Early Lung Function Testing in Infants with Aortic Arch Anomalies Identifies Patients at Risk for Airway Obstruction

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Abstract

Background: Aortic arch anomalies (AAA) are rare cardio-vascular anomalies. Right-sided and double-sided aortic arch anomalies (RAAA, DAAA) are distinguished, both may cause airway obstructions. We studied the degree of airway obstruction in infants with AAA by neonatal lung function testing (LFT).

Patients and Methods: 17 patients (10 RAAA and 7 DAAA) with prenatal diagnosis of AAA were investigated. The median (range) post conception age at LFT was 40.3 (36.6–44.1) weeks, median body weight 3400 (2320–4665) g. Measurements included tidal breathing flow-volume loops (TBFVL), airway resistance (R_{aw}) by bodyplethysmography and the maximal expiratory flow at functional residual capacity ($V'_{max}FRC$) by rapid thoracic-abdominal compression (RTC) technique. $V'_{max}FRC$ was also expressed in Z-scores, based on published gender-, age and height-specific reference values.

Results: Abnormal lung function tests were seen in both RAAA and DAAA infants. Compared to RAAA infants, infants with DAAA had significantly more expiratory flow limitations in the TBFVL, (86% vs. 30%, p<0.05) and a significantly increased R_{aw} (p = 0.015). Despite a significant correlation between R_{aw} and the Z-score of $V'_{max}FRC$ (r = 0.740, p<0.001), there were no statistically significant differences in $V'_{max}FRC$ and it's Z-scores between RAAA and DAAA infants. 4 (24%) infants (2 RAAA, 2 DAAA) were near or below the 10th percentile of $V'_{max}FRC$, indicating a high risk for airway obstruction.

Conclusion: Both, infants with RAAA and DAAA, are at risk for airway obstruction and early LFT helps to identify and to monitor these infants. This may support the decision for therapeutic interventions before clinical symptoms arise.

Introduction

Aortic arc anomalies (AAA) are rare congenital cardiac anomalies; they represent approx. 1–3% of all cardiovascular anomalies [1]. In right-sided aortic arches (RAAA) the aorta originates from the left ventricle and takes a rightward turn before its descent through the mediastinum, whereas double-sided aortic arch anomalies (DAAA) are combinations of a right-sided and a left sided aortic arch [2]. This duplication often forms a vascular ring around the trachea and/or oesophagus, which tends to compress these [3,4,5]. Likewise, a RAAA, together with the ligamentum arteriosum (the remnant of the ductus arteriosus Botalli) may also cause compression of the mediastinal structures by forming a so called aortic sling. Therefore, both anomalies may cause stridor, cough, dyspnoea, dysphagia and recurrent lower airway infections [6,7,8,9]. Based on surgical series, DAAA are the most common causes of vascular rings, followed by a right aortic arch with an aberrant left subclavian and left ductal ligament [10]. According to Bonnard et al. the majority (94%) of symptomatic

AAA were successfully treated with surgical repair [8]. Hence, there is commonly a low threshold for early corrective surgery in these patients.

AAA can be identified by fetal ultrasound as early as 12 weeks gestational age (GA) [11]. The postnatal diagnosis of AAA can be made by echocardiography, barium swallow studies, magnetic resonance imaging (MRI), or computer tomography (CT) [12,13]. While echocardiography allows sufficient imaging of the great vessels, airway obstruction is either confirmed by indirect imaging studies like barium swallow [14], or by CT or MRI, which are associated with either high doses of radiation and/or high costs [6]. Therefore, lung function tests (LFT) have been suggested as non-invasive, non-radiating diagnostic tests to diagnose and monitor the progression of airway obstruction in patients with AAA [15]. However, possibly due to lack of systematic investigations, only little data exists on LFT in children with AAA [15,16].

We hypothesized that lung function testing in the neonatal period allows the identification and monitoring of patients with

AAA. We aimed to investigate newborn infants with AAA and to describe the typical LFT findings.

Methods

Ethics statement

Neonatal lung function testing (LFT) was approved by the Charité University Hospital's ethics committee (ID 54/92). Written parental consent was obtained before each individual LFT.

Subjects

This was a retrospective study from a large tertiary referral centre for congenital abnormalities (Charité University Medical Centre Berlin). All surviving neonates with a prenatal diagnosis of AAA, born between January 2005 and March 2011, were included in the study. Postnatal management included admission to the neonatal intensive care unit for observation of cardiac or respiratory symptoms and further diagnostic echocardiography.

Protocol

Whenever possible, tests were performed around discharge from the unit. A single operator performed the LFTs in our lung function laboratory. Patients were not investigated if they had symptoms of an active respiratory tract infection (RTI), or had suffered a RTI within 2 weeks prior to the scheduled LFT. Before LFT, body weight was measured with a standard digital scale to
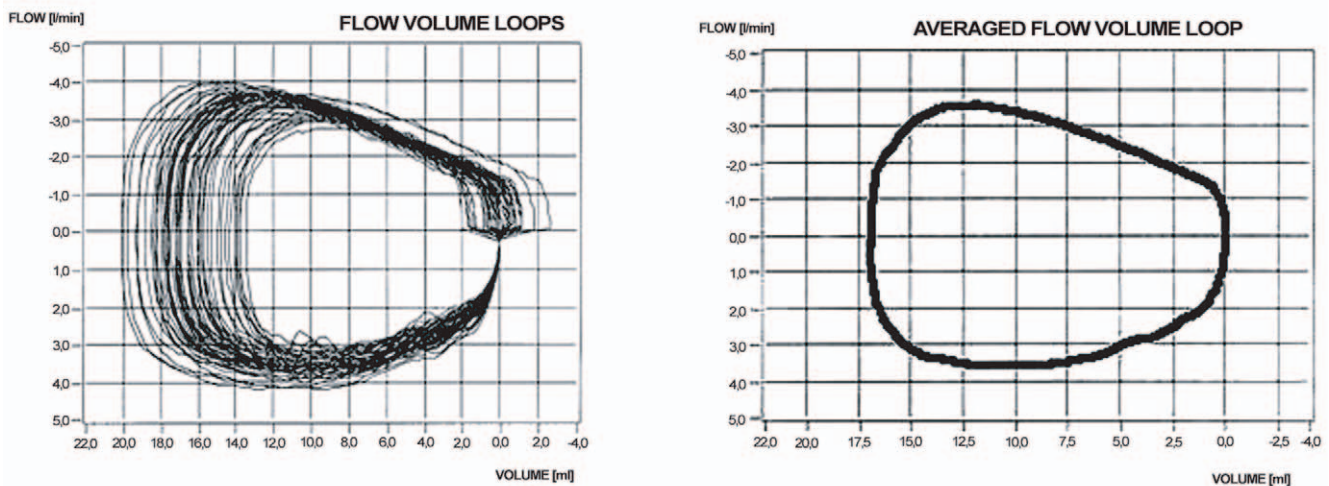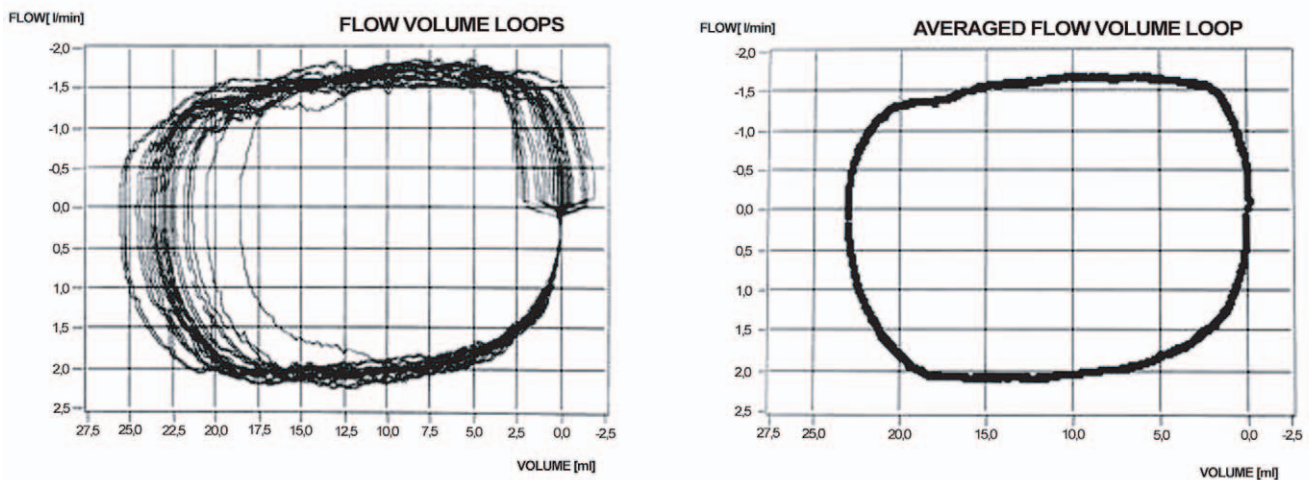
Figure 1. Consecutively measured tidal breathing flow-volume loops of newborns. Loops of a healthy newborn (1A) and loops of an infant with DAAA (1B), which illustrates the characteristic inspiratory and expiratory flow limitations. The left side of the figures show a series of consecutive breathing cycles and the right side the calculated averaged loop (by definition: inspiration shown on lower part of the graph, expiration on the top part of the graph).
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Table 1. Comparison of patient characteristics of infants with right-sided (RAAA) and double-sided aortic arch anomaly (DAAA) (presented as median (range) or n (%)).

	RAAA n = 10	DAAA n = 7	p-value
At birth			
Gestational age (weeks)	38.5 (36–41)	40 (36–41)	0.520
Birth weight (g)	3295 (2800–3665)	3420 (2330–4150)	0.435
Male	5 (50%)	2 (29%)	0.622
At time of measurement			
Age (days)	6.5 (3–22)	9 (5–34)	0.202
Post conceptional age (weeks)	39.4 (36.6–44.1)	40.9 (37.3–44.0)	0.305
Body weight (g)	3250 (2605–3780)	3550 (2320–4665)	0.353
Body length (cm)	50 (46–55)	53 (44–56)	0.224

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the nearest 10 grams (Seca®, Hamburg, Germany), body length from crown to heel was measured by an inelastic tape to the nearest centimetre.

Infants were studied after having received chloral hydrate (50 mg kg^{-1}) given orally 30–60 min before LFT. Sleeping infants were measured in supine position with the neck in a neutral position, supported by a neck roll. Three independent lung function tests were used to asses upper airway obstructions: the shape of the flow-volume measured during tidal breathing (TBFVL), the measurement of airway resistance using baby bodyplethysmography and the measurement of forced expiratory flow at functional residual capacity (V'$_{max}$FRC).

TBFVLs were measured using custom made equipment based on the flow-through technique [17]. Briefly, the facemask is continuously rinsed thoroughly by a constant background flow, which eliminates apparatus dead space thus allowing long-term measurements. Depending on the variability of the breathing pattern 20–60 consecutive breaths were measured and an averaged breathing loop was calculated as described previously [18]. As shown in Fig. 1 upper-airway obstructions cause a horizontal flattening of the inspiratory and/or expiratory limb so

that the TBFVL became a rectangular shape, as described by Leonhardt et al. [19].

The airway resistance (R$_{aw}$) was measured by baby-body-plethysmography (Jaeger Master Screen/Babybody, VIASYS, Würzburg, Germany) [20]. Upper airway obstructions cause an increase in R$_{aw}$, however, the measured R$_{aw}$ is highly method- and growth-dependent and there are no accepted reference ranges [21].

With the same equipment V'$_{max}$FRC were measured using the rapid thoracic-abdominal compression (RTC) technique, according to international guidelines [22]. V'$_{max}$FRC was also expressed in standard deviation scores (Z-scores) based on sex-, age and hight-specific reference values of healthy infants published by Hoo et al. [23].

During the pulmonary function tests, heart rate and oxygen saturation were monitored continuously by pulse oximetry (model N-200; Nellcor, Hayward, California).

Statistical methods

Patient's characteristics and the results of LFT were described by incidences or median and range. For the comparison between infants with RAAA and DAAA the exact Fischer test or Mann-Whitney rank test was used as appropriate. Regression analysis was used to investigate the relationship between the Z-score of V'$_{max}$FRC and R$_{aw}$. Statistical analysis was performed using Statgraphics Centurion® software (Version 15.0, Statpoint Inc., Herndon, Virginia, USA). A level of statistical significance of $p < 0.05$ was accepted.

Results

Patients

Seventeen patients with AAA (10 RAAA, 7 DAAA) were analysed. The median (range) post conceptional age at LFT was 40.3 (36.6–44.1) weeks and the median body weight was 3400 (2320–4665) grams. There was no statistically significant difference between the infants with RAAA or DAAA at birth or at the time of LFT, as shown in Table 1.

Lung function measurements

LFT were performed around the 40th post conceptional week (term). The results are shown in table 2: The TBFVL indicated significantly more expiratory flow limitations in infants with DAAA compared to infants with RAAA. The combination of inspiratory and expiratory flow limitation was only seen in four infants with DAAA. Figure 1 illustrates a characteristic example of a typical TBFVL, as seen in DAAA patients.

Table 2. Comparison of the results of lung function testing in infants with right-sided and double-sided aortic arch anomaly (presented as median (range) or n (%), statistically significant p-values are printed in bold).

	RAAA n = 10	DAAA n = 7	p-value
Shape of the TBFVL			
Inspiratory flow limitation	2 (20%)	4 (57%)	0.162
Expiratory flow limitation	3 (30%)	6 (86%)	**0.049**
Combined inspiratory and expiratory flow limitation	0 (0%)	4 (57%)	**0.015**
Measurements of airway resistance			
R$_{aw}$ (kPa/L/s)	1.58 (0.35–5.9)	3.09 (1.05–12.93)	0.097
R$_{aw}$ (kPa/L/s) >2.81 kPa/L/s	2 (20%)	6 (86%)	**0.015**
Measurement of V'$_{max}$FRC			
V'$_{max}$FRC (mL/s)	95.5 (19–182)	75 (53–168)	0.435
Z-Score V'$_{max}$FRC	−0.16 (−1.87–1.07)	−0.93 (−1,58–0.77)	0.283

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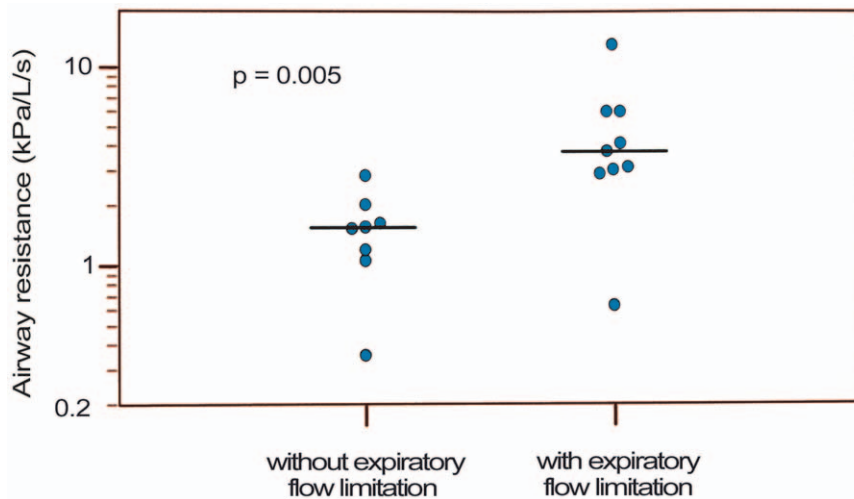
Figure 2. Expiratory flow limitation of the TBFVL and its impact on airway resistance (R_{aw} is presented on a logarithmical scale and the horizontal bar represents the median).
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An expiratory flow limitation was associated with a significantly increased R_{aw} (Fig. 2). However, there were differences in R_{aw} between infants with RAAA and DAAA. As shown in table 2, 6/7 (86%) infants with DAAA had an increased R_{aw} (p = 0.015) above the group median of all infants (2.81 cmH$_2$O/L/s).

Despite a significant correlation between R_{aw} and the Z-score of $V'_{max}FRC$ (r = 0.740, p<0.001) there were no statistically significant differences in $V'_{max}FRC$ and the Z-scores of $V'_{max}FRC$ between RAAA and DAAA infants. As shown in Fig. 3, four (24%) infants (2 RAAA, 2 DAAA) were near or below the 10th percentile of $V'_{max}FRC$, which is indicative for a high risk of airway obstructions.

Discussion

The study has shown that most infants with AAA have normal LFT at term. However, infants with DAAA as well as RAAA are at increased risk of airway obstruction, and these infants can clearly be identified by early LFT.

The risk of airway obstruction is higher in infants with DAAA compared to infants with RAAA. Combined in- and expiratory flow limitation (illustrated by the typical rectangular TBFVL, Fig. 1) was only seen in infants with DAAA. Most DAAA infants showed increased R_{aw} and their median R_{aw} was almost twice that of infants with RAAA, as shown in Table 2.

There is a lack of LFT studies in infants with AAA and this is to date the largest aggregation of early, pre-surgical lung function testing of such infants. Previously, Thomson et al. compared pre- and postoperative LFT in six children with vascular rings, also using a Jaeger Baby-Plethysmograph® [15]: All patients had pathologic LFT and evidence of tracheal compression; four infants had decreased values for FRC [15]. Also, and similar to our study, Amirav et al. found significantly increased R_{aw} and decreased values for $V'_{max}FRC$ [16].

To date, the gold standard for confirming the diagnosis of AAA is by contrast CT or MRI [12]. Comparative studies of LFT and imaging studies have not yet been performed. Performing LFT in
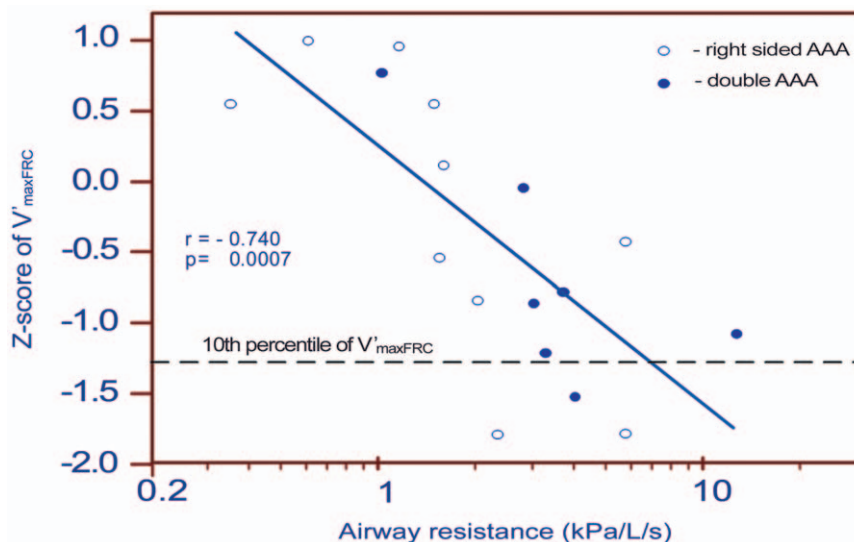
Figure 3. Correlation between Z-score of $V'_{max}FRC$ and R_{aw} of infants with AAA.
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AAA offers the advantage of using a non-invasive method, which spares the patient a high load of radiation (CT) or intensive apparatus and cost generating investigations (MRI/CT). We believe that early LFT can serve as a non-invasive tool for diagnosing the extent of airway compression by the shape of the TBFVL, the elevation in R_{aw} and $V'_{max}FRC$ reduction.

The decision for corrective surgery is traditionally based on the patient's clinical presentation. However, one patient from our analysis with a preoperative diagnosis of RAAA was intra-operatively found to have DAAA. Interestingly, this patient had a longstanding history of >3 clinical symptoms related to AAA, including recurrent respiratory infections. The TBFVL at term showed the typical configuration of a DAAA infant. His R_{aw} at term (3.71 cmH$_2$O/L/s) was higher than the median found in our RAAA group (1.58 cmH$_2$O/L/s) and even higher than that for the DAAA group (3.09 cmH$_2$O/L/s). Also, his $V'_{max}FRC$ of 64 L/s was well below the median (95.5 L/s) found for RAAA infants.

Three neonatal lung function tests were used in this study. These tests assessed different aspects of airway obstruction. The TBFVL demonstrates flow limitations, which are predictive for airway obstruction [19]. However, TBFVL have the disadvantage that they not only reflect lung mechanics but also the patients' voluntary breathing patterns [24]. As for the other tests, R_{aw} primarily describes the conductivity of the upper airways, while $V_{max}FRC$ mostly describes small airway conductivity [22]. Our study has shown that the combination of these three methods can reliably identify the presence and the degree of airway obstruction in AAA patients.

Our study has several limitations. Firstly, RAAA and DAAA are rare malformations. The small number of patient data in our study limits its statistical power and increases the risk of a type II error.

Only a limited number of measurements were available for comparing subgroups. Thus, the absence of significant differences in R_{aw} and $V_{max}FRC$ between both patient groups may be due to the low sample size and the high inter subject variability of lung function parameters. Furthermore, to date no age-dependent reference values exist for R_{aw}, mainly because these values are highly dependent on the method of measurement and of the infants' growth [21,25]. Although we believe to have found a clinically useful interpretation of R_{aw} by using the relationship between R_{aw} and the Z-score of $V'_{max}FRC$, this has not been previously studied and requires further investigation.

In conclusion, and different to previous common belief, we found that both groups of AAA patients (RAAA and DAAA) are at risk for airway obstruction. Early LFT helps to identify and to monitor such infants. Early LFT may support the decision for a surgical intervention even before clinical symptoms arise.

Acknowledgments

Author Contributions

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