



Original Article

Abdominal Skeletal Muscle Index as a Potential Novel Biomarker in Adult Fontan Patients

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ABSTRACT

Background: Fontan palliation results in a chronic multisystem disorder with diminished exercise capacity and increased risk of muscle wasting. The aims of this study were to assess the feasibility of skeletal muscle mass measurements in Fontan patients undergoing magnetic resonance imaging liver surveillance to compare muscle mass with a historic control and to assess its correlation with cardiorespiratory fitness.

Methods: Skeletal muscle area (SMA) and skeletal muscle index (SMI) were measured at T12 and L3. A young, healthy historic cohort was used as a comparison group.

RÉSUMÉ

Contexte : L'intervention palliative de Fontan engendre une atteinte multiviscérale chronique, notamment une diminution de la capacité à l'effort et une hausse du risque d'atrophie musculaire. L'étude visait à évaluer la possibilité de mesurer la masse musculaire squelettique des patients ayant subi une intervention de Fontan et faisant l'objet d'une surveillance du foie par imagerie par résonance magnétique, afin de comparer les résultats à ceux d'une cohorte historique témoin et d'en évaluer la corrélation avec la capacité cardiorespiratoire.

Méthodologie : La surface musculaire squelettique (SMS) et l'indice musculaire squelettique (IMS) ont été mesurés en T12 et en L3. Une

Patients with a functionally univentricular heart have a poor survival outlook when left untreated. The Fontan operation,¹ which redirects all systemic venous return directly into the pulmonary arteries without ventricular power augmentation as the final step in the surgical palliation in most patients with single-ventricle physiology, has significantly improved survival with many patients surviving now into adulthood. However, the absence of a subpulmonary right ventricle creates a chronic state of heart failure with definable structural myocardial abnormalities, functional impairment, neurohormonal activation, and venous congestion.² The Fontan circulation unsurprisingly is associated with significant morbidity and premature mortality^{3,4} due to both cardiovascular

complications and extracardiac multiorgan system dysfunction. The average 40-year-old Fontan patient is expected to have the same life expectancy of a 75-year-old in the general population.⁵

Muscle wasting in the context of such chronic conditions has been described to be associated with adverse outcomes, including in the elderly⁶ and those with congestive heart failure,⁷⁻⁹ cancer,¹⁰ chronic obstructive pulmonary disease,¹¹ and chronic kidney disease.¹² Not surprisingly, a high prevalence of skeletal muscle wasting in the Fontan population, measured by dual x-ray absorptiometry, has been demonstrated.¹³ Measurement of abdominal skeletal muscle, most commonly obtained at the third lumbar vertebra (L3), is an alternative and widely described tool to define sarcopenia in non-Fontan populations.¹⁴⁻¹⁶ The recent recommendation for routine abdominal cross-sectional imaging for surveillance of potential liver disease¹⁷ makes secondary analysis of cross-sectional abdominal imaging an attractive and easily accessible tool to measure abdominal skeletal muscle mass in the Fontan population. The aims of the present study were to assess feasibility and reproducibility of determining

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Ethics Statement: The research reported has adhered to the relevant ethical guidelines.

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See page 60 for disclosure information.

Results: Forty patients with a Fontan circulation (mean age, 25.5 ± 7.9 years; 50% were men) were included. Measurements of SMA and SMI were feasible and highly reproducible. Mean SMA and SMI were significantly lower in women compared with men at both T12 (SMA: 25.1 ± 4.9 cm² vs 33.5 ± 8.4 cm², $P < 0.001$; SMI: 9.7 ± 2.1 cm²/m² vs 11.3 ± 2.7 cm²/m², $P = 0.045$) and L3 (SMA: 121 ± 12 cm² vs 162 ± 24 cm², $P < 0.001$; SMI: 46.9 ± 7.0 cm²/m² vs 54.5 ± 7.4 cm²/m², $P = 0.002$). Mean SMI at L3 was significantly lower in the male Fontan population compared with the healthy historic cohort (54.5 ± 7.4 cm²/m² vs 60.9 ± 7.8 cm²/m², $P < 0.001$), but was similar for women (46.9 ± 7.0 cm²/m² vs 47.5 ± 6.6 cm²/m², $P = 0.692$). SMI at L3, but not at T12, was positively correlated with peak oxygen consumption, oxygen pulse, and workload. Four patients (10%) met criteria for muscle wasting in the sarcopenic range based on L3 measurements.

Conclusions: Abdominal skeletal muscle mass can be reproducibly determined on surveillance liver magnetic resonance imaging scans. Muscle wasting appears to occur commonly in Fontan patients. Further research is needed to better define the value of SMI as a biomarker in the Fontan population.

skeletal abdominal muscle mass secondarily from routinely obtained liver surveillance magnetic resonance imaging (MRI) scans in an adult Fontan population and to assess its correlation with cardiopulmonary capacity. Additionally, we sought to assess whether muscle mass at the 12th thoracic vertebra (T12), which is readily accessible on cardiac MRI, correlates well with more standardized markers of sarcopenia at L3.

Materials and Methods

Study population

This was a retrospective study performed at Cincinnati Children's Hospital Medical Center. The study protocol was approved by the local institutional review board with a waiver of documentation of informed consent. All patients with a history of Fontan surgery who underwent liver or abdominal MRI between 2000 and 2018 were included. Liver MRI is performed as part of the institutional Fontan surveillance protocol at least every 3 years in all adult patients. Patients aged < 17 years and patients with MRI scans that did not include T12 and L3 or were of insufficient quality were excluded.

Data collection

Patient charts were screened, and baseline and demographic characteristics, imaging results, cardiopulmonary exercise test results, hemodynamic data assessed by cardiac catheterization, and laboratory and outcome data were

cohort historique de sujets jeunes et en santé a servi de groupe témoin.

Résultats : Quarante patients ayant subi une intervention de Fontan (âge moyen, $25,5 \pm 7,9$ ans; 50 % des sujets étaient de sexe masculin) ont été admis dans l'étude. Il a été possible d'obtenir des mesures de la SMS et de l'IMS hautement reproductibles. Les valeurs moyennes de la SMS et de l'IMS étaient significativement plus faibles chez les femmes que chez les hommes, tant en T12 (SMS : $25,1 \pm 4,9$ cm² vs $33,5 \pm 8,4$ cm², $p < 0,001$; IMS : $9,7 \pm 2,1$ cm²/m² vs $11,3 \pm 2,7$ cm²/m², $p = 0,045$) qu'en L3 (SMS : 121 ± 12 cm² vs 162 ± 24 cm², $p < 0,001$; IMS : $46,9 \pm 7,0$ cm²/m² vs $54,5 \pm 7,4$ cm²/m², $p = 0,002$). L'IMS moyen en L3 était significativement plus bas chez les hommes ayant subi une intervention de Fontan que chez ceux de la cohorte historique de témoins en santé ($54,5 \pm 7,4$ cm²/m² vs $60,9 \pm 7,8$ cm²/m², $p < 0,001$), mais comparable chez les femmes ($46,9 \pm 7,0$ cm²/m² vs $47,5 \pm 6,6$ cm²/m², $p = 0,692$). L'IMS mesuré en L3 était corrélé positivement avec la consommation maximale d'oxygène, le pouls d'oxygène et la charge d'effort, ce qui n'était pas le cas de l'IMS mesuré en T12. Selon les mesures effectuées en L3, quatre patients (10 %) répondaient aux critères d'atrophie musculaire de la sarcopénie.

Conclusions : La masse musculaire squelettique abdominale peut être déterminée de façon reproductible à partir des clichés d'imagerie par résonance magnétique obtenus aux fins de la surveillance du foie. Il semble que les patients ayant subi une intervention de Fontan présentent fréquemment une atrophie musculaire. Des recherches plus poussées s'imposent afin de mieux définir l'utilité de l'IMS comme biomarqueur au sein de la population des patients ayant subi une intervention de Fontan.

extracted. The date of the liver/abdominal MRI served as the predefined baseline time point, and all other data were obtained most closely to the MRI.

Muscle measurements

Muscle measurements were obtained from the most recent liver or abdominal MRI within the study inclusion period. Skeletal muscle area (SMA) was assessed on axial views at the levels of the 12th thoracic (T12) and third lumbar (L3) vertebral body. Muscle measurements were performed on T1 sequences or, if not available, on T2 or mDixon sequences. All included patients underwent muscle measurements at both T12 and L3. Abdominal muscle area at L3 is a frequently used and standardized marker to assess muscle mass.¹⁴⁻¹⁶ We also performed measurements at T12 because this vertebral level has a higher likelihood of being included on cardiac MRI scans in those patients for whom no abdominal MRI is available. Muscles included in the measurement at T12 included back muscles only (Fig. 1A). Total abdominal and back muscles were included at L3 (Fig. 1B). The muscles were traced as outlined in Figure 1A and B to calculate the muscle area. To avoid inclusion of extensive fat tissue in the muscle measurements, manual adjustments to the tracing have been performed. The SMA was reported in centimeters squared, and the skeletal muscle index (SMI) was calculated by indexing the SMA to the height in square meters (cm²/m²) as previously described.¹⁸ The rationale behind this adjustment is a strong correlation between absolute muscle mass and height.¹⁹ All measurements were generated using Vitrea Core software (Toshiba Medical Systems, Minnetonka, MN) and

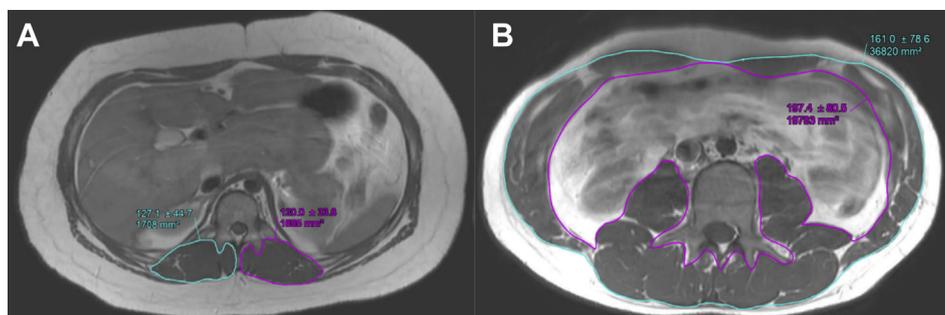


Figure 1. Back muscles at the level of the 12th thoracic vertebral body (A). Abdominal skeletal muscles at the level of the third lumbar vertebral body (B).

were performed by one reader (M.P.). One-quarter of the measurements at each vertebral level were repeated by the same reader and by a second reader (S.S.) at 2 different occasions with an interval of more than 30 days to assess intraobserver and interobserver variability. All images were blinded for this purpose.

Derstine et al.²⁰ defined normal values for abdominal SMA and SMI using axial computed tomography images based on a large, healthy US population. Cutoff values for the SMI to describe muscle wasting in the sarcopenic range were defined in that study as mean $- 2 \times$ standard deviation. These proposed SMI cutoff values at L3 were used in the present study to define muscle wasting in the sarcopenic range ($<45.4 \text{ cm}^2/\text{m}^2$ for men, $<34.4 \text{ cm}^2/\text{m}^2$ for women).

Cardiopulmonary exercise testing

All patients had undergone a standardized exercise test on a cycle ergometer or treadmill depending on patient and clinician preference. The cardiopulmonary exercise testing, which was performed most closely to the MRI, was used for study analyses. A ramp protocol was used for the cycle ergometer, and a modified Bruce protocol was used for the treadmill. The protocol allowed patients to reach exhaustion after approximately 10 minutes of exercise. Expired gases were measured continuously using breath-by-breath gas analysis. Simultaneous ECG monitoring, heart rate, and blood pressure measurements were performed throughout the test. Oxygen consumption (VO_2), carbon dioxide production, and ventilation were obtained. Cardiopulmonary exercise testing parameters were measured as previously described.²¹ Before the exercise test, all patients had undergone pulmonary function testing in which forced vital capacity and forced expiratory volume in 1 second were measured.

Statistical analyses

Continuous variables were expressed as mean \pm standard deviation. Categorical variables were reported as numbers and percentages. Comparisons between 2 groups were performed by unpaired *t* test for continuous variables and by chi-square test for categorical variables. Comparisons between multiple groups were performed by Kruskal–Wallis test. Correlation analyses were performed using the Pearson correlation test. Test–retest analyses were performed using the intraclass correlation coefficient (ICC) to determine intraobserver and interobserver variability in SMA measurements at T12 and L3. A *P* value < 0.05 was considered statistically significant.

All statistical analyses were performed using commercially available software packages (IBM SPSS Statistics, Version 22, Chicago, IL; and GraphPad Prism version 8.0, GraphPad Software, La Jolla, CA).

Results

A total of 40 patients were included. Their mean age was 25.5 ± 7.9 years, and 50% ($n=20$) were men. Seven patients (17.5%) had an atriopulmonary connection, 22 patients (55%) had a lateral tunnel, and 11 patients (27.5%) had an extracardiac conduit. Baseline characteristics are detailed in Table 1.

Intraobserver and interobserver reliability

There was excellent intraobserver reliability with an ICC for repeated measurements of SMA at T12 and L3 of 0.98 (95% CI, 0.93–0.99) and 0.98 (95% CI, 0.92–0.99), respectively, and good interobserver reliability with an ICC for SMA at T12 and L3 of 0.76 (95% CI, -0.80 –0.95) and 0.83 (95% CI, 0.20–0.96), respectively.

SMA and index at T12 and L3 in the Fontan population

Mean SMA at T12 and L3 was $29.3 \pm 8.0 \text{ cm}^2$ and $141 \pm 28 \text{ cm}^2$, and mean SMI was $10.5 \pm 2.5 \text{ cm}^2/\text{m}^2$ and $50.7 \pm 8.1 \text{ cm}^2/\text{m}^2$, respectively. Mean SMA and SMI were significantly lower in women compared with men at both T12 (SMA: $25.1 \pm 4.9 \text{ cm}^2$ vs $33.5 \pm 8.4 \text{ cm}^2$, $P < 0.001$; SMI: $9.7 \pm 2.1 \text{ cm}^2/\text{m}^2$ vs $11.3 \pm 2.7 \text{ cm}^2/\text{m}^2$, $P = 0.045$) and L3 (SMA: $121 \pm 12 \text{ cm}^2$ vs $162 \pm 24 \text{ cm}^2$, $P < 0.001$; SMI: $46.9 \pm 7.0 \text{ cm}^2/\text{m}^2$ vs $54.5 \pm 7.4 \text{ cm}^2/\text{m}^2$, $P = 0.002$). There was no difference in SMA at T12 ($P = 0.176$) and L3 ($P = 0.633$) when stratified according to different body mass index groups ($<20 \text{ kg}/\text{m}^2$, 20.1 – $25 \text{ kg}/\text{m}^2$, 25.1 – $30 \text{ kg}/\text{m}^2$, $>30 \text{ kg}/\text{m}^2$).

SMA index at L3 compared with a historic cohort

The mean age in the historic control population was somewhat higher compared with the Fontan population in the present study (men in that study: 30.9 ± 6.1 years vs 25.9 ± 5.9 years in the current study, $P < 0.001$, mean age for women in that study 31.2 ± 6.1 years vs 25.0 ± 9.6 years in the current study, $P < 0.001$). Despite the younger age of the population in the present study, the mean SMI at L3 was significantly lower in the male Fontan population compared with the healthy historic cohort ($54.5 \pm 7.4 \text{ cm}^2/\text{m}^2$ vs $60.9 \pm 7.8 \text{ cm}^2/\text{m}^2$,

Table 1. Patient characteristics

Variable	N	Value
Age (y), mean ± SD	40	25.5 ± 7.9
Male sex, n (%)	40	20 (50)
Weight (kg), mean ± SD	40	70.2 ± 12.7
Height (cm), mean ± SD	40	167.0 ± 9.5
BMI (kg/m ²), mean ± SD	40	25.2 ± 4.6
Oxygen saturation at rest (%), mean ± SD	39	92.6 ± 4.2
Age at Fontan operation (y), mean ± SD	39	4.4 ± 3.8
Protein losing enteropathy, n (%)	40	2 (5)
Fontan type	40	
Atriopulmonary, n (%)		7 (17.5)
Lateral tunnel, n (%)		22 (55.0)
Extracardiac conduit, n (%)		11 (27.5)
Ventricular morphology	40	
Left, n (%)		27 (67.5)
Right, n (%)		11 (27.5)
Biventricular/indeterminate		2 (5)
Cardiac MRI findings		
Ejection fraction (%), mean ± SD	28	50.6 ± 7.2
EDVi* (mL/m ²), mean ± SD	27	97.6 ± 28.4
Moderate or more AV regurgitation, n (%)	31	2 (5)
Haemodynamics (cardiac catheterization)		
EDP (mm Hg), mean ± SD	26	10.6 ± 4.5
Fontan pressure (mm Hg), mean ± SD	25	13.0 ± 3.5
Exercise parameters		
Peak VO ₂ (mL/kg/min), mean ± SD	38	23.3 ± 6.8
VO ₂ at AT (mL/kg/min), mean ± SD	34	17.1 ± 5.1
Peak O ₂ pulse (mL/beat), mean ± SD	35	11.0 ± 3.4
VE/VCO ₂ slope, mean ± SD	36	37.9 ± 7.2
Peak VE (L/min)	35	71.8 ± 25.8
MVV (L/min)	31	121 ± 34
Workload (watts), mean ± SD	36	135 ± 42
FEV1 (L), mean ± SD	32	3.2 ± 0.9
FVC (L), mean ± SD	32	3.8 ± 1.0
FEV1/FVC, mean ± SD	32	83.3 ± 7.8
Outcomes		
Death, n (%)	40	1 (2.5)
Heart transplantation, n (%)	40	0
Ventricular assist device, n (%)	40	0
Heart transplantation evaluation, n (%)	40	3 (7.5)
Unscheduled hospitalization, n (%)	40	21 (52.5)

AT, anaerobic threshold; AV, aortic valve; BMI, body mass index; EDP, end-diastolic pressure; EDVi, end-diastolic volume indexed; FEV1/FVC, forced expiratory volume at 1 second/forced vital capacity; MRI, magnetic resonance imaging; MVV, maximum voluntary ventilation; SD, standard deviation; VE, minute ventilation; VO₂, oxygen consumption.

*When 2 ventricles contributed to the systemic circulation, both volumes were included.

$P < 0.001$, Fig. 2A). However, for women, the SMI at L3 was similar to the historic control ($46.9 \pm 7.0 \text{ cm}^2/\text{m}^2$ vs $47.5 \pm 6.6 \text{ cm}^2/\text{m}^2$, $P = 0.692$, Fig. 2B). On the basis of values from the healthy historic control group, 3 (15%) male and 1 (5%) female Fontan patients had an SMI in the sarcopenic range. Patients with an SMI in the sarcopenic range were older, and there was a trend toward lower peak workload when compared with Fontan patients with an SMI in the normal range. However, these differences were not statistically significant (Table 2).

Skeletal muscle index, exercise capacity, and other clinical parameters

Patients with a higher SMI at L3 achieved a higher peak VO₂ ($r = 0.323$, $P = 0.048$, Fig. 3A), a higher peak O₂ pulse ($r = 0.363$, $P = 0.032$, Fig. 3B), and a higher workload

($r = 0.355$, $P = 0.034$). Peak minute ventilation was significantly higher in patients with higher SMI at L3 ($r = 0.375$, $P = 0.026$) (Table 3). SMI at T12 was not correlated with VO₂ ($r = -0.115$, $P = 0.492$), O₂ pulse ($r = 0.224$, $P = 0.195$), workload, or minute ventilation ($r = -0.037$, $P = 0.833$) (Table 3). Mean time interval between MRI and cardiopulmonary exercise test was 1.9 ± 3.0 years. There was no correlation between SMI at T12 and L3 with laboratory data (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, creatinine, serum albumin), hemodynamic data (end-diastolic pressure, Fontan pressure), ejection fraction, age, age at Fontan surgery, and type of Fontan. Results were unchanged after performing correlation analyses with SMA, SMA indexed to height, and SMA indexed to body surface area instead of SMI.

Comparison of skeletal muscle at L3 and T12

Comparison of skeletal muscle at L3 and T12 was performed to assess the validity of using T12 as a potential surrogate in Fontan patients when L3 measurements were not available. There was a moderate correlation of SMA and SMI at level L3 and T12 (SMA: $r = 0.648$, $P < 0.001$; SMI: $r = 0.553$, $P < 0.001$).

Discussion

In this study, we took advantage of MRI-based cross-sectional imaging performed for routine liver surveillance in patients after the Fontan procedure and quantified abdominal skeletal muscle mass secondarily to the primary indication, which was to assess radiologic features of Fontan-associated liver disease. We confirmed that it is possible to obtain previously standardized and reproducible assessment of abdominal skeletal muscle mass. These standardized assessments have been shown to correlate well with outcomes in chronic disorders, including heart failure.

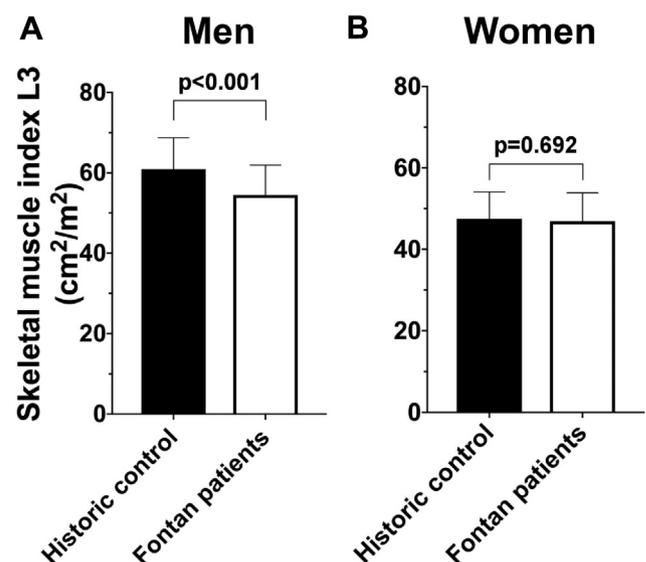


Figure 2. Skeletal muscle index (SMI) at L3 in male (A) and female (B) Fontan patients compared with a historic cohort of healthy young adults.

Table 2. Comparison of Fontan patients with and without muscle wasting in the sarcopenic range based on muscle measurements at L3

Variable	No sarcopenia	N	Sarcopenia	N	P value
Age (y), mean ± SD	24.9 ± 7.9	36	30.9 ± 5.9	4	0.150
Age at Fontan operation (y), mean ± SD	4.3 ± 3.8	35	5.3 ± 3.5	4	0.602
Saturation (%), mean ± SD	92.4 ± 4.3	35	94.3 ± 2.9	4	0.419
Fontan type		36		4	0.446
Atriopulmonary, n (%)	7 (19.4)		0		
Lateral tunnel, n (%)	20 (55.6)		2 (50)		
Extracardiac conduit, n (%)	9 (25)		2 (50)		
Peak VO ₂ (mL/kg/min), mean ± SD	23.5 ± 7.0	34	21.7 ± 5.1	4	0.620
Peak O ₂ pulse (mL/beat), mean ± SD	10.9 ± 3.3	31	11.7 ± 5.0	4	0.685
Workload (watts), mean ± SD	138 ± 42	32	109 ± 33	4	0.195

Sarcopenic range is defined as an SMI at L3 of < 45.4 cm²/m² for men and < 34.4 cm²/m² for women based on Derstine et al.²⁰
SD, standard deviation; VO₂, oxygen consumption.

Although women in our Fontan population had a lower SMI compared with men, consistent with a healthy historic cohort,²⁰ they did not have significantly different SMI from healthy controls. The reason why SMI at L3 was lower in the male Fontan cohort, but not in the female Fontan cohort, when compared with a healthy historic cohort is not entirely clear. Different metabolic parameters, different Fontan disease stages, different levels of exercise in the daily life, or the comparison with a historic cohort might play a role.

Additionally, we have shown that abdominal SMI is significantly correlated with cardiorespiratory fitness in this population. Specifically, SMI at L3 was positively correlated with peak VO₂, oxygen pulse, and workload. Further, we have shown that compared with reference values from the literature,²⁰ SMI was significantly lower in our male Fontan population and 1 in 10 Fontan patients met criteria for muscle wasting in the sarcopenic range.

The present study demonstrates a readily accessible way to measure abdominal skeletal muscle and muscle wasting derived from MRI scans in Fontan patients and shows that in an unselected population, deficiencies in skeletal muscle are apparent. As such, abdominal SMI measured at L3 on routine abdominal MRI in Fontan patients may represent a biomarker of physiologic capacity.

Frailty and muscle wasting in the Fontan population

Despite the enormous success of Fontan palliation in patients born with a functionally univentricular heart, the Fontan circulation predisposes to late cardiovascular and extra-cardiovascular organ complications with an associated incremental burden of hospital admission and mortality. The

Fontan circulatory state is recognized as a heart failure syndrome with neurohormonal activation,²² liver disease,²³ lymphatic dysfunction,²⁴ and kidney disease.²⁵

Frailty is a common syndrome in patients with chronic heart failure and is associated with an increased risk of death and hospitalization.^{10,26-28} The complex and multifactorial nature of frailty hinders a uniform definition.²⁹⁻³¹ However, common features of frailty include a state of vulnerability and limited physical performance. Sarcopenia, defined as a loss of muscle mass and muscle strength,³² is an important component of the frailty syndrome. Muscle wasting is frequently present in patients with chronic heart failure¹⁰ and itself is associated with increased morbidity and mortality.³³ In our cohort of unselected Fontan patients, who had an abdominal MRI as part of our routine surveillance protocol, we found 1 in 10 Fontan patients to have muscle mass reduced to the sarcopenic range.

Appendicular and leg lean mass measured by total body dual x-ray absorptiometry have been shown to be reduced in Fontan patients.^{13,34} Data in a small cohort of 16 Fontan patients showed a high prevalence of arm and leg muscle wasting, with one-quarter having muscle wasting in the sarcopenic range.¹³ Reduced skeletal mass was associated with impaired exercise capacity and was positively correlated with peak VO₂^{13,34} and oxygen pulse.¹³ Abdominal skeletal muscle is an alternative, frequently used, and well-described biomarker to characterize muscle wasting in different disease entities.¹⁴⁻¹⁶ The advantage of abdominal skeletal muscle mass assessment is that these muscle groups are included in routine surveillance imaging of the liver, and thus additional dedicated imaging is not required. To the best of our knowledge,

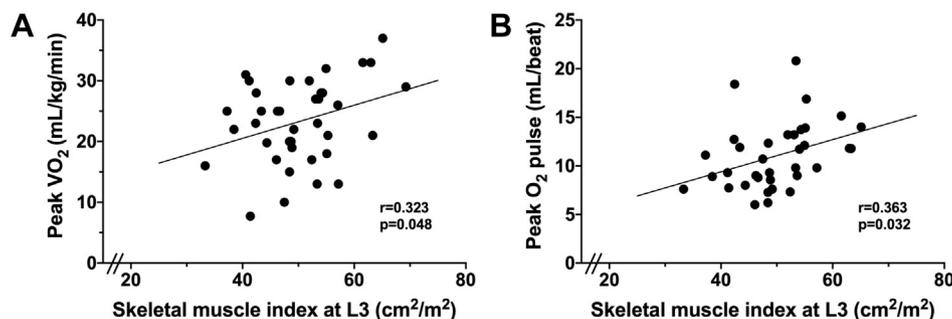


Figure 3. SMI at L3 is weakly but positively correlated to peak oxygen consumption (VO₂) (A) and peak O₂ pulse (B).

Table 3. Correlation between SMI and exercise parameters

Variable	N	L3 (cm ² /m ²)		T12 (cm ² /m ²)	
		Pearson correlation, r	P value	Pearson correlation, r	P value
Peak VO ₂ (mL/kg/min)	38	0.323	0.048	-0.115	0.492
VO ₂ at AT (mL/kg/min)	40	0.236	0.179	-0.142	0.422
Peak O ₂ pulse (mL/beat)	35	0.363	0.032	0.224	0.195
VE/VCO ₂ slope	36	-0.187	0.276	-0.118	0.494
Workload (watts)	36	0.355	0.034	0.045	0.795
Peak VE (L/min)	35	0.375	0.026	-0.037	0.833
MVV (L/min)	31	0.261	0.155	0.057	0.762

AT, anaerobic threshold; MVV, maximum voluntary ventilation; SMI, skeletal muscle area; VCO₂, carbon dioxide production; VE, minute ventilation; VO₂, oxygen consumption.

a correlation between abdominal skeletal muscle and exercise capacity in the Fontan population has not yet been demonstrated, and the present study is the first to introduce this concept to the Fontan population. We were able to confirm the prior observations by Cordina et al.¹³ and Avitabile et al.,³⁴ who looked at the association between peripheral skeletal muscle and function, and in this study we could derive similar results based on abdominal SMI at level L3, but not T12.

L3 is an accepted level for abdominal skeletal muscle mass assessment.¹⁴⁻¹⁶ In this study, we also explored muscle mass assessment at T12 because this level is likely to be included in the imaged field of view for cardiac MRI and thus might represent an additional level readily available for assessment of skeletal muscle mass. Unfortunately, in our study, skeletal muscle assessments at T12 were not predictive of function. However, because of the positive correlation between SMI at levels L3 and T12, it is possible that in a larger sample SMI at T12 might also correlate with cardiopulmonary exercise parameters. On the other hand, the inclusion of the psoas muscle group at L3 might represent the peripheral muscle bulk more accurately and thus might explain its better correlation with physical capacity.

This proof-of-concept study was meant to introduce the practical potential of abdominal SMI as an accessible biomarker in the Fontan population, which can easily be obtained from abdominal MRI scans without adding additional diagnostic costs and risks. A larger cohort with matched control groups should be used to better define the phenotype of Fontan patients with muscle wasting and to better describe the use of SMI as a biomarker and its correlation with outcome in the Fontan population.

Limitations

Several limitations have to be acknowledged. Because of the low sample size, we were not able to perform outcome analyses, which should be addressed in future research to better define the clinical significance of SMI as a potential outcome predictor in Fontan patients. The relatively long interval between MRI and exercise testing somewhat limits the power of correlation between the 2, especially in older patients in whom the functional capacity might change in a shorter period of time. The use of historic data as a comparison cohort might introduce a systematic error given the different methods of measuring SMI (computed tomography in the historic control vs MRI in the present cohort). A selection bias might have been introduced by excluding patients with non-MRI-conditional cardiovascular

implantable electronic devices and patients with insufficient MRI data. Our institutional policy is to perform a liver MRI in all patients, even in those with less severe Fontan-associated liver disease, and thus selection bias toward patients with advanced liver disease should be low. In addition, clinical data on routine physical activity of the included study population are lacking, which is an important factor in the interpretation of the results of muscle wasting and physical capacity. It is possible that the level of physical activity contributes to the different results in male and female Fontan patients when compared with the historic control group. The results of our study should be confirmed in comparison with an age-, sex-, and body mass index-matched control group, including the assessment of regular exercise.

Conclusions

The complex interplay among metabolic factors, cardiac function, and physical capacity in the Fontan population is reflected in the skeletal muscle. SMI can be easily obtained from abdominal cross-sectional imaging without additional risks and costs. A correlation with cardiorespiratory fitness makes abdominal SMI an interesting biomarker in the risk stratification of Fontan patients. We think that future research to better define its value as a biomarker in the growing adult Fontan population is important.

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Disclosures

The authors have no conflicts of interest to disclose.

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