Postnatal Lung Function in Congenital Cystic Adenomatoid Malformation of the Lung

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Background. **Management of prenatally diagnosed but postnatal asymptomatic pulmonary lesions remains controversial. The aim of this study was to investigate the effect of congenital cystic adenomatoid malformation of the lung (CCAM) on postnatal lung function tests (LFT) and to elucidate whether LFTs help identify infants who would benefit from early surgery.**

Methods. **The LFTs were performed in 26 CCAM infants at a median (interquartile range) postmenstrual age of 42.4 (39.6 to 44.0) weeks and compared with LFT from 30 healthy controls. The LFT included the measurement of tidal breathing, functional residual capacity by body plethysmography, respiratory mechanics (respiratory compliance), and respiratory resistance by occlusion test and blood gas analysis.**

Results. **The CCAM infants showed a restrictive ventilation disorder with increased respiratory rates ($p = 0.006$) and marginally decreased tidal volumes ($p = 0.043$). Furthermore, respiratory compliance was significantly reduced as compared with controls ($p < 0.001$). No statistically significant differences were seen in the respiratory resistance, functional residual capacity, and capillary blood gases. Particularly in CCAM infants who had surgery in the first 2 years of life, a marked reduction of respiratory compliance ($p < 0.001$) was seen preoperatively.**

Conclusions. **Congenital cystic adenomatoid malformation can cause restrictive ventilation disorders, which can be detected and monitored by postnatal LFT. Thus, LFT represents an additional tool to support the decision for or against surgical intervention.**

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Congenital bronchopulmonary malformations comprise a large group of thoracic lesions with diverse clinical presentations. Although the overall incidence is low (4.85 per 10,000 fetuses [1] for all congenital thoracic malformations), they account for significant morbidity and mortality in the pediatric population. Since the advent of high resolution prenatal ultrasound, these lesions are frequently detected *in utero* [2]. Numerous different types of malformations share a cystic appearance in prenatal and postnatal imaging: bronchopulmonary sequestration, bronchogenic cyst, congenital lobar emphysema, and congenital cystic adenomatoid malformations (CCAM). Of these entities, CCAM is associated with the most controversy concerning nomenclature and therapeutic management [3, 4]. Various subtypes have been recognized. The most commonly used classification is that of Stocker and colleagues [5], who distinguish between type 1 lesions characterized by large cysts up to 10 cm diameter, type 2 CCAM with more uniform cysts of less than 2 cm diameter, and type 3 lesions, which are solid on macroscopic examination. Although the Stocker classification of CCAM is used by most authors, this concept has recently been challenged [6], and to date there is no universally accepted classification of CCAM subtypes.

The natural course of these malformations is highly variable. Prenatally, large space-occupying lesions may cause fetal hydrops or even fetal demise, but spontaneous resolution is not uncommon [3]. In the neonate, clinical manifestation may range from severe respiratory insufficiency to the complete absence of symptoms [7]. Complications can, however, include pneumothorax, recurrent infections, or pulmonary hemorrhage [8]. In addition, an association of CCAM with several types of malignant tumors has been described [9–11]. The optimal therapeutic management of CCAM is the subject of an ongoing debate: while surgical excision usually seems the straightforward approach in symptomatic infants, the necessity and timing of surgical resection in children with radiologic evidence of CCAM but no symptoms remains controversial. Advantages of early resection include prevention of malignant transformation, possible facilitation of compensatory lung growth, and the low rate of complications in elective versus emergency surgery [8]. Furthermore, a parenchyma-saving operative approach (preferring segmentectomy or wedge resection over lobectomy or pneumonectomy) has been demonstrated to

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Abbreviations and Acronyms

CCAM	=	congenital cystic adenomatoid malformation
C_{rs}	=	respiratory compliance
FRC_{pleth}	=	functional residual capacity measured by body plethysmography
LFT	=	lung function test
MV	=	minute ventilation
R_{aw}	=	airway resistance
RR	=	respiratory rate
R_{rs}	=	respiratory resistance
$V'_{max}FRC$	=	maximal flow at functional respiratory capacity
V_T	=	tidal volume

be safe and effective [12]. Those in favor of an expectant management emphasize the low overall rate of long-term complications in CCAM, the possibility of spontaneous resolution, and avoidance of the risks of unwarranted surgery [13]. Owing to the above debate, and in addition to the fact that even otherwise innocuous neonatal or infant surgery has been associated with subsequent subtle problems in behavior, language, or cognition [14–17], it would be helpful to identify infants with CCAM in whom surgery could safely be deferred until they are least 3 years of age.

We speculate that lung function testing (LFT) in the neonatal period and preoperatively may help to quantify the extent of impairment in lung function and to identify patients whose pulmonary function will remain low, indicating that they will in future require surgery. Data on pulmonary function testing in children and especially infants with CCAM are sparse and have mainly addressed the issue of compensatory lung growth after surgery [18, 19]. Therefore, the aim of our study was to compare early lung function measurements between CCAM infants and healthy controls and to investigate possible differences in infants who underwent lung surgery within the first 2 years of life and those who were managed conservatively.

Material and Methods

Subjects

We retrospectively analyzed the postnatal lung function measurements of 26 infants with CCAM who were investigated between 1993 and 2013 in our neonatal lung function laboratory. Data from these infants were compared with 30 pulmonary healthy controls enrolled from previous studies [20, 21], matched on a patient-by-patient basis for postmenstrual age and body weight. The CCAM was diagnosed by prenatal ultrasound (n = 22), postnatal x-ray (n = 20), or computerized tomography or magnetic resonance tomography (n = 14). Not included in the study were infants with other pulmonary malformations such as bronchopulmonary sequestrations or bronchogenic cysts. Furthermore, infants with congenital diaphragmatic hernia, congenital heart disease, neuromuscular disease, or thoracic wall deformities were not included. All parents provided written informed consent before each LFT, and the Institutional Data Safety Committee and University Departmental Ethics Committee approved this study.

Lung Function Testing

All LFTs were performed in clinically stable children who had no history of upper or lower airway infections in the 3 weeks preceding the tests. Before the LFT, body weight was measured by electronic scales to the nearest 10 g (Seca, Hamburg, Germany), and body length (crown to heel) was measured to the nearest 5 mm. The departmental protocol for LTF has been published previously [22].

Briefly, after a temperature stabilization period of at least 30 minutes, all devices were calibrated before measurement according to the manufacturer's guidelines. At 15 to 30 minutes before the LFT, sleep was induced by oral administration of chloral hydrate (50 mg kg^{-1}). Sleeping infants were measured in a supine position with the neck in a neutral position and supported by a neck roll. A compliant silicon mask (Infant mask, size 1; Vital Signs Inc, Totowa, NJ) was tightly placed over the nose and mouth of each subject. After waiting for 5 to 20 minutes, tidal breathing parameters (tidal volume, respiratory rate, minute ventilation) were measured using the SensorMedics 2600 (SensorMedics Corp, Yorba Linda, CA). After that respiratory lung mechanics (respiratory compliance [C_{rs}] and respiratory resistance [R_{rs}]) were measured by occlusion technique using the same equipment. Between 5 and 15 occlusions were performed and the mean of 5 valid measurements of C_{rs} and R_{rs} reported. Airway resistance (R_{aw}) and functional residual capacity (FRC_{pleth}) were measured using a constant volume baby body plethysmograph (CareFusion, Höchberg, Germany) Up to 5 technically satisfactory measurements were obtained and the mean of 3 to 5 valid measurements was calculated. All flow and volume values were related to the body weight on the day of measurement in order to reduce the intersubject variability.

All measurements were carried out by the same operator (S.W.). An arterialized capillary blood gas sample was taken at the end of the LFT (ABL800 FLEX; Radiometer, Brønshøj, Denmark). Heart rate and oxygen saturation were monitored continuously by a pulse oximeter (N-200; Nellcor, Hayward, CA) during the LFT.

Statistical Methods

Patient characteristics and lung function parameters are given as rates or median and interquartile range. Data were compared between CCAM infants and controls by the Fisher exact test, Mann-Whitney rank test, or Kruskal-Wallis rank test as appropriate. Statistical analysis was performed using Statgraphics Centurion software (Version 16.0; Statpoint Inc, Herndon, Virginia) and MedCalc (Version 9.2.0.2; MedCalc Software, Mariakerke, Belgium). A p value less than 0.05 was considered statistically significant.