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Lung function in patients with a congenital heart defect

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Lung function in patients with a congenital heart defect

DISSERTATION

Julia Theresa Hock

Topic-specific publications

Interim and partial results of the study were presented at the following **congresses**:

AEPC 2019: **Hock J**, Oberhoffer R, Ewert P, Hager A: Decreased Total Lung Capacity in Patients with Tetralogy of Fallot. *Talk.*

AEPC 2021: **Hock J**, Bessar M, Ewert P, Dalla Pozza R, Hager A: Prevalence of obstructive and restrictive lung pattern in adults with congenital heart disease. *Poster.*

Hock J, Bessar M, Ewert P, Dalla Pozza R, Hager A: Reduced spirometric volumes in children with a right heart defect – are they all restrictive? *Poster.*

ESC Preventive Cardiology 2022: **Hock J**, Nagdyman N, Meierhofer C, Ewert P, Hager A: Are there correlations between lung volume and exercise capacity in children and adolescents with native Ebstein's Anomaly? *Poster.*

AEPC 2022: **Hock J**, Bessar M, Ewert P, Hager A: What about the lungs? Body plethysmography in patients with congenital heart disease. *Poster.*

ESC Preventive Cardiology 2023: **Hock J**, Bessar M, Dalla Pozza R, Ewert P, Hager A: Some results are striking - what about lung function in adults with congenital heart disease? *ePoster.*

Hock J, Bessar M, Dalla Pozza R, Ewert P, Hager A: More likely normal lungs in nowadays children with a congenital heart defect? *ePoster.*

The following **papers** were written and are currently submitted or published:

Bessar M, **Hock J**, Ewert P, Hager A. Preserving the Lung Functions in Patients with Congenital Heart Defect: Advantage of Catheterization Therapy over Surgical Closure. *Submitted for publication.*

Hock J, Bessar M, Ewert P, Hager A. Body plethysmography – additional information on exercise capacity? *Submitted for publication.*

Hock J, Willinger L, Pozza RD, Ewert P, Hager A. Abnormalities in pulmonary function and volumes in patients with CHD: a systematic review. Cardiol Young. 2023 Feb;33(2):169-181. doi: 10.1017/S1047951122004103. Epub 2023 Jan 5. Erratum in: Cardiol Young. 2023 Feb;33(2):182. PMID: 36601957.

Furthermore, **Mohammed Bessar** used parts of the data for his Medical Doctor thesis entitled "Body plethysmography in congenital heart disease." In the thesis, patients with an isolated shunt are examined regarding their lung function.

Table of contents

Abstract

Due to the high survival rate, functional outcomes in patients with a congenital heart defect (CHD) have gained more and more attention in recent years. The physical and mental constitution of young, and old patients is of great interest. Especially in coping with every-day life, patients need to have sufficient functional capacity.

Exercise performance is one of the strongest predictors of morbidity and mortality in CHD patients and is often impaired. In addition, lung function, an additional functional outcome, which is one of the decisive factors for good exercise capacity, frequently occurs reduced in patients with various CHD. This is significantly related to the underlying heart defect, but also to the patients' lifestyles and generally the current times and therefore also the surgical decade and treatment concepts used for the patient. There are only few studies that have investigated the lung function of CHD patients by means of a "large lung function test" (body plethysmography). Both, the time required and the cost-benefit ratio, play a role here.

This study aimed to investigate most lung parameters in a large cohort of CHD patients. The results were divided by children and adults and separated regarding respective heart defect categories.

The data show that many patients with congenital heart defects have worse results of lung volumes and function. There is no significant difference in frequency between children and adults.

Most patients who have reduced volumes have small lungs (restriction). Here the data show a correlation with surgery; only a few patients have obstruction in lung function.

Nevertheless, more than one third of all patients have abnormal results in spirometry and body plethysmography. Even though the latter revealed that a significant proportion (22 out of 52 initially defined as preserved ratio impaired spirometry) had abnormal lung function, but the reason could not be specified due to lack of tests. These patients show a non-specific pattern.

Additionally, patients with a surgical intervention are more likely to have noteworthy results. Since lung function is (also) related to performance - and because of this and to improve the quality of life of patients with CHD, it is necessary and recommended that a regular lung function test is performed. Changes in the results should lead to further testing and training - thus guaranteeing lifelong monitoring and support for the patient.

List of Figures

List of Tables

List of Abbreviations

95%CI 95 percent confidence interval
CHD congenital heart defect
CPAP continuous positive airway pressure
EA Ebstein's anomaly
ERV expiratory reserve volume
FEF forced (mean) expiratory flow
FEV1 forced expiratory volume in one second
FRC functional residual capacity
FVC forced vital capacity
GLI Global Lung Initiative
IC inspiratory capacity
ICD implantable cardioverter defibrillator
L liter
LHO left heart obstruction
LLN lower limit of normal
n number of patients
PRISm preserved ratio impaired spirometry
RHO right heart obstruction
RV residual volume
SD standard deviation
SVC slow vital capacity
TCPC total cavopulmonary connection
TGA transposition of the great arteries
TLC total lung capacity
TV tidal volume
VC ventilatory capacity
VT breathing volume
VTG volume of thoracic gas
X-ray radiography

1 Introduction

During the last decades, medical, interventional, and surgical treatment in patients with a congenital heart defect (CHD) progressed dramatically, leading to a nowadays significantly improved survival [1-3]. As "staying alive" became self-evident, "staying healthy" became the focus of research in this cohort. However, studies have shown that especially in patients over the age of 40, co-morbidities are common [4-6] and it can be expected that this will even increase during the next decades. Next to different organic damages in specific sub-groups (e.g. liver disease in Fontan patients [5] or nephrological issues in cyanotic patients), further functional impairments occur in this cohort. Functional outcomes including exercise capacity, but also lung function and volumes, can give a first hint on late-onset morbidities, mortality, and there is a correlation with the quality of life [7-9]: CHD patients show reduced lung volumes [10-12], a lack of exercise capacity [13-16], and also health-related physical fitness or quality of life is often reduced or at least affected [13-15,17]. These results also depend on the decade of birth (progress in surgery, primary, secondary, and tertiary care) and the patient's current age.

One main aspect of research during the last few years was mainly patients' quality of life, [13,15,17-20] next to trainability (physically and mentally) [21-26], and further lifestyle changes [27]. These research questions have been investigated extensively, also in CHD patients.

However, the lungs as the closest organ to the heart were mostly left aside – though it is well known that CHD patients' lung volumes are often reduced [10,28-30].

Prospective studies are rare over a wide range of CHDs [31]. Therefore, this project aims to prospectively evaluate lung volumes and function in children and adults with a CHD and compare the results in sub-groups to state a trend in expectations. Further, it is ensured that any suspicious result was examined by a lung specialist.

2 Medical Background

In the center of the thorax, the heart and the lungs form an inseparable unit, the basis for the functions of all other organs in the body (Figure 1). If either of the organs has developed an anomaly, the other may suffer from this – less space, worse function, or probable damage from the other one (Figure 2).

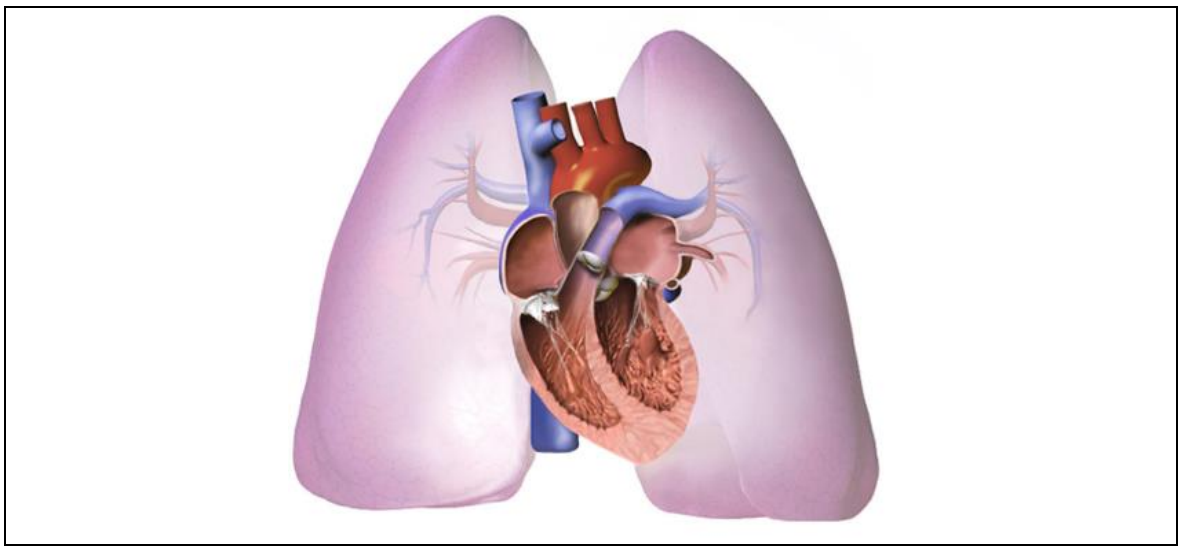
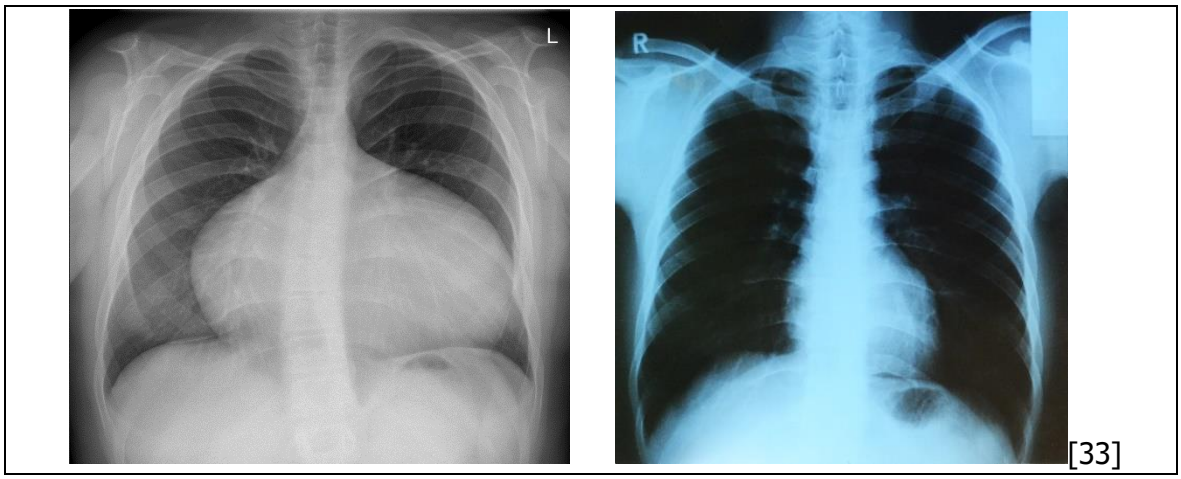


Figure 1: Cardiopulmonary system: positional relationship [32]



[33]

Figure 2: X-ray image in a patient with congenital heart defect and a healthy one

left: X-ray image of a normal heart-thoracic-lung arrangement [33]; right: example of an X-ray from an Ebstein's anomaly (own data)

2.1 Normal heart and normal lungs

A normal heart consists of four chambers, two great arteries, pulmonary veins, and the vena cava (Figure 3). The blood circulation works as follows:

Spent, deoxygenated blood from the body flows via the inferior and superior vena cava into the right atrium; from there via the tricuspid valve into the right ventricle and via the pulmonary valve into the lungs. Here the blood is enriched with oxygen (ventilation see chapter 2.2) and reaches the left atrium via the pulmonary veins. It enters the left ventricle via the mitral valve, where it then leaves the heart via the aorta and supplies the body with oxygen. After the oxygen has been "consumed", the circulation starts all over again. [34,35]

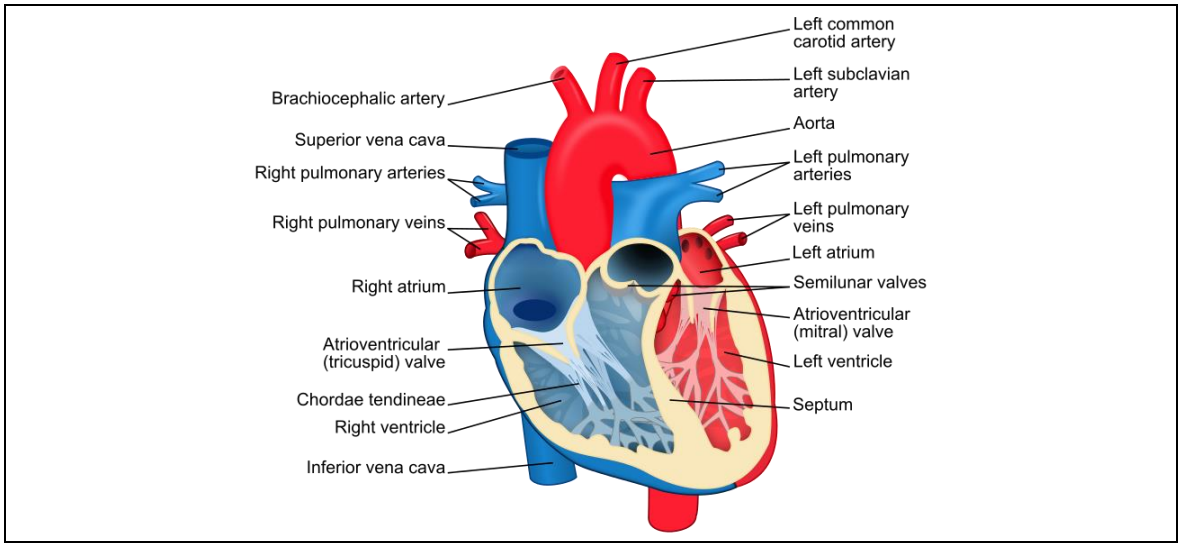


Figure 3: Normal heart with chambers, arteries, veins and valves [36]

The respiratory system consists of all airways between outside air and alveoli. The different parts are, from the upper part to lower part, the nasal cavity where the air is warmed and moistened and cilia trap the smallest foreign bodies; followed by the larynx that closes the access to the intrathoracic airways during swallowing via glottis, and the trachea. The lower airways consist of the lungs including bronchiole and alveoli (Figure 4). [37]

It seems to be obvious that if one part does not work properly, the whole system might be affected.

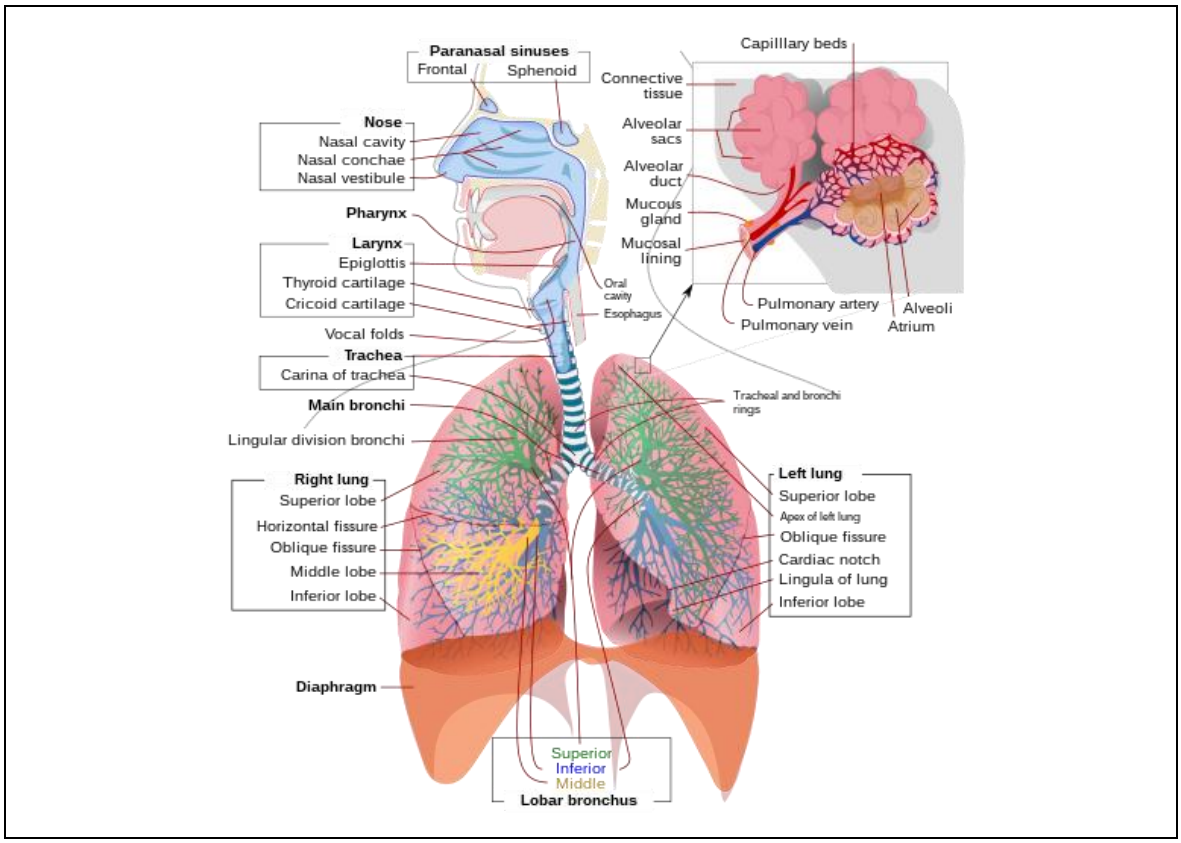


Figure 4: Respiratory system [38]

2.2 Cardiopulmonary interaction under physiologic conditions

Ventilation affects human's hemodynamic which is affected by the heart (Figure 5).

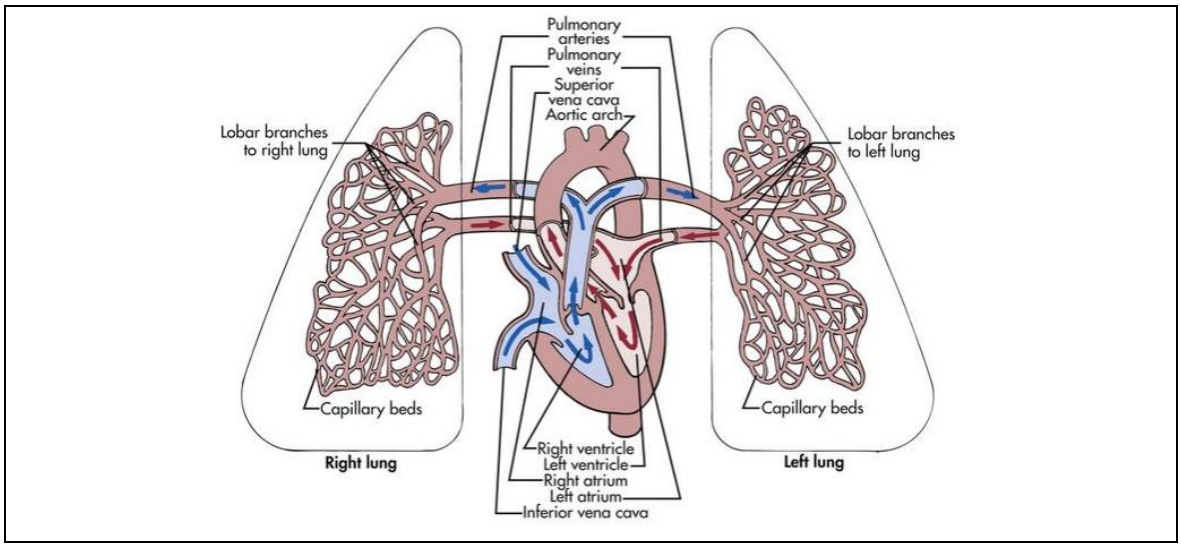


Figure 5: Blood circulation in cardiopulmonary interaction

Picture taken from: https://u.osu.edu/smoot.43/pathophysiology-of-pulmonary-embolism/ [39]
Blue: deoxygenated blood, red: oxygenated blood

Pinsky defines ventilation as follows:

> "1) Spontaneous ventilation is exercise; 2) changes in lung volume alter autonomic tone and pulmonary vascular resistance and can compress the heart in the cardiac fossa; and 3) spontaneous inspiratory efforts decrease intrathoracic pressure, increasing venous return and impeding left ventricular ejection, whereas positive-pressure ventilation decreases venous return and unloads left ventricular ejection." [40]

With spontaneous inspiration, the intrathoracic pressure decreases [40]. Furthermore the heart rate increases with inspiration [41]. In some trained patients or children, breathing is even visible in the electrocardiogram. It is called respiratory arrhythmia [42] and shows a well-adapted heart and autonomic function concerning changes in breathing.

However, changes in intrathoracic pressure affect the heart in both – venous return and systemic outflow due to changes in pressure in the arteries and veins [40]. Any imbalance within this system may affect the other organ.

Since shortness of breath is a common complaint, especially in elderly patients, the heart should always be part of the medical examination when somebody has issues breathing. Moreover, chest pain is another reason for patients to get a consult [43]. In both cases the leading question is – are the complaints refer to their heart or their lungs?

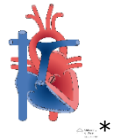
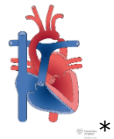
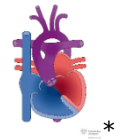
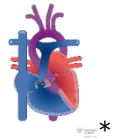
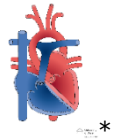
As mentioned, if the heart does not work properly, this may have an impact on the lungs. For example, in heart failure patients' blood can no longer be sufficiently transported into the body, so. Therefore, it congests in the lung veins. Consequently, the lung capillaries are affected, blood flows from those to the alveoli and finally the gas exchange, that is oxygen uptake and carbon dioxide emission, decreases. The patient seems to get less air, although they have an increased respiratory rate - and contrary to what symptoms like shortness of breath might indicate, it is actually heart failure that is responsible for this [43].

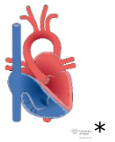
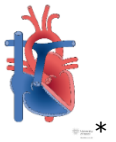
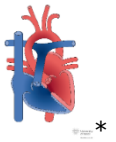
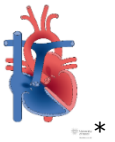
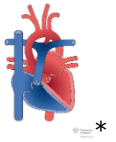
2.3 Congenital heart defects

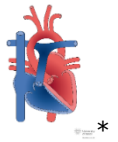
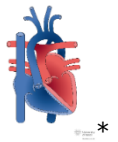
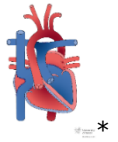
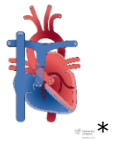
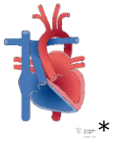
Congenital heart defects (CHD) are the most common congenital defect in newborns with a prevalence of about 1% in infants [44,45]. Many patients reach adulthood due to recent medical advances [4-6,46]. However, a higher survival rate also leads to increased comorbidities in these patient group. Furthermore, side effects or late impacts of the defect arise more often. Already in children, deficits in several functional outcomes are present [13-15,18,47]. Therefore, it is important to assess more than "only the heart" during routine follow up. Some patients with CHD seem to be more affected concerning their lungs compared to others. Especially in those with a right heart obstruction (e.g. tetralogy of Fallot or pulmonary atresia), decreased lung volumes and impaired lung functions are expected [31]. Table 1 gives an overview of CHD that were investigated in this study.

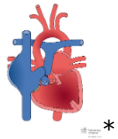
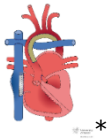
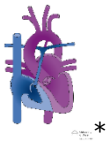
However, up to now, no large study including a various range of CHD was performed to prove this with both, spirometry, and body plethysmography.

Table 1: Overview of congenital heart defect with descriptions

Classification	Underlying heart defect	Description [46,48]	
Left heart obstruction	Aortic stenosis	○ Stenosis: bicuspid aortic valve; left ventricular outflow tract obstruction; forms: valvular, subvalvular, supravalvular.	 *
	Coarctation of the Aorta	○ Organic stenosis at the physiological constriction between the subclavian artery and the aortic orifice, based on ductal tissue surrounding the aortic wall in a pincer-like manner. ○ Part of a generalized arteriopathy and not just a circumscritical narrowing of the aorta.	 *
Right heart obstruction	Truncus arteriosus communis	○ Aorta and truncus pulmonalis are not completely separated during fetal development, both arteries originate together from the heart, often ventricular septal defect. ○ Categorized under "right heart obstruction", because patients show these typical conditions after primary surgical repair, using an implanted right ventricle outflow conduit.	 *
	Tetralogy of Fallot	○ Displacement of the infundibulum septum to the right, anterocephalically. ○ Obstruction of the right ventricular outflow tract. ○ Large, subaortic, "malalignment" ventricular septal defect. ○ Aorta riding over the ventricular septal defect (>50%). ○ Right ventricle hypertrophy (consecutive).	 *
	Pulmonary valve stenosis	○ Stenosis of pulmonary artery. ○ Forms: subvalvular, valvular, supravalvular, peripheral.	 *

Ebstein's anomaly	Grade of severity depends on grade of tricuspid regurgitation	○ One or more leaflets of the tricuspid valve malformed; displacement determines the severity. ○ Tricuspid valve regurgitation, dysfunction of the left ventricle, mitral valve abnormalities, an interatrial connection (patent foramen ovale or atrial septal defect) ○ Threatening arrhythmias are common; cardiomyopathy component	 *
Isolated shunt	Atrial septal defect type II (as example)	○ Ostium secundum defect: in the region of the oval fossa. ○ Atrial septal defect type I; partial atrial-valve septal defect: Immediately cranial to the atrioventricular valve plane. Atrioventricular septal portions are absent and there is abnormal atrioventricular valve anatomy. ○ Sinus venosus defect: Outside the fossa ovalis, in each case at the junction of the superior or inferior vena cava with the atrium (cranial in the superior type, caudal in the inferior type).	 *
	Perimembranous ventricular septal defect	○ Small to medium-sized ventricular septal defects have a volume load to the pulmonary circulation, left atrium, and left ventricle. ○ Large defects result in an additional pressure volume load for the right ventricle and pulmonary circulation.	 *
	Complete atrioventricular septal defect	○ Deep-seated atrial septal defect Type I, inlet ventricular septal defect. ○ Gap formation in the anterior left-sided- and septal right-sided AV valve leaflets. ○ All four cardiac cavities are in communication with each other. ○ Atrioventricular valves are at the same level and form a common atrial-valvular valve orifice from four to seven leaflet parts. ○ Unbalanced atrioventricular septal defect: "left or right dominance," when the common valve is predominantly assigned to one ventricle and the other is hypotrophic, otherwise balanced (equilibrated) type.	 *
	Patent ductus arteriosus	○ Vascular connection between aorta and left pulmonary artery. ○ Essential for fetal circulation (ductus arteriosus botalli). ○ Persistent ductus arteriosus botalli if, after birth, the connection stays un-occluded > 3 months.	 *

	Patent foramen ovale	○ Foramen ovale is a valve-like connection between the two atria. ○ Essential to stay open in fetal circulation, closes after birth and adheres during life. ○ Patent foramen ovale is a lack of adherence, causing reopening and right to left shunt in certain conditions like Valsalva maneuver or right heart failure.	
Transposition of the great arteries	D-transposition of the great arteries	○ Aorta arises from the morphologically right ventricle. ○ Pulmonary artery arises from the morphologically left ventricle (ventriculo-arterial discordance). ○ Aorta ascends ventrally and/or to the right of the pulmonary artery. ○ Great vessels run parallel without crossing each other ("D- Transposition of the great arteries").	
	D-transposition of the great arteries after atrial redirection (Mustard procedure; Senning procedure – autologous material)	○ Right atrium excision of the atrial septum down to a narrow groin fixation of a reverse patch (baffle) of pericardium, Dacron, or Gore-Tex. ○ Patch dilatation of the pulmonary vein atrium frequently. ○ Systemic venous blood → newly created systemic venous atrium → mitral valve → morphological left ventricle → pulmonary artery. ○ Pulmonary venous blood → dorsal and lateral to the systemic venous tunnel → tricuspid valve → morphologic right ventricle → Aorta.	
	D-transposition of the great arteries after arterial switch operation (Jatene procedure)	○ Ventrally located aorta positioned peripheral to the coronary artery ostia and the dorsally located pulmonary artery at the same level. ○ Excision of the coronary arteries. ○ Relocation of the ascending aorta behind the pulmonary artery. ○ Connection with the stump of the coronary artery carrying pulmonary artery. ○ Reconstruction of the former aortic stump connection with the pulmonary artery ventral to the "neoaorta".	
	Congenitally corrected transposition of the great arteries	○ Atrioventricular discordance. ○ Transposition of the great vessels (ventriculoarterial discordance). ○ Atrioventricular valves, coronary arteries, and conduction system are inverted.	

Fontan circulation	Fontan-Lins/Kreutzer	○ Right atrium to pulmonary arteria connection for various types of univentricular hearts.	 *
	Fontan-Björk	○ Connection between right atrium and right ventricle for some types of tricuspid atresia.	no picture available
	Total cavopulmonary connection	○ With lateral tunnel for hypoplastic left heart syndrome (current surgical palliation).	 *
Cyanosis	Example: pulmonary atresia with intact ventricular septum with hypoplastic right ventricle and cyanosis	○ Oxygen saturation at rest is below 90%. ○ Includes Eisenmenger patients or failing palliation or failing of the repair.	 *

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2.4 Lung volumes and function

The amounts of air that can be mobilized by the lungs are referred to as volumes [49]. They can be measured by a lung volume test using a flow-volume-curve and additional by a body plethysmography that precisely measures all volumes (due to Boyle and Gay-Lussac combined gas law [50,51]). This makes up part of a lung's function. But the term lung function usually refers to how the human utilizes the air which takes place in the bronchioles and alveoli (diffusion and perfusion) [49]. However, to simplify reading, the term lung function and lung volumes are used equally.

A spirometry (lung volume test) can quantify the forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and related flow-volumes such as forced expiratory flow (FEF25-FEF75, as a first hint on pulmonary suspiciousness). A body plethysmography measures further volumes such as total lung capacity (TLC), residual volume (RV) or functional residual capacity (FRC). All volumes are important to exclude possible impairments or diseases from differential diagnosis.

Potential correlation with a heart defect

Different studies have already shown that patients with CHD are more likely to show reduced lung volumes, represented in impaired results in FVC and FEV1 but normal ratio in spirometry [11,29,30,52]. Also, a recently published systematic review by Hock et al. showed, that overall, about one third to half of all patients' lung function volumes are reduced [31]. However, reasons for these results are mainly unknown – and will presumably also be difficult to justify in the future due to the complexity of the subject.

3 Material and Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethical board of the Technical University of Munich (project number: 110/19 S). It was retrospectively registered at the Deutsches Register für klinische Studien (DRKS00021120). Its design is a cross-sectional study with retro- and prospective details. All patients (or parents in case of children) were informed and signed a consent form in advance of participating (cf. Appendix). Next to data from lung function tests, medical records were included to evaluate the patients' medical background (e.g. surgery, co-morbidity etc.).

Julia Hock was responsible for testing and calculations. She performed about 55% of all measurements, taught colleagues, supervised other technicians, and entered the data into the database. Eventually, she conducted all statistical analyses in this thesis.

3.1 Aim of the study

The leading question of this study is: "What about lung volumes and ventilatory disorders in patients with congenital heart defect?" The research aims to investigate a large cohort of patients with different kinds of congenital heart defects.

3.2 Lung function tests

All tests were performed with the body plethysmography BPd-HP (Figure 6) including lung function laboratory HDpft 2000 and were assessed with the software KoKo Px v7. Measured parameters are given in Figure 7 and Table 2. All tests were performed following the latest ATS and ERS guidelines [53-56].

Figure 6: Body plethysmograph (KoKo) that was used for the study

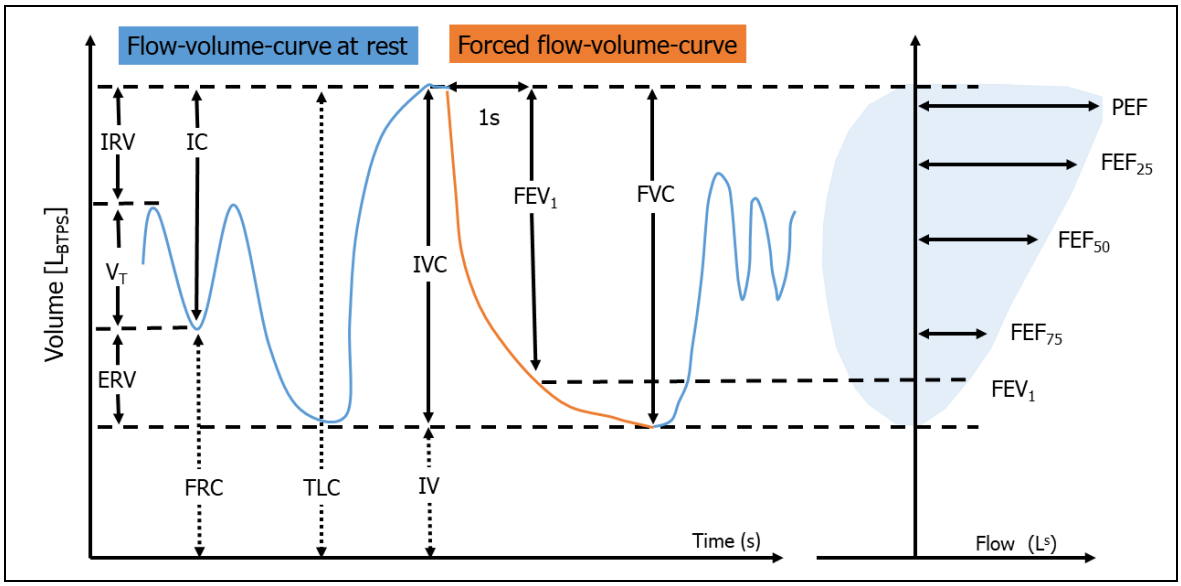

Figure 7: Static and dynamic lung function parameters and expiratory flows (modified from Criée et al., Figure 1 [57])

L: litre, BTPS: body temperature and pressure saturated, IRV: inspiratory reserve volume, VT: tidal volume, ERV: expiratory reserve volume, TLC: total lung capacity, IVC: inspiratory volume capacity, RV: residual volume, FEV1: forced expiratory volume in 1 second, FVC: forced expiratory volume, s: second, PEF: peak expiratory flow, FEF: forced expiratory flow

Table 2: Volumes that can be measured by lung function tests [50,51,56,58,59]

Test	Parameter	Meaning/calculation
Spirometry	FVC	forced vital capacity
	FEV1	forced expiratory volume in 1 second
	FEF25-75	forced (mean) expiratory flow (related to the percentage of exhaled FVC)
	IC	inspiratory capacity
	IVC	inspiratory vital capacity
	ERV	expiratory reserve volume
	VT	breathing volume
Body plethysmography	FRC	functional residual capacity
	VTG	volume of thoracic gas
	TLC	total lung capacity
	RV	residual volume

During the data collection, the machine had to be re-calibrated three times. All tests were re-performed after each calibration by the same expert to decrease the risk of calibration bias.

Spirometry

A spirometry is a test that mainly assesses the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1). Each patient underwent the examination at least three times. Afterward, according to ATS [54,55], the test with the best result (sum of FEV1 and FVC) was used for study investigation. As reference values, the latest Global Lung Initiative references were used (GLI-2021) [56,58].

Strategy for analyses were performed as suggested in Stanojevic et al. (Figure 8).

Figure 9 shows a normal spirometry.

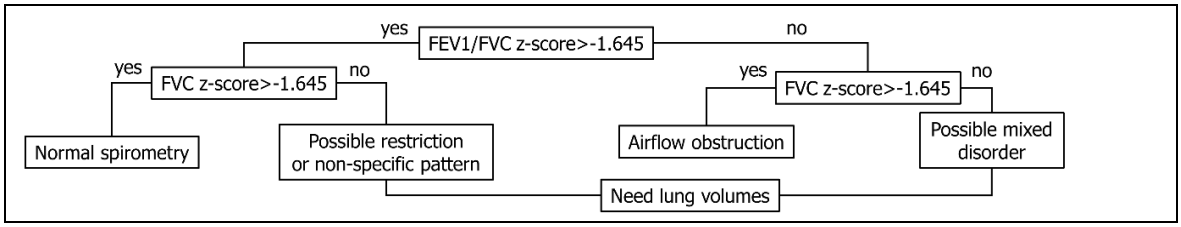

Figure 8: Examination strategy in spirometry for retrospective analyses (modified from Stanojevic et al., Figure 8 [56])

FEV1: forced expiratory volume in one second, FVC: forced vital capacity

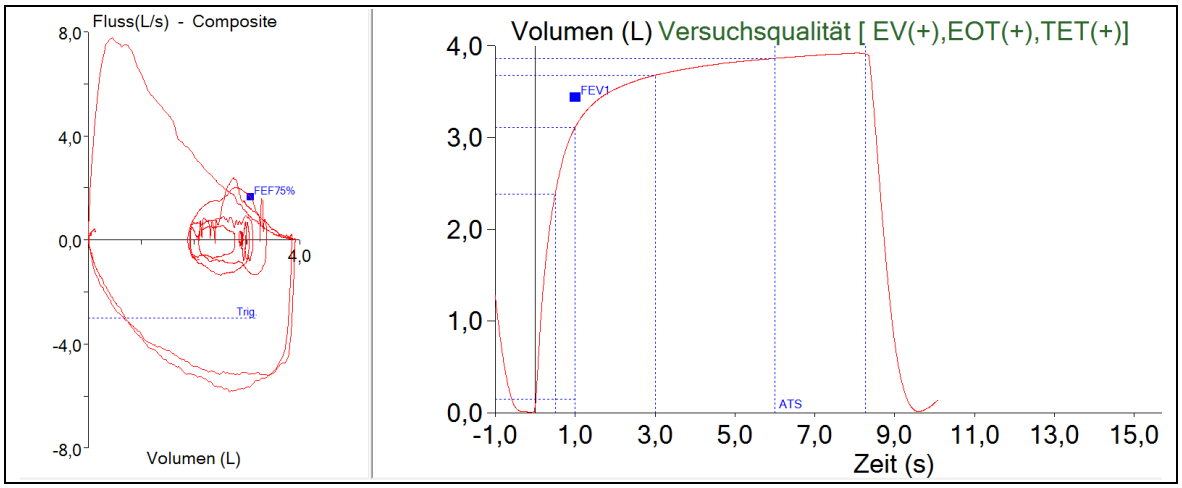

Figure 9: Normal flow–volume (left) and volume–time display in spirometry (right) from the software

L: litre, s: second, FEF: forced expiratory flow, Trig.: trigger, FEV1: forced expiratory flow in one second, EV: extrapolated volume, EOT: end of test, TET: total expiratory time

Results with a z-score < -1.645 in FVC, a z-score < -1.645 in FEV1 and normal FEV1/FVC were classified as preserved ratio impaired spirometry (PRISm [56,60], Figure 10). In PRISm pattern, the graphical lower limits of normal (LLN, equivalent to z-score of -1.645), represented as a horizontal line for the volume and vertical line for the speed, are not reached (Figure 10).

Patients can show normal values in FVC, but since they have difficulties in exhaling volume, their FEV1 is reduced with preserved ratio. These results are determined as "undefined pattern" since no definition is provided.

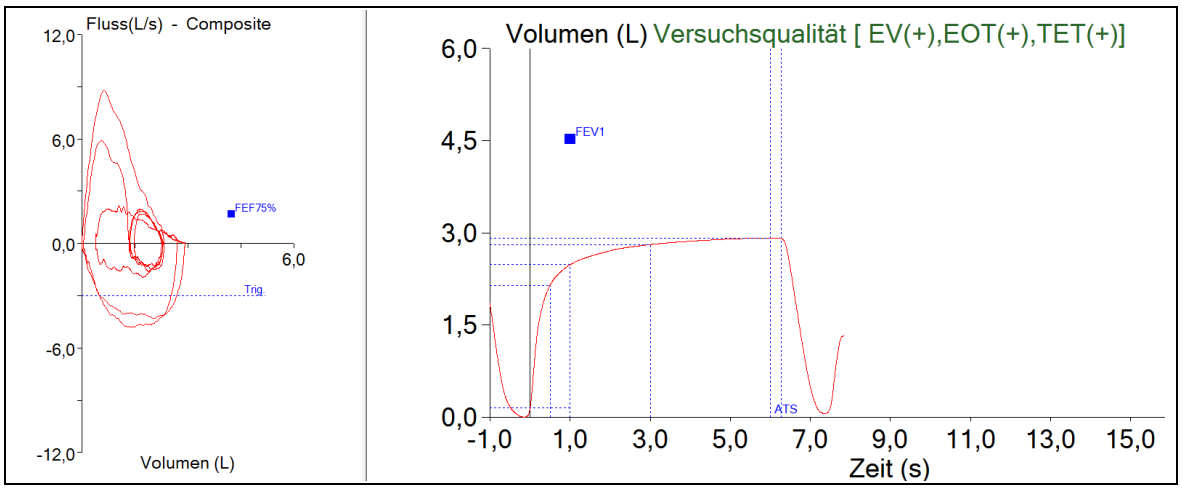

Figure 10: Preserved ratio impaired spirometry (PRISm)

PRISm: the flow is quick, but the reference values are not reached (FEV1/FVC normal, FVC and FEV1 z-score < -1.645), L: litre, s: second, FEF: forced expiratory flow, Trig.: trigger, FEV1: forced expiratory flow in 1 second, EV: extrapolated volume, EOT: end of test, TET: total expiratory time

In an obstructive pattern the ratio of FEV1/FVC is below the LLN (Figure 11, right: FEV1 not reached and less steep).

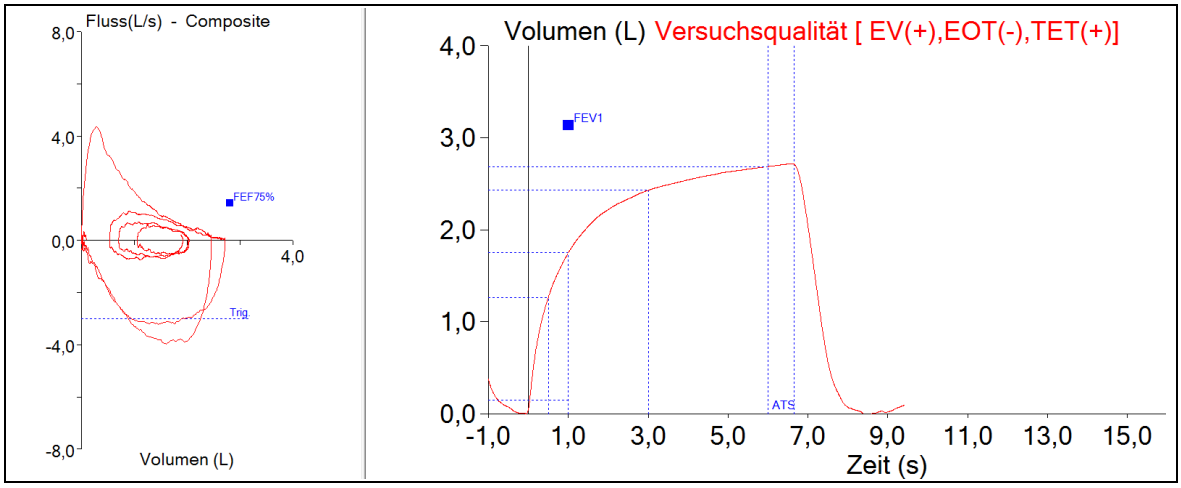

Figure 11: Obstructive pattern in spirometry

Obstructive: the flow is significantly reduced (FEV1/FVC < -1.645), L: litre, s: second, FEF: forced expiratory flow, Trig.: trigger, FEV1: forced expiratory flow in 1 second, EV: extrapolated volume, EOT: end of test, TET: total expiratory time

As suggested in the examination strategy, if a suspicious flow-volume-curve is seen, a body plethysmography should be performed to find out, whether there is another lung function problem. These examination results should always be examined more closely to detect possible (non-)reversible lung diseases and, if necessary, to treat them. However, in this study each patient underwent a body plethysmography afterwards, anyway.

Body plethysmography

After a valid spirometry test, all patients performed a body plethysmography test, following the current operator's manual [61] from KoKo GmbH® (former nSpire health GmbH®; KoKo Px v7 Operator's Manual): First the patient takes a breath and then reestablishes tidal breathing at the functional residual capacity position. Afterwards, the shutter closes, and the patient breathes three times with a frequency of 30-60 breathes per minute. After re-opening, the patient first breathes normally and then breathes (slowly) to maximum point of inspiration followed by maximum point of expiration. After that the patient breathes normal and finally the collection of the airway resistance data is performed with a breathing frequency of 90-120 breathes per minute. If the volume of thoracic gas (VTG) maneuver is improperly performed it can be reinitiated. Total lung capacity was calculated with the expiratory vital capacity method: average functional residual capacity (FRC) + average inspiratory capacity (IC), what is equal to residual volume (RV) + maximum ventilatory capacity (VC).

The test execution has the same purpose, but the method of execution differs a bit from other machines used in Western Europe. Before the statistical analysis, however, all tests had to be re-examined, since in some cases incorrect measurements were made in the event of technical problems. That led to a significant reduction of subjects included (Figure 14).

Figure 12 shows an example of a well-performed body plethysmography with normal results, performed with the KoKo machine.

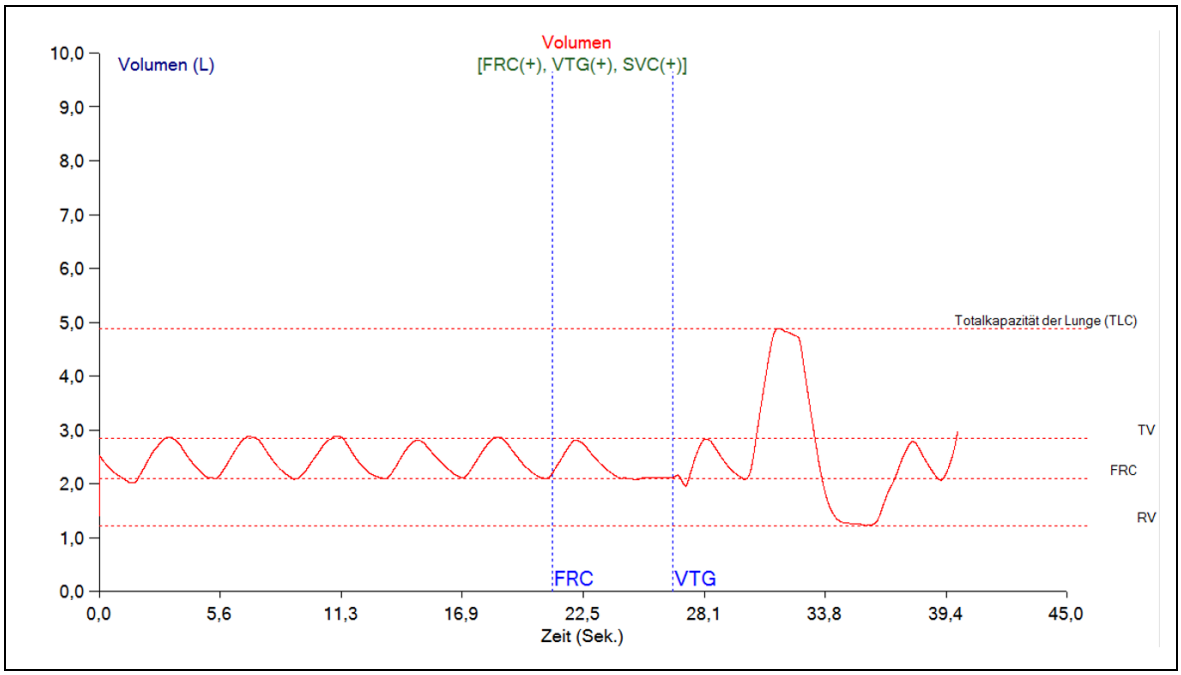

Figure 12: Body plethysmography in a healthy subject

L: litre, FRC: functional residual capacity, SVC: slow vital capacity, TLC: total lung capacity, TV: tidal volume, Sek.: second

As reference, latest data from Stanojevic et al. [56] were used and strategy for interpretation can be seen in Figure 13.

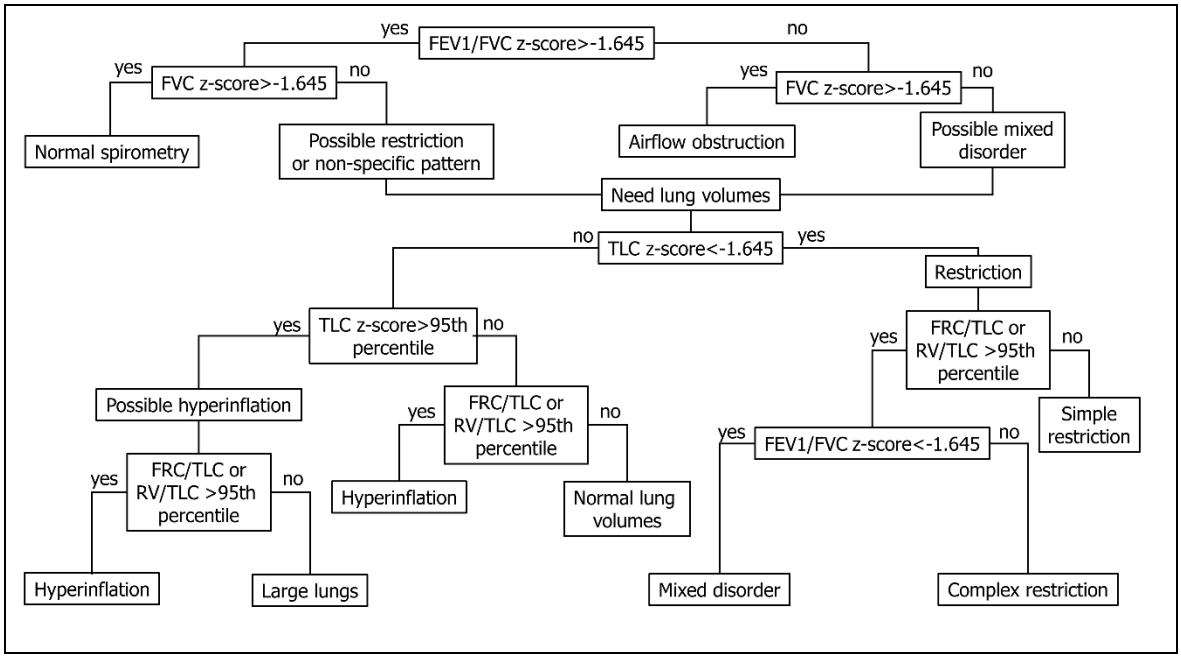

Figure 13: Approach for interpreting results in spirometry and body plethysmography (modified from Stanojevic et al., Figure 8 and 10 [56])

FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, TLC: total lung capacity, FRC: functional residual capacity, RV: residual volume

3.3 Patients

Included CHDs were: Aortic stenosis, coarctation of the aorta (both categorized as left heart obstruction, LHO); truncus arteriosus communis, tetralogy of Fallot and pulmonary stenosis (categorized as right heart obstruction, RHO); Ebstein's anomaly (EA); transposition of the great arteries (TGA after Senning/Mustard/Rastelli procedure and CCTGA as TGA others and surgical repair with atrial switch as another group); atrial or ventricular septal defect, atrioventricular septal defect, partial or total anomalous pulmonary venous return, patent ductus arteriosus or foramen ovale (categorized as isolated shunt); Fontan circulation (in children: after total cavopulmonary connection, TCPC), and cyanotic patients (oxygen saturation <90% at rest including palliated or native CHD).

Lung function in retrospective analysis

All data from the local database were retrospectively analyzed. A total of 13,994 spirometry tests were performed between July 2001 and October 2022. After exclusion of double, not included CHD category and exclusion of obvious invalid tests, 4,023 spirometries were analyzed.

Lung function in prospective analysis

From April 2018 to October 2022 five-hundred-forty-two (542) patients participated in the cross-sectional prospective study. Details on inclusion and exclusion criteria can be seen in Figure 14 and patients' underlying CHD contribution in Table 3. After the exclusion of invalid tests in body plethysmography (n=199), and exclusion of some patient groups (e.g. Marfan, regurgitation of the aortic or pulmonic valve only, patients with arrhythmia only, or onco-logic patients), 244 CHD patients (and 33 healthy reference subjects, tested randomly) were included in data analyses.

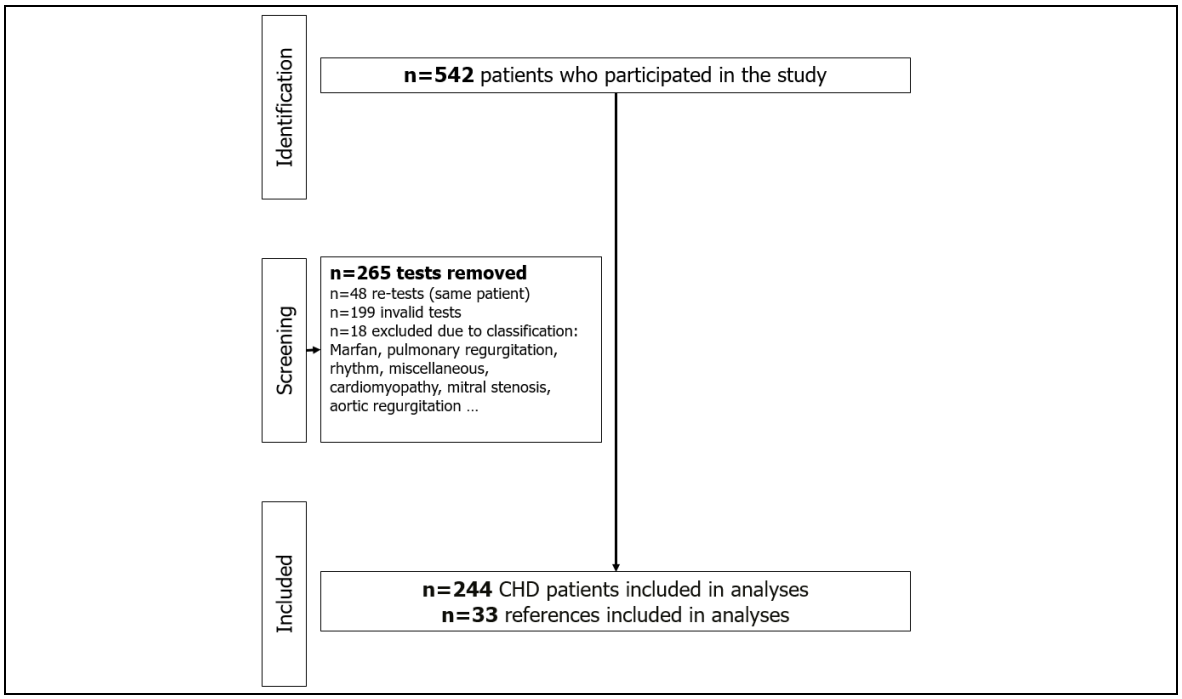

Figure 14: Inclusion of the patients

CHD: congenital heart defect

Table 3: Underlying congenital heart defect contribution

Congenital heart defect	Number of patients	Group
AS	22 (3 children)	Left heart obstruction (n=35)
CoA	13 (1 child)	
Fallot	70 (22 children)	Right heart obstruction (n=87)
PS	9 (2 children)	
TAC	8 (4 children)	
EA	23 (5 children)	Ebstein's anomaly (n=23)
TGA art. Switch	19 (5 children)	TGA after arterial switch (n=19)
TGA Senning/Mustard	21	TGA (Senning/ CCTGA/other) (n=30)
TGA divers	5	
CCTGA	4	
PFO	1	Isolated shunt (n=25)
PDA	1	
ASD	11 (7 children)	
AVSD	5 (2 child)	
VSD	6 (1 child)	
TAPVR	1 child	
Fontan circulation	21 (5 children, 12 TCPC overall)	Fontan circulation (n=21)
Cyanotic	4	Cyanotic (n=4)
Normal references	33 (3 children)	normal references

AS: aortic stenosis, CoA: Coarctation of the Aorta, EA: Ebstein's Anomaly, PS: pulmonary stenosis, TAC: truncus arteriosus communis, TGA: transposition of the great arteries, art.: arterial, CCTGA: congenitally corrected transposition of the great arteries, PFO: persistent foramen ovale, PDA: patent ductus arteriosus, ASD: atrial septal defect, VSD: ventricular septal defect, AVSD: atrioventricular septal defect, TAPVR: total anomalous pulmonary venous return, TCPC: total cavopulmonary connection

Table 4 gives an overview of patients' characteristics and pre-interventions or surgeries. Additionally, comorbidities are provided.

Table 4: Study characteristics in adults and children

	Adults												
CHD	**n (female)**	**Age (years)**	**Height (cm)**	**Weight (kg)**	**BMI (kg/m²)**	**Surgery (%/n)**	**Sternotomy (%/n)**	**Thoracotomy (%/n)**	**PM/ICD (%/n)**	**Only cath.**	**Native (%)**	**Comorbidity (%)**	**Lung disease (%)**
Overall	186 (83)	31.9 ± 10.4	172.1 ± 9.1	70.1 ± 12.7	23.6 ± 3.6	156 (84%)	148 (80%)	27 (15%)	21 (11%)	10 (5%)	17 (9%)	91 (49%)	16 (9%)
LHO	31 (9)	27.8 ± 7.6	173.5 ± 9.4	72.6 ± 14.5	24.0 ± 4.3	19 (61%)	11 (36%)	10 (32%)	3 (10%)	2 (7%)	9 (29%)	12 (39%)	2 (7%)
RHO	59 (24)	30.4 ± 10.7	173.1 ± 9.0	70.9 ± 12.1	23.6 ± 3.6	56 (95%)	56 (95%)	8 (14%)	4 (7%)	2 (3%)	0	25 (42%)	6 (10%)
EA	18 (12)	35.2 ± 13.5	170.9 ± 9.4	71.6 ± 13.2	24.4 ± 3.5	12 (67%)	12 (67%)	1 (6%)	2 (11%)	0	6 (33%)	9 (50%)	0
Isolated shunt	14 (9)	32.7 ± 16.0	169.0 ± 8.0	65.2 ± 9.8	22.8 ± 2.1	7 (50%)	7 (50%)	0	0	5 (36%)	1 (7%)	5 (36%)	1 (7%)
TGA switch	14 (4)	26.6 ± 2.9	175.7 ± 9.4	71.3 ± 10.4	23.1 ± 2.6	14 (100%)	14 (100%)	0	1 (7%)	0	0	6 (43%)	1 (7%)
TGA other**	30 (12)	34.7 ± 7.7	172.3 ± 8.5	67.9 ± 12.0	22.8 ± 3.0	29 (97%)	26 (97%)	4 (13%)	7 (23%)	1 (3%)	0	18 (60%)	1 (3%)
Fontan	16 (11)	31.4 ± 8.2	166.4 ± 8.5	68.1 ± 14.8	24.6 ± 4.8	16 (100%)	16 (100%)	4 (25%)	4 (25%)	0	0	12 (72%)	2 (13%)
Cyanosis	4 (2)	43.1 ± 6.8	170.3 ± 11.2	71.6 ± 19.6	24.4 ± 4.0	3 (75%)	3 (75%)	0	0	0	1 (25%)	4 (100%)	3 (75%)

Children

CHD group	n (girls)	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)	Surgery (%/n)	Ster-notomy (%/n)	Thora-cotomy (%/n)	PM (%/n)	Only cath.	Native (%)	Comor-bidity (%)	Lung disease (%)
Overall	58 (16)	14.0 ± 2.5	161.9 ± 14.0	53.1 ± 15.4	19.8 ± 3.4	45 (78%)	45 (78%)	3 (5%)	1 (2%)	5 (9%)	7 (12%)	14 (24%)	2 (3%)
LHO	4 (2)	14.4 ± 1.4	168.3 ± 8.0	62.0 ± 12 8	21.9 ± 4.5	1 (25%)	1 (25%)	0	0	1 (25%)	2 (50%)	0	0
RHO	28 (2)	14.4 ± 2.5	161.4 ± 13.7	52.1 ± 13.8	19.6 ± 3.2	27 (96%)	27 (96%)	2	0	1 (4%)	0	6 (21%)	1 (4%)
EA	5 (2)	12.5 ± 2.1	161.6 ± 13.5	52.2 ± 17.1	19.5 ± 4.0	2 (40%)	2 (40%)	0	0	0	3 (60%)	0	0
Isolated Shunt	11 (5)	13.7 ± 2.9	161.7 ± 18.2	55.0 ± 21.0	20.2 ± 4.1	5 (46%)	5 (46%)	0	1 (9%)	3 (27%)	2 (18%)	4 (36%)	1 (9%)
TGA switch	5 (0)	12.7 ± 2.4	155.4 ± 11.8	45.2 ± 7.6	18.7 ± 1.8	5 (100%)	5 (100%)	0	0	0	0	0	0
TCPC	5 (1)	14.5 ± 2.6	166.4 ± 14.4	56.0 ± 17.8	19.8 ± 4.1	5 (100%)	5 (100%)	1 (20%)	0	0	0	4 (80%)	0
Cyanosis	0	-	-	-	-	-	-	-	-	-	-	-	-

** Senning/Mustard/Rastelli procedure and CCTGA

CHD: congenital heart defect, LHO: left heart obstruction, RHO: right heart obstruction, EA: Ebstein's Anomaly, TGA: transposition of the great arteries, TCPC: total cavopulmonary connection, BMI: body mass index, PM: pacemaker, ICD: implantable cardioverter defibrillator, cath.: catheter

3.4 Statistical analyses

All analyses were performed with SPSS (version 28.0, IBM Corporation, Armonk, NY, USA).

Methodology

Data are presented in mean ± standard deviation (SD). Due to better comparisons, even in those with low number of subjects, mean ± SD was used. Data are provided as raw values or z-scores, if possible. If necessary, percentage were used. For statistical analyses, correlations (Pearson and Spearman), Student's T-tests and Mann-Whitney-U tests were performed, where appropriate. A two-sided p-value of <0.050 was considered significant.

References and normal values

For reference values, latest Global Lung Initiative data were used (GLI-2021) [56,58]. The cut-off for normal spirometry results is a z-score ≥ -1.645 in FVC, FEV1 and its ratio. Z-scores are adjusted for sex, age, and height as well as race (in this cohort only Caucasian were examined due to lack of reference values).
If FVC and FEV1 were below this, a PRISm pattern in spirometry was defined. A ratio in FEV1/FVC with $z < -1.645$ was defined as obstructive pattern. Results with only FVC or FEV1 < -1.645 were named "undefined pattern" since no reference for naming was given.
If a PRISm pattern was seen, further statistical calculations were performed with the results of the body plethysmography, as mentioned in Table 5, following Figure 13. Any suspicious results were re-evaluated with the physician's letter and if the examination was abnormal, patients were advised to see a pulmonary specialist. Results should be sent to the German Heart Center of Munich to ensure a good clinical practice.

Table 5: Evaluation strategy in spirometry and body plethysmography results (modified from Stanojevic et al., Table 5 and Table 7 [56])

Spirometry				
	FVC	FEV1	FEV1/FVC	Comments
PRISm	↓	↓	normal/↑	TLC needed to confirm restriction (TLC_z< -1.645)
obstructive pattern	normal	normal/↓	↓	
mixed disorder	↓	↓	↓	
non-specific pattern	↓	↓	normal	normal TLC → additional tests needed (e.g. bronchodilator response)
muscle weakness/suboptimal effort	↓	↓	normal	lack of sharp PEF

Body plethysmography						
	FRC	RV	TLC	FRC/TLC	RV/TLC	Comments
large lungs	↑	↑	↑	normal	normal	normal above upper limit of normal
obstruction	normal/↑	normal/↑	↑	normal/↑	↑	hyperinflation if FRC/TLC and RV/TLC are elevated
simple restriction	↓	↓	↓	normal	normal	
complex restriction	↓	↓	normal/↑	normal	↑	e.g. due to small airway disease with gas trapping and obesity
mixed disorder	↓	normal/↓	normal/↑	normal/↑	normal/↑	typically, with FEV1/FVC < -1.645

PRISm: preserved ration impaired spirometry, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, PEF: peak expiratory flow, e.g.: exempli gratia (for example), FRC: functional residual volume, RV: residual volume, TLC: total lung capacity, ↑ with z-score > 2.0, ↓ with z-score < -1.645

4 Results

4.1 Retrospective analyses

Results of spirometry in retrospectively analyzed data are shown in Table 6. As in literature [31], also our database proves that approximately half of the patients show abnormal of at least distinctive spirometry results with a wide range within the different heart defects (reaching from 38-80% of abnormal results). These results were the baseline of the prospective study.

The next step was to find out, whether these patients have an abnormal lung function. This can only be tested with body plethysmography and was conducted as a prospective study.

Table 6: Results in spirometry in retrospectively analysed data

CHD category	n (female//children)	Normal results (n/%)	PRISm* (n/%)	Obstructive pattern** (n/%)	Mixed disorder (n/%)	*Only FVC_z <-1.645	*Only FEV1_z <-1.645
Overall	4,023 (1,824//824)	1,966 (49%)	1,242 (31%)	201 (5%)	211 (5%)	176 (4)	227 (6%)
Left heart obstruction	883 (298//199)	514 (58%)	175 (20%)	53 (6%)	34 (4%)	48 (5%)	60 (7%)
Right heart obstruction	1,019 (486//215)	432 (42%)	384 (38%)	49 (5%)	64 (6%)	47 (5%)	43 (4%)
Ebstein's anomaly	271 (162//41)	188 (70%)	47 (17%)	9 (3%)	6 (2%)	4 (2%)	17 (6%)
Isolated shunt	743 (435//149)	408 (55%)	190 (26%)	49 (7%)	32 (4%)	20 (3%)	44 (6%)
TGA after arterial switch	190 (54//75)	102 (52%)	45 (24%)	10 (5%)	4 (2%)	16 (8%)	13 (7%)
TGA (Senning, CCTGA and other)	444 (178//27)	212 (48%)	153 (35%)	19 (4%)	16 (4%)	25 (6%)	19 (4%)
Fontan circulation	298 (125//100)	84 (28%)	153 (51%)	8 (3%)	16 (5%)	15 (5%)	22 (7%)
Cyanotic	175 (86//18)	27 (15%)	95 (54%)	4 (2%)	39 (22%)	1 (1%)	9 (5%)

CHD: congenital heart defect, TGA: transposition of the great arteries, CCTGA: congenitally corrected transposition of the great arteries; PRISm: preserved ratio impaired spirometry, *FEV1 and FVC z-scores< -1.645 with normal FEV1/FVC, **FEV1/FVC z-score< -1.645; Reference for normal data from Hall et al. (GLI-2021) [58]
*: undefined pattern

4.2 Prospective analyses

4.2.1 CHD patients

A total of 244 patients with 99 females were included (27.6 ± 11.9 years n=58 with age < 18 years). Overall, 7% (18) had a lung-affecting disease. One hundred-five patients (43%) had co-morbidities not affecting the lung directly (e.g. former borreliosis, iron deficiency, arterial hypertension …) (Table 4). Six CHD patients were (former) smokers, five suffered from asthma (one exercise-induced and four allergic), three had diaphragmatic problems (two paresis and one hernia). Four patients had scoliosis, two were diagnosed with pulmonary arterial hypertonia. Further four patients had either vocal cord paresis, cerebral paresis, under continuous positive airway pressure therapy or long-stretch tracheal stenosis.

Table 7 shows raw data of the study results.

Table 7: Results in spirometry and body plethysmography in CHD patients

Adults								
CHD	**FVC_z**	**FEV1_z**	**FEV1/FVC_z**	**FEF25-75_z**	**TLC_z**	**FRC_z**	**RV_z**	**RV/TLC_z**
Overall (n=186)	-1.08 ± 1.16	-1.20 ± 1.23	-0.29 ± 1.04	-0.73 ± 1.18	-0.58 ± 1.16	-0.47 ± 1.14	0.59 ± 0.82	1.13 ± 0.92
LHO (n=31)	-0.69 ± 1.10	-0.93 ± 1.33	-0.52 ± 1.16	-0.86 ± 1.26	-0.11 ± 1.00	-0.06 ± 0.91	0.82 ± 0.64	1.18 ± 0.86
RHO (n=59)	-1.52 ± 1.12	-1.65 ± 1.04	-0.30 ± 0.95	0.99 ± 1.06	-0.98 ± 1.15	-0.86 ± 1.11	0.49 ± 0.89	1.20 ± 1.00
EA (n=18)	-0.69 ± 0.81	-0.85 ± 1.25	-0.32 ± 1.19	0.57 ± 1.38	-0.22 ± 0.82	0.07 ± 0.84	0.71 ± 0.67	1.08 ± 0.71
Isolated shunt (n=14)	-0.06 ± 0.75	-0.44 ± 0.97	-0.66 ± 0.0.79	-0.75 ± 0.90	0.46 ± 1.12	0.03 ± 1.27	0.96 ± 0.77	1.03 ± 0.62
TGA switch (n=14)	-1.17 ± 1.29	-1.05 ± 1.36	0.13 ± 1.10	-0.26 ± 1.27	-0.47 ± 1.35	-0.21 ± 1.04	0.79 ± 0.70	1.32 ± 0.73
TGA other** (n=30)	-0.85 ± 1.03	-0.77 ± 0.98	0.12 ± 0.90	-0.19 ± 1.06	-0.57 ± 0.97	-0.29 ± 0.98	0.53 ± 0.58	1.01 ± 0.58
Fontan (n=16)	-1.40 ± 0.86	-1.47 ± 1.02	-0.23 ± 0.93	-0.80 ± 1.05	-1.19 ± 1.00	-1.38 ± 1.39	-0.06 ± 1.18	0.56 ± 1.29
Cyanosis (n=4)	-3.18 ± 0.90	-3.65 ± 0.98	-1.75 ± 1.40	-1.95 ± 1.66	-2.03 ± 0.65	-0.90 ± 0.97	0.92 ± 0.60	2.78 ± 1.20

Children								
CHD	**FVC_z**	**FEV1_z**	**FEV1/FVC_z**	**FEF25-75_z**	**TLC_z**	**FRC_z**	**RV_z**	**RV/TLC_z**
Overall (n=58)	-1.03 ± 1.28	-0.98 ± 1.24	0.04 ± 1.03	-0.66 ± 0.98	-0.40 ± 1.12	-0.93 ± 1.17	0.27 ± 0.69	0.67 ± 0.73
LHO (n=4)	-0.59 ± 1.39	-0.46 ± 1.17	0.24 ± 1.22	0.23 ± 1.12	-0.15 ± 0.6	-0.85 ± 0.92	0.26 ± 0.39	0.50 ± 0.70
RHO (n=28)	-1.73 ± 0.86	-1.60 ± 0.80	0.18 ± 1.04	0.99 ± 0.80	-0.96 ± 0.87	-1.21 ± 0.95	0.20 ± 0.70	0.80 ± 0.70
EA (n=5)	0.15 ± 1.00	-0.03 ± 1.58	-0.39 ± 1.18	-0.68 ± 0.13	0.67 ± 1.03	-0.00 ± 1.22	0.75 ± 0.64	0.81 ± 0.53
Isolated shunt (n=11)	-0.46 ± 1.30	-0.59 ± 1.33	-0.29 ± 1.10	-0.65 ± 1.17	-0.36 ± 2.03	-1.07 ± 1.35	0.12 ± 0.64	0.34 ± 0.76
TGA switch (n=5)	0.41 ± 1.05	0.47 ± 0.96	0.06 ± 1.09	0.11 ±0.62	0.83 ± 0.94	0.58 ±0.63	0.63 ± 0.59	0.81 ± 0.97
TCPC (n=5)	-1.35 ± 1.25	-1.18 ± 1.25	0.21 ± 0.57	-0.29 ± 0.90	-0.40 ± 0.86	-1.03 ± 1.61	0.29 ± 0.95	0.71 ± 1.22
Cyanosis	-	-	-		-			-

** Senning/Mustard/Rastelli procedure and CCTGA

CHD: congenital heart defect, LHO: left heart obstruction, RHO: right heart obstruction, EA: Ebstein's Anomaly, TGA: transposition of the great arteries, CCTGA: congenitally corrected transposition of the great arteries, TCPC: total cavopulmonary connection

Spirometry

From all patients, 66% had normal results (in adults 60%, in children 55%).
However, in adults, seventy-five patients had remarkable results – most of them (n=39, 68% with impaired spirometry) showed a PRISm. Further ten (5%) had obstructive impairments and eight (4%) had both. In 18 patients, an undefined pattern was diagnosed with either low FVC_z or low FEV1_z.
In children, results are similar: 26 children have noteworthy results with 13 (77% with impaired spirometry) PRISm, three (5%) obstructive and one (2%) combined patterns and further nine an undefined one. Table 8 shows the origin CHD of these patients.

Table 8: Classification of results in spirometry

Adults					
CHD	***PRISm**	****obstructive pattern**	**mixed disorder**	*****only FVC_z <-1.645**	*****only FEV1_z <-1.645**
Overall (n=186)	39 (21%)	10 (5%)	8 (4%)	4 (2%)	14 (8%)
LHO (n=31)	2		3		3
RHO (n=59)	19	5	1	1	4
EA (n=18)	2	2	1	1	
Isolated shunt (n=14)	1	2			
TGA switch (n=14)	3	1		1	2
TGA other£ (n=30)	6			1	3
Fontan (n=16)	4		1		2
Cyanosis (n=4)	2		2		
Children					
Overall (n=58)	13 (22%)	3 (5%)	1 (2%)	6 (10%)	3 (5%)
LHO (n=4)				1	
RHO (n=28)	11		1	4	3
EA (n=5)		1			
Isolated shunt (n=11)	1	2		1	
TGA switch (n=5)					
TCPC (n=5)	1				
Cyanosis					

*: FVC_z and FEV1_z < -1.645 and FEV1/FVC_z normal
**: normal FVC_z and FEV1_z and FEV1/FVC_z < -1.645
***: undefined pattern
£: Senning/Mustard/Rastelli procedure and CCTGA
CHD: congenital heart defect, PRISm: preserved ratio impaired spirometry, LHO: left heart obstruction, RHO: right heart obstruction, EA: Ebstein's Anomaly, TGA: transposition of the great arteries, CCTGA: congenitally corrected transposition of the great arteries, TCPC: total cavopulmonary connection

Body plethysmography

Table 5 and Figure 13 show how in the present study results were interpreted, following the latest guidelines [56].

Having a closer look on the formerly defined patients with PRISm (Table 8), these patients (n=52) show the following results: thirty of 52 patients (12% overall) have a small lung with a TLC_z < -1.645. The other 22 patients with TLC_z ≥ -1.645 can only be defined as a "non-specific pattern" [62].

This group with a small lung includes 25 adults (13.4%, mean age 32.5 ± 10.8 years, 8 females) and 5 children (8.6%, mean age 14.1 ± 2.2 years, 2 girls).

Their underlying CHDs were: 1 LHO (3%), 18 RHO (60%), 1 EA (3%), 2 isolated shunts (7%), 1 TGA switch (3%), 4 TGA other (13%), 2 with a Fontan circulation (7%) and 1 with a cyanosis.

Since the CHD distribution is uneven, the percentage in the whole cohort is:

1/35 in LHO (3%), 18/87 in RHO (21%), 1/23 in EA (4%), 2/25 in isolated shunts (8%), 1/19 in TGA switch (5%), 4/30 in TGA other (13%), 2/21 in Fontan circulation (10%) and 1/4 in cyanotic patients (25%).

One patient had a simple restriction (small lung: z-score in FVC, FEV1 and TLC < -1.645) and seven a complex restriction (with additional RV_z > -1.645 and RV/TLC_z > -1.645). However, one of these supposed complex restrictions originally showed "muscle weakness" with a lack of sharp peak expiratory flow (Figure 15, patient with TGA after switch), which should have already been noticed during spirometry.

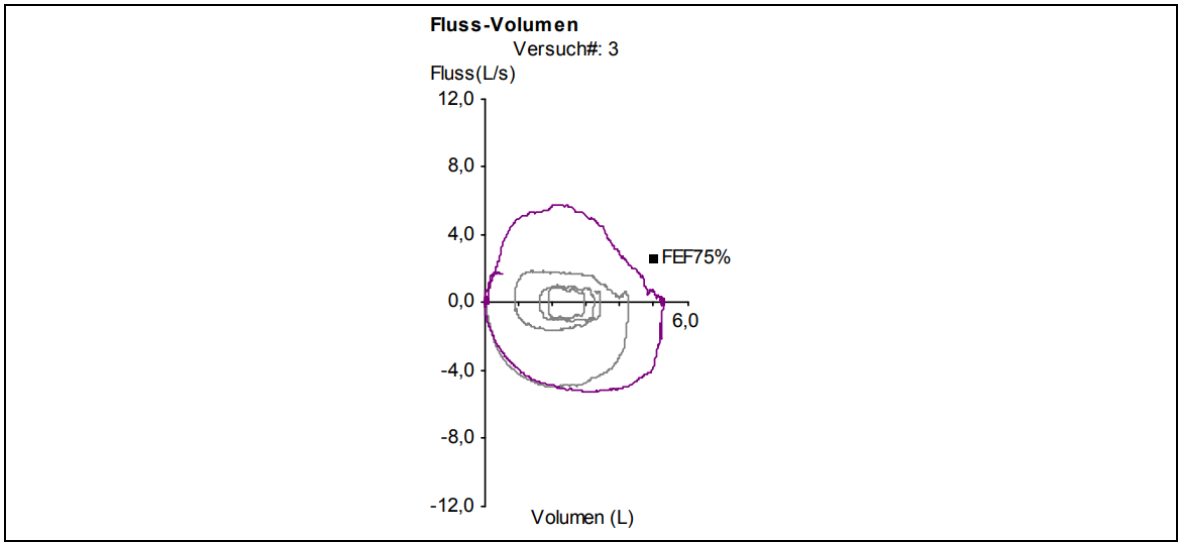

Figure 15: Probable muscle weakness in a supposed preserved ratio impaired spirometry

L/s: litre per second, FEF: forced expiratory flow

The volumes in the other six patients were already abnormal in spirometry: four showed a PRISm pattern and two a mixed one. In three patients, a co-existing lung disease was previously defined: allergic asthma, severe kyphoscoliosis, and former pneumothorax. However, only in one patient results are confirmed by reduced functional residual capacity (FRC_z < -1.645, patient with kyphoscoliosis).

Furthermore, following the current guidelines from Stanojevic et al., only patients showing an obstructive pattern in spirometry can be defined as "obstructive" [56]. In this study sample, 13 patients (three children) showed obstructive results in spirometry (FEV1/FVC_z < -1.645). Further examinations should be a bronchodilator or allergic tests to examine possible treatments.

Comparisons between subgroups of interventions

Overall, small lungs seem more likely to affect patients with RHO and surgical intervention. In patients with small lungs, one had not undergone any intervention or surgery at the testing time, categorized in cyanosis. However, overall, the number of surgical interventions reaches from one to six. Mean age at first surgical repair was 2.7 ± 4.0. All patients who underwent surgical repair had a sternotomy, eight additionally a thoracotomy. Three had a co-morbidity affecting the lung volumes (diaphragmatic paralysis, pulmonary arterial hypertonia, severe scoliosis). Eighteen had a co-morbidity in general (e.g. spastic hemiparesis, genetics, and cerebral disorders). Six patients had a pacemaker/ICD with one to seven interventions (change or re-surgery due to infect).

Comparing these patients (n=30) with those who have no conspicuous results (normal lungs, n=160), data show that they have had more surgeries (2.5 ± 1.3 vs. 1.2 ± 1.0, p<0.001, 95%CI: 0.80 – 1.83). However, age at first surgery did not differ significantly (2.7 ± 4.1 vs. 4.0 ± 8.5, p=0.441, 95%CI: -4.46 – 1.95).

For analyzing interventional groups, data from undefined pattern were excluded from analysis (n=27). Values from those with surgical repair and native patients (including those who underwent a catheter only), as well as thoracotomy were compared against sternotomy.

Results show that a noteworthy lung function appears more often in patients with surgical intervention (Table 9). However, also in patients with no surgical intervention it appears that the lung function volumes are at least reduced.

Comparing sternotomy and thoracotomy, results are similar. Only small lungs are more often diagnosed in patients who underwent a thoracotomy (27% vs. 12%, p=0.049).

As a next step, correlations between number of surgery and outcomes were calculated. The number of surgeries significantly influences FVC_z (r=-0.477, p<0.001), FEV1_z (r=-0.480,

p<0.001), and TLC_z (r=-0.426, p<0.001). However, number of surgeries due to pacemaker/ICD do not influence any results. Furthermore, age at first surgical intervention (independently if sternotomy or thoracotomy) does not influence pulmonary outcome (Table 9).

Table 9: Results in comparing different circumstances in patients

Group	Surgical repair (n=201)	Native*** (n=43)	p-value¥	Sternotomy (n=171)	Thoracotomy (n=30)	p-value¥
normal lung pattern	123 (60%)	37 (86%)	**0.001§**	109 (64%)	14 (47%)	0.103§
PRISm	50	2	**0.002§**	38	12	0.064§
obstructive pattern	10	3	0.706§	9	1	1.000§
mixed disorder	9	0	0.367§	6	3	0.135§
small lung*	29	1	**0.037§**	21	8	**0.049§**
non-specific pattern**	21	1	0.139§	17	4	0.527§

***including those with no intervention and those with catheter only
¥: significant with p<0.500, highlighted bold
§: two-tailed Fisher's exact test
FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, TLC: total lung capacity, ICD: implantable cardioverter defibrillator; PRISm: preserved ratio in spirometry *PRISm and TLC_z < -1.645, **PRISm and TLC_z ≥ -1.645

4.2.2 References (control cohort) and comparisons

The reference cohort consists of 33 subjects with 21 females (30.7 ± 11.3 years, n=3 with age < 18 years).

Two subjects suffer from exercise-induced or allergic asthma, three were (former) smokers. None had any severe or treatment-needed lung disease. Co-morbidities were not investigated.

Their results in spirometry show in FVC_z -0.15 ± 0.83, FEV1_z -0.41 ± 0.81, FEV1/FVC_z -0.51 ± 0.81 and FEF25-75_z -0.51 ± 0.99. Body plethysmography shows in FRC_z -0.18 ± 0.96, RV_z 0.55 ± 0.68, TLC_z 0.06 ± 0.86 and RV/TLC_z 0.72 ± 0.69, representing roughly normal values in the examined cohort.

Only three subjects had an abnormal lung function: two showed an obstructive pattern in spirometry (one with asthma) and one had a preserved ratio impaired spirometry (PRISm).

Afterwards, all patients with a CHD (n=244) were compared to data from the reference cohort (n=33) and show significant reduced values in FVC_z (-1.07 ± 1.19 vs. -0.15 ± 0.83, p<0.001, 95%CI: -1.343 – -0.503), FEV1_z (-1.15 ± 1.24 vs. -0.41 ± 0.96, p=0.001, 95%CI: -1.177 – -0.297), and TLC_z (-0.55 ± 1.16 vs. 0.06 ± 0.84, p=0.004, 95%CI: -1.02 – -0.20).

5 Discussion

An impaired lung function increases the risk of mortality significantly [63-67]. In patients with congenital heart defects, follow-up examinations often overlook the fact that the lungs may also be affected due to the heart defect itself [11,68,69], due to interventions [70] or due to lack of exercise capacity [10,12,71-73], and therefore influence survival [74-76]. Thus, lung volume may be reduced, the function may be impaired or diseases of the pulmonary vessels may be present or occur in the future [77].

The present study shows that up to one-third of the patients show abnormalities in the results of spirometry. Undefined patterns with only one parameter decreased (FVC_z or FEV1_z but not both or its ratio) cannot be interpreted since references do not define them. However, if only the FVC_z is decreased, it is more likely that the test was performed insufficiently. A re-test should be examined. In patients with only the FEV1_z below -1.645, a slight obstruction may be diagnosed. These patients should undergo more frequent re-tests, to see, whether an obstructive pattern occurs. In these investigated patients in this study, FEF25-FEF75_z is simultaneously decreased, which can be a first hint on future obstruction, however a diagnosis cannot be made [78]. Nonetheless, a possible disease value can only be confirmed by means of further diagnostics - including body plethysmography.

Patients with right heart obstruction (in both, children, and adults) show the lowest results in FVC_z and FEV1_z as well as in TLC_z, showing mostly a restriction. This may be due to the direct effect of reduced blood circulation in the lungs as previously described in a lung function training study [79].

A disturbed blood circulation into the lungs may affect the results in adult patients with TGA after Senning/Mustard due to systemic right ventricle after surgical palliation [80]. Since nowadays, surgical repair is performed differently, no children with this surgery were investigated in the present study. In those patients, who underwent arterial switch, results show no noteworthy results. However, in adults with TGA switch, lung volumes are sometimes conspicuous and need to undergo further examinations.

Patients with Fontan circulation (or TCPC in children, and young adults) show slightly higher, but still results often below the lower limit of normal (LLN). This may have similar reasons as it does in RHO and TGA patients. Over the decades, results remain similar. However, more specific studies comparing the underlying CHD in Fontan or TCPC should be performed (e.g. hyperplastic ventricles against atresia of the valves).

Patients with EA show mainly normal results. This is surprising since 67% of the adults and 50% of the children underwent a surgical repair. However, since the patient's age at surgical intervention, variates in this CHD category, a summarizing result is not easy. Lung volumes seem not to be affected – which is encouraging news for these patients. Additionally, it should motivate patients to prevent their lung function from later onset impairments due to lifestyle.

Patients with isolated shunts (with or without intervention) should have normal results in lung function since an effect on the lung should not apply. In sum, they have results below the median in z-score but show best results in adult CHD patients. A recently submitted study from Bessar et al. has proven this [81]. However, a certain number of abnormal lung functions can also be expected in the general population. The patients who come to Deutsches Herzzentrum München are also usually no small, "simple" shunts, but more complex CHDs. This may lead to a selection bias and result in more abnormal results.

Cyanotic patients (only in the group of adults) show all impaired lung function: two with PRISm and two with mixed disorder. Three of four have a previously diagnosed lung comorbidity. However, independently from individual constitution in these patients, a lung function test should be part of routine follow-up since any decreases in volumes may affect their daily life. Since the present study, the number of patients is significantly underrepresented, future investigations should be performed.

The basic question regarding lung volumes in patients with CHD is, where the PRISm flow-volume-curve originates. Is it a small lung (small FVC, FEV1 and TLC) or is it hyperinflation (small FVC, FEV1 and normal TLC with increased RV/TLC). The new guidelines show that a "simple" diagnosis with normal lung size is not (any longer) easily possible despite limited spirometry [56]. Whereas previously it was referred to as hyperinflation, nowadays it is referred to as a "non-specific pattern". This change in the guidelines also shows that lung function research has not yet been exhausted in this respect.

What does this mean for the patient population of children, adolescents, and adults with congenital heart defect? Every patient should have a pulmonary function test (and cardiopulmonary exercise test) as part of the routine examination. This should be done as early as possible, so that changes in the course of the results can be documented and interventions can be made as early as possible. In patients with cystic fibrosis, for example, - a severe chronic, genetic lung disease - measures (medication, etc.) are already taken in the case of small changes to counteract a deterioration [82].

What might be the reasons? Is it possible to prevent patients from lung morbidities? That is a new or at least more likely new research field. The guidelines show, that after surgical intervention (no matter if thoracotomy, sternotomy, or catheter), lungs need to be trained [83,84]. Latest studies have shown, that isolated lung training (inspiratory volume-oriented breathing training or inspiratory muscle training) improves patients' exercise capacity and lung function [79] – or at least there is no deterioration seen [24,26,85].

However, long lasting late onset injuries may not affect patient's lives at first, but over time affect them in terms of health-related quality of life, exercise capacity etc.

Some studies have already shown that there is a correlation between functional outcome and health-related quality of life. Abassi et al. have shown a correlation between FVC, FEV1 and quality of life scores in children with CHD [69]. Furthermore, Callegari et al. show that FEV1 and quality of life terms in patients after Fontan palliation are associated [29].

However, (health-related) quality of life is discussed contradictory in literature. Some studies show low [29,86] and others normal or even better results compared to peers [15,17]. It is therefore indispensable to assess functional outcome and quality of life [20].

There are studies that show that training in lung function and exercise capacity increases quality of life in severely sick patients. Mereles et al. investigated patients with chronic pulmonary hypertension and proved that a 15-weeks exercise and respiratory training improves both – functional outcome and quality of life [87]. Other studies are needed to help patients to start, remain and continue with an active lifestyle - life-long training is advisable and recommended.

6 Conclusions

More than one third of the evaluated subjects show impaired results in spirometry – in adults more likely than in children, and in right heart obstructive CHDs more likely than in left heart obstructive CHDs. However, in patients with noteworthy results in spirometry, a body plethysmography is recommended and should be performed to exclude a possible severe lung function impairment. Regular controls are needed to re-evaluate possible changes. Since surgical interventions influence the outcome, lung function training is recommended and should be used in all patients. Education regarding the importance of good lung function - and its relationship to exercise capacity - must be made clear to patients early on.

7 Limitations

The collection of data in this study started initially in February 2017. Unfortunately, all data collected between 02/2017 and 04/2018 could not be included due to a technical issue (calibration). About 100 tests had to be excluded. Furthermore, between 2018 and 2021 several technical issues occurred leading to an exclusion of further 199 tests. This leads to an additional selection bias. During the pandemic, from 03/2020-07/2020 no data could be collected. Additionally, afterwards only patients with a negative COVID-19 test were allowed to perform a body plethysmography. Therefore, this also leads to a selection bias and may have prevented a (significant) proportion of abnormal lung functions.

The pandemic in recent years has shown how quickly a disease can attack the lung tissue, damaging and in some cases irreversibly destroying it [88,89]. COVID-19 disease can have many severe effects on patients. Many complain of shortness of breath, impaired performance, or general fatigue even weeks after the disease. Some of the patients examined here were also confirmed to be infected with COVID-19 (recovered at the testing time). As a rule, they had a mild course (from no symptoms to fever/flu). All patients examined here wanted to know after the lung function measurement whether and how the lung volumes had changed. Fortunately, we were able to show a pre-test before the pandemic for each of them. Without having analysed the data separately (due to the small number of cases), it can be said that the results remained the same. Further studies could prove this in a larger patient population in our clinic - as there are probably sufficient comparative tests here.

Furthermore, the small number of controls including fewer female in the CHD group also may influence results (though data are standardized due to z-score).

Since two people examined the patients, there may have been a bias in the selection, consent, and performance of the tests. Similar limitations can be applied to the evaluation of collected data.

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Appendix

Patient's informed consent

Klinik für Kinderkardiologie und
angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
– Klinik an der Technischen Universität München –

Prof. Dr. med. P. Ewert - Lazarettstraße 36 - 80636 München

PATIENTENINFORMATION

zur Studie

Lungenfunktion bei Patienten mit angeborenem Herzfehler

Sehr geehrte Patientin, Sehr geehrter Patient,

man kann sagen, dass Lunge und Herz eine Einheit bilden. Zum einen muss alles, was vom (rechten) Herz gepumpt wird, durch die Lungen durch, zweitens teilen sich Lungen und Herz den begrenzten Brustkorb. Während das Herz im Rahmen Ihrer Untersuchungen routinemäßig kontrolliert wird, wollen wir im Rahmen einer Studie auch Ihre Lungenfunktion (Spirometrie, Bodyplethysmographie und Diffusionskapazität) testen.

Zweck der Studie

Im Rahmen dieser Studie soll erstmals beschrieben, ob Patienten mit angeborenem Herzfehler eine normale Lungenfunktion haben, und wie die Lungenfunktion vom Herzfehler beeinflusst wird. Ferner untersuchen wir Zusammenhänge mit der körperlichen Leistungsfähigkeit und Lebensqualität.

Ablauf der Studie:

Die Messung der Lungenfunktion ist eine zusätzliche Untersuchung zu Ihren normalen Untersuchungen im Rahmen Ihres Ambulanztermins und dauert ca. 20-40 Minuten.

Risiken und Nebenwirkungen (ggf. auch Nutzen für den Patienten)

Es werden nur etablierte Untersuchungen angewandt, die in unserer Ambulanz regelmäßig stattfinden. Aufgrund eines möglicherweise ungewohnt tiefen und langen Atmens beim Test kann es kurz zu Schwindel oder Benommenheit kommen. Nichts davon ist gefährlich. Die Ergebnisse werden direkt in Anschluss mit Ihnen besprochen.

Vertraulichkeit

Die ärztliche Schweigepflicht bleibt gewahrt. Alle Daten werden ausschließlich pseudonymisiert ausgewertet und veröffentlicht. Die Bestimmungen des Datenschutzes werden eingehalten.

Freiwilligkeit

Die Teilnahme an der Studie ist freiwillig. Sie können die Zusage jederzeit ohne Angabe von Gründen und ohne, dass Ihnen Nachteile entstehen, zurückziehen.

Vielen Dank für die Zeit, die Sie sich genommen haben, um diese Information zu lesen.

EU-Datenschutz-Grundverordnung

Gemäß der europäischen Datenschutzgrundverordnung (DSGVO) haben Sie u.a. das Recht auf:

- Auskunft über die Verarbeitung Ihrer persönlichen Daten
- Berichtigung oder Löschung Ihrer persönlichen Daten
- Widerruf Ihrer gegebenen Einwilligung mit Wirkung auf die Zukunft
- Beschwerde bei der Datenschutzaufsichtsbehörde

Postanschrift: Lazarettstraße 36, 80636 München, Telefon (089) 1218-0, Telefax (089) 1218-3013, e-Mail: Prof.Ewert@dhm.mhn.de

U 1 Maillingerstraße 20 21 Lothstraße

Sollten Sie Fragen zur Datenverarbeitung und zur Einhaltung datenschutzrechtlicher Anforderungen haben, können Sie sich an den Datenschutzbeauftragten (DSB) Ihrer Klinik oder das zentrale Datenmanagement wenden:

Datenschutzbeauftragter Ihrer Klinik	**Zentrales Datenmanagement**
Deutsches Herzzentrum München - Klinik an der Technischen Universität München - Lazarettstraße 36 80636 München Telefon: 089/1218-0 E-Mail: Datenschutzbeauftragter@dhm.mhn.de	Deutsches Herzzentrum München - Klinik für angeborene Herzfehler und Kinderkardiologie - Lazarettstraße 36 80636 München Telefon: 089/1218-0 E-Mail: StudienzentrumKK@dhm.mhn.de

Sollten Sie sich bei der Aufsichtsbehörde beschweren wollen, können Sie sich an den Landesdatenschutzbeauftragten wenden:

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Homepage: http://www.datenschutz-bayern.de

Darüber hinaus können Sie sich weiterhin auch an Ihren Prüfarzt wenden:

Prüfarzt
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Deutsches Herzzentrum München
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Prof. Dr. med. Alfred Hager
(Studienleitung, Leiter Ambulanz DHM)

Seite **2** von **2**

Klinik für Kinderkardiologie und
angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
– Klinik an der Technischen Universität München –

Prof. Dr. med. P. Ewert · Lazarettstraße 36 · 80636 München

ELTERNINFORMATION

zur Studie

Lungenfunktion bei Patienten mit angeborenem Herzfehler

Liebe Eltern,

man kann sagen, dass Lunge und Herz eine Einheit bilden. Zum einen muss alles, was vom (rechten) Herz gepumpt wird, durch die Lungen durch, zweitens teilen sich Lungen und Herz den begrenzten Brustkorb. Während das Herz im Rahmen der Untersuchungen Ihres Kindes routinemäßig kontrolliert wird, wollen wir im Rahmen einer Studie auch die Lungenfunktion Ihres Kindes (Spirometrie, Bodyplethysmographie und Diffusionskapazität) testen.

Zweck der Studie

Im Rahmen dieser Studie soll erstmals beschrieben, ob Patienten mit angeborenem Herzfehler eine normale Lungenfunktion haben, und wie die Lungenfunktion vom Herzfehler beeinflusst wird. Ferner untersuchen wir Zusammenhänge mit der körperlichen Leistungsfähigkeit und Lebensqualität.

Ablauf der Studie:

Die Messung der Lungenfunktion ist eine zusätzliche Untersuchung zu den normalen Untersuchungen Ihres Kindes im Rahmen des Ambulanztermins und dauert ca. 20-40 Minuten.

Risiken und Nebenwirkungen (ggf. auch Nutzen für den Patienten)

Es werden nur etablierte Untersuchungen angewandt, die in unserer Ambulanz regelmäßig stattfinden. Aufgrund eines möglicherweise ungewohnt tiefen und langen Atmens beim Test kann es kurz zu Schwindel oder Benommenheit ihres Kindes kommen. Nichts davon ist gefährlich. Die Ergebnisse werden direkt in Anschluss mit Ihnen und Ihrem Kind besprochen.

Vertraulichkeit

Die ärztliche Schweigepflicht bleibt gewahrt. Alle Daten werden ausschließlich pseudonymisiert ausgewertet und veröffentlicht. Die Bestimmungen des Datenschutzes werden eingehalten.

Freiwilligkeit

Die Teilnahme an der Studie ist freiwillig. Sie und/oder Ihr Kind können die Zusage jederzeit ohne Angabe von Gründen und ohne, dass Ihnen oder Ihrem Kind Nachteile entstehen, zurückziehen.

Vielen Dank für die Zeit, die Sie sich genommen haben, um diese Information zu lesen.

EU-Datenschutz-Grundverordnung

Gemäß der europäischen Datenschutzgrundverordnung (DSGVO) haben Sie u.a. das Recht auf:

- Auskunft über die Verarbeitung Ihrer persönlichen Daten
- Berichtigung oder Löschung Ihrer persönlichen Daten
- Widerruf Ihrer gegebenen Einwilligung mit Wirkung auf die Zukunft
- Beschwerde bei der Datenschutzaufsichtsbehörde

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Sollten Sie Fragen zur Datenverarbeitung und zur Einhaltung datenschutzrechtlicher Anforderungen haben, können Sie sich an den Datenschutzbeauftragten (DSB) Ihrer Klinik oder das zentrale Datenmanagement wenden:

Datenschutzbeauftragter Ihrer Klinik
Deutsches Herzzentrum München
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E-Mail: Datenschutzbeauftragter@dhm.mhn.de

Zentrales Datenmanagement
Deutsches Herzzentrum München
- Klinik für angeborene Herzfehler und Kinderkardiologie -
Lazarettstraße 36
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Telefon: 089/1218-0
E-Mail: StudienzentrumKK@dhm.mhn.de

Sollten Sie sich bei der Aufsichtsbehörde beschweren wollen, können Sie sich an den Landesdatenschutzbeauftragten wenden:

Bayerischer Landesdatenschutzbeauftragter
Postfach 221219
80502 München
Telefon: 089/2672-0
Telefax: 089/212672-50
E-Mail: poststelle@datenschutz-bayern.de
Homepage: http://www.datenschutz-bayern.de

Darüber hinaus können Sie sich weiterhin auch an Ihren Prüfarzt wenden:

Prüfarzt
Prof. Dr. med. Alfred Hager
Deutsches Herzzentrum München
Klinik für angeborene Herzfehler und Kinderkardiologie
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Prof. Dr. med. Alfred Hager
(Studienleitung, Leiter Ambulanz DHM)

Seite **2** von **2**

Klinik für Kinderkardiologie und
angeborene Herzfehler

Direktor: Prof. Dr. med. P. Ewert

Deutsches Herzzentrum München
des Freistaates Bayern
– Klinik an der Technischen Universität München –

Prof. Dr. med. P. Ewert · Lazarettstraße 36 · 80636 München

KINDERINFORMATION

zur Studie

Lungenfunktion bei Patienten mit angeborenem Herzfehler

Hallo,

man kann sagen, dass die Lunge und das Herz zusammengehören. Alles, was durch Dein Herz geht, muss auch durch die Lunge. Um das Herz kümmern sich die Ärzte bei der Untersuchung, wir wollen uns Deine Lunge anschauen.

Zweck der Studie

Wir wollen uns zum ersten Mal anschauen, wie die Lunge bei Kindern wie Dir eigentlich genau ist. Auch wollen wir gucken, wie fit Du bist und wie gut es Dir geht.

Ablauf der Studie:

Die Messung der Lungenfunktion ist eine zusätzliche Untersuchung und dauert ca. 20-40 Minuten.

Risiken und Nebenwirkungen (ggf. auch Nutzen für den Patienten)

Es werden mit Dir nur Untersuchungen gemacht, die hier regelmäßig stattfinden. Weil Du während dem Test ungewohnt tief und lange atmest, kann Dir schwindelig werden. Das ist aber nicht schlimm. Die Ergebnisse werden direkt in Anschluss mit Dir besprochen.

Vertraulichkeit

Die Ärzte dürfen nicht außerhalb der Klinik über die Ergebnisse reden. Alle Daten, die wir von Dir erheben, werden ohne, dass Dein Name oder andere konkrete Daten genannt werden, ausgewertet. Natürlich halten wir uns auch an den Datenschutz!

Freiwilligkeit

Die Teilnahme an der Studie ist freiwillig. Du kannst jederzeit und ohne zu sagen warum, Deine Teilnahme beenden. Das hat auch keine Konsequenzen.

Vielen Dank für die Zeit, die Du Dir genommen hast, um diese Information zu lesen.

[redacted]
Mohammed Bessar
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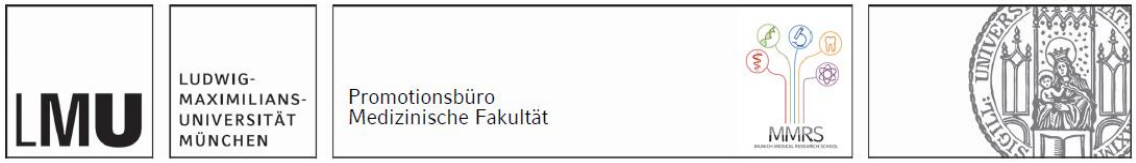
Secondly, I want to thank all my colleagues thanks to who the daily work was entertaining, exciting, but also instructive and fun. Special thanks to Mohammed Bessar, who participated this project and without whom that good numbers of patients could not have been tested.
Last, but not least thanks to my family and friends – without your support and deep trust in my skills this and more would not have happened.

Affidavit



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