REGULAR ARTICLE

Paediatric apnoeas are not related to a specific respiratory virus, and parental reports predict hospitalisation

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ABSTRACT

Aim: The aim of this study was to determine the frequency of apnoeas in previously healthy young infants with acute respiratory tract infection (ARI) and correlate their occurrence with isolated micro-organisms, clinical findings, disease severity and outcome.

Methods: We performed reverse transcriptase real-time polymerase chain reaction (RT-PCR) on the nasal wash specimens of a prospective cohort study of 582 children with ARI. Clinical data on a subgroup of 241 infants under three months of age, with and without apnoeas, were compared.

Results: Our study found that 19 (7.9%) of the 241 infants under three months old had a history of apnoeas: eight had a respiratory syncytial virus (RSV), five had a different virus than RSV and seven RT-PCR results were negative. Infants with apnoeas were more likely to have cyanosis, had longer hospital stays and required extra oxygen for a longer period. Most patients with parental reported apnoeas also experienced apnoeas during hospitalisation.

Conclusion: This study observed apnoeas irrespective of the isolated micro-organism, and we hypothesise that they were related to the pathophysiology of the respiratory infection and not to the micro-organism itself. Parental reported apnoeas were a major warning sign and predicted that apnoeas would occur in hospital.

INTRODUCTION

Acute respiratory tract infection (ARI) is the leading cause of hospitalisation in young children (1), and the respiratory syncytial virus (RSV) is responsible for approximately 45–80% of those admissions, depending on the season. Since 1970s, RSVs have been recognised as the key organism associated with apnoeas (2,3). In paediatric intensive care unit (PICU) settings, these RSV infections often require mechanical ventilation, but resolve within the days of onset (4).

Apnoeas are characterised by the absence of airflow, and their pathophysiology is diverse and comprises several mechanisms. Some researchers have suggested that the infant's immature brainstem respiratory centre plays a role, and an exaggerated inhibitory response leads to reduced breathing effort (5,6). A second proposed mechanism was related to the infectious status of the respiratory system, regardless of the causative organism. In a prospective study, respiratory arrest was associated with a strong inflammatory response in the mucosa (7). A third proposed mechanism referred to the stimulation of stretch receptors in the lungs, causing a reflectory negative feedback to respiration, known as the Hering–Breuer reflex (8–10). This reflex is sometimes stronger due to general malaise and muscle fatigue (11–13). A fourth proposed mechanism was an obstruction of the airways by mucus plugging and stasis in the nose and, or, small airways. Obstructive apnoeas may also lead to subsequent central apnoeas (10).

In the literature, apnoeas have been strongly associated with RSV, and they may be the first sign of disease (14,15).

Key notes

- This study of previously healthy young infants under three months of age with acute respiratory tract infections found that 19/241 (7.9%) had a history of apnoeas.
- We observed apnoeas irrespective of the isolated micro-organism and hypothesise that they were related to the pathophysiology of the respiratory infection and not to the micro-organism itself.
- Parental reported apnoeas were a major warning sign and predicted that apnoeas would occur in hospital.

However, since the introduction of real-time reverse transcriptase polymerase chain reaction (RT-PCR) in general practice, more viruses have also been associated with apnoeas (2,15–20).

Studies have consistently maintained that the major risk factors for the development of ARI-related apnoeas are prematurity, an early postnatal onset at less than two months of age and a history of apnoea or cyanosis and comorbidity, especially of the respiratory tract (2,4,5,14,21,22).

However, it is not known what effect the individual viruses have on apnoeas. So far, researchers have suggested that RSV is the most important virus, based on frequency. But perhaps we need to broaden our scope to include other viruses as well. This study aimed to answer two clinical questions: is it just RSV infected infants that need hospitalisation based on the risk of apnoeas and which parameters add to clinical decision-making regarding the need for hospital admission? To answer these questions, we studied the incidence of apnoeas and clinical characteristics in formerly healthy infants presenting with respiratory symptoms to their paediatrician.

METHODS
Patients and study design
This study was a substudy of the Evaluation of Viral Diagnostics on Respiratory Infections in Children (EVIDENCE) trial, a multicentre randomised clinical trial designed to evaluate the clinical impact of rapidly communicating RT-PCR results to paediatricians who saw paediatric patients who presented with acute respiratory symptoms. The study comprises 582 previously healthy children from 0 to 12 years of age. The study protocol has already been described elsewhere (19). The research was conducted during two winter seasons at two hospitals in the Netherlands, the Reinier de Graaf Hospital in Delft and the Groene Hart Ziekenhuis in Gouda, between November 2007 and May 2008 and October 2008 and March 2009. The inclusion criteria were children with respiratory symptoms and suspected ARIs in the two hospitals' emergency departments, outpatient clinics and paediatric wards. Most of the children were referred to the hospitals after initial assessments by their primary care physicians, which is a common practice in the Netherlands. We excluded children with underlying anatomical airway abnormalities, neuromuscular impairment or other significant underlying disorders, such as syndromal disorders that included psychomotor retardation, malignancies and cardiac pathology. All newborn infants hospitalised since birth were also excluded. No restrictions were placed on including patients with asthma or suspected asthma.

To analyse the incidence and clinical characteristics of the children with apnoeas, we only selected infants who were younger than three months from the EVIDENCE data set, because the risk of apnoeas is highest in this age group (2,14,21).

The regional medical ethics committee approved the trial protocol, and all parents provided written, informed consent.

Data collection and nasal wash specimens
Clinical data were prospectively collected using a standardised form, and missing data, as well as laboratory and radiologic reports, were retrieved from the hospitals' medical records.

In addition to the standard hospital protocols, RT-PCR assays for 15 viruses and two bacteria were performed on all nasal wash specimens (Table S1). *Bordetella pertussis* was only tested if there was a clinical suspicion. Duplex RT-PCR assays were performed with all nasal wash specimens using assays developed in-house. The RT-PCR method and validation procedure have already been described elsewhere (19).

Definitions
Apnoea was defined as one or more episodes of respiratory pauses, regardless of duration, that were observed by parents or guardians, physicians or nurses and resulted in hospitalisation. During hospitalisation, the definition of apnoea agreed by the American Academy of Pediatrics was used: an unexplained episode of cessation of breathing for 20 seconds or longer or a shorter respiratory pause associated with bradycardia, cyanosis, pallor and, or, marked hypotonia (23).

The disease severity score (DSS) used in this study, which was designed to determine the severity of the respiratory illness, was a modification of the severity score developed by Gern et al. (24). A score of zero to seven represented mild disease, while 8–18 indicated moderate disease and 19–27 indicated severe disease (Table S2).

Statistical analysis
The statistical package SPSS version 18.0 was used to analyse the data (SPSS Inc, Chicago, USA). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, and the Mann–Whitney U-test was used for continuous variables. To present the risk factors for apnoea, the odds ratio (OR) and 95% confidence interval (95% CI) were calculated from two-by-two tables. When the 95% CI included one, no significant association between a risk factor and apnoea existed. Statistical significance was defined as $p < 0.05$.

RESULTS
A total of 241 infants under three months of age were included in this analysis, and 19 (7.9%) had apnoeas during the course of their disease. We divided the 241 infants into two groups based on the presence (n = 19) or absence (n = 222) of apnoeas (Table 1). Both groups were comparable with regard to gender, gestational age and birth weight, but the apnoea group tended to be younger at presentation: 10 infants with apnoeas (52.6%) were younger than one month at the time of diagnosis. Only two patients with apnoeas were older than three months. These two infants both were born after full-term delivery, both experienced apnoeas as result of gastro-oesophageal reflux disease, and they were not included in this analysis.

Table 1 Patient characteristics and clinical findings in the apnoea and nonapnoea groups

	Apnoea n = 19	No apnoea n = 222	p value
Patient demographics			
Male, n (%)	9 (47.4)	129 (58.1)	0.364[†]
Gestational age ≤ 35 weeks, n (%)	3 (15.8)	13 (5.9)	0.120[‡]
Birth weight, median (g)	n = 16	n = 136	
	3070.0	3537.5	0.184*
Age at diagnosis, median (months)	0.95	1.44	0.065*
Time course of apnoeas			
Before admission, n/total infants (%)	**17/19 (89)**	**0 (0)**	**<0.001[†]**
During hospitalisation, n/hospitalised (%)	**12/18 (67)**	**0 (0)**	**<0.001[†]**
Continuous monitoring of vital signs, n (%)	18 (100)	158 (94)	0.287[†]
Findings at admission			
Disease severity score (DSS), median	**15.00**	**8.00**	**0.006***
DSS Categories, n (%)			
<=7/reference	**3 (15.8)**	**108 (48.6)**	
8–18	**11 (57.9)**	**80 (36.0)**	**0.022[†]**
19+	**5 (12.8)**	**34 (15.3)**	
Presence of fever, n (%)	5 (26.3)	70 (31.5)	0.637[†]
Presence of wheezing, n (%)	6 (31.6)	50 (22.5)	0.398[‡]
Presence of cough, n (%)	13 (68.4)	152 (68.5)	0.997[†]
Presence of rhinorrhoea, n (%)	15 (89.6)	199 (78.9)	0.243[‡]
Presence of cyanosis, n (%)	**14 (73.7)**	**77 (34.7)**	**0.001[†]**
Presence of tachypnoea, n (%)	6 (31.6)	96 (43.2)	0.323[†]
Presence of retractions, n (%)	9 (47.4)	90 (40.5)	0.562[†]
DSS without apnoea, median	11.00	8.00	0.271*
Hospitalisation and disease course			
Hospitalisation, n (%)	18 (94.7)	168 (75.7)	0.057[†]
Duration of hospitalisation, median (days)	**6.00**	**3.00**	**0.003***
PICU admission, n (%)	**4 (21.1)**	**0 (0)**	**<0.001[‡]**
Duration of extra oxygen use, median (days)	n = 18	n = 168	
	3.00	**0.00**	**0.003***

Significant differences are noted as bold. DSS, disease severity score; PICU, paediatric intensive care unit.

*For continuous variables, Mann–Whitney U-tests were used.

†For categorical variables, chi-square tests were used.

‡For categorical variables, Fisher's exact test was used because of the expected frequencies less than five.

Of the 19 apnoeic episodes, 17 were reported by the parents or guardians before admission to the hospital, and the other two were not reported and occurred during hospitalisation when the infants were monitored for vital signs using a cardiorespiratory monitor (Table 1). One infant with a parent reported apnoea, and a DSS of 11, was not admitted to the hospital because of their excellent clinical condition after a short observation period in the outpatient clinic. The remaining 18 infants were hospitalised, and 12 of them also experienced apnoeas during hospitalisation, just like they did at home.

Infants with apnoeas had a significantly longer duration of hospitalisation, received more oxygen and presented with cyanosis more frequently (Table 1). The median DSS was significantly higher in infants with, than without, apnoeas: 15.0 compared to 8.0 (p = 0.006). As apnoea itself was included in the DSS, we recalculated the difference between the apnoea and nonapnoea groups after excluding apnoea from the DSS. As shown in Table 1, once this was performed, the DSS lost its significance.

Four infants (21.1%) in the apnoea group were eventually admitted to a PICU, compared to none in the nonapnoea group (p < 0.001), and the median DSS of the infants admitted to the PICU was 26.5.

In addition to Table 1, the clinical data of each of the 19 patients with apnoeas are presented in Table 2. These include descriptions of the apnoeas, length and frequency of pauses, degree of oxygen desaturation, heart rate changes and interventions required to treat the hypoxia, when available.

The RT-PCT test was negative in seven infants (36.8%) in the apnoea group, compared with 53 (23.0%) in the nonapnoea group, but this difference was not statistically significant (Table 3). In the infants with apnoea, no positive RT-PCR tests for adenovirus, human metapneumovirus and parainfluenza virus were found, whereas those viruses were often present in the nonapnoea group. The percentage of RSV as the causative agent for ARI was equal in both groups. One infant in the subgroup with apnoeas was positive for the influenza virus as well as for *Bordetella pertussis*. In the other infants, only a single virus was detected. RT-PCR detected either two or three viruses in 38 infants (17.1%) in the nonapnoea group.

Although the detected viruses did not differ significantly between both groups, it is evident that nonRSV viruses also led to apnoeas. The percentage of apnoeas in the different PCR groups is shown in Table 4.

DISCUSSION

Our data show that apnoeas are not just caused by RSV. These findings are in line with the recent publications that suggested that apnoeas result from general inflammatory responses, rather than from a specific microorganism (7). In our study, parental reports of apnoeas at home significantly predicted apnoeas in the hospital. Another study has published similar risk factors (20).

Most studies on apnoeas have primarily focused on the relationship with RSV. Epidemics occur each winter that lead to many young infants under the age of three months being hospitalised. The high frequency of RSV infections is probably responsible for the idea that RSV itself induces apnoeas. As RSV is highly associated with apnoeas (2,3), several guidelines recommend hospitalising young infants with an RSV infection even if there are no clinical signs that warrant hospital care (25). In contrast to these recommendations, our study revealed that the same proportion of apnoeas was also observed in nonRSV infections and that they occurred irrespective of the causative micro-organism.

Table 2 Characteristics and clinical findings for each patient in the apnoea group

Patient	Age in months	GA/BW	Medical history	Parental reported apnoea	Description of clinically observed apnoea	Maximum desaturation (%)	Bradycardia (beats/min)	Diagnosis at discharge	PICU	LOS	DSS	PCR results
1	0.95	39 5/7 3865	No	Absence of breathing for 15 seconds after vomiting during breastfeeding. Self-correcting	None	–‡‡	–	ARI/GERD‡	No	2	3	Neg
2	1.7	39 1/7 4210	No	Recurring periods of the absence of breathing after coughing. Cyanosis of lips. Recovery after moderate stimulation	Paroxysmal coughing	79	–	ARI	No	8	12	IV§ BP¶
3	0.72	37 2/7 3085	No	Absence of breathing for 15–20 seconds	Recurring absent breathing CPAP and caffeine during PICU admission	65	50	ARI	Yes	2	15	HBoV**
4	0.33	39 5/7 3440	No	Absence of breathing for several seconds	Absent breathing in emergency room. Severe dyspnoea	85	–	Bronchiolitis	No	10	27	RSV
5	0.62	36 6/7 2835	Yes*	Hypotonia and alarm on sleep apnoea baby pad activated four times. Recovery after moderate stimulation	Multichannel registration: short central apnoeas	86	–	ARI/GERD‡	No	7	9	Neg
6	2.13	36 3/7 3125	No	None reported	Detoriation of respiratory condition and apnoeas. Mechanical ventilation during PICU admission	–	–	Bronchiolitis Pneumonia	Yes	10	26	RSV HCoV††
7	0.23	40 0/7 2640	No	Recurring episodes of hypotonia and cyanosis of the face. Self-correcting	None. Desaturation during sleep	89	–	–	No	2	4	Neg
8	0.23	40 3/7 3360	No	Cyanosis of the face	Rapid detoriation of respiratory condition and apnoeas	55	50	Sepsis	No	10	4	Neg
9	0.69	42 0/7 4480	No	None reported	Three episodes of absent breathing after coughing Severe mucus production	73	–	Bronchiolitis	No	6	16	RSV
10	2.79	41 3/7 4000	No	Cyanosis of the face during feeding	None	–	–	Bronchiolitis	No	4	11	RSV
11	2.43	36 4/7 2890	No	Three episodes of absent breathing for several seconds. Somnolence	Frequent episodes of absent breathing for several seconds. Severe mucus production and coughing	85	–	Bronchiolitis Pneumonia	No	6	15	RSV
12	0.95	40 4/7 3600	No	Recurring episodes of absent breathing. Cyanosis of the face and somnolence. Recovery after moderate stimulation	Absent breathing for several seconds. Exhaustion. No mechanical ventilation during PICU admission	87	60	Bronchiolitis Pneumonia	Yes	6	27	RSV

Table 2 (Continued)

Patient	Age in months	GA/BW	Medical history	Parental reported apnoea	Description of clinically observed apnoea	Maximum desaturation (%)	Bradycardia (beats/min)	Diagnosis at discharge	PICU	LOS	DSS	PCR results
13	1.08	35 5/7 2693	No	Three episodes of cyanosis of the face after coughing. Self-correcting	Several episodes of absent breathing for several seconds. Cyanosis of the face. Coughing	66	–	ARI	No	7	21	Neg
14	1.05	33 1/7 2390	No	Cyanosis of the face	Detoriation of respiratory condition and apnoeas. Mechanical ventilation during PICU admission	38	–	Bronchiolitis	Yes	15	27	RSV
15	2.46	39 1/7 3475	Yes[†]	Absence of breathing several seconds. Hypotonia and somnolence	Five episodes of absent breathing during sleep and during feeding	76	80	Bronchiolitis	No	1	16	Neg
16	0.66	36 6/7 3060	No	Cyanosis of the face	Recurring periods of absent breathing for several seconds. Recovery after moderate stimulation	72	79	ARI	No	7	11	HCoV
17	1.05	36 6/7 3080	No	Rhinitis, short period of absent breathing	No clinical admission. Excellent condition during observation in emergency room	–	–	ARI	No	–	11	HRV
18	1.9	40 0/7 3270	No	Two episodes of absent breathing for several seconds after coughing. Recovery after moderate stimulation	Two episodes of absent breathing for several seconds. Cyanosis of the face. Recovery after moderate stimulation	86	50	Bronchiolitis	No	4	16	RSV
19	0.52	38 0/7 2460	No	Absent breathing for 15–20 seconds. Pale face	None. Superficially breathing pattern	87	–	ARI, Premature breathing pattern	No	1	9	Neg

*Premature breathing with apnoeas first days of live; caffeine therapy.
†RSV bronchiolitis at age six weeks; mechanical ventilation for one week.
‡GERD: gastro-oesophageal reflux disease.
§Influenza virus.
¶*Bordetella Pertussis.*
**Human Bocavirus.
††Human Coronavirus.
‡‡Missing data.

Table 3 Laboratory findings in the apnoea and nonapnoea groups

	Apnoea n = 19	No apnoea n = 222	p Value
Viruses*			
Adenovirus, n (%)	0 (0)	5 (2.3)	N/A
Human bocavirus, n (%)	1 (5.3)	1 (0.45)	0.152[†]
Human coronavirus, n (%)	2 (10.5)	26 (11.7)	1.000[†]
Human metapneumovirus, n (%)	0 (0)	16 (7.2)	N/A
Influenzavirus, n (%)	1 (5.3)	19 (8.6)	1.000[†]
Negative, n (%)	7 (36.8)	53 (23.9)	0.267[†]
Parainfluenzavirus, n (%)	0 (0)	9 (4.1)	N/A
Rhinovirus, n (%)	1 (5.3)	30 (13.5)	0.481[†]
Respiratory syncytial virus, n (%)	8 (42.1)	100 (45.0)	1.000[†]
Other findings			
Bordetella pertussis, n (%)	1 (5.3)	0 (0)	N/A
Chlamydophila pneumonia, n (%)	0 (0)	1 (0.45)	N/A
Mycoplasma pneumonia, n (%)	0 (0)	4 (1.8)	N/A

N/A, not applicable.

*Total proportions exceed 100% because pathogens in mixed infections were also counted individually.

†For categorical variables, Fisher's exact test was used because of expected frequencies less than five.

Table 4 Percentage of apnoeas in the different PCR groups

PCR result	Percentage apnoeas (n/N)
RSV	7.4% (8/108)
Non-RSV	7.0% (12/171)
Other virus than RSV identified	4.5% (5/111)
No virus identified	11.7% (7/60)

We could not find a statistically significant difference between apnoeas and any specific virus, but our sample size was probably too small to answer that question. Our findings were in line with a prospective multicentre study that demonstrated a similar apnoea risk across the major viral pathogens (20).

Definitions of apnoea differ in the literature (23,26), and this makes it difficult to determine their incidence accurately. To compare our study with the literature, we focused on apnoeas at home, namely a parental reported history of respiratory arrest at home, in common with most of the other researchers (15). A minimum duration of the respiratory arrest was not included in this definition. Most infants with ARI-associated apnoeas receive their care in a general hospital. As a result, the registration of apnoeas during hospitalisation in our study was less accurate than in a PICU setting and was probably under-reported. Furthermore, the phenomenon of apnoea remains a subjective observation when it is not measured with close monitoring of vital parameters, breathing patterns and airflow. Despite these issues, our results stress that parental observations of apnoeas should be taken seriously and are a strong predictor of apnoeas in hospital (Tables 1 and 2).

Young age is an important risk factor for the occurrence of apnoeas (3,4). In our initial cohort, 21 (3.5%) of the 582 children had apnoeas, and only two of these were older than three months. This incidence in the initial cohort, or 19/241 (7.9%) in the age-restricted group, corresponded to the results described in a review, in which the overall apnoea rate ranged from 1.2% to 23.8% (15). The variations in incidence detected by this review were the result of different definitions of apnoea and the age ranges that were included.

When we refer to the possible mechanisms of apnoeas, young age is likely to be associated with immaturity of the brainstem respiratory centre and is likely to partly contribute to the occurrence of apnoeas (6,27,28). The correlation of apnoeas with the DSS supports the view that the inflammatory reaction itself is an important factor when it comes to increasing the risk of apnoeas (7). Activation of the laryngeal chemoreceptors by inflammatory cytokines leads to prolonged respiratory arrest between two breaths (6), and this view is further supported by the observation that apnoeas mainly occur in children with an involvement of the lower respiratory tract. These are both situations in which hypoxia and hypercapnia are more likely to occur. However, the inflammatory response is only partly responsible, because the significance of the DSS decreased after excluding apnoea from the scoring system. Without extensive breathing registration, it is not possible to establish the relative contribution of the brainstem respiratory centre and the inflammatory status. Four of the infants with apnoea in our study were only diagnosed with an upper respiratory tract infection, and one of these infants suffered from choking periods due to nasal obstruction. As young children obligatory breathe through their nose (29), apnoeas may occur without lower respiratory tract involvement. Excessive mucus production or plugging in these children causes mechanical airway blockage that can easily be resolved by rinsing the nose with saline or using suction or decongestive medication.

Apnoeas predicted a more unfavourable clinical course. Four of the 19 nineteen (21%) infants in our study were eventually admitted to a PICU due to respiratory insufficiency. Although the DSS in our study was not validated to predict PICU admittance, the scores of the infants admitted to the PICU were significantly higher than those who stayed on a paediatric ward. A retrospective study of 43 RSV-positive patients who were admitted to a PICU for apnoeas found that the risk factors were younger age, lower admission weight, lower gestational age, admission from the emergency room and the lack of hyperthermia (30). From a clinical point of view, it would be helpful if the DSS could predict which infants with apnoeas required PICU care.

CONCLUSION

Apnoeas were observed in about 7% of infants with ARIs under the age of three months, irrespective of the isolated micro-organism. The most likely causes were general inflammatory responses, an immature brainstem or blocked

nose. Viral testing for an RSV should not be used to identify infants who need to be hospitalised.

The only parameter that significantly predicted the occurrence of apnoeas during hospital admission in our study was parental reports of apnoeas at home.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Microorganisms that were tested in nasal wash specimens.
Table S2 Modified disease severity score after Gern et al. (24).