Cardiology in the Young

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Abnormalities in pulmonary function and volumes in patients with CHD: a systematic review

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Review

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Abstract

Background: Lung function and cardiac function are naturally correlated by sharing the thoracic cage and handling the whole cardiac output sequentially. However, lung function studies are rare in patients with CHD, although results worthy of investigation could be expected. This review summarises existing studies with the lung function parameters (spirometry and body plethysmography) in CHD patients during the last decade. *Methods:* A systematic review was performed in the relevant database (PubMed, Cochrane, and Scopus) in studies including paediatric and adult patients with CHD where lung parameters (spirometry, body plethysmography) were investigated from January 2010 to December 2020. Two independent reviewers evaluated the studies according to the Study Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Heart, Lung, and Blood Institute *Results:* Eight studies investigated patients with Fontan palliation including 704 patients (306 female). Four studies included patients after repaired tetralogy of Fallot examining 219 patients (103 female), with one study using double. Further six studies included 3208 (1324 female) children and adults with various CHDs. Overall, four studies were categorised as "good", ten as "fair", and four as "poor". While the measurements were consistently standardised, references to calculate %predicted differed substantially across all studies. All evaluated studies showed reduced forced vital capacity in the majority of CHD patients. *Conclusions:* Many CHD patients have a reduced forced vital capacity independent of their underlying defect. Spirometry should not only follow a standardised measure according to ATS (update 2019) but also stick to the 2012 GLI reference values

A CHD is the most common anomaly given by birth[1] with a prevalence of 7.32 per 1000 births in Europe. Infants are more likely to grow up and reach adolescence and adulthood.[2] Medical care, especially in a specialised tertiary care centre becomes more important. However, "late" on-set comorbidities such as liver diseases in Fontan patients, cancer, or a decrease in exercise capacity occur more often than in the normal population.[3–5] Already in childhood, low exercise capacity,[6–9] a higher risk of impaired functional outcomes such as motor competence – not only fine and gross motoric but also strength,[10,11] – or subsequent medical issues are frequent.[12,13]

The heart can particularly affect lung volumes and their function due to the common limited space in the thoracic cage. Second, lung development may already be affected by abnormal blood flow during embryonic development,[14,15] especially if the pulmonary blood flow is affected (for example, in the absence of a pulmonary valve or severe stenosis, or on the other side severe recirculation in a large septum defect). Third, consecutive palliative surgeries (like staged palliation of univentricular hearts) can influence thoracic compliance and growth, cause pleural adhesions, and alter lung function.[16,17] Müller et al. have shown that lung volumes correlate with the number of thoracotomies.[18] However, comprehensive knowledge of lung function in CHD is still lacking. Former studies concentrated on the late effects of surgery.[18,19] Therefore, the present systematic review aims to investigate (me) the state of the literature in the context of lung function testing in CHD within the last decade as well as (II) its quality and methodology and consequences for future studies.

Material and Method

Objective

This study investigates lung function parameters in patients with a congenital heart defect to figure out whether abnormalities are more likely, common, or rare. Furthermore, highlighting patients under risk is elaborated and examination strategies are provided.

Searching strategy

The review was performed systematically. Relevant databases were chosen: PubMed, Cochrane, and Scopus. We only included studies published in English with full-text available. Final data research update was performed in July 2021. A standardised protocol was used for population, intervention, comparison, outcome, method (PICO-C),[20] and applied as follows:

- *"Congenital heart defect" OR "Congenital heart disease" OR "Congenital heart defects" OR "Congenital heart diseases" OR "Fallot" OR "Ebstein" OR "Eisenmenger" OR "Transposition of the great arteries" OR "Fontan" OR "Cavopulmonary" OR "Cavo-Pulmonary" OR "septal defect"AND*
- *"lung function" OR "lung volume" OR "Spirometry" OR "Bodyplethysmography" OR "lung capacity" OR "body box" OR "pulmonary function" OR "Body plethysmography".*

Furthermore, only studies from January 2010 to December 2020 (the last decade) were analysed.

Data collection

Data from children, adolescents, and adults with CHD were included in the review. All relevant studies were screened for eligibility with title and abstract. Inclusion criteria consisted of CHD patients as subjects and lung volumes (e.g. forced vital capacity). Lung volumes must have been measured standardised and this also had to be noted in the manuscript. Furthermore, literature for the reference values had to be reported. Both % of predicted values and z-score were considered.

Two reviewers conducted a full-text analysis. If at least one of them considered the published study as eligible, the study was included in the review.

Rating of the studies

Studies, which were included in the review, were rated by The National Heart, Lung, and Blood Institute "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies". The rating consists of "yes", "no", and "other" (e.g. cannot determine). Following their guidelines, the rating of the studies depends on their individual "risk of bias". Therefore, if the two reviewers concluded that a study has a (high) risk of bias, it was rated lower than studies with no or low risk of bias. There is no strict guideline for the number of "yes" leading to a better conclusion. Studies with another design than cohort or cross-sectional (e.g. Fritz et al.[21]) were excluded due to their character of inclusion and exclusion criteria leading to a risk of bias in subjects' lung function. Only one intervention study[22] was included since no exclusion criteria that may influence the outcome (lung function) were reported.

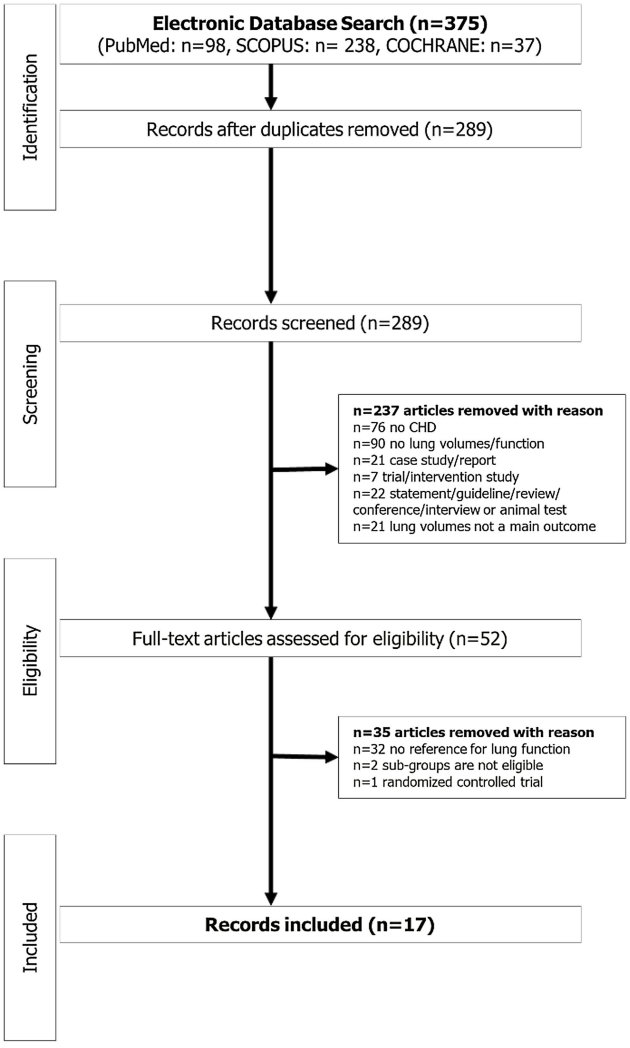

Fig. 1 Study concept and exclusion criteria.

Results

Selected studies

Figure 1 shows the inclusion and exclusion process of the review. After full-text analyses (n = 52), 32 studies were excluded because no established reference was provided (e.g. only "[. . .] with <80% predicted [. . .]") or their origin for reference values was missed. Two studies were excluded since the sub-groups were not eligible (e.g. reduced lung volumes in CHD patients vs. normal results in CHD patients) and one further study due to its randomised controlled trial nature which has a risk of bias due to in- and exclusion criteria.[21] However, the intervention study from Hedlund et al.[22] was included since the inclusion criteria consisted of parameters that will not affect lung function in CHD patients (e.g. myocarditis or moved to another geographical region). Only baseline characteristics were used for analyses.

Study quality

All studies stated that they performed a standardised lung function test, which guarantees comparability between results. Classification of CHD was well described and results were given

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Table 1. Quality assessment according to the NHLBI quality assessment tool for observational cohort and cross-sectional studies.

Study	Type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality range
Fontan patients (n = 7)																
Idorn et al. 2014	CSS	√	√	√	–	–	–	–	–	√	NA	√	–	NA	√	Poor
Opotowsky et al. 2014	CSS	√	√	√	√	–	–	–	√	√	NA	√	–	NA	√	Good
Turquetto et al. 2017	CSS	√	√	–	√	–	–	–	√	√	NA	√	–	NA	√	Fair
Hedlund et al. 2018	IS	√	√	–	√	–	√	√	√	√	NA	√	–	√	√	Good
Shafer et al. 2018**	CS	√	√	CD	√	–	√	–	√	√	–	√	–	NA	√	Fair
Liptzin et al. 2018¥	CSS	√	√	CD	–	–	–	–	√	–	NA	√	–	NA	√	Poor
Callegari et al. 2019	CSS	√	√	CD	√	–	–	–	NA	√	NA	√	–	NA	√	Fair
Guenette et al. 2019	CSS	√	√	CD	–	–	–	–	√	√	NA	√	–	NA	√	Poor
TOF patients (n = 4)																
Demirpence et al. 2015	CSS	√	√	√	–	–	–	–	√	√	NA	√	–	NA	√	Fair
Cohen et al. 2017¥	CSS	√	√	CD	√	–	√	√	√	√	–	√	–	√	√	Good
Shafer et al. 2018**	CS	√	√	CD	√	–	√	–	√	√	–	√	–	NA	√	Fair
Powell et al. 2019	CSS	√	√	CD	–	–	–	–	√	√	NA	√	–	NA	–	Fair
all CHD patients (n = 6)																
Alonso-Gonzalez et al. 2013	CS	√	√	CD	√	–	√	√	√	√	–	√	–	√	√	Fair
Ginde et al. 2013	CSS	√	√	CD	–	–	–	–	√	√	NA	√	–	NA	√	Poor
Hawkins et al. 2014¥	CSS	√	√	√	–	–	–	–	√	√	NA	√	–	NA	√	Fair
Abassi et al. 2019	CSS	√	√	–	√	–	–	–	√	√	NA	√	–	NA	√	Good
Morales Mestre et al. 2019	CSS	√	√	CD	√	–	–	–	√	√	NA	√	–	NA	√	Fair
Fabi et al. 2020	CSS	√	√	CD	–	–	–	–	√	√	NA	√	–	NA	√	Fair

**study double since both, Fontan and TOF patients were investigated; ¥ for this study no mean ± SD was given.
Abbreviations: NHLBI: The National Heart, Lung, and Blood Institute, Q: question, CSS: cross-sectional study, CS: cohort study, IS: Intervention Study.
Question 1. Research question, Questions 2 and 3. Study population, Question 4. Groups recruited from the same population and uniform eligibility criteria, Question 5. Sample size justification, Question 6. Exposure assessed prior to outcome measurement, Question 7. Sufficient timeframe to see an effect, Question 8. Different levels of the exposure of interest, Question 9. Exposure measures and assessment, Question 10. Repeated exposure assessment, Question 11. Outcome measures, Question 12. Blinding of outcome assessors, Question 13. Follow-up rate, Question 14. Statistical analyses.
"√" fulfilled, "–" not fulfilled, CD: cannot determine, NA: not applicable.

precisely in almost all studies. Only Abassi et al.[23] used an uncommon classification of CHD. All studies investigated at least spirometry parameters (forced vital capacity and forced expiratory volume in 1 s, FEV1). Only six studies investigated total lung capacity or residual volume by body plethysmography and diffusion capacity measurement.[22,24–28] The number of individuals studied ranged from 17[25] to 168[24] and includes 380 body plethysmography tests as well as 4131 spirometry tests.

Study quality ratings

The quality of studies in this NHLBI tool does not depend on the total score as it is in others.[29] Each study is rated individually. If in one study the independent reviewers were not in agreement with the quality range, they discussed the risk of bias due to missing or insufficient provided information in the study. The lower the risk, the higher the rating.

Table 1 shows the result of the NHLBI study rating. All studies provided a research question and defined a study population (Q1 and Q2). The study population (Q3 and Q4) is often sufficiently described, but more often it was not determined. A selection bias in subjects must be assumed in these studies. No study included a justification of sample size which may be the nature of limited subjects due to this special cohort and second due to the character of cross-over studies (Q5). However, also in these cohorts, a power-analyses should be done in advance. Some questions can only be answered with "not applicable" (e.g. Q 10) due to the nature of the CHD: patients are born with this condition and therefore the exposure measurement cannot be "repeated". Another risk is the lack of blinding of studies, which no study fulfilled (Q12). However, in each patient group, it was already clear that all of them suffer from a CHD since they visit a specialised clinic (Q8–Q10).

Four studies were rated as good[22,23,30,31] indicating a low risk of bias. Nine studies[24,28,32–38] were considered "fair" with a lower internal validity in the view of the reviewers. The other studies[25–27,39] showed a higher risk of bias (e.g. missing a control group from a similar population) and further weaknesses also compared to the other studies.

Study characteristics

Seven studies[22,25–28,30,32,33] investigated patients with Fontan palliation (or children after total cavopulmonary connection, TCPC) including 704 patients (306 female). Four studies[31,32,34,35] included patients after repaired tetralogy of Fallot. These studies examined 219 patients (103 female). Further six studies[23,24,36–39] included 3,208 children and adults with various CHDs (1324 female).

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Overall, 14 studies[23–28,30,31,33–35,37–39] were cross-sectional studies, two cohort studies[32,36] and one intervention study.[22] All studies refer to a local/national or worldwide reference, 7 of the 14 cross-sectional studies compared results with age and gender-matched healthy reference cohorts.[23–25,28,34,35,37] The other studies used healthy reference cohorts only. The two cohort studies used either norm references[36] or an age-matched reference cohort with CHD.[32] Hedlund et al.[22] included a matched cohort in their 12-week intervention study. Table 2 provides more detailed information on all studies.

Lung function tests and reference norms

All selected studies refer to cohort studies investigating healthy subjects. It is striking that there is hardly any agreement between the studies concerning the norm values: Abassi et al.,[23] as well as Morales Mestre et al.,[38] used the current 2012 GLI references from the Global Lung Initiative published by Quanjer et al.[40] Two studies referred to Brusasco et al.,[41] and a further five to Pellegrino et al.[42] The other studies used local or national studies as references,[34,43–45] comparatively old references,[46–50] or other references.[51] Therefore, statistical analysis with an, e.g., meta-analysis is not practicable. Furthermore, since the results are mainly in common (Fig 2) between the studies, there was no benefit in calculating effect size.

Discussion

Despite the heterogeneous quality of the studies and the use of different reference values in the studies, Fontan and tetralogy of Fallot patients, as well as cohorts of mixed CHDs, showed mainly a reduced forced vital capacity with about 50% of patients in the striking result range.

Lung volumes in CHD patients

Studies on Fontan patients

Seven studies investigated patients with Fontan palliation or total cavopulmonary connection, the "modern" palliation.[22,25–28,30,32,33] Hedlund et al. performed an intervention study, Shafer et al. a cohort studies, and the remaining a cross-sectional studies. All studies showed mild to significant limitations in terms of lung volumes in children and adolescents with CHD. Opotowsky et al.[30] highlight that almost half of 260 included patients were below the lower limit of normal in forced vital capacity (represented in 80% of predicted with their reference).

Remarkable is that studies that included children[22,26,28] show much higher and more likely normal volumes in forced vital capacity and FEV1 (≥80% of predicted). These studies on children include patients with the nowadays common surgical repair which probably leads to better functional outcomes.[8] However, results are significantly lower compared to healthy peers.

Studies investigating adults[25,32,33] show significantly lower results in lung volumes (~60–75% of predicted). It may be concluded that the current surgical procedure "protects" children's lung function – or that nowadays patients are more likely to perform sports and exercise, and therefore, their lung volumes may be less affected and more likely in a normal range. Daily exercise and sports lead to better exercise capacity[52,53] which vice versa correlates with lung volumes and function.[22,23,28,52,54]

Moreover, Guenette et al.[25] showed that total lung capacity and diffusion capacity is lower in their Fontan cohort. Low total lung capacity represents a small lung. Additionally, lungs may be affected in diffusion by the passive circulation after the Fontan procedure, presented in diffusion capacity. Unfortunately, in this study, no data on diffusion capacity/VA were reported. Further studies are needed with much larger sample sizes (in this study only 17 patients were included) to re-evaluate these findings.

All included studies demonstrate lower values than the reference (<80% of predicted or < −1.645 in z-score) or even impairments in FVC and FEV1. Almost no patient showed obstructive patterns [27]. Strikingly, some studies show that body plethysmography (TLC and RV) is normal, with only 165 Fontan patients underwent this test.[26–28]

Studies on TOF patients

Four studies[31,32,34,35] examined a total of 219 patients with repaired tetralogy of Fallot. Shafer et al. conducted a cohort study and the other three cross-sectional studies. As in Fontan patients, also in this cohort, children show better results compared to adults. Demirpençe et al. and Powell et al. show only a slight decrease in forced vital capacity and FEV1 in their investigated children with results below 80% of predicted. Cohen et al. studied 122 adult patients with tetralogy of Fallot and their results show mild impairments in 19% and moderately to severe impairments in further 19% of the patients. Also, Shafer et al. provide impaired results in tetralogy of Fallot patients with forced vital capacity in % of predicted 62.8 ± 16.7 and FEV1: 59.0 ± 15.3. It seems, that again, children who undergo surgical repair "today" benefit from improvements in surgical intervention regarding the results in lung volumes. Future studies should evaluate this hypothesis – it is questionable, if the lung function parameters are better or if they decrease later on – or if for example daily activity and sports play a role.[55]

None of the reviewed studies performed body plethysmography in tetralogy of Fallot patients. It is advisable to test those with a restrictive pattern (forced vital capacity <80% of predicted) regarding their total lung capacity to eliminate the risk of hyperinflation (normal total lung capacity while forced vital capacity is reduced leading to a high residual volume).[56]

Studies with all CHD patients

The last six studies,[23,24,36–39] that are included in this review, deal with various kinds of CHD. Mainly, the heart defects were separated following different possibilities: e.g. left heart lesion (as aortic stenosis), right heart lesion (as tetralogy of Fallot), and other lesions (as transposition of the great arteries),[37] data were presented for each CHD separately,[23,39] or other different groupings were made.[23,24,36,38]

However, the main results are similar compared to those with Fontan or tetralogy of Fallot patients: while children[23,24,38] have fairly normal lung volumes, adults more often show reduced or impaired results.[36,39] The study by Hawkins et al. included both age groups and found decreased lung volume results in 20% of all their subjects.[37] Anatomical basics, heart surgery, and the number of surgeries can favour these decreased lung volumes.[36,37] Again, no study investigated total lung capacity or RV in the patients. Overall, the results show that approximately half of all investigated patients have a restrictive pattern in spirometry.

Figure 2 summarises the main results of all studies, separated in CHD. It has to be mentioned that in this figure, the studies from Liptzin et al, Cohen et al., and Hawkings et al. are not presented. None of these studies reported mean or medians as results, only the numbers of impaired results were given.

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Table 2. Study characteristics and outcomes.

Study	CHD, n (female)	Healthy CG (n)	CHD diagnosis (n)	Age ± SD (range) [IQR25;IQR75] in CHD	Outcome measures in lung volumes	Reference for lung volumes	Main results
Fontan patients (n = 8)							
Idorn et al., 2014	87 (38)		Fontan	16.3 ± 7.6	FVC, FEV1, FEV1/FVC, VC, FRC, ERV, RV, TLC, VC, DLCO (n = 10), DLCO/VA	Stanojevic et al., 2008 and Zapletal, Šamánek, & Paul, 1987	FVC: 91.4 ± 14.4 %predicted or z-score −0.73 ± 1.23, FEV1: 89.5 ± 14.0 or z-score −0.30 ± 1.08, FEV1/FVC: 101.3 ± 7.6 or z-score: 0.30 ± 1.26; TLC: 90.7 ± 12.1 or z-score −0.74 ± 1.46, RV: 108.0 ± 31.4 or z-score 0.24 ± 1.07; DLCO: 61.0 ± 13.7 or z-score −2.85 ± 1.26, DLCO/VA: 70.3 ± 14.5 or z-score −2.38 ± 1.20
Opotowsky et al., 2014	260 (105)	–	Fontan	13.1 ± 3	FVC, FEV1, FEV1/FVC	Brusasco, Crapo, Viegi, American Thoracic, & European Respiratory, 2005 and NHANES III	FVC: 45.8% < lower limit of normal (LLN); FEV1/FVC: 7.8% < LLN
Turquetto et al., 2017	27 (15)	Age and gender matched (27)	Fontan	Male 18 (15-29), female 22 (15-25)	FVC, FEV1, FV1/FVC, FEFmax, FEF25-75, TGV, IC, TLC, RV, RV/TLC, DLCO	Pereira, Sato, & Rodrigues, 2007	Only important parameters (ANOVA One-way, Post Hoc Scheffe): FVC: male 83 ± 11 versus 103 ± 14 %predicted and female 75 ± 16 versus 88 ± 12 % predicted (p < 0.001), FEV1: male 80 ± 9 versus 97 ± 11 % predicted and female 76 ± 16 versus 99 ± 12 % predicted (p < 0.001), FEV1/FVC: n.s.; TLC: male 91 ± 18 versus 117 ± 22 %predicted and female 77 ± 12 versus 97 ± 8 %predicted, RV: n.s.; DLCO: male 58 ± 9 versus 98 ± 19 %predicted and female 66 ± 15 versus 84 ± 8 %predicted (p < 0.001)
Hedlund, Ljungberg, Soderstrom, Lundell, & Sjoberg, 2018	30 (14)	matched *n* = 25 (12)	Fontan	14.2 ± 3.2 (8.9–20.4)	FVC, FEV1, FEV1/FVC, FEF50, FEF75; TLC, FRC, RV; DLCO	Hedenstrom, Malmberg, & Agarwal, 1985; Hedenstrom, Malmberg, & Fridriksson, 1986	FVC: 86 ± 17 versus 97 ± 13 % predicted (p = 0.010), VC: 87 ± 15 versus 97 ± 11 % predicted (p = 0.006) and DLCO 60 ± 11 versus 87 ± 10% predicted (p < 0.001)

(*Continued*)

Table 2. (*Continued*)

Study	CHD, n (female)	Healthy CG (n)	CHD diagnosis (n)	Age ± SD (range) [IQR25;IQR75] in CHD	Outcome measures in lung volumes	Reference for lung volumes	Main results
Shafer, Opotowsky, & Rhodes, 2018**	Fontan: 27 (11)	age-matched Fontan: 70 (35)	Fontan: cases (death) vs. controls	Cases Fontan: 28.9 ± 10.7	FVC, FEV1, FEV1/FVC	Ginde et al., 2013 referring Pellegrino et al., 2005	Fontan: FVC: 67.4 ± 19.1 versus 77.6 ± 14.9 %predicted (p = 0.007), FEV1: 67.8 ± 19.1 versus 78.4 ± 13.9 % predicted (p = 0.015), FEV1/FVC: N/A.
Liptzin et al., 2018¥	51 (27)	–	Fontan: fenestrated vs. infenestrated	Median 10.8 (3.3-21.3)	FVC, FEV1, FEV1/FVC, TLC, DLCO	Eigen et al., 2001, Wang, Dockery, Wypij, Fay, & Ferris, 1993, Hankinson, Odencrantz, & Fedan, 1999, Zapletal et al., 1987, and Quanjer et al., 1993	Results are given in median (range): FVC N/A, FEV1: 85 (59–114) % predicted, FEV1/FVC: N/A; TLC: 94 (70–112) % predicted, DLCO: 85.5 (57–151) %predicted (n = 20); Normal function: n = 8 (21%); Airway obstruction and/or air trapping n = 12 (32%); n = 2 reversibility on pulmonary function testing, n = 11 history of reversibility on pulmonary function testing, n = 1 symptoms of asthma (cough/wheeze with exercise and/or at night-time), n = 1 asthma; n = 7 (18%) evidence of restriction; *n* = 1 mixed pattern, n = 7 <DLCO
Callegari et al., 2019	205 (88)	–	Fontan	25.6 ± 10.8 (all subjects)	FVC, FEV1, FEV1/FVC	Morris, 1976 and Quanjer et al., 1995	FVC: 71.1 ± 16.9%pred (p < 0.001), FEV1: 74.7 ± 17.8% pred (p < 0.001), FEV1/FVC: n.s.
Guenette et al., 2019	17 (8)	17 (8)	Fontan	31.8 ± 11.0	FVC, FEV1, FEV1/FVC, TLC, DLCO	Tan et al., 2011 and Gutierrez et al., 2004	FVC: 76 ± 13 versus 98 ± 12 % predicted (p < 0.001); FEV1: 74 ± 11 versus 94 ± 12 % predicted (p < 0.001); FEV1/FVC: n.s.; TLC: 74 ± 9 versus 91 ± 12 % predicted (p < 0.001); DLCO: 67 ± 12 versus 98 ± 18 %predicted (p < 0.001)
TOF patients (n = 4)							
Demirpençe et al., 2015	25 (14)	age and sex-matched *n* = 25	TOF	11.6 ± 2.7	FVC, FEV1, FEV1/FVC, FEF25-75, PEF	Oneş, Somer, Sapan, Dişçi, & Guler, 2004	FVC: 79 ± 15 versus 91 ± 13 % predicted, p = 0.005); FEV1: 79 ± 15 versus 92 ± 15% predicted (p = 0.005); FEV1/FVC: n.s.;

Table 2. (*Continued*)

Cohen et al., 2017[¥]	122 (59)	–	TOF	31 ± 10.1	FVC, FEV1, FEV1/FVC Normal: predicted FVC 70%, Mildly impaired: predicted FVC, 70 to 60%, moderately to severely impaired: FVC < 60%; FEV1/FVC <70% and FVC >70%: sole obstructive pattern	"Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society," 1991	Normal: n = 76 (61%), mildly impaired: n = 22 (19%), moderately to severely impaired: n = 23 (19%); FEV1/FVC <70% n = 3 (2%); FVC <70% and FEV1/FVC <70% n = 2 (2%)
Shafer et al., 2018**	TOF. 15 (6)	age-matched Fontan: 70 (35) TOF: 45 (21)	TOF: cases (death) vs. controls	Cases TOF: 42.0 ± 15.2	FVC, FEV1, FEV1/FVC	Ginde et al., 2013 reffering Pellegrino et al., 2005	TOF: FVC: 62.8 ± 16.7 versus 75.0 ± 14.0 %predicted (p = 0.006), FEV1: 59.0 ± 15.3 versus 73.3 ± 15.8 % predicted (p = 0.006), FEV1/FVC: N/A.
Powell, Mays, Knecht, & Chin, 2019	57 (24)	Age matched *n* = 57 (24)	TOF: 2 groups (transannular patch as subgroup)	24.7 ± 13.8	FVC, FEV1, FEV1/FVC	Goldman & Becklake, 1959	FVC: 79.4 ± 18.6 versus 93.9 ± 10.1 %predicted (p < 0.05), FEV1: 75.9 ± 19.9 versus 91.2 ± 17.7 %predicted (p < 0.05), FEV1/FVC: n.s.
all CHD patients (n = 6)							
Alonso-Gonzalez et al., 2013	1,188 (555)	–	all CHD	33.2 ± 13.1	FVC, FEV1, FEV1/FVC Normal: predicted FVC > 70%, Mildly impaired: predicted FVC, 70 to 60%, moderately to severely impaired: FVC < 60%; FEV1/FVC < 70% and FVC > 70%: sole obstructive pattern	"Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society," 1991	All: FVC: 69.7 ± 17.5 % predicted; FEV1: 72.7 ± 18.0 % predicted; FEV1/FVC: 0.89 ± 0.08; Normal lung function: n = 628 (52.9%), mildly impaired: n = 207 (17.4%), moderately to severely impaired: n = 353 (29.7%); Exclusion of sole obstructive pattern with FEV1/FVC < 70%; n = 59 patients
Ginde et al., 2013	100 (57)	–	CoA (n = 19), TOF (n = 17), left ventricular outflow tract obstructive lesions (n = 12), septal defects (n = 11), Fontan (n = 9); TGA after atrial switch (n = 9); ccTGA (n = 7); Ebstein's anomaly (n = 7); PS (n = 5), TGA after arterial switch (n = 4)	Median: 31 (18-63)	FVC, FEV1, FEV1/FVC, FEF25-75	Pellegrino et al., 2005	Normal: n = 50, reduced lung volumes n = 44, mixed restrictive and obstructive pattern n = 4; (n = 2 indeterminate); Most likely abnormal (>50%): TOF, single ventricle, PS

(*Continued*)

Table 2. (*Continued*)

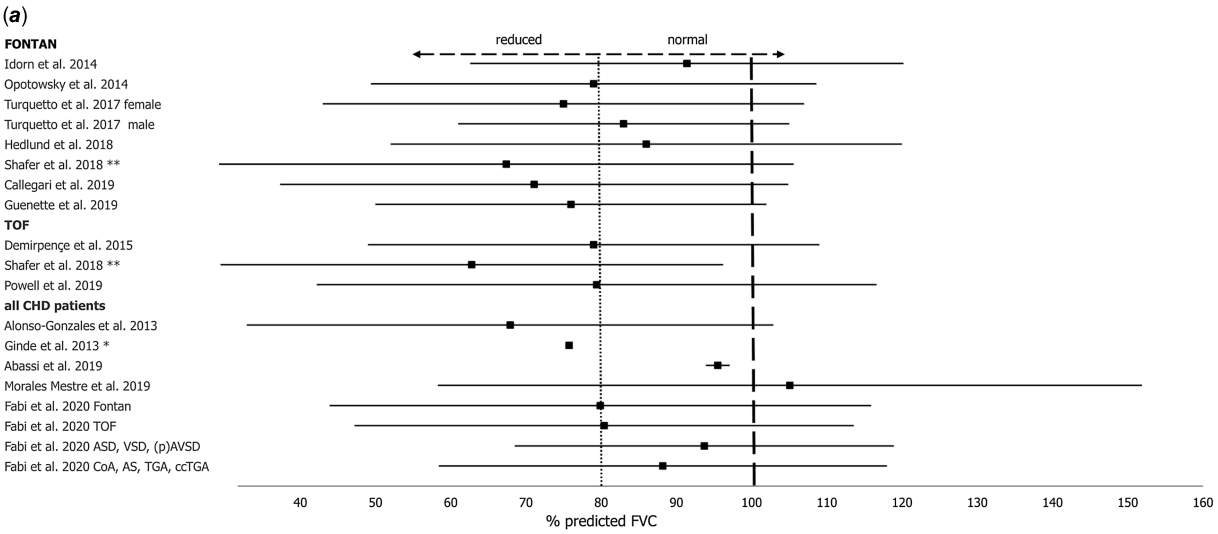
Study	CHD, n (female)	Healthy CG (n)	CHD diagnosis (n)	Age ± SD (range) [IQR25;IQR75] in CHD	Outcome measures in lung volumes	Reference for lung volumes	Main results
Hawkins, Taylor, Sillau, Mitchell, & Rausch, 2014[¥]	Tests: 876 (294)	age and gender-matched n of tests = 220 (85)	surgical and non-surgical repair; nonsurgical group: left-sided lesions, right-sided lesions, other lesions;	15.5 ± 7.7	FVC, FEV1, FEV1/FVC	Pellegrino et al., 2005	Prevalence in reduced lung function: Overall: 19.7% versus 13.2% ($p = 0.03$); surgical versus non-surgical versus CG: 25.5% versus 8.6% versus 13.2% ($p < 0.0001$) – OR: surgical versus CG 3.64 (95% confidence interval [CI], 2.19–6.03) and nonsurgical versus CG 2.25 (95%CI, 1.44–3.51); Sternotomy and thoracotomy are most often associated with reduced lung function.
Abassi et al., 2019	555 (229)	age and gender matched $n = 279$	Heterotaxy (3), venous return anomaly (14), atria and interatrial anomaly (32), atrioventricular junctions and valves anomaly (28), complex atrioventricular connection anomaly (6), UVH (36), VSD (50), TGA (75), complex ventricular outflow anomaly (117), AS/Shone complex (60), PS (45), extrapericardial arterial trunks anomaly (80), coronary artery anomaly (7)	12.2 ± 3.3	FVC, FEV1, FEV1/FVC	Quanjer et al., 2012	FVC: 95.5 ± 0.8 versus 104.5 ± 1.1%predicted, z-score: −0.4 ± 1.5 versus −0.4 ± 1.3 ($p < 0.0001$), (except complex atrioventricular connection anomaly; especially: heterotaxy, UVH, complex ventricular outflow anomaly; FEV1: 97.3 ± 0.7 versus 106.7 ± 1.0% predicted, z-score: −0.5 ± 1.4 versus 0.4 ± 1.2 ($p < 0.0001$), (except heterotaxy, venous return anomaly, complex atrioventricular connection anomaly); FEV1/FVC: n.s.
Morales Mestre, Reychler, Goubau, & Moniotte, 2019	321 (124)	–	All CHD: 4 severity groups using the modified Ross classification (1: no limitations or symptoms; 2: Mild tachypnea or diaphoresis with feeding in infants;	13.4 ± 4.6 [4.4; 22.3]	FVC, FEV1, FEV1/FVC, FEF25-75	Quanjer et al., 2012	FVC: differ significantly but is normal range ($p < 0.001$); FEV1: differs significantly but the normal range ($p = 0.002$)

Table 2. (*Continued*)

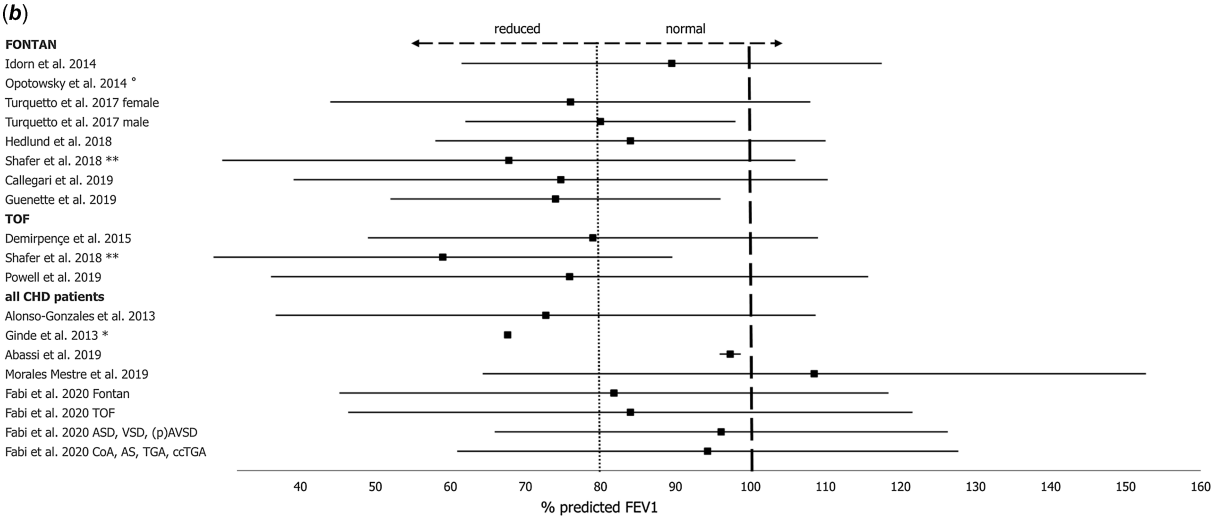
			dyspnea at exertion in older children; no growth failure, 3: Marked tachypnea or diaphoresis with feeding or exertion and prolonged feeding times with growth failure from congestive heart failure, 4: Symptomatic at rest with tachypnea, retractions, grunting, or diaphoresis)				
Fabi et al., 2020	168 (65)	52 (17)	group 1 (increased pulmonary flow): ASD, VSD, (p) AVSD; group 2 (reduced pulmonary flow): TOF, PA-iVS; group 3: TCPC; group 4 (normal flow): CoA, AS, TGA, ccTGA	n.a.	FVC, FEV1, FEV1/FVC, FEF25-75, PEF; TLC, VC, RV, RV/TLC, IC, ERV, Raw; DLCO, DLCO/AV	Brusasco et al., 2005 and Pellegrino et al., 2005	Group 1 versus CG: n.s.; Group 2 versus CG: reduced in VC ($p = 0.001$), IC ($p < 0.001$), FVC ($p < 0.001$), FEV1 ($p < 0.001$), DLCO ($p < 0.001$); Group 3 versus CG: reduced in FVC ($p = 0.001$), FEV1 ($p < 0.001$), DLCO ($p < 0.001$), DLCO/AV ($p < 0.001$); Group 4: n.s.

**study double since both, Fontan and TOF patients were investigated; ¥ for this study no mean ± SD was given

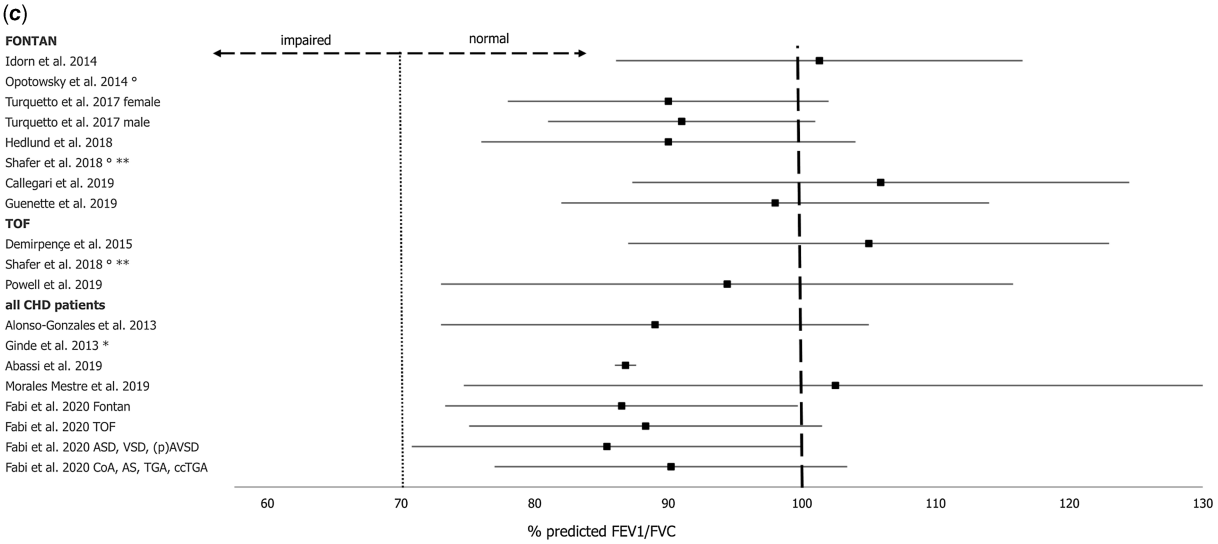
Abbreviations: ANOVA: analyses of variance, AS: aortic stenosis, ASD: atrial septal defect, AV: volume of the alveolar, ccTGA: congenital corrected transposition of the great arteries, CHD: congenital heart disease, CG: control group, CoA: coarctation of the aorta, DLCO: transfer factor of the lung for carbon monoxide (diffusion capacity), ERV: expiratory reserve volume, FEF: forced expiratory flow, FEV1: forced expiratory volume in 1 s, FRC: functional residual capacity, FVC: forced vital capacity, IC: inspiratory capacity, IQR: interquartile range, LLN: lower limit if normal, n: number of subjects, MIP: maximum inspiratory pressure, N/A: not applicable (data not given in results), NHANES: National Health and Nutrition Examination Survey, (p)AVSD: (partial) atrioventricular septal defect, PA-iVS: pulmonary atresia with intact ventricular septum, PEF: peak expiratory flow, PS: pulmonary stenosis, RV: residual volume, SD: standard deviation, SNIP: sniff nasal inspiratory pressure, TCPC: total cavopulmonary connection, TGA: transposition of the great arteries, TLC: total lung capacity, TOF: tetralogy of Fallot, UVH: univentricular heart, VC: vital capacity, VSD: ventricular septal defect.



Forrest plot in forced vital capacity (FVC): mean ± 2 standard deviations (SD) with 80% as threshold of normal results



Forrest plot in forced expiratory volume in 1 second (FEV1): mean ± 2 standard deviations (SD) with 80% as threshold of normal results



Forrest plot in FEV1/FVC: mean ± 2 standard deviations (SD) with 70% as threshold of normal results

Fig. 2 Forrest plots in FVC, FEV1, and its ratio.
* no SD given, ° no data available, ** study double since both, Fontan and TOF patients were investigated. Abbreviations: FVC: forced vital capacity, FEV1: forced expiratory volume in 1 seconds, TOF: Tetralogy of Fallot, CHD: congenital heart disease, ASD: atrial septal defect, VSD: ventricular septal defect, (p)AVSD: (partial) atrioventricular septal defect, CoA: coarctation of the Aorta, AS: aortic stenosis, TGA: transposition of the great arteries, ccTGA: congenitally corrected transposition of the great arteries.

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Clinical impact

The studies in this review show that about half of all investigated patients have fairly normal or only mild restrictive patterns occur (Table 2, Fig 2). Lung physiology in patients with CHD can be affected by several factors. Due to decreased blood flow antenatal, as neonates and infants,[14,15] maldevelopment of the lungs may result in possible reductions in lung volumes.[19]

Surgical palliation or repair already takes place in early childhood.[57] At this time, lung growth is not yet complete. Underlying restrictions may improve or even disappear with time. Therefore, lower restrictions compared to studies with adults are not surprising since they often underwent surgical interventions later in age compared to today – which has to be investigated in future studies. Surgical improvements during the last decades additionally enhanced children's clinical situation. Future studies should evaluate, if these children can maintain their "good" and normal volumes or if there may be a point of change during their lifetime, as we know from exercise capacity, the natural decline with time increases during the decades.[58]

Remarkably, all included studies report an increased likelihood that patients in whom the pulmonary circulation is affected (tetralogy of Fallot, Fontan, and pulmonary stenosis) have lower values in spirometry or body plethysmography.[23,39] In patients with left heart lesions, reviewed studies suggest fewer reduced or striking lung volume parameters.[24,38]

Secondly, lung volume reductions might be the result of a compliance lack in the thoracic cage: growth of the ribs, as well as adhesions in the pleural space, can reduce forced vital capacity. In a recent study, we could confirm that the reduction in lung volume is associated with the number of thoracotomies,[18] which supports this hypothesis of thoracic limitations. This reason can be improved by inspiratory training, which not only improves lung volume but also exercise capacity.[54]

Thirdly, the reduced lung volume can be due to the lack of exercise. The adult patients with CHD experience during their childhood due to overprotection by parents and physicians.[59] Nowadays, there are liberal recommendations for physical activity and sports.[60] So, this should be confined to very few patients with CHD.

Only rarely the reduction of the lung volume is the result of a persistent post-operative phrenic palsy.[61] However – none of them highlighted any co-morbidities in the investigated patients. Further studies need to implement possible co-factors which influence lung parameter results (such as asthma and diaphragmatic palsy).[19]

Last but not least, heart failure with increased left or right heart might be present in early childhood and not be completely reversible with treatment. This condition will increase with time when more patients with CHD of moderate or severe complexity reach adulthood and step into a vicious cycle of heart failure, valve dysfunction and repeated surgery. As the heart and lung share the same thoracic cavity, every kind of dilatation or hypertrophy of a cardiac chamber results in a reduced lung volume.

Whatever the reason is, reductions in lung volumes are negatively associated with exercise performance,[55] and mortality,[36] and may indirectly also affect the heart itself. Patients with reduced or impaired lung function can only benefit if diagnosed early and treated if needed.

Therefore, at least a spirometry needs to be performed in every patient with CHD to detect initial restrictions of the lung volumes and possibly counteract deterioration through, for example, targeted sports[52] or respiratory training.[21,54] And the test needs to be interpreted in the context of the individual condition of the patient and the CHD by a trained person to guarantee the best result for both – the patient and the attending physicians.

Limitations

The sample size of the included studies reaches from 17 patients[25] to 1188 in Alonso-Gonzales et al.[36] Studies with no individual reference cohort consist of >50 subjects (two studies) or even >100 included patients. No study has applied a power analysis in its methods that justify the number of included patients. Furthermore, most of the included patients suffered from TOF or Fontan which makes it more difficult to precise results in general.

Studies that did not implement certain references for lung volumes were excluded since only a certain reference guarantees appropriate results which significantly reduced the number of studies.

Conclusion and Clinical Recommendation

Children, adolescents, and adults with CHD are affected by reduced forced vital capacity, measured via spirometry. Restrictive patterns are common. Further studies with more precise and different subgroups (in only one to two CHDs) are needed to further specify which CHD patients are at higher risk of decreased lung volumes. Furthermore, greater emphasis should be placed on body plethysmography, as possible restrictive patterns in the lung-volume pattern may originate from air trapping or other lung diseases.

All three aspects mentioned above (limited space in the thoracic, developmental limitations in the lungs, and risk of surgical interventions) need to be clarified. There is at least a nationalwide need for a common database to stratify risk factors in CHD patients and to point out to parents and patients also concerning possible promotion and improvement possibilities in lung function. As seen in Fig 2, although patients reach normal values in forced vital capacity, FEV1 (above 80% of predicted), and its ratio are most likely below the reference represented as 100%.

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