17$), annuloplasty ($n=3$) or commissuroplasty ($n=3$). AVSD type (complete, intermediate, partial) was not associated with requirement of LAVV reoperation ($p=0.781$). LAVV regurgitation at discharge after AVSD repair or before in-hospital reoperation was graded absent/ mild in 205 patients, moderate in 70 patients, and severe in 9 patients. Expectedly, the degree of LAVV regurgitation strongly correlated with the necessity of LAVV reoperation ($p<0.001$). LAVRI significantly differed between patients with absent/ mild and patients with moderate/ severe LAVV regurgitation at discharge (3.0 cm^2/m^2 [IQR 1.51] vs. 2.53 cm^2/m^2 [IQR 1.34], $p=0.007$). Median LAVV inflow pressure gradient at discharge did not significantly differ between patients with and without requirement for LAVV reoperation (1.80 mmHg [IQR 2.16] vs. 1.67 mmHg [IQR 1.53], $p=0.20$).

LAVRI was significantly lower in patients requiring LAVV reoperation compared to patients without an indication for reoperation (1.92 cm^2/m^2 [IQR 1.31] vs. 2.91 cm^2/m^2 [IQR 1.37], $p=0.002$, Fig. 3b). Patients with an LAVRI ≤ 2.03, equalling the 25th percentile of the BVR cohort, had a significantly higher risk for a reoperation addressing the LAVV (Odds Ratio: 5.79 [95% CI 1.99–16.86], $p=0.002$).

Surgical Strategy in Unbalanced AVSD

Of 68 patients undergoing UVP, 34 patients were palliated with Fontan completion and 34 patients were interstage including 21 patients with superior cavopulmonary anastomosis and 13 patients with an aortopulmonary shunt at last follow-up. Forty-six patients were characterized by right ventricular dominance and twelve patients by left ventricular dominance. In the UVP cohort, complex AVSD was diagnosed significantly more frequent than in the BVR cohort: Right ventricular outflow tract obstruction/ pulmonary atresia occurred in 35 patients, coarctation of the aorta/

Table 2 Echocardiographic parameters according to surgical strategy

Echocardiographic parameter/index	BVR	UVP	*p*-value
VSD size (cm)	0.73 [0.53]	0.89 [0.41]	**< 0.001**
mAVVI	0.49 [0.08]	0.35 [0.17]	**< 0.001**
LAVRI (cm^2/m^2)	2.80 [1.44]	1.18 [1.64]	**< 0.001**
VCR	0.93 [0.36]	0.55 [0.52]	**< 0.001**
RV/LV inflow angle (°)	97.71 [28.99]	75.71 [26.07]	**< 0.001**

Statistically significant results are given in bold letters

Data are presented as median [IQR]

mAVVI modified atrioventricular valve index, *BVR* biventricular repair, *LAVRI* left atrioventricular valve reduction index, *RV/LV* right ventricular/left ventricular, *UVP* univentricular palliation, *VCR* ventricular cavity ratio, *VSD* ventricular septal defect

Table 3 Area under the curve from receiver operating characteristic curve analysis of echocardiographic indices with regard to discrimination between BVR and UVP

Parameter	AUC	*p*-value	95% CI
VSD size (cm)	0.329	**< 0.001**	0.238–0.420
mAVVI	0.782	**< 0.001**	0.685–0.878
LAVRI (cm^2/m^2)	0.792	**< 0.001**	0.709–0.878
VCR	0.721	**< 0.001**	0.614–0.828
RV/LV inflow angle (°)	0.756	**< 0.001**	0.675–0.836

Statistically significant results are given in bold letters

AUC area under the curve, *BVR* biventricular repair, *CI* confidence interval, *LAVRI* left atrioventricular valve reduction index, *mAVVI* modified atrioventricular valve index, *RV/LV* right ventricular/left ventricular, *UVP* univentricular palliation, *VCR* ventricular cavity ratio, *VSD* ventricular septal defect

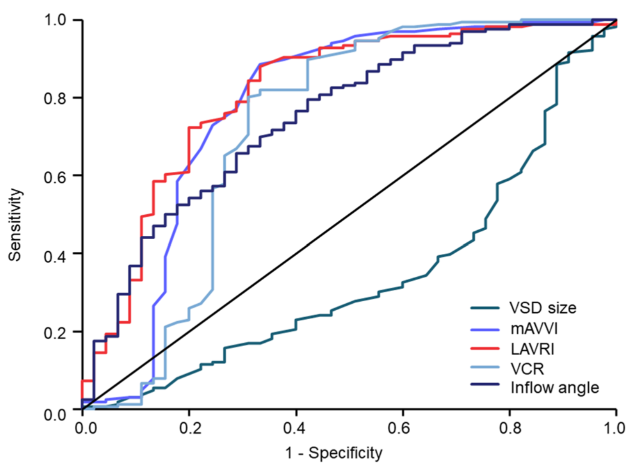


Fig. 4 Receiver operating curve analysis of each echocardiographic index concerning prediction of surgical strategy. *mAVVI* modified atrioventricular valve index, *BVR* biventricular repair, *LAVRI* left atrioventricular valve reduction index, *RV/LV* right ventricular/left ventricular, *VCR* ventricular cavity ratio, *VSD* ventricular septal defect

interrupted aortic arch in 14 patients, total or partial anomalous pulmonary venous connection in 28 patients, double outlet right ventricle in 19 patients, heterotaxy in 33 patients, and malposition of the great arteries in 37 patients (all $p \leq 0.007$, Table 1). Echocardiographic parameters and indices comparing patients who underwent BVR and UVP are listed in Table 2: LAVRI measurement was available in 46 of 68 patients (67.65%) and significantly differed between patients receiving UVP and BVR (1.18 cm^2/m^2 [IQR 1.64] vs. 2.80 cm^2/m^2 [IQR 1.44], $p < 0.001$, Table 2, Fig. 3c). In patients with right-dominant unbalanced AVSD median LAVRI was 0.83 cm^2/m^2 [IQR 1.12] and 3.24 cm^2/m^2 [IQR 1.59] in patients characterized by left ventricular dominance ($p < 0.001$). VSD size, mAVVI, VCR, and RV/LV inflow angle significantly diverged between patients undergoing BVR or UVP (Table 2). ROC analysis showed acceptable discrimination between surgical strategies for LAVRI, mAVVI, VCR, and inflow angle and unsatisfying discrimination for VSD size (Table 3, Fig. 4). Based on area under the curve (AUC) calculations, the accuracy of LAVRI in discriminating between BVR and UVP was superior to the other echocardiographic indices (Table 3, Fig. 4).

Fourteen patients diagnosed with unbalanced AVSD were considered suitable for biventricular approach: Twelve patients received primary biventricular repair and 2 patients biventricular conversion from prior single ventricle palliation (one-and-a-half biventricular repair with surgical correction of AVSD and leaving the superior cavopulmonary anastomosis in one and staged conversion with initial repair of total anomalous pulmonary venous return, secondary Kawashima operation and final Kawashima take-down and surgical AVSD repair in the other patient). Ten patients were characterized by right ventricular dominance and four patients by left ventricular dominance. Mortality and LAVV reoperation rate did not significantly differ between patients with balanced and unbalanced AVSD receiving BVR ($p_1 = 0.360$; $p_2 = 0.358$). In patients with unbalanced AVSD, partial or no cleft closure was performed significantly more frequent than in patients with balanced AVSD ($n_1 = 7/14$ (50.0%) vs. $n_2 = 29/270$ (10.74%), $p = 0.001$). In this particular patient cohort, LAVRI was significantly lower than in patients with balanced AVSD anatomy receiving BVR (1.55 cm^2/m^2 [IQR 2.15] vs. 2.87 cm^2/m^2 [IQR 1.37], $p = 0.002$). Postoperative course did not significantly vary between patients with balanced and unbalanced AVSD receiving BVR in terms of total hospital and intensive care unit (ICU) stay (total hospital stay: 10 days [IQR 8.0] vs. 12.0 days [IQR 9.0], $p_1 = 0.390$, ICU stay: 5.0 days [IQR 6.0] vs. 6.0 days [IQR 7.0], $p_2 = 0.092$). In patients with unbalanced AVSD a trend toward longer ventilation time was observed (105.0 h [IQR 183.0] vs. 53.0 h [IQR 111.75], $p = 0.042$].

Discussion

Despite improved survival rates of patients with AVSD, two major issues remain controversial concerning surgical AVSD repair: First, the reoperation rate of the LAVV and second the suitability for biventricular approach in unbalanced AVSD anatomy. In this study we introduced the left atrioventricular valve reduction index (LAVRI) for preoperative estimation of the resulting left atrioventricular valve area after complete cleft closure. We evaluated the usability of LAVRI in facilitating surgical decision-making concerning primary LAVV repair, estimating the risk of LAVV reoperation and predicting the suitability for biventricular approach in unbalanced AVSD.

Primary LAVV Repair and Risk of LAVV Reoperation

Late outcomes after surgical correction of AVSD are compromised by the substantial risk for reoperation of the LAVV, which results in considerable mortality and morbidity of this particular patient cohort [1–4]. Normal karyotype, moderate or severe pre– and postoperative LAVV regurgitation, LAVV dysplasia, and double orifice have been identified as risk factors for LAVV reoperation [1–4, 13]. Despite primary LAVV repair with complete cleft closure, deterioration of the LAVV competence is common after AVSD repair and contributes to an increased risk for reoperation [14]. In our cohort, LAVV reoperation occurred in 8.80% of patients after AVSD repair. Major causes for moderate or severe LAVV regurgitation requiring reoperation were dehiscence of the cleft suture, incomplete cleft closure or LAVV anomalies (such as double orifice and deficient mural or bridging leaflets), which were not addressed during primary LAVV repair. Complete cleft closure is generally favored to minimize reoperation risk, but pre- and intraoperative decision-making remains challenging since the LAVV apparatus is still fragile and prone to laceration at the age of 3 to 6 months, when AVSD repair is usually performed [1–4, 14]. Depending on atrioventricular valve morphology, equilibrating the optimal balance between residual LAVV regurgitation and a stenotic valve function may represent an enormous technical challenge. Our retrospective analysis revealed the feasibility of our developed LAVRI in assessing surgical options of primary LAVV repair: In patients with a LAVRI > 2.0 cm^2/m^2 the cleft was preferably closed completely, whereas in patients with a LAVRI ≤ 2.0 cm^2/m^2, LAVV cleft could only be closed partially or not closed at all (Fig. 2). In this patient cohort LAVV reoperation occurred significantly more frequent due to the development of moderate or severe LAVV regurgitation during follow-up. Additionally, a LAVRI ≤ 2.0 cm^2/m^2 was associated with an almost sixfold higher risk for LAVV reoperation. The preoperative prediction of an increased reoperation risk in patients with a LAVRI ≤ 2.0 cm^2/m^2 might be useful to provide more detailed information concerning the expected long-term outcome and prepare parents and treating physicians for a possible need of a LAVV reoperation after initial repair.

Suitability for BVR in Unbalanced AVSD

Due to the wide spectrum of unbalanced AVSD anatomy, no universal consensus exists, which parameters define the preferable surgical strategy and facilitate decision-making concerning the feasibility of biventricular approach [7, 15, 16]. Since mortality rates of patients with unbalanced AVSD undergoing single ventricle palliation are substantial, a biventricular repair should be favored [17, 18]. Del Nido et al. demonstrated a significant survival benefit in patients who received biventricular conversion from prior single ventricle palliation or staged biventricular recruitment compared to patients with definite univentricular palliation, even at the expense of a significantly higher number of postsurgical re-operations and re-interventions [11].

Since feasibility of biventricular repair depends on various anatomic features, such as ventricular size, AV valve morphology, inflow geometry, VSD size or associated cardiac malformations, a single echocardiographic index alone cannot adequately determine the appropriateness of surgical strategy. Generally, all indices evaluated in our study, except VSD size, proved satisfying identifiers of the magnitude of ventricular imbalance and were strongly associated with surgical strategy. Two fundamental factors seem crucial for BVR in unbalanced AVSD: First, AVSD anatomy including the size of left and right ventricular cavity and the extent of the disproportion of the atrioventricular junction and second the associated cardiac malformations.

The introduced LAVRI proved usable in predicting surgical strategy for primary LAVV repair in balanced AVSD and suitability for biventricular approach in unbalanced AVSD. In patients with unbalanced AVSD with dominant right ventricle receiving BVR, complete cleft closure was not feasible due to a small LAVV area (LAVRI ≤ 2.0 cm^2/m^2). These patients received primary LAVV repair with no or only partial cleft closure since the cleft was frequently the only component of the LAVV opening area. In these patients, frequency of LAVV reoperation was not higher compared to patients with balanced AVSD repaired with only partial or without cleft closure ($n_1 = 1/7$ (14.29%) vs. n_2 7/29 (24.14%), $p = 0.503$).

Conclusion

The introduced LAVRI is strongly associated with surgical strategy for balanced and unbalanced AVSD and may, therefore, prove valuable in the planning of surgical procedures and the prediction of postoperative results. Moreover, it adequately differentiates between ventricular imbalance suitable or unsuitable for biventricular repair. Surgical decision-making for biventricular approach in unbalanced AVSD cannot be based on one single index but combining LAVRI with previously reported echocardiographic indices might substantially increase accuracy of preoperative assessment and in turn result in improved surgical outcomes.

Limitations

There are several limitations to this study. This is a retrospective, single-center study with a small patient cohort. Further studies, preferably with a larger patient cohort and in a multi-center setting, are needed to evaluate the suitability of LAVRI in defining surgical strategy. The number of patients with unbalanced AVSD receiving BVR in our study is small; results of morbidity and mortality after BVR might change in a larger patient cohort. The skewed distribution of patients receiving UVP and BVR might confound the capacity of echocardiographic indices in defining surgical strategy. Additionally, no ventricular growth strategies were performed in our institution. Therefore, decision-making for BVR in unbalanced AVSD was performed based on preoperatively preexistent anatomic features without consideration of possible growth potential. Additionally, MRI analysis and measurement of ventricular end-diastolic volumes was not performed in this study, which is only based on echocardiographic evaluation of ventricular size and AV valve disproportion.

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Compliance with Ethical Standards

Conflict of interest All authors declare not to have any conflicts of interest.

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Die Ergebnisse dieser Studie verdeutlichen die Notwendigkeit einer dezidierten präoperativen Echokardiographie zur Indikationsstellung der Durchführung einer univentrikulären Palliation mittels Fontan-Operation bei Patientinnen und Patienten mit ventrikulärer Imbalance. Die nachfolgende Arbeit befasst sich mit der Inzidenz, dem klinischen Spektrum und den Risikofaktoren für das Auftreten einer FALD als häufigste Sekundärorganerkrankung nach einer Fontan-Operation.

4.2 Krankheitsspektrum sowie potentielle Einflussfaktoren auf die Entstehung und Ausprägung der FALD

In der vorliegenden Studie

Schleiger, A., Salzmann, M., Kramer, P., Danne, F., Schubert, S., Bassir, C., Müller, T., Müller, H.P., Berger, F., Ovroutski, S. Severity of Fontan-associated liver disease correlates with Fontan hemodynamics. Pediatric Cardiology, 02/2020; 736-746, 41.

erhielten 145 Fontan-Patientinnen und –Patienten unterschiedlichen Alters ein dezidiertes hepatologisches Nachsorgeprogramm, welches die Durchführung einer laborchemischen Analyse, einer standardisierten Lebersonographie sowie einer transienten Elastographie (TE) beinhaltete. Neben der hepatologischen Nachsorge wurden eine Echokardiographie, eine Testung der kardiopulmonalen Belastbarkeit mittels Spiroergometrie sowie eine invasive Messung der Fontan-Hämodynamik mittels Herzkatheteruntersuchung durchgeführt. Im Rahmen der Studie konnte nachgewiesen werden, dass bei 70 % der eingeschlossenen Fontan-Patientinnen und –Patienten eine FALD vorlag. Die Mehrheit der untersuchten Personen wies eine deutliche Erhöhung der γGT und des Bilirubins auf. Die häufigsten sonographisch detektierbaren morphologischen Veränderungen umfassten ein heterogenes Leberparenchym, eine Dilatation sowie Kaliberschwankungen der Lebervenen sowie eine Dysmorphie der Leberlappen. Bei 20 Patientinnen und Patienten wurde eine fortgeschrittene Leberzirrhose diagnostiziert. Die Messwerte der TE befanden sich bei allen untersuchten Personen außerhalb des für andere Lebererkrankungen definierten Normwertbereiches. Diese Studie belegte zusätzlich einen Zusammenhang zwischen einer kompromittierten Fontan-Hämodynamik und der Ausprägung von FALD. Patientinnen und Patienten mit einer sonographisch nachweisbaren Leberzirrhose wiesen eine deutlich reduzierte kardiopulmonale Belastbarkeit auf. Zusätzlich konnten bei diesen Personen im Rahmen einer Herzkatheteruntersuchung signifikant erhöhte Druckwerte im Fontan-Kreislauf, den Lebervenen und im Systemventrikel gemessen werden. Eine multivariate Risikofaktoranalyse identifizierte die Zeit nach der Fontan-Operation als wesentlichen Risikofaktor für die Entstehung der FALD.

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ORIGINAL ARTICLE

Severity of Fontan-Associated Liver Disease Correlates with Fontan Hemodynamics

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Abstract

Fontan-palliated patients are at risk for the development of Fontan-associated liver disease (FALD). In this study, we performed a detailed hemodynamic and hepatic assessment to analyze the incidence and spectrum of FALD and its association with patients' hemodynamics. From 2017 to 2019, 145 patients underwent a detailed, age-adjusted hepatic examination including laboratory analysis (FibroTest®, $n=101$), liver ultrasound ($n=117$) and transient elastography (FibroScan®, $n=61$). The median patient age was 16.0 years [IQR 14.2], and the median duration of the Fontan circulation was 10.3 years [IQR 14.7]. Hemodynamic assessment was performed using echocardiography, cardiopulmonary exercise capacity testing and cardiac catheterization. Liver ultrasound revealed hepatic parenchymal changes in 83 patients (70.9%). Severe liver cirrhosis was detectable in 20 patients (17.1%). Median liver stiffness measured by FibroScan® was 27.7 kPa [IQR 14.5], and the median Fibrotest® score was 0.5 [IQR 0.3], corresponding to fibrosis stage ≥ 2. Liver stiffness values and Fibrotest® scores correlated significantly with Fontan duration ($P_1=0.013$, $P_2=0.012$). Exercise performance was significantly impaired in patients with severe liver cirrhosis ($P=0.003$). Pulmonary artery pressure and end-diastolic pressure were highly elevated in cirrhotic patients ($P_1=0.008$, $P_2=0.003$). Multivariable risk factor analysis revealed Fontan duration to be a major risk factor for the development of FALD ($P<0.001$, OR 0.77, CI 0.68–0.87). In the majority of patients, hepatic abnormalities suggestive of FALD were detectable by liver ultrasound, transient elastography and laboratory analysis. The severity of FALD correlated significantly with Fontan duration and impaired Fontan hemodynamics. A detailed hepatic assessment is indispensable for long-term surveillance of Fontan patients.

Keywords Fontan-associated liver disease · Liver cirrhosis · Fontan surveillance · Fontan hemodynamics · Risk factors for FALD

Introduction

The Fontan operation was introduced in 1968 by François M. Fontan as surgical palliation of tricuspid atresia [1]. Despite various modifications concerning surgical techniques, it has remained the palliative standard procedure for patients with univentricular physiology. With advances in surgical techniques, perioperative management, diagnostic capacities and adequate patient selection, early- and long-term survival of Fontan-palliated patients has improved over the past few decades [2–4]. Since the majority of Fontan patients reaches adulthood, there is growing evidence of end-organ dysfunction, especially affecting the liver [5, 6]. Fontan-associated liver disease (FALD) includes all abnormalities in liver structure and function which result from the non-physiological Fontan

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circulation: liver fibrosis, liver cirrhosis and hepatocellular carcinoma [7–10]. The etiology of FALD seems to be multifactorial, involving hypoxic and ischemic liver insults before and during the multi-step surgical palliation pathway for patients with univentricular anatomy [11]. The hallmarks of the Fontan circulation—diminished cardiac output and chronic central venous congestion—augment the structural and functional alteration of the liver: impaired hepatic vein drainage, sinusoidal dilatation and hemorrhagic necrosis result in the development of perisinusoidal and pericentral fibrosis leading to FALD [11]. Although various studies focus on the detection of FALD, hepatic assessment is not routinely included in Fontan surveillance, and risk factors for FALD development have not yet been identified.

In this study we performed a detailed hemodynamic and hepatic assessment to examine the incidence and spectrum of FALD and to analyze its association with hemodynamic parameters determined by echocardiography, cardiopulmonary exercise capacity testing and cardiac catheterization.

Patients and Methods

Patients

From July 2017 to July 2019, 145 of 475 (30.5%) Fontan patients treated in our institution underwent a detailed, age-adjusted hepatic assessment including liver ultrasound and laboratory analysis in patients > 7 years of age, and additional transient elastography in patients > 14 years. Hemodynamic assessment consisted of echocardiography and cardiopulmonary exercise testing. Cardiac catheterization was performed in patients with a clinical indication for an invasive evaluation of hemodynamics, e.g. clinical deterioration, impaired exercise capacity or decreased oxygen saturation. Two patients who received the Fontan operation as adults and died from early Fontan failure were excluded from further analysis. In patients with elevated liver enzymes and bilirubin, other causes for liver disease, such as infectious hepatitis, were ruled out. In our analysis, FALD was defined as the combination of elevated liver enzyme or bilirubin levels and abnormal liver ultrasound findings in accordance with reports of other investigators [12, 13]. Following the findings of Horowitz et al. [14] and Moon et al. [15], the combination of heterogeneous echotexture, surface nodularity, lobar atrophy or hypertrophy, and splenomegaly defined ultrasonographic diagnosis of liver cirrhosis. The study was approved by the institutional review board and the institutional ethics committee (decision number EA2/127/16). Informed consent was obtained from all individual participants included in the study.

Laboratory Assessment

Liver function was evaluated using the liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (γGT), total bilirubin, α_2-macroglobulin, apolipoprotein A_1 and haptoglobin. The laboratory parameters alanine aminotransferase, γ-glutamyltransferase, total bilirubin, α_2-macroglobulin, apolipoprotein A_1 and haptoglobin were measured in accordance with recommendations required by BioPredictive (Paris, France) to calculate biomarker fibrosis scores with FibroTest®. FibroTest® was computed on the BioPredictive website (www.biopredictive.com). The calculated Fibrotest® score was converted to liver fibrosis stage according to the METAVIR histological classification for liver biopsies [16].

Liver Ultrasound and Transient Elastography

Following our protocol for hepatic Fontan surveillance, patients between 7 and 18 years of age underwent liver ultrasound by an experienced pediatric radiologist, while patients older than 18 years were referred to an experienced hepatologist. Liver ultrasound was performed following a multidisciplinary-developed protocol including measurement of liver and spleen size, examination of liver parenchyma and liver vein morphology, signs of portal hypertension, and Doppler sonography of liver vessels. Transient elastography (TE, FibroScan®, Echosens, France) was performed using a size M transducer in Fontan patients older than 14 years. A median value of 10 measurements of the right lobe of the liver was calculated. In patients with abnormal abdominal anatomy, e.g. situs inversus or heterotaxy, transient elastography was not considered diagnostically conclusive. Liver stiffness was reported in kilopascals (kPa).

Hemodynamic Assessment

Hemodynamic assessment was performed following our protocol for Fontan surveillance and included echocardiography and cardiopulmonary exercise capacity testing. Echocardiographic systolic function of the single ventricle was graded as normal/mildly, moderately or severely impaired according to visual assessment of ventricular contractility performance. The degree of atrioventricular (AV) valve regurgitation was classified as none/mild, moderate or severe referring to the width of the colour Doppler regurgitation jet. Functional cardiopulmonary capacity testing was performed following a standardized institutional protocol using a cycle ergometer. Exercise was continued to the point of patients' maximum tolerance. Maximal oxygen uptake (VO_2 max) was measured in ml/kg/min and normalized in % of predicted VO_2 max using age-, gender- and body dimension-adjusted normative values suggested by Cooper et al. [17]. Cardiac catheterization was performed in patients with a clinical indication for an invasive hemodynamic evaluation (s.a.). The standard catheterization protocol included measurement of pulmonary artery pressure (PAP), systemic ventricular end-diastolic pressure (EDP), liver vein pressure (LVP) and liver vein wedge pressure (LVWP). Transpulmonary gradient (TPG) was calculated by the difference between mean pulmonary artery pressure and pulmonary capillary wedge pressure.

Statistical Analysis

Demographic and surgical data were obtained from the medical records of the German Heart Center Berlin/ Department of Pediatric Cardiology at Charité Universitätsmedizin Berlin. Data are expressed as median and interquartile range calculated as 75th minus 25th percentile. Fontan duration was defined as the time between the date of Fontan operation and end of follow-up. Correlation analysis was performed using the Spearman or Kruskal–Wallis *H* test. The impact of ventricular function and the degree of AV valve regurgitation on the development of FALD were analyzed using the chi-square test. Risk factors for the development of FALD were evaluated using logistic regression analysis. Variables with $P<0.1$ were included in a multivariable regression model. Statistic analysis was performed using the SPSS statistical software program SPSS for Windows (version 23, IBM Corp., Armonk, NY, USA). A P value <0.05 was considered significant.

Table 1 Patient characteristics

Demographic assessment	No. (%)/median [IQR]
Patient age (years)	16.0 (14.2)
Age at Fontan operation (years)	3.5 (3.3)
Duration of Fontan circulation (years)	10.3 (14.7)
Gender	
Male	71 (49.0)
Underlying anatomy	
Tricuspid atresia	45 (31.0)
Double inlet left ventricle	21 (14.5)
Hypoplastic left heart syndrome	22 (15.2)
Complex transposition of great arteries	11 (7.6)
Unbalanced AVSD	16 (11.0)
RV hypoplasia with PA/IVS	11 (7.6)
Other	19 (13.1)
Predominant ventricular morphology	
Left	95 (66.5)
Right	50 (34.5)
Fontan type	
Intracardiac lateral tunnel	22 (15.2)
Extracardiac conduit	109 (75.2)
Other	14 (9.7)
Fenestration	
Primary	61 (14.5)
Secondary	6 (4.1)
PLE	12 (8.3)

AVSD atrioventricular septal defect, *RV* right ventricle, *PA/IVS* pulmonary atresia with intact ventricular septum, *PLE* protein-losing enteropathy

Results

Patient Characteristics

Table 1 displays baseline patient characteristics of the total cohort. From July 2017 to July 2019, 145 Fontan-palliated patients received a detailed, age-adjusted hepatic assessment in our institution. The total cohort consisted of 80 pediatric (55.2%) and 65 adult patients (44.8%). The median patient age was 16.0 years [IQR 14.2], and median age at Fontan operation was 3.7 years [IQR 3.3]. The most common underlying morphologies are listed in Table 1 and consisted of tricuspid atresia ($n=45$, 31.0%), double inlet left ventricle ($n=21$, 14.5%) and hypoplastic left heart syndrome ($n=22$, 15.2%). Left ventricular dominance was found in 95 patients (65.5%). Absent sinus rhythm was found in 41 patients (28.3%), 29 of whom required a permanent pacemaker. The median duration of Fontan circulation was 10.3 years [IQR 14.7]. The Fontan procedure was performed using extracardiac conduit in 109 patients (75.2%), intracardiac lateral tunnel in 22 patients (15.2%) and other surgical modifications in 14 patients (9.7%). Sixty-one patients (42.1%) received primary fenestration. In 29 patients the fenestration was closed by intervention after a median time of 1.6 years [IQR 2.4]. Two patients (1.4%) were diagnosed with plastic bronchitis and 12 patients (8.3%) with protein-losing enteropathy. At the time of investigation, one patient with plastic bronchitis and seven patients with protein-losing enteropathy were in stable remission.

Laboratory Assessment

The results of laboratory analysis for the total cohort are listed in Table 2. According to age-adjusted standard values of our laboratory, alanine aminotransferase (ALT) was elevated in 31 patients, aspartate aminotransferase (AST) in 27 patients, γ-glutamyltransferase (γGT) in 115 patients and bilirubin in 32 patients. Thrombocytopenia was found in 37 patients. The median Fibrotest® fibrosis score was 0.5 [IQR 0.3]. With regard to the Fibrotest® calculation, fibrosis was staged F2 in the majority of our patients ($n=49$; Table 2).

Table 2 Results from hemodynamic and hepatic assessment

Hepatic assessment	Median (IQR)	No. (%) abnormal
Laboratory analysis		
AST (U/l)	36.6 (13.5)	27/133 (20.3)
ALT (U/l)	34.7 (16.5)	31/133 (23.3)
γGT (U/l)	71.1 (43.0)	115/133 (86.5)
Bilirubin (mg/dl)	1.0 (0.6)	32/130 (24.6)
Thrombocytes (K/µl)	207.2 (87.0)	37/133 (27.8)
Fibrotest®		
F0		6/101 (5.9)
F1		8/101 (7.9)
F2		49/101 (48.5)
F3		24/101 (23.8)
F4		14/101 (13.9)
Liver ultrasound findings		
Hepatomegaly		17/117 (14.5)
Splenomegaly		38/117 (32.5)
Heterogeneous parenchymal echotexture		83/117 (70.9)
Lobar atrophy/hypertrophy		27/117 (23.1)
Liver vein dilatation		69/117 (59.0)
Abnormal liver vein architecture		32/117 (27.4)
Hyperechogenic lesions		10/117 (8.5)
Surface nodularity		18/117 (15.4)
Ascites		13/117 (11.1)
Transient elastography	27.7 (14.5)	
Hemodynamic assessment		
Impairment of ventricular function		
None/mild		122/145 (84.1)
Moderate		20/145 (13.8)
Severe		3/145 (2.1)
AV valve insufficiency		
None/mild		122/145 (84.1)
Moderate		21/145 (14.5)
Severe		2/145 (1.4)
PAP (mmHg)	12.0 (4.0)	
EDP (mmHg)	8.0 (3.8)	
TPG (mmHg)	3.5 (3.0)	
LVP (mmHg)	12.0 (5.0)	
LVWP (mmHg)	13.0 (4.0)	

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *γGT* γ-glutamyltransferase, *PAP* pulmonary artery pressure, *EDP* end-diastolic ventricular pressure, *TPG* transpulmonary gradient, *LVP* liver vein pressure, *LVWP* liver vein wedge pressure

Liver Ultrasound and Transient Elastography

Liver ultrasound revealed hepatic parenchymal changes in 83 patients (Table 2). The most common ultrasound findings were heterogeneous echotexture ($n=83$), liver vein dilatation ($n=69$), altered liver vein morphology ($n=32$) and segmental hypertrophy or atrophy ($n=25$). Hyperechogenic lesions were present in 10 patients, and sonographic signs of liver cirrhosis were detectable in 20 patients (17.1%). Median TE values were 28.0 kPA [IQR 13.7] in the pediatric and 27.6 kPa [IQR 14.5] in the adult population. Both values were well above pediatric and adult TE cutoff values of 6.8 kPa and 7.5 kPA for severe liver fibrosis suggested by Fitzpatrick et al. [18] and Stebbing et al. [19]. Liver stiffness values were significantly higher in patients with sonography-detectable liver cirrhosis than in patients without ($P=0.017$). Fibrotest® fibrosis score correlated mildly with liver stiffness values measured by Fibroscan®

($P = 0.045$). No correlation was found between sonographic evidence of structural hepatic damage and Fibrotest® fibrosis score ($P = 1.297$).

Hemodynamic Assessment

Echocardiographic examination was available in 145 patients and revealed no or mild impairment of systolic function in 122 patients, moderate impairment in 20 patients and severe impairment in three patients (Table 2). AV valve insufficiency was graded none or mild in 122 patients, moderate in 21 patients and severe in two patients. No correlation was found between systolic ventricular function, the degree of AV valve insufficiency and the incidence and severity of FALD in the form of liver cirrhosis.

Exercise capacity testing was performed in 123 patients (84.8%). Median VO_2 max was 25.6 ml/min/kg [IQR 8.5], equalling 64.8% [IQR 24.4] of age-, gender-, weight- and height-adjusted normative values. Normalized maximal oxygen uptake correlated strongly with the incidence of FALD ($P = 0.012$) and ultrasonography-detectable liver cirrhosis (Fig. 1; $P = 0.003$).

Seventy-six patients (53.1%) received invasive hemodynamic evaluation using cardiac catheterization; results are shown in Table 2. Invasive pressure measurement revealed a median PAP of 12.0 mmHg [IQR 4.0], EDP of 8.0 mmHg [IQR 3.8] and a median TPG of 3.5 mmHg [IQR 3.0]. Median liver vein pressure was 12.0 mmHg [IQR 5.0] and liver vein wedge pressure 13.0 mmHg [IQR 4.0]. PAP, EDP and LVWP were significantly higher in patients with sonography-detectable cirrhosis ($P_1 = 0.008$, $P_2 = 0.003$, $P_3 = 0.029$; Fig. 2). TPG did not correlate with the presence of liver cirrhosis ($P = 0.175$). Liver vein wedge pressure correlated strongly with liver stiffness values measured by Fibroscan® ($P_1 = 0.005$). The presence of a primary fenestration had no statistically significant impact on the incidence of FALD ($P = 0.138$) or liver cirrhosis ($P = 0.299$).

The Impact of Fontan Duration on Hemodynamics and FALD

In our cohort, Fontan duration showed a strong correlation with Fontan hemodynamics and hepatic abnormalities: pulmonary artery pressure significantly increased with the duration of the Fontan circulation ($P = 0.026$). A significant decrease in exercise capacity was detected with prolonged time post-Fontan ($P < 0.001$). Liver stiffness values measured by transient elastography and fibrosis score calculated by Fibrotest® both correlated strongly with the duration of the Fontan circulation ($P_1 = 0.013$, $P_2 = 0.012$; Fig. 3). Fontan duration was significantly longer in patients with severe liver cirrhosis than in patients without (20.9 years [IQR 11.6] vs. 8.6 years [IQR 11.6], $P < 0.001$; Fig. 4).

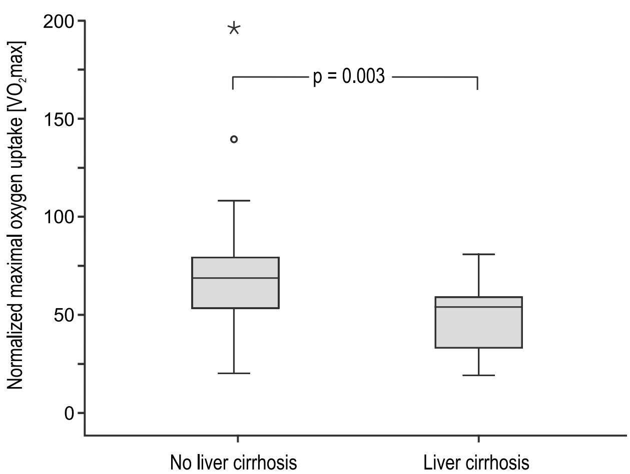


Fig. 1 Relationship between exercise capacity (maximal oxygen uptake, VO_2max) and liver cirrhosis. Data are shown as box plots representing two patient groups: patients with liver cirrhosis ($n = 19$) and without liver cirrhosis ($n = 81$). The top and the bottom of the rectangle indicate the 75th and 25th percentiles, and the middle horizontal line the median value. The vertical line extends from the maximal to the minimal VO_2max value of each group

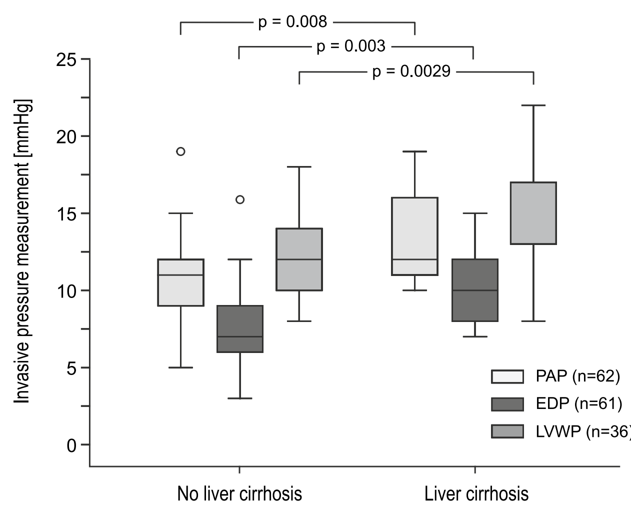


Fig. 2 Correlation between invasively measured hemodynamic parameters and liver cirrhosis. Data are shown as box plots representing two patient groups: patients with and without liver cirrhosis. The top and the bottom of the rectangle indicate the 75th and 25th percentiles, and the middle horizontal line the median value. The vertical line extends from the maximal to the minimal invasively measured pressure in each group. Light gray box plots display values of pulmonary artery pressure of patients with liver cirrhosis ($n = 14$) and without liver cirrhosis ($n = 48$). Gray box plots with dashed black lines represent end-diastolic pressure of patients with liver cirrhosis ($n = 14$) and patients without ($n = 47$). Dark gray box plots display liver vein wedge pressure in cirrhotic ($n = 9$) and non-cirrhotic patients ($n = 29$). *PAP* pulmonary artery pressure, *EDP* end-diastolic pressure, *LVWP* liver vein wedge pressure

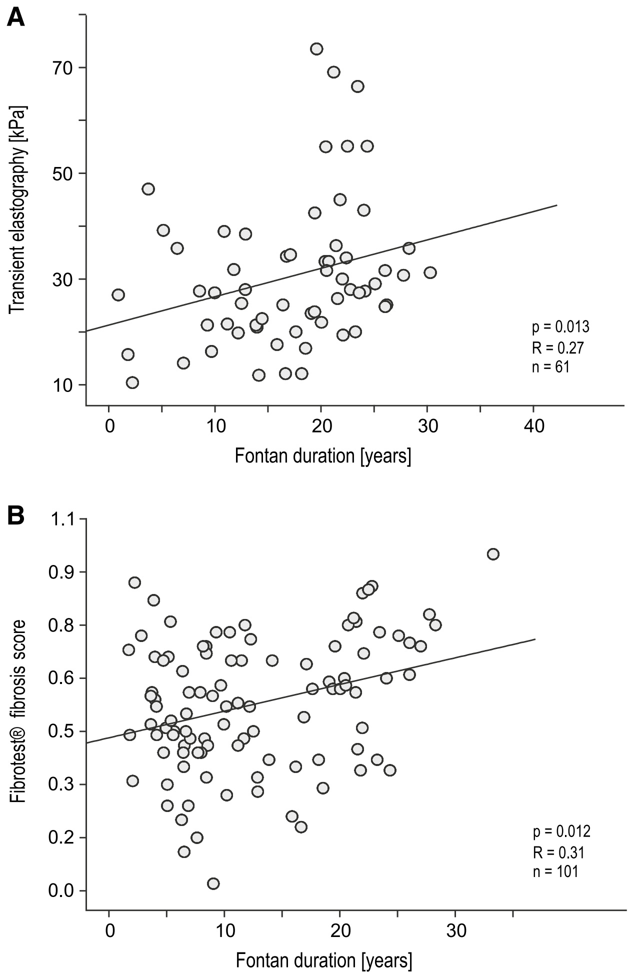


Fig. 3 Scatter diagrams with regression lines representing the correlation between the duration of the Fontan circulation (ordinate) and liver stiffness values measured by transient elastography (abscissa, **a**) and Fibrotest® fibrosis score (abscissa, **b**)

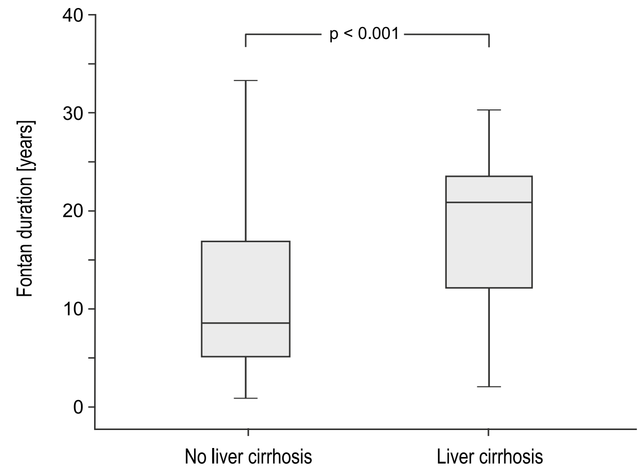


Fig. 4 Correlation between the duration of the Fontan circulation and liver cirrhosis. Data are shown as box plots representing two patient groups: patients with liver cirrhosis ($n=20$) and those without liver cirrhosis ($n=100$). The top and the bottom of the rectangle indicate the 75th and 25th percentiles, and the middle horizontal line the median value. The vertical line extends from the maximal to the minimal time post Fontan of each group

Risk Factor Analysis for the Development of FALD

Univariable risk factor analysis revealed Fontan duration, Fontan type and the absence of sinus rhythm to be significantly associated with FALD development (Table 3). Of the possible risk factors investigated in multivariable regression analysis, Fontan duration was found to be an independent risk factor for FALD (Table 3). Ventricular morphology did not influence FALD manifestation.

Algorithm for Hemodynamic and Hepatic Fontan Surveillance

Based on the findings presented in this study, we developed an algorithm for Fontan surveillance, which is demonstrated in Figs. 5, 6 and 7. We recommend annual or biannual referral of every Fontan-palliated patient to a specialized center for hemodynamic assessment including a detailed clinical examination, electro- and echocardiography, exercise capacity testing and laboratory analysis. In the case of clinical deterioration, cyanosis, reduced cardiopulmonary performance, arrhythmia, impaired ventricular function or increased AV valve regurgitation, a cardiac catheterization and/or MRI might be indicated for further hemodynamic evaluation. Additionally, a screening for second-organ diseases such as renal failure, frailty, chronic venous insufficiency and especially Fontan-associated liver disease should be performed.

According to our findings, in the majority of patients, the first hepatic abnormalities are evident 4 or 5 years after the Fontan operation. Therefore, we recommend a routine hepatic assessment including laboratory analysis (e.g. liver enzymes, bilirubin, thrombocytes) and liver ultrasound from the age of 7 years. Patients with a complicated course after the Fontan operation including early Fontan failure should receive routine hepatic surveillance before reaching 7 years of age. Patients with signs of liver cirrhosis should be referred to an experienced hepatologist and monitored closely for development of hepatocellular carcinoma or portal hypertension, including measurement of alpha-fetoprotein, liver sonography in 6-month intervals and performance of gastroscopy for diagnosis and treatment of gastroesophageal varices. In patients with tumor-suspicious lesions, a liver MRI is indicated.

Our findings underline the strong interrelation between Fontan hemodynamics and the development of Fontan-associated liver disease. Therefore, a detailed hepatic assessment

Table 3 Uni- and multivariable risk factor analysis for the development of FALD

Variable	Univariable analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Systemic ventricle	0.83	0.35–2.0	0.681			
Fontan type	0.36	0.11–1.14	**0.082**	0.3	0.05–0.12	0.443
Sinus rhythm	0.24	0.06–0.41	**0.008**	0.21	0.08–0.26	0.298
Fontan duration	0.78	0.72–0.89	**< 0.001**	0.77	0.68–0.87	**< 0.001**

OR odds ratio, *CI* confidence interval

P values considered statistically significant are highlighted in bold

should be performed when a patient presents with impaired hemodynamics (Figs. 5, 6). Conversely, progression of hepatic damage such as an increase in liver enzymes, sonographic signs of severe liver fibrosis or liver cirrhosis, or liver stiffness values > 30 kPA should prompt a detailed hemodynamic evaluation (Fig. 7).

Since every Fontan-palliated patient has a unique anatomy, this algorithm should only be considered as a recommendation for patients with an uncomplicated clinical course after Fontan operation and without signs of Fontan failure. The diagnostic and therapeutic approach should be individualized for each Fontan patient.

Discussion

Fontan-associated liver disease is the most common second-organ dysfunction in Fontan-palliated patients, and is associated with increased morbidity and mortality [20–22]. This is the first study to perform a detailed, noninvasive hepatic assessment to examine the incidence and spectrum of FALD and to analyze its association with hemodynamic parameters determined by echocardiography, exercise capacity testing and cardiac catheterization.

Over the past few years, various invasive and noninvasive diagnostic instruments have been proposed for the detection of FALD, including liver biopsy, laboratory assessment, liver ultrasound, liver CT or MRI, and transient elastography [11–13, 23]. Although histopathological evaluation is considered the gold standard in the diagnosis of liver disease, in our study we focused on noninvasive assessment, considering that liver biopsy is associated with increased risk due to anticoagulation treatment and the unique vein anatomy of Fontan patients. Concerning long-term surveillance, noninvasive diagnostic instruments also appear to be more feasible and reproducible in the clinical setting.

Noninvasive Diagnostic Instruments for the Detection of FALD

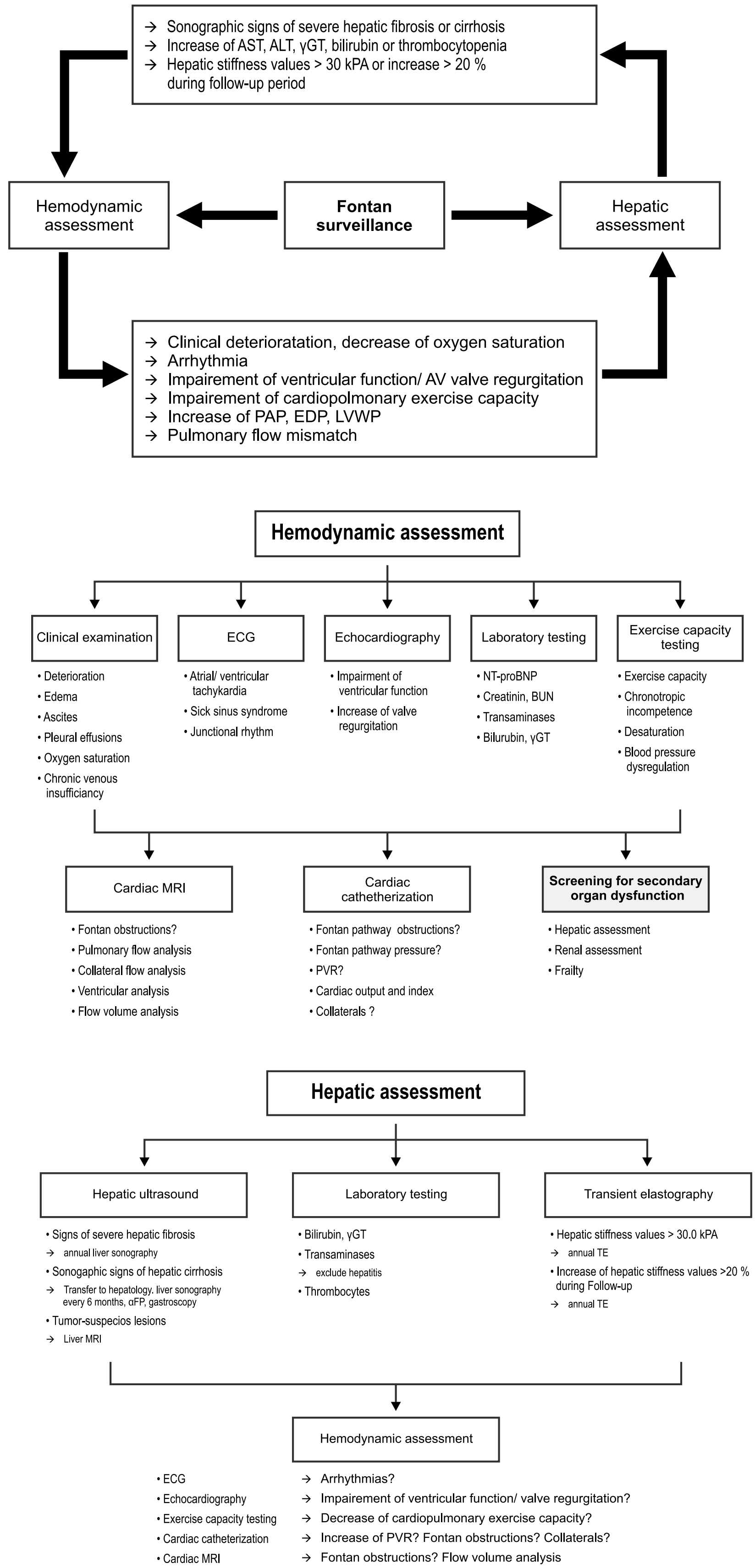
Transient Elastography

Transient elastography is considered a rapid and noninvasive diagnostic instrument to assess liver fibrosis by measuring liver stiffness [11]. Various studies report performing transient elastography in pediatric and adult Fontan patients with inconsistent results concerning correlation of TE values and Fontan duration, Fontan pressure or laboratory parameters [12–14]. In our cohort, a strong correlation was found between liver stiffness values and the duration of the Fontan circulation and liver fibrosis score calculated by Fibrotest®. TE values did not correlate with pulmonary artery pressure or EDP, suggesting that venous congestion does not mainly interfere with liver stiffness measurement. Moreover, in patients with sonographic detectable cirrhosis TE values were significantly higher than in patients without. These findings indicate TE might be useful to detect structural hepatic damage in Fontan patients. Nevertheless, normative liver stiffness values have to be validated for this particular patient cohort using laboratory tests and liver ultrasound.

Liver Ultrasound

Liver ultrasound is one of the most important diagnostic instruments for the detection of severe hepatic damage, such as liver cirrhosis. In our cohort, liver ultrasound revealed hepatic parenchymal changes in the majority of our patients. Severe liver cirrhosis was diagnosed based on sonographic scoring in 20 patients [14, 15]. Tumor-suspicious lesions were detected by liver ultrasound in three patients, but hepatocellular carcinoma was excluded by MRI. Based on its feasibility and reliability in the detection of hepatic damage

Figs. 5–7 Algorithm for hemodynamic and hepatic assessment of Fontan-palliated patients. *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γGT* γ-glutamyltransferase, *kPA* kilopascal, *PAP* pulmonary artery pressure, *EDP* end-diastolic ventricular pressure, *LVWP* liver vein wedge pressure, *ECG* electrocardiogram, *AV* atrioventricular, *BUN* blood urea nitrogen, *TE* transient elastography



liver, ultrasound should be performed in every Fontan patient during follow-up.

Laboratory Assessment

Laboratory assessment revealed an elevation of γGT in 86.5% of the total cohort. γGT is an enzyme located on the external surface of cellular membranes. The hallmarks of Fontan hemodynamics—low cardiac output and chronic venous congestion—may diminish vascular supply of intrahepatic bile ducts, leading to endothelial injury and release of γGT. Moreover, as a marker of increased oxidative stress, elevated γGT is associated with augmented risk of cardiovascular disease and heart failure [24]. γGT elevation is common in FALD but does not seem to correlate with its extent. In our cohort, the liver fibrosis score calculated by Fibrotest® showed a strong correlation with the duration of the Fontan circulation, a mild correlation with liver stiffness values measured by Fibroscan®, but no correlation with liver ultrasound findings. Given these incoherent results, further studies are needed to evaluate the predictive ability of the Fibrotest® fibrosis score with regard to liver fibrosis in Fontan patients.

All in all, our study demonstrates that one diagnostic instrument alone is ineffective in detecting Fontan-associated liver disease. Therefore, we propose the combination of laboratory analysis, transient elastography and liver ultrasound as basic hepatic screening for FALD in Fontan patients.

Impact of Fontan Hemodynamics on FALD

The development of Fontan-associated liver disease is based on a multi-step etiology including hypoxic insults, chronic venous congestion and low cardiac output [6]. This study revealed a high incidence of FALD among our patients based on laboratory and sonographic abnormalities found during examination. The severity of FALD varied between slightly elevated liver enzymes, minimal hepatic parenchymal changes and severe hepatic damage in the form of liver cirrhosis. In patients diagnosed with FALD, Fontan duration was significantly longer than in patients without (14.2 years [IQR 13.3] vs. 5.1 years [IQR 3.7]; $P<0.001$). This significant correlation was also detected in patients with severe liver cirrhosis.

In our study, PAP, EDP and LVWP were not associated with the incidence of FALD, but correlated strongly with its severity. Cardiopulmonary exercise capacity was significantly decreased in patients diagnosed with both FALD and severe liver cirrhosis. Since PAP, EDP and LVWP exhibit a small variance and are not highly elevated in compensated Fontan patients compared with patients suffering from Fontan failure, a statistically significant increase might only become evident in patients with severe, but not mild, organ damage. In comparison, cardiopulmonary exercise testing seems to be more sensitive to detecting changes in Fontan hemodynamics. This might be explained by chronic venous congestion leading to diminished preload reserve in Fontan patients, which can be demonstrated by worsened cardiopulmonary performance. Our results confirm that impaired hemodynamics lead to severe hepatic damage. Conversely, these findings underline the importance of monitoring end-organ damage to detect impairment of Fontan hemodynamics. Further studies are needed to analyze and grade the severity of Fontan-associated liver disease and investigate the impact of hemodynamic changes during follow-up.

Risk Factor Analysis

Univariable risk factor analysis revealed Fontan duration, Fontan type and absent sinus rhythm to be risk factors for FALD. The influence of Fontan type (intracardiac/lateral tunnel vs. extracardiac conduit) on FALD manifestation may reflect the change in surgical technique from late to early Fontan era, and underlines the importance of time post-Fontan in the development of end-organ damage.

The importance of atrial contraction in Fontan hemodynamics and the negative effect of arrhythmias and pacemaker dependency on long-term outcome in Fontan patients have already been described by other investigators [25]. Our results imply that absent atrial contraction leads to impaired atrial filling, reduced ventricular preload and diminished cardiac output. The consequences are elevated atrial and central venous pressure, which increases venous congestion and may aggravate the development of FALD.

In multivariable analysis, Fontan duration was found to be the strongest independent risk factor for FALD. These results underline the fact that FALD manifestation is inevitable. Consequently, a detailed hepatic assessment is mandatory in long-term surveillance of Fontan patients.

Algorithm for Fontan Surveillance

Based on our findings, we developed a diagnostic algorithm for hemodynamic and hepatic Fontan surveillance. This algorithm highlights the strong interrelation between Fontan hemodynamics and the development of Fontan-associated liver disease: progression of hepatic damage should result in a detailed hemodynamic evaluation and vice versa.

Conclusion

Fontan-associated liver disease is the most common second-organ dysfunction in Fontan-palliated patients. In 70.9% of our patients, hepatic abnormalities suggestive of FALD were detectable by liver ultrasound, transient elastography and laboratory analysis. The incidence and spectrum of FALD correlate strongly with exercise capacity and Fontan hemodynamics. Fontan duration was found to be an independent risk factor for the development of FALD. FALD surveillance is imperative in the monitoring of Fontan-palliated patients.

Limitations

There are several limitations to this study which should be noted. First, this is a prospective, cross-sectional study which includes many diagnostic instruments for hepatic and hemodynamic assessment. Therefore, not every patient received every diagnostic procedure mentioned, due to either death, noncompliance, movement, or missing indication for invasive procedures (e.g. cardiac catheterization). Second, we focused on noninvasive diagnostic instruments to detect Fontan-associated liver disease. Therefore, histological assessment to evaluate the extent and severity of liver alterations is missing. Third, although liver disease is common in Fontan patients, no universal definition of FALD exists, and further studies are needed to implement terminology and diagnostic and therapeutic algorithms. Fourth, risk factor analysis was limited by the number of patients included in the study.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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Der Untersuchung der Inzidenz, des Spektrums der klinischen Manifestation und der potentiellen Risikofaktoren für die Entstehung der FALD folge eine Graduierung der Schweregrade der FALD anhand eines neu eingeführten FALD-Scores. Weiterhin wurde der Zusammenhang zwischen den FALD Schweregraden und der Hämodynamik der Fontan-Zirkulation und insbesondere dem Versagen der Fontan-Zirkulation ermittelt.

4.3 Erkennen eines Versagens der Fontan-Zirkulation durch Graduierung der FALD

Im Rahmen der Arbeit,

Schleiger, A., Kramer, P., Salzmann, M., Danne, F., Schubert, S., Bassir, C., Müller, T., Tacke, F., Müller, H.P., Berger, F., Photiadis, J., Ovroutski, S. Evaluation of Fontan failure by classifying the severity of Fontan-associated liver disease: a single-center cross sectional study. European Journal of Cardio-Thoracic Surgery, 10/2020, 341-348, 59.

welche 129 Fontan-Patientinnen und -Patienten einschloss, wurde anhand von Ergebnissen aus Laborwertanalyse, TE und Lebersonographie ein Score zur Graduierung der FALD entwickelt. Der FALD-Score errechnet sich aus der Summe der mittels Laborwertanalyse, TE und Lebersonographie detektierten Abnormalitäten, für welche jeweils ein Punkt vergeben wird (erreichbare Punktzahl: 0-14). Anhand des FALD-Score konnte FALD in die drei Schweregrade mild (≤3 Punkte), moderat (4-5 Punkte) und schwer (≥6 Punkte) aufgeteilt werden. Diese Arbeit konnte einen signifikanten Zusammenhang zwischen der Ausprägung von FALD und der Fontan-Hämodynamik belegen. Patientinnen und Patienten mit einer als moderat oder schwer klassifizierten FALD wiesen eine signifikant reduzierte kardiopulmonale Belastbarkeit, eine moderate Einschränkung der systolischen Funktion des Systemventrikels sowie deutlich erhöhte invasiv gemessene Drücke im Fontan-Kreislauf und im Systemventrikel auf. Bei 21/129 Personen lag ein klinisch manifestes Versagen der Fontan-Zirkulation vor; bei der Mehrheit der Betroffenen wurde FALD als schwergradig klassifiziert. Bei einem *Cut-off*-Wert von ≥6 Punkten konnte der entwickelte FALD-Score mit einer Sensitivität von 90,5 % und Spezifität von 71,3 % zwischen Personen mit und ohne Versagen der Fontan-Zirkulation unterscheiden.

Ein Zugriff auf die Originalarbeit ist unter Schleiger et al., Evaluation of Fontan failure by classifying the severity of Fontan-associated liver disease: a single-center cross sectional study. Eur J Cardiothorac Surg. 2020; 28:ezaa310. https://doi.org/10.1093/ejcts/ezaa310 möglich.

Nach Etablierung einer Schweregradeinteilung der FALD durch Einführung eines FALD-Score sowie Überprüfung seiner Anwendbarkeit zur Detektion eines Versagens der Fontan-Zirkulation wurde das Ausmaß einer funktionellen Leberschädigung durch die pathologische Fontan-Zirkulation durch Erfassung der enzymatischen Leberfunktion untersucht.

4.4 Zeitlicher Zusammenhang zwischen dem Auftreten von FALD-spezifischen morphologischen Veränderungen und einer Einschränkung der enzymatischen Leberfunktion

Die Arbeit

Schleiger, A., Kramer, P., Sallmon, H., Jentsch, J. Pileckaite, M., Danne, F., Schafstedde, M., Müller, H.P., Müller, T., Tacke, F., Jara, M., Stockmann, M., Berger, F., Ovroutski, S. Morphologic alterations precede functional hepatic impairement as determined by ^{13}C-Methacetin liver function breath test in adult Fontan patients. Frontiers in Cardiovascular Medicine, 12/2021; 8:764009.

untersuchte den Zusammenhang zwischen dem Auftreten von morphologischen Veränderungen der FALD und der enzymatischen Leberfunktion. Ein nicht-invasives Verfahren zur Erfassung der enzymatischen Leberfunktion ist der ^{13}C-Methacetin Leberfunktionsatemtest (*maximal liver function capacity test,* LiMAx-Test). Hierbei wird intravenös die isotopenmarkierte Substanz ^{13}C-Methacetin appliziert und in der Leber über das hepatozyten-spezifische Enzym CYP1A2 zu Paracetamol und $^{13}CO_2$ metabolisiert. $^{13}CO_2$ wird während der Untersuchung kontinuierlich in der Ausatemluft der Patientinnen und Patienten gemessen und korreliert mit der quantitativen enzymatischen Leberfunktion. Diese wurde im Rahmen dieser Arbeit bei 39 erwachsenen Fontan-Patientinnen und -Patienten mittels LiMAx-Test gemessen und mit Ergebnissen von Lebersonographie, Laborwertanalyse und TE verglichen. Bei der Mehrheit der Studienteilnehmer:innen war die Leberfunktion normwertig, während bei 11/39 Untersuchten eine milde bis moderate Leberfunktionseinschränkung nachweisbar war. Ein Zusammenhang zwischen dem Vorliegen und der Anzahl der sonographisch detektierbaren hepatischen Veränderungen, der TE-Messwerte und der enzymatischen Leberfunktion ließ sich nicht belegen, während eine signifikante Korrelation zwischen den Laborparametern γGT und Bilirubin und den LiMAx-Test Werten bestand. Die basierend auf dem FALD-Score ermittelten Schweregrade der FALD korrelierten nicht mit der gemessenen enzymatischen Leberfunktion.

Im Rahmen dieser Arbeit konnte erstmalig nachgewiesen werden, dass die mittels LiMAx-Test erfasste enzymatische Leberfunktion trotz Vorliegen von laborchemischen und morphologischen FALD-spezifischen Veränderungen bei der Mehrheit der Patientinnen und Patienten erhalten bleibt und erst bei Vorliegen einer Leberzirrhose eine moderate Einschränkung aufweist.

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ORIGINAL RESEARCH
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Morphologic Alterations Precede Functional Hepatic Impairment as Determined by ^{13}C-Methacetin Liver Function Breath Test in Adult Fontan Patients

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Objectives: Fontan-associated liver disease (FALD) is the most common end-organ dysfunction affecting up to 70–80% of the Fontan population. The clinical significance of FALD is incompletely understood and no unambiguous correlation between hepatic function and FALD severity has been established. In this study, we sought to evaluate maximal liver function capacity with liver maximum function capacity test (LiMAx®) in adult Fontan patients.

Methods: Thirty-nine adult Fontan patients (median age: 29.4 years [IQR 23.4; 37.4], median follow-up after Fontan operation: 23.9 years [IQR 17.8;26.4]) were analyzed in a cross-sectional observational study using LiMAx® test (Humedics GmbH, Berlin, Germany), laboratory testing, transient elastography (TE) and hepatic ultrasound. The LiMAx® test is based on the metabolism of ^{13}C-methacetin, which is administered intravenously and cleaved by the hepatic cytochrome P4501A2 to paracetamol and $^{13}CO_2$, which is measured in exhaled air and correlates with maximal liver function capacity.

Results: Maximal liver function capacity assessed by LiMAx® test was normal in 28 patients (>315 µg/h*kg) and mildly to moderately impaired in 11 patients (140–314 µg/h*kg), while no patient displayed severe hepatic impairment (<139 µg/kg*h). No correlation was found between maximal liver function capacity and hepatic stiffness by TE ($r^2 = -0.151$; $p = 0.388$) or the presence of sonographic abnormalities associated with FALD ($r^2 = -0.204$, $p = 0.24$). There was, however, an association between maximal liver function capacity and the laboratory parameters bilirubin ($r^2 = -0.333$, $p = 0.009$)

and γ-glutamyl transferase ($r^2 = -0.367$; $p = 0.021$). No correlation was detected between maximal liver function capacity and the severity of FALD ($r^2 = -0.235$; $p = 0.152$).

Conclusion: To the best of our knowledge, this is the first study to evaluate maximal liver function capacity using LiMAx® test in Fontan patients, which is a useful complementary diagnostic instrument to assess chronic hepatic injury. Maximal liver function capacity was preserved in most of our adult Fontan patients despite morphologic evidence of FALD. Moreover, maximal liver function capacity does not correlate with the extent of FALD severity evaluated by sonography or laboratory analysis. Thus, the development and progression of FALD in Fontan patients is not a uniform process and diagnostics of chronic hepatic injury during follow-up should encompass various modalities.

Keywords: Fontan-associated liver disease, enzymatic liver function, hepatic assessment, second-organ dysfunction, Fontan failure

INTRODUCTION

Over the past decades, survival of Fontan-palliated patients significantly improved with the majority of patients now reaching adulthood (1, 2). Nevertheless, the unphysiological Fontan circulation leads to progressive end-organ damage in the long-term (3–5). Fontan-associated liver disease (FALD) is the most common end-organ dysfunction and affects up to 70–80% of the adult Fontan population (5, 6). FALD manifestations vary from slightly elevated serum liver enzymes and mild hepatic parenchymal changes to end-stage liver cirrhosis (5, 6). The clinical significance of FALD is incompletely understood, and its diverse manifestations need to be put into clinical context when making therapeutic decisions. In a previous study, we proposed a scoring system (FALD score) to grade FALD severity based on a combination of laboratory parameters, hepatic ultrasound and transient elastography (TE). Our results revealed that the FALD score significantly correlated with Fontan hemodynamics and reliably discriminated between patients with and without Fontan failure (7). Liver-associated morbidity and mortality are well-described in the adult Fontan population and constitute major risk factors limiting survival after cardiac transplantation (8, 9). Therefore, reliable diagnostic modalities are indispensable to monitor hepatic end-organ damage and to determine the optimal timing for cardiac transplantation.

Since conventional liver function tests are often insensitive indicators of early disease stages, Stockmann et al. introduced the liver maximum capacity test (LiMAx®) for exact determination of quantitative enzymatic liver function and prediction of outcome after hepatectomy (10). The test is based on the enzymatic function of the cytochrome P4501A2 (CYP1A2) system, which is exclusively expressed in hepatocytes and is proportional to the hepatic parenchymal volume (10). As methacetin is exclusively metabolized by CYP1A2, the intravenous administration of ^{13}C-methacetin and the continuous real-time breath analysis of exhaled $^{13}CO_2$ provides an exact quantification of maximal liver capacity.

The aims of this study were to determine maximal liver function capacity with the LiMAx® test in adult Fontan patients, in comparison to the results of other hepatic diagnostic modalities and to analyze its relationship with the severity of FALD.

METHODS

Study Design and Patients

From 2019 to 2021 we performed a cross-sectional observational study including 39 adult Fontan patients, who successively presented in our outpatient clinic for follow-up and received measurement of maximal liver function capacity using the LiMAx® test. Exclusion criteria consisted of patient age < 18 years and/or intolerance to paracetamol or methacetin. The study was approved by the institutional review board and ethics committee (decision number: EA2/127/18). Informed written consent was obtained from all individual participants prior to inclusion.

FALD Diagnostics

Our institutional protocol and diagnostic algorithm for hepatic assessment of Fontan palliated patients has previously been described in detail and consists of laboratory analyses, hepatic ultrasound and liver stiffness measurement by TE (5). The laboratory parameters alanine-aminotransferase (ALT), γ-glutamyltransferase (γGT), total bilirubin, α_2-macroglobulin, apolipoprotein A_1 and haptoglobin were required to calculate a biomarker fibrosis score with FibroTest®. FibroTest® was computed on Biopredictive website (Paris, France; www.biopredictive.com). The calculated Fibrotest® score was converted into liver fibrosis stages according to METAVIR histological classification for liver biopsies (11). The calculation of the FALD score has previously been described in detail (7). Briefly, scoring points assigned for each hepatic abnormality detected in the diagnostics mentioned above were summed up for the final FALD score (7). In addition, patients received a standardized LiMAx® test as described by Stockmann et al. (10). Briefly, after 4 h of fasting, patients were placed in a resting horizontal position. Ten minutes prior to the injection of ^{13}C-methacetin, the baseline $^{13}CO_2/^{12}CO_2$ ratio was recorded.

A solution of 2 mg/kg body weight ^{13}C-labeled methacetin was intravenously injected as a bolus over a maximum of 30 s followed by 20 mL 0.9% sodium chloride solution. ^{13}C-methacetin is metabolized by the hepatozyte-specific CYP1A2 system into paracetamol and $^{13}CO_2$, which is exhaled and measured in expired air (**Supplementary Figure 1**). Each LiMAx® test analyzed 46 breath samples per patient and the result is given in μg/kg*h (**Supplementary Figure 2**).

STATISTICAL ANALYSIS

Data were obtained from medical records of the German Heart Centre Berlin. Patients' characteristics were expressed as median and interquartile range [IQR]. Fontan follow-up duration was defined as the interval between Fontan operation and last follow-up. Correlations between maximum liver capacity and laboratory parameters, TE, the number of hepatic abnormalities detected by ultrasound and the FALD score were assessed using Spearman's correlation. Associations between FALD severity graded as mild, moderate, and severe and maximal liver function capacity was analyzed using Kuskal Wallis and Wilcoxon tests as appropriate. Statistical analyses were performed using SPSS statistical software (version 23, IBM Corp., NY, USA). A $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics of the entire cohort are listed in **Table 1**. Median patient age was 29.4 years [IQR 23.4, 37.4] and median follow-up after Fontan operation 23.9 years [IQR 17.8, 26.4]. The most common underlying cardiac morphologies were tricuspid atresia ($n = 10$), double inlet left ventricle ($n = 11$) and unbalanced atrioventricular septal defect ($n = 3$). Fontan modifications included extracardiac conduit in 13 patients, lateral tunnel in 16 patients and atriopulmonary/atrioventricular connection (APC/AVC) or other modifications in 10 patients. Systolic ventricular function was normal or mildly impaired in the majority of the cohort ($n = 33$). Atrioventricular valve regurgitation was classified as absent or mild in 30 patients, moderate in 8 patients and severe in 1 patient. In 4 patients cardiac transplantation was performed, 2 patients died after transplantation. In addition, 1 patient died on mechanic circulatory support prior to cardiac transplantation.

TABLE 1 | Patient characteristics.

Patient age (years)	29.4 [23.4;37.4]
Age at Fontan operation (years)	6.5 [3.5;12.9]
Follow-up after Fontan (years)	23.9 [17.8;26.4]
Cardiac anatomy	
Double inlet left ventricle	11 (28.2%)
Tricuspid atresia	10 (25.6%)
Unbalanced AVSD	3 (25.6%)
Complex TGA	3 (25.6%)
Hypoplastic left heart syndrome	2 (5.1%)
Other	10 (15.5%)
Left ventricular morphology	27 (69.2%)
Fontan type	
Intracardiac TCPC	16 (41.7%)
Extracardiac TCPC	13 (33.3%)
APC/AVC/other	10 (30.3%)
Impairment of systolic ventricular function	
None	12 (30.8%)
Mild	21 (53.8%)
Moderate	5 (12.8%)
Severe	1 (2.6%)
Atrioventricular valve insufficiency	
None	13 (33.3%)
Mild	17 (43.6%)
Moderate	8 (20.5%)
Severe	1 (2.6%)

Data are presented as median [IQR] or frequencies (%).
APC, Atriopulmonary connection; AVC, Atrioventricular connection; AVSD, Atrioventricular septal defect; IQR, interquartile range; TCPC, total cavopulmonary connection; TGA, Transposition of great arteries.

Hepatic Assessment

Results from laboratory analysis, TE, hepatic ultrasound and the LiMAx® test are reported in **Table 2**. According to age-adjusted institutional reference values, ALT was elevated in 6 patients, aspartate aminotransferase (AST) in 7 patients, γGT in 31 patients and bilirubin in 13 patients. Thrombocytopenia was found in 12 patients. Median Fibrotest® fibrosis score was 0.6 [IQR 0.4, 0.6]. Referring to Fibrotest® calculation, fibrosis was staged F2 in the majority of our patients ($n = 12$; **Table 2**). Ultrasound revealed hepatic parenchymal changes in all patients (**Table 2**). The most common ultrasound findings were heterogeneous echotexture ($n = 35$), liver vein dilatation ($n = 31$), altered liver vein morphology ($n = 25$) and segmental hypertrophy or atrophy ($n = 11$). Hyperechogenic lesions were present in 7 patients. In 7 patients, sonographic signs of liver cirrhosis were detectable. Median TE values were 20.0 kPA [IQR 15.0, 34.3]. FALD was graded as mild in 6, moderate in 11 and severe in 22 patients based on the FALD score (7).

Median maximal liver function capacity was 350.0 μg/kg*h [IQR 288.0; 470.0] corresponding to a normal hepatic function (≥ 315 μg/kg/h) based on previously published normative values (12). In 11 patients, a moderate hepatic impairment was detected (140–314 μg/kg*h), while none had severely impaired maximal liver function capacity (≤ 139 μg/kg*h). As shown in **Figure 1**, hepatic function as assessed by LiMax® tended to decrease with a longer follow-up after Fontan operation ($r^2 = -0.333$, $p = 0.038$). A significant correlation between maximal liver function capacity and the laboratory parameters bilirubin ($r^2 = -0.421$, $p = 0.009$) and γGT ($r^2 = -0.367$; $p = 0.021$) was detected. However, no significant correlations were found between maximal liver function capacity and Fibrotest® fibrosis score ($r^2 = -0.335$, $p = 0.052$), TE ($r^2 = -0.151$, $p = 0.388$) or the number of hepatic abnormalities detected by liver ultrasound ($r^2 = -0.204$, $p = 0.24$). Seven of thirty-nine patients were diagnosed with liver cirrhosis based on sonography, in these patients maximal liver function capacity was significantly reduced as compared to patients without liver cirrhosis (274.5 μg/kg*h [IQR 216.3; 346.0] vs. 384.0 μg/h*kg [IQR 320.0; 497.5], $p = 0.025$).

TABLE 2 | Hepatic assessment.

	Median [IQR]	Outside RR/N (%)
Laboratory parameters		
ALT (U/l)	30.0 [25.0; 38.0]	6/39 (15.4%)
AST (U/l)	30.0 [26.0; 34.0]	7/39 (17.9%)
γGT (U/l)	87.0 [54.0; 125.0]	31/39 (79.5%)
Total bilirubin (mg/dl)	0.9 [0.7; 1.6]	13/39 (33.3%)
Thrombocytes (K/μl)	159.0 [137.0; 211.0.]	12/39 (30.8%)
Fibrotest®	0.6 [0.4; 0.7]	
F0		4/34 (11.8%)
F1		6/34 (17.6%)
F2		12/34 (35.3%)
F3		8/34 (23.5%)
F4		8/34 (23.5%)
TE (kPa)	20.0 [15.0; 34.3]	
< 21.2 kPa		18/34 (52.9%)
21.3–27.6		2/34 (5.9%)
27.7–35.7		8/34 (23.5%)
> 35.8 kPa		7/34 (20.6%)
Hepatic ultrasound findings		
Hepatomegaly		9/35 (25.7%)
Splenomegaly		9/35 (25.7%)
Heterogeneous liver parenchyma		35/35 (100.0%)
Segmental atrophy/hypertrophy		11/35 (31.4%)
Hepatic vein dilatation		31/35 (88.6%)
Abnormal hepatic vein architecture		35/35 (100.0%)
Hyperechogenic lesions		7/35 (20.0%)
Surface nodularity		7/35 (20.0%)
Ascites		4/35 (11.4%)
FALD score/ FALD severity	6.0 [5, 8]	
Mild		6/39 (15.4%)
Moderate		11/39 (28.2%)
Severe		22/39 (56.5%)
Maximal liver function capacity		
LiMax® test (μg/kg*h)	350.0 [288.0; 470.0]	
Hepatic metabolic impairment		
None (> 315 μg/kg*h)		28/39 (71.8%)
Moderate (140–315 μg/kg*h)		11/39 (28.2%)
Severe (0–139 μg/kg*h)		0/39 (0.0%)

Data are presented as median [IQR] or frequencies (%).
AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; γGT, γ-Glutamyl-aminotransferase; IQR, interquartile range; kPa, Kilopascal; RR, reference range; TE, Transient elastography.

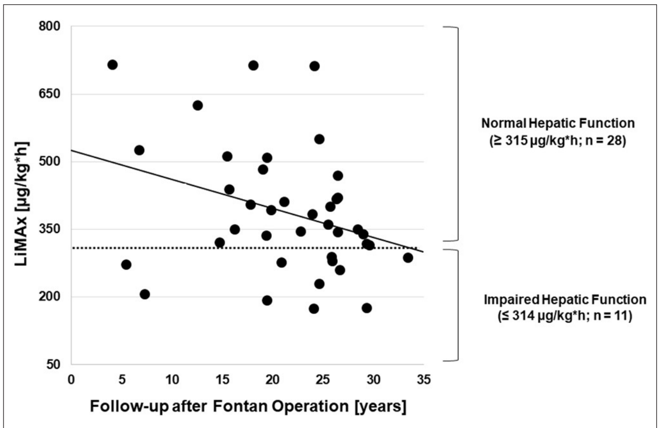

FIGURE 1 | Correlation between the follow-up time after Fontan operation and maximal liver function capacity ($n = 39$).

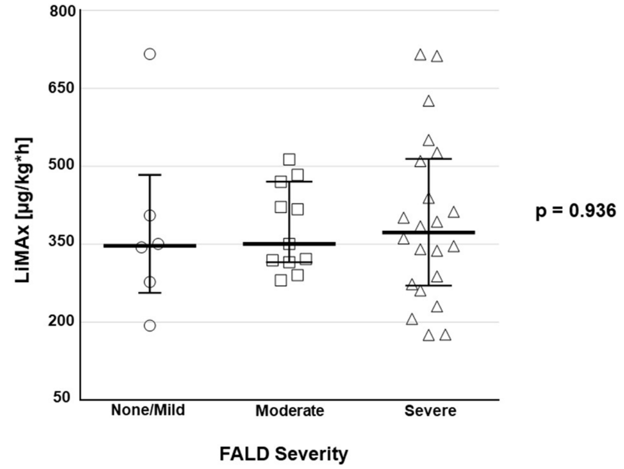

FIGURE 2 | Boxplots depict maximal liver function capacity according to the classification of FALD severity [absent/ mild ($n = 6$), moderate ($n = 11$), severe ($n = 22$)].

No correlation was observed between maximal liver function capacity and the FALD score ($r^2 = -0.237$; $p = 0.152$). Also, maximal liver function capacity did not differ significantly between varying degrees of FALD severity ($p = 0.936$; **Figure 2**).

DISCUSSION

Fontan-associated liver disease (FALD) encompasses all abnormalities in liver structure and function which are associated with the unphysiological Fontan circulation (3–6). Affecting up to 80% of the Fontan population, it is the most common second-organ disease (7–9). Various studies focused on the detection and monitoring of FALD, but its clinical significance and importance for therapeutic decision-making remains unclear. The LiMAx® test was successfully evaluated in several clinical settings such as hepatic surgery, hepatic transplantation, sepsis, and hepatic cirrhosis (10, 12–15). To the best of our knowledge, we herein provide the first results on maximal liver function capacity measured by LiMAx® in Fontan patients in comparison with other diagnostic modalities and FALD severity. Of note, maximal liver function capacity was normal in the majority of our patients although more than half of our cohort had FALD graded as severe. In addition, no clear correlation of maximal liver function capacity with TE and sonographic hepatic abnormalities was detected. We only found a relationship between the laboratory parameters bilirubin and γGT and LiMAx® values. An increase of laboratory parameters associated with cholestasis is the most common abnormality in Fontan patients as well as in patients with congestive hepatopathy (16). The degree of cholestasis is known to be related to increases in right atrial pressure and to the severity of tricuspid valve regurgitation in patients with right heart failure (17, 18). The underlying mechanism is supposed to be the compression of bile canaliculi and small ductules by centrally congested sinusoids (16). Additionally, diminished cardiac output results in reduced vascular supply and increased oxidative stress leading to necrosis of centrilobular hepatocytes and ischemic damage of the intrasinusoidal endothelium (16), which might not only be detected by increased indicators of cholestasis but also by reduced maximal liver function capacity.

The major finding of our study is the missing correlation between FALD severity and maximal liver capacity measured by the LiMAx® test. This important result suggests that the progress of hepatocyte-specific damage is decelerated and enzymatic liver function remains preserved for a considerably long time in the majority of patients during the morphologic development and progression of FALD. This finding may have important implications for the routine hepatic follow-up of Fontan patients and for the evaluation of failing Fontan patients for cardiac transplantation. Assessing maximal liver function capacity may help to identify failing Fontan patients that require a combined cardiac and liver transplantation. In line with these findings, we previously reported remarkable hepatic remodeling in a patient with normalization of hepatic stiffness values and regression of sonographic signs of hepatic cirrhosis after cardiac transplantation (7). This observation underlines that certain FALD-specific abnormalities are potentially reversible, which might be explained by the missing or slow progression of hepatic injury revealed by our measurements of maximal liver function capacity.

Maximal Liver Function Capacity and Evaluation for Cardiac Transplantation

Cardiac transplantation is currently the only remaining treatment option for patients with refractory Fontan failure since effective evidence-based medical heart failure therapies are virtually non-existent, and mechanic circulatory support is not well-established in Fontan-palliated patients (19, 20). However, cardiac transplantation remains a high risk surgical procedure in the adult Fontan population and hepatic end-organ damage contributes to post-transplant morbidity and mortality (8, 9). Moreover, no guidelines exist for the optimal timing for cardiac transplantation in Fontan patients which may result in a delayed listing for transplantation with already advanced second-organ damage that may negatively impact transplantation outcome. In our cohort, maximal liver function capacity was significantly reduced in patients listed or evaluated for listing for cardiac transplantation ($n = 4$) compared to the remaining cohort (288.0 μg/kg*h [IQR 182.8, 331.5] vs. 361.0 μg/kg*h [IQR 302.5, 454.5], $p = 0.035$). This observation suggests that FALD was rather progressed in these patients, already resulting in functional impairment of the liver which in turn might indicate that listing for cardiac transplantation needs to be considered early. In a previous study, we emphasized on the importance of FALD monitoring to determine the optimal timing for cardiac transplantation and proposed the FALD score as a tool to grade FALD severity and facilitate surveillance of FALD progression (7). The LiMAx® test may represent a valuable complementary additional diagnostic modality in the hepatic assessment of Fontan patients since it provides a reproducible quantitative measurement of enzymatic hepatocyte function. Since a deterioration of maximal liver function capacity seems to occur relatively late during the disease course, its occurrence should trigger an evaluation for cardiac transplantation.

CONCLUSION

We herein demonstrate that maximal liver function capacity as measured by the LiMAx® test is generally well-preserved in Fontan patients despite morphologic evidence of advanced FALD. Our findings suggest that the development and progression of FALD is not a uniform process and diagnostics of chronic hepatic injury during follow-up after Fontan operation should encompass various modalities. Specifically, morphologic changes as detected by ultrasound and/or TE seem to precede functional impairment as evidenced by preserved hepatic function in several patients with significant structural anomalies.

Limitations

There are several limitations to this study. This is a cross-sectional single center trial with a comparably small patient cohort. Future studies, preferably in a multi-institutional setting, are necessary to comprehensively evaluate the assessment of hepatic function in Fontan palliated patients. Methacetin is only approved in adult patients, therefore pediatric patients could not be included in this study. After intravenous injection ^{13}C methacetin undergoes a hepatic microsomal deacylation into paracetamol and $^{13}CO_2$, which is transported to the lung as bicarbonate. Inter – and intraindividual bicarbonate kinetics might influence the respiratory $^{13}CO_2$ excretion by delayed liberation of transiently trapped $^{13}CO_2$. Moreover, although our results suggests an earlier appearance of morphologic changes as compared to functional impairments the temporal relationships of FALD progression and changes of maximal liver function capacity cannot be determined by our cross-sectional study design and requires longitudinal studies. Additional diagnostic modalities such as histological analyses from biopsies or hepatic magnetic resonance imaging were not included in our routine hepatic assessment and the relationship between Fontan hemodynamics and hepatic function was not addressed in this study and needs to be evaluated in the future. The FALD score and gradation of FALD severity have not been evaluated or validated in large patient cohorts or multicenter settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Charité-Universitätsmedizin

Berlin (desicion number EA2/127/18). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS and SO: conceptualization. AS, NJ, and MP: data collection. AS, FD, PK, MS, HS, H-PM, and TM: investigation. AS: formal analysis and writing original draft. SO, FB, FT, MJ, and MS: supervision. SO, PK, FB, FT, HS, and TM: writing review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.764009/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Nach der erstmaligen Erfassung der enzymatischen Leberfunktion bei Fontan-Patientinnen und –Patienten mittels LiMAx-Test und dem Vergleich der gemessenen Werte mit den Ergebnissen der nicht-invasiven diagnostischen Modalitäten wie Laborwertanalyse, Lebersonographie und TE wurde der Zusammenhang zwischen der enzymatischen Leberfunktion und der Fontan-Hämodynamik untersucht.

4.5 Einfluss der Fontan-Hämodynamik auf die enzymatische Leberfunktion

Die Arbeit

Schleiger, A., Kramer, P., Sallmon, H., Jentsch, J., Pileckaite, M., Danne, F., Schafstedde, M., Müller H.P., Müller, T., Tacke F., Jara, M., Stockmann, M., Berger F., Ovroutski, S. Functional hepatic deterioration determined by ^{13}C-Methacetin breath test is associated with impaired hemodynamics and late Fontan failure in adults. Frontiers in Cardiovascular Medicine, 09/2022; 9:952080.

analysierte den Zusammenhang zwischen der Hämodynamik der Fontan-Zirkulation und der enzymatischen Leberfunktion. Im Rahmen der Arbeit wurde bei 59 adulten Fontan-Patientinnen und -Patienten ein LiMAx-Test sowie ein ausführliches hämodynamisches Assessment mittels Echokardiographie, Spiroergometrie und Herzkatheteruntersuchung durchgeführt. Bei 15/59 Personen lag ein klinisch manifestes Versagen der Fontan-Zirkulation vor. Im Rahmen dieser Arbeit konnte nachgewiesen werden, dass die enzymatische Leberfunktion bei Patientinnen und Patienten mit einem erhöhten Mitteldruck im Fontan-Kreislauf sowie einem erhöhten Füllungsdruck im singulären Systemventrikel mild bis moderate Beeinträchtigungen aufwies. Bei Personen mit einem manifesten Versagen der Fontan-Zirkulation waren die LiMAx-Test Werte signifikant reduziert.

Die Ergebnisse dieser Studie verdeutlichen, dass die mittels LiMAx-Test erfasste enzymatische Leberfunktion von der Hämodynamik der Fontan-Zirkulation beeinflusst wird. Insbesondere das Vorliegen eines manifesten Versagens der Fontan-Zirkulation resultiert in einer deutlichen Reduktion der enzymatischen Leberfunktion.

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Functional hepatic deterioration determined by ^{13}C-methacetin breath test is associated with impaired hemodynamics and late Fontan failure in adults

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Background: Despite improved survival a substantial number of Fontan patients eventually develop late failure. Fontan-associated liver disease (FALD) is the most frequent end-organ dysfunction. Although impaired hemodynamics and Fontan failure correlate with FALD severity, no association between hepatic functional metabolic impairment and Fontan hemodynamics has been established.

Hypothesis: Metabolic liver function measured by liver maximum function capacity test (LiMAx®) correlates with Fontan hemodynamics and Fontan failure.

Methods: From 2020 to 2022, 58 adult Fontan patients [median age: 29.3 years, IQR (12.7), median follow-up time after Fontan operation: 23.2 years, IQR (8.7)] were analyzed in a cross-sectional study. Hemodynamic assessment included echocardiography, cardiopulmonary exercise testing and invasive hemodynamic evaluation. Fontan failure was defined based on commonly applied clinical criteria and our recently composed multimodal Fontan failure score.

Results: LiMAx® test revealed normal maximum liver function capacity in 40 patients (>315 μg/h*kg). In 18 patients a mild to moderate impairment was detected (140–314 μg/h*kg), no patient suffered from severe hepatic deterioration (≤139 μg/kg*h). Fontan failure was present in 15 patients. Metabolic liver function was significantly reduced in patients with increased pulmonary artery pressure ($p = 0.041$. $r = -0.269$) and ventricular end-diastolic pressure ($p = 0.033$, $r = -0.325$), respectively. In addition, maximum liver function capacity was significantly impaired in patients with late Fontan failure (289.0 ± 99.6 μg/kg*h vs. 384.5 ± 128.6 μg/kg*h, $p = 0.007$).

Conclusion: Maximum liver function capacity as determined by LiMAx® was significantly reduced in patients with late Fontan failure. In addition, elevated pulmonary artery pressure and end-diastolic ventricular pressure were associated with hepatic functional metabolic impairment.

KEYWORDS

late Fontan failure, Fontan-associated liver disease, end-organ dysfunction, Fontan hemodynamics, metabolic liver function

Introduction

Despite its tremendous success in treating patients with univentricular anatomy, the Fontan operation remains a palliative procedure, which is characterized by abnormal hemodynamics (1, 2). In the long-term course, chronic venous congestion and low cardiac output lead to progressive clinical heart failure with limited treatment options (3, 4). The relative scarceness of effective pharmacological therapies and the limited applicability of mechanical circulatory support restrict end-stage therapeutic strategies to cardiac transplantation, which itself is associated with considerable morbidity and mortality (5, 6). The indications and optimal timing of cardiac transplantation in Fontan patients are still subject of ongoing debate. The urgency of addressing these issues is illustrated by the fact that within the next decades a significant increase in adult Fontan patients experiencing hemodynamic compromise and subsequently cardio-circulatory demise can be expected (7).

Liver-associated morbidity and mortality are well described in the adult Fontan population and constitute major risk factors significantly impacting survival rates after cardiac transplantation (8, 9). Additionally, the indication for a combined heart and liver transplantation is currently subject of ongoing debate. Therefore, reliable diagnostic modalities are required to monitor hepatic end-organ damage, determine the optimal timing for cardiac transplantation and define the indications for a combined heart-liver transplantation. The liver maximum capacity test (LiMAx®) has been developed to quantitatively determine metabolic liver function. Methacetin is exclusively metabolized by the cytochrome P4501A2 (CYP1A2) system, which exclusively exists in hepatocytes (10). Therefore, enzymatic cleavage of intravenously administrated ^{13}C-methacetin into $^{13}CO_2$, reliably correlates with hepatic parenchymal volume and metabolic function (10). Previously, we have demonstrated that structural hepatic alterations antecede functional hepatic impairment as assessed by LiMAx®, with maximum liver function capacity being well preserved in the majority of Fontan patients (11). However, the potential impacts of late Fontan failure and hemodynamics on metabolic liver function are unknown.

Herein, we aimed to analyze the potential associations between maximum liver function capacity and (I) Fontan hemodynamics by clinical, echocardiographic and invasive assessments and (II) late Fontan failure.

Methods

Study design and patients

From 2019 to 2022 58 adult Fontan patients, who successively presented in our outpatient clinic for follow-up, were included in our cross-sectional observational study. All patients received measurement of maximal liver function capacity using LiMAx® test as well as a detailed hemodynamic and hepatic assessment. Exclusion criteria were intolerance to methacetin or paracetamol and/or patient age below 18 years. The institutional review board and ethics committee approved the study (decision number: EA2/127/18). All individual participants consented to participate in the study prior to inclusion.

Hemodynamic assessment

Hemodynamic assessment included clinical evaluation, echocardiography, cardiopulmonary exercise testing (CPET) and cardiac catheterization. Systolic ventricular function was measured by echocardiography based on the modified Simpson's method (12). Atrioventricular valve incompetence (AVVI) was classified as absent/mild, moderate or severe by visual assessment of the regurgitation jet dimensions in color Doppler sonography. CPET was performed following a standardized institutional protocol using a cycle ergometer. Peak oxygen uptake (VO_2peak) was measured in ml/kg*min and normalized in % of age-, gender- and body dimension-adjusted reference values. Cardiac catheterization included measurements of mean pulmonary artery pressure (mPAP) and systemic ventricular end-diastolic pressure (SVEDP). Transpulmonary pressure gradient (TPG) was calculated as the difference between mPAP and pulmonary capillary wedge pressure. Cardiac output (CO) and pulmonary vascular resistance (PVR) were determined by Fick's principle using oximetry (13). For comparability, CO and PVR are indexed to body-surface area (Cardiac index, CI, $l/min/m^2$; pulmonary vascular resistance index, PVRi, WU^*m^2). Fontan failure was defined as severe dysfunction of the Fontan circulation caused by impaired ventricular function, moderate to severe atrioventricular valve incompetence, increased pulmonary vascular resistance, recurrent arrhythmia or therapy-refractory protein-losing enteropathy based on commonly applied clinical criteria (14) and our previously described Fontan failure score (15). Briefly, the score includes a set of 15 clinical, echocardiographic, invasive hemodynamic and laboratory parameters and is calculated by assigning one score point for each score item beyond the defined threshold with a range from 0 to 15 points. A score $\geq$ 8 score points detects late Fontan failure with a sensitivity of 99.3 % and a specificity of 53.9 % (15).

Hepatic assessment

Hepatic assessment was performed based on our previously published institutional protocol (16) and consisted of laboratory analyses, hepatic ultrasound and liver stiffness measurement by transient elastography (TE). FibroTest® was computed on Biopredictive website (Paris, France; www.biopredictive.com).

Maximal liver function capacity

The LiMAx® test was performed following the standardized protocol of Stockmann et al. (10).

Briefly, a body weight-adjusted solution (2 mg/kg) of ^{13}C-labeled methacetin was administered intravenously. The hepatocyte-specific CYP1A2 system metabolizes ^{13}C-labeled methacetin into paracetamol and $^{13}CO_2$, which is continuously measured in the exhaled air. The LiMAx test result is calculated based on the individually determined maximum delta-over-baseline ratio of $^{13}CO_2/^{12}CO_2$ (10).

Statistical analysis

Data were collected from medical records of the German Heart Centre Berlin. Data are expressed as median and interquartile range, which were calculated as the 75th minus 25th percentile. Fontan follow-up duration was defined as the interval between Fontan operation and last follow-up. Correlations between maximum liver capacity, echocardiographic, hemodynamic and hepatic parameters as well as the Fontan failure score were assessed using Spearman's correlation and Mann-Whitney U test. Statistical analyses were performed using SPSS statistical software (version 23, IBM Corp., NY, USA). A p-value <0.05 was considered statistically significant.

Results

Patient cohort

Patient characteristics of the entire cohort are provided in Table 1. Median patient age was 29.3 years (IQR 12.7) and median follow-up time after Fontan operation 23.2 (IQR 8.7). The most common underlying cardiac morphologies were tricuspid atresia (n = 18), double inlet left ventricle (n = 15) and unbalanced atrioventricular septal defect (n = 9). Fontan modifications consisted of extracardiac conduit in 22 patients, lateral tunnel in 17 patients and atriopulmonary/ atrioventricular connection (APC/AVC) in 19 patients. From the study cohort, 3 patients died during follow-up; 2 patients after cardiac transplantation and 1 patient on mechanical circulatory support. Two additional patients successfully underwent cardiac transplantation.

Hemodynamic assessment

Results of hemodynamic assessment are presented in Table 2. Systolic ventricular function was preserved/ mildly impaired in 47 patients, moderately impaired in 9 patients and severely impaired in 2 patients. AVVI was classified as absent/mild in 44 patients, moderate in 13 patients and severe in 1 patient. Median percentage of reference VO_2peak was 44.4 % (IQR 21.3) in the entire cohort. Invasive hemodynamic evaluation revealed mPAP, SVEDP and TPG to be within normal reference ranges (Table 1). Calculated median CI was 2.2 $L/min/m^2$ (IQR 0.8) and median PVRi 2.3 WU^*m^2 (IQR 1.1). Late Fontan failure was diagnosed in 15 patients.

Hepatic assessment

Results of hepatic assessment are listed Table 3. The laboratory parameters Alanin-Aminotransferase (ALT), Aspartat-Aminotransferase (AST), bilirubin and thrombocytes did not significantly differ between patients with and without Fontan failure, whereas γ-glutamyl-transferase (γGT) was significantly increased in patients with a failing Fontan circulation (p = 0.017). Results from hepatic ultrasound revealed that surface nodularity, ascites and segmental atrophy/ hypertrophy were more frequently detected in patients with Fontan failure (Table 3). Additionally, liver stiffness values measured by TE were significantly higher in patients with a failing Fontan circulation (p = 0.001), whereas Fibrotest® fibrosis score did not differ between patients with and without Fontan failure.

TABLE 1 Patient characteristics.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Patient age (years)	29.3 (12.7)	27.8 (10.9)	36.3 (22.0)	0.093
Age at Fontan operation (years)	5.7 (9.0)	4.6 (8.3)	11.4 (7.8)	**0.035**
Follow-up after Fontan (years)	23.2 (8.7)	23.0 (9.1)	24.6 (11.1)	0.214
Cardiac anatomy (n)				0.541
Tricuspid atresia	18 (31.0%)	14 (32.6%)	4 (26.7%)	
Double inlet left ventricle	15 (25.9%)	11 (26.2%)	4 (26.7%)	
Hypoplastic left heart syndrome	2 (3.5%)	1 (2.3%)	1 (6.7%)	
Complex TGA	3 (5.1%)	2 (4.7%)	1 (6.7%)	
Unbalanced AVSD	9 (15.5%)	5 (11.6%)	4 (26.7%)	
Other	11 (18.9%)	9 (20.9%)	2 (13.3%)	
Left ventricular morphology (n)	39 (67.2%)	31 (72.1%)	8 (53.3%)	0.213
Fontan type (n)				0.373
Extracardiac conduit	22 (37.9%)	16 (37.2%)	6 (40.0%)	
Intracardiac lateral tunnel	17 (29.3%)	12 (27.9%)	5 (33.3%)	
APC / AVC	19 (32.8%)	15 (34.9%)	4 (26.7%)	

Data are presented as median and interquartile range or frequencies and %. Statistically significant results are given in bold letters. APC, atriopulmonary connection; AVC, atrioventricular connection; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries.

TABLE 2 Hemodynamic assessment.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Ejection fraction (%)	48.0 (11.3)	50.0 (9.0)	40.0 (16.5)	**<0.001**
$\leq$ 45% (n)	18/54 (33.3%)	9/41 (22.0%)	9/13 (69.2%)	**0.005**
AV valve regurgitation (n)				
Absent/mild	44/58 (75.9%)	36/43 (83.7%)	8/15 (53.3%)	0.056
Moderate	13/58 (22.4%)	7/43 (16.3%)	6/15 (40.0%)	
Severe	1/58 (1.7%)	0 (0.0%)	1 (6.7%)	
Cardiopulmonary exercise testing VO_2peak (% of reference)	44.4 (21.3)	46.0 (24.5)	30.4 (31.4)	**<0.001**
< 50% of reference (n)	31/50 (62.0%)	19/37 (51.4%)	12/13 (92.3%)	**0.008**
Transcutaneous oxygen saturation (%)				
at rest	93.0 (4.3)	95.0 (4.0)	92.0 (5.0)	**0.004**
at VO_2peak	92.0 (9.8)	92.0 (9.0)	88.0 (11.0)	0.222
mPAP (mmHg)	12.0 (6.3)	10.0 (4.0)	17.0 (6.0)	**<0.001**
$\geq$ 15 mmHg (n)	16/58 (27.6%)	5/43 (11.6%)	11/15 (73.0%)	**<0.001**
SVEDP (mmHg)	10.0 (7.0)	9.0 (6.0)	14.5 (4.8)	**<0.001**
$\geq$ 12 mmHg (n)	20/43 (46.5%)	8/29 (27.6%)	12/14 (85.7%)	**0.001**
TPG (mmHg)	3.5 (1.0)	4.0 (1.0)	3.0 (5.0)	0.551
CO (L/min)	3.9 (1.4)	3.9 (1.4)	4.1 (1.8)	0.664
CI (L/min*m²)	2.2 (0.8)	2.3 (0.8)	2.1 (0.7)	0.18
PVR (WU)	0.9 (0.6)	0.8 (0.6)	1.1 (0.9)	0.117
PVRi (WU*m²)	1.7 (1.1)	1.6 (1.0)	2.0 (1.9)	0.117
$\geq$ 2.5 WU*m² (n)	10/55 (18.2%)	4/40 (10.0%)	6/15 (40.0%)	**0.018**

Data are presented as median and interquartile range or frequencies (%). Statistically significant results are given in bold letters. AV, atrioventricular; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; SVEDP, systemic ventricular end-diastolic pressure; TPG, transpulmonary pressure gradient.

TABLE 3 Hepatic assessment.

	Entire cohort (n = 58)	No Fontan failure (n = 43)	Fontan failure (n = 15)	*P*-value
Laboratory parameters				
ALT (U/l)	30.1 (7.5)	30.6 (7.3)	30.0 (10.0)	0.901
AST (U/l)	31.0 (12.8)	31.4 (12.9)	27.5 (15.7)	0.189
γGT (U/l)	91.8 (60.5)	79.2 (61.0)	119.8 (51.4)	**0.017**
Total bilirubin (mg/dl)	1.0 (0.7)	1.0 (0.7)	1.0 (1.4)	0.195
Thrombocytes (K/μl)	164.5 (69.5)	165.0 (69.0)	155.0 (74.0)	0.683
Fibrotest® Fibrosis Score	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.434
TE (kPa)	19.4 (19.2)	16.2 (13.0)	33.7 (21.0)	**0.001**
Hepatic ultrasound findings (n)				
Hepatomegaly	11/54 (20.4 %)	8/40 (20.0 %)	3/14 (21.4 %)	1.0
Splenomegaly	13/54 (24.1 %)	6/40 (15.0 %)	7/14 (50.0 %)	**0.025**
Heterogeneous liver parenchyma	52/54 (96.3 %)	38/40 (95.0 %)	14/14 (100.0 %)	1.0
Segmental atrophy/hypertrophy	16/54 (29.6 %)	10/40 (25.0 %)	6/14 (42.9 %)	0.38
Hepatic vein dilatation	48/54 (88.9 %)	36/40 (90.0 %)	12/14 (85.7 %)	0.643
Abnormal hepatic vein architecture	38/54 (70.4 %)	26/40 (65.0 %)	11/14 (78.6 %)	0.507
Hyperechogenic lesions	10/54 (18.5 %)	7/40 (17.5 %)	3/14 (21.4 %)	0.708
Surface nodularity	8/54 (14.8 %)	3/40 (7.5 %)	5/14 (35.7 %)	**0.021**
Ascites	7/54 (13.0 %)	1/40 (2.5%)	6/14 (42.9%)	**0.001**
Maximum liver function capacity (μg/kg/h)	355.0 (160.8)	390.0 (162.0)	288.0 (140.0)	**0.007**

Data are presented as median and interquartile range or frequencies (%). Statistically significant results are given in bold letters. ALT, Alanin-Aminotransferase; AST, Aspartat-Aminotransferase; γGT, γ-glutamyl-transferase; kPA, Kilopascal; TE, transient elastography.

Maximal liver function capacity

Median maximum liver function capacity was 355.0 μg/kg*h (IQR 160.8), which corresponds to a normal hepatic function (≥ 315 μg/kg*h). In 18 patients maximum liver function capacity was moderately impaired (140–314 μg/kg*h), while no patient suffered from severe hepatic damage (≤ 139 μg/kg*h). No correlation was detected between systolic ventricular function or the extent of AVVI and maximum liver function capacity ($p = 0.178$, r = 0.186 and $p = 0.873$, r = −0.016, respectively). Additionally, no association was found between VO_2peak and LiMAx® test results ($p = 0.356$, r = 0.133). No correlation was detected between maximal liver function capacity and resting or peak oxygen saturation ($p_1 = 0.202$, r = 01.7; $p_2 = 0.056$, r = −0.267). In patients with mPAP ≥ 15 mmHg maximal liver function capacity was significantly reduced compared to patients with mPAP < 15 mmHg [294.0 μg/kg*h (IQR 126.0) vs. 388.5 μg/kg*h (IQR 177.0), $p = 0.019$, Figure 1A]. An SVEDP ≥ 12 mmHg was also associated with decreased maximum liver function capacity [331.5 μg/kg*h (IQR 136.5) vs. 401.0 μg/kg*h (IQR 173.0), $p = 0.029$; Figure 1B]. Finally, in patients with late Fontan failure, maximal liver function capacity was significantly impaired as compared to patients without evidence of Fontan failure [288.0 μg/kg/*h (IQR 140.0) vs. 390.0 μg/kg*h (IQR 162.0), $p = 0.007$; Figure 1C].

Discussion

This is the first study to describe the association between Fontan hemodynamics, Fontan failure and maximum liver function capacity assessed by LiMAx®. Briefly, no correlation was detected between echocardiographic parameters or CPET results and metabolic liver function. Additionally, hemodynamic parameters such as CI and PVRi also showed no association with results from the LiMAx® test. However, maximum liver function capacity was significantly decreased in patients with increased mPAP (≥15 mmHg), and those with increased SVEDP (≥12 mmHg) as well as in patients with Fontan failure. In these patients, hepatic functional impairment was graded as moderate whereas no severe hepatic failure was detected.

The LiMAx® test was introduced to accurately quantify metabolic liver function based on the hepatocyte-specific cytochrome P4501A2 (CYP1A2) system and was evaluated in several clinical settings (17–19). We previously described the missing correlation between maximum liver function capacity and results from other diagnostic modalities such as laboratory parameters, TE and hepatic ultrasound (11). The major finding of our previous study was that metabolic liver function was preserved in the majority of adult Fontan patients even in those with clear evidence of advanced FALD.

Due to the non-physiological hemodynamics, failure of the Fontan circulation is inevitable in the long term (20–22).

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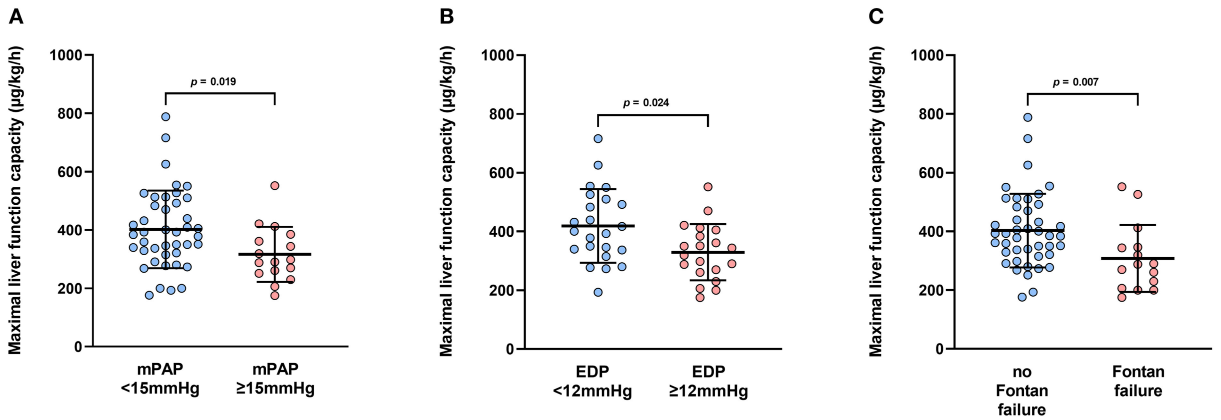

FIGURE 1
(A) Boxplots depict maximal liver function capacity according to mean pulmonary artery pressure (mPAP). mPAP < 15 mmHg: n = 42; mPAP <15 mmHg: n = 15. **(B)** Boxplots depict maximal liver function capacity according to systemic ventricular end-diastolic pressure (SVEDP). SVEDP < 12 mmHg: n = 23; SVEDP <12 mmHg: n = 19. **(C)** Boxplots depict maximum liver function capacity according to the presence of Fontan failure. Fontan failure; n = 15; no Fontan failure, n = 43.

Since therapeutic strategies are limited, cardiac transplantation remains the only viable end-stage treatment option but is associated with considerable mortality and morbidity (23). Additionally, guidelines for the timing of cardiac transplantation are missing and delayed listing may result in progressing secondary end-organ damage, which significantly contributes to post-transplant mortality (8, 9). Fontan-associated liver disease (FALD) is the most frequent end-organ dysfunction and encompasses all abnormalities in both liver structure and function with the end-stage being severe liver cirrhosis or hepatocellular carcinoma (24, 25). The indication for a combined heart and liver transplantation in failing Fontan patients is currently subject of ongoing debate. The decision whether a patient may benefit from single or multi-organ transplantation is challenging due to the lack of sound data to support or refute any given approach. Whereas successful isolated heart transplantation has been reported in the presence of hepatic cirrhosis (26), feasibility of combined heart and liver transplantation has also been demonstrated (27, 28). The most commonly encountered scenario in Fontan patients considered for cardiac transplantation is the inevitable presence of some degree of liver fibrosis with most patients demonstrating 'cirrhotic' alterations on imaging. However, it has been shown that cirrhosis on biopsy is less common and often does not correlate with imaging modalities such as ultrasound, magnetic resonance imaging or computed tomography (29). These discrepancies between imaging and biopsy findings complicate the interpretation and classification of FALD and its clinical significance for therapeutic decision making.

The LiMAx® test may represent a valuable complementary diagnostic modality in the hepatic assessment of Fontan patients and provides a reproducible quantitative measurement of hepatocyte function. Since a deterioration of maximum liver function capacity seems to occur relatively late during the disease course, when a significant impairment of Fontan hemodynamics and Fontan failure is already evident, its occurrence may prove as a valuable indicator for the requirement of a timely evaluation for cardiac transplantation. In our cohort, maximum liver function capacity was moderately reduced in patients who received cardiac transplantation [247.0 µg/kg*h (IQR 148.8) vs. 369.5 µg/kg*h (IQR 182.5), $p =$ 0.029), however, none of these patients fulfilled the criteria for a combined heart and liver transplantation such as hepatocellular carcinoma or severe liver cirrhosis. In patients who survived cardiac transplantation, improvements in morphological and laboratory FALD parameters were detected. This observation has also been reported by other institutions and might underline the remarkable hepatic potential for regeneration (11, 30, 31). Therefore, patients with mild to moderate impairment of metabolic liver function might be appropriate candidates for isolated cardiac transplantation, whereas a severely impaired maximum liver function capacity may indicate the necessity of a combined heart and liver transplantation. Since both, FALD and Fontan failure, are characterized by a slow progress and are often clinically disguised by patient's adaptation to their chronically reduced output state and clinical deterioration, it seems advisable to perform repeated measurement of maximum liver function capacity during long-term follow-up, however, based on the currently available data, no precise intervals can be recommended. In patients with severe hemodynamic and hepatic impairment a yearly evaluation might be required followed by the consultation of an experienced hepatologist.

However, further well-conducted research efforts are warranted to address these questions, including additional studies, which compare maximum liver function capacity before and after cardiac transplantation as well as explore correlations of hepatic metabolic function with histologic findings of liver biopsies.

Limitations

This study has several limitations. Since this is a cross-sectional single center study with a comparably small patient cohort, future multi-institutional studies are necessary to evaluate metabolic liver function in larger patient cohorts. Additionally, the longitudinal relationship between Fontan hemodynamics and hepatic function was not addressed by this study. Since the parameters SVEDP and PAP are included in the calculation of the Fontan failure score, the association between LiMAx and Fontan failure might be confounded. However, considering that SVEDP and PAP are only 2 of 15 parameters used for score calculations, the confounding effect seems negligible. Additionally, all of the 15 Fontan failure patients fulfill the clinical consensus definition criteria of Fontan failure (14). Parts of the data of our current study cohort (n = 38/58, 65%) have previously been published in a study with a different scope focusing on morphologic hepatic assessment (11).

Conclusions

We herein demonstrate that maximum liver function capacity measured by the LiMAx® test is impaired in patients with impaired Fontan hemodynamics and Fontan failure. Hence, the LiMAx® test represents a valuable complementary diagnostic modality for FALD and might be useful in evaluating the indication for combined heart and liver transplantation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethikkommission der Charité, Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization and formal analysis: AS, PK, and SO. Data collection: AS, NJ, MP, and PK. Investigation: AS, PK, FD, H-PM, TM, and HS. Supervision: FB and FT. Writing original draft: AS. Writing review and editing: PK and SO. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Nach dem Herstellen eines kausalen Zusammenhangs zwischen der Einschränkung der enzymatischen Leberfunktion und dem Vorliegen einer kompromittierten Fontan-Hämodynamik wurden die positiven Effekte eines körperlichen Ausdauertrainings als potentielle nicht-pharmakologische Therapieoption zur Verzögerung des Auftretens eines Fontan-Versagens sowie der konkomitanten Sekundäroraganerkrankungen untersucht. Bei limitierter Studienlage erfolgte zunächst eine longitudinale klinische Studie zur Analyse der Sicherheit und Durchführbarkeit eines mehrmonatigen heim-basierten Ausdauertrainings mit der Hauptfrage nach Verbesserung der kardiopulmonalen Belastbarkeit und der subjektiven Lebensqualität.

4.6 Positive Auswirkungen von heim-basiertem Ausdauertraining auf die kardiopulmonale Belastbarkeit von Fontan-Patientinnen und -Patienten

Im Rahmen der Arbeit

Dirks, S., Kramer, P., **Schleiger, A.**, Speck H.M., Wolfarth B., Thouet T., Berger, F., Sallmon, H., Ovroutski, S. Home-based long-term physical endurance and inspiratory muscle training for children and adults with Fontan circulation – initial results from a perspective study. Frontiers in Cardiovascular Medicine, 02/2022, 8:784648.

wurden die positiven Effekte eines individualisierten heim-basierten Ausdauertrainings auf die Fontan-Zirkulation untersucht. Hierfür wurden 18 Fontan-Patientinnen und –Patienten unterschiedlichen Alters und Geschlechts eingeschlossen, welche über einen Zeitraum von zehn Monaten ein individuell konzipiertes Ausdauer- sowie Atemtraining von 90 Minuten pro Woche absolvierten. Die Studienteilnehmer:innen wurden vor Studieneinschluss, nach einem Zeitraum von vier sowie zehn Monaten mittels einem kardiopulmonalen Belastbarkeitstest (Spiroergometrie) sowie einer Bodyplethysmographie untersucht und füllten zusätzlich einen Fragebogen zur Erfassung der Lebensqualität aus (PedsQL^{TM}). Nach einem Trainingszeitraum von zehn Monaten konnten die maximale gewichtsbezogene Leistung (Watt/kg) sowie die maximalen in- und exspiratorischen Drücke signifikant gesteigert werden, während die gewichtsbezogene maximale Sauerstoffkapazität (VO_{2max}) keine relevante Elevation aufwies. Die mittels PedsQL^{TM} erfasste Lebensqualität konnte durch das Fahrradtraining bei den untersuchten Personen nicht nachweislich verbessert werden.

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ORIGINAL RESEARCH
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Home-Based Long-Term Physical Endurance and Inspiratory Muscle Training for Children and Adults With Fontan Circulation—Initial Results From a Prospective Study

Stefan Dirks [1], Peter Kramer [1], Anastasia Schleiger [1], Hans-Martin Speck [1], Bernd Wolfarth [2], Thomas Thouet [2], Felix Berger [1,3,4], Hannes Sallmon [1,3†] and Stanislav Ovroutski [1†]*

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Background: Patients with congenital heart disease (CHD)—including those after Fontan operation—are encouraged to be physically active.

Aim: To prospectively determine the effects of an individually adapted, home-based cycle ergometer endurance training in combination with inspiratory muscle training (IMT) in pediatric and adult Fontan patients. We, herein, report the results of the initial 10-months follow-up (phase 1).

Methods: 18 patients (median age 16.5 years; range 10-43 years) completed baseline check-ups, and 4 and 10 months follow-up visits, which each included cardiopulmonary exercise testing (CPET), bodyplethysmography (including measurement of respiratory muscle strength), and a quality of life questionnaire (PedsQL™). The training program consisted of a home-based cycle ergometer endurance training on a "Magbike® AM-5i/3i" (DKN Technology®, Clermont-Ferrand, France) and IMT with a handheld "POWERbreathe® Medic plus" device. Patients performed 90 min of endurance training per week in addition to IMT (30 breaths per day, 6-7 times per week). After the first 4 months, patients underwent additional interval training.

Results: After 10 months of training, we observed significant increases in maximum relative workload (W/kg, $p = 0.003$) and in maximum inspiratory (MIP, $p = 0.002$) and expiratory (MEP, $p = 0.008$) pressures. Peak VO_2 values did not increase significantly as compared to baseline ($p = 0.12$) in the entire cohort ($n = 18$), but reached statistical significance in a subgroup analysis of teenage/adult patients ($n = 14$; $p = 0.03$). Patients' subjective quality of life did not show any significant changes after 10 months of training.

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Discussion: In Fontan patients, an individually adapted home-based training is safe and associated with improvements in some CPET variables. However, these improvements did not translate into an improved QoL after 10 months. With an unclear, but most likely negative, impact of the COVID-19 pandemic, improvements in QoL may become evident during further follow-up (phase 2 of the study).

Keywords: Fontan circulation, cardiopulmonary exercise testing (CPET), endurance training, inspiratory muscle training (IMT), quality of life

INTRODUCTION

The development of the Fontan operation and its subsequent modifications represent a mainstay of surgical palliation in children with single-ventricle malformations (1). Due to continuous refinements in surgical techniques, perioperative care, and medical and interventional treatment strategies, which have resulted in improvements in early and late mortality, a growing number of affected children enter into adolescence and adulthood (2–4). Nonetheless, the basic hemodynamic limitations of the Fontan circulation and major long-term comorbidities have remained vastly unchanged (4–6).

Specifically, increased pulmonary vascular resistance and a non-pulsatile pulmonary flow pattern may lead to systemic venous congestion and reduced ventricular preload, thereby decreasing efficacy of the Frank-Starling mechanism. In addition, a decreased heart rate reserve, ventricular fibrosis and/or hypertrophy, and an impaired systolic and/or diastolic function all result in a reduced capacity to increase stroke volume and cardiac output during physical activity (2, 5). Furthermore, Fontan patients exhibit a restrictive lung function pattern, an impaired pulmonary diffusing capacity, and a reduced maximal oxygen uptake (7), which, in turn, are associated with decreases in health-related quality of life (8–11) and exercise tolerance (12–14).

Despite these intrinsic limitations, short term exercise programs and endurance training have been shown to positively effect stroke volume, cardiac output, and lung function, thereby increasing overall physical function, exercise capacity, and quality of life (15–18). Furthermore, inspiratory muscle training (IMT) has been shown to improve cardiac output (19). Thus, patients with congenital heart disease (CHD)—including those after Fontan operation—are encouraged to be physically active and exercise training is recommended on an individual basis (20).

Recently, CHD sports programs were designed to specifically address training and medical needs of CHD patients in several countries. However, a widespread geographic distribution of the Fontan population may limit access to those programs. Therefore, home-based programs have been introduced which demonstrated a similar efficacy as compared to hospital-based programs without an increasing rate of adverse events (17, 21–26). These results led to the recent recommendation to integrate home-based exercise training programs in the follow-up care of patients undergoing Fontan surgery (17, 23). However, efficacy results of individually adapted, home-based training protocols specifically designed for Fontan patients are still sparse. Therefore, we aimed to prospectively determine the effects of an individually adapted, home-based cycle ergometer endurance training (including interval training) in combination with IMT in a cohort of pediatric and adult Fontan patients. Herein, we report the initial results of a 10-months follow-up.

METHODS

Study Design and Population

We conducted a single center prospective study on the long-term impact of a home-based training with individually prescribed and adapted endurance training in combination with inspiratory muscle training (IMT). The endurance training protocol (see below) was developed in co-operation with the Department of Sports Medicine at Charité—Universitätsmedizin Berlin. Patients were enrolled between March 2018 to March 2021. The study is divided into two study periods, with follow-up examinations in phase 1 taking place after 4 and 10 months, while follow-up visits in phase two are planned after 16 and 22 months of training. Herein, we report the results from phase 1.

Participants with Fontan circulation had to be at least 6 years of age. Informed consent of patients or legal guardians was obtained prior to enrollment. The study was reviewed and approved by the Institutional Review Board of Charité—Universitätsmedizin Berlin (EA2/244/17). The patients' medical history and routine cardiac examination were reviewed, and upon inclusion patients underwent a baseline check-up which encompassed cardiopulmonary exercise testing (CPET), bodyplethysmography, including measurement of respiratory muscle strength (CASETM ES Version 6.73, GE Health Care, Germany) (27) and a standardized health-related quality of life questionnaire (PedsQL™–Pediatric Quality of Life Inventory)—including the cardiac module (28). Within the PedsQL™, different questions are allocated to several sub-categories (psychosocial, physical health, heart problems and treatment, treatment anxiety, cognitive problems, and communication). Childrens' body weight was evaluated using the reference values of the KiGGS' data (29). Lung function was evaluated using the GLI reference values (30, 31). Blood pressure values were evaluated according to the recommendations of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (32).

Training Protocol

The training program consisted of a home-based cycle ergometer endurance training on a "Magbike® AM-5i/3i" (DKN Technology®, Clermont-Ferrand, France). Training was adapted individually to each patient's pre-training and check-up values. Patients performed 90 min of training per week, in 3 or 6 sessions of 30 or 15 min at a time, respectively (**Table 1**). Workload was set in 5 watts steps to 55% of maximum workload obtained during the latest check-up, respectively. After the first follow-up visit (4 months), patients underwent additional interval training (four intervals of 4 min at 80% of the maximum workload separated by 4 min of rest). For safety reasons, patients were urged to perform their training only when a person, who could assist or send for help in case of medical problems, was present. Prior to the initiation of home-based training, all patients underwent a baseline check-up, including CPET evaluation. If no adverse events, including symptomatic hyotonia, syncope, severe desaturation or arrhythmias occurred, patients were eligible for home-based training. An individual safety heart rate limit was set for each patient (blood pressure and saturation monitoring was not available at home in most patients). In addition to endurance training, the study participants executed an inspiratory muscle training with a handheld "POWERbreathe® Medic plus" device (POWERbreathe®, Winsen, Germany) with adjustable expiratory resistance. Inspiratory muscle training was performed at least 6 times a week for 30 consecutive slow and deep breaths. The effort was to be assessed on the 6-20 Borg scale. Participants were to adjust the resistance to achieve a value of 12-15 on the Borg scale.

Monitoring of the training included a training diary, filled out by the participants or their parents, which was checked on a monthly basis. Regular phone calls complemented the assessments of compliance and supported motivation. Based on the interviews, compliance was excellent among all 18 patients who completed the study (completion of at least 85% of the prescribed exercises). Of note, 7/25 initially enrolled patients had to be excluded before final analyses due to a low compliance or voluntary termination of the study.

TABLE 1 | Study protocol.

Baseline		
	CPET + Body + MIP/MEP + QoL	
Training period 1		
16 weeks (4 months)	Inspiratory muscle training (IMT)	30-50% of MIP 1 x 30 breaths per day (6-7 x per week)
	Ergometry	55% of W at VO2max at baseline 3 x 30 min per weeks or 6 x 15 min
	Training diary	Monthly check + weekly calls
Follow-up 1		
16 weeks (4 months)	CPET + Body + MIP/MEP + QoL	
Training period 2		
24 weeks (10 months)	Inspiratory muscle training (IMT)	1 x 30 breaths per day with adapted pressure (6-7 x per week)
	Ergometry	Adapt: 55% of W at VO2max at follow-up 1 2 x 45 min per weeks or 5 x 18 min + Interval training (4 x 4 min at 80% W at VO2max with 3 min of recovery each)
	Training diary	Monthly check + weekly calls
Follow-up 2		
24 weeks (10 months)	CPET + Body + MIP/MEP + QoL	

Body, bodyplethysmography; CPET, cardiopulmonary exercise testing; MEP, Maximum expiratory pressure; MIP, maximum inspiratory pressure.

Statistics

Statistical analysis was carried out using SPSS Version 25 (SPSS Inc., Chicago, IL, USA) In all analyses at least one variable was not in normal distribution, therefore non-parametric tests were used. Differences between groups (the three time points) were analyzed by the non-parametric Friedman test for three or more paired samples. P-values < 0.05 were considered statistically significant. In addition, a-priori power analysis was performed to estimate the required sample size (based on anticipated changes in the PedsQL scores): Assuming a sample size of $n = 20$, significant changes can be seen with a minimal effect size of 0.66 (power 80%, alpha-level 0.05), which would be equivalent to, e.g., an increase of 5% (standard deviation 8%). With only $n = 10$ children enrolled, the required effect size would have to be 0.95 (power 80%, alpha-level 0.05), e.g., equivalent to an increase of 12% (standard deviation 13%).

RESULTS

Demographics

A total of 25 patients were initially enrolled in the study, out of which 18 patients (median age 16.5 years; range 10-43 years) were included in the final analyses. Seven out of the 25 initially enrolled patients were excluded due to a low compliance or voluntary termination of the study. Compliance was assessed by means of a training diary and weekly telephone interviews with patients and parents. These calls were also supposed to work as a motivational strategy. 11/18 (61.1%) were male and 7/18 (38.9%) female. Baseline body weight in adults ranged between 37 and 84 kg (median 65 kg), while in children weight ranged between the 5th and 79th percentile (median 35th percentile). Details on the underlying congenital cardiac malformation are provided in **Table 2**. Of note, three patients (16.7 %) had evidence of an open fenestration at the latest echocardiography before initiation of training and two patients (11.1%) had an epicardiac pacemaker. Cardiac medication remained stable during the study period in all 18 patients. The median oxygen saturation at rest was 97% (range 89-100%). At baseline, the mean resting systolic and diastolic blood pressures in adults were 121 (range 69-143) mmHg and 79 (range 50-86) mmHg. In children, the mean resting systolic blood pressures at baseline was at the 71st (range 4th to 99th)

TABLE 2 | Baseline patients' characteristics.

	Age	Gender	Height (cm)	Weight (kg) baseline/4 months/10 months	Age at Fontan completion	Cardiac malformation	Comment	Medication	Mean pulmonary artery pressure [mmHg]
01	22	F	169	62/55/55	2	TA, PA, intact VS	Fenestration	VKA	14
02	13	F	153	40/43/45	4	PA, VSD, TGA	-	ACEI, VKA	11
03	15	F	170	50/50/51	3	TA, VSD, pulmonary artery ligation	-	VKA	11
04	12	M	158	40/42/45	3	TA, TGA, VSD, s/p Damus-Kaye-Stansel operation	-	VKA	-
05	43	M	167	69/70/70	17	TA, PA, VSD, occlusion left subclavian artery	-	ACEI, HCT, MCRA, VKA, Propafenone, Ivabradine	-
06	12	M	148	49/51/54	3	TA, VSD, sick sinus syndrome	DDD-Pacemaker	ACEI, PDE5 inhibitor, VKA	14
07	20	M	185	68/67/67	5	TA, VSD, coarctation of the aorta, DORV, s/p Damus-Kaye-Stansel operation	-	VKA	13
08	24	M	190	71/70/70	3	TA	-	ASA, HCT	14
09	26	M	187	84/86/88	6	TA	-	VKA	12
10	24	F	156	37/38/38	3	DILV, sick sinus syndrome, AV Block II°	-	ACEI, VKA	11
11	12	M	143	46/47/49	3	HLHS, coarctation of the aorta	Fenestration	ACEI, VKA	-
12	11	M	143	29/31/31	4	DORV, DILV, PS	-	VKA	-
13	11	M	149	38/40/41	3	MA, DORV, VSD	-	ACEI, HCT, VKA	-
14	11	M	150	46/49/51	3	TA, VSD, PS	DDD-Pacemaker	ACEI, VKA	7
15	10	F	135	32/36/39	9	PA, VSD, tricuspid valve dysplasia	Fenestration	ACEI, PDE5 inhibitor, VKA	11
16	18	F	164	57/60/59	3	TA, PS	-	ASA	8
17	27	F	162	58/59/60	24	DORV,VSD,TGA, RVOT stenosis	Fenestration	HCT, MCRA, VKA	12
18	36	F	158	60/59/60	9	DILV, VSD, PS	-	ACEI , ASA	13

DILV, double inlet left ventricle; DORV, double outlet right ventricle; F, female; HLHS, hypoplastic left heart syndrome; M, male; MA, mitral atresia; PA, pulmonary atresia; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; TA, tricuspid atresia; TGA, transposition of great arteries; VS, ventricular septum; VSD, ventricular septal defect; ACEI, ACE inhibitors; ASA, acetylsalicylic acid; HCT, hydrochlorothiazide; MCRA, mineralocorticoid receptor antagonist; VKA, vitamin K antagonist.

percentile. 13/18 patients underwent cardiac catheterization during the 5 years preceding baseline (median 8 months). Invasively obtained mean pulmonary artery pressures (mPAP) ranged between 7 and 14 mmHg (median 12 mmHg), indicating stable Fontan circulation (**Table 2**). The remaining patients showed no indication for invasive diagnostics due to reassuring general condition, echocardiographic results and high oxygen saturations (33).

Cardiopulmonary Function

Cardiopulmonary function was evaluated at baseline, and after 4 and 10 months of training (**Table 3**). After 10 months of follow-up, peak VO_2 values did not increase significantly as compared to baseline (mean 26.50 ± 2.10 ml/min/kg to 28.10 ± 1.95 ml/min/kg; $p = 0.12$) (**Figure 1**). Of note, in the sub-cohort of teenage/adult patients (patients who turned 13 or older during the study period, $n = 14$), the increase in peak VO_2

TABLE 3 | Cardiopulmonary exercise testing (CPET, all patients, $n = 18$).

	Baseline	4 months	10 months	P
HF (rest) [bpm]	91.50 ± 3.28	91.44 ± 3.85	85.41 ± 3.33	0.09
HF (max) [bpm]	158.67 ± 7.56	165.22 ± 6.39	161.59 ± 7.63	0.12
Heart rate reserve [bpm]	67.17 ± 6.93	73.78 ± 5.50	76.18 ± 6.16	0.058
Max. power/weight [W/kg]	1.92 ± 0.15	2.14 ± 0.16	2.17 ± 0.19	**0.003**
VO_2max [ml/min/kg]	26.50 ± 2.10	26.99 ± 1.98	28.10 ± 1.95	0.12
AT/reference [%]	48.88 ± 4.08	47.88 ± 3.51	52.00 ± 4.06	0.12
VE/VCO_2 slope	33.02 ± 1.32	33.42 ± 1.10	32.51 ± 1.45	0.07
TCS (rest) [%]	96.18 ± 0.82	95.53 ± 0.97	95.94 ± 0.63	0.98
TCS (max. capacity) [%]	92.67 ± 1.07	92.44 ± 1.15	92.00 ± 1.18	0.29
VC_{insp}/reference [%]	77.75 ± 5.05	81.21 ± 4.78	81.55 ± 4.64	0.87
TLC/reference [%]	85.64 ± 3.64	85.61 ± 3.82	85.28 ± 4.42	0.98
FEV_1/VC_{insp} [%]	92.83 ± 1.95	92.76 ± 1.66	90.91 ± 2.33	0.16
MEP [kPa]	6.87 ± 0.80	7.71 ± 0.84	8.17 ± 1.00	**0.008**
MIP [kPa]	6.41 ± 0.63	8.90 ± 0.89	8.95 ± 0.97	**0.002**

Baseline results and results after 4 and 10 months of training are shown with corresponding P-values (non-parametric Friedman test for three or more paired samples). Significant values are shown in bold. All CPETs were maximal test (RER > 1.0). HF, heart frequency; AT, anaerobic threshold; TCS, transcutan oxygen saturation; FEV1, forced expiratory pressure in 1 s; VCinsp, inspiratory vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; TLC, total lung capacity.

reached statistical significance after 10 months of training (23.50 ± 3.86 ml/min/kg to 26.09 ± 2.00 ml/min/kg; $p = 0.03$, **Figure 1**; **Table 4**). Slope values did not decrease significantly during the 10-months training period, in both the overall cohort ($p = 0.07$, **Table 3**) and the sub-cohort of teenage/adult patients ($p = 0.09$, **Table 4**). In addition, in the total cohort maximum relative workload increased within 10 months of training from a mean of 1.92 ± 0.15 W/kg to 2.17 ± 0.19 W/kg ($p = 0.03$) (**Table 3**; **Figure 1**).

Furthermore, in both cohorts no significant changes in resting heart rate or functional heart rate reserve could be demonstrated (**Table 3**). Of note, at baseline, there was no significant difference in the drop of oxygen saturation during exercise when comparing patients with and those without fenestration ($U = 19.5$, $Z = -0.748$, $p = 0.477$). Consistently, these results did not change after 10 months of training ($U = 12.0$, $Z = -1.022$, $p = 0.307$).

Pulmonary Function

9/18 (53%) showed normal pulmonary function, while 6/18 (35%) exhibited a restrictive and 2/18 (12%) an obstructive pattern at baseline. One patient did not tolerate bodyplethysmography at baseline. As expected, vital capacity (VC), total lung capacity (TLC) and FEV1/VC did not show any significant improvements after 10 months of training. However, in the cohort of patients from all age groups maximal inspiratory pressure significantly increased from 6.41 ± 0.63 to 8.95 ± 0.97 kPa ($p = 0.002$; **Table 3**; **Figure 2**) and maximal expiratory pressure from 6.87 ± 0.80 to 8.17 ± to 1.00 kPa ($p = 0.008$, **Table 3**; **Figure 2**). Again, similar results were obtained from the sub-cohort analysis of teenage/adult patients (**Table 4**)

Quality of Life

Patients' subjective quality of life as determined by the PedsQL^{TM} questionnaires did not show any significant changes after 10 months of training (in neither of the sub-categories - psychosocial, physical health, heart problems and treatment, treatment anxiety, cognitive problems and communication, data not shown).

DISCUSSION

We herein show, that an individually adapted home-based training is safe and associated with improvements in some CPET variables. However, these improvements did not translate into an improved QoL after 10 months. Importantly, none of the patients experienced any adverse events during home-based training such as syncope, symptomatic arrhythmia or acute hospitalization.

During the last decades, survival rates in children with CHD have increased substantially. Currently, more than 97% of children with CHD can be expected to reach adulthood (2, 34–36). With an improved long-term survival, aspects of long-term morbidity, cardiopulmonary capacity, pulmonary function, reproductive and psychosocial health and quality of life require closer attention. In patients with Fontan circulation, exercise capacity has been reported to be reduced to about 50-60% (10, 13). However, impaired exercise capacity is known to be associated with adverse outcome in CDH patients, including Fontan patients. Furthermore, CPET is indicated in Fontan patients with pulmonary vascular disease (37) and should be performed on a regular basis in all Fontan patients if possible (38).

Paridon et al. observed peak VO_2 values within the normal range in only 28% of patients. However, a majority of individuals (63%) exhibited an anaerobic threshold within the normal range, suggesting that many Fontan patients tolerate a high level of submaximal and non-maximal activity (3). Thus, endurance training at the lower end of the individually tolerated workload (defined as W/kg at VO_2max = 100%) seems adequate for Fontan patients. However, long-term data

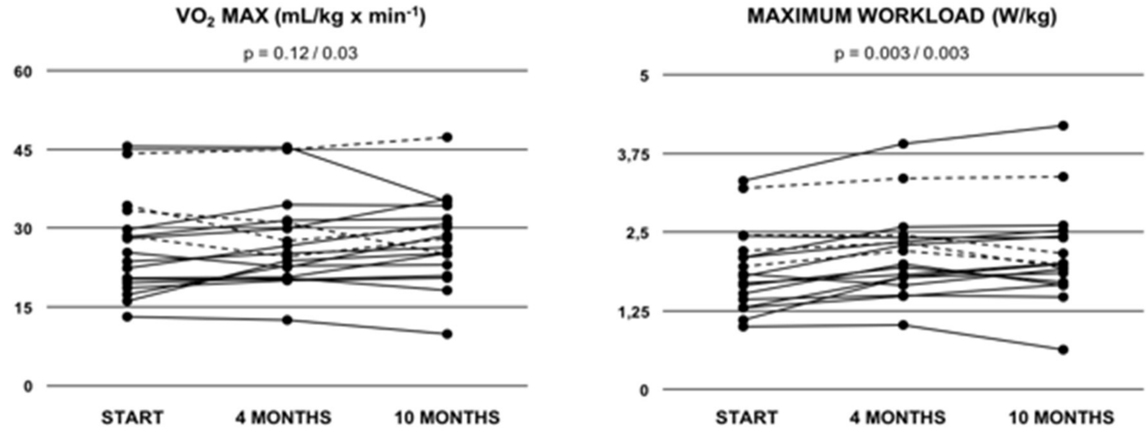

FIGURE 1 | Peak oxygen uptake (VO_2 MAX) and maximum relative workload (W/kg) in Fontan patients during the 10-months training period. Values are given at baseline (start), and after 4 and after 10 months of combined endurance and inspiratory muscle training. Each line represents one patient. Full lines represent teenage/adult patients, while dashed lines indicate patients who remained younger than 13 years throughout the study period. The first *p*-value refers to the total cohort of 18 patients, while the second *p*-value refers to the teenage/adult subgroup analyses only ($n = 14$).

TABLE 4 | Cardiopulmonary exercise testing (CPET, teenage/adult subgroup, $n = 14$).

	Baseline	4 months	10 months	*P*
HF (rest) [bpm]	89.29 ± 4.08	90.36 ± 4.88	83.14 ± 3.71	0.23
HF (max) [bpm]	155.21 ± 8.76	162.21 ± 7.62	157.79 ± 8.51	0.11
Heart rate reserve [bpm]	65.93 ± 7.78	71.86 ± 6.24	74.64 ± 6.71	0.085
Max.power/weight [W/kg]	1.75 ± 0.15	2.00 ± 0.15	2.02 ± 0.17	**0.003**
VO_2max [ml/min/kg]	23.50 ± 3.86	25.43 ± 2.15	26.09 ± 2.00	**0.03**
AT/reference [%]	42.46 ± 2.94	44.94 ± 3.69	48.07 ± 3.38	0.09
VE/VCO_2 slope	32.17 ± 1.71	33.14 ± 1.42	31.31 ± 1.61	0.09
TCS (rest) [%]	95.92 ± 0.98	95.36 ± 1.10	95.92 ± 0.67	0.97
TCS (max. capacity) [%]	92.43 ± 1.31	91.93 ± 1.33	92.31 ± 1.42	0.42
VC_{insp}/reference [%]	71.15 ± 5.12	70.21 ± 4.94	69.00 ± 5.50	0.56
TLC/reference [%]	90.48 ± 2.26	91.13 ± 1.96	89.70 ± 3.00	0.61
FEV_1/VC_{insp} [%]	92.23 ± 4.78	96.14 ± 5.12	103.64 ± 4.11	0.09
MEP [kPa]	6.25 ± 0.80	8.84 ± 1.08	7.87 ± 1.18	**0.045**
MIP [kPa]	6.63 ± 0.73	9.35 ± 1.04	8.38 ± 1.07	**0.014**

Baseline results and results after 4 and 10 months of training are shown with corresponding p-values (non-parametric Friedman test for three or more paired samples). Significant values are shown in bold. All CPETs were maximal test (RER > 1.0). HF, heart frequency; AT, anaerobic threshold; TCS, oxygen saturation; FEV1, forced expiratory pressure in 1 s; VCinsp, inspiratory vital capacity; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; TLC, total lung capacity.

on training studies is still sparse in the Fontan population. A recent review article (39) showed that out of 245 individuals reported in the literature, only 88 (36%) patients trained for more than 3 months and only 30 individuals (12%) trained in studies lasting longer than 8 months. We, herein, report on the 10-months follow-up of 18 patients who underwent an individually adapted, home-based ergometer endurance training (including interval training) in combination with IMT.

Cardiopulmonary Impact

Exercise intolerance in Fontan patients is caused by multiple factors, which include the lack of a subpulmonary ventricle (pump function), chronotropic incompetence, restrictive lung function, reduced muscle mass, and general deconditioning, among others (40, 41). While healthy people improve their cardiac output by increasing both heart rate and stroke volume during exercise, in the Fontan circulation, increases in heart rate are crucial to enhance cardiopulmonary exercise capacity due to a reduced capacity to increase preload (lack of a subpulmonary ventricle) (42). In addition, heart rate reserve is further reduced in several patients by medication and/or iatrogenic damage of the sinus node (43). After 10 months of training, we did not see significant reductions in resting heart rate or increases in functional heart rate reserve (**Tables 3**, **4**). Due to the limited size of our total cohort, a meaningful sub-cohort analysis of patients on specific antiarrhythmic medications and/or sick sinus syndrome was not feasible. However, heart rate reserve

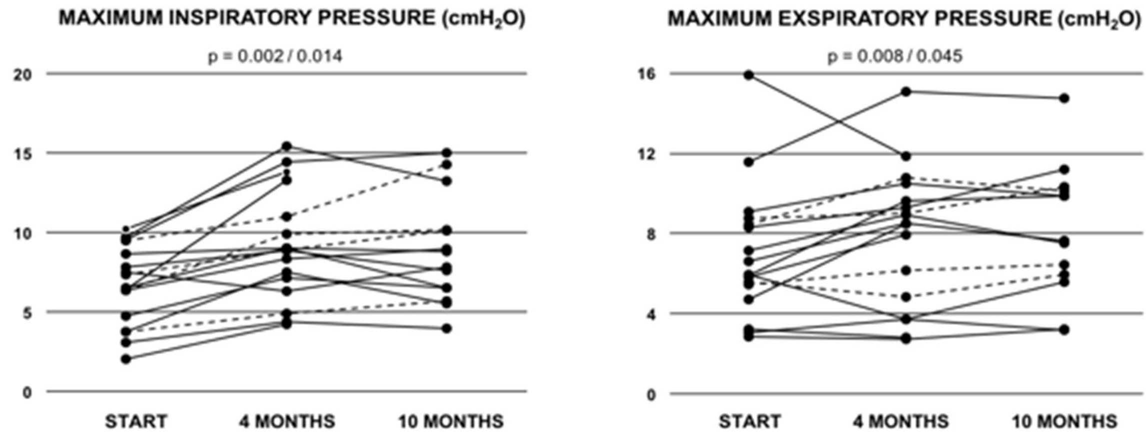

FIGURE 2 | Maximum inspiratory pressure (MIP) and maximum exspiratory pressure (MIP) in Fontan patients during the 10-months training period. Values are given at baseline (start), and after 4 and after 10 months of combined endurance and inspiratory muscle training. Each line represents one patient. Full lines represent teenage/adult patients, while dashed lines indicate patients who remained younger than 13 years throughout the study period. The first *p*-value refers to the total cohort of 18 patients, while the second *p*-value refers to the teenage/adult subgroup analyses only ($n = 14$).

between patients with and those without pacemaker did not differ significantly ($p = 0.9$). This was also true when all patients with impaired chronotopy (antiarrhythmic medication with betablockers, ivabradin or pacemaker patients) were compared to patients without pacemakers or antiarrhythmic medication (data not shown). Thus, it remains unclear if the lack of significant improvements in functional heart rate reserve after training represents an intrinsic limitation in all Fontan patients or if medications and specific heart rhythm anomalies are responsible for these results. Furthermore, it is likely that subtle improvements may only become evident during a longer training period.

Besides heart rate reserve, peak VO_2 and VE/VCO_2 slope are major indicators of cardiopulmonary exercise capacity. Healthy people reach their maximum of peak VO_2 at early adulthood, with values beginning to drop around the age of 30 years. However, in Fontan patients peak VO_2 values already start to decrease disproportionally early during adolescence (10, 44). In our teenage/adult cohort we were able to demonstrate significant improvements in peak VO_2 after 10 months of training, while we did not see significant improvements in the total cohort of 18 patients. In their recent review article incorporating 16 studies on endurance training in Fontan patients, Scheffers et al. report that only 9 out of 16 reviewed studies demonstrated improvements in peak VO_2 (39). Differences in results among studies are likely caused, at least in part, by different follow-up durations as functional parameters, such as peak VO_2 and slope, usually require some time of training before significant improvements become evident.

Of note, previous studies demonstrated significantly lower oxygen saturation values at rest (45) and a pronounced systemic desaturation during exercise in patients with fenestration as compared to those without fenestration (46). In the cohort presented herein, we were unable to confirm these results as our results did not show any differences in saturation values between groups. However, our study only included four patients with fenestration precluding a statistically meaningful subgroup analysis. In addition, the presence of fenestrations was documented by echocardiography preceding the baseline evaluation only. Thus, their hemodynamic relevance remains unclear in our patients. Of note, we did not observe any significant differences (CPET, pulmonary function, QoL) between the patients with and those without fenestration (data not shown).

Pulmonary Function

About one third of the patients in our cohort exhibited a restrictive breathing pattern at baseline, in line with previous reports on lung function test results in Fontan patients (7, 47). The observed restrictive breathing pattern is likely caused by multiple factors, which include diaphragmatic paralysis (48, 49) and a reduced thoracic mobility due to repeated thoracotomies with presence of less flexible scar tissue (49). Previous results on the impact of different physical training programs on lung function testing in Fontan patients revealed conflicting results. While, similar to our results, Fritz et al. failed to show significant improvements in vital capacity, total lung capacity and Tiffeneau-Index (FEV1/VC) after daily inspiratory muscle training over 10 months (50), Hedlund et al. demonstrated an increased vital capacity after endurance training (7).

We observed significant increases in maximum power/weight ratio, as well as in maximum inspiratory (MIP) and expiratory (MEP) pressures after 10 months of combined endurance and inspiratory muscle training. MIP and MEP values at baseline ranged between the 3rd and 25th percentile (P3-P25) and increased to P10-P50 during training (51). Laohachai et al. (19) previously reported that improvements in MIP were associated with positive effects on cardiac output in Fontan patients after 6-week of IMT. Thus, one might speculate that higher inspiratory muscle strength may increase pulmonary blood flow (by improving the "thoracic pump") and subsequently improve preload, cardiac output and exercise capacity (19). Furthermore, the combination of different training modalities, such as IMT and endurance training may, at least theoretically, booster the positive effects of training in Fontan patients as an improved "thoracic pump" and an overall improved cardiorespiratory capacity both enhance overall physical fitness at multiple circulatory target sites.

Quality of Life

Although we did observe improvements in several parameters of cardiopulmonary exercise capacity, those changes did not translate into patients' subjective quality of life as determined by the PedsQL questionnaires after 10 months of training. Previously, several authors found improvements in quality of life indices by training interventions in Fontan patients (11, 18, 28, 37, 52), while others reported unchanged QoL (23). Although several factors, such as differences in training protocols, duration and compliance, might contribute to these discrepancies in previously reported results, self-reported QoL is generally influenced by a variety of possible confounders (parenteral influence, bias by peer comparison, etc.). In addition, some categories of the quality-of-life questionnaire, such as "treatment anxiety" and "cognitive problems and communication" are unlikely to change by physical training programs.

Furthermore, a home-based training, as performed here, almost completely lacks the social benefit of training together. However, home-based protocols may enable an easy individual adaptation of training plans and facilitate inclusion of more patients as compared to a standard group training at a certain location. While we believe that a longer follow-up may be required to detect improvements in QoL, the study was conducted during a time heavily affected by the COVID-19 pandemic with its detrimental effects on families, social life, school, work, and activities, which likely had a negative impact on general QoL. In this regard, several patients affected by CHD and especially older Fontan patients reduced many of their social activities in order to decrease their risk of infection. Of note, the PedsQL questionnaire had been initially designed for patients up to 18 years. However, in order to allow for comparative analyses we used PedsQL in all patients (children, teenagers and adults). Furthermore, adult patients with Fontan circulation often face specific challenges, which are similar to their situation during childhood (high dependence on parental support etc.).

Limitations

In addition to the previously mentioned confounders, such as the co-occurrence of the COVID-19 pandemic, further limitations apply when interpreting the results presented in this study. First, the number of patients is limited and patients differed in regard to underlying age, gender, cardiac defect, surgical modifications, and medical treatment. Nevertheless, compared to previously reported studies on physical training in Fontan patients, our cohort is of comparably large size and followed-up for a relatively long period of time (10 months during phase 1). In addition, differences in motivation, other health-related problems, and differences in socio-economic backgrounds, supervision by parents, self-awareness of benefit, cognitive abilities and technical execution of training represent further confounders that were unaccounted for in this analysis (27). In addition, due to learning effects, lung function tests are known to improve over time, especially in patients that perform lung function tests for the first time. While we cannot rule out the possibility that learning effects might have contributed to the results, CPET testing and assessment of inspiratory muscle strength is routinely performed during follow-up for all Fontan patients and we usually do not see improvements over time. However, the well-known effects of learning cannot firmly be ruled out. Furthermore, Fontan patients are especially prone to malnutrition and often exhibit a body composition with low muscle mass. Thus, the combined effect of nutritional management together with different physical training programs needs to be evaluated in further studies.

CONCLUSIONS

In conclusion, we show that individually adapted aerobic endurance training in combination with IMT is safe and associated with improvements in certain CPET variables in Fontan patients in a home-based setting. While some CPET measures improved, these improvements did not (yet) translate into an improved QoL. With an unclear, but most likely negative, impact of the COVID-19 pandemic, improvements in QoL may be expected during further follow-up (phase 2 of the study). Additional research efforts on the long-term role of individualized training programs are warranted in order to facilitate improvements (or to prevent premature deterioration) of physical endurance and QoL in Fontan patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Charité Institutional Review Board (EA2/244/17). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SD, PK, HS, and SO planned and conducted the study. SD and H-MS wrote the manuscript. All authors contributed to data collection, analysis, interpretation, and approved the final version of the manuscript.

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5. Diskussion

5.1 Echokardiographische Parameter zur Indikationsstellung einer univentrikulären Palliation bei Patientinnen und Patienten mit ventrikulärer Imbalance

Das breite Spektrum der anatomischen Varianten eines unbalancierten AVSD erschwert die Definition von echokardiographischen Parametern, welche zur Festlegung einer geeigneten chirurgischen Strategie herangezogen werden können.[76-78] Die Durchführbarkeit einer biventrikulären Korrektur ist von mehreren anatomischen Voraussetzungen abhängig, welche in der Entscheidungsfindung berücksichtigt werden sollten.[16] Hierzu gehören die Volumina des rechten und linken Ventrikels, die Größe und Morphologie der gemeinsamen Atrioventrikularklappe, die Geometrie der Ein- und Ausflusstrakte, die Größe des Ventrikelseptumdefektes sowie die Art und Anzahl der konkomitanten kardialen Malformationen. Durch diese Vielzahl an Einflussfaktoren kann ein einzelner echokardiographischer Parameter nicht zur Entscheidung zwischen einer univentrikulärer Palliation und einer biventrikulären Korrektur herangezogen werden. Jeder im Rahmen unserer Studie untersuchte echokardiographische Parameter – ausgenommen der Größe des Ventrikelseptumdefektes – hat sich als valide zur Identifikation des Ausmaßes der ventrikulären Imbalance und somit Festlegung der operativen Strategie erwiesen. Durch die Berechnung der linksventrikulären Atrioventrikularklappenfläche nach komplettem chirurgischem Verschluss des *Cleft* trägt der neu eingeführte LAVRI sowohl zur Einschätzung der Möglichkeit einer biventrikulären chirurgischen Korrektur als auch des Reoperationsrisikos im Bereich der linksventrikulären Atrioventrikularklappe nach erfolgter Korrekturoperation (*Cut-off* Wert ≤2.0 cm^2/m) bei. Eine Validierung des Parameters in prospektiven multizentrischen Studien mit einer größeren Patientenanzahl ist jedoch erforderlich. Ein weiterer ausstehender

Forschungsaspekt ist die Anwendbarkeit von präoperativ erfassten echokardiographischen Parametern, insbesondere des LAVRI, für die Selektion von geeigneten Patientinnen und Patienten für biventrikuläre Rekrutierungs- oder Konversionsstrategien.[18,19] Diese werden bisher in einigen Zentren erfolgreich durchgeführt und stellen weiterhin eine große interdisziplinäre Herausforderung dar, so dass aktuell keine klare Therapieempfehlung zur Anwendung dieser vorliegt. Trotz zufriedenstellender kurz – und mittelfristiger Ergebnisse ist der Nutzen dieser operativen Strategien im Hinblick auf die Gesamtüberlebensprognose für Personen mit ventrikulärer Imbalance nicht belegt. Im Gegenteil scheint sich die Langzeitüberlebensprognose nach erfolgreicher Fontan-Operation in den letzten Jahrzehnten auch für Patientinnen und Patienten mit unbalanciertem AVSD verbessert zu haben.[79]

5.2 FALD als Langzeitkomplikation einer univentrikulären Palliation

Die Fontan-assoziierte Lebererkrankung stellt die häufigste Sekundärorganerkrankung bei Patientinnen und Patienten mit einer Fontan-Zirkulation dar und ist mit einer erhöhten Mortalität und Morbidität assoziert.[80] Das frühzeitige Erkennen ihres Vorliegens und Progresses ist zur Prognoseeinschätzung und Risikostratifizierung für diese Patientenkohorte von erheblicher Bedeutung.[79] Der schleichende Krankheitsprogress, das verzögerte Auftreten von klinischen Symptomen und die Diskrepanz zwischen Ergebnissen von nicht-invasiven und histopathologischen Untersuchungen erschweren die Interpretation der Untersuchungsbefunde, ihre Einordnung in den klinischen Kontext sowie das Ableiten von Therapiempfehlungen.[57] Der zentrale Forschungsschwerpunkt dieser Arbeit umfasste eine Klassifizierung und Graduierung der FALD, um eine

Interpretationsgrundlage für die diversen Manifestationsformen dieser Erkrankung zu etablieren. Weitere Schwerpunkte stellten die Untersuchung eines Zusammenhangs zwischen der Hämodynamik der Fontan-Zirkulation und der Entstehung sowie dem Progress der FALD sowie umgekehrt die Nutzbarkeit dieses Zusammenhangs zur frühzeitigen Detektion eines Versagens der Fontan-Zirkulation dar.

5.2.1 Diagnostische Modalitäten zur frühzeitigen Erkennung der FALD

In der vorliegenden Arbeit wird ein großer Fokus auf die Anwendung von nicht-invasiven diagnostischen Modalitäten, wie Laborwertanalyse, Lebersonographie und TE, sowie der Messung der enzymatischen Leberfunktion mittels LiMAx-Test zur Detektion der FALD gelegt. Vorteile dieser Auswahl sind eine einfache Durchführung und Reproduzierbarkeit der Untersuchungen sowie deren mühelose Integration in die klinische Routine. Obwohl die Leberbiopsie weiterhin den Goldstandard für die Diagnostik von akuten und chronischen Lebererkrankungen darstellt, wird ihre Durchführung bei Fontan-Patientinnen und –Patienten nur bei besonderen klinischen Fragestellungen, wie der Evaluation für eine Herzlebertransplantation, empfohlen.[80] Hintergründe sind eine fehlende einheitliche histopathologische Schweregradklassifizierung der FALD, welche durch das Vorliegen von periportaler und zentrolobulärer Fibrose ein eigeständiges und neuartiges histologisches Krankheitsbild darstellt.[81]

Die Interpretation von Ergebnissen der TE als nicht-invasives Diagnostikum zur Erfassung des hepatischen Fibrosegrades ist bei Patientinnen und Patienten mit einer Fontan-Zirkulation ebenfalls erschwert. Basierend auf der chronischen systemvenösen und hepatischen Kongestion lagen die TE Messwerte in der untersuchten Kohorte deutlich oberhalb der für andere Lebererkrankungen definierten

Referenzwerte.[82,83] Eine Korrelation zwischen TE Messwerten und dem histologischen Fibrosegrad der Leber konnte in vergleichenden Studien nicht nachgewiesen werden.[84,85] Nach dem aktuellen Kenntnisstand sollten die Ergebnisse der TE nicht punktuell sondern im longitudinalen Verlauf beurteilt werden. Für eine konkrete Interpretation der Ergebnisse einer TE bei Fontan-Patientinnen und –Patienten sind eine weitere Validierung und Definition von Referenzwerten erforderlich.

Im Rahmen der laborchemischen Analyse konnte gezeigt werden, dass bei der Mehrheit der untersuchten Personen eine Erhöhung der γGT und des Bilirubins vorlag. Untersuchungen von Patientinnen und Patienten mit einer chronischen Rechtsherzinsuffizienz konnten einen Zusammenhang zwischen dem Ausmaß der systemvenösen Kongestion und dem Anstieg der beiden Cholestaseparameter belegen.[86,87] Als dem zu Grunde liegender Mechanismus wird eine Kompression der *Canaliculi biliferi* und *Ductuli biliferi interlobulares* durch die massiv dilatierten Lebersinusoide angenommen. Zusätzlich führt ein vermindertes Herzzeitvolumen zu einer reduzierten hepatischen Perfusion, welche in vermehrtem oxidativen Stress und konsekutiv in einer Nekrose der zentrolubulären Hepatozyten sowie einer ischämisch-bedingten Schädigung des intrasinusidalen Endothels resultiert.[88] Diese Annahme wird durch die Korrelation der Cholestaseparameter mit der mittels LiMAx Test erfassten enzymatischen Leberfunktion unterstützt.

Die häufigsten sonographisch detektierbaren Leberveränderungen umfassen ein heterogenes Leberparenchym, eine Atrophie des rechten und Hypertrophie des linken Leberlappens, Oberflächennodularität, Lebervenendilatation und –kaliberschwankungen sowie hyperechogene Läsionen. Diese sind in der Regel benigne und weisen histologische Merkmale von Regeneratknötchen sowie einer fokalen nodulären Hyperplasie auf.[89] Bei einer Minderheit unserer untersuchten

Kohorte konnten in Rahmen der Lebersonographie tumorverdächtige Läsionen detektiert werden, so dass eine weiterführende diagnostische Abklärung mittels Kontrastmittelsonographie oder Magnetresonanztomographie erforderlich war. Maligne Prozesse konnten bei erfreulicherweise bei allen untersuchten Personen ausgeschlossen werden.

Der LiMAx-Test basiert auf der Metabolisierung von dem isotopenmarkierten ^{13}C-Methacetin durch das hepatozyten-spezifischen Zytochrome P4501A2-(CYP1A2) System zu Paracetamol und $^{13}CO_2$, welches kontinuierlich in der Exspirationsluft der untersuchten Patientinnen und Patienten gemessen wird. Der LiMAx-Test wurde bereits für unterschiedliche Fragestellungen in die klinische Routine zur Erfassung der maximalen Leberfunktionskapazität integriert.[90-92] Bisher existieren nur wenige Studien, welche die enzymatische Leberfunktion von Fontan-Patientinnen und –Patienten untersuchen. Im Rahmen der vorliegenden Arbeit konnte gezeigt werden, dass die mittels LiMAx-Test erfasste hepatozyten-spezifische enzymatische Leberfunktion trotz einer hohen Anzahl von FALD-spezifischen morphologischen und laborchemischen Veränderungen bei der Mehrzahl der Patientinnen und Patienten erhalten war. Eine milde bis moderate Einschränkung der LiMAx Werte war lediglich bei Personen mit einer sonographisch detektierbaren Leberzirrhose nachweisbar. Daher liegt die Vermutung naheliegend, dass morphologische und laborchemische Veränderungen einer funktionellen Einschränkung der Leber vorangehen bzw. dass diese sich erst in späten Krankheitsstadien der FALD manifestiert.

Der LiMAx-Test stellt eine sinnvolle Ergänzung zur nicht-invasiven Diagnostik dar und kann die Interpretation der nachgewiesenen morphologischen oder laborchemischen Veränderungen unterstützen. Weiterhin ist die Quantifizierung der enzymatischen Leberfunktion als longitudinaler Verlaufsparameter geeignet, so dass bei

Verschlechterung weiterführende diagnostische oder therapeutische Schritte ohne Zeitverzögerung initiiert werden können.

5.2.2 Einflussfaktoren für die Entstehung und den Progress der FALD

Die Entstehung der FALD unterliegt einer multifaktoriellen Genese, welche das Vorliegen einer chronischen venösen Kongestion, eines reduzierten Herzzeitvolumens sowie multipler hypoxisch-ischämischer Insulte beinhaltet. Im Rahmen dieser Arbeit konnte nachgewiesen werden, dass eine eingeschränkte systolische Funktion des Systemventrikels, erhöhte Pulmonalarterienmitteldrücke sowie erhöhte end-diastolische Füllungsdrücke des Systemventrikels signifikant mit der morphologischen Ausprägung und funktionellen Einschränkung der FALD korrelieren. Insbesondere ein Pulmonalarterienmitteldruck ≥15 mmHg und ein end-diastolischer Ventrikeldruck ≥12 mmHg waren mit einer signifikant eingeschränkten enzymatischen Leberfunktion sowie einer schweren Ausprägung der FALD assoziiert, welche an der Art und Anzahl von morphologischen und laborchemischen FALD-spezifischen Veränderungen gemessen wurde. Ähnlich wie bei einer durch schwere Rechtsherzinsuffizienz verursachten kongestiven Hepatopathie sind Faktoren wie das Vorliegen von tachykarden Herzrhythmustörungen, die Abwesenheit eines Sinusrhythmus, ein erhöhter pulmonalvaskulärer Widerstand, eine reduzierte systolische Ventrikelfunktion sowie die Schwere der Atrioventrikularklappeninsuffizienz für die Entstehung und Ausprägung der FALD ausschlaggebend.[93-96] Als weiterer wesentlicher Risikofaktor für die Entstehung der FALD wurde im Rahmen dieser Arbeit die Zeit nach der Fontan-Operation identifiziert. Diese Beobachtung ist kohärent mit Ergebnissen von anderen Arbeitsgruppen, welche einen signifikanten Anstieg der FALD-Inzidenz 15 Jahre nach Durchführung der Fontan-Operation beschreiben.[80,97,98] Das zirrhosefreie Überleben nach Komplettierung der Fontan-Zirkulation wird mit 99 % nach 10 Jahren, 94 % nach 20 Jahren und 57 % nach 30 Jahren angegeben.[99] Die kumulativen Inzidenzraten für die Entstehung eines HCC betragen 0,8 %, 2,9 % und 13,3 % nach einem Zeitraum von 10, 20 und 30 Jahren nach Durchführung der Fontan-Operation.[100] Diese Inzidenzraten sind deutlich höher als bei der gleichaltrigen europäischen Bevölkerung[101]; zusätzlich ist das Manifestationsalter bei Erstdiagnose des HCC deutlich niedriger als bei Patientinnen und Patienten mit anderen hepatologischen Grunderkrankungen.[102] Die Genese des HCC ist bei einem hohen Anteil von 40-50 % der Fontan-Patientinnen und –Patienten nicht mit der Antedeszens einer Leberzirrhose assoziiert.[103] Das junge Alter bei Erstmanifestation und die erschwerte Diagnostik des HCC durch das Fehlen einer vorangehenden Leberzirrhose unterstreichen die Bedeutung und rechtfertigen die Indikation für ein frühzeitiges und standardisiertes FALD Screening.[103]

5.2.3. Relevanz der FALD in der Diagnostik und Therapie des Fontan-Versagens

Das Versagen der Fontan-Zirkulation ist eine schwerwiegende und unvermeidbare Langzeitkomplikation der unphysiologischen Fontan-Hämodynamik.[11,20] Innerhalb der nächsten Dekade wird ein signifikanter Anstieg der Anzahl von erwachsenen Fontan-Patientinnen und –Patienten mit einer kompromittierten Fontan-Zirkulation erwartet, so dass die frühzeitige Detektion und Initiierung einer adäquaten Therapie einen hohen Stellenwert in der aktuellen kardiovaskulären Forschung einnehmen.[104,105] Das zeitnahe Erkennen des Fontan-Versagens stellt aufgrund der uneinheitlichen Definition, der hohen phänotypischen Variabilität sowie des schleichenden Krankheitsprozesses eine große Herausforderung in der Betreuung von Fontan-

Patientinnen und -Patienten dar. Im Rahmen dieser Arbeit konnte nachgewiesen werden, dass eine kompromittierte Fontan-Hämodynamik mit der morphologischen und funktionellen Ausprägung der FALD korreliert. Weiterhin wurde erstmalig ein Scoring-System zur systematischen Graduierung und Schweregradeinteilung der FALD eingeführt, welches effizient zwischen Personen mit und ohne Vorliegen eines Fontan-Versagens differenzieren kann. Der eingeführte FALD-Score ist durch eine simplifizierte Handhabung charakterisiert und kann somit leicht in die klinische Routine intergiert werden. Da *Cut-off* Werte ≥ 6 Punkte eine hohe Sensitivität und Spezifität für das Vorliegen eines Fontan-Versagens aufweisen, sollte bei Betroffenen eine detaillierte weiterführende Diagnostik zur Risikostratifizierung durchgeführt werden. Der nachgewiesene Zusammenhang zwischen einer kompromittieren Fontan-Hämodynamik und dem Auftreten und der Ausprägung von FALD akzentuiert die Notwendigkeit eines frühzeitigen und regelmäßigen Monitorings von Sekundärorganerkrankungen sowie eine Integration dieser in die Definition des Fontan-Versagens. Zusätzlich sollte diese Assoziation zur rechtzeitigen Initiierung einer adäquaten medikamentösen, interventionellen oder chirurgischen Therapie genutzt werden, da eine Optimierung der Fontan-Hämodynamik einigen Fallberichten zufolge in einer Regression von FALD-spezifischen Veränderungen resultierte.[106,107]

5.2.4. Bedeutung der FALD für die Evaluation für eine Herz- und Herzlebertransplantation

Die therapeutischen Optionen eines Fontan-Versagens sind weiterhin limitiert. Eine leitliniengerechte medikamentöse antikongestive Therapie kann die klinischen Symptome eines progredienten Fontan-Versagens reduzieren, trägt jedoch zu keinem nachweisbaren Überlebensvorteil, wie bei Personen mit einer biventrikulären

Anatomie, bei.[32,108] Eine mechanische Kreislaufunterstützung stellt bei Patientinnen und Patienten mit einer Fontan-Zirkulation aufgrund der limitierten Möglichkeiten eines adäquaten Ersatzes des fehlenden subpulmonalen Ventrikels bisher keine etablierte Therapieoption dar.[37,109] Eine Herztransplantation verbleibt somit die *ultima ratio*, ist jedoch insbesondere bei erwachsenen Fontan-Patientinnen und –Patienten mit einer erhöhten Mortalität und Morbidität assoziiert.[38,39] Das Vorliegen von hepatischen oder renalen Sekundärorganerkrankungen trägt in dieser Kohorte zu einer deutlich verschlechterten Überlebensprognose nach einer Herztransplantation bei.[110,111] Insbesondere der MELD-IX Score hat sich in mehreren Studien als ein valider Prädiktor für die Früh- und Spätmortalität nach einer Herztransplantation bei adulten Fontan-Patientinnen und -Patienten erwiesen.[111,112] Eine fortgeschrittene FALD sollte *per se* keine Transplantationsindikation darstellen, jedoch kann ihr Progress auf eine Verschlechterung der Fontan-Hämodynamik und ein beginnendes Fontan-Versagen hinweisen und sollte weiterführende diagnostische Maßnahmen initiieren. Eine einheitliche und Konsensus-orientierte Definition von Listungskriterien für eine Herztransplantation ist für Fontan-Patientinnen und –Patienten bisher nicht etabliert. Die Anwendung des FALD-Scores zur Einschätzung des FALD Schweregrades sowie des LiMAx-Testes zur Quantifizierung der enzymatischen Leberfunktion könnten hierfür eine Grundlage darstellen, um die mit einem Fontan-Versagen einhergehenden Sekundärorgandysfunktionen frühzeitig zu erkennen und den Transplantationserfolg zu optimieren.

Die Indikationsstellung für eine kombinierte Herzlebertransplantation stellt ebenfalls eine große Herausforderung bei dieser Kohorte dar. Die Datenlage zur Indikation einer kombinierten Herzlebertransplantation bei Patientinnen und Patienten mit schwerer Leberfibrose oder -zirrhose ist zurzeit kontrovers. Während einige Zentren über zufriedenstellende Ergebnisse nach Durchführung des Zweihöhleneingriffs berichten[113,114], konnte ein Überlebensnachteil nach singulärer Herztransplantation bei an einer Leberzirrhose erkrankten Personen nicht nachgewiesen werden.[115,116] Insbesondere das hohe Regenerationspotential der Leber mit der Möglichkeit einer Regression von FALD-spezifischen Veränderungen nach einer durchgeführten Herztransplantation sollte in den Indikationskriterien für eine kombinierte Herzlebertransplantation berücksichtigt werden.[106,107] Neben einer Leberbiopsie zur Verifizierung einer manifesten Leberzirrhose könnte die Erfassung der enzymatischen Leberfunktion zur Indikationsstellung für die Notwendigkeit einer zusätzlichen Lebertransplantation hilfreich sein.

5.3 Einfluss eines individualisierten heim-basierten Ausdauertrainings auf die kardiopulmonale Belastbarkeit und Lebensqualität von Fontan-Patientinnen und -Patienten

Durch den medizinischen Fortschritt der letzten Jahrzehnte hat sich die Überlebensprognose von Fontan-Patientinnen und -Patienten deutlich verbessert, so dass der Fokus der medizinischen Therapie auf den Erhalt der Lebensqualität und somit auf die Verbesserung der kardiopulmonalen und respiratorischen Belastbarkeit gerückt ist. Die körperliche Leistungsfähigkeit ist bei Personen mit einer Fontan-Zirkulation reduziert und entspricht 50-60 % der alters- und geschlechtsspezifischen Normwerte.[61,117] Als Ursachen für diese Belastungsintoleranz werden das Fehlen eines subpulmonalen Ventrikels, eine chronotrope Inkompetenz, eine reduzierte Muskelmasse sowie eine restriktive Lungenfunktion beschrieben.[118] Da eine reduzierte kardiopulmonale Belastbarkeit mit negativen unerwünschten Ereignissen assoziiert ist,[66,119,120] wird die Durchführung eines regelmäßigen körperlichen und respiratorischen Ausdauertrainings allen Fontan-Patientinnen und –Patienten empfohlen.[31,121] Im Rahmen der vorliegenden Arbeit konnte nachgewiesen werden, dass die regelmäßige Durchführung eines individualisierten, heim-basierten körperlichen und respiratorischen Ausdauertrainings über einen Zeitraum von zehn Monaten die relative körperliche Leistung sowie die maximalen inspiratorischen und exspiratorischen Drücke der Studienteilnehmer:innen signifikant verbessert hat. Eine statistisch relevante Veränderung anderer Indikatorparameter der kardiopulmonalen Leistungsfähigkeit wie der Herzfrequenzreserve oder der VO_{2max} konnte während des Studienzeitraums nicht nachgewiesen werden. Während bei gesunden Individuen die VO_{2max} im jungen Erwachsenenalter ihr Maximum erreicht, wird bei gleichaltrigen Fontan-Patientinnen und -Patienten bereits eine stetige Abnahme dieser beobachtet.[122] Das Alter bei Beginn des Ausdauertrainings scheint ein ausschlaggebender Faktor für eine mögliche Verbesserung der kardiopulmonalen Indikatorparameter zu sein: Im Rahmen der durchgeführten Studie konnte eine signifikante Steigerung der kardiopulmonalen Belastbarkeit bei pädiatrischen Patientinnen und Patienten und jungen Adoleszenten, jedoch nicht auf die Gesamtkohorte bezogen, beobachtet werden. Das Fehlen einer Abnahme der Indikatorparameter der kardiopulmonalen Belastbarkeit über den Trainingszeitraum könnte bei adulten Fontan-Patientinnen und –Patienten aufgrund der kontinuierlichen Regression dieser mit zunehmendem Alter und Dauer der Fontan-Zirkulation bereits als Therapieerfolg gewertet werden. Zusätzlich wird die Sicherheit der Durchführung eines heim-basierten Ausdauertrainings bei Personen mit einer Fontan-Zirkulation in dieser Studie verdeutlicht, da während des gesamten Studienzeitraums keine unerwünschten Ereignisse aufgetreten sind.

Bei einem Drittel der Studienteilnehmer:innen lag eine restriktive Lungenfunktion vor, welche durch Komorbiditäten, wie eine einseitige Zwerchfellparese oder eine durch zahlreiche Voroperationen bedingte erhöhte Thoraxrigidität, verursacht wird. Ergebnisse von Studien, welche eine Verbesserung der Lungenfunktion bei Fontan-Patientinnen und –Patienten durch regelmäßiges respiratorisches Muskeltraining untersucht haben, sind widersprüchlich.[73,123,124] Ursachen für diese Diskrepanzen könnten unterschiedliche Studienprotokolle mit Abweichungen hinsichtlich der Art, Dauer und Intensität des respiratorischen Muskeltrainings darstellen. Eine weitere essentielle Voraussetzung für die Effektivität eines heim-basierten Trainings stellt die intrinsische Motivation der Studienteilnehmer:innen dar. Trainingsprogramme, welche von geschulten Instruktoren supervidiert werden, sind mit einer höheren Komplettierungsrate und einem besseren messbaren Trainingserfolg assoziiert.[125] Der direkte Vergleich der Ergebnisse eines heim-basierten und eines im Krankenhaus durchgeführten Trainingsprogramms konnte bei Patientinnen und Patienten mit einer Fontan-Zirkulation jedoch keine signifikanten Unterschiede hinsichtlich des Trainingseffektes feststellen.[126] Trotz kontroverser Studienergebnisse hinsichtlich Trainingseffektivität hat regelmäßiges respiratorisches Muskeltraining eine hohe Relevanz für die Fontan-Hämodynamik: Eine Erhöhung der inspiratorischen Muskelkraft führt konsekutiv zu einer Steigerung der pulmonalen Perfusion und damit der Vorlast und des Schlagvolumens des Systemventrikels, so dass sowohl das Herzzeitvolumen als auch die kardiopulmonale Belastbarkeit erhöht werden.[124]

Die durchgeführte Studie konnte eine signifikante Verbesserung einiger Indexparameter der kardiopulmonalen und respiratorischen Leistungsfähigkeit belegen, während die subjektive durch PedsQL^{TM} Fragebögen erfasste Lebensqualität nicht durch regelmäßiges körperliches Ausdauertraining gesteigert werden konnte. Die Datenlage zur Verbesserung der subjektiv empfundenen Lebensqualität durch regelmäßiges körperliches Training bei Fontan-Patientinnen und -Patienten ist diskrepant.[70,73] Ursachen für diese unterschiedlichen Studienergebnisse könnten multiple Störvariablen sein, welche bei selbst ausgefüllten Fragebögen gehäuft vorkommen. Den wichtigsten konfundierenden Faktor stellt die Antwortverzerrung durch den Einfluss von Eltern oder den Vergleich mit Peergruppen dar. Weiterhin beinhaltet der Fragebogen Module wie „Behandlungsangst“ und „Kognitive Probleme und Kommunikation“, welche nicht durch ein körperliches Ausdauertrainingsprogramm beeinflusst werden können.

Der wichtigste Aspekt für die fehlende Verbesserung der im Rahmen der durchgeführten Studie erfassten Lebensqualität ist die Koinzidenz mit der Coronavirus SARS-CoV-2-Pandemie, welche die Lebensqualität der Gesamtbevölkerung und insbesondere chronisch erkrankter Menschen durch soziale Isolation sowie finanzielle und gesundheitliche Ängste erheblich einschränkte.

6. Zusammenfassung und Ausblick

In der vorliegenden Arbeit wurden sechs Publikationen zu dem Thema Langzeitkomplikationen der univentrikulären Palliation mit dem Schwerpunkt der Fontan-assoziierten Lebererkrankung als häufigste Sekundärorganerkrankung vorgestellt. Die Arbeiten umfassten eine retrospektive Auswertung von präoperativen echokardiographischen Parametern von Patientinnen und Patienten mit einem AVSD zur dezidierten Therapieplanung und Indikationsstellung für eine univentrikuläre Palliation bei ventrikulärer Imbalance. Weiterhin wurden Querschnittstudien zur Erfassung der morphologischen und funktionellen Merkmale der FALD als häufigste Langzeitendorgankomplikation der Fontan-Zirkulation durchgeführt. Den Schwerpunkt der Studien stellten die Untersuchung der Einflussparameter auf die Entstehung und den Progress dieser Sekundärorganerkrankung dar. Zuletzt wurde eine prospektive Studie zur Untersuchung der positiven Effekte von kardiopulmonalem und respiratorischen Ausdauertraining auf die Fontan-Zirkulation vorgestellt.

Zusammenfassend konnte gezeigt werden, dass die Entstehung und Ausprägung der FALD mit der Dauer der Fontan-Zirkulation und der Fontan-Hämodynamik assoziiert ist. Anhand der morphologischen und laborchemischen FALD-spezifischen Veränderungen wurde ein FALD-Score entwickelt, welcher eine Schweregradklassifikation der Erkrankung sowie eine frühzeitige Detektion eines Versagens der Fontan-Zirkulation erlaubt. Zusätzlich konnte nachgewiesen werden, dass die laborchemischen und morphologischen FALD-Merkmale einer funktionellen hepatischen Beeinträchtigung vorangehen.

In weiterführenden Studien sollen die Effekte einer endovaskulären Therapie von Obstruktionen im Fontan-Kreislauf auf die Ausprägung der FALD untersucht werden. Weiterhin soll überprüft werden, ob die Durchführung eines heim-basierten körperlichen und respiratorischen Ausdauertrainings als nicht-pharmakologische Therapieoption das Auftreten eines Versagens der Fontan-Zirkulation und den Progress der FALD verzögern kann.

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9. Erklärung § 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

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