Impact of bronchopulmonary dysplasia on pulmonary function during childhood: a systematic review

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Abstract:

Introduction: Bronchopulmonary dysplasia (BPD) is a multifactorial chronic lung disease that contributes to disruption of pulmonary development. It may impair pulmonary function in early childhood and persist throughout school-age, adolescence, and into adulthood.

Objective: To analyze, through a systematic review, the impact of BPD on pulmonary function in early childhood.

Methods: Systematic searches were performed in three electronic databases (Medline, SciELO and PEDro). Two independent examiners analyzed the titles, abstracts and full texts, considering the following study inclusion criteria: studies of pulmonary function in up to 5-year-old children diagnosed with BPD in the neonatal period.

Results: Initially, 1789 articles were identified, and the final sample included 22 articles. It could be observed that children diagnosed with BPD in early childhood showed expiratory flow limitation and reduced functional residual capacity. However, pulmonary function in children with a history of BPD remains reduced when compared with healthy full-term children. Moreover, there are no positive responses in pulmonary function values with the use of bronchodilators.

Conclusion: Children with BPD show changes in pulmonary function, which may improve with growth, and most of them do not respond positively to bronchodilators.

Keywords: bronchopulmonary dysplasia, lung diseases, infant, respiratory function testing, child.

INTRODUCTION

Neonatal chronic lung disease, also known as bronchopulmonary dysplasia (BPD), is defined as the need for respiratory support with oxygen and/or mechanical ventilation in the first 28 days of life[1-4]. Children who developed the disease in the postnatal period may show abnormalities in pulmonary function[5].

Currently, pulmonary function testing in early childhood, i.e., the time period ranging from 0 to 6 years including infants and preschoolers, can be performed by examinations, such as rapid chest compression, single breath occlusion, plethysmography and helium dilution[6]. Studies indicate that infants with BPD show compromised pulmonary function in the first years of life, with significant expiratory flow limitation, namely, forced expiratory volume in one second (FEV1), mean forced expiratory flow (FEF25-75%), as well as reduced pulmonary compliance, increased pulmonary resistance, higher respiratory rate, reduced functional residual capacity (FRC) and residual volume[7-24].

These results are characteristics of ventilatory and functional changes, the knowledge of which may provide a better understanding of the disease and, consequently, improve treatment and preventive strategies to manage the disease. Therefore, this study aimed to analyze the impact of bronchopulmonary dysplasia on the pulmonary function of infants and preschool children between 0 and 4 years of age.

METHODS

Search Strategy

The literature review strategy included electronic searching using three bibliographic online databases: SciELO (Scientific Electronic Library Online), PEDro (Physio-

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therapy Evidence Data base) and Medline (Medical Literature Analysis and Retrieval System Online via Ovid. The publications were selected until the date of online searching, i.e., September 2016, regardless of the language.
The authors developed a search strategy for Medline (via OVID web) and PEDro, which are shown in (Figure 1), due to the absence of this type of publication on the topic. The following keywords were used for the SciELO database: displasia broncopulmonar, bronchopulmonary dysplasia.

Selection Strategy

The articles were screened by 2 examiners, who independently analyzed the results of the online search for potentially eligible articles. The publications which met all previously established inclusion criteria were selected, and doubtful cases were discussed. First, the reviewers read the titles, followed by an analysis of the abstracts.

The studies that proved to be eligible were reviewed in full, in agreement with the recommendations of the Main Items for Reporting Systematic Reviews and Meta-analysis (PRISMA)[25,26] (Figure 2).

Analysis of data

Inclusion criteria were: clinical trials that assessed pulmonary function of infants and preschool children aged 0-4 years with a diagnosis of BPD in the neonatal period. The diagnosis of BPD was defined as the need for supplemental oxygen above 21% during 28 days or more.[24] Studies that were not available through the Program Manager Bibliographic Commuting (Comut), the newspaper's website or Ovid database, were not used for analysis.newspaper's website or Ovid database, were not used for analysis.

Figure 1: search strategy

Medline (ovid web)

1. Randomized controlled trials as topic/
2. Randomized controlled trial/
3. Random allocation/
4. Double blind METHODS/
5. Single blind method/
6. Clinical trial/
7. Exp clinical trials as topic/
8. (Clinic* adj trial*1).Mp.
9. ((Singl* or doubl* or tripl*) adj (blind*3 or mask*3)).Mp.
10. Placebos/
11. Placebo*.Mp.
12. Randomly allocated.Mp.
13. (Allocated adj2 random).Mp.
14. 1 Or 14
15. Bronchopulmonary dysplasia/
16. Pulmonary dysplasia
17. Infant, premature, diseases/
18. Respiratory distress syndrome newborn/
19. Respiratory system abnormalities/
20. Pulmonary fibrosis/
21. Or/17-22
22. Lung volume measurements/
23. Respiratory function tests/
24. Pulmonary function test*.Mp.
25. Exercise test/
26. Exercise tolerance/
27. Spirometry/
28. Lung capacity
29. Vital capacity/
30. Airway resistance/

31. Or/24-32
32. Infant, newborn/
33. Infant, low birth weight/
34. Infant, premature/
35. Neonate.mp.
36. Child*.mp.
37. Pediatr*.mp.
38. Adolescent*.mp.
39. School age.mp.
40. Child, Preschool/
41. or/34-42
42. 16 and 23 and 33 and 43

PEDro
Strategy 1
Field Title/abstract: Bronchopulmonary dysplasia
Field Therapy: respiratory therapy
Field METHODS: clinical trial
Field Problem: No appropriate

Strategy 2
Field Title/abstract: Bronchopulmonary dysplasia
Field Therapy: respiratory therapy
Field METHODS: clinical trial
Field Problem: impaired ventilation

SciELO

Displasia broncopumonar or bronchopulmonary dysplasia [all indexes]

■ RESULTS

A total of 1789 articles were identified, 61 titles of which were selected for analysis of their respective abstracts. Next, 33 articles were shortlisted for full review, and 11 were excluded because they did not meet the inclusion criteria. The final sample consisted of 22 articles as shown in the flowchart (figure 2).

Of the 22 articles included (table 1), 12 assessed children with a history of BPD at different moments (longitudinal)[7-16,27,28] and the maximum follow-up was the interval between the neonatal hospital stay and five years of life. The remaining ten reviewed studies performed pulmonary function testing in one single moment (transversal).[17-22,29-32]

Figure 2: Flowchart showing selection of articles for review (adapted from Moher et al. 2009)
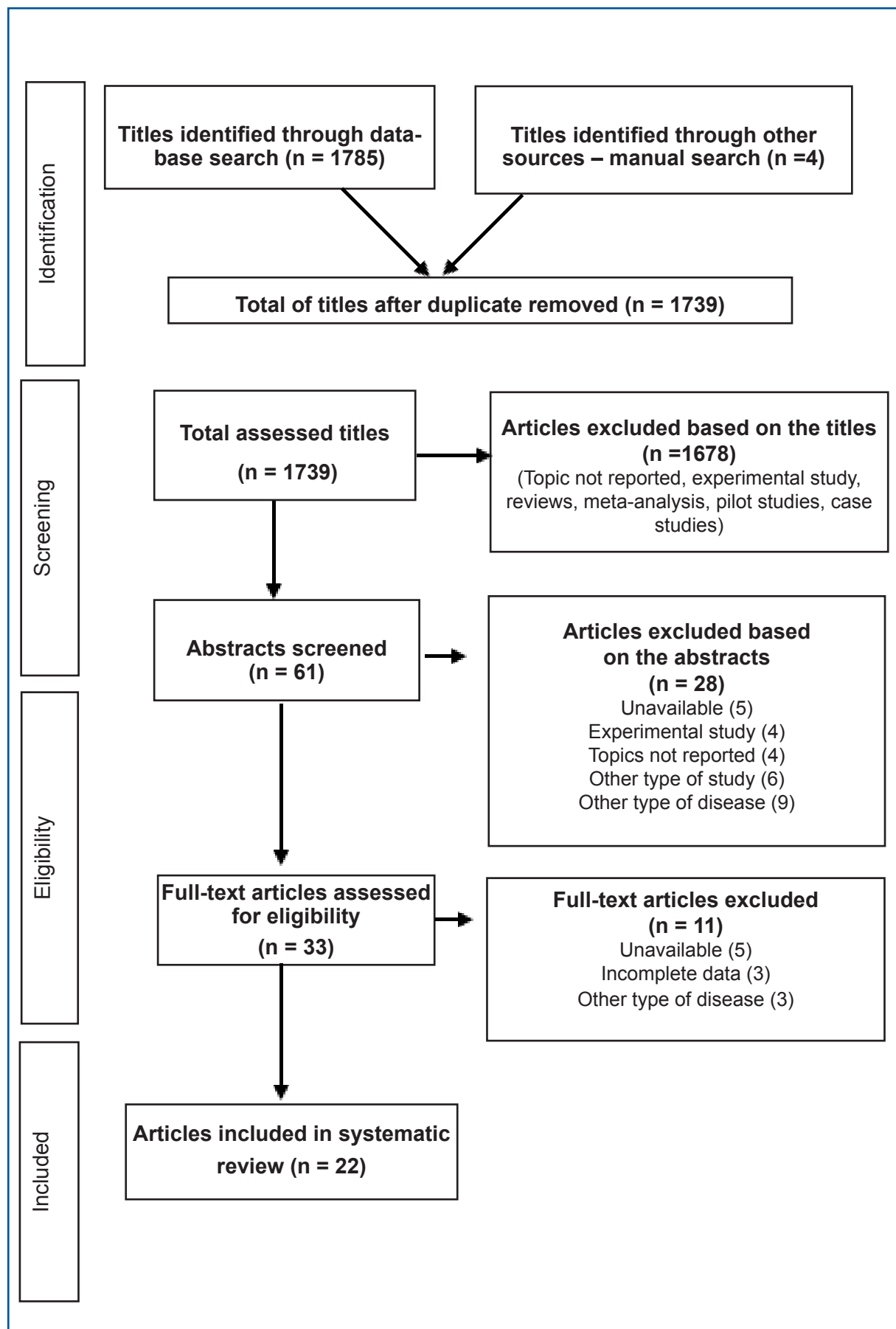
Table 1: Summary of articles selected for systematic review

Author, Year	Results
Tepper et al., 1986	Compared to CG, BPDG had lower FRC up to 10.5 months of PCA; BPDG showed decreased corrected and absolute expiratory flows compared to CG. The linear regression slope of the VMA-XFRC x length was lower in BPDG, indicating low AWs growth.
Hjalmarson et al., 2005	Severe BPD showed reduced FRC, less efficient gas mixture and higher specific conductance, compared with CG, mild and moderate BPD.
Farstad et al.,1995	RSR was higher in BPDG than in CG with 50 weeks of CA, but decreased with 120 weeks. Analysis of the VMAXFRC showed that 80% of the children with BPD and 58% of CG had severe peripheral obstruction with 50 weeks; no controls with 120 weeks (p <0.05) and 38% BPDG with severe obstruction.
Schmalisch et al., 2005	Differences between children with BPD and CG were found during tidal breathing of 0.45 vs 0.65; RR: 55.4 vs 39.2.
Filbrun et al., 2011	In the first evaluation, FEV0.5, FEV75, FEV 25-75 showed significant reduced values. In the re--evaluation, mean lung volume and flow remained close to the initial values, below the predicted, indicating lack of pulmonary growth. Children with above-average growth showed improved FVC, FEV0.5, TLC, and RV/TLC.
Baraldi et al., 1997	Severe changes in the mechanical properties of the RSR lung were found during the acute phase of BPD. The progressive improvement occurred from 3 months. At 24 months of age, RSR reached the normal range.
Schmalisch, 2012.	There was no significant difference between the groups regarding RR, TRR and AWs, or blood gas levels. CV, EV, pulmonary compliance and FRC were lower in children with BPD compared to CG. However, these differences became non-significant after normalization of body weight.
Boeck et al.,1998	There was no significant decrease in lung resistance after inhalation of salbutamol or ipratropium bromide in patients with BPD.
Pérez et al., 1999	Mean values for compliance and RSR were within normal range; mean value for peak expiratory flow time was below normal, indicating airway obstruction.
Robin et al., 2004	BPDG showed lower FEV0.5, FEV75, FEV25-75; and FRC, RV, and RV/TLC higher than CG. In BPDG, 17 patients underwent a bronchodilator testing and only 6 showed bronchodilator response.
Thunqvist et al., 2014	Only FRC values and RS compliance at 18 months were not below the normal values; all other lung function measurements were significantly below normative values. During follow-up at 6 and 18 months, NB with respiratory symptoms had lower values of maximum and mean forced expiratory peak, and RS compliance value compared to individuals without symptoms.
May et al., 2011	NB who developed moderate/severe BPD had lower FRC values and compliance over the entire 28 day period, compared to those who did not develop BPD. The rate of improvement in FRC and compliance over the first 28 days was higher in NB with moderate/severe BPD.
Balinotti et al., 2010	Individuals with BPD had a significant decrease in lung diffusion compared to CG subjects. Pulmonary capacity was significantly lower for individuals with BPD compared to CG.
Mahut et al., 2007	Most children showed low VmaxFRC values, suggesting an obstructive pattern. Strong correlations were observed between FRC measurements and oxygen exposure.
Mallory et al., 1991	During the first 6 months of age in both groups, FVC was significantly lower in BPDG, compared to normal value. At 24 and 36 months of age, mean FVC was even lower in Group B than in Group A, but the difference was not significant.
Vural et al., 1996	Significant relationships were found between thoracic distension and duration of positive inspiratory pressure (P <0.05, r = 0.43), duration of positive expiratory pressure (P <0.05, r = 0.45), total time of oxygen therapy; between total lung resistance and duration of mechanical ventilation with high frequency (P <0.05: r = 0.52); between hypoxemia and time of oxygen therapy with FiO 2> -60% (P <0.05; r = 0.54).
Khoulood et al., 2010	Children with BPD had low expiratory airflow at 6, 12, and 24 months, respectively, with no significant improvement over time. FRC has increased significantly over time.
Vrijlandt et al., 2007	The resonance frequency was higher in BPD compared to non-BPD (mean of 26.8 vs 22.7, P <0.001) and lower mean reactance X4-24 (hPa.s / l) (- 3.0 vs. -1.9, P< 005).
Greenough et al., 2005	Children with BPD showed significantly lower pulmonary values, compared with non-BPD children.
Kavvadia et al., 1998	FRC at 14 and 28 days were lower in group A than in group C (P <0.01). Group B showed lower difference (P <0.05) at 28 days, when compared to group C.
Wei et al., 2013	In moderate and severe BPD groups, RR was higher than in the non- BPD group. In the BPD group, FRC was higher than the moderate and severe groups.
Fouzas et al., 2013	Capnography waveforms in phase II (SII) and III (SIII) were more pronounced in children with BPD compared to healthy preterm and full-term infants.

Legend: CG: control group; BPDG: group with bronchopulmonary dysplasia; FRC: functional residual capacity; PCA: post- conceptional age; AWs: airways; RSR: respiratory system resistance; CA: corrected age; RR: respiratory rate; FEV0.5: forced expiratory volume at half second; FEV75: forced expiratory volume at 75% of curve of forced vital capacity; FEV25-75: forced expiratory volume between 25 and 75% curve of forced vital capacity; FVC: forced vital capacity; TLG: total lung capacity; RV: residual volume; RV/TLC: residual volume and total lung capacity ratio; TRR: total respiratory resistance; CV: current volume; EV: expiratory volume; RS: respiratory system; NB: new-born; FiO2: fraction of inspired oxygen.

DISCUSSION

Notably, maintaining the integrity of the respiratory system in the first two years of life is essential and will determine the improvement of gas exchange and respiratory reserve after infancy[33] as this is the period of greatest alveolar growth[34]. In this review, the studies suggest that respiratory symptoms and pulmonary function seem to improve in early childhood[7,8,10,12,27] with the growth and development of the child with a history of BPD. Farstad et al.[12] found that, at 50 weeks of corrected age (CA), 80% of the children with BPD in their study sample had severe peripheral obstruction, compared to 58% of preterm infants without BPD. In the reevaluation period (120 weeks of CA), only 38% of the children with BPD presented with severe obstruction versus no preterm children. According to Sanchez et al.[35] the progressive improvement of capacity and flow-volume curves in this population is proportional to the increase in weight and length of infants. On the other hand, Hjalmarson et al.[13] observed that the pulmonary function in infants using bronchodilators remains reduced even after normalization of weight, compared to healthy infants. However, these alterations may not be significant considering the normal values of pulmonary function parameters[12,17]. In this context, some authors[7,8,10] point out that improved pulmonary function during infancy is more evident in children with moderate/severe BPD, compared to those with mild BPD, or in preterm infants without BPD[28].

It is well-established that some complications caused by BPD in early childhood may favor high rates of respiratory infections, recurrent wheezing and hospital readmissions[12,28,33,34,36]. According to a study conducted by Tepper et al.[14] 55% of infants with BPD required prehospitalization during the first year of life due to diseases of the lower respiratory tract. The incidence of respiratory morbidity and prehospitalization has been lower in healthy full-term infants[28], as well as in preterm infants who developed respiratory distress syndrome[12] when compared to infants with bronchopulmonary dysplasia . However, Mahut et al.[29] observed that there is no difference in pulmonary function among BPD infants with frequent symptoms and those with fewer or no symptoms, and all of them showed reduced FRC. These results suggest that pulmonary function as well as other factors may be involved in the high susceptibility to respiratory infections in this population.

Another topic identified in the current review is the response of BPD children to bronchodilators. The selected studies demonstrate no reduction in inspiratory and expiratory resistance after the use of bronchodilators in most children with a history of BPD.

Children who respond to these medications show greater abnormalities in pulmonary function parameters than non-responders[22,32]. According to Fakhoury et al.[23] up to 3 years of age, only 20 to 30% of children with moderate to severe BPD show bronchodilator response. Therefore, this drug should not be indicated for all patients with BPD, but only for responders or patients show worsening in wheezing during acute respiratory exacerbation[22,32].

Current articles and reviews have shown limited pulmonary function, functional capacity and quality of life of schoolchildren[37] and adults[38] with BPD. However, the impact of BPD on infants and preschool children has not been often discussed. This review was able to collect results of current studies about the disease in this age group. A limitation of this review is the lack of classification of the methodological quality, by means of valid instruments.

In summary, children with a history of BPD usually show alterations in pulmonary function in the first three years of life, which seems to improve with growth and become non-significant after body weight adequacy. However, when comparing BPD children with full-term children, this limitation can still be observed. Also, most BPD children do not show positive response in pulmonary function after the use of inhaled bronchodilator. But, responders have compromised pulmonary function.

Admittedly, there is a gradual improvement of pulmonary function in the first years of life. Therefore, public health professionals involved in the care of this population should consider the importance of nutritional aspects and prevention of respiratory infections in this period, in order to allow conditions for adequate pulmonary growth and development. This may attenuate alterations in pulmonary function due to neonatal injury. Furthermore, early identification of possible impairment of pulmonary function may help pediatricians and/or pulmonologists to prevent disease complications by means of strategies, e.g., to encourage children to keep regular physical activities as soon as possible, and to refer patients for physical therapy as a preventive measure or during acute respiratory events.

CONCLUSION

It could be observed that children diagnosed with BPD during the neonatal period showed expiratory flow limitation and reduced FRC when assessed in early childhood, compared to healthy full-term and preterm children. Most children show improved values of pulmonary function with growth and normalization of weight.

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Resumo

Introdução: A displasia broncopulmonar (DBP) é uma doença pulmonar crônica multifatorial que interrompe o desenvolvimento pulmonar, podendo repercutir em comprometimento da função pulmonar na primeira infância, que pode perdurar durante a idade escolar, adolescência, até a idade adulta.

Objetivo: Analisar, através de uma revisão sistemática, as repercussões da DBP na função pulmonar de crianças na primeira infância.

Método: Foram realizadas buscas sistematizadas em três bases de dados eletrônicas (Medline, SciELO e PEDro). Dois examinadores independentes analisaram sistematicamente os títulos, resumos e textos na íntegra, considerando os seguintes critérios de inclusão: estudos que avaliaram a função pulmonar de crianças com até 5 anos de idade que apresentaram diagnóstico de DBP no período neonatal.

Resultados: Inicialmente foram identificados 1789 artigos, sendo que a amostra final foi composta de 22 artigos. Evidenciou-se que crianças com DBP apresentam na primeira infância limitação dos fluxos expiratórios e redução da capacidade residual funcional. Estas alterações podem ser normalizadas ou minimizadas com o crescimento e adequação de peso, porém, a função pulmonar das crianças com história de DBP continua reduzida em comparação a crianças hígidas nascidas a termo. Ainda, a maioria delas não apresenta respostas positivas nos valores de função pulmonar com o uso de broncodilatadores.

Conclusão: Crianças com DBP apresentam alterações na função pulmonar, podendo melhorar com o crescimento, sendo que a maioria não responde positivamente ao broncodilatador.

Palavras-chave: displasia broncopulmonar, doenças pulmonares, lactente, testes de função respiratória, criança.