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Small airway patency in infants with apparent life-threatening events

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Abstract A reduction in specific airway conductance has been reported in infants with a history of an apparent life-threatening event (ALTE). It is unclear, however, whether this reflects upper or lower airway narrowing. We performed a controlled study to determine small airway patency in infants with ALTE. Lung function tests were performed in 26 infants with a history of ALTE and 27 healthy controls. Partial expiratory flow-volume curves were obtained during quiet sleep using the rapid chest compression technique; thoracic gas volume (TGV) and expiratory airway resistance (RAW) were measured by whole body plethysmography. Compliance of the respiratory system (Crs) was measured using the single breath occlusion technique. The median maximal flow at functional residual capacity ($\dot{V}_{max}$FRC) was 85 ml/s (range 10–198 ml/s) in patients and 123 (range 47–316 ml/s) in controls ($P = 0.003$). $\dot{V}_{max}$FRC corrected for TGV was 0.5 s^{-1} (range 0.06–1.3 s^{-1}) and 0.9 s^{-1} (range 0.4–1.8 s^{-1}), respectively ($P = 0.001$). TGV, RAW and Crs were not significantly different between patients and controls.

Conclusion Reduced small airway patency may play a role in the pathogenesis of ALTE.

Key words Lung function · Conductive airways · Sudden infant death

Abbreviations *ALTE* apparent life-threatening event · *Crs* compliance of the respiratory system · *RAW* respiratory airway resistance · *sGAW* specific airway conductance · *SID* sudden infant death · *TGV* thoracic gas volume · $\dot{V}_{max}FRC$ maximal flow at functional residual capacity

Introduction

In infants suffering apparent life-threatening events (ALTE), a reduction in specific airway conductance has been reported [5]. No information, however, was provided as to whether this reduction was due to upper and/or lower airway narrowing. We therefore undertook a study to determine small airway patency in infants with ALTE.

Patients

During a 2-year period, 26 infants were studied. They had been referred to the Royal Brompton National Heart and Lung Hospital, London, UK, the Academic Department of Paediatrics, Stoke-on-Trent, UK, and the Department of Paediatric Pulmonology, Hannover Medical School, Hannover, Germany, for cardiorespiratory evaluation because they had experienced at least one episode of cyanosis or pallor for which they had received vigorous stimulation and/or cardiopulmonary resuscitation by

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Table 1 Clinical details of patients and controls. Medians (and ranges) are given where appropriate. There was no significant difference between patients and controls for any of these variables. (*IPPV* intermittent positive pressure ventilation, *BPD* bronchopulmonary dysplasia)

	Patients (n = 26)	Controls (n = 27)
Gestational age at birth (weeks)	37 (25–40)	37 (29–42)
Post-conceptional age at ALTE (weeks)	41 (36–75)	NA
Post-conceptional age at study (weeks)	51 (39–83)	52 (39–82)
Weight at study (g)	4942 (2480–9900)	5740 (2920–9020)
Length at study (cm)	59 (47–74)	60 (48–73)
Gender (male/female)	16/10	16/11
Infants whose mothers smoked in pregnancy	8	5
Infants in whom at least one parent smoked	14	8
Infants with parental asthma and/or atopy	10	12
Infants born at <37 weeks gestational age	12	13
Infants with history of IPPV	6	4
Infants with history of BPD	1	0
Infants with history of cough and/or wheeze	5	4

their caregivers for which no attributable cause had been identified by the referring hospitals. Infants were only eligible to the study if their ALTE had been sufficiently severe to result in documented acidosis (arterial pH < 7.32 and base excess < −6 mMol/l) on admission to hospital and/or had required artificial ventilation as judged by their attending physicians, and/or if a further ALTE showing definite hypoxaemia (arterial oxygen saturation ≤80% for >20 s) had been documented during recordings of physiological signals. Clinical details of these 26 patients are summarised in Table 1. Three patients were subsequently found to have abnormal EEG changes immediately prior to subsequent ALTE even though their standard EEG recordings had been normal and referring paediatricians had considered that a diagnosis of epilepsy was unlikely. A diagnosis of seizure induced hypoxaemic episodes was established [3]. Since they had originally fulfilled the entry criteria to the study (see above), it was not deemed acceptable to exclude these patients retrospectively from the study. In all other patients, the mechanism for their events remained unknown. One additional patient did not sleep following sedation and had, therefore, no lung function tests performed; the parents of two other patients who fulfilled the above criteria did not consent to the study.

These patients were compared with a group of 27 control infants who had no history of ALTE, but similar gestational ages at birth, postnatal ages and gender. Fourteen infants were siblings of sudden infant death (SID) victims, two were twins of patients with ALTE, and 11 had been born preterm (<37 weeks) but were otherwise healthy and had no history or evidence of chronic lung disease. All ALTE patients and the siblings of SID victims were discharged on a transcutaneous oxygen monitor [12]; no infant died. Written informed consent was obtained from parents of all infants and ethical approval given to this study.

Methods

Lung function tests were only performed if the infant had not suffered a respiratory tract infection during the previous 3 weeks. The median interval between the first ALTE and the lung function test was 7 weeks. All tests were performed by one of two examiners (H.H. or J.S.). Following sedation with chloral hydrate (50–100 mg/kg orally), partial expiratory flow-volume curves were obtained during quiet sleep using the rapid chest compression technique [7]. Flow and volume signals were measured by a Fleisch pneumotachograph (size 0, linear ±2% from 33–217 ml/s) using a baby plethysmograph unit (Fenyves and Gut, Switzerland). Jacket pressure was started at 30 cm H_2O and increased until no further increase in maximal flow at functional residual capacity ($\dot{V}_{max}$FRC) was noted. At least five partial expiratory flow-volume manoeuvres were performed at this pressure and the mean of the three best values analysed.

Thoracic gas volume (TGV) and expiratory airway resistance (RAW) were measured by whole body plethysmography (Fenyves and Gut, Switzerland) with the infants breathing air at BTPS conditions (37°C, barometric pressure, air saturated with water to 100%). The volume of the bodyplethysmograph was 152 l. The mean of five individual measurements was calculated for each infant. Since a different model of body plethysmograph was used for the lung function tests of the six patients studied in Hannover, data on RAW and TGV from these patients were not included in the study in order to minimise potential influences from different equipment. Specific airway conductance (sGAW) was calculated as 1/(TGV · RAW).

Compliance of the respiratory system (Crs) was measured 5–10 times in each patient using the single breath occlusion technique [7]. Measurements were only accepted if mouth pressure reached a plateau of at least 0.1 s during the occlusion and repeated measurements in the same patient varied by less than 10%.

Statistics

Data was entered into a personal computer (Apple Macintosh) and analysed with the help of a statistics package (Statview 4.02). Groups (patients and controls) were compared using the analysis of variance (ANOVA) and the two tailed Mann-Whitney-U test.

Results

Technically satisfactory measurements of $\dot{V}_{max}$FRC were obtained in all subjects. The median jacket pressure

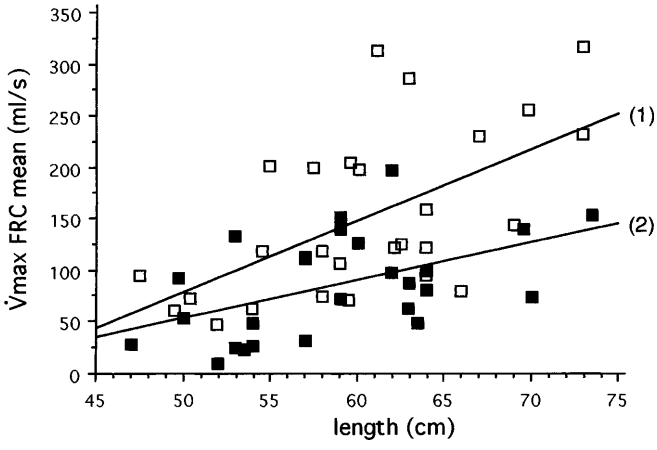

Fig. 1 $\dot{V}_{max}$FRC (ml/s) versus length (cm) in all 26 patients and 27 controls: ■ patients with ALTE, □ controls. The regression equation for the controls (*1*) has an intercept of −267 and a slope of 6.94, the equation for patients (*2*) has an intercept of −129 and a slope of 3.66

Table 2 Results of lung function test in patients and controls. Medians and ranges are given

	Patients/*n*	Controls/*n*	*P*-value
TGV/kg (ml/kg)	29.0 (21.1–43.4)/17	26.4 (17.7–33.0)/23	0.5
RAW (kPa · s/l)	2.5 (0.5–8.0)/17	2.1 (1.1–5.0)/23	0.2
sGAW (1/s · kPa)	2.43 (0.62–21.0)/17	3.10 (0.96–12.0)/23	0.2
Crs/kg (ml/kPa · kg)	11.6 (4.8–17.2)/12	11.4 (6.9–14.8)/10	0.8
$\dot{V}_{max}$FRC (ml/s)	85 (10–198)/26	123 (47–316)/27	0.003
$\dot{V}_{max}$FRC/TGV (1/s)	0.5 (0.1–1.3)/17	0.9 (0.4–1.8)/23	0.001

resulting in the best $\dot{V}_{max}$FRC was 46 cm H_2O in the patients (range 32–70) and 52 cm H_2O in the controls (range 32–73). $\dot{V}_{max}$FRC increased with length (Fig. 1). The regression equations for controls and ALTE patients had slopes of 6.94 and 3.66, respectively, with a correlation coefficient of 0.5 in both groups. $\dot{V}_{max}$FRC was significantly lower in patients than in controls. This difference remained statistically significant when $\dot{V}_{max}$FRC values were corrected for lung volume (Table 2). Analysis of variance demonstrated that these differences were independent of age, gestational age, gender, history of parental smoking and history of parental asthma and/or atopy.

Technically satisfactory measurements for TGV and RAW were obtained in 17 patients and 23 controls; Crs was measured in 12 patients and 10 controls. There were no statistically significant differences between cases and controls for any of these variables (Table 2). There was, however, a trend towards higher values for TGV and RAW and lower sGAW in the patients.

Re-analysis of the data without the three patients with seizure induced hypoxaemic events did not significantly alter our results (data not shown, but available on request).

Discussion

This group of infants with severe ALTE showed a significantly reduced $\dot{V}_{max}$FRC, a measurement generally regarded as a sensitive parameter of small airway patency. Lung function tests were performed after a median interval of 7 weeks following the ALTE and it is unlikely that the reduction of $\dot{V}_{max}$FRC is secondary to the event. A reduced $\dot{V}_{max}$FRC indicates a reduced airway calibre before tidal breathing is significantly affected and obstruction becomes clinically apparent [14]. The significant decrease in $\dot{V}_{max}$FRC observed in our patients was accompanied by only slightly increased values for RAW and TG and only slightly decreased values for sGAW. Kao and Keens [5] found decreased sGAW in a group of ALTE patients who, similar to our patients, did not show clinical signs of airway obstruction. These authors, however, were unable to determine the site of airway narrowing in their patients. Our data indicate that small airway patency may be the relevant mechanism and extend the observation by Kao and Keens.

What are the mechanism(s) whereby a reduced small airway calibre may be involved in the pathogenesis of ALTE? At least two possibilities may be considered. Firstly, reduced small airway patency may facilitate progressive closure of small airways, particularly in the presence of bronchial hyperreactivity, respiratory tract infections, and/or disturbances in surfactant function [6, 11]. If pulmonary blood flow continues to unventilated areas of the lung, this may result in severe hypoxaemia due to both hypoventilation and intrapulmonary shunting, leading to a clinical picture of ALTE [10]. Secondly, a reduction in the calibre of the peripheral airways may be associated with a reduced size of the *upper* airways as well, thereby potentially making obstructive apnoeas more likely to occur. However, the latter mechanism seems less likely in our patients, since one would then expect them to have not only a significantly increased $\dot{V}_{max}$FRC, but also higher values for RAW, which they had not.

Our results have been obtained in infants with ALTE and should not, therefore, be uncritically extended to SID, particularly as none of our patients subsequently died suddenly and unexpectedly. Nevertheless, there are certain physiological and epidemiological features which are characteristic of both ALTE and SID [6, 10]. Furthermore, we confined our study to ALTE patients fulfilling high risk criteria for SID as defined by Oren et al. [9]. In the following, we will therefore discuss our findings with regard to these common features of both ALTE and SID.

Reduced airway patency is a characteristic of several conditions linked to ALTE and SID: both occur more frequently in boys than in girls [4, 8, 13]; $\dot{V}_{max}$FRC is also significantly lower in boys [1, 14]. Smoking during pregnancy, an important risk factor for ALTE and SID [4, 8], has also been demonstrated to result in lower values for $\dot{V}_{max}$FRC [2]. The same is also true for premature birth: infants who are born before term but are otherwise healthy are not only at increased risk of ALTE and SID [4, 15], but do also have lower values for $\dot{V}_{max}$FRC. The latter persist throughout the 1st year of life [14]. Finally, ALTE occur most frequently between 2 and 4 months of age. This peak coincides with the physiological nadir in $\dot{V}_{max}$FRC [6].

The ALTE patients studied here were also predominantly between 2 and 4 months of age, 59% were male and 44% had been born at <37 weeks gestation. Distributions of postconceptional age, gestational age and gender were similar in both cases and controls. Comparisons between the two groups with regard to other possible risk factors for ALTE revealed that 8 out of 27 cases had a history of smoking during pregnancy (compared to 5 controls), and 1 had a history of BPD

(oxygen therapy had been discontinued well before her ALTE). These differences are not statistically significant, but are in line with epidemiological data on the prevalence of these risk factors amongst patients with ALTE. However, analysis of variance demonstrated that the differences in $\dot{V}_{max}$FRC between cases and controls could not be explained by different prevalences of these risk factors.

Some limitations need to be considered. About half of the control infants were siblings of SID victims, potentially causing selection bias. However, our data on $\dot{V}_{max}$FRC in these siblings were comparable to reference data from the literature [7, 14]. The patients studied here were from tertiary referral centres and may thus not be representative of all patients with ALTE. We have therefore been careful not to generalise our finding of a reduced small airway patency made in this selected group of patients with severe ALTE to all patients with such events.

In conclusion, our data suggest that some infants with ALTE have a reduced patency of their peripheral airways. This provides further evidence that mechanisms other than those related to central respiratory control may be involved in the pathogenesis of these potentially fatal events.

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