

# Biphasic (Subtherapeutic) Levodopa-Induced Respiratory Dysfunction in Parkinson Disease

Veerle A. van de Wetering-van Dongen, MSc, Alberto J. Espay, MD, MSc, Luca Marsili, MD, PhD, Andrea Sturchio, MD, Susanne Ten Holter, MD, Bastiaan R. Bloem, MD, PhD, and Maarten J. Nijkrake, PhD

## Correspondence

Ms. van de Wetering-van Dongen  
veerle.vandewetering-vandongen@  
radboudumc.nl

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## Abstract

### Objective

To evaluate 3 cases illustrating a rarely recognized phenotype of Parkinson disease (PD), namely, biphasic levodopa-induced respiratory dysfunction manifesting as dyspnea.

### Methods

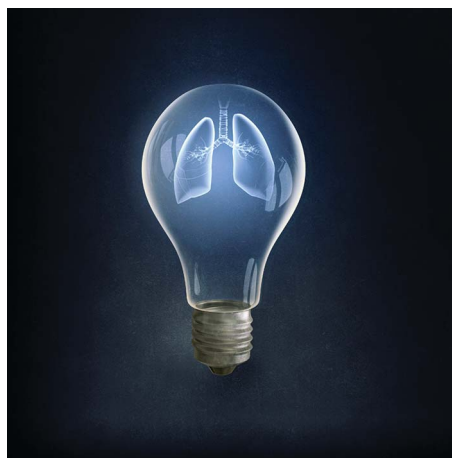
To appreciate the nature of the fluctuations of respiratory function in response to levodopa, we measured changes in respiratory muscle control before and after the best therapeutic response to levodopa in 3 PD patients with fluctuating dyspnea.

### Results

Episodes of breathlessness were accompanied by shallow tachypnea and reduced respiratory muscle control, as measured by maximal expiratory pressure, peak cough flow, and forced expiratory volume in 1 second.

### Conclusions

The spectrum of respiratory dysfunction in PD includes a biphasic reduced respiratory muscle control accompanying periods when the effect of levodopa is subtherapeutic. This biphasic levodopa-related complication represents a rarely recognized nonmotor phenomenon in PD. Management requires increasing the levodopa dose, shortening the interdose interval, or implementing a program of continuous dopaminergic stimulation.



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Respiratory dysfunction in Parkinson disease (PD) is incompletely understood but seems largely related to cardinal motor features such as bradykinesia, chest wall rigidity, and dystonia.<sup>1</sup> These motor features may influence the breathing pattern so that both respiratory muscle control and strength are reduced, thus causing upper airway obstructions and restrictive respiratory dysfunction.<sup>2</sup> In addition, chest wall rigidity limits lung expansion and increases the risk of atelectasis.<sup>3</sup> Signs of impaired inspiratory muscle strength and control are found already early in the disease in terms of a reduced inspiratory mouth pressure.<sup>4</sup>

The effects of levodopa on respiratory functions are somewhat controversial. A meta-analysis supports a positive effect of levodopa on respiratory functioning by improving forced vital capacity (FVC) and peak cough flow (PCF) during the “on” medication state

Department of Rehabilitation (VAvdW-vD, MJN), Radboud University Medical Center, Donders Center for Brain, Cognition and Behavior, Nijmegen, the Netherlands; Department of Neurology (AJE, LM, AS), UC Gardner Neuroscience Institute, Gardner Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, OH; and Department of Neurology (STH, BRB), Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Center of Expertise for Parkinson and Movement Disorders, Nijmegen, the Netherlands.

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compared with the “off” state.<sup>5</sup> However, the long-duration response of respiratory function to levodopa remains unclear.<sup>6,7</sup> We describe 3 patients with PD reporting breathlessness before and after the best therapeutic response to levodopa, suggesting a biphasic respiratory dysfunction, a previously rarely recognized nonmotor phenomenon in PD.

### Case 1

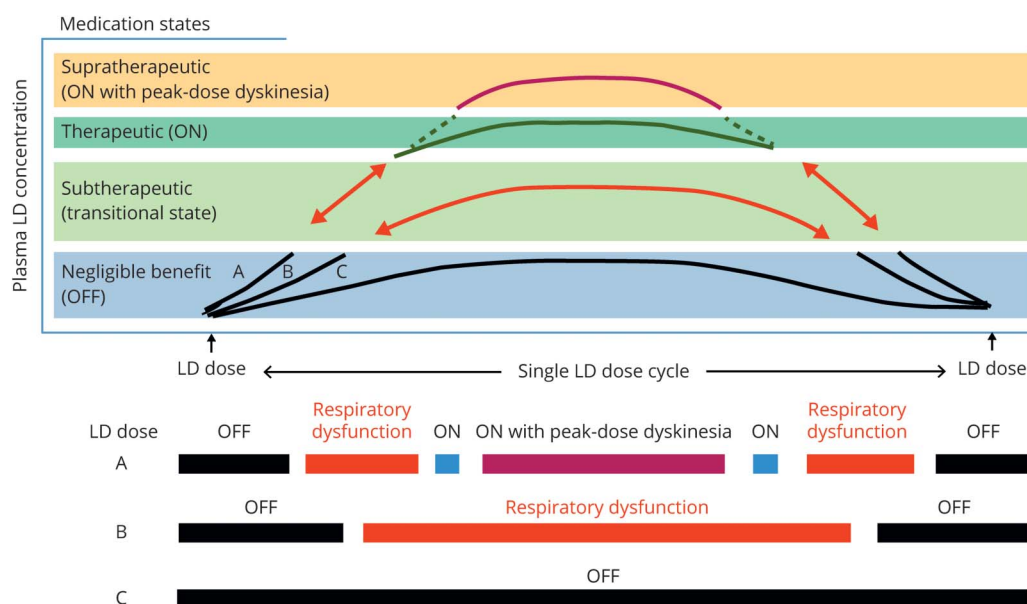
This nonsmoking 69-year-old woman, with a prior history of arterial hypertension, had tremor-dominant PD for 2 years. She responded positively to levodopa/carbidopa 100/25 mg 5 times daily. Soon after treatment initiation, she started experiencing breathlessness after taking each medication. This feeling persisted for around 45 minutes (“before the best on-state”). During these moments, she described a sensation of emptiness in her lungs, as if her chest was tightened by a chain. She could not be active during these episodes, forcing her to remain seated until she entered her on-state, at which point this sensation disappeared. Two hours after she had taken medication and just before she needed to take her next dose, similar breathlessness reappeared. A similar pattern appeared throughout all medication cycles. To objectively document her respiratory symptoms, we quantified motor functioning (Movement Disorders Society–Unified Parkinson Disease Rating Scale [MDS-UPDRS] part III), vital signs (heart rate, pulse oximetry, and blood pressure), and respiratory function tests (FVC, forced expiratory volume in 1 second [FEV<sub>1</sub>], maximum inspiratory pressure [MIP], maximum

expiratory pressure [MEP], and PCF). Assessments were made in the (1) “off-state,” >12 hours after her last dose; (2) “before on-state,” 30 minutes after intake of a supra-maximal levodopa dose (150% of normal dose); and (3) “supra on-state,” 60 minutes after intake of a supramaximal levodopa dose (figure). The 150% dose was 1.5 dispersible tablet “125” Madopar, containing levodopa 150 mg and benserazide 37.5 mg. All respiratory function tests (FEV<sub>1</sub>, MEP, and PCF) decreased during the “before on-state” and increased to higher, near “off-state” values in the “supra on-state” (table). No differences were found for FVC during the medication challenge. Both UPDRS part III and MIP improved in the “supra on-state” compared with the “off-state.” MIP did not evidently decrease in the “before on-state.” Based on these findings, the levodopa dose was increased by 50 mg at every other dose. The biphasic episodes of breathlessness did not fully disappear but were perceived as less troublesome.

### Case 2

This nonsmoking 67-year-old man, with a history of arterial hypertension and third-degree atrioventricular block, was diagnosed with PD 5 years before this evaluation. He was initially treated with 4 tablets, 3 times daily of levodopa/carbidopa 50/12.5 mg. Two years previously, this was changed to 3 tablets, 4 times daily. Over the past 14 months, he experienced an unpleasant tightness around his chest, neck, and face and a shortness of breath soon after taking each medication dose. These sensations persisted for around 45 minutes (“before ON state”) but disappeared during a

**Figure** Diagrammatic Relationship of Biphasic Respiratory Dysfunction in the Levodopa Dose Cycle of Cases 1, 2, and 3



Scenario A: a true biphasic pattern of respiratory dysfunction occurs before and after a full-ON medication state. Scenario B: because the on-state is associated with a narrow therapeutic window and, in some cases, severe peak-dose dyskinesia, a lower dose may avoid peak-dose dyskinesia at the expense of biphasic respiratory dysfunction lasting most of the cycle in a square-wave pattern. Scenario C: to avoid both severe peak-dose dyskinesia and respiratory dysfunction, some patients may opt to remain in a “light” off-state, an undermedicated state below the transitional state. LD = levodopa.

**Table** Respiratory Function Tests and Vital Signs in the Levodopa Dose Cycle of Cases 1 and 2

	Off-state	Before on-state	Supra on-state
<b>Case 1</b>			
<b>FVC (L, % of predicted)</b>	2.51, 99%	2.48, 98%	2.49, 98%
<b>FEV<sub>1</sub> (L, % of predicted)</b>	1.88, 88%	1.02, 48%	1.20, 57%
<b>MIP in cm H<sub>2</sub>O</b>	53	52	61
<b>MEP in cm H<sub>2</sub>O</b>	66	57	76
<b>PCF (L/m)</b>	259	199	274
<b>Heart rate (bpm)</b>	86	80	75
<b>SaO<sub>2</sub></b>	99	98	99
<b>Blood pressure</b>	178/107	140/90	135/86
<b>UPDRS part III</b>	37		16
<b>Case 2</b>			
<b>FVC (L, % of predicted)</b>	5.08, 115%	4.97, 112%	—
<b>FEV<sub>1</sub> (L, % of predicted)</b>	4.03, 119%	3.9, 115%	—
<b>MIP in cm H<sub>2</sub>O</b>	46	54	—
<b>MEP in cm H<sub>2</sub>O</b>	96	125	—
<b>PCF (L/m)</b>	502	326	—

Abbreviations: bpm = beats per minute; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; PCF = peak cough flow; UPDRS = Unified Parkinson Disease Rating Scale part III.

All respiratory function tests were captured in the sitting position and according to the procedure of the American Thoracic Society (ATS) and European Respiratory Society (ERS).

subjectively good “on-state.” Approximately 2 hours after having taken his medication and just before he needed his next dose, the same episode reappeared. A similar pattern was found during the other 3 medication cycles of the day. Switching to levodopa/benserazide at the same dose was tried to reduce this symptoms but did not alter the problem. We measured motor functioning (UPDRS part III, item 3.14) and respiratory function tests (FVC, FEV<sub>1</sub>, PCF, and MIP) during an outpatient visit to evaluate him during (1) an “off-state,” after 6.5 hours without medication and (2) “before on-state,” 30 minutes after intake of a supramaximal levodopa dose (125% of normal dosage) (figure). The 125% dose consisted of a dispersible tablet containing levodopa/benserazide 200/50 mg. During the “off-state,” we observed left-sided predominant rigidity and bradykinesia (UPDRS part 3, item 3.14 was scored as 3/4) with right arm and leg dystonic posturing associated with a feeling of tightness around the chest. During the “before on-state,” there was improvement of rigidity and bradykinesia (UPDRS part 3, item 3.14 decreased to 2/4), but dystonic dyskinesia increased in the right hand with clear dystonic posturing of his neck and orofacial region. The tightness around his chest, neck, and face worsened, and he reported shortness of breath. Respiratory function tests showed only a decrease in PCF in the “before on-state” (table). Other respiratory function tests showed no substantial differences between the

“off-state” and “before on-state.” Based on these findings, the dose of 50/12.5 mg levodopa/benserazide remained the same, at 3 tablets each, but the frequency increased from 4 to 5 times a day. He experienced improvement of his symptoms with only a slight residual shortness of breath shortly after taking his medication.

### Case 3

This 68-year-old woman with a 7-year history of PD, heralded by left foot tremor, started to experience motor fluctuations with left leg pain and chorea during wearing-off periods within 1 year after being initiated on levodopa/carbidopa 50/12.5 mg (half of a 100/25 tablet) 3 times daily. These off periods resolved by increasing levodopa/carbidopa to 100/25 mg 4 times daily. However, within 3 years after symptom onset, levodopa was associated with troublesome upper-body-predominant peak-dose dyskinesia, which prompted a reduction in the dose, but at the price of a reemergence of wearing-off-related left leg pain and choreoathetosis. These periods also became associated with intense, disabling shortness of breath (videos 1 and 2). She was eventually switched to extended-release levodopa/carbidopa (Rytary, Amneal Pharmaceuticals) 195/48.75 mg, 2 capsules 4 times daily. The episodes of difficulty breathing continued to be timed between 30 and 45 minutes before the optimal effect of each dose (“before on-state”) and 3 hours after the

full effect of each dose. Some episodes lasted longer, spanning more than 1 dose cycle (as she explains in video 1). Some accompaniments included a sensation of “ear popping,” excess phlegm, and “an ocean roaring in my head.” She used menthol cough drops and sodium chloride nasal spray to attenuate these episodes. She also observed that chewing ice could provide immediate relief or “clog me more.” During these periods, she noted painful left foot inversion with toe curling. She was started on continuous 16-hour levodopa subcutaneous infusion (experimental but open-label ND0612, NeuroDerm), increasing the levodopa-equivalent dose from 780 mg to 1500 mg/d, which markedly reduced the frequency and severity of these respiratory episodes.

### Data Availability

Any anonymized data not published within the article can be shared by request from any qualified investigator.

## Discussion

These 3 patients reported episodes of breathlessness in the “before on-state” and “before off-state,” suggesting a biphasic respiratory dysfunction that coincided with a subtherapeutic dopaminergic tone. We were able to document reduced respiratory muscle control, as measured by PCF, during the episodes of breathlessness during the “before on-state” compared with both the “off-state” and the “supra on-state.” These cases illustrate biphasic respiratory dysfunction as a rarely recognized type of nonmotor fluctuation and a significant source of disability, a target for levodopa dose evaluation and adjustment (figure).

These observations suggest that the pharmacokinetic profile of levodopa is capable of inducing respiratory dysfunction. Although peak-dose respiratory dyskinesia has been described previously, the biphasic dysfunction identified here has not been previously documented.<sup>8–10</sup> The fact that the respiratory dysfunction in all patients improved following increases in dopaminergic tone supports the hypothesis that their respiratory dysfunction was hypodopaminergic in nature, justifying the increase in individual levodopa doses, a reduction in their interdose interval, or a consideration of a treatment system providing more continuous dopaminergic stimulation.

Although the biphasic pattern seems consistent in all cases, their clinical presentation and respiratory muscle control, perceptions of breathlessness, and motor function differed somewhat. It is known that the internal respiratory control is disturbed in PD, but its mechanism is not fully understood.<sup>2</sup> With the data available, we can not ascertain whether there is a relationship between the expressions of respiratory dyskinesia and motor features such as chest wall rigidity and bradykinesia.<sup>1</sup> Additional research should determine the extent to which motor (dyskinesia,

dystonia, rigidity, and bradykinesia) or nonmotor features (anxiety, cognition, and mood) are associated with or contribute to the development of biphasic respiratory dysfunction, the level of respiratory system with which they interfere, and the underlying mechanisms. Proper recognition of nonmotor manifestations of biphasic dyskinesia and prompt consideration of strategies that avoid transitional, subtherapeutic levels of levodopa are important to mitigate this source of disability. As suggested by the third patient, one promising therapeutic option is to resort to more continuous dopaminergic stimulation, such as infusion systems of levodopa or apomorphine. It may also be worthwhile to examine the effects of subthalamic or pallidal deep brain stimulation, which have been previously shown capable of alleviating peak-dose respiratory dyskinesia.<sup>9,10</sup>

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## Appendix Authors

Name	Location	Contribution
<b>Veerle A. van de Wetering-van Dongen, MSc</b>	Radboud University Medical Center; Donders Center for Brain, Cognition and Behavior, Department of Rehabilitation; Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Alberto J. Espay, MD, MSc</b>	UC Gardner Neuroscience Institute, Department of Neurology, Gardner Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, OH	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
<b>Luca Marsili, MD, PhD</b>	UC Gardner Neuroscience Institute, Department of Neurology, Gardner Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, OH	Major role in the acquisition of data and analysis or interpretation of data
<b>Andrea Sturchio, MD</b>	UC Gardner Neuroscience Institute, Department of Neurology, Gardner Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, OH	Major role in the acquisition of data and analysis or interpretation of data
<b>Susanne Ten Holter, MD</b>	Radboud University Medical Center; Donders Institute for Brain, Cognition and Behaviour; Department of Neurology; Center of Expertise for Parkinson & Movement Disorders; Nijmegen, the Netherlands	Major role in the acquisition of data and analysis or interpretation of data

## Appendix (continued)

Name	Location	Contribution
<b>Bastiaan R. Bloem, MD, PhD</b>	Radboud University Medical Center; Donders Institute for Brain, Cognition and Behaviour; Department of Neurology; Center of Expertise for Parkinson & Movement Disorders; Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
<b>Maarten J. Nijkrake, PhD</b>	Radboud University Medical Center; Donders Center for Brain, Cognition and Behavior, Department of Rehabilitation; Nijmegen, the Netherlands	Drafting/revision of the manuscript for content, including medical writing; study concept or design; and analysis or interpretation of data

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