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Clinical

Respiratory dysfunction in Parkinson's disease

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Abstract

Respiratory dysfunction has been associated with Parkinson's disease since it was first described in 1817. The respiratory symptoms observed in Parkinson's disease patients vary greatly. Most patients remain asymptomatic, whereas others present with acute shortness of breath and even stridor.

In August 2016, an electronic literature search was conducted using PubMed and Google Scholar. Results were screened and studies reporting on respiratory dysfunction associated with Parkinson's disease were included.

Respiratory dysfunction is due to a combination of factors including restrictive changes, upper airway obstruction, abnormal ventilatory drive and response to medications.

Much debate surrounds the mechanism underlying respiratory dysfunction in Parkinson's disease, its prevalence and the effect of levodopa on respiration. It is clear from this review that larger studies, comparing patients of similar disease duration and severity using the same pulmonary function parameters, are required to provide a better understanding of the pathophysiology underlying respiratory dysfunction in Parkinson's disease.

Keywords dyspnoea, Parkinson's disease, pulmonary function tests, respiratory dysfunction

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Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder associated with tremor, rigidity, bradykinesia and postural instability. These abnormalities are not limited to the extremities but also affect the striated muscle within the upper airways and chest wall. Respiratory dysfunction has been associated with PD since James Parkinson first described it in 1817,[1] and it remains one of the most common causes of death in these patients.

Patients with PD may present with a variety of respiratory symptoms ranging from dyspnoea without any overt clinical evidence of respiratory dysfunction, exertional dyspnoea, daytime somnolence due to nocturnal hypoxia and acute stridor. The majority, however, remain asymptomatic even with grossly abnormal pulmonary function tests.[2] This may be due to the motor manifestations of their PD limiting their exercise tolerance; it may also be due to the heterogeneous nature of PD and how it affects each patient differently.

Shortness of breath in PD can be very distressing for patients and clinicians alike. Extensive investigations are carried out, often repeatedly during recurrent admissions, looking for infection, pulmonary emboli, heart failure and anxiety. Although these are possible in PD patients and should be excluded, clinicians must remember that PD itself and its medications can lead to shortness of breath through various mechanisms. Efficient ventilation depends on several factors including adequate airways, sufficient respiratory muscular function and a chemoreceptor drive to breathing.

PD can affect each of these to a varying degree. Several patterns of respiratory dysfunction have been described in PD, including: restrictive changes secondary to chest wall rigidity and reduction in lung volume secondary to kyphoscoliosis, upper airway obstruction, abnormal ventilatory control, diaphragmatic dyskinesias and pleuropulmonary complications of medications. In addition, although rare, shortness of breath is an important non-motor wearing off symptom.

There is controversy as to whether levodopa improves or worsens respiratory function. This review will not cover in detail the respiratory complications of PD but rather look at the spectrum of respiratory dysfunction in PD as well as the effects of levodopa on pulmonary function tests.

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Search strategy

An electronic literature search was conducted in August 2016, using PubMed and Google Scholar. The following search term were used: 'Parkinson's disease' combined with the Boolean operator 'AND' and each of the following terms: 'respiratory disorder'; 'respiratory dysfunction'; 'pulmonary disorder'; 'pulmonary dysfunction'. After duplicates were removed, the titles were initially scanned and abstracts of interest were reviewed. Only articles in the English language were included. The reference lists of all relevant articles were hand-searched for additional suitable articles.

Studies were included if they studied respiratory dysfunction in PD. Studies were excluded if they included the following criteria: (a) respiratory complications of PD; (b) animal studies; (c) neurological disorders other than PD, e.g. multi-system atrophy, dystonia, multiple sclerosis; and (d) conference abstracts. The literature search yielded 49 non-duplicated articles, of which 23 were suitable. After hand-searching the reference lists, a further two were included. The studies were undertaken between 1966 and 2016, and included small numbers of patients ranging from 12 to 78.

Findings

Upper airway obstruction

Upper airway obstruction (UAO) has been reported in over 33% of PD patients.[2,3] The most common and frequently reported manifestation of upper airway dysfunction is hypophonia, which affects up to 70% of patients.[4] Other potential features include 'shaky' voice, wheeze, and stridor.

Two other types of UAO have been described; both are often asymptomatic.[3] Prior to this classification, there was no general consensus as to the cause or site of obstruction. The first type of UAO, also referred to as 'respiratory flutter', is characterised by UAO with superimposed rapid oscillations of the supraglottic structures and vocal cords, which are apparent on flow volume loops generated by spirometry measurements. On direct fibreoptic visualisation, these oscillations correspond to the rhythmic 4–8 Hz resting tremor seen in PD patients. Vincken et al.[3] reported this to be present in 78% of their cohort and it is thought to be due to basal ganglia dysfunction.

The second type of UAO is characterised by irregular abrupt changes in the flow volume loop, which at times leads to complete obstruction. There is rounding off of the expiratory phase and a delayed peak. This was thought to be less common than the first type, occurring in only 22% of patients. However a more recent study[2] reported this as the most common type, observed in 82% of their cohort. This may be explained by the fact that a higher proportion of patients included in the first study had a peripheral tremor.[3]

The prevalence of UAO in PD patients ranges from 6.7% to 67%.[5,6] The differences in rates reported depended on whether levodopa was administered during the study or whether it was withheld.

In those patients whose levodopa was withheld, UAO was associated with abnormal inspiratory and expiratory flow rates in 62% of patients[6] consistent with older reports.[7,8] However, these older studies included patients with Parkinsonism and post-encephalitic Parkinsonism.

Lower rates of obstructive respiratory dysfunction were observed when levodopa was continued.[5,9] This suggests UAO may be sensitive to levodopa. Additional evidence for the positive effect of levodopa on UAO comes from reports of UAO with stridor and respiratory failure occurring when levodopa is stopped.[4] This is important to consider, especially in acutely unwell patients and those in the peri-operative period.

There is limited research looking at the relationship between UAO and other symptoms associated with PD. UAO has been observed in patients with a higher degree of rigidity, bradykinesia[6] and tremor.[8] A recent case-control study showed a negative correlation between UAO and the patient's age.[10] UAO has also been associated with a higher degree of dorsal column arthrosis, most likely due to restriction in movement.[6] Pulmonary function tests are not only limited by cervical restriction but also affected by thoraco-abdominal movements. In patients with PD, a reduction in percentage vital capacity correlates with chest movements, and a reduction in percentage forced vital capacity (FVC) correlates with abdominal movements.[11]

The overall prevalence of UAO appears to be diminishing in PD patients. This may reflect the increasing diagnostic accuracy of UAO and its management or it may reflect a therapeutic effect of levodopa.[5] It may also reflect the types of patients studied. Earlier studies investigating respiratory dysfunction in PD included patients who were post encephalopathic, smokers, ex-smokers and patients with chronic obstructive pulmonary disease, which may bias their results.

Restrictive respiratory dysfunction

The mechanisms underlying the restrictive pattern of respiratory dysfunction observed in PD patients are not fully understood. It is likely to result from a combination of factors including increased rigidity of the chest wall, a theory supported by electromyographic studies of respiratory muscles[12] which reveal abnormal activity throughout the respiratory cycle with a frequency similar to 4–8 Hz; reduction in lung volume secondary to kyphoscoliosis leading to reduced ventilation; and pleuropulmonary changes secondary to long term ergot-derived dopamine agonist use.

The frequency of restrictive respiratory dysfunction reported in PD varies from 28%[6] to 94%,[13,14] depending on the cohort studied, the severity of the disease and whether patients were taking levodopa or not. Typical symptoms are those of exertional dyspnoea.

Since Sabate et al. in 1996,[6] higher incidences of restrictive respiratory disease have been observed in PD patients[13–15] and a link between this and the motor manifestations of PD has been described. A restrictive pattern has been shown to correlate with falls and freezing but not with tremor, rigidity or bradykinesia.[6] There is also a correlation with a moderate decrease in dorsal extension of the cervical neck.[6] However, other studies dispute this finding. One reported a significant correlation between restrictive respiratory dysfunction and the severity of PD, as well as, to a lesser extent, the duration of the disease.[15] Another reported rigidity and bradykinesia correlate with a restrictive pattern, especially in female PD patients, but no link to tremor was noted.[16]

The effect of levodopa on restrictive respiratory disease is controversial. Some authors have shown an improvement in respiratory function after levodopa[13,14,16] whereas others did not.[17] These discrepancies may be due to differences in the patient's age, disease duration and severity and techniques used to assess respiratory function as well as the parameters measured.

Abnormal central control of ventilation

Dyspnoea in PD can occur through both a central and peripheral mechanism. It is defined by the American Lung Association as a 'subjective experience of breathing discomfort that derives from interactions among multiple physiological, psychological, social and environmental factors'.[18]

As discussed, many patients have respiratory dysfunction; yet the majority remain asymptomatic and do not report dyspnoea. The reason for this may be twofold. First, as the disease progresses, the motor manifestations of PD limit a patient's exercise tolerance and so respiratory problems may not manifest themselves. Second, PD patients have been shown to have an impaired perception of dyspnoea (POD). Those who report dyspnoea with no objective evidence of respiratory dysfunction are often mistakenly diagnosed as anxious or depressed. An increased and a decreased POD have been reported in PD patients.[17,19] An impaired POD may be due to peripheral factors, e.g. muscle weakness, restrictive respiratory pattern or UAO, or it may be due to an abnormal respiratory drive.

Normally the respiratory drive is influenced by hypercapnia. However, in PD there is a reduced response to carbon dioxide.[20] This abnormality of central ventilatory control may be explained, in part, by the Braak hypothesis,[21] which suggests there is early brainstem involvement in PD with selective degeneration of the dopaminergic cells in the medulla.[3,17] The carotid body is highly dopaminergic and plays a role in the ventilatory response to hypoxia. Seccombe et al.[20] did not find an abnormal response to mild hypoxia, contradicting previous studies that showed patients in the early stages of PD to have a subnormal response to hypoxia,[19, 22] in addition to a reduced POD and a normal response to hypercapnia.[19] The mild hypoxia challenge used in the first study may account for the lack of response seen.

The reduced POD reported is not consistent with a more recent study,[23] which showed PD patients to have a heightened POD that decreased significantly after levodopa administration, yet still remained higher than normal subjects. The patients studied may explain this increased POD reported, as in contrast to the first paper,[19] they had longstanding PD and had abnormal pulmonary function tests. Thus, mechanical ventilatory factors may have contributed to the increased POD they reported.

Levodopa leads to a significant improvement in POD without an improvement in pulmonary function tests, suggesting that levodopa is acting centrally.[17,20] There is a paucity of evidence for investigations into brainstem-mediated function in these patients; however, it seems plausible that as PD progresses with further loss of dopaminergic cells in the midbrain and basal ganglia, there is also further loss in the medulla, thus leading to a worsening of respiratory function and ventilation.

In addition to levodopa, specific inspiratory muscle training has been shown to decrease POD by improving inspiratory muscle strength and endurance. Despite this, there was no associated improvement in quality of life assessed using questionnaires.[22]

Drugs and respiratory dysfunction

Levodopa is the gold standard treatment for PD, but its effects on respiratory function are not clear. There are reports that levodopa improves both UAO and restrictive respiratory dysfunction,[2,9,13,16] has no effect[7] or even worsens respiratory function.[17,24] One study demonstrated an improvement in respiratory musculature and pulmonary function tests following apomorphine.[25]

The differences reported in these studies may be accounted for by the number of patients studied, disease duration and severity, and the severity of the respiratory disease. As PD progresses, levodopa becomes less efficacious. Respiratory dysfunction has been shown to worsen as disease progresses[4] and one wonders whether respiratory dysfunction also becomes less responsive to levodopa?

Upper airways obstruction

Levodopa has been shown to induce significant variations in peak expiratory flow and UAO ratios with a reduction in UAO.[9,26] It has also been linked to an increase in total lung capacity;[26] however, a more recent study showed no increase in total lung capacity.[9] Obenour et al.[7] found no change in pulmonary function tests following levodopa administration and Lim et al.[27] actually found an improvement in FVC and forced expiratory volume in one second (FEV1) when levodopa was stopped. However, it must be noted that these changes were small and did not reach statistical significance.[27]

Restrictive respiratory dysfunction

A meta-analysis, consisting of four trials with 73 patients in total, concluded levodopa improved FVC and peak expiratory flow but had no effect on FEV1 and the FEV1/FVC ratio.[28]

Side effects of Parkinson's disease medications

Levodopa and ergot-derived dopamine agonists may also induce respiratory dysfunction in PD. Levodopa-induced diaphragmatic dyskinesias may lead to rapid strenuous and distressful dyspnoea.[29,30] Additionally, dyspnoea may also occur as a wearing off phenomenon in PD patients taking levodopa. Pleuropulmonary fibrosis and pleural effusions have been reported in patients taking ergot-derived dopamine agonists. It usually develops within three years of starting these medications, although it has been reported in a patient after 11 years.[31]

Conclusion

Respiratory dysfunction remains the most common cause of death in patients with PD. There are several possible mechanisms for the respiratory dysfunction observed in PD patients and it is likely to be due to a combination of these.

The prevalence of both obstructive and restrictive pulmonary dysfunction varies greatly between studies. The discrepancies noted can be explained by the number of patients studied (as very small numbers were included in each publication); the past medical history of the patients included; the pulmonary function test parameters used; and whether levodopa was held or continued during the study. It may also be explained by the heterogeneous nature of PD itself.

The role of levodopa in respiratory dysfunction is controversial. Only one meta-analysis including four studies was found in our search. More studies are required with larger numbers of patients to conclusively ascertain its effects on both obstructive and restrictive respiratory dysfunction in PD and to investigate whether it is worth considering starting levodopa early in these patients in order to prevent further progression of their respiratory dysfunction.

Greater awareness of respiratory dysfunction in PD may better equip clinicians to identify signs and symptoms earlier, thus avoiding extensive unnecessary investigations but also preventing complications. It may also prompt clinicians to ask about respiratory symptoms in PD patients, leading to appropriate investigations being conducted early on. Currently there is no evidence base for conducting pulmonary function tests in asymptomatic patients. Yet we know the majority remain asymptomatic, even with profoundly abnormal pulmonary function tests. To help clinicians identify those who should be investigated, it would be useful if studies were carried out that looked at whether investigating asymptomatic patients is feasible and valid. There is strong evidence that longitudinal spirometry measurements of acceptable quality can be obtained in patients with PD, even when motor fluctuations are present[32] and it would also allow clinicians to monitor progress during treatment and exercise programmes.

It is of vital importance that more systematic studies are conducted to investigate respiratory dysfunction in PD, as well as the effect of levodopa on respiratory dysfunction, respiratory muscle strength and its effect on central ventilatory control.

References

1 Parkinson J. *An Essay on the Shaking Palsy*. London: Whittingham and Rowland for Sherwood, Neely, and Jones; 1817.
2 Hovestadt A, Bogaard JM, Meerwaldt JD et al. Pulmonary function in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989; 52: 329–33.
3 Vincken WG, Gauthier SG, Dollfuss RE et al. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med* 1984; 311: 438–42.
4 Shill H, Stacy M. Respiratory Complications of Parkinson's disease. Semin Respir Crit Care Med 2002; 23: 261–6.
5 Izquierdo-Alonso JL, Jiménez-Jiménez FJ, Cabreara-Valdivia F et al. Airway dysfunction in patients with Parkinson's disease. *Lung* 1994; 172: 47–55.
6 Sabate M, Gonzalez I, Ruperez F et al. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci* 1996; 138: 114–9.
7 Obenour WH, Stevens PM, Cohen AA et al. The causes of abnormal pulmonary function in Parkinson's disease. *Am Rev Respir Dis* 1972; 105: 382–7.
8 Neu HC, Connolly JJ Jr, Schwertley FW et al. Obstructive respiratory dysfunction in Parkinsonian patients. *Am Rev Respir Dis* 1967; 95: 33–47.
9 Herer B, Arnulf I, Housset B. Effects of levodopa on pulmonary function in Parkinson's disease. *Chest* 2001; 119: 387–93.
10 Owolabi LF, Nagoda M, Babadhani M. Pulmonary function tests in patients with Parkinson's disease: A case – control study. *Niger J Clin Pract* 2016; 19: 66–70.
11 Tamaki A, Matsuo Y, Yanagihara T et al. Influence of thoracoabdominal movement on pulmonary function in patients with Parkinson's disease: comparison with healthy subjects. *Neurorehabil Neural Repair* 2000; 14: 43–7.
12 Estenne M, Hubert M, De Troyer A. Respiratory muscle involvement in Parkinson's disease. *N Engl J Med* 1984; 311: 1516–7.
13 Sathyaprabha TN, Kapavarapu PK, Pal PK et al. Pulmonary functions in Parkinson's disease. *Indian J Chest Dis Allied Sci* 2005; 47: 251–7
14 De Pandis MF, Starace A, Stefanilli F et al. Modification of respiratory function parameters in patients with severe Parkinson's disease. *Neurol Sci* 2002; 23: S69–70.
15 Wang Y, Shao W, Gao L et al. Abnormal pulmonary function and respiratory muscle strength findings in Chinese patients with Parkinson's disease and multiple system atrophy–comparison with normal elderly. *PloS ONE* 2014; 9(12).
16 Pal PK, Satyaprabha TN, Tuhina P et al. Pattern of subclinical

pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord* 2007; 22: 420–4.
17 Weiner WJ, Goetz CG, Nausieda PA et al. Respiratory dyskinesias: extrapyramidal dysfunction and dyspnea. *Ann Intern Med* 1978; 88: 327–31.
18 American Thoracic Society; Dyspnea. Mechanism, assessment and management: A consensus statement. *Am J Respir Crit Care Med* 1999; 159: 321–49.
19 Onodera H, Okabe S, Kikuchi Y et al. Impaired chemosensitivity and perception of dyspnoea in Parkinson's disease. *Lancet* 2000; 356: 739–40.
20 Seccombe LM, Giddings HL, Rogers PG et al. Abnormal ventilatory control in Parkinson's disease – further evidence for non-motor dysfunction. *Respir Physiol Neurobiol* 2011; 179: 300–4.
21 Braak H, Brack E. Pathoanatomy of Parkinson's disease. *J Neurol* 2000; 247(suppl 2): 3–10.
22 Serebrovskaya T, Karaban I, Mankovskaya I et al. Hypoxic ventilatory responses and gas exchange in patients with Parkinson's disease. *Respiration* 1998; 65: 28–33.
23 Inzelberg R, Peleg N, Nisipeanu P et al. Inspiratory muscle training and the perception of dyspnea in Parkinson's disease. *Can J Neurol Sci* 2005; 32: 213–7.
24 De Keyser J, Vincken W. L-dopa-induced respiratory disturbance in Parkinson's disease suppressed by tiapride. *Neurology* 1985; 35: 235–7.
25 De Bruin PF, de Bruin VM, Lees AJ et al. Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis* 1993; 148: 1576–80.
26 Nakano KK, Bass H, Tyler HR. Levodopa in Parkinson's disease: effect on pulmonary functions. *Arch Intern Med* 1972; 130: 346–8.
27 Lim A, Leow L, Huckabee ML et al. A pilot study of respiratory and swallowing integration in Parkinson's disease: 'on' and 'off' levodopa. *Dysphagia* 2008; 23: 76–81.
28 Monteiro L, Souza-Machado A, Valderramas S et al. The effect of levodopa on pulmonary function in Parkinson's disease: a systematic review and meta-analysis. *Clin Ther* 2012; 34: 1049–55.
29 Mehanna R, Jankovic L. Respiratory problems in neurologic movement disorders. *Parkinsonism Relat Disord* 2010; 16: 628–38.
30 Xie T, Guan R, Staisch J et al. Respiratory dyskinesia in a patient with Parkinson's disease successfully treated with STN DBS. *Neurology* 2015; 85: 479–80.
31 Tintner R, Manian P, Gauthier P et al. Pleuropulmonary fibrosis after long-term treatment with dopamine agonist pergolide for Parkinson's disease. *Arch Neurol* 2005; 62: 1290–95.
32 Hampson NB, Kieburtz KD, LeWitt PA et al. Prospective evaluation of pulmonary function in Parkinson's disease patients with motor fluctuations. *Int J Neurosci* 2016; 26: 1–20.