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ORIGINAL ARTICLE

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A restrictive ventilatory pattern is common in patients with univentricular heart after Fontan palliation and associated with a reduced exercise capacity and quality of life

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Abstract

Aim: The Fontan circulation is highly dependent on ventilation, improving pulmonary blood flow and cardiac output. A reduced ventilatory function is reported in these patients. The extent of this impairment and its relation to exercise capacity and quality of life is unknown and objective of this study.

Methods: This multicenter retrospective/cross-sectional study included 232 patients (140 females, age 25.6 ± 10.8 years) after Fontan palliation (19.8% atrioventricular connection; 20.3% atriopulmonary connection; 59.9% total cavopulmonary connection). Resting spirometry, cardiopulmonary exercise tests, and quality-of-life assessment (SF-36 questionnaire) were performed between 2003 and 2015.

Results: Overall, mean forced expiratory volume in one second (FEV_1) was 74.7 ± 17.8%predicted (%pred). In 59.5% of the patients, FEV_1 was <80%pred., and all of these patients had FEV_1/forced vital capacity (FVC) > 80%, suggestive of a restrictive ventilatory pattern. Reduced FEV_1 was associated with a reduced peakVO_2 of 67.0 ± 17.6%pred. ($r = 0.43$, $P < .0001$), even if analyzed together with possible confounding factors (sex, BMI, age, years after palliation, number of interventions, scoliosis, diaphragmatic paralysis). Synergistically to exercise capacity, FEV_1 was associated to quality of life in terms of physical component summary ($r = 0.30$, $P = .002$), physical functioning ($r = 0.25$, $P = .008$), bodily pain ($r = 0.22$, $P = .02$), and general health ($r = 0.16$, $P = .024$). Lower FEV_1 was associated with diaphragmatic paralysis ($P = .001$), scoliosis ($P = .001$), higher number of interventions ($P = .002$), and lower BMI ($P = .01$). No correlation was found to ventricular morphology, type of surgeries, or other perioperative/long-term complications.

Conclusions: This study shows that the common restrictive ventilatory pattern in Fontan patients is associated with lower exercise capacity and quality of life. Risk factors are diaphragmatic paralysis, scoliosis, a high total number of interventions and low BMI.

KEYWORDS
CPET, Fontan, quality of life, spirometry, ventilatory function

1 | INTRODUCTION

The Fontan palliation for patients with single ventricle anatomies was developed in the 70s.[1] Different surgical variants have been proposed since its first introduction: atriopulmonary connection (APC), atrioventricular connection (AVC), and total cavopulmonary connection (TCPC). The introduction of appropriate surgical techniques[2] led to a significant improvement in the survival of these patients.[3] This approach is now performed in all functional univentricular hearts (UVH) unable to sustain the systemic and pulmonary circulation separately.[4] However, this palliation has intrinsic limitations[5] and the circumvention and management of long-term complications is still a major topic in the care of these patients.[6] As a result of a multifactorial process, Fontan patients often have a severe decline in the cardiorespiratory response to exercise.[7,8]

In UVH, the single ventricle is the systemic ventricle and the passive pulmonary blood flow[9] is substantially enhanced by the ventilatory movements and by the skeletal muscular pump of the veins.[10] Weakness in skeletal muscles is common in Fontan patients[11] and the presence of an impaired ventilation[12] with restrictive spirometry and reduced lung volumes was reported.[13] A reduced lung perfusion can lead to a reduced preload of the single ventricle.[14]

Nevertheless, the specific impact of the ventilatory function on the hemodynamic status and on the clinical outcomes of these patients has not been evaluated in detail yet.[15] Therefore, this analysis investigates the extent of ventilatory impairment in Fontan patients, its predictors in the clinical/surgical history and its consequences on the subsequent outcomes in terms of exercise capacity and quality of life (QoL).

2 | METHODS

This is a multicenter retrospective/cross-sectional study that involved the Department of Pediatric Cardiology and Congenital Heart Disease, *Deutsches Herzzentrum München*, Technical University of Munich and the Department of Women's and Children's Health, Pediatric Cardiology, University of Padua. Patients with UVH and Fontan circulation are followed on a lifelong basis in both institutions.

Inclusion criteria consisted of patients with a Fontan circulation of at least 7 years of age. Exclusion criteria involved patients with a chromosome abnormality, patients not able to perform a reliable exercise test, transplanted patients, pregnant patients, or deceased patients.

The medical history of the patients was analyzed to define cardiac anatomy and surgical history. The associated complications were classified as present or absent at latest follow-up. The presence of diaphragmatic paralysis, atrioventricular valve regurgitation (AVVR), scoliosis, plastic bronchitis (PB), protein loosing enteropathy (PLE), total number of interventions (defined as any procedure involving a sternotomy or thoracotomy), and arrhythmias (defined as need of a pacemaker implantation or cardiac ablation) were considered as complications. The NT-proBNP levels were measured in venous blood at steady state. As NT-proBNP was markedly skewed, a logarithmic transformation was performed.

Spirometry was repeated at least three times to ensure reproducibility.[16] The test session was considered finished when the difference between the two largest forced vital capacities (FVC) and forced expiratory volumes in one second (FEV_1) measurements was within 0.2 L. Spirometry values were normalized per age, sex, and height. Reference values were used from Morris[17] and for those younger than 21 years from Quanjer.[18] The presence of a highly probable restrictive ventilatory pattern was defined by FEV_1 < 80% of the predicted value, associated with a Tiffeneau-Pinelli index >80%. An obstructive pattern was defined by FEV_1 < 80% of the predicted value associated to a Tiffeneau-Pinelli index <80%.

To evaluate the health-related self-perceived quality-of-life of the study patients, the questionnaire 36-item short form (SF-36) was used in patients >14 years of age. This questionnaire has proven itself useful in various medical specialties without any bias for symptoms of a specific disease.[19] The SF-36 is a multidisciplinary instrument to evaluate QoL related to the health status, and focuses on eight categories with scores ranging from 0 (bad) to 100 (best) using subscales with 2-10 entries.[19] The patients had to complete it autonomously. Individual age- and sex-related reference values were drawn from Bullinger et al.[20]

Cardiopulmonary exercise test (CPET) was performed with a treadmill or a cycle ergometer with a ramp protocol. The tests were performed according to the guidelines of the American Heart Association.[21,22] In Munich, the exercise test featured a breath-by-breath gas exchange analysis (after 2010, with an Encore V_{max}29, CareFusion Corporation, San Diego, California; before 2010, V_{max}229, SensorMedics, Viasys Healthcare, Yorba Linda, California) with continuous ECG Monitoring. Pulse oximetry (SpO_2) (Nonin7750, Nonin Medical Inc., Plymouth, Minnesota) was performed with a forehead sensor. In Padua, the test featured a continuous ECG monitoring (Case8000, General Electrics, Waukesha, Wisconsin). Most of the patients completed a treadmill test (COSMOS model T170 DE-med), while patients who would benefit of a sitting position used a cycle ergometer (Excalibur Sport Lode, Groeningen, The Netherlands). The test had a breath-by-breath gas exchange analysis (Masterscreen CPX Jaeger, CareFusion, Hoechberg, GE). As resting values were considered mean values of the raw data for 3-minute sitting without cycling and peak values were mean values of the raw data during the 30-second time interval when peakVO_2 was measured. For patients younger than 18 years of age, reference values were calculated according to Cooper,[23] for those 25 years old and older according to Gläser[24] and for the patients between 18 and 25 years the values were extrapolated from pediatric equations. A coefficient of 0.9 was multiplied to the peakVO_2 values obtained at the treadmill. The breath reserve was calculated as $1 - VE_{max}/FEV_1/35$, the HRmax%predicted (%pred). as HR_{max}/(220-age) (IF age > 20), or HR_{max}/(200) (IF age < 20) and the maximal systolic blood pressure according to Heck.[25] The eligible patients underwent the tests in one of the two centers, in a time frame of six months without the intercurrence of significant events.

Statistical analysis was performed using SPSS 22.0.0 (SPSS Inc, IBM Company, Chicago, Illinois). The continuous variables are expressed as mean ± SD, categorical data as counts and percentages.

Deviation of the whole group from the reference values was tested in a one sample *t* test; groups' comparison was performed using two-sample *t* tests. Levene's test for equality of variance was used to analyze if the variability in the two groups was significantly different. The ordinal, nominal, and dichotomical variables were evaluated with contingency tables and compared with chi-square tests. The predictability of the continuous variables was evaluated by means of Pearson correlations and stepwise multiple regressions, with the criteria probability of F to enter $P < .05$, probability of F to be removed $P > .1$. Significance is defined by values of $P < .05$.

The study was conducted in accordance with the declaration of Helsinki (revision 2013) and all patients or guardians gave written informed consent for participation in the study. Local ethical committees in Munich and Padua approved the study.

3 | RESULTS

3.1 | Study subjects

In total, 232 patients (mean age 25.6 ± 19.8 years) 19.2 ± 7.93 years after Fontan operation were included in the analysis. Type of Fontan connection was APC in 20.3%, AVC in 19.8%, and TCPC in 59.9% (37.2% with an extracardiac conduit and 22.4% with an intraatrial tunnel). Baseline characteristics of all patients are summarized in Table 1.

3.2 | Spirometry

In 205 patients, a reliable resting spirometry test was performed (Table 2). FEV_1 was significantly reduced to 74.7 ± 17.8%pred compared with the predicted values ($P < .001$).[17,18] FVC was reduced to 71.1 ± 16.9%pred compared with the predicted values[17,18] ($P < .001$). One hundred twenty-two patients (59.5%) had an impaired ventilatory function with FEV_1 < 80%pred. All these 122 patients had a FEV_1/FVC ratio >80% and a FEV_1 < 80%pred associated with a FEV_1/FVC ratio <80% was not found.

3.3 | Exercise capacity

A total of 214 patients performed a reliable CPET test. Mean peakVO_2 was 25.7 ± 8.3 ml/kg/min (67.0 ± 17.6%pred.). In patients <20 years of age, peakVO_2 was 71.9 ± 16.5%pred. vs 64.1 ± 17.5%pred. in patients > 20 years of age ($P < .002$). SpO_2 showed an average decrease of 4% from baseline value during exercise testing. The complete results of CPET are summarized in Table 3.

3.4 | Quality of life

The SF-36 was completed by 133 patients older than 14 years of age. The results are expressed as %predicted (Table 4). The mean scores were significantly reduced in the categories of physical functioning ($P < .001$), physical role functioning ($P = .005$), general health ($P < .001$), vitality ($P = .02$), social role functioning ($P = .01$), emotional role functioning ($P = .001$), and health transition ($P = .02$), compared to the expected values.

TABLE 1 Baseline characteristics of the study population

Study population	232 (100)
Age (y)	25.6 ± 10.8
Male	92 (39.7)
Female	140 (60.3)
Follow-up (y)	19.2 ± 7.9
Weight (kg)	54.66 ± 19.16
Height (cm)	159 ± 16.6
BMI	20.76 ± 4.52
Ventricle anatomy	
LV	176 (75.9)
RV	49 (21.1)
LV/RV[a]	6 (2.6)
Unclear	1 (0.4)
Type of palliation	
AVC	46 (19.8)
APC	47 (20.3)
TCPC	139 (59.9)
Condition at follow-up	
Total number of interventions[b]	3.4 ± 1.4
NT-pro-BNP (ng/L)	352.05 ± 630.69
Long-term complications	
Diaphragmatic paralysis	14 (6.0)
PB	6 (2.6)
PLE	16 (6.9)
Scoliosis	15 (6.5)
AVVR	119 (51)
Arrhythmia[c]	61 (27)
Length of hospitalization	30.2 ± 23.2

Notes: Data presented as mean ± SD, categorial data as counts (n) and percentages (%).
Abbreviations: APC, atriopulmonary connection; AVC, atrioventricular connection; AVVR, atrioventricular valve regurgitation; cm, centimeter; kg, kilogram; LV, left ventricle; PB, plastic bronchitis; PLE, protein loosing enteropathy; RV, right ventricle; TCPC, total cavopulmonary connection; y, years.
[a]All hearts with two ventricles where a biventricular correction could not be performed.
[b]Defined as any procedure involving a sternotomy or thoracotomy.
[c]Defined as need of cardiac ablation or pacemaker.

3.5 | Analysis of the predictors of the ventilatory function

The independent predictors of FEV_1, defined with a multiple regression model (R^2adj. = 0.20), were: diaphragmatic paralysis ($P = .001$), scoliosis ($P = .001$), the total number of interventions ($P = .002$), and a lower BMI ($P = .01$). No correlation was found between ventilatory function at follow-up and type of UVH or of Fontan palliation, years

TABLE 2 Results of spirometry tests

Variables	205 (88)
FEV_1%pred.*	74.7 ± 17.8
FEV_1/FVC%pred.*	105.9 ± 9.3
FEV_1 > 80%pred.*	83 (40.5)
FEV_1 < 80%pred.*	122 (59.5)
FEV_1 < 80%pred.* and FEV_1/FVC%pred. > 80%*	122 (59.5)
FEV_1 < 80%pred.* and FEV_1/FVC%pred. > 80%*	0 (0)

Data presented as mean ± SD, categorial data as counts (n), and percentages (%).
Abbreviations: FEV_1, forced expiratory volume in one second; FVC = forced vital capacity; %pred.*, percentage of age- and sex-related values.

TABLE 3 Results of cardiopulmonary exercise tests

Variables	214 (92)
$PeakVO_2$ (ml/kg/min)	25.70 ± 8.31
$PeakVO_2$%pred.*	67.01 ± 17.63
HR (max)%pred.*	78.4 ± 13.0
SpO_2 (rest)	92.77 ± 5.18
SpO_2 (max)	88.51 ± 7.26
$PETCO_2$ (at)	32.72 ± 3.74
VE/VCO_2 (slope)	34.33 ± 7.08
VE (max)	55.91 ± 21.92
VT (peak)	1.34 ± 0.54
BR	28.4 ± 28.1
SBP (max)%pred.*	95.3 ± 15.2

Data presented as mean ± SD.
Abbreviations: BR, breathing reserve; HR, heart rate; $PeakVO_2$, peak oxygen uptake; $PETCO_2$, end-tidal CO_2; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation; VE, minute ventilation; VE/VCO_2, minute ventilation/carbon dioxide production; %pred.*, percentage of age- and sex-related values.

TABLE 4 Results of quality of life questionnaire SF-36

Variables	133 (57)	*P* value
Physical functioning %pred.*	85.56 ± 19.51	<.001
Physical role functioning %pred.*	91.71 ± 32.88	.005
Bodily pain %pred.*	97.70 ± 33.42	.49
General health %pred.*	84.91 ± 28.24	<.001
Vitality %pred.*	94.31 ± 26.91	.02
Social role functioning %pred.*	95.55 ± 21.13	.01
Emotional role functioning %pred.*	89.82 ± 34.43	.001
Mental health %pred.*	100.7 ± 23.64	.74
Health transition %pred.*	107.6 ± 36.72	.2

Data presented as mean (±SD).
Abbreviation: %pred. *, percentage of age- and sex-related values.

passed from the Fontan palliation, NT-pro-BNP, somatic features (sex, weight, age), and other perioperative/long-term complications (AVVR, PB, PLE, arrhythmias).

3.6 | Correlation with exercise capacity

A total of 196 patients performed a reliable spirometry and as well as a reliable CPET. Patients with a restrictive pattern of lung function in spirometry (FEV_1 <80% of the predicted value, associated with a Tiffeneau-Pinelli index >80%) had $peakVO_2$%pred. of 61.98 ± 15.71% vs 73.50 ± 17.60% of those with a preserved lung function ($P < .0001$). The correlation between FEV_1 and $peakVO_2$%pred was $r = 0.43$, $P < .0001$ (Figure 1). The details of the correlation between CPET results and FEV_1 %pred. are displayed in Table 5.

NT-pro-BNP, FEV_1%pred., and the time period since Fontan operation were found to be independent predictors of $peakVO_2$%pred ($P < .0001$). In the same multiple regression analysis (R^2adj. = 0.33), sex, age, and the predictors of ventilatory function itself (scoliosis, diaphragmatic paralysis, total number of interventions) were excluded as possible confounding factors.

3.7 | Correlation with quality of life

FEV_1%pred. was found to correlate with the scores (%pred.) of the SF-36 in the categories of physical component summary ($r = 0.30$, $P = .002$) (Figure 2), physical functioning ($r = 0.25$, $P = .008$), bodily pain ($r = 0.22$, $P = .02$), and general health ($r = 0.16$, $P = .01$) (Figure 3). Multiple regressions analysis showed, that these relations were independent from $peakVO_2$%pred. (physical component summary: R^2adj. = 0.12; physical functioning: R^2adj. = 0.13; bodily pain: R^2adj = 0.05; general health: R^2adj = 0.08).

4 | DISCUSSION

In this clinical multicenter study, we could demonstrate that there is a high prevalence of a restrictive ventilatory pattern in spirometry in patients with UVH and Fontan circulation. We found total number of interventions, long-term complications (scoliosis, diaphragmatic paralysis) and low BMI to be associated with this form of deterioration in ventilatory function, which directly and independently correlates with exercise capacity and several aspects of quality of life.

The heart and the lungs are intimately connected: first, due to their anatomical localization and, second, because of their functional interaction in several different ways. Not only in UVH but also in patients with congenital heart disease in general it is known, that an impaired ventilatory function is often present and that it is related to the complexity of the anatomical defect and surgical history.[26] In 2001, a first clinical study evaluated lung function data in Fontan patients.[27] FVC and FEV_1 were found to be impaired in 58% of patients, with a high prevalence of a restrictive lung function pattern. The central role of the lungs in UVH was also highlighted by Opotowsky et al,[12] who found a reduced FVC in 45.8% of these patients. Our analysis of the predictors of an impaired ventilatory function showed that it was independently and indirectly influenced by the presence of diaphragmatic paralysis and scoliosis, a higher number of surgical interventions, and reduced BMI.

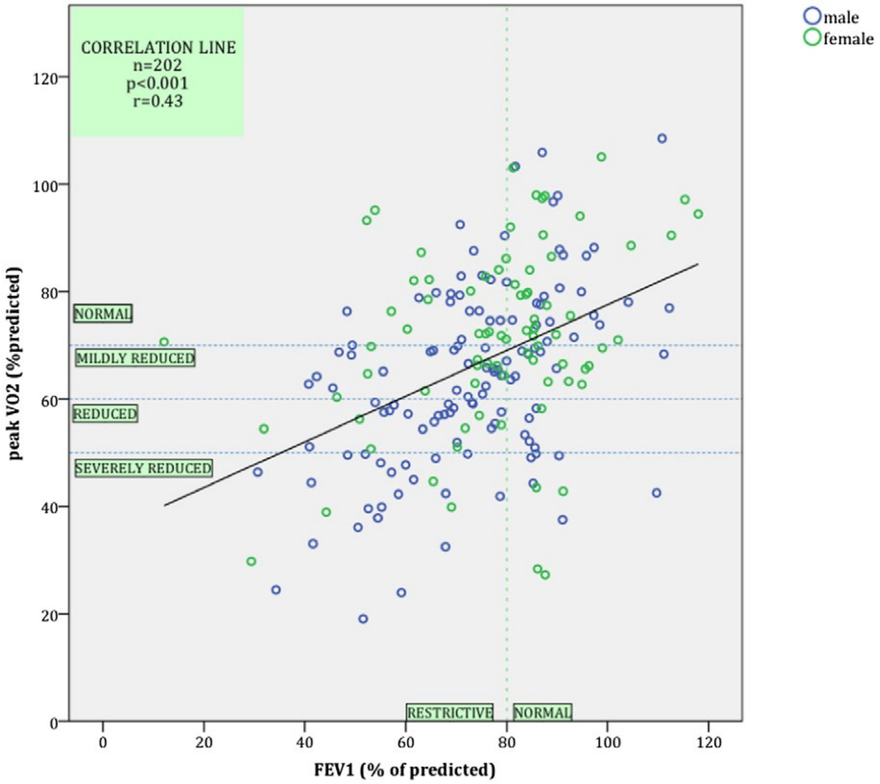

FIGURE 1 Linear and direct relationship between FEV_1 and $peakVO_2$ in patients after Fontan palliation (r = 0.43, P < .0001, n = 202)

TABLE 5 Correlation FEV_1 (%pred.*)/CPET

Variables	r	P value
$PeakVO_2$ (ml/kg/min)	0.23	.001
$PeakVO_2$ (%predicted)	0.43	<.0001
VE/VCO_2 (slope)	−0.22	.001
HR (max) (%pred.*)	0.28	<.0001
SpO_2 (max)	0.17	.02
RER (max)	0.42	<.0001
VE (max)	0.44	<.0001
VT (peak)	0.48	<.0001
Breath reserve	0.43	<.0001

Abbreviations: HR, heart rate; $PeakVO_2$, peak oxygen uptake; RER, respiratory exchange ratio; SpO_2, peripheral oxygen saturation; VE, minute ventilation; VE/VCO_2, minute ventilation/carbon dioxide production; VT, tidal volume; %pred.*, percentage of age- and sex-related values.

A diaphragmatic dysfunction reduces the ventilatory function of about 25%,[28] a deficit that, in otherwise healthy subjects, is compensated by the accessory muscles and stability of the thoracic cage. However, this mechanism is often impaired in Fontan patients, due to reduced muscle force and an unstable thoracic cage after multiple thoracotomies.[29] In addition, a high prevalence of scoliosis of about 9% was reported in these patients,[30] with an incidence of 6% in our patient group. It is postulated, that a reduced lung function in the setting of scoliosis refers to an abnormal development of the thorax including the respiratory muscles,[30] where the reduction in lung volumes correlates with the degree of the spinal curvature.[31] The correlation of an impaired ventilatory function to the number of interventions is in line, as it has to be assumed that every thoracotomy reduces the mobility of the thoracic cage by adding scar tissue,[13] leading to the necessity of an increased muscle force to achieve the maximal inspiration. This constitutes a relevant finding: due to the several steps of the Fontan pathway, patients are exposed to a high number of surgeries, influencing the stability of the thorax with the above-mentioned consequences on thorax shape and consecutive reduced ventilatory function parameters.

A preserved ventilatory function serves as main propulsive force for the pulmonary circulation in Fontan patients.[32] In fact, 63% of the systemic venous return occurs during inspiration, when the blood stream to the lung increases because of the negative intrathoracic pressure.[28] The key role of the inspiratory muscles was recently confirmed by Laohachai et al,[11] who explored the consequences of a 6-week inspiratory muscle training (IMT) in Fontan patients. Even after such a short training period, an improved ventilatory efficiency (defined as VE/VCO_2) and cardiac function could be described. Wu et al[13] obtained similar results in a small cohort of Fontan patients after a 12-week program of IMT, showing an improvement in $peakVO_2$ and ventilatory efficiency.

Not only the preserved "thoracic pump" plays a key role in maintaining an adequate systemic venous return in Fontan circulation.[13] In fact, the deteriorated skeletal muscles force of cachectic patients reduces the impact of the peripheric muscles, the "muscle pump,"

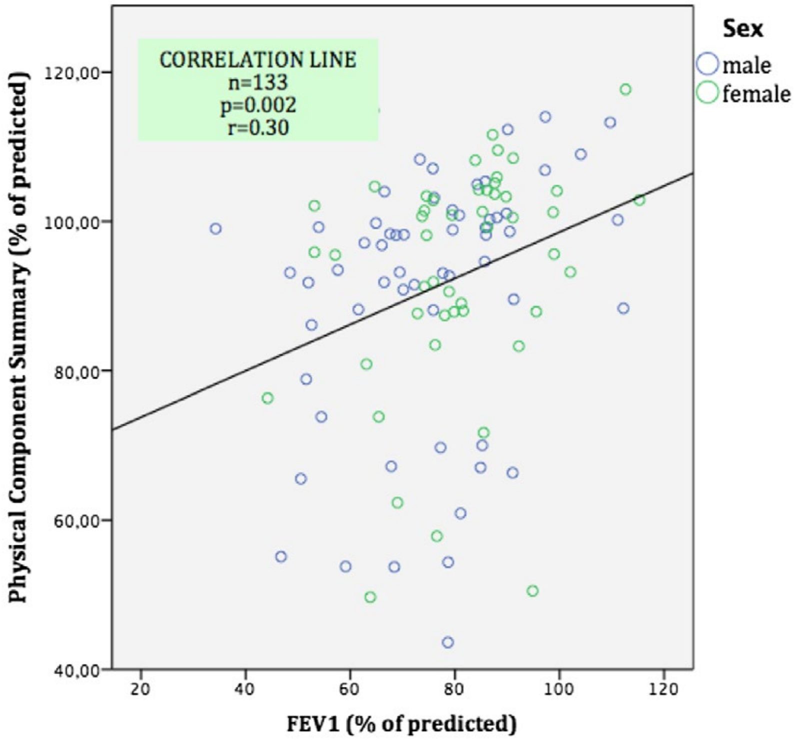

FIGURE 2 Linear and direct relationship between FEV_1 and physical component summary (%predicted) in patients after Fontan palliation (r = 0.30, P = .002, n = 133)

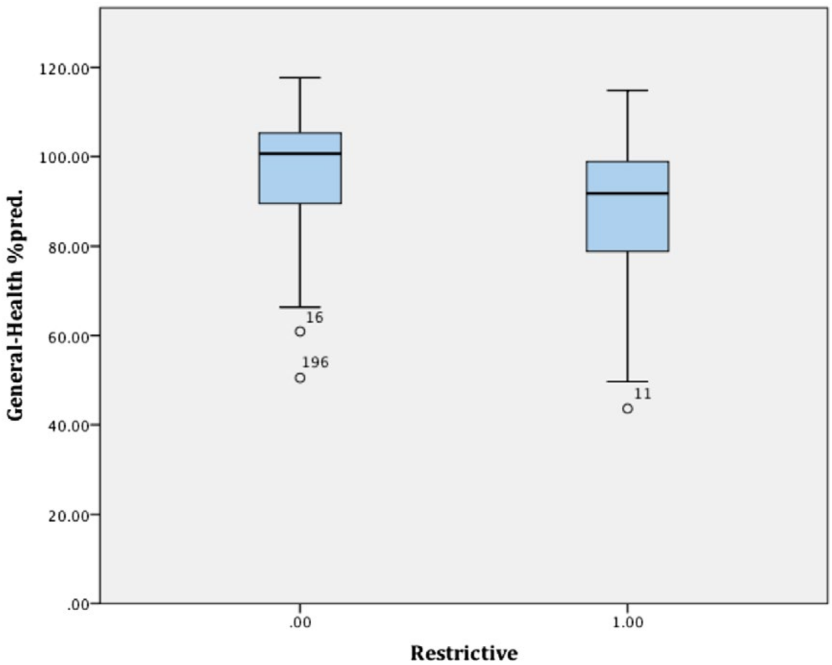

FIGURE 3 Box plot showing the difference of the mean values of general health (%predicted) in relation to the presence of restrictive pattern (P = .03)

to the venous blood return.[33] In accordance to our finding, Cordina et al confirmed a negative impact of a reduced BMI on ventilatory function.[34]

However, all the described predictors of FEV_1 together accounted only for 22% of FEV_1's variation. In fact, the prevalence of abnormal ventilatory function is much higher than that of diaphragmatic paralysis, scoliosis, or low BMI. This suggests that other, and more generally applicable factors, which were not considered in our analysis, exist additionally. A pathological development of the lung tissue was appointed as probable reason.[35] In fact, lung function tests[32] showed that the lungs of patients with UVH in Fontan circulation are relatively small. Development of the lungs starts in the last trimester of pregnancy and 95% of the alveolar surface is formed after birth: physical activity, somatic growth, and pulmonary blood supply strongly influence lung growth and development.[15] Unfortunately, Fontan patients experience all the conditions that could deteriorate alveolar growth, such as long and multiple hospitalizations, iatrogenic damage to the pulmonary vascular system during interventions and impaired somatic development due to malnutrition and restriction to exercise. According to these assumptions, a relationship between the fetal-infant environment and the lung function in adult life has been suggested.[36]

Lungs reduced in size also have a diminished vascular bed,[32] an anatomical condition that can enhance the presence of an impaired exercise capacity. The circulation of a Fontan patient deals with a "paradox,"[37] where a high-pressure systemic venous system is associated to a reduced venous pressure in the pulmonary circulation. Moreover, the flow in the pulmonary vessels cannot be adequately increased during exercise because of the lack of a subpulmonary ventricle. In fact, in a biventricular circulation, even though the apices of the lungs are less perfused than the basis, the pressure of the pulmonary circulation rises during exercise and the blood flow in the superior pulmonary lobes is augmented in order to decrease the respiratory mismatch and increase the cardiac output. Therefore, it could be speculated, that a vascular bed reduced in size that can only partially be increased during maximal exercise, leads to both an augmentation in death space ventilation and to an inappropriate augmentation of the cardiac stroke volume. This dysfunction causes, as ripple effect, a diminished exercise capacity. Our cohort of Fontan patients shows an imparted ventilatory efficiency, meaning a high VE/VCO_2 slope, and an inappropriate augmentation of the preload of the single ventricle was demonstrated in literature.[6] Moreover, VE/VCO_2 slope is positively influenced by an increase in FEV_1, leading to the assumption that a better ventilatory function improves the ventilation/perfusion ratio. This was confirmed by the positive correlation between FEV_1 and SpO_2. Going along with our thesis, the maximal hearth rate achieved during the CPET was positively influenced by a preserved ventilatory function. In fact, regarding the limitation to exercise, our analysis showed that the patients with an inadequate ventilatory function were restricted on the cardiac level, rarely having a decreased breathing reserve. Therefore, we can conclude that a decreased FEV_1 relevantly exacerbates cardiac limitation to exercise.

We found, that the ventilatory function acts as an independent and direct predictor of exercise capacity, while NT-pro-BNP and the years passed from Fontan palliation show an inverse correlation with peakVO_2%pred. It is a very important and innovative result, which emphasizes the independent role of the lungs in a Fontan circulation. Aging enhances the decline of peakVO_2, a concept already evident in literature.[38] Moreover, an increase in NT-pro-BNP could be representative of AVVR or myocardial failure, which obviously impair the cardiac performance. A direct relationship between FEV_1 and NT-pro-BNP was not found in our analysis.

As survival improved due to modification of surgical techniques as well as to improved surveillance and catheter interventional techniques in the last decades, QoL of Fontan patients becomes more important in follow-up.[39] We could show that most of the patients enjoy an acceptable QoL, while the presence of a normal ventilatory function is associated with higher scores in many categories of SF-36. In fact, any physical limitation could invalidate both physical and psychological aspects.[40] In our study population, the mean score of every category of the SF-36 showed no relevant difference in comparison to the expected scores of a healthy comparison group. As explanation to such high scores, it has been suggested that the patients cope with their pathology and express their feelings more realistic than their peers, a fact that is already known from childhood oncology patients.[41,42] The presence of a normal psychosocial status was a common finding in our population, as already found in other similar patients cohorts.[43] With the ventilatory function we could describe an independent and relevant predictor of QoL in Fontan patients. Interestingly, a preserved lung function affects not only the plain physical sphere of the perceived QoL, but also the general perception of the health status. Therefore, it can be speculated, that a specific intervention aimed to enhance the ventilatory function, such as IMT, can lead to an add-on effect on many levels, improving not only mere physical aspects (such as exercise capacity), but also the general attitude toward life, as seen in other studies.[44]

4.1 | Study limitations

In this study, no body plethysmography was available, and the restrictive ventilatory pattern could only be deduced from the spirometry results. Regarding the predictors of a restrictive lung disease, early development factors could not be analyzed. The long-term complications and comorbidities were only evaluated as present or not present. Smoking behavior, pharmacological therapy, and parameters of ultrasound other than AVVR were not examined. Moreover, for every patient only punctual data were available and therefore no evolution of ventilatory function over time was possible.

4.2 | Conclusion

Fontan patients have a high prevalence of a restrictive ventilatory function and a reduced FEV_1 correlates directly with exercise capacity and QoL. Even if the presence of a ventilatory restriction currently does not suggest any specific treatment, the measurement of abnormal spirometry variables may be used for a better risk stratification in Fontan patients. Furthermore, is fundamental to prevent the risk factors of an impaired ventilatory function and, if they are already present, treat them promptly. Some pilot studies proposed IMT as specific treatment with encouraging results. However, the efficacy of similar interventions should be tested prospectively with larger patients' cohorts.

CONFLICT OF INTEREST

All authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Alessia Callegari: Design of the study, Data collection/analysis, drafting/approval of article.

Rhoia Neidenbach: Data collection, Critical revision/approval of article.
Ornella Milanesi: Design of the study, Critical revision/approval of article.
Biagio Castaldi: Data collection/analysis, Critical revision/approval of article.
Martin Christmann: Interpretation of data, Critical revision/approval of article.
Masamichi Ono: Data collection, Critical revision/approval of article.
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