



HAL
open science

Atteinte ventilatoire dans la maladie de Parkinson : du symptôme à l'atteinte objective

Guillaume Baille

► **To cite this version:**

Guillaume Baille. Atteinte ventilatoire dans la maladie de Parkinson : du symptôme à l'atteinte objective. Médecine humaine et pathologie. Université de Lille, 2019. Français. NNT : 2019LILUS023 . tel-02921548

HAL Id: tel-02921548

<https://theses.hal.science/tel-02921548>

Submitted on 25 Aug 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

UNIVERSITE DE LILLE
ECOLE DOCTORALE BIOLOGIE-SANTE DE LILLE

Thèse d'Université

**Atteinte ventilatoire dans la maladie de Parkinson :
du symptôme à l'atteinte objective**

Présentée et soutenue publiquement le 14 octobre 2019
par le Docteur Guillaume BAILLE

JURY

Madame le Professeur Cécile Chenivresse, Lille
Madame le Professeur Capucine Morélot-Panzini, Paris
Monsieur le Professeur David Maltete, Rouen
Madame le Docteur Christine Brefel-Courbon, Toulouse
Monsieur le Professeur Luc Defebvre, Lille
Madame le Professeur Caroline Moreau, Lille

présidente
rapporteur
rapporteur
examinatrice
co-directeur de thèse
co-directrice de thèse

Directeur de l'UR INSERM 1171 : Professeur Régis Bordet

UNIVERSITE DE LILLE
ECOLE DOCTORALE BIOLOGIE-SANTE DE LILLE

Thèse d'Université

**Atteinte ventilatoire dans la maladie de Parkinson :
du symptôme à l'atteinte objective**

Présentée et soutenue publiquement le 14 octobre 2019
par le Docteur Guillaume BAILLE

JURY

Madame le Professeur Cécile Chenivesse, Lille
Madame le Professeur Capucine Morélot-Panzini, Paris
Monsieur le Professeur David Maltete, Rouen
Madame le Docteur Christine Brefel-Courbon, Toulouse
Monsieur le Professeur Luc Defebvre, Lille
Madame le Professeur Caroline Moreau, Lille

présidente
rapporteur
rapporteur
examinatrice
co-directeur de thèse
co-directrice de thèse

Directeur de l'UR INSERM 1171 : Professeur Régis Bordet

AUTEUR : Nom : Baille

Prénom : Guillaume

Date de soutenance : 14 octobre 2019

Titre de la thèse : Atteinte ventilatoire dans la maladie de Parkinson : du symptôme à l'atteinte objective

Mots-clés : maladie de Parkinson, troubles ventilatoires, dyspnée, explorations fonctionnelles respiratoires, signes axiaux, signes non-moteurs.

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus fréquente. Parmi les nombreux signes cliniques rapportés par les patients et observés par les médecins, les manifestations respiratoires sont encore très peu étudiées.

Premièrement, la dyspnée, signe fonctionnel invalidant et altérant la qualité de vie, semble fréquente dans la MP mais sa prévalence et ses caractéristiques (dimension perceptive et réponse émotionnelle notamment) doivent être précisées. L'objectif de l'étude DYSPARK était de mieux définir le profil des patients dyspnéiques, le retentissement de la plainte respiratoire et de corréliser ses caractéristiques avec des éléments cliniques de la MP afin de mieux appréhender sa physiopathologie.

Deuxièmement, les anomalies ventilatoires objectives (explorations fonctionnelles respiratoires - EFR) sont encore mal connues dans la MP, de même que leur évolution. Une altération des volumes pulmonaires ou une atteinte de la musculature respiratoire pourraient avoir un retentissement sur le cours évolutif de la maladie. L'objectif de l'analyse d'une sous-population de la cohorte PRODIGY-PARK était de déterminer de façon prospective, sur 5 ans, le cours évolutif des données en EFR et leur impact pronostique potentiel.

Composition du jury :

Présidente : Madame le Professeur Cécile Chenivesse

Rapporteurs : Madame le Professeur Capucine Morélot-Panzini, Monsieur le Professeur David Maltete

Examineur : Madame le Docteur Christine Brefel-Courbon

Directeurs de recherche : Monsieur le Professeur Luc Defebvre, Madame le Professeur Caroline Moreau

REMERCIEMENTS

Madame le Professeur Capucine Morélot-Panzini, vous m'avez fait l'honneur de participer au comité de suivi de thèse avec le **Monsieur le Professeur David Maltete**. Vos remarques au cours des deux premières années de ce projet ont permis de combiner au mieux vos expertises respectives dans le domaine de la dyspnée et des mouvements anormaux.

Madame le Docteur Christine Brefel-Courbon, vous avez accepté de prendre part au jury de thèse et votre expérience des signes non-moteurs de la maladie de Parkinson est un plus dans l'évaluation de ce travail.

Madame le Professeur Cécile Chenivresse, je pense que tu sais ô combien je suis reconnaissant pour ta réactivité, tes conseils et ta bonne humeur et pour avoir tenté de me donner le point de vue du pneumologue dans cette problématique.

Madame le Professeur Caroline Moreau, merci d'avoir su écouter mes idées, mes hypothèses et d'avoir surtout pu les canaliser tout au long de mon clinicat.

Monsieur le Professeur Luc Defebvre, merci de m'avoir accompagné tout au long de ces presque dix années (depuis l'externat) et de m'avoir aidé à devenir un meilleur médecin, un meilleur pédagogue, un meilleur neurologue, en bref, un meilleur homme. J'espère avoir pu un peu prendre exemple sur votre rigueur au cours de ce travail de thèse.

Je tiens à remercier également le **Docteur Thierry Perez** pour son regard critique et pertinent sur les analyses EFR et le **Professeur Kathy Dujardin** avec qui les premiers échanges ont

m'ont permis de mieux appréhender le problème respiratoire du point de vue de la neuropsychologie et du spectre des troubles anxieux.

Merci à **Marie Pleuvret** d'avoir mené la cohorte PRODIGY-PARK d'une main de fer. Enfin, je remercie le **Professeur Michelle R Ciucci** pour ces échanges enrichissants sur la nécessité de s'efforcer à mener de front recherche clinique et fondamentale dans ce domaine encore trop peu étudié.

SOMMAIRE

Travaux scientifiques conduits pendant la thèse	6
RESUME	8
ABSTRACT	9
INTRODUCTION GENERALE.....	11
1. Les signes non-moteurs de la maladie de Parkinson	11
2. La dyspnée : signe ventilatoire subjectif	13
3. Les explorations fonctionnelles respiratoires	17
4. Atteinte ventilatoire objective dans la maladie de Parkinson.....	19
Objectifs du travail	30
Etude 1	31
La dyspnée : un symptôme méconnu de la maladie de Parkinson.....	31
Etude 2.....	34
La dyspnée est un symptôme spécifique de la maladie de Parkinson.....	34
Etude 3.....	50
Atteinte précoce des muscles inspiratoires dans la maladie de Parkinson.....	50
Etude 4.....	62
Anomalies ventilatoires dans la maladie de Parkinson : suivi à 5 ans.....	62
Discussion générale.....	82
Perspectives	98
Références bibliographiques	100

Travaux scientifiques conduits pendant la thèse

Les travaux présentés dans cette thèse d'université ont été conduits dans le laboratoire de l'UR INSERM 1171 (troubles cognitifs dégénératifs et vasculaires, Pr Bordet) de l'université de Lille, les services de neurologie et pathologie du mouvement et d'explorations fonctionnelles respiratoires du CHU de Lille.

Publications

Cette thèse est organisée autour d'une revue de la littérature publiée et de quatre articles. Deux sont publiés, un a été accepté et un dernier a été soumis dans des revues scientifiques internationales avec comité de lecture.

BAILLE G, DE JESUS AM, PEREZ T, DEVOS D, DUJARDIN K, CHARLEY CM, DEFEBVRE L, MOREAU C. Ventilatory Dysfunction in Parkinson's Disease. J Parkinsons Dis. 2016 Jun 16;6(3):463-71. doi: 10.3233/JPD-160804. Review.

BAILLE G, CHENIVESSE C, PEREZ T, MACHURON F, DUJARDIN K, DEVOS D, DEFEBVRE L, MOREAU C. Dyspnea: an underestimated symptom in Parkinson's disease. Parkinsonism and Related Disorders (2018), 2019 Mar;60:162-166.

BAILLE G, PEREZ T, DEVOS D, MACHURON F, DUJARDIN K, CHENIVESSE C, DEFEBVRE L, MOREAU C,. Dyspnea is a specific symptom in Parkinson's disease. Accepté dans Journal of Parkinson's disease le 25/07/2019.

BAILLE G, PEREZ T, DEVOS D, DEKEN V, DEFEBVRE L, MOREAU C. Early occurrence of inspiratory muscle weakness in Parkinson's disease. PLoS ONE 2018 13(1): e0190400.

BAILLE G, CHENIVESSE C, PEREZ T, DEKEN V, DEVOS D, DEFEBVRE L, MOREAU C. Impaired lung function in Parkinson's disease: a 5-year follow-up study. Soumis le 19/0/07/2019 pour Parkinsonism & Related Disorders.

Communications lors de réunion scientifique internationale

Communication orale

BAILLE G, PEREZ T, MACHURON F, DEFEBVRE L, CHENIVESSE C, MOREAU C. Dyspnea: an underestimated non-motor symptom in Parkinson's disease? European Academy of Neurology Lisbonne 2018

BAILLE G, CHENIVESSE C, PEREZ T, DEKEN V, DEVOS D, DEFEBVRE L, MOREAU C. Ventilatory impairment in Parkinson's disease: a 5 years follow-up study. European Academy of Neurology Oslo 2019

Communications écrites

BAILLE G, PEREZ T, DEVOS D, DEFEBVRE L, MOREAU C. Ventilatory disturbance in early-stage disease : a prospective study. European Academy of Neurology Copenhagen 2016

BAILLE G, PEREZ T, DEVOS D, DEFEBVRE L, MOREAU C. Pulmonary dysfunction in Parkinson's disease: a feature of early disease ? Movement Disorders Congress Berlin 2016

BAILLE G, DEVOS D, HUIN V, PEREZ T, SABLONNIERE B, DEFEBVRE L, MOREAU C. Axial signs in early-stage Parkinson's disease : an influence of the genotype ? Movement Disorders Congress Vancouver 2017

BAILLE G, DEVOS D, HUIN V, PEREZ T, SABLONNIERE B, DEFEBVRE L, MOREAU C. Gene polymorphisms may influence axial signs's onset in early-stage Parkinson's disease. European Academy of Neurology Amsterdam 2017

BAILLE G, PEREZ T, MOREAU C, CHENIVESSE C, DEFEBVRE L. Prevalence and characteristics of dyspnea in Parkinson's disease. International Society for the Advancement of Respiratory Psychophysiology Lille 2017

BAILLE G, PEREZ T, MACHURON F, DEFEBVRE L, CHENIVESSE C, MOREAU C. Dyspnea in Parkinson's disease : a biomarker of disease's severity ? Movement Disorders Congress Hong-Kong 2018

BAILLE G, CHENIVESSE C, PEREZ T, DEKEN V, DEVOS D, DEFEBVRE L, MOREAU C. Long term evolution of ventilatory function in Parkinson's disease. Movement Disorders Congress Nice 2019

RESUME

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus fréquente. Parmi les nombreux signes cliniques rapportés par les patients et observés par les médecins, les manifestations respiratoires sont encore très peu étudiées.

Premièrement, la dyspnée, signe fonctionnel invalidant et altérant la qualité de vie, semble fréquente dans la MP mais sa prévalence et ses caractéristiques (dimension perceptive et réponse émotionnelle notamment) doivent être précisées. L'objectif de l'étude DYSPARK était de mieux définir le profil des patients dyspnéiques, le retentissement de la plainte respiratoire et de corrélérer ses caractéristiques avec des éléments cliniques de la MP afin de mieux appréhender sa physiopathologie.

Deuxièmement, les anomalies ventilatoires objectives (explorations fonctionnelles respiratoires - EFR) sont encore mal connues dans la MP, de même que leur évolution. Une altération des volumes pulmonaires ou une atteinte de la musculature respiratoire pourraient avoir un retentissement sur le cours évolutif de la maladie. L'objectif de l'analyse d'une sous-population de la cohorte PRODIGY-PARK était de déterminer de façon prospective, sur 5 ans, le cours évolutif des données en EFR et leur impact pronostique potentiel.

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disease. Among the numerous signs reported by the patients and observed by the physicians, respiratory manifestations are one the least explored.

Firstly, dyspnea, debilitating symptom that can impair the quality of life, seems to be frequent in PD, but its prevalence and its clinical characteristics (perceptive aspect and emotional response) need to be determined. The objective of the DYSPARK project was to define the clinical profile of dyspneic PD patients, the consequence of the shortness of breath and to correlate its clinical features with the motor and non-motor aspects of the disease.

Secondly, objective ventilatory abnormalities (pulmonary function testings – PFT) and the change over time are not well defined in PD. A diminution of lung volumes or impaired respiratory muscles could influence the outcome of the disease. The aim of the analysis of a group of patients from the PRODIGY-PARK cohort was to prospectively assess (5 years follow-up) the PFT data and their possible prognostic impact.

PREAMBULE

Ce travail de thèse a été réalisé dans le cadre des cohortes PRODIGY PARK 1 et 2 (Prospective Assessment of Dysarthria and Other Dopaminergic and Non Dopaminergic Axial Signs in PD) cohort (ClinicalTrials.gov: NCT 02627664). Ce projet s'intéresse à l'apparition des signes axiaux dans la maladie de Parkinson, à savoir la dysarthrie, les troubles de la déglutition, l'instabilité posturale et le freezing de la marche. Grâce à une coopération étroite avec le Dr Thierry PEREZ et le Pr Cécile CHENIVESSE, pneumologue dans le service des explorations fonctionnelles respiratoires du CHU de Lille, nous avons pu dédier une partie des ressources à l'étude des troubles ventilatoires dans la maladie de Parkinson.

INTRODUCTION GENERALE

1. Les signes non-moteurs de la maladie de Parkinson

La maladie de Parkinson (MP) est la 2^{ème} maladie neurodégénérative la plus fréquente après la maladie d'Alzheimer. Elle touche 1,6% des personnes âgées de plus de 65 ans et plus de 150 000 personnes sont traitées en France pour une MP [1,2]. En partie du fait du vieillissement de la population, sa prévalence devrait doubler entre 2005 et 2030 [3].

La physiopathologie de la MP est encore mal connue mais les dépôts d'alpha-synucléine sont la marque anatomopathologique de la maladie et la déplétion dopaminergique est responsable en grande partie des signes moteurs. Ces dépôts et la neurodégénérescence sont diffus avec une progression caudo-rostrale des lésions au niveau du tronc cérébral [4]. La localisation des agrégats d'alpha-synucléine explique les symptômes prodromaux de la MP (constipation, troubles de l'humeur, hyposmie ou troubles du comportement en sommeil paradoxal). Bien que certains de ces symptômes soient utilisés pour définir des critères de « MP prodromale » [5], en 2019, le diagnostic de MP repose encore sur des éléments cliniques moteurs [6]. En effet, le syndrome parkinsonien est défini par l'association de la bradykinésie avec au moins un autre symptôme parmi tremblement de repos et hypertonie plastique. Cependant, les patients parkinsoniens rapportent de nombreux signes non-moteurs (SNM), au moment du diagnostic et parfois avant l'apparition des premiers signes moteurs. Ces symptômes sont de plus en plus pris en compte pour le diagnostic de MP. En effet, dans les critères de MP de 2015, « l'absence d'un syndrome non-moteur classique de la MP dans les cinq premières années d'évolution (troubles du sommeil, dysautonomie, hyposmie, troubles du comportement) » constitue un drapeau rouge et doit faire évoquer un diagnostic différentiel. De plus, depuis quelques années, les fluctuations non-motrices (FNM) ont été reconnues comme partie intégrante de la phase de complications motrices [7,8]. Les mécanismes sous-jacents sont encore mal compris (notamment le lien avec le système dopaminergique) mais

une meilleure compréhension des SNM pourrait permettre de mieux caractériser phénotypiquement la MP et peut-être déterminer des facteurs pronostiques [9,10]. Leur impact sur la qualité de vie des patients est important [11,12], il est donc nécessaire de mieux les prendre en charge. Néanmoins, la diversité [13] et la non-spécificité des SNM décrits dans la MP rendent leur diagnostic parfois difficile [14], et pour cela, plusieurs questionnaires de dépistage ont été créés [15, 16]. Il est toutefois impossible d'être exhaustif et l'évaluation de la prévalence des SNM dans la MP au sein de la plus grande cohorte publiée a d'ailleurs utilisé un questionnaire semi-dirigé [17]. La fatigue, l'anxiété, les douleurs des membres inférieurs et l'insomnie étaient les signes les plus rapportés dans cette étude.

Parmi SNM rapportés par les patients parkinsoniens (tableau 1), la dyspnée est parmi les moins étudiés. Même si dans une étude observationnelle, la plupart des cas de plaintes respiratoires étaient liés à une pathologie cardiaque ou pulmonaire [18], beaucoup de cliniciens ignorent encore que la dyspnée est classée comme SNM de la MP [13].

Tableau 1 : principaux signes non-moteurs de la maladie de Parkinson (issu de Bonnet et al., 2012 [19], adapté de [20]).

- (a) Neuropsychiatric symptoms:
 - (1) Depression
 - (2) Anxiety
 - (3) Apathy
 - (4) Hallucinations, delusions, illusions
 - (5) Delirium (may be drug induced)
 - (6) Cognitive impairment (dementia, MCI)
 - (7) Dopaminergic dysregulation syndrome (usually related to levodopa)
 - (8) Impulse control disorders (related to dopaminergic drugs).
- (b) Sleep disorders:
 - (1) REM sleep behaviour disorder (possible premotor symptoms)
 - (2) excessive daytime somnolence, narcolepsy type "sleep attack"
 - (3) restless legs syndrome, periodic leg movements
 - (4) insomnia
 - (5) sleep disordered breathing
 - (6) non-REM parasomnias (confusional wandering)
- (c) Fatigue:
 - (1) central fatigue (may be related to dysautonomia)
 - (2) peripheral fatigue.
- (d) Sensory symptoms:
 - (1) pain
 - (2) olfactory disturbance

- (3) hyposmia
- (4) functional anosmia
- (5) visual disturbance (blurred vision, diplopia; impaired contrast-sensitivity).
- (e) Autonomic dysfunction:
 - (1) bladder dysfunction (urgency, frequency, nocturia)
 - (2) sexual dysfunction (may be drug-induced)
 - (3) sweating abnormalities (hyperhydrosis)
 - (4) orthostatic hypotension.
- (f) Gastrointestinal symptoms:
 - (1) dribbling of saliva
 - (2) dysphagia
 - (3) ageusia
 - (4) constipation
 - (5) nausea
 - (6) vomiting.
- (g) Dopaminergic drug-induced behaviour NMS:
 - (1) hallucinations, psychosis, delusions
 - (2) dopamine dysregulation syndrome
 - (3) impulse control disorders.
- (h) Dopaminergic drug-induced other NMS:
 - (1) ankle swelling
 - (2) dyspnea
 - (3) skin reactions
 - (4) subcutaneous nodules
 - (5) erythematous
- (i) Nonmotor fluctuations:
 - (1) dysautonomia
 - (2) cognitive/psychiatric
 - (3) sensory/pain
 - (4) visual blurring
- (j) Other symptoms:
 - (1) weight loss
 - (2) weight gain.

2. La dyspnée : signe ventilatoire subjectif

La dyspnée a été définie par l'American Thoracic Society comme « Expérience subjective d'inconfort respiratoire se manifestant par des sensations qualitativement différentes, variant en intensité. Cette sensation résulte de l'interaction entre différents facteurs physiologiques, psychologiques, sociaux et environnementaux et peut induire des réactions secondaires physiologiques et comportementales » [21].

Il s'agit d'un symptôme fréquent dans les pathologies respiratoires, cardiaques et psychiatriques (attaque de panique par exemple). En neurologie, les pathologies neuromusculaires sont bien connues des cliniciens comme étant à l'origine d'une dyspnée. Par exemple, pour évaluer la sévérité de sclérose latérale amyotrophique (SLA), 2/12 items de

l'Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) prennent en compte ce symptôme [22].

Concernant les pathologies dégénératives extrapyramidales, dès la première description de la maladie, James Parkinson rapportait des difficultés respiratoires ("He fetched his breath rather hard" [23]). Même si l'existence d'une plainte respiratoire dans la MP doit faire rechercher une origine cardiaque ou pulmonaire [18], la fréquence de la dyspnée dans la MP [24] semble supérieure à celle de la population générale âgée de plus de 65 ans [25].

Par ailleurs, la dyspnée est un marqueur de mauvaise qualité de vie et est associée à une perte d'autonomie chez les sujets âgés [26]. De plus, Barone et al. ont montré qu'il s'agit du cinquième SNM le plus gênant dans la MP [17]. Malgré ces données, peu d'études se sont intéressées à l'évaluation spécifique de la dyspnée dans la MP comme nous l'avons rapporté dans une revue de la littérature au début de notre travail de thèse [27].

Cependant, le diagnostic de dyspnée, comme c'est le cas pour les pathologies pulmonaires telles que l'asthme ou la broncho-pneumopathie chronique obstructive (BPCO), peut être compliqué du fait de son caractère multidimensionnel, [26,27]. En effet, la dyspnée nécessite une évaluation en plusieurs étapes. D'abord, la subjectivité du symptôme oblige le clinicien à demander simplement, sans cotation de sévérité, si oui ou non le patient ressent ou a ressenti des difficultés pour respirer normalement. Ensuite, il faut prendre en compte les trois aspects de la dyspnée : l'aspect sensoriel, l'aspect émotionnel et l'impact engendré [28].

L'aspect perceptif doit être évalué qualitativement car les patients peuvent rapporter à la fois la nécessité de devoir fournir un effort mental ou physique pour respirer, une sensation d'oppression thoracique ou un manque d'air. Ces sensations sont bien distinctes et pourraient correspondre à des mécanismes physiopathologiques sous-jacents différents [28, 29]. La sensation d'oppression thoracique est la plus décrite dans l'asthme qui engendre un syndrome obstructif [30]. La sensation d'effort à fournir serait davantage liée à un défaut de la

mécanique respiratoire (paroi thoracique ou muscles respiratoires), alors que la sensation de manque d'air proviendrait de la dissociation entre la commande motrice et l'ampleur de la ventilation produite (troubles des échanges gazeux).

Ces distinctions basées en partie sur des études cliniques permettent de mieux comprendre la physiologie respiratoire et les différentes structures en jeu dans la ventilation « normale » [31, 32]. Le tronc cérébral est la structure du système nerveux central comportant les centres de la respiration [33]. Au niveau de la protubérance, le groupe respiratoire pontique est composé des centres pneumotaxique et apneustique qui régulent de façon autonome les groupes neuronaux situés dans le bulbe rachidien. A ce niveau, on distingue le groupe respiratoire dorsal qui commande via le nerf phrénique la contraction du diaphragme, principal muscle inspiratoire et le groupe respiratoire ventral qui peut être activé volontairement pour mettre en jeu les muscles accessoires (figure 1).

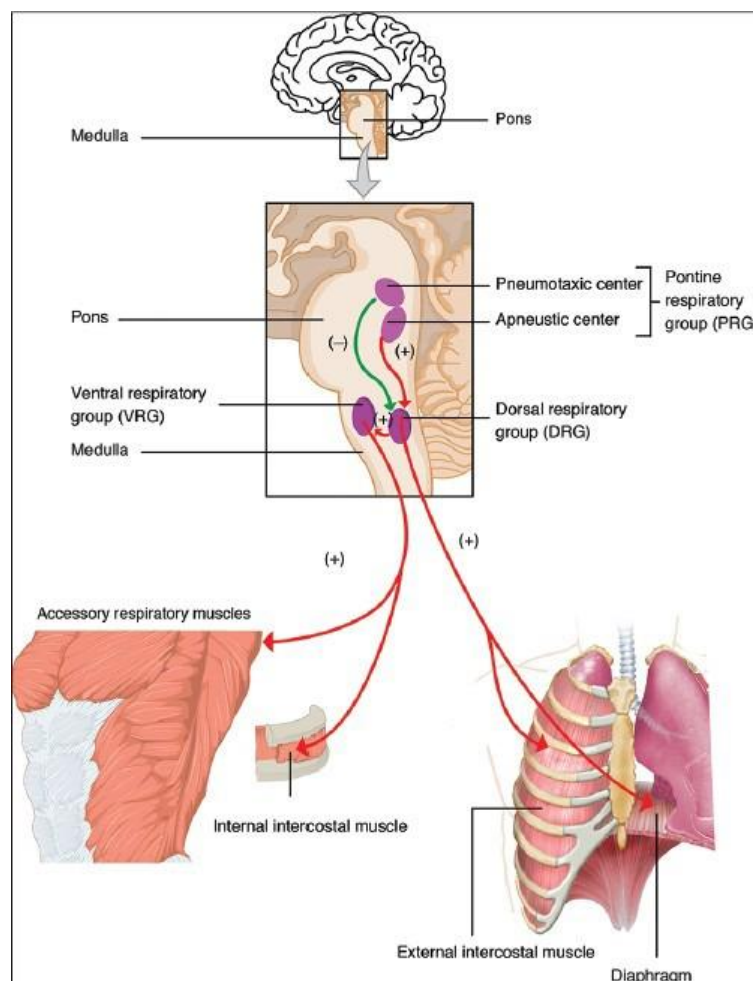


Figure 1 : Schéma des centres respiratoires du tronc cérébral. (+): stimulation. (-): inhibition. (issu de Anatomy and Physiology, OpenStax College resource Unit 5 Chapter 22)

Dans la MP, selon le modèle de Braak [4], la neurodégénérescence affecte de façon précoce les structures du tronc cérébral, notamment de la protubérance. On pourrait donc s'attendre à une déficience de la commande ventilatoire au cours de la maladie qui engendrerait une dyspnée [34,35].

Au-delà des afférences motrices pour provoquer l'inspiration, les afférences sensorielles jouent un rôle primordial dans le contrôle ventilatoire. En effet, les mécanorécepteurs de la plèvre renvoient les informations au tronc cérébral. La finalité de la ventilation étant les échanges gazeux, l'efficacité du processus est également évaluée par des chémorécepteurs périphériques situés dans les corpuscules carotidiens et aortiques, dont les informations sont relayées respectivement par le nerf glossopharyngien et par le nerf vague au cerveau. Le fonctionnement de ces chémorécepteurs dépend en partie de cellules dopaminergiques [36,37] et la perte de ces neurones dans la cadre de la MP pourrait induire une mauvaise réponse à l'hypoxie [38,39], elle-même à l'origine d'une dyspnée.

D'autres afférences sensorielles ont pour destination le cortex cérébral, en particulier l'insula antérieure, structure faisant partie du système limbique [40]. Von Leupoldt et al. ont mis en évidence des circuits neuronaux communs entre les voies nociceptives et celles liées à la dyspnée [41]. Sur le même modèle que celui de la douleur, il est donc nécessaire de prendre en compte l'aspect émotionnel de la dyspnée. Celui-ci doit être évalué de manière qualitative et quantitative en déterminant notamment le caractère désagréable de la sensation et l'intensité des émotions générées (colère, peur, angoisse...). La dyspnée est donc anxiogène mais les troubles anxieux peuvent aussi se manifester par des troubles somatoformes avec par exemple une sensation d'inconfort respiratoire. Par ailleurs, dans une étude transversale, 34% des patients parkinsoniens répondaient aux critères DSM IV pour au moins un trouble

anxieux. Néanmoins, dans la classification des SNM de la MP proposée par Susan & Lang [13], la dyspnée est classée à la fois comme signe « dysautonomique » et « sensoriel » mais pas dans comme signe « neuropsychiatrique ». Selon cette classification, la dyspnée est le seul SNM à être intégré à deux catégories différentes. Il est donc indispensable de mieux caractériser les différents aspects de ce symptôme dans la MP.

Le retentissement de la dyspnée sur les activités de la vie quotidienne et l'autonomie est le troisième aspect à évaluer. Les échelles de Borg et modified Medical Research Council (mMRC) sont couramment utilisées en neurologie dans ce but [42, 43]. Cependant, à cause de la limitation physique liée au syndrome akinéto-rigide et aux troubles de la marche dans la MP, ces échelles ne semblent pas les plus adaptées pour l'évaluation de la dyspnée dans cette maladie.

La dyspnée est donc un symptôme multidimensionnel qui pourrait être lié, par plusieurs mécanismes physiopathologiques, à la MP. Au-delà de l'aspect purement fonctionnel, il peut s'agir également d'un signe d'alarme d'une atteinte pulmonaire objective (par exemple la complication d'une pneumopathie). Afin de déterminer l'existence ou non d'un trouble ventilatoire et de la préciser, il faut recourir à des explorations fonctionnelles respiratoires (EFR).

3. Les explorations fonctionnelles respiratoires

Ce terme regroupe l'ensemble des examens destinés à l'exploration de la fonction ventilatoire. Elle comprend l'étude i) des volumes pulmonaires et des débits respiratoires (spirométrie ou pléthysmographie), ii) l'activité des muscles respiratoires iii), des échanges gazeux au repos ou à l'effort, iv) du sommeil (polygraphie ou polysomnographie) et v) le contrôle de la ventilation. L'interprétation des EFR se fait en fonction du terrain du patient (tabagisme,

exposition professionnelle), de sa plainte (dyspnée) et de l'examen clinique. Dans ce manuscrit, nous traiterons des volumes pulmonaires et des muscles respiratoires.

La spirométrie dépend de manœuvres volontaires et peut se réaliser de façon « simple » ou « forcée ». Cette dernière évalue les débits d'air (figure 2). Elle s'interprète en fonction de l'âge, de la taille et du poids du patient [44]. Les anomalies à la spirométrie peuvent être d'ordre quantitatif ou qualitatif (aspect de la courbe principalement pour la spirométrie forcée) et permettent de déterminer si le patient présente ou non un trouble ventilatoire (TV). Schématiquement, deux types de TV sont définis : d'une part, le TV obstructif (TVO) et, d'autre part, le TV restrictif (TVR). Le premier est défini par un coefficient de Tiffeneau (qui est égal à $VEMS/CVF$) inférieur à 0,7. Les principales étiologies des TVO sont les pathologies bronchiques comme l'asthme ou la BPCO. Le TVR correspond à une baisse de la capacité pulmonaire totale (CPT) qui doit être inférieure à 80% de la valeur théorique. Les principales étiologies sont les anomalies de la cage thoracique, de la cavité pleurale ou les pneumopathies interstitielles.

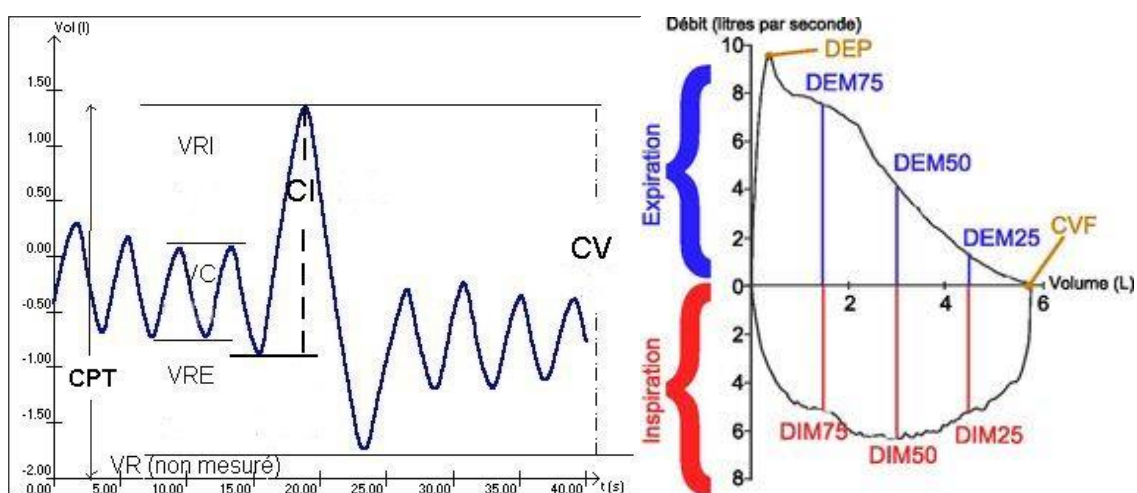


Figure 2 : à gauche les volumes pulmonaires obtenus en spirométrie (CPT : capacité pulmonaire totale, VR : volume résiduel, VRI : volume résiduel inspiratoire, VC : volume courant, VRE : volume résiduel expiratoire, CI : capacité inspiratoire, CV : capacité vitale. A droite : courbe débit-volume : DEP : débit expiratoire de pointe, DEM : débit expiratoire moyen, DIM : débit inspiratoire moyen, CVF : capacité ventilatoire forcée

L'activité des muscles respiratoires est évaluée de façon classique par la mesure des pressions buccales et nasales. Elles sont obtenues par des manœuvres volontaires qui sont simples à réaliser et bien tolérées par le patient. Les indices les plus couramment utilisés pour mesurer l'activité des muscles respiratoires sont la pression inspiratoire et la pression expiratoire maximales (respectivement P_Imax et P_Emax). D'autres méthodes permettent d'évaluer la force musculaire inspiratoire et expiratoire : le sniff nasal inspiratory pressure (SNIP) en réalisant un reniflement rapide et le débit expiratoire à la toux. Le diaphragme est le principal muscle inspiratoire mais ces manœuvres simples évaluent également les muscles accessoires inspiratoires (intercostaux externes, scalène ou sterno-cleïdo-mastoïdien) et expiratoires (intercostaux internes et muscles de la paroi abdominale). La fonction diaphragmatique peut être étudiée isolément par stimulation du nerf phrénique, qui, dans notre centre, est réalisée par stimulation magnétique [45]. L'avantage de cette technique est qu'elle ne dépend pas de la motivation du patient.

Indispensables dans les pathologies neuromusculaires comme la SLA où elles font partie des recommandations de bonne pratique [46], les EFR ne sont pas intégrées dans la prise en charge des pathologies dégénératives extrapyramidales. Cependant, depuis plusieurs années, de nombreuses études ont mis en évidence des anomalies de la fonction ventilatoire dans la MP [27, 47, 48].

4. Atteinte ventilatoire objective dans la maladie de Parkinson

En initiant ce travail de thèse, nous avons publié une revue de la littérature sur ce sujet [25-copie de cet article pages suivantes).

Afin de couvrir l'ensemble de la problématique des troubles ventilatoires dans la MP, nous avons recensé les articles s'intéressant à la dyspnée, aux volumes pulmonaires, à la fonction musculaire respiratoire, aux troubles du sommeil et à la réponse à l'hypoxie. Concernant les volumes pulmonaires, les données existantes dans la littérature sont contradictoires quant à la

présence d'un TVO ou d'un TVR dans la MP. Il en est de même pour l'activité des muscles respiratoires.

Les limites des études déjà publiées étaient les suivantes : i) petits effectifs, ii) cohortes le plus souvent composées de patients au stade avancé de la MP, iii) absence de suivi longitudinal de la fonction ventilatoire, iv) très peu d'évaluation des EFR en condition « off drug ». Ces différents éléments ont été pris en compte pour établir nos différents objectifs de thèse.

Review

Ventilatory Dysfunction in Parkinson's Disease

Guillaume Baille^a, Anna Maria De Jesus^b, Thierry Perez^b, David Devos^c, Kathy Dujardin^a, Christelle Monaca Charley^d, Luc Defebvre^a and Caroline Moreau^{a,*}

^a*Service de Neurologie et Pathologie du Mouvement, Pôle de neurosciences et appareil locomoteur, CHRU de Lille, Lille, France / INSERM UMR 1171, LILLE France, Troubles cognitifs dégénératifs et vasculaires, Lille, France*

^b*Service d'Explorations Fonctionnelles Respiratoires, Hôpital Albert Calmette, CHRU de Lille, Lille, France*

^c*Service de Pharmacologie Médicale, Université de Lille, CHRU de Lille, France / INSERM UMR 1171, Lille, France*

^d*Unité des Troubles du Sommeil et de la Vigilance, CHRU de Lille/INSERM UMR 1171, Lille, France*

Accepted 16 May 2016

Abstract. In contrast to some other neurodegenerative diseases, little is known about ventilatory dysfunction in Parkinson's disease (PD). To assess the spectrum of ventilation disorders in PD, we searched for and reviewed studies of dyspnea, lung volumes, respiratory muscle function, sleep breathing disorders and the response to hypoxemia in PD. Among the studies, we identified some limitations: (i) small study populations (mainly composed of patients with advanced PD), (ii) the absence of long-term follow-up and (iii) the absence of functional evaluations under "off-drug" conditions. Although there are many reports of abnormal spirometry data in PD (mainly related to impairment of the inspiratory muscles), little is known about hypoventilation in PD. We conclude that ventilatory dysfunction in PD has been poorly studied and little is known about its frequency and clinical relevance. Hence, there is a need to characterize the different phenotypes of ventilation disorders in PD, study their relationships with disease progression and assess their prognostic value.

Keywords: Parkinson's disease, pathophysiology, ventilatory function, review

INTRODUCTION

Ventilatory dysfunction is known to have a role in the pathogenesis and progression of neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis [1–4]. However, little is known about the association between Parkinson's disease (PD) and ventilatory dysfunction – despite the fact that James Parkinson noted the presence of respiratory abnormalities in his initial description of

the disease ("He fetched his breath rather hard . . .", [5]). Furthermore, it is well known that aspiration pneumonia and pulmonary embolism are among the main causes of death in PD patients [6, 7]. Ventilatory changes in PD might affect the patient's quality of life by reducing levels of physical activity. However, ventilatory dysfunction in PD patients has not been well characterized even if, in 2010, a general review about respiratory problems in neurologic disorders was published [8]. Nowadays, there are a number of outstanding questions. What are the frequency and the severity of ventilatory dysfunction in PD? When does it start? How might ventilatory dysfunction influence the course of the disease in terms of the phenotype and prognosis? Is it respon-

*Correspondence to: Caroline Moreau, MD, PhD, Service de Neurologie et Pathologie du Mouvement, Pôle de neurosciences et appareil locomoteur, CHRU de Lille/INSERM UMR 1171, F-59037 Lille, France. Tel.: +003320446752; Fax: +0033204 46680; E-mail: caroline.moreau@chru-lille.fr.

sive to dopaminergic treatments? Here, we performed a review of the spectrum of ventilatory disorders in PD. Identified publications were classified into five groups, depending on the topic: (i) dyspnea, (ii) lung volumes, (iii) respiratory muscle function and (iv) sleep breathing disorders, (v) response to hypoxemia. Lastly, we discuss these impairments' putative involvement in the neurodegenerative process.

LITERATURE SEARCH STRATEGY

We performed a systematic review of available literature in Pubmed with the appropriate search terms. Relevant publications in any language were identified by searching the PubMed bibliographic database (<http://www.ncbi.nlm.nih.gov/pubmed/>) up 1950 until January 2015 with combinations of the keywords "pulmonary function AND Parkinson", "lung AND Parkinson", "breathing disorders AND Parkinson" (excluding nocturnal disorders), "ventilation AND Parkinson" and "hypoxemia AND Parkinson". When relevant, additional references found in the identified publications were included in the review. Thus, we also considered reports of "breathing sleep disorders" in PD focusing on the articles about the impact of antiparkinsonian drugs.

DYSPNEA

Dyspnea corresponds to the subjective experience of respiratory discomfort, and consists of distinct sensations that vary in intensity [9]. The phenomenon appears to result from the erroneous integration of sensory afferents but also has a marked emotional component [10]. Dyspnea is a marker for poor quality of life and is associated with a loss of autonomy in ambulatory elderly patients [11]. Very few studies assessed dyspnea in PD (Table 1).

Dyspnea and fluctuations

In an observational study including all patients attended in a Movement Disorders department, most of the dyspnea was due to cardio-pulmonary diseases [12]. Using the classification of non-motor fluctuations in PD [13], dyspnea can be considered as an "autonomic disorder" (with cough and stridor) or as a "sensory disturbance". Among non-motor fluctuations, in a cohort composed of advanced-PD patients, 40% reported dyspnea [14]. Several studies have shown that the perception of dyspnea is

impaired in PD patients [15, 16]. This misperception was associated with symptoms of anxiety and non-motor fluctuations [17, 18]. Indeed, PD patients report that they feel dyspnea more frequently in the "off-drug" condition [14, 19].

Impact of treatments on dyspnea

However, dopamine does not seem to be the only neurotransmitter involved in dyspnea. Although there is still a doubt about the role of serotonin [20], anti-inflammatory drugs like steroids may interfere in dyspnea sensation [21]. After the administration of L-DOPA, improvements in lung function were not correlated with the reduction in the symptoms reported by the patients [15]. Paradoxically, antiparkinsonian medications can trigger dyspnea. Thus, L-DOPA-induced dyskinesia has been reported as a possible cause of dysregulated breathing [22], perhaps as a result of the loss of muscle control. Likewise, a longitudinal study has shown that dyspnea can be a side effect of subthalamic nucleus deep brain stimulation [23]. The authors mentioned the following mechanisms underlying this phenomenon: An alteration of dyspnea perception, a bronchoconstriction, a disturbance in upper airway control or a disturbed respiratory muscle control. Surprisingly, a fixed epiglottis has been observed in subthalamic nucleus deep brain stimulation patients [24].

Therefore, the precise mechanisms of dyspnea and the effect of treatments remain unknown.

LUNG VOLUMES

Restrictive patterns

Since the 1960 s, many studies have used spirometry to assess lung capacity in PD patients (Table 2). Even though the pulmonary fibrosis caused by ergotamine derivatives has become very rare, restrictive pulmonary syndrome has been reported in patients with severe PD (i.e. Hoehn & Yahr scores between III and V [25]). Nevertheless, in this paper, the severity of the restrictive patterns is unknown as their definition was based on a qualitative analyze of the low-flow volume loop. The precise prevalence of these patterns in PD remains unclear but a recent study found 56.7% of restrictive pulmonary dysfunction in a 30 patients cohort with a mean disease duration of 4.9 years \pm 3.1 [26]. The loss of chest wall compliance and the camptocormia have been suggested as a mechanism [27, 28]. Actually, chest expansion was

Table 1

Summary of the literature data on dyspnea in PD. HY: Hoehn and Yahr, DBS: Deep brain stimulation. VIM : Ventrale intermediate nucleus of the thalamus, NA: Not available

Study	Number of patients	Disease duration (year)	Clinical scores	Control group	Misperception of dyspnea	Main results
[16]	25		HY 2–3	Yes	Yes	Impaired perception of dyspnea
[14]	50	12.7 ± 5.4	UPDRS III 44.4 ± 13.4 "on drug"			90% of patients with dyspnea on "off drug" condition
[15]	20	7.5 ± 1.1	HY 2–3	Yes	Yes	No link between reduction in dyspnea and increase in lung volumes
[23]	13	Patients with DBS	NA	Yes (VIM)	Yes	link between DBS and dyspnea

much lower in PD than in control group ($1.8 \text{ cm} \pm 0.8$ vs. $4.3 \text{ cm} \pm 1.0$). A gender effect has been suggested: Women may present a more severe restrictive syndrome, even after adjustment for the severity of PD [29, 30]. Beyond the severity, restrictive patterns affected more women (more than 50%) than men (about 10% - [29]). On the contrary, in a kinematic and spirometric analysis of PD subjects suffering from a speech deficit, no lung volumes abnormalities was observed [31]. Nevertheless, most of the studies used the forced vital capacity (FVC) to define the restrictive pattern although the guidelines recommend using the total lung capacity (TLC).

Obstructive patterns

An analysis of the flow-volume curve highlighted a severe obstructive pulmonary syndrome in patients with advanced-PD [32], and some researchers have reported abnormalities in the upper airways [33, 34]. Some of the participants in these studies were patients with active tobacco intoxication [35, 36], and so the results may also have depended on the patients' willingness to perform the test. Furthermore, once more, upper airway obstruction was set from the flow-volume loop tracing with difficulty to assess quantitatively. Therefore, the frequency of upper airway obstruction remains unknown even if some researchers estimated an occurrence between one fifth and two-third of the patients [30, 35, 36]. After testing 58 PD patients, Sabaté et al. suggested that the obstructive pulmonary syndrome was associated with bradykinesia, hypertonia and radiologic signs of cervical and dorsal arthrosis [30]. In contrast, no obstructive pulmonary syndrome was found in a cohort of 12 patients with advanced-PD (even in the "off-drug" condition) [25]. In 1989, a respiratory flutter phenomenon (flow-volume loop oscillation of

4–8 Hz) was observed (see Fig. 1; [32]) and found to be correlated with dyskinesia and tremor. It should be due to a vibration of the vocal cords and the supraglottic structures. However, this feature does not seem to be specific for PD since it was described in other extrapyramidal disorders [33]. At last, two studies have highlighted the occurrence of mixed pulmonary dysfunction (association of obstructive and obstructive ventilatory syndromes) in PD patients [28, 30].

Effect of antiparkinsonian drugs on lungs volumes

Regarding the dopasensitivity, some researchers consider that the effect of L-DOPA in the restrictive syndrome is only partial [29] although others did not highlight any signification variation due to treatment [25]. Yet, even on "on drug condition", FVC remained below the norm [29]. Some researchers suggest that acute and chronic administration L-DOPA can improve the flow-volume curve [35, 36]. These results must be interpreted with caution, since some of the studies included patients with asthma or obstructive bronchopulmonary disease [35, 36]. Furthermore, it has been suggested that obstructive pulmonary syndrome is due to bronchoconstriction caused by sympathetic hyperactivation [37].

RESPIRATORY MUSCLES

Inspiratory and expiratory muscles weakness

Several studies have evidenced weakness of both inspiratory and expiratory muscles in PD (Table 3; [26, 38–41]). The maximal inspiratory mouth pressures (MIP) seems to be more affected than the maximal expiratory mouth pressure (MEP) according to several researchers [26, 42]. Besides, in this latter

Table 2

Summary of the literature data on pulmonary function and PD. HY: Hoehn and Yahr, NS: Not significant, UPDRS: Unified Parkinson's Disease Rating Scale, MSA: Multiple system atrophy

Study	Number of patients	Disease duration (year)	Clinical scores	Control group	Spirometry	Dopasensitivity	Main results
[37]	31				obstruction	No	bronchoconstriction due to hyperactivity of the sympathetic system
[34]	23				proximal obstruction		
[36]	6				obstruction		partial
[33]	27				proximal obstruction		
[32]	31		12 HY3, 11 HY4, 8 HY5		obstruction		link with PD progression
[32]	31	8			mixed		description of ventilatory flutter
[31]	19			Yes			no impact of lung volumes on dysarthria
[28]	63	5 ± 0.68			mixed		link with UPDRS III score
[30]	58				mixed		link with clinical aspects of PD (bradykinesia, hypertonia, dorsal and cervical arthrosis)
[48]	review			review			restriction associated with hypertonia, obstruction pulmonary syndrome associated with upper airway obstruction
[35]	21	5 (mean)	HY 2-4		obstruction	Yes	lung volumes improved by L-DOPA
[27]	40	/	HY 1-3	Yes	restriction		
[46]	21			Yes	obstruction		abnormal agonist-antagonist muscle activity impacts on lungs volumes
[25]	12		HY 3-5		restriction	NS	no obstructive syndrome, even in the "off-drug" condition
[29]	53	2.8 in women, 3.2 in men	UPDRS 45 off, 14.6 on		restriction	partial	female patients had worse pulmonary function
[26]	30	4.9 ± 3.1	UPDRS 32.4 "on drug"	Yes (and MSA)	mixed		correlation with motor section of UPDRS

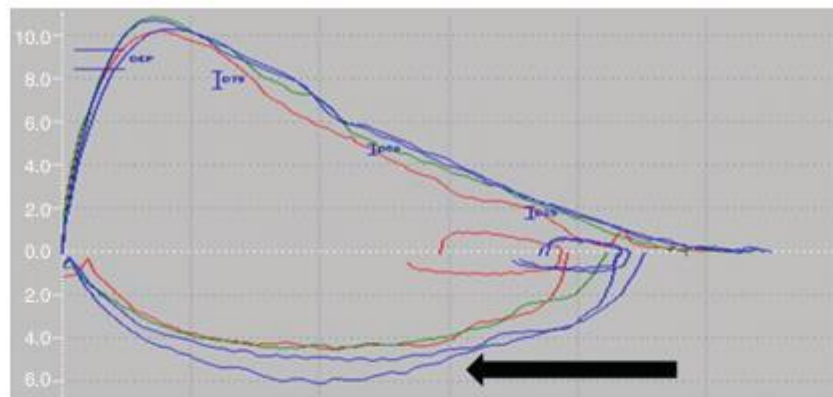


Fig. 1. A flow-volume loop in a PD patient (personal observation). Ordinate: Flow (L/s), Abscissa: Volume (L). Ventilatory flutter is predominant during inspiration (black arrow).

Table 3

Summary of the literature data on respiratory muscle weakness and PD. HY: Hoehn and Yahr, inspi: Inspiratory muscles, expi: Expiratory muscles, NS: Not significant. UPDRS: Unified Parkinson's Disease rating Scale

Study	Number of patients	Disease duration (year)	Clinical scores	Control group	Muscles	Dopasensitivity	main results
[36]	6				Inspi and expi	Yes	
[40]	9	2 to 14	HY 1-3	Yes			
[42]	10	6 to 20	HY 2-4		inspi	Yes (apomorphine)	due to lack of muscle coordination
[27]	40		HY 1-3	Yes	normal		
[39]	66		HY 3-5	Yes	inspi and expi		abnormal response to mild hypoxia
[29]	35	3		Yes	inspi and expi	Yes	
[41]	26	9.1 ± 0,3	UPDRS 43 "on drug"	Yes	inspi and expi	NS	respiratory muscle weakness in early-stage PD correlation with motor section of UPDRS
[26]	30	4.9 ± 3.1	UPDRS 32.4 "on drug"	Yes (and MSA)	inspi and expi		

paper, inspiratory muscles weakness is very severe [42]. The correlation with respiratory symptoms remains unclear, since some of the studies included patients with severe PD and limitations in their activities of daily living. There are few studies of the pathophysiology of this respiratory muscle weakness. Tremor (mainly action tremor) may be involved [43] or jerky movements of the diaphragm [44]. Accessory muscles seem to be affected in PD, although data on diaphragm function in PD are scarce. Vercueil et al. observed a differential impact of the disease on inspiratory muscles (preservation of diaphragmatic activity and impaired accessory inspiratory muscles, mainly intercostal muscles) [45]. A link between respiratory muscles disturbance and impaired lung volumes has been suggested [46]. Spirometry results would be the consequence of a reduced efficiency

during repetitive motor tasks. Furthermore, respiratory muscles strength seems to decrease with the course of the disease since a negative correlation was highlighted between MIP, MEP and the motor section of UPDRS [26].

Effect of antiparkinsonian drugs on respiratory muscles

Continuous subcutaneous infusion of Apomorphine has a positive effect on upper airways and chest wall muscle coordination [42]. But the MIP was not normalized. Other researchers did not find any significant effect of L-DOPA on mouth pressure values [41]. Likewise, two other studies did not evidence any respiratory muscle weakness in PD patients [23, 33]. Lastly, it is still not clear whether the onset of muscle

Table 4
Summary of the literature data on dyspnea and PD. HY: Hoehn and Yahr

Study	Number of patients	Disease duration (year)	Clinical scores	Control group	Main results
[56] (article in Russian)	7				abnormal response to hypoxemia
[57]	19	5.7 ± 0.3	HY 3–5		reduced response to hypoxia
[58]	12	9.3 ± 4.6	HY 1.5 ± 0.7	Yes	reduced response to hypoxia

weakness occurs early in PD, although Guedes et al. has suggested that this is indeed the case. Yet, the mean disease duration in their cohort was 9.1 ± 0.3 years [41].

SLEEP BREATHING DISORDERS

Occurrence of sleep apnea syndrome in PD

It has been known for decades that PD is associated with sleep disorders such as insomnia, excessive daytime sleepiness, REM (rapid-eye movement) and sleep behavioral disorders. However, there is still debate as to the prevalence of sleep apnea syndrome (SAS) in PD patients [47]. According to Shill et al. [48], the presence of restrictive or obstructive patterns in PD could be a predisposition to SAS. Some researchers have reported an abnormally high prevalence of SAS in PD (relative to healthy, age-matched controls), whereas others have reported normal or below-normal values [47, 49–51]. The body mass index was a major source of bias in these studies, and most of the patients included were suffering from late-stage PD. Moreover, no predictive clinical features of SAS have been identified [51]. Some researchers have mentioned peripheral SAS caused by upper airway obstruction [48]. However, an occurrence of 48% of sleep breathing disorders with a predominance of central SAS has been observed [52].

Interestingly, a recent study found that 43.3% of *de novo* PD patients (with a mean ± SD duration of disease of 9.7 ± 9.5 months) had an apnea-hypopnea index higher than 5 per hour [53]. The researchers observed an average of 15.9 ± 20.9 desaturation episodes per hour. Nevertheless, the study lacked an age-matched control group. Furthermore, no other studies (except those with obese patients) have evidenced significant oxyhemoglobin desaturation [47]. In conclusion, there is some evidence of mild nocturnal desaturation in early-stage PD but the underlying mechanisms have not been characterized. The functional consequences of these sleep breathing disorders are unclear, although vigilance does not seem to be affected [54].

Impact of antiparkinsonian drugs on sleep breath disorders

No effect of antiparkinsonian drugs was reported in a review about treatment of sleep disorders in PD [55]. In a study, dopamine agonist enhanced the risk of central SAS (mainly during REM-sleep) without any difference in terms of Epworth Sleepiness Scale [53].

THE RESPONSE TO HYPOXIA

In 1998, Serebrovskaya et al. showed that PD patients had abnormally low alveolar ventilation during severe hypoxia [56]. This result could not be attributed to a mechanical restriction of lung function. It is suggested that the altered response to minor and major hypoxia resulted from a PD-associated impairment of chemoreception [56]. Other researchers confirmed these results in patients with advanced disease [16] and patient with early-stage disease [57]. Other studies found a reduced ventilatory response to hypercapnia [58]. The putative mechanism is related to low ventilatory chemosensitivity and autonomic dysfunction.

INVOLVEMENT IN THE NEURODEGENERATIVE PROCESS

Neurodegeneration of the substantia nigra pars compacta (the hallmark of PD) is accompanied by extensive loss of neurons in extranigral sites, including the brainstem nuclei involved in sleep physiology and respiratory control [59, 60]. This localized neurodegeneration in some parts of the brainstem may account for the occurrence of ventilatory disorders in PD. However, a number of questions have yet to be resolved.

- (i) Since hypoxemia has already been described as one of the mechanisms of cell death in PD [61], does the alteration in pulmonary function accelerate the disease progression? Do cerebral or brainstem structures morphometric alterations

impact on the occurrence of ventilator disorders? In a cerebral MRI study, Gama et al. found an association between excessive daytime sleepiness and middle cerebellar peduncle atrophy in PD [62]. It would be interesting to perform a polysomnography and MRI study in this type of patient population.

(ii) When does hypoxemia occur? Asymptomatic hypoxemic episodes seem to occur even in *de novo* untreated patients [49], although larger patient vs. control cohort studies are required.

(iii) If hypoxemia does occur, can it influence the disease phenotype? As already observed in non-parkinsonian elderly patients [63], Neikrug et al. also highlighted obstructive SAS as a predictor of cognitive impairment in PD [64]. However, in a cohort of 740 early-stage PD patients, pulmonary dysfunction was not found to be a risk factor for cognitive impairment [65]. The main limit of this study is the absence of precise evaluation of the ventilatory function. Furthermore, motor status before and after the treatment of sleep apnea in PD patients has never assessed. However, some researchers found evidence of an abnormally low sympathetic response to hypoxia in patients with PD [57]. Here again, only a large, prospective cohort follow-up will be able to address this point.

CONCLUSION

Ventilatory dysfunction is an underestimated feature of PD. The heterogeneity of the papers hinders the assessment of the frequency and the severity of lung volumes alterations (restrictive and obstructive patterns), the respiratory muscles weakness and the dyspnea, even in advanced PD. The effect of antiparkinsonian drugs is still controversial. Among the studies included in this paper, we identified some limitations: (i) small study populations (mainly composed of patients with advanced PD), (ii) the absence of long-term follow-up and (iii) the absence of functional evaluations under "off-drug" conditions.

Recent data suggested that ventilator dysfunction could affect even early-stage. However, there are too few literature data to adequately confirm this hypothesis.

In conclusion, future research will have to investigate (i) the prevalence of respiratory dysfunction in early-stage patients, (ii) the pathophysiological mechanisms underlying this dysfunction and (iii) any long-term correlations between respiratory muscle

weakness, altered lung volumes, breathing sleep disorders and the onset of motor and non-motor signs of PD.

Our manuscript was copy-edited by David Fraser (Biotech Communication SARL).

REFERENCES

- [1] Troussière A-C, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, Pasquier F, & Bombois S (2014) Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry*, **12**, 1405-1408.
- [2] Kim S-M, Kim H, Lee J-S, Park KS, Jeon GS, Shon J, Ahn SW, Kim SH, Lee KM, Sung JJ, & Lee KW (2013) Intermittent hypoxia can aggravate motor neuronal loss and cognitive dysfunction in ALS mice. *PLoS One*, **11**, e81808.
- [3] Moreau C, Devos D, Gosset P, Brunaud-Danel V, Tonnel AB, Lassalle P, Defebvre L, & Destée A (2010) Mechanisms of deregulated response to hypoxia in sporadic amyotrophic lateral sclerosis: A clinical study. *Rev Neurol (Paris)*, **3**, 279-283.
- [4] Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM, & Swerdlow RH (2008) Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology*, **3**, 210-216.
- [5] Parkinson J (2002) An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci*, **2**, 223-236.
- [6] Ebihara S, Saito H, Kanda A, Nakajoh M, Takahashi H, Arai H, & Sasaki H (2003) Impaired efficacy of cough in patients with Parkinson disease. *Chest*, **3**, 1009-1015.
- [7] Fontana GA, Pantaleo T, Lavorini F, Maluccio NM, Mutolo D, & Pistolesi M (1998) Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med*, **2**, 458-464.
- [8] Mehanna R, & Jankovic J (2010) Respiratory problems in neurologic movement disorders. *Parkinsonism Relat Disord*, **10**, 628-638.
- [9] Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, & O'Donnell DE; American Thoracic Society Committee on Dyspnea (2012) An official American Thoracic Society statement: Update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*, **4**, 435-452.
- [10] Chenivesse C, Chan P-Y, Tsai H-W, Wheeler-Hegland K, Silverman E, von Leupoldt A, Similowski T, & Davenport P (2014) Negative emotional stimulation decreases respiratory sensory gating in healthy humans. *Respir Physiol Neurobiol*, **204**, 50-57.
- [11] Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, & Burr ML (2001) Dyspnoea and quality of life in older people at home. *Age Ageing*, **2**, 155-159.
- [12] Yust-Katz S, Shitrit D, Melamed E, & Djaldetti R (2012) Respiratory distress: An unrecognized non-motor phenomenon in patients with parkinsonism. *J Neural Transm*, **1**, 73-76.
- [13] Susan HF, & Lang AE (2007) Motor and nonmotor fluctuations. *Handbook of Clinical Neurology*. Elsevier, Edinburgh-Toronto, pp. 159-184.
- [14] Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, & Chérif AA (2002) Nonmotor fluctuations in

- Parkinson's disease: Frequent and disabling. *Neurology*, **3**, 408-413.
- [15] Weiner P, Inzelberg R, Davidovich A, Nisipeanu P, Magadle R, Berar-Yanay N, & Carasso RL (2002) Respiratory muscle performance and the Perception of dyspnea in Parkinson's disease. *Can J Neurol Sci*, **1**, 68-72.
- [16] Onodera H, Okabe S, Kikuchi Y, Tsuda T, & Itoyama Y (2000) Impaired chemosensitivity and perception of dyspnoea in Parkinson's disease. *Lancet*, **9231**, 739-740.
- [17] Storch A, Schneider CB, Wolz M, Stürwald Y, Nebe A, Odin P, Mahler A, Fuchs G, Jost WH, Chaudhuri KR, Koch R, Reichmann H, & Ebersbach G (2013) Nonmotor fluctuations in Parkinson disease: Severity and correlation with motor complications. *Neurology*, **9**, 800-809.
- [18] Leentjens AFG, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, & Starkstein SE (2012) Anxiety and motor fluctuations in Parkinson's disease: A cross-sectional observational study. *Parkinsonism Relat Disord*, **10**, 1084-1088.
- [19] Bayulkem K, & Lopez G (2010) Nonmotor fluctuations in Parkinson's disease: Clinical spectrum and classification. *J Neurol Sci*, **1-2**, 89-92.
- [20] Martinez JA, Rocha FS, Sobrani E, Galhardo FP, & Terra Filho J (2002) Effects of ondansetron on respiratory pattern and sensation of experimentally induced dyspnea. *Sao Paulo Med J*, **5**, 141-145.
- [21] Kallas de Carvalho F, Filho JT, Vianna EO, Silva GA, & Martinez JA (2002) Do steroids interfere in dyspnoea sensation? *Respir Med*, **7**, 511-514.
- [22] Rice JE, Antic R, & Thompson PD (2002) Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord*, **3**, 524-527.
- [23] Chalif JI, Sitsapesan HA, Pattinson KTS, Herigstad M, Aziz TZ, & Green AL (2014) Dyspnea as a side effect of subthalamic nucleus deep brain stimulation for Parkinson's disease. *Respir Physiol Neurobiol*, **192**, 128-133.
- [24] Yanase M, Kataoka H, Kawahara M, Hirabayashi H, Yamanaka T, Hirano M, & Ueno S (2008) Fixed epiglottitis associated with subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*, **3**, 332-333.
- [25] De Pandis MF, Starace A, Stefanelli F, Marruzzo P, Meoli I, De Simone G, Prati R, & Stocchi F (2002) Modification of respiratory function parameters in patients with severe Parkinson's disease. *Neurol Sci Suppl*, **2**, 69-70.
- [26] Wang Y, Shao WB, Gao L, Lu J, Gu H, Sun LH, Tan Y, & Zhang YD (2014) 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*, **12**, e116123.
- [27] Cardoso SRX, & Pereira JS (2002) Analysis of breathing function in Parkinson's disease. *Arq Neuropsiquiatr*, **1**, 91-95.
- [28] Izquierdo-Alonso JL, Jiménez-Jiménez FJ, Cabrera-Valdivia F, & Mansilla-Lesmes M (1994) Airway dysfunction in patients with Parkinson's disease. *Lung*, **1**, 47-55.
- [29] Pal PK, Sathyaprabha TN, Tuhina P, & Thennarasu K (2007) Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord*, **3**, 420-424.
- [30] Sabaté M, González I, Ruperez F, & Rodríguez M (1996) Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci*, **1-2**, 114-119.
- [31] Murdoch BE, Chenery HJ, Bowler S, & Ingram JC (1989) Respiratory function in Parkinson's subjects exhibiting a perceptible speech deficit: A kinematic and spirometric analysis. *J Speech Hear Disord*, **4**, 610-626.
- [32] Hovestadt A, Bogaard JM, Meerwaldt JD, van der Meché FG, & Stigt J (1989) Pulmonary function in Parkinson's disease. *J Neurol Neurosurg Psychiatr*, **3**, 329-333.
- [33] Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, & Cosio M (1984) Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med*, **7**, 438-442.
- [34] Nakano KK, Bass H, & Tyler HR (1972) Levodopa in Parkinson's disease: Effect on pulmonary function. *Arch Intern Med*, **3**, 346-348.
- [35] Herer B, Arnulf I, & Housset B (2001) Effects of levodopa on pulmonary function in Parkinson's disease. *Chest*, **2**, 387-393.
- [36] Bateman DN, Cooper RG, Gibson GJ, Peel ET, & Wandless I (1981) Levodopa dosage and ventilatory function in Parkinson's disease. *Br Med J (Clin Res Ed)*, **6285**, 190-191.
- [37] Obenour WH, Stevens PM, Cohen AA, & McCutchen JJ (1972) The causes of abnormal pulmonary function in Parkinson's disease. *Am Rev Respir Dis*, **3**, 382-387.
- [38] Sathyaprabha TN, Kapavarapu PK, Pall PK, Thennarasu K, & Raju TR (2005) Pulmonary functions in Parkinson's disease. *Indian J Chest Dis Allied Sci*, **4**, 251-257.
- [39] Haas BM, Trew M, & Castle PC (2004) Effects of respiratory muscle weakness on daily living function, quality of life, activity levels, and exercise capacity in mild to moderate Parkinson's disease. *Am J Phys Med Rehabil*, **8**, 601-607.
- [40] Tzelepis GE, McCool FD, Friedman JH, & Hoppin FG Jr (1988) Respiratory muscle dysfunction in Parkinson's disease. *Am Rev Respir Dis*, **2**, 266-271.
- [41] Guedes LU, Rodrigues JM, Fernandes AA, Cardoso FE, & Parreira VF (2012) Respiratory changes in Parkinson's disease may be unrelated to dopaminergic dysfunction. *Arq Neuropsiquiatr*, **11**, 847-851.
- [42] De Bruin PF, de Bruin VM, Lees AJ, & Pride NB (1993) Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis*, **6**, 1576-1580.
- [43] Brown P, Corcos DM, & Rothwell JC (1997) Does parkinsonian action tremor contribute to muscle weakness in Parkinson's disease? *Brain*, **3**, 401-408.
- [44] Estenne M, Hubert M, & De Troyer A (1984) Respiratory-muscle involvement in Parkinson's disease. *N Engl J Med*, **23**, 1516-1517.
- [45] Vercueil L, Linard JP, Wuyam B, Pollak P, & Benchetrit G (1999) Breathing pattern in patients with Parkinson's disease. *Respir Physiol*, **2-3** 163-172.
- [46] Polatli M, Akyol A, Cildag O, & Bayülkem K (2001) Pulmonary function tests in Parkinson's disease. *Eur J Neurol*, **4**, 341-345.
- [47] Da Silva-Júnior FP, do Prado GF, Barbosa ER, Tufik S, & Togeiro SM (2014) Sleep disordered breathing in Parkinson's disease: A critical appraisal. *Sleep Med Rev*, **2**, 173-178.
- [48] Shill H, & Stacy M (1998) Respiratory function in Parkinson's disease. *Clin Neurosci*, **2**, 131-135.
- [49] Maria B, Sophia S, Michalis M, Charalampos L, Andreas P, John ME, & Nikolaos SM (2003) Sleep breathing disorders in patients with idiopathic Parkinson's disease. *Respir Med*, **10**, 1151-1157.
- [50] Diederich NJ, Vaillant M, Leischen M, Mancuso G, GolINVAL S, Nati R, & Schlessner M (2005) Sleep apnea syndrome in

- Parkinson's disease. A case-control study in 49 patients. *Mov Disord*, **11**, 1413-1418.
- [51] Trotti LM, & Bliwise DL (2010) No increased risk of obstructive sleep apnea in Parkinson's disease. *Mov Disord*, **13**, 2246-2249.
- [52] Valko P, Hauser S, Sommerauer M, Werth E, & Baumann CR (2014) Observations on sleep-disordered breathing in idiopathic Parkinson's disease. *PLoS One*, **6**, e100828.
- [53] Joy SP, Sinha S, Pal PK, Panda S, Philip M, & Taly AB (2014) Alterations in Polysomnographic (PSG) profile in drug-naïve Parkinson's disease. *Ann Indian Acad Neurol*, **3**, 287-291.
- [54] Monaca C, Duhamel A, Jacquesson JM, Ozsancak C, Destée A, Guieu JD, Defebvre L, & Derambure P (2006) Vigilance troubles in Parkinson's disease: A subjective and objective polysomnographic study. *Sleep Med*, **5**, 448-453.
- [55] Trotti LM, & Bliwise DL (2014) Treatment of the sleep disorders associated with Parkinson's disease. *Neurotherapeutics*, **1**, 68-77.
- [56] Serebrovskaya T, Karaban I, Mankovskaya I, Bernardi L, Passino C, & Appenzeller O (1998) Hypoxic ventilatory responses and gas exchange in patients with Parkinson's disease. *Respiration*, **1**, 28-33.
- [57] Seccombe LM, Rogers PG, Hayes MW, Farah CS, Veitch EM, & Peters MJ (2013) Reduced hypoxic sympathetic response in mild Parkinson's disease: Further evidence of early autonomic dysfunction. *Parkinsonism Relat Disord*, **11**, 1066-1068.
- [58] Seccombe LM, Giddings HL, Rogers PG, Corbett AJ, Hayes MW, Peters MJ, & Veitch EM (2011) Abnormal ventilatory control in Parkinson's disease—further evidence for non-motor dysfunction. *Respir Physiol Neurobiol*, **2-3** 300-304.
- [59] Diederich NJ, & McIntyre DJ (2012) Sleep disorders in Parkinson's disease: Many causes, few therapeutic options. *J Neurol Sci*, **1-2**, 12-19.
- [60] Braak H, Del Tredici K, Rüb U, Rüb U, de Vos RA, Jansen Steur EN, & Braak E (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*, **2**, 197-211.
- [61] Olanow CW (2007) The pathogenesis of cell death in Parkinson's disease. *Mov Disord Suppl*, **17**, S335-S342.
- [62] Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, & de Bruin PF (2010) Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. *Parkinsonism Relat Disord*, **4**, 275-279.
- [63] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, Ancoli-Israel S, & Stone KL (2011) Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA*, **6**, 613-619.
- [64] Neikrug AB, Maglione JE, Liu L, Natarajan L, Avanzino JA, Corey-Bloom J, Palmer BW, Loreda JS, & Ancoli-Israel S (2013) Effects of sleep disorders on the non-motor symptoms of Parkinson disease. *J Clin Sleep Med*, **11**, 1119-1129.
- [65] Uc EY, McDermott MP, Marder KS, Anderson SW, Litvan I, Como PG, Auinger P, Chou KL, & Growdon JC; Parkinson Study Group DATATOP Investigators (2009) Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. *Neurology*, **18**, 1469-1477.

Objectifs du travail

L'objectif principal de notre thèse était de mieux préciser l'atteinte ventilatoire dans la MP en s'intéressant à la fois au symptôme (la dyspnée) et à l'atteinte objective en EFR dès le stade précoce de la maladie.

Ce travail s'est décomposé en quatre étapes. La première a consisté en une évaluation de la prévalence de la dyspnée dans une population de patients parkinsoniens non-déments à tous les stades de la maladie de Parkinson (étude DYSPARK – étude n°1). Dans une seconde étape, nous avons étudié les caractéristiques cliniques de la dyspnée dans cette pathologie en utilisant une échelle multidimensionnelle (étude DYSPARK - étude n°2). Dans la troisième étape nous avons tenté de préciser s'il existe une atteinte objective des EFR au stade précoce de la MP et analyser l'évolution à 2 ans (étude Prodigy-Park1 – étude n°3). La quatrième étape a consisté en une poursuite du suivi longitudinal à 5 ans de la cohorte de l'étude n°3 (étude Prodigy-Park2 - étude n°4). Enfin, nous avons réalisé une mesure des pressions buccales chez les patients de l'étude n°4.

Etude 1

La dyspnée : un symptôme méconnu de la maladie de Parkinson.

BAILLE G, CHENIVESSE C, PEREZ T, MACHURON F, DUJARDIN K, DEVOS D, DEFEBVRE L, MOREAU C. Dyspnea : an underestimated symptom in Parkinson's disease. *Parkinsonism and Related Disorders*, 2019 Mar;60:162-166..

1. Objectifs de l'étude

La première étape de cette thèse a consisté en l'étude de la prévalence de la dyspnée dans une population de patients parkinsoniens consécutifs issus de la cohorte NS Park et pris en charge au CHU de Lille. Basée sur les données de la littérature, notre hypothèse était que 30% des patients atteints de MP se plaignait de dyspnée au cours du mois précédent et que la présence du symptôme était associée à l'évolution et à la sévérité de la maladie.

2. Méthodes

Les patients inclus répondaient aux critères de MP et devaient avoir un score à la MoCA > 24/30. L'existence d'une pathologie cardiaque, pulmonaire ou ORL et/ou un examen cardio-pulmonaire anormal étaient des critères d'exclusion. La question suivante a été posée aux participants de l'étude : "au cours du dernier mois, avez-vous ressenti un essoufflement et/ou avez-vous eu des difficultés pour respirer normalement ?" En cas de réponse positive à un des 2 items, le patient était considéré comme dyspnéique.

Nous avons ensuite comparé les caractéristiques cliniques motrices (score MDS-UPDRS III et IV, score de Hoen & Yahr), non-motrices (MDS-UPDRS I, II, HAD anxiété et dépression, MoCA) et la qualité de vie (PDQ8) des patients dyspnéiques à celles des patients non-dyspnéiques.

3. Résultats

Sur les 153 patients inclus (âge moyen = $63,9 \pm 7,4$ ans ; durée moyenne d'évolution de la MP = $9,2 \pm 6,1$ années), la fréquence de la dyspnée était de 39,2% (31,5–47). Au plus le score Hoen et Yahr était élevé, au plus la proportion de patients dyspnéiques était importante ($p < 0,001$). En ajustant sur la durée d'évolution de la maladie, les patients parkinsoniens non dyspnéiques avaient un score MDS-UPDRS I (7,0 (5,0 ; 9,0) vs 15,5 (11,5 ; 19,0) ($p < 0,001$)), II (5,0 (3,0 ; 6,0) vs 11,0 (7,0 ; 15,5) $p < 0,001$)), III (25,0 (18,0 ; 34,0) vs 43,0 (35,5 ; 50,5) $p < 0,001$)), et IV (7,0 (6,0 ; 9,0) vs 11,0 (7,0 ; 13,0) $p < 0,001$)) significativement plus faible, un score à la MoCA significativement plus élevé (27,0 (26,0 ; 29,0) vs 25,0 (23,0 ; 26,0) $p < 0,001$)). D'autres SNM (évalués par le score MDS-UPDRS I) étaient fortement associés à la présence d'une dyspnée : les troubles cognitifs (OR, 7,5 ; 95% IC [3,9-14,6]), la fatigue (OR 6,16 ; 95% IC [3,30 ; 11,51]) et la constipation (OR, 4,2 ; 95% IC [2,4-7,3]).

4. Conclusion

Dans la population de notre étude, la dyspnée est un SNM de la MP et semble avoir un impact sur l'autonomie. Sa présence est liée à la sévérité motrice et non-motrice de la maladie et aux fluctuations motrices. La dyspnée étant une expérience subjective pluridimensionnelle, il est nécessaire de mieux la caractériser chez les patients parkinsoniens afin de mieux comprendre sa physiopathologie.



Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Dyspnea: An underestimated symptom in Parkinson's disease

Guillaume Baille^{a,*}, Cécile Chenivresse^b, Thierry Perez^b, François Machuron^c, Kathy Dujardin^a, David Devos^a, Luc Defebvre^a, Caroline Moreau^a^a Department of Neurology, Expert Center for Parkinson's Disease, INSERM UMR_S1171, Lille University Medical Center, LICEND COEN Center, Lille, F-59000 France^b CHU Lille, Service de Pneumologie et Immuno-Allergologie, Centre de Compétence pour les Maladies Pulmonaires Rares, Univ. Lille, INSERM U1019, CHU, Institut Pasteur de Lille, F-59000 Lille, France^c Univ. Lille, CHU Lille, EA 2694 - Santé Publique: Épidémiologie et Qualité des Soins, Department of Biostatistics, F-59000 Lille, France

ARTICLE INFO

Keywords:

Dyspnea

Non-motor symptoms

Respiratory disturbance

ABSTRACT

Introduction: Dyspnea is one of the least well-characterized non-motor symptoms (NMS) associated with Parkinson's disease (PD).**Objective:** To determine the frequency of dyspnea in a large, single-center cohort of consecutive PD patients with no history of lung or heart disease, and to compare clinical features in dyspneic vs. non-dyspneic patients.**Methods:** Patients with abnormal cardiovascular and pulmonary results in a clinical examination were excluded. A positive response to at least one question ("In the last month, have you suffered from breathlessness?" and "In the last month, have you had trouble breathing normally?") was considered to signify the experience of dyspnea. MDS-UPDRS, global cognitive performance, non-motor symptoms and quality of life were assessed.**Results:** In the cohort of 153 non-demented PD patients (mean age \pm standard deviation: 63.9 ± 7.4 ; mean disease duration: 9.2 ± 6.1 years), the mean [95% confidence interval (CI)] frequency of dyspnea was 39.2% (31.5–47). After adjustment for disease severity, PD patients with dyspnea had a significantly higher Movement Disorders Society Unified Parkinson's Disease Rating Scale part I, II and IV scores, a higher HAD anxiety and depression scores and a significantly higher 8-item Parkinson's Disease Questionnaire.**Conclusion:** Dyspnea is a frequent NMS in PD. Its pathophysiology and prognostic value need more investigation.

1. Introduction

Dyspnea is one of the least well-characterized non-motor symptoms (NMSs) associated with Parkinson's disease (PD). Dyspnea has been defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity ... [it] derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses [1]." Dyspnea is a common symptom of respiratory, cardiac, neuromuscular, and psychological disorders. In an observational study of patients attending a movement disorders department, most cases of dyspnea were associated with heart and lung diseases [2]. However, many clinicians are unaware that dyspnea is also listed as a NMS of PD [3].

In neurodegenerative diseases such as amyotrophic lateral sclerosis, the associated neuromuscular impairment of respiratory muscles means that dyspnea is a frequent symptom. In PD, the precise mechanisms involved in dyspnea remain unknown [4]. Furthermore, the literature data on the frequency of dyspnea in PD are contradictory: a prevalence

of 40% was reported in a cohort of 50 fluctuating PD patients [5], whereas the PRIAMO study of 1072 patients found a value of only 11.5% [6]). Since dyspnea is a marker for poor quality of life and is associated with a loss of autonomy in ambulatory elderly patients [7], a specific study of dyspnea in PD is lacking, even more in patients without fluctuations.

The diagnosis of dyspnea can still be challenging; the multi-dimensional, subjective aspect of this diagnosis might account for the wide range of prevalence values reported to date. It is a self-reported symptom and must not be mistaken with tachypnea or intercostal indrawing. Therefore, without an active approach, physicians can miss the existence of the dyspnea. Furthermore, dyspnea is the only NMS included in two different categories (dysautonomia and sensorial) in the classification developed by Susan & Lang [3].

The primary objective of the present study was to determine the prevalence and clinical characteristics of dyspnea in a large cohort of PD patients. The secondary objective was to compare the clinical features between dyspneic and non dyspneic PD patients.

* Corresponding author. Department of Neurology and Movement Disorders, Lille University Medical Center, Lille, France.

E-mail address: guillaume.baille@chru-lille.fr (G. Baille).<https://doi.org/10.1016/j.parkreldis.2018.09.001>

Received 7 June 2018; Received in revised form 29 August 2018; Accepted 2 September 2018

1353-8020/© 2018 Elsevier Ltd. All rights reserved.

Etude 2

La dyspnée est un symptôme spécifique de la maladie de Parkinson.

BAILLE G, PEREZ T, DEVOS D, MACHURON F, DUJARDIN K, DEFEBVRE L, CHENIVESSE C, DEFEBVRE L, MOREAU C.

Dyspnea is a specific symptom in Parkinson's disease.

Accepté dans Journal of Parkinson's disease le 25/07/2019

1. Objectifs de l'étude

La deuxième étape de cette thèse a consisté en l'étude des caractéristiques de la dyspnée dans une population de patients parkinsoniens consécutifs issus de la cohorte NS Park et pris en charge au CHU de Lille. Il s'agit de la sous-population présentant une dyspnée issue de l'étude précédente.

Pour la première fois, l'échelle MDP a été administrée chez des patients atteints de la MP. Il était donc difficile d'émettre des hypothèses précises quant aux résultats, mais nous suspicions que les caractéristiques cliniques de la dyspnée dans la MP différaient de celles dans les pathologies pulmonaires telles que l'asthme ou la BPCO. L'objectif de cette étude était de déterminer les caractéristiques sensorielles et émotionnelles de la dyspnée dans la MP.

2. Méthodes

Le questionnaire MDP était administré aux patients dyspnéiques de la cohorte DYSPARK (60/153). Cela permettait de calculer le score de perception immédiate (A1), de déterminer le meilleur qualificatif sensoriel (SQ) s'appliquant au ressenti de chaque patient et d'évaluer la réponse émotionnelle (A2).

3. Résultats

Les patients étaient dyspnéiques depuis en moyenne $4,6 \pm 2,4$ ans, avec un début de la symptomatologie pour la grande majorité après le début de signes moteurs. Le retentissement moyen de la dyspnée en mMRC était de $1,3 \pm 0,8$. Les meilleurs qualificatifs sensoriels (SQ) rapportés étaient l'hyperpnée (35%), l'effort musculaire respiratoire (25%) et la sensation de manque d'air (20%). L'hyperpnée et le manqué d'air étaient les sensations avec l'intensité la plus importante ($3,7 \pm 2,5$ et $3,3 \pm 3,4$ respectivement). Parmi les réponses émotionnelles (A2), l'anxiété avait la plus grande intensité rapportée ($4,0 \pm 3,3$). L'intensité globale des SQ était corrélée avec le score d'anxiété du HAD ($p=0,02$; $r=0,3$), le score de dépression du HAD ($p=0,03$; $r=0,28$) et la qualité de vie (PDQ8 - $p=0,004$; $r=0,37$). L'intensité de la réponse émotionnelle globale (A2) était corrélée avec le score d'anxiété du HAD ($p<0,001$; $r=0,49$), le score de dépression du HAD ($p=0,03$; $r=0,28$) et la qualité de vie (PDQ8 - $p<0,001$; $r=0,42$).

4. Conclusion

La dyspnée semble être un symptôme avec des caractéristiques spécifiques à la MP. Corréler les différents qualificatifs sensoriels avec les données objectives en EFR permettraient de mieux comprendre la physiopathologie des troubles ventilatoires dans la MP.

Dyspnea is a specific symptom in Parkinson's disease

Guillaume Baille MD ¹, Thierry Perez MD ², David Devos MD, PhD ⁴, François Machuron MS ³, Kathy Dujardin PhD¹, Cécile Chenivresse MD, PhD² Luc Defebvre MD, PhD, ¹Caroline Moreau MD, PhD ¹

1. Department of Neurology, Expert Center for Parkinson's Disease, INSERM UMRS_1171, Lille University Medical Center, LICEND COEN center, Lille, F-59000 France
2. CHU Lille, Lung Function Department, Univ Lille, INSERM 1019, CNRS UMR 8204, Institut Pasteur de Lille, Center for Infection and Immunity of Lille, Lille, France
3. Univ. Lille, CHU Lille, EA 2694 - Santé Publique: Épidémiologie et Qualité des Soins, Department of Biostatistics, F-59000 Lille, France
4. CHU Lille, Department of Allergy and Respiratory Medicine, Competence Center for rare lung diseases, Univ. Lille, CNRS, INSERM, Institut Pasteur de Lille, U1019 - UMR 8204 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille France
5. CHU Lille, Department of Medical Pharmacology, Lille University INSERM 1171, Lille, France

Version acceptée dans la revue Journal of Parkinson's disease.

Corresponding author: Caroline Moreau, caroline.moreau@chru-lille.fr, +33320445962

CHU Lille, Service de Pneumologie et Immuno-Allergologie, Centre de Compétence pour les Maladies Pulmonaires Rares, Univ. Lille, INSERM U1019, CIIL, Institut Pasteur de Lille, F-59000 Lille, France

Keywords : Parkinson's disease, dyspnea, non-motor symptom, anxiety, ventilatory dysfunction

Abstract = 171/250

Words = 1713

References = 22/40

Figures = 2/2

Authors' role (1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique)

GB: 1A, 1B, 1C, 3A

TP: 1A, 2C, 3B

DD: 2C, 3B

FM: 2A, 2B

KD: 1A

CC: 1A, 2C, 3B

LD: 2C, 3B

CM: 1A, 1B, 2C, 3B

Disclosures:

GB, TP, FM, KD and CC have no disclosure.

DD has received PHRC grants from the French Ministry of Health and research funding from the ARSLA charity, France Parkinson charity and European Commission (H2020). He served on advisory boards, served as a consultant and given lectures for pharmaceutical companies such as Apopharma, Orkyn, Air Liquide, Aguettant, Everpharma, Boston Scientific.

LD has received grants from France Parkinson charity and served on advisory boards for Orkyn, Zambon and Abbvie and gave a lecture (honorary) for UCB.

CM has served as CSO InBrain Pharma and Scientific advisor for Apopharma, Orkyn/ Air Liquide and Boston Scientific.

Abstract (171/250)

Background

Dyspnea is a multidimensional sensation that is reported in Parkinson's disease (PD). The multidimensional dyspnea profile (MDP) questionnaire can help to distinguish the perceptible dimension and the emotion response.

Objective

The aim was to assess the clinical features associated with dyspnea using the MDP questionnaire in order to determine which aspects of the symptom was linked with anxiety, depression or motor severity of the disease.

Methods

Non-demented patients were asked whether they experienced shortness of breath in the last month. In case of positive answer, dyspnea was assessed by the MDP. MDS-UPDRS, global cognitive performance, non-motor symptoms and quality of life were assessed.

Results

60/153 patients were dyspneic since 4.6 ± 2.4 years. The most frequent best sensory quality (SQ) described were: hyperpnoea (35%), physical breathing effort (25%) and air hunger (20%). Hyperpnoea and air hunger had the highest SQ intensity. Anxiety had the highest intensity in the emotional domain.

Conclusion

Dyspnea is a frequent symptom in PD, with specific presentations and two main aspects: one related with anxiety and another with ventilation control impairment.

Introduction:

Non-motor symptoms are frequent in Parkinson's disease (PD). Among them, dyspnea is reported between 11.5% and 40% of the patients [1-3]. Even if other causes are excluded, it seems to be a symptom due to the neurodegenerative process [4]. As dyspnea is disabling for elderly and in PD [2,5] and perceived as stressful, a better clinical assessment could improve the management of dyspneic PD patients. Furthermore, a controversy still exists regarding the existence and the pathophysiology of respiratory disturbance in PD [6]. Determining the clinical features of dyspnea in PD could help us to better understand the underlying mechanisms in this disease. On one side, shortness of breath could be a somatic expression of anxiety [7]. But on the other side, MRI data and clinical observation tends to classify dyspnea and ventilatory dysfunction as a dysautonomic symptom [8-10]. Four main contributors to ventilatory dysfunction have been identified: an obstructive element, a restrictive component, potential drug effects (i.e levodopa induced diaphragmatic dyskinesias) and an abnormal central control of ventilation.

Dyspnea is a complex and multidimensional sensation and it needs specific tools to be screened properly. Classically, shortness of breath is mainly assessed through the disability associated with breathlessness by using the mMRC scale (from 0 (no disability) to 4 (complete disability) [11], however, this scale only questions the patient about the functional impairment due to dyspnea. Since physical autonomy is disabled in neurological diseases like PD (due to akinesia, hypertonia or gait), other questionnaires are needed in order to screen the symptom and not only its consequences when the patient makes effort. Recently, the multidimensional dyspnea profile (MDP) questionnaire has been developed to distinguish sensory and emotional aspects of the dyspnea [12 – more details in supplementary data 2]. The best sensory quality (which means the quality that most accurately describes the sensation - SQ) and the severity of the emotional response domain may differ between airway, lung or neuromuscular diseases [13,14].

The aim of our study was to assess the clinical features of dyspnea using the MDP questionnaire. Our hypothesis was that dyspnea in PD is an individualized symptom with two distinct aspects: one strongly linked with emotional response domain and particularly anxiety and another one associated with ventilation control impairment due to dysautonomia.

Method

Between october 2016 and march 2017, in a single-center study (movement disorders clinic), consecutive PD patients were asked whether they experienced dyspnea. The inclusion criteria were i) physician-diagnosed PD (according to the Movement Disorders Society Clinical Diagnostic Criteria for PD (2015)) ii) age between 18 and 85, iii) experience of dyspnea in the last month. The exclusion criteria were (i) atypical parkinsonism, (ii) cognitive impairment (as evidenced by a Montreal Cognitive Assessment (MoCA) score < 24 out of 30 [15]), (iii) a pulmonary, cardiac or ENT pathology (affecting the upper airways) that may lead to dyspnea, (iv) intercurrent pulmonary, cardiac or ENT infection in the last month and (v) abnormal cardiac and/or pulmonary results in a clinical examination. An ethical standards committee approved the procedures.

Patients were asked the two following questions: “In the last month, have you experienced breathlessness” and “In the last month, did you feel discomfort while breathing?” Dyspnea was diagnosed if the answer to at least one question was “yes”. Respiratory disability was assessed using the mMRC scale: zero for dyspnea only with strenuous exercise; 1 for dyspnea when hurrying or walking up a slight hill; 2 if the patient walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own; 3 if the patient stops for breath after walking 100 yards (91 m) or after a few minutes; 4 if the patient is too dyspneic to leave house or breathless when dressing [10]. Patients with fluctuations (n=52) were also asked to determine if the symptom was associated with motor fluctuations (if dyspnea was more predominant during self-reported “on drug” or “off drug” conditions, or “undetermined if the patients was not able to precise this point) and the clinical features of dyspnea were assessed by the MDP. In this study, the patients were instructed to focus on their worst breathing experience in the preceding 4 weeks. First, the patients were asked to rate unpleasantness of breathing sensations (A1 – numerical rating scale - maximum 10). Secondly, they are asked to determine if sensory qualifiers applies or not to describe the dyspnea (SQ – 5 different sensations – Table 1) and then, which of the 5 sensations most accurately applied. Thirdly, the patients are asked to rate each of the sensory qualifiers that apply (numerical rating scale from 0 to 10 for each item – maximum 50). The immediate perception response score is equal to the sum of A1 plus the numerical rating of each sensory qualifier. Lastly, they are asked to rate each of 5 breathing-related emotions (numerical rating scale from 0 to 10 for each item –maximum 50). The emotional response domain (A2) is the sum of the numerical rating of each emotion.

The neurological examination included the Movement Disorders Society Unified-Parkinson’s Disease Rating Scale (MDS-UPDRS [16]), the Hoehn and Yahr score (H&Y [17]), the Hospital Anxiety and Depression scale (HAD [18]), and the 8-item Parkinson’s Disease Questionnaire (to assess quality of life (PDQ8) [19]).

The quantitative variables were described using the mean and the standard deviation or the median and the interquartile range (IQR). The normality of the distributions was verified with the help of graphs and the Shapiro-Wilk test. The qualitative variables were described using frequencies and percentages. Relationship between variables has been appreciated with the help of Spearman’s correlation coefficients. The Hotelling–Williams procedure tests whether or not two non-independent correlation coefficients are significantly different. The threshold of significance was 0.05. The analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA).

Results

Among the 153 patients of our cohort (flow chart in supplementary data 1), sixty patients (39.2% - more details in [3]) reported dyspnea (age = 64.9 ± 8.3 years, sex ratio (M/F) = 31/29, disease duration = 12.0 years (8.0; 16.0) (Table 1). The duration of dyspnea was 4.6 ± 2.4 years with much more occurrence of the dyspnea during wearing-off times (48.3%) than during biphasic and peak-dose dyskinesia (6.7%). The mean degree of disability associated with dyspnea assessed by the mMRC scale was 1.3 ± 0.8 .

MDP data are in Table 1. The most frequent SQ described by the patients were: hyperpnoea (35%), physical breathing effort (25%) and air hunger (20%). Hyperpnoea and air hunger were the SQ with the highest intensity (respectively 3.7 ± 2.5 and 3.3 ± 3.4). Regarding the emotional response domain (A2), anxiety had the highest intensity (4.0 ± 3.3).

The intensity of the global SQ was correlated with the MDS-UPDRS I score (Non-motor Experiences of Daily Living - $p=0.002$; $r=0.39$), the MDS-UPDRS II score (Motor Experiences of Daily Living – $p=0.004$; $r=0.36$), the MDS-UPDRS III (Motor Examination – $p=0.03$; $r=0.29$), the Hoehn & Yahr score (global motor severity of the PD – $p=0.03$; $r=0.29$), the HAD anxiety score ($p=0.02$; $r=0.3$), the HAD depression score ($p=0.03$; $r=0.28$) and the quality of life (PDQ8 - $p=0.004$; $r=0.37$).

The intensity of emotions (A2) was correlated with the MDS-UPDRS I (Non-motor Experiences of Daily Living - $p<0.001$; $r=0.49$), the MDS-UPDRS II (Motor experiences of daily life – $p=0.03$; $r=0.28$), the HAD anxiety ($p<0.001$; $r=0.49$), the HAD depression ($p=0.03$; $r=0.28$) and the quality of life (PDQ8 - $p<0.001$; $r=0.42$). HAD anxiety score had a stronger statistical correlation with A2 (intensity of emotional response domain) than with the immediate perception response score (0.3 vs 0.49, $p=0.03$).

Discussion

In our study, dyspnea seems to be a specific symptom with variable characteristics. Indeed, hyperpnoea was the best sensory quality for 35% of the participants and in a cohort of patients with amyotrophic lateral sclerosis, “air hunger” was the best sensory quality for almost half of the patients [14]. In chronic obstructive pulmonary disease, “air hunger” (27%), followed by “breathing a lot” (19%) were the most chosen qualities [13]. Therefore, “parkinsonian dyspnea “ seems to have a specific profile, different to that observed either in lung or in neuromuscular diseases.

With the different sensory qualities, MDP can also help us to better understand the pathophysiology of dyspnea in PD. Hyperpnoea may be the consequence of a muscles command dysfunction due to hypertonia and lack of coordination. Some authors highlighted an abnormal ventilatory control in PD patients [20] and further investigations are needed to determine if dyspnea is associated with autonomic and/or cognitive dysfunction (as attention deficit or hallucinations) in the disease. Regarding the emotional response scores, in our cohort, dyspnea was associated with anxious and depressive feelings. These results are not specific of PD. Yet, fear and frustration are not described with such intensity in lung or neuromuscular diseases [13,14]. It may reflect the difficulty for PD patients to control properly the respiratory muscles, unlike in asthma for example [21]. Only a study assessing MDP and pulmonary function tests in PD patients could confirm this hypothesis.

Our study suffers from several limitations. Firstly, we did not perform pulmonary function testing in our study. These data might help to understand better the pathophysiological mechanisms underlying dyspnea. By assessing dyspnea and PFT in a prospective cohort, correlations with obstructive/restrictive patterns could be done. Then, we could determine if the respiratory sensations are associated with an objective lung dysfunction and are related with lack of ventilatory control (i.e. dysautonomia) or with anxiety, as part of non-motor fluctuations. Secondly our cohort was recruited from a single center (a tertiary hospital). Nevertheless, the mean age, disease duration and non-motor scores were similar to those published for other cohorts [22]. A multicenter international cohort could

avoid this bias. Lastly, we cannot rule out self-reporting bias among the patients. Some participants might have not perceived their dyspnea because of a disease-related physical limitation or might even have mistaken it for a motor impairment. We did not restrict the definition of dyspnea to respiratory disability since we screened it with an open-ended question.

Conclusion

Dyspnea is a specific symptom in PD with clinical features distinct from what is observed in neuromuscular or cardiac diseases. An individualized and specific clinical approach is needed to better understand the underlying mechanisms of this respiratory symptom. We also need to determine the clinical features that could be warning signs to perform pulmonary function testings or trigger specific care of non-motor symptoms.

References

1. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meo G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrone R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group. (2009) The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord.*, **11**, 1641-9.
2. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Chérif AA. (2002) Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology*, **3**, 408-13.
3. Baille G, Chenivresse C, Perez T, Machuron F, Dujardin K, Devos D, Defebvre L, Moreau C. (2019) Dyspnea: an underestimated symptom in Parkinson's disease. *Parkinsonism Relat Disorders*, **60**, 162-166.
4. Yust-Katz S, Shitrit D, Melamed E, Djaldetti R. Respiratory distress: an unrecognized non-motor phenomenon in patients with parkinsonism. (2012) *J Neural Transm (Vienna)*, **1**, 73-6.
5. Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, & Burr ML (2001) Dyspnoea and quality of life in olderpeople at home. *Age Ageing*, **2**, 155-159.
6. Baille G, De Jesus AM, Perez T, Devos D, Dujardin K, Charley CM, Defebvre L, Moreau C. (2016) Ventilatory Dysfunction in Parkinson's Disease. *J Parkinsons Dis*, **3**, 463-71.
7. Leentjens AFG, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, & Starkstein SE (2012) Anxiety and motor fluctuations in Parkinson's disease: A cross-sectional observational study. *Parkinsonism Relat Disord*, **10**, 1084–1088.
8. Secombe LM, Rogers PG, Hayes MW, Farah CS, Veitch EM, & Peters MJ (2013) Reduced hypoxic sympathetic response in mild Parkinson's disease: Further evidence of early autonomic dysfunction. *Parkinsonism Relat Disord*, **11**, 1066-1068.
9. Meissner WG, Vital A, Ghorayeb I, Guehl D, Tison F. (2010) Dyspnea as first sign of autonomic failure in postmortem confirmed multiple system atrophy. *Mov Disord*, **12**, 1997-8.

10. Lee SY, Chen MH, Chiang PL, Chen HL, Chou KH, Chen YC, Yu CC, Tsai NW, Li SH, Lu CH, Lin WC. (2018) Reduced gray matter volume and respiratory dysfunction in Parkinson's disease: a voxel-based morphometry study. *BMC Neurol*, **1**, 73.
11. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA (1999) Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease *Thorax*, **7**, 581-6.
12. Banzett RB, O'Donnell CR, Guilfoyle TE, Parshall MB, Schwartzstein RM, Meek PM, Gracely RH, Lansing RW (2015) Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. *Eur Respir J*, **6**, 1681-91.
13. Morélot-Panzini C, Gilet H, Aguilaniu B, Devillier P, Didier A, Perez T, Pignier C, Arnould B, Similowski T (2016) Real-life assessment of the multidimensional nature of dyspnoea in COPD outpatients. *Eur Respir J*, **6**, 1668-79.
14. Morélot-Panzini C, Perez T, Sedkaoui K, de Bock E, Aguilaniu B, Devillier P, Pignier C, Arnould B, Bruneteau G, Similowski T (2018) The multidimensional nature of dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: Air hunger, anxiety and fear. *Respir Med*, **145**, 1-7.
15. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*, **4**, 695–9.
16. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe W, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N; Movement Disorder Society UPDRS Revision Task Force (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*, **15**, 2129-70.
17. Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression and mortality. *Neurology*, **5**, 427–42.
18. Zigmond A.S., Snaith R.P (1983) The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand*, **67**, 361-370.
19. Jenkinson C, Fitzpatrick R, Peto V (1998) The Parkinson's disease questionnaire; User manual for the PDQ-39, PDQ-8 and PDQ summary index. *Oxford: Health Services Research Unit, Department of Public Health, University of Oxford*.
20. Seccombe LM, Giddings HL, Rogers PG, Corbett AJ, Hayes MW, Peters MJ, Veitch EM (2011) Abnormal ventilatory control in Parkinson's disease—further evidence for non-motor dysfunction. *Respir Physiol Neurobiol*, **2-3**, 300-4.
21. Clanton TL, Levine S. (2009) Respiratory muscle fiber remodeling in chronic hyperinflation: dysfunction or adaptation? *Journal of Applied Physiology*, **1**, 324 - 35.

22. T. Maeda, Y. Shimo, S.W. Chiu, T. Yamaguchi, K. Kashihara, Y. Tsuboi, M. Nomoto, N. Hattori, H. Watanabe, H. SaikiJ-FIRST group (2017) Clinical manifestations of nonmotor symptoms in 1021 Japanese Parkinson's disease patients from 35 medical centers, *Parkinsonism Relat Disord*, **38**, 54–60.

Table 1: clinical features of the patients.

Parameter	Overall population N=60
Age (years), mean \pm SD	64.9 \pm 8.3
Sex, M/F	31/29
Smoking, n (%)	
Never smokers	46 (76.7)
Former smokers	11 (18.3)
Current smokers	3 (5.0)
Disease duration (years), median [IQR]	12.0 (8.0 ; 16.0)
Duration of dyspnea (years), mean \pm SD	4.6 \pm 2.4
Dyspnea onset before motor symptoms of PD, n (%)	2 (5.0)
Occurrence of dyspnea, n (%)*	
“on drug”	4 (7.7)
“off drug”	26 (50)
Undetermined	22 (42.3)
mMRC, mean \pm SD (/4)	1.3 \pm 0.8
MDP, breathing discomfort (A1) (/10), mean \pm SD	5.0 \pm 2.3
MDP, best Sensory Quality (SQ), n (%)	
Physical breathing effort	15 (25.0)
Air hunger	12 (20.0)
Tightness	11 (18.3)
Mental breathing effort	1 (1.7)
Hyperpnoea	21 (35.0)
MDP, Intensity of Sensory Quality (SQ) (/10), mean \pm SD	
Physical breathing effort	2.9 \pm 2.9
Air hunger	3.3 \pm 3.4
Tightness	2.8 \pm 3.1
Mental breathing effort	1.6 \pm 2.0
Hyperpnoea	3.7 \pm 2.5
MDP, Sensory Dimension (/50), mean \pm SD	19.1 \pm 6.0

MDP, Emotional Response Domain (/50), mean \pm SD	16.9 \pm 9.2
MDP, Intensity of Emotions (A2) (/10), mean \pm SD	
Depressed	2.0 \pm 2.0
Anxious	4.0 \pm 3.3
Angry	0.8 \pm 1.5
Frustrated	2.6 \pm 2.2
Afraid	2.8 \pm 3.7

SD: Standard Deviation; M: male; F: female; IQR: Interquartile Range; mMRC: modified Medical Research Council; MDP: Multidimensional Dyspnea Profile. * only for patients with fluctuations (n=52)

Table 2: Correlation between the MDP scores and clinical features of PD patients.

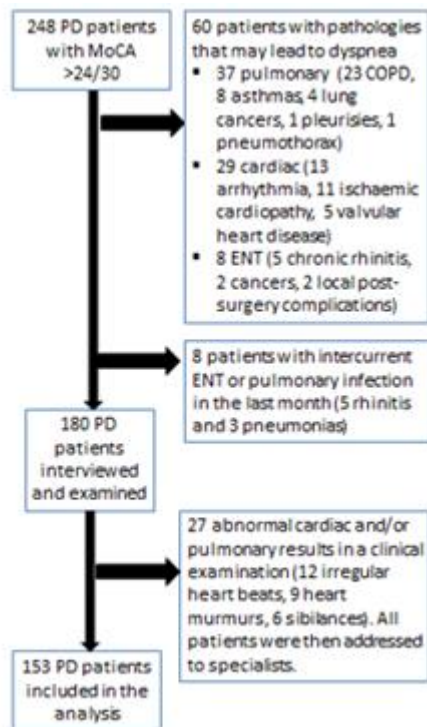
MDP domain and item	mMRC N=60	MDS- UPDRSI N=60	MDS- UPDRSII N=60	MDS- UPDRSIII N=60	MDS- UPDRS IV N=53	MoCA N=60	HAD Anxiety N=60	HAD Depression N=60	PDQ8 N=60
A1. Immediate unpleasantness of dyspnoea	0.46^a	0.47	0.23	0.04	0.22	0.10	0.38	0.21	0.31
SQ1. Breathing requires work or effort	0.11	0.15	0.27	0.21	-0.20	-0.25	-0.27	0.18	0.20
SQ2. Not enough air, smothering or hunger for air	0.20	0.23	-0.03	-0.04	0.20	0.22	0.36	-0.01	0.06
SQ3. Chest and lungs feel tight or constricted	-0.01	0.11	0.14	0.24	0.15	-0.05	0.32	0.14	0.15
SQ4. Breathing requiring mental effort or concentration	0.17	0.01	0.05	-0.03	-0.01	-0.27	-0.25	-0.06	0.00
SQ5. Breathing a lot	-0.17	-0.13	0.11	0.16	0.05	-0.36	-0.14	0.10	0.11
<i>Immediate perception response score</i>	0.35	0.39	0.36	0.29	0.19	-0.19	0.30	0.28	0.37
A2.1. Depressed	0.10	0.37	0.18	0.11	-0.05	-0.18	0.14	0.40	0.43
A2.2. Anxious	0.36	0.29	0.12	0.05	0.20	0.10	0.47	0.08	0.21
A2.3. Frustrated	0.20	0.18	0.26	0.21	-0.07	-0.30	-0.20	0.15	0.15
A2.4. Angry	0.34	0.17	0.26	0.07	0.21	-0.14	0.13	-0.01	0.14
A2.5. Afraid	0.47	0.35	0.04	0.03	0.17	-0.03	0.53	0.11	0.25
<i>Emotional response score</i>	0.48	0.49	0.28	0.15	0.21	-0.03	0.49	0.28	0.42
<i>Hotelling–Williams p value^b</i>	0.16	0.27	0.34	0.15	0.88	0.095	0.030	0.95	0.59

MDP: Multidimensional Dyspnea Profile; mMRC: modified Medical Research Council; MDS-UPDRS: Movement disorders society-Unified Parkinson's disease rating scale; MoCA: Montréal Cognitive Assessment; HAD: Hospital Anxiety and Depression scale; PDQ: Parkinson's disease questionnaire.

^a Spearman correlation coefficients. Statistically significant correlations are shown in bold.

^b The Hotelling–Williams procedure tests whether or not two non-independent correlation coefficients are significantly different. Here, the correlations between the immediate perception response score and the lung function outcomes are compared with the correlations between the emotional response score and the lung function outcomes.

SUPPLEMENTARY DATA 1



Flow chart from Baille et al. Parkinsonism and Related Disorders 2018

SUPPLEMENTARY DATA 2

Multidimensional Dyspnea Profile page 1 of 4

name/code _____ date&time

MULTIDIMENSIONAL DYSPNEA PROFILE

©2011 R.B.Banzett. All Rights Reserved.

Script for first time use:

The purpose of this questionnaire is to help us understand how your breathing feels. There are no right or wrong answers. We want to know what you tell us about your own breathing.

On this page we ask you to tell us how unpleasant your breathing feels. On a later page we will ask you about the intensity or strength of your breathing sensations. The distinction between these two aspects of breathing sensation might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low, and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases.

A1 Scale

Use this scale to rate the **unpleasantness or discomfort** of your breathing sensations, how **bad** your breathing feels [felt].

Please focus on the period when _____

← ← 0 1 2 3 4 5 6 7 8 9 10
PLEASANT NEUTRAL UNBEARABLE

Below are phrases or terms arranged in groups of similar meaning.

Step 1: Check each group that describes how your breathing feels [felt] during _____ (indicate focus period).
Step 2: Please also mark *one* group that most accurately describes how your breathing feels [felt].

If ANY term in the group applies, choose that group.	Step 1		Step 2
	DOES NOT APPLY	DOES APPLY	MOST ACCURATELY DESCRIBES
My breathing requires muscle work <i>or</i> effort			
I am not getting enough air <i>or</i> I am smothering <i>or</i> I feel hunger for air			
My chest and lungs feel tight <i>or</i> constricted			
My breathing requires mental effort <i>or</i> concentration			
I am breathing a lot			

Use these scales to rate the intensity of the breathing sensations you feel [felt] (like the loudness of sound, regardless of whether the sensation is pleasant or unpleasant; for example a sensation could be intense without being unpleasant).

Please focus on the period when _____

If ANY term in the group applies, rate that group.	NONE										AS INTENSE AS I CAN IMAGINE	
	0	1	2	3	4	5	6	7	8	9		10
My breathing requires muscle work <i>or</i> effort												
I am not getting enough air <i>or</i> I am smothering <i>or</i> I feel hunger for air												
My chest and lungs feel tight <i>or</i> constricted												
My breathing requires mental effort <i>or</i> concentration												
I am breathing a lot												
Other*												

*If you need to, you can add additional descriptions of your breathing sensations.

Multidimensional Dyspnea Profile page 4 of 4 name/code _____ date&time _____
A2 Scales

When your breathing doesn't feel normal, you may experience emotions or 'feelings'. Using the scales below, please tell us about how your breathing sensations made you feel – rate zero for any emotion you did not feel.

Please focus on feelings during the period when _____.

	NONE										THE MOST I CAN IMAGINE
Depressed	0	1	2	3	4	5	6	7	8	9	10
Anxious	0	1	2	3	4	5	6	7	8	9	10
Frustrated	0	1	2	3	4	5	6	7	8	9	10
Angry	0	1	2	3	4	5	6	7	8	9	10
Afraid	0	1	2	3	4	5	6	7	8	9	10
Other?	0	1	2	3	4	5	6	7	8	9	10

Etude 3

Atteinte précoce des muscles inspiratoires dans la maladie de Parkinson.

BAILLE G, PEREZ T, DEVOS D, DEKEN V, DEFEBVRE L, MOREAU C.

Early occurrence of inspiratory muscle weakness in Parkinson's disease. PLoS ONE 2018 13(1): e0190400.

1. Objectifs de l'étude

La troisième étape a consisté en une évaluation des EFR au stade précoce de la MP et d'analyser ensuite leur évolution 2 ans plus tard. Les patients étaient issus de la cohorte Prodigy-Park1. L'hypothèse était que, au vu du modèle de Braak [4], la fonction ventilatoire allait être affectée de manière objective dès les premières années de la MP. Concernant l'évolution à 2 ans, à partir des données de la littérature [27], nous avons mis l'hypothèse d'une progression des anomalies en EFR.

2. Méthodes

Nous avons comparé les données en EFR de 41 patients au stade précoce de la MP (âge moyen : $61,7 \pm 7,7$ ans ; durée moyenne d'évolution de la maladie : $1,9 \pm 1,7$ années et de 36 sujets sains appariés sur l'âge. Nous avons réalisé des évaluations neurologiques (MoCA, UPDRS I, II, III et IV) et en EFR (mMRC pour évaluer le retentissement de la dyspnée ; CPT, CVF, VEMS pour les volumes pulmonaires ; SNIP et PImax pour les muscles respiratoires, pour les 2 groupes. Les évaluations EFR n'ont été répétées à 2 ans que dans le groupe de patients parkinsoniens.

3. Résultats

A l'inclusion, le déficit de la musculature inspiratoire était la seule différence significative entre les deux groupes (53,7% pour le groupe de patients parkinsoniens vs 25% dans le groupe contrôle). SNIP et P_{Imax} étaient significativement inférieurs dans le groupe de patients parkinsoniens ($p=0,004$ et $p=0,0035$ respectivement).

Après 2 ans de suivi et l'introduction d'un traitement antiparkinsonien chronique ou la majoration des doses (augmentation de la dose moyenne d'équivalent L-DOPA de $234,3 \pm 324,2$ mg), SNIP et P_{Imax} avaient tendance à être plus élevés ($p=0,056$ et $0,055$ respectivement). Les modifications des volumes pulmonaires n'étaient pas significatives. Enfin, les patients parkinsoniens avec un déficit de la musculature inspiratoire précoce ne présentaient pas un moins bon pronostic moteur (évolution du score UPDRS III $4,4 \pm 8,4$ vs $5,2 \pm 9$ – $p=0,84$).

4. Conclusion

L'atteinte de la force inspiratoire semble précoce chez certains patients atteints de la MP. Les EFR sont stable à 2 ans d'évolution, ce qui pourrait s'expliquer par une durée de suivi insuffisante ou par un discret effet positif de l'instauration du traitement antiparkinsonien. Une prolongation du suivi à long terme paraît donc nécessaire afin de mieux comprendre l'histoire naturelle des troubles ventilatoires dans la MP et leur impact pronostique.

RESEARCH ARTICLE

Early occurrence of inspiratory muscle weakness in Parkinson's disease

Guillaume Baille^{1,2}, Thierry Perez^{2,3}, David Devos^{1,2,4}, Valérie Deken⁵, Luc Defebvre^{1,2}, Caroline Moreau^{1,2*}

1 Department of Neurology and Movement Disorders, Lille University Medical Center, Lille, France, **2** INSERM UMR 1171, University of Lille, Lille, France, **3** Lung Function Department, Lille University Medical Center, Lille, France, **4** Department of Medical Pharmacology, Lille University Medical Center, Lille, France, **5** Department of Biostatistics, Lille University Medical Center, Lille, France

* caroline.moreau@chru-lille.fr



Abstract

Introduction

In Parkinson's disease (PD), respiratory insufficiency (including functional and muscle disorders) can impact dysarthria and swallowing. Most studies of this topic have been performed retrospectively in populations of patients with advanced PD. The objective of the present study was to characterize lung function (under off-drug conditions) in early-stage PD patients at baseline and then again two years later.

Methods

Forty-one early-stage PD patients (mean \pm SD age: 61.7 ± 7.7 ; mean \pm SD disease duration: 1.9 ± 1.7 years) were prospectively enrolled and compared with 36 age-matched healthy controls. Neurological evaluations and pulmonary function testing were performed in the off-drug condition at the inclusion visit and then two years later.

Results

Pulmonary function testing did not reveal any restrictive or obstructive disorders; at baseline, inspiratory muscle weakness was the only abnormality observed in the PD group (in 53.7% of the patients, vs. 25% in controls; $p = 0.0105$). The PD patients had a lower mean maximal inspiratory mouth pressure than controls and a lower sniff nasal inspiratory pressure. Two years after the initiation of chronic treatment with antiparkinsonian medications, the maximal inspiratory mouth pressure and the sniff nasal inspiratory pressure tended to be higher. Lastly, overall motor outcomes were not significantly worse in patients with inspiratory muscle weakness than in patients without inspiratory muscle weakness.

Conclusion

Inspiratory muscle weakness seems to be common in patients with early-stage PD, and was seen to be stable over a two-year period. Additional long-term follow-up studies are required to specify the impact of this new feature of PD.

OPEN ACCESS

Citation: Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C (2018) Early occurrence of inspiratory muscle weakness in Parkinson's disease. PLoS ONE 13(1): e0190400. <https://doi.org/10.1371/journal.pone.0190400>

Editor: Randi Starrfelt, Kobenhavns Universitet, DENMARK

Received: April 6, 2017

Accepted: December 14, 2017

Published: January 12, 2018

Copyright: © 2018 Baille et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was funded by the French Association France Parkinson in 2011. Caroline MOREAU is scientific advisor for Abbvie, Medtronic et Bial. David Devos is scientific advisor for Orkyn, Aguetant, Apopharma. Luc Defebvre is scientific advisor for Abbvie, Zambon, Aguetant. Thierry Perez, Valerie DEKEN and Guillaume Baille have nothing to disclose.

Competing interests: Caroline Moreau is scientific advisor for Abbvie, Medtronic and bill. David Devos is scientific advisor for Orkyn, Aguetant, Apopharma. Luc Defebvre is scientific advisor for Abbvie, Zambon and Aguetant. Other authors have nothing to disclose. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disease [1]. Although patients with PD complain of many non-motor symptoms, the diagnosis of this condition is still based on the observation of motor signs (such as rest tremor, akinesia, and rigidity). When considering non-motor symptoms, pulmonary dysfunction has been described as a dysautonomic sign of PD in several studies; however, the prevalence of this dysfunction has probably been underestimated. The literature data diverge; some researchers have evidenced changes in lung volumes in PD patients (such as an airflow limitation [2,3], a restrictive pattern [4,5,6] or a mixed pattern [7,8]), whereas others have reported ventilatory muscle weakness [9,10]. Furthermore, most studies have been performed in the "on-drug" condition in advanced PD patients (i.e. more than 5 years after disease onset), and we are not aware of any long-term follow-up studies.

According to Braak et al., alpha synuclein deposition and neuron loss start in the caudal part of the brainstem [11]. Given the physiology of respiratory control, structures in the pons and the medulla oblongata might be affected by the initial neurodegeneration in PD [12]. Early alpha synuclein deposition in the nuclei responsible for coordinating ventilation or analyzing the peripheral detection of hypoxemia or hypercapnia might have a harmful impact on respiration. Impaired lung function in PD may be involved in the pathophysiology of axial symptoms such as dysarthria (respiratory muscle weakness, possibly leading to hypophonia [13]) and swallowing disorders (with a shorter period of apnea during the pharyngeal phase of deglutition [14]).

The objective of the present study was to prospectively assess pulmonary function in a cohort of early-stage PD patients at inclusion and then two years later (i.e. after the initiation of chronic treatment with dopaminergic medications). In view of Braak's model, we hypothesized that pulmonary function would be worse in early-stage PD patients than in healthy controls.

Methods

In this prospective pilot study, all the participants belonged to the "Prospective Assessment of Dysarthria and Other Dopaminergic and Non Dopaminergic Axial Signs in PD" cohort (PRO-DYGI-PARK; ClinicalTrials.gov: NCT 02627664) and were included during an inclusion visit between September 2011 and December 2012. All of the patients (i) met the UK Brain Bank criteria [15], (ii) had a Hoehn and Yahr score below 3 [16], and (iii) had been diagnosed and included early in the course of PD (i.e. a disease duration of less than 5 years, as determined by the onset of the first motor symptoms reported by the patient). None of the patients suffered from a concomitant respiratory disease. Likewise, patients with an ear, nose or throat disease (a tumor, an infection or a functional disorder of the vocal cords) or severe cognitive disturbance (as defined by a Mini-Mental State Examination score of less than 24 out of 30 [17]) were excluded. Thirteen of the 41 (32%) patients were had not been treated with parkinsonian medication at inclusion. The remaining 28 (68%) patients had been receiving stable, moderate doses of dopaminergic drugs for at least one month prior to inclusion. With the exception of the neuropsychological assessment, all examinations were performed in the "off-drug" condition. (i.e. at least 12 hours after the last administration of antiparkinsonian medication, typically taken the previous evening).

The study was approved by the local investigational review board (*Comité de Protection des Personnes Nord Ouest IV*, Lille, France: reference: 11/07 2010-A01391-38), and all participants gave their written, informed consent. We compared the patients' baseline pulmonary function testing (PFT) data with those recorded for a historical cohort of 36 gender- and age-matched

(± 5 years) healthy controls and volunteers for a lung examination (mean \pm SD age: 61 ± 5.2). All patients were tested in an outpatient clinic.

Clinical examinations were performed by a neurologist with experience in the diagnosis and management of movement disorders. We scored parts I (non-motor aspects of experiences of daily living), II (motor aspects of experiences of daily living), part III (motor examination) and IV (motor complications) of the Unified Parkinson's Disease Rating Scale (UPDRS [18]). Antiparkinsonian medications were assessed and expressed as the levodopa equivalent daily dose (LEDD) [19].

Pulmonary function testing was performed in Lille University Medical Center's lung function department. Dyspnea was assessed on the Medical Research Council scale [20], which ranges from 0 ("not troubled by breathlessness except with strenuous exercise") to 4 ("too breathless to leave the house or breathless when dressing or undressing"). Spirometry and lung volume measurements (nitrogen washout) were measured with a HypAir Compact+[®] system (Medisoft Group, Sorinnes, Belgium). We measured the total lung capacity (TLC), forced vital capacity (FVC), and the forced expiratory volume in one second (FEV1). Respiratory muscle assessment was also performed with a HypAir Compact+[®] system, with measurement of the maximal inspiratory mouth pressure (MIP) and the sniff nasal inspiratory pressure (SNIP). The PFT procedures complied with European Respiratory Society's guidelines on defining an obstructive, restrictive or mixed pattern of respiratory impairment [21]. The respiratory muscle pressures were interpreted with regard to the predicted values published by Uldry et al. [22]. Inspiratory muscle weakness was defined as concomitant changes in the MIP and SNIP (below the lower limit of normal, i.e. the 5th percentile). The PFT was performed at the inclusion visit (V1) for both groups and then two years later (V2) for the PD group only. The neuropsychological examination included the Montreal Cognitive Assessment [23]. Quantitative variables were expressed as the mean \pm SD (for normally distributed variables) or the median [interquartile range]. Qualitative variables were expressed as the number (percentage). The normality of the data distribution was assessed using histograms and the Shapiro-Wilk test. A bivariate analysis was performed using Student's t test for quantitative variables (or a Mann-Whitney U test for non-normally distributed variables) and a chi-squared test for categorical variables (or Fisher's exact test if the expected cell frequency was <5). An analysis of covariance was used to assess changes over time in clinical parameters for PD patients with or without inspiratory muscle weakness. The change over time in clinical quantitative variables was assessed using Student's paired t test or (for non-normally distributed variables) a Wilcoxon paired test. Correlations between two quantitative variables were evaluated by calculating Pearson's coefficient or (for non-normally distributed variables) Spearman's coefficient. The threshold for statistical significance (two-tailed) was set to $p < 0.05$. All statistical analyses were performed using SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

Results

After a two-year follow-up period, the study population comprised 41 patients (25 men and 16 women; mean \pm SD age: 61.7 ± 7.7 years; mean disease duration: 1.9 ± 1.7 years) and was divided into two subgroups (according to the clinical phenotype). There were 15 participants in the "tremor-predominant" group and 26 in the "akinetic-rigid" group (Table 1).

Comparison of PD patients with controls

The clinical and PFT data are summarized in Table 1. The mean TLC ($p = 0.004$), the mean FEV1 ($p = 0.002$) and the mean FVC ($p = 0.002$) were significantly higher in the PD group than in the control group. Inspiratory muscle weakness was also more prevalent in the patient group than in

the control group ($p = 0.011$). Both the mean MIP and mean SNIP were significantly lower in the patient group than in the control group ($p = 0.035$ and $p = 0.004$, respectively).

Comparison of treated with drug-naïve patients

With the exception of FEV1 ($p = 0.03$), the drug-naïve and treated PD patients did not differ significantly with regard to the PFT results (Table 2); this was true for the SNIP ($p = 0.52$), the MIP ($p = 0.12$), and the proportion of patients with inspiratory muscle weakness ($p = 0.51$).

The LEDD and the PFT results

For treated PD patients at V1 ($n = 28$), no correlation was observed between the LEDD on one hand and FEV1 ($p = 0.55$, $r = 0.12$), FVC ($p = 0.083$, $r = 0.04$), FEV1/FVC ($p = 0.82$, $r = 0.04$), TLC ($p = 0.33$, $r = 0.19$), MIP ($p = 0.11$, $r = -0.32$) or SNIP ($p = 0.46$, $r = -0.15$) on the other.

Table 1. A comparison between PD patients and healthy subjects.

	PD patients n = 41	Controls n = 36	p
Age (years)	61.7 ± 7.7	61 ± 5.2	0.65***
Gender (M/F)	25/16	24/12	0.60*
Phenotype	- 15 tremor-predominant (36.6%) - 26 akinetic-rigid (63.4%)	NA	NA
Disease duration (years)	1.9 ± 1.7	NA	NA
LEDD (mg)	304.2 ± 310	NA	NA
Treatment	-13 drug-naïve (32%) -9 taking levodopa alone (22%) -19 taking levodopa and dopaminergic agonists (46%)	NA	NA
MoCA (out of 30)	27 ± 2.2	NA	NA
UPDRS part I (out of 16)	5.1 ± 3.7	NA	NA
UPDRS part II (out of 52)	5.9 ± 4.2	NA	NA
UPDRS part III (out of 108)	19 ± 8.3	NA	NA
UPDRS part IV (out of 23)	0.8 ± 1.1	NA	NA
Symptomatic patients (MRC ≥ 1)	17 (41%)	NA	NA
MRC dyspnea scale (out of 4)	0.6 ± 0.8	NA	NA
Tobacco use	5 (12.2%)	8 (22.2%)	0.24*
Active smoking	1	2	NA
Obstructive pattern	6 (14.6%)	4 (11.1%)	0.74**
FEV1/FVC (%)	75.1 ± 7.2	75.5 ± 5.9	0.80*
Restrictive pattern	1	2	NA
FEV1 (% predicted)	106.3 ± 13.3	97.7 ± 17.5	0.002***
FVC (% predicted)	111.9 ± 14.9	101.6 ± 12.3	0.002***
TLC (% predicted)	111.8 ± 17.4	101 ± 14.3	0.004***
Inspiratory muscle weakness	22 (53.7%)	9 (25%)	0.011**
MIP (% predicted)	75.2 ± 34.2	90.6 ± 26.1	0.035***
SNIP (% predicted)	71.8 ± 30.9	89.7 ± 18.6	0.004***

M: male, F: female, LEDD: levodopa equivalent daily dose, MoCA: Montréal Cognitive Assessment, UPDRS: Unified Parkinson's Disease Rating Scale, MRC: Medical Research Council; FEV1: forced expiratory volume in one second, FVC: forced vital capacity, TLC: total lung capacity, MIP: maximal inspiratory mouth pressure, SNIP: sniff nasal inspiratory pressure. NA: not applicable

* in a chi-squared test

** in Fisher's exact test

*** in Student's test

<https://doi.org/10.1371/journal.pone.0190400.t001>

Table 2. A comparison between drug-naïve and treated PD patients.

	Drug-naïve PD patients n = 13	Treated PD patients n = 28	p
Age (years)	61.1 ± 7.6	62 ± 7.8	0.74
Gender (M/F)	8/5	17/11	0.96
MRC dyspnea scale (out of 4)	0.23 ± 0.44	0.75 ± 0.84	0.06
FEV1/FVC (%)	75.7 ± 5.5	74.8 ± 7.9	0.8
FEV1 (% predicted)	112.6 ± 13.9	103.4 ± 12.2	0.03*
FVC (% predicted)	116.4 ± 12.7	109.7 ± 15.6	0.13
TLC (% predicted)	112.6 ± 21.9	111.4 ± 15.3	0.66
Inspiratory muscle weakness	6 (46.2%)	16 (57.1%)	0.51
MIP (% predicted)	89.3 ± 39	69.3 ± 30.8	0.12
SNIP (% predicted)	74.2 ± 31.6	70.8 ± 31.3	0.52

M: male, F: female, MRC: Medical Research Council; FEV1: forced expiratory volume in one second, FVC: forced vital capacity, TLC: total lung capacity, MIP: maximal inspiratory mouth pressure, SNIP: sniff nasal inspiratory pressure.

* in a U Mann Withney test

<https://doi.org/10.1371/journal.pone.0190400.t002>

The motor phenotype and the PFT results

Akinetic-dominant PD patients had a significantly higher FVC ($p = 0.05$) and a significantly lower FEV1/FVC ($p = 0.005$), relative to tremor-dominant PD patients (Table 3). There were no other subgroup differences in the PFT results.

Changes over time at V2

The changes over time in clinical features and PFT data between V1 and V2 are summarized in Table 4. With the exception of the UPDRS part I score ($p = 0.096$), the MIP ($p = 0.055$) and the SNIP ($p = 0.056$), all clinical parameters had significantly worsened after two years of follow-up. The LEDD was significantly higher ($p < 0.0001$), and the FEV1/FVC was significantly lower ($p = 0.002$). The correlation between the LEDD and changes in FEV1/FVC was not statistically significant ($p = 0.55$). Patients with a higher LEDD tended to have higher MIP ($p = 0.02$, $r = 0.37$) and SNIP ($p = 0.05$, $r = 0.53$) values—greater respiratory muscle strength, in other words.

Table 3. A comparison between tremor and akinetic dominant PD patients.

	Tremor-dominant PD patients n = 15	Akinetic-dominant PD patients n = 26	p
Age (years)	60.4 ± 9.2	62.5 ± 6.7	0.4
Gender (M/F)	8/7	17/9	0.45
MRC dyspnea scale (out of 4)	0.73 ± 0.88	0.5 ± 0.71	0.44
FEV1/FVC (%)	79.3 ± 7.6	72.7 ± 5.8	0.005*
FEV1 (% predicted)	103.1 ± 13	108.41 ± 13.4	0.26
FVC (% predicted)	109.5 ± 13.7	115.3 ± 14.6	0.05*
TLC (% predicted)	112.6 ± 21.9	111.4 ± 15.3	0.7
Inspiratory muscle weakness	9 (60%)	13 (50%)	0.54
MIP (% predicted)	74.4 ± 41.3	75.6 ± 31.1	0.61
SNIP (% predicted)	75.2 ± 28.6	70 ± 32.4	0.46

M: male, F: female, MRC: Medical Research Council; FEV1: forced expiratory volume in one second, FVC: forced vital capacity, TLC: total lung capacity, MIP: maximal inspiratory mouth pressure, SNIP: sniff nasal inspiratory pressure.

* in a U Mann Withney test

<https://doi.org/10.1371/journal.pone.0190400.t003>

Table 4. Changes over time in clinical and PFT parameters between V1 and V2.

	V1	V2	delta	p
UPDRS I (out of 16)	5.1±3.7	6.3 ± 3.8	1.2 ± 4.4	0.01*
UPDRS II (out of 52)	5.9±4.2	7.2 ± 4.9	1.3 ± 3.7	0.028*
UPDRS III (out of 108)	19.0±8.3	23.5 ± 10.0	4.6 ± 8.6	0.002*
UPDRS IV (out of 23)	0.8±1.1	2.0 ± 2.0	1.2 ± 2.1	0.001*
LEDD (mg)	304.2±310.0	538.5 ± 360.9	234.3 ± 324.2	<0.0001*
MoCA	27.0±2.2	27.1 ± 2.2	0.1 ± 1.9	0.80*
FEV1/FVC (%)	75.1 ± 7.2	72.2 ± 5.9	-2.7 ± 5.0	0.002*
FVC (% predicted)	111.9 ± 14.9	114.7 ± 14.2	1.9 ± 7.5	0.13*
FEV1 (% predicted)	106.3 ± 13.3	105.4 ± 15.0	-0.9 ± 6.2	0.36*
TLC (% predicted)	111.8 ± 17.4	109.5 ± 16.8	-2.6 ± 17.2	0.36*
MIP (% predicted)	75.2 ± 34.2	77.5 ± 22.9	4.0 ± 25.1	0.055**a
Median [IQR]	68 [53–93]	76 [66–97]	5 [–2–14]	
SNIP (% predicted)	71.8 ± 30.9	76.5 ± 17.6	5.2 ± 28.2	0.056a**
Median [IQR]	71 [50.5–88]	81 [71–90]	8.5 [–2.5–17]	

equivalent daily dose, MoCA: Montréal Cognitive Assessment, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, TLC: total lung capacity, MIP: maximal inspiratory mouth pressure, SNIP: sniff nasal inspiratory pressure.

a: non-significant difference.

* in Student's paired test

** in a Wilcoxon paired test

<https://doi.org/10.1371/journal.pone.0190400.t004>

Effect of the inspiratory muscle phenotype on disease outcomes

There was no significant difference between the two subgroups of PD patients (i.e. those with vs. without inspiratory muscle weakness) in terms of the clinical outcome ($p = 0.84$ for the UPDRS part III score) or the change in LEDD ($p = 0.83$) (Table 5).

The impact of motor fluctuations on PFT

At V2, the UPDRS IV score was seen to be correlated with the MIP ($p = 0.005$, $r = -0.43$) and the SNIP ($p = 0.05$, $r = -0.3$) but not with FEV1 ($p = 0.55$, $r = 0.12$) or FVC ($p = 0.68$, $r = 0.06$).

Discussion

The present study's main findings were as follows: (i) significant inspiratory muscle weakness (as measured by the maximal inspiratory mouth pressure and sniff nasal inspiratory pressure)

Table 5. Comparison (in an analysis of covariance) of clinical changes between V1 and V2 in PD patients with and without inspiratory muscle weakness.

	PD patients with inspiratory muscle weakness n = 22	PD patients with normal inspiratory muscle strength n = 19	p
Change in the UPDRS part I score	0.3± 4.8	2.2± 3.8	0.94
Change in the UPDRS part II score	1.1 ± 4	1.5± 3.4	0.96
Change in the UPDRS part III score	4.4± 8.4	5.2 ± 9	0.84
Change in the UPDRS part IV score	1.3± 2.5	1.1 ± 1.7	0.35
Change in the LEDD	187.2± 371.5	288.8± 258.3	0.83

UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: levodopa equivalent daily dose.

<https://doi.org/10.1371/journal.pone.0190400.t005>

can be observed in the early stages of PD, (ii) antiparkinsonian medication does not seem to affect the PFT results, and (iii) the maximal inspiratory mouth pressure and sniff nasal inspiratory pressure tended to be higher at V2 (i.e. after the initiation of chronic treatment with antiparkinsonian medication).

To the best of our knowledge, the present study is the first to have prospectively assessed inspiratory muscle weakness in early-stage PD patients. Interestingly, antiparkinsonian medications may be responsible (at least in part) for the maintenance of the MIP and SNIP values after two years. Although dopamine is not known to increase muscle strength, it might sustain the PFT results by improving muscle coordination.

Inspiratory muscle strength was impaired in PD patients (relative to healthy controls), as characterized by lower % predicted MIP and SNIP values (according to Uldry et al., 1995). Other studies have yielded similar results for the MIP, albeit in later stages of the disease (e.g. a mean disease duration of over 5 years and a Hoehn and Yahr score sometimes higher than 2 [24,25,9,10]). At V1, the statistically significant patient vs. control differences in lung volumes were not clinically significant; this contrasts with the many literature reports of an airway obstruction and, in some cases, a restrictive syndrome [2,3,7,8,26,27,28]. However, these studies did not include patients with promptly diagnosed, early-stage PD; in contrast, the mean disease duration in our study was 1.9 ± 1.7 years. Furthermore, the drug-naïve patients and the treated patients (at V1) did not differ with regard to the PFT data in general and inspiratory muscle weakness in particular, and the LEDD and PFT results were not correlated. Hence, one can suppose that ventilatory dysfunction is part of the pathophysiological process, rather than an effect of treatment with dopaminergic medications. However, these results need to be confirmed in a larger population.

In agreement with other reports [29,30], our patients' mean UPDRS III scores worsened by 2.1% over two years. The LEDD also increased, and FEV1/FVC decreased significantly. We cannot rule out a role of age in these changes, although there is a lack of detailed data on this topic in the literature. When considering inspiratory muscle strength, the changes over time in MIP and SNIP were non-significant. Factors other than age may explain these results. We did not observe any relationships between changes in pulmonary function and a clinical decline. Increases in the LEDD were not associated with changes in FEV1/FVC. Our present results cannot be directly compared with those of other studies in which lung volume dopasensitivity was assessed following an acute administration of levodopa (with conflicting results) [2,5,6]. However, we observed that changes in the MIP and the SNIP were correlated with an increase in the LEDD. De Bruin et al. observed that the MIP increased after an acute apomorphine injection [24]. Acute levodopa was found to produce an improvement in inspiratory muscle function in anesthetized dogs [31], and dopamine improved diaphragm function during acute respiratory failure in patients with chronic obstructive pulmonary disease [32]. In our cohort, motor fluctuations (mainly induced by levodopa treatment) had a negative impact on MIP and SNIP. Therefore, our results raise the question of whether dopaminergic drugs have a differential effect on ventilatory function, with a potentially positive effect of chronic levodopa administration and a potentially negative impact of acute levodopa intake [33].

The impact of impaired pulmonary function on the cognitive course of PD has never been assessed. In a cohort of 740 PD patients followed up for 6.5 years, the presence of lung function disorders was not a prognostic factor for the occurrence of cognitive disorders [34]. However, the researchers did not objectively measure MIP, SNIP and lung volumes in PFT. We did not observe any changes in cognitive function in our study population—probably because the follow-up period of two years was too short and our cognitive assessment was not detailed enough.

Our study had some limitations. Firstly, PFT was not performed for the control group at V2. However, the results were unlikely to have declined by more than by the predicted values in healthy subjects with normal baseline values. Only Enright et al. highlighted a slight decrease in MIP (of between 0.8 and 2.7 cm/H₂O per year) in a cohort of 4443 subjects over the age of 65 [35]. Secondly, the level of effort required by the PFT procedure (which requires voluntary maneuvers) may have had an effect on the quality of the data. Again, the value in the control group was clinically normal. A non-volitional technique (such as transcranial magnetic stimulation) could be used to assess diaphragm strength and respiratory muscle recruitment more specifically in PD. Thirdly, we did not assess the dopasensitivity of the PFT results. Fourthly, very few PD patients had undergone a polysomnographic assessment, although the relationship between PD and sleep disorders is well known. Indeed, respiratory sleep disorders can be the first clinical expression of diaphragm dysfunction. Moreover, obstructive sleep apnea can lead to intermittent hypoxemia and cognitive disorders. Lastly, our follow-up period (two years) may have been too short to evidence an effect of inspiratory muscle weakness on the course of PD.

Conclusion

Inspiratory muscle strength appears to be impaired in very early-stage PD patients. After two years, it was not clear whether muscle weakness had progressed. Levodopa may have a positive effect on inspiratory muscle strength. Pathophysiological studies are needed to assess the impact of potential respiratory involvement on PD in more detail. The chronic hypoxemia caused by pulmonary dysfunction may notably have a role in the neurodegenerative process, as has already been suggested for amyotrophic lateral sclerosis [36] and Alzheimer's disease [37]. However, extended follow-up of our cohort will be required to assess the clinical prognosis of patients with early-onset inspiratory muscle weakness.

Supporting information

S1 File. Supporting information: Raw values of the patients (demographical and pulmonary functional testing).
(XLS)

Author Contributions

Conceptualization: David Devos, Caroline Moreau.

Data curation: Guillaume Baille.

Formal analysis: Guillaume Baille.

Funding acquisition: Caroline Moreau.

Methodology: Thierry Perez, David Devos, Valérie Deken, Luc Defebvre, Caroline Moreau.

Project administration: Caroline Moreau.

Software: Guillaume Baille, Valérie Deken.

Supervision: Thierry Perez, Luc Defebvre, Caroline Moreau.

Validation: David Devos, Valérie Deken, Luc Defebvre, Caroline Moreau.

Visualization: Thierry Perez, Caroline Moreau.

Writing – original draft: Guillaume Baille.

Writing – review & editing: Thierry Perez, David Devos, Valérie Deken, Luc Defebvre, Caroline Moreau.

References

1. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord.* 2014; 29(13):1583–90. <https://doi.org/10.1002/mds.25945> PMID: 24976103
2. Herer B, Arnulf I, Housset B. Effects of levodopa on pulmonary function in Parkinson's disease. *Chest.* 2001; 119(2):387–93. PMID: 11171713
3. Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med.* 1984; 311(7):438–42. <https://doi.org/10.1056/NEJM198408163110704> PMID: 6749190
4. Cardoso SRX, Pereira JS. Analysis of breathing function in Parkinson's disease. *Arq Neuropsiquiatr.* 2002; 60(1):91–5. PMID: 11965415
5. De Pandis MF, Starace A, Stefanelli F, Marruzzo P, Meoli I, De Simone G, et al. Modification of respiratory function parameters in patients with severe Parkinson's disease. *Neurol Sci.* 2002; 23(2):69–70.
6. Pal PK, Sathyaprabha TN, Tuhina P, Thennarasu K. Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord.* 2007; 22(3):420–4. <https://doi.org/10.1002/mds.21330> PMID: 17230476
7. Izquierdo-Alonso JL, Jiménez-Jiménez FJ, Cabrera-Valdivia F, Mansilla-Lesmes M. Airway dysfunction in patients with Parkinson's disease. *Lung.* 1994; 172(1):47–55. PMID: 8295432
8. Sabaté M, González I, Ruperez F, Rodríguez M. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci.* 1996; 138(1–2):114–9. PMID: 8791248
9. Sathyaprabha TN, Kapavarapu PK, Pall PK, Thennarasu K, Raju TR. Pulmonary functions in Parkinson's disease. *Indian J Chest Dis Allied Sci.* 2005; 47(4):251–7. PMID: 16255396
10. Guedes LU, Rodrigues JM, Fernandes AA, Cardoso FE, Parreira VF. Respiratory changes in Parkinson's disease may be unrelated to dopaminergic dysfunction. *Arq Neuropsiquiatr.* 2012; 70(11):847–51. PMID: 23175196
11. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003; 24(2):197–211. PMID: 12498954
12. Kazemi H, Johnson DC. Respiration. In: *Encyclopedia of the Human Brain*, VS Ramachandran. (Ed), Academic Press, San Diego, CA 2002. Vol 4, p.209–216.
13. Hammer MJ. Aerodynamic assessment of phonatory onset in Parkinson's disease: evidence of decreased scaling of laryngeal and respiratory control. *J Parkinsons Dis.* 2013; 3(2):173–9. <https://doi.org/10.3233/JPD-130180> PMID: 23750188
14. Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. *Dysphagia.* 2011; 26(3):218–24. <https://doi.org/10.1007/s00455-010-9289-x> PMID: 20623304
15. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatr.* 1988; 51(6):745–52.
16. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967; 17(5):427–42. PMID: 6067254
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12(3):189–98. PMID: 1202204
18. Martínez-Martín P, Gil-Nagel A, Gracia LM, Gómez JB, Martínez-Sarriés J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Mov Disord.* 1994; 9(1):76–83. <https://doi.org/10.1002/mds.870090112> PMID: 8139608
19. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord.* 2010; 25(15):2649–53. <https://doi.org/10.1002/mds.23429> PMID: 21069833
20. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999; 54(7):581–6. PMID: 10377201
21. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Standardisation of the measurement of lung volumes. *Eur Respir J.* 2005; 26(3):511–22. <https://doi.org/10.1183/09031936.05.00035005> PMID: 16135736

22. Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. *Thorax*. 1995; 50(4):371–5. PMID: [7785009](https://pubmed.ncbi.nlm.nih.gov/7785009/)
23. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005; 53(4):695–9. <https://doi.org/10.1111/j.1532-5415.2005.53221.x> PMID: [15817019](https://pubmed.ncbi.nlm.nih.gov/15817019/)
24. De Bruin PF, de Bruin VM, Lees AJ, Pride NB. Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis*. 1993; 148(1):1576–80.
25. Haas BM, Trew M, Castle PC. Effects of respiratory muscle weakness on daily living function, quality of life, activity levels, and exercise capacity in mild to moderate Parkinson's disease. *Am J Phys Med Rehabil*. 2004; 83(8):601–7. PMID: [15277961](https://pubmed.ncbi.nlm.nih.gov/15277961/)
26. Obenour WH, Stevens PM, Cohen AA, et al. The causes of abnormal pulmonary function in Parkinson's disease. *Am Rev Respir Dis*. 1972; 105(3):382–7. <https://doi.org/10.1164/arrd.1972.105.3.382> PMID: [5011667](https://pubmed.ncbi.nlm.nih.gov/5011667/)
27. Bateman DN, Cooper RG, Gibson GJ, McCutchen JJ. Levodopa dosage and ventilatory function in Parkinson's disease. *Br Med J (Clin Res Ed)*. 1981; 283(6285):190–1.
28. Bogaard JM, Hovestadt A, Meerwaldt J, vd Meché FG, Stigt J. Maximal expiratory and inspiratory flow-volume curves in Parkinson's disease. *Am Rev Respir Dis*. 1989; 139(3):610–4. <https://doi.org/10.1164/ajrccm/139.3.610> PMID: [2923359](https://pubmed.ncbi.nlm.nih.gov/2923359/)
29. Reinoso G, Allen JC, Au W-L, Seah SH, Tay KY, Tan LC. Clinical evolution of Parkinson's disease and prognostic factors affecting motor progression: 9-year follow-up study. *Eur J Neurol*. 2015; 22(3):457–63. <https://doi.org/10.1111/ene.12476> PMID: [24888502](https://pubmed.ncbi.nlm.nih.gov/24888502/)
30. Harrison MB, Wylie SA, Frysinger RC, Patrie JT, Huss DS, Currie LJ, et al. UPDRS activity of daily living score as a marker of Parkinson's disease progression. *Mov Disord* 2009; 24(2): 224–30. <https://doi.org/10.1002/mds.22335> PMID: [18951537](https://pubmed.ncbi.nlm.nih.gov/18951537/)
31. Fujii Y. Olprinone/dopamine combination for improving diaphragmatic fatigue in pentobarbital-anesthetized dogs. *Curr Ther Res Clin Exp*. 2006; 67(3):204–13. <https://doi.org/10.1016/j.curtheres.2006.06.003> PMID: [24678096](https://pubmed.ncbi.nlm.nih.gov/24678096/)
32. Aubier M, Murciano D, Menu Y, Boczkowski J, Mal H, Pariente R. Dopamine effects on diaphragmatic strength during acute respiratory failure in chronic obstructive pulmonary disease. *Ann Intern Med*. 1989; 110(1):17–23. PMID: [2908830](https://pubmed.ncbi.nlm.nih.gov/2908830/)
33. Rice JE, Antic R, Thompson PD. Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord*. 2002; 17(3):524–7. <https://doi.org/10.1002/mds.10072> PMID: [12112201](https://pubmed.ncbi.nlm.nih.gov/12112201/)
34. Uc EY, McDermott MP, Marder KS, Anderson SW, Litvan I, Como PG, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. *Neurology*. 2009; 73(18):1469–77. <https://doi.org/10.1212/WNL.0b013e3181bf992f> PMID: [19884574](https://pubmed.ncbi.nlm.nih.gov/19884574/)
35. Enright PL, Kronmal RA, Manolio MB, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *Am J Respir Crit Care Med* 1994; 149(2 Pt 1):430–438.
36. Kim S-M, Kim H, Lee J-S, Park KS, Jeon GS, Shon J, et al. Intermittent hypoxia can aggravate motor neuronal loss and cognitive dysfunction in ALS mice. *PLoS ONE*. 2013; 8(11):e81808. <https://doi.org/10.1371/journal.pone.0081808> PMID: [24303073](https://pubmed.ncbi.nlm.nih.gov/24303073/)
37. Shiota S, Takekawa H, Matsumoto S-E, Takeda K, Nurwidya F, Yoshioka Y, et al. Chronic intermittent hypoxia/reoxygenation facilitate amyloid- β generation in mice. *J Alzheimers Dis*. 2013; 37(2):325–3 <https://doi.org/10.3233/JAD-130419> PMID: [23948880](https://pubmed.ncbi.nlm.nih.gov/23948880/)

Etude 4

Anomalies ventilatoires dans la maladie de Parkinson : suivi à 5 ans.

BAILLE G, CHENIVESSE C, PEREZ T, DEKEN V, DEVOS D, DEFEBVRE L, MOREAU C.

Impaired lung function in Parkinson's disease: a 5-year follow-up study.

Version soumise à Parkinsonism & Related Disorders le 19/07/2019.

1. Objectifs de l'étude

La quatrième étape a consisté en une évaluation des EFR 5 ans après l'inclusion dans la cohorte Prodigy Park. Les caractéristiques cliniques, l'évolution au cours du temps et la physiopathologie des troubles ventilatoires dans la MP sont encore méconnus. Les objectifs cette étude étaient : i) d'évaluer l'évolution des volumes pulmonaires et de la fonction musculaire respiratoire avec un recul de 5 ans, ii) de déterminer le facteur pronostique (moteur et non-moteur) de cette dysfonction ventilatoire dans le cours évolutif de la maladie.

2. Méthodes

Vingt-sept patients au stade précoce de la MP (âge moyen à l'inclusion = $67,3 \pm 7,6$ ans ; durée moyenne d'évolution = $1,9 \pm 1,6$ ans). L'examen neurologique (UPDRS I, II, III et IV), l'évaluation neuropsychologique (MoCA, LARS, HDRS) et les explorations fonctionnelles respiratoires ont été réalisés à l'inclusion et 5 ans plus tard. La mesure de la pression buccale par stimulation magnétique transcrânienne a été mesurée chez 21 sujets lors de la visite à 5 ans.

3. Résultats

Après 5 ans, la capacité vitale ($\Delta = -5,4\%$ théorique ; $p=0,001$), la capacité fonctionnelle respiratoire ($\Delta = -17,6\%$ théorique ; $p= 0,002$), le volume expiratoire maximum seconde ($\Delta = -3,7\%$ théorique ; $p=0,006$) et la capacité pulmonaire totale ($\Delta = -12\%$ théorique ; $p=0,0008$) diminuaient significativement. La pression inspiratoire maximale, la pression expiratoire maximale, le SNIP et le débit expiratoire à la toux sont restés stables. La décroissance de la capacité vitale n'était corrélée ni avec l'évolution de la fonction musculaire respiratoire, ni avec la pression buccale. Les données EFR à l'inclusion n'étaient pas associées avec un moins bon pronostic moteur (UPDRS III) ou non-moteur (UPDRS I, MoCA) à 5 ans.

4. Conclusion

Dans notre cohorte, les volumes pulmonaires diminuaient façon significative après 5 ans de suivi, au contraire de la fonction musculaire respiratoire qui restait stable. La rigidité de la paroi thoracique pourrait expliquer ces résultats. Par ailleurs, la fonction diaphragmatique semble atteinte chez une partie des patient parkinsoniens.

Impaired lung function in Parkinson's disease: a 5-year follow-up study.

Guillaume Baille MD ^{1,2}, Cecile Chenivesse MD, PhD³, Thierry Perez MD^{3,4}, Valérie Deken⁵, David Devos MD, PhD ², Luc Defebvre MD, PhD ^{1,2}, Caroline Moreau MD, PhD ^{1,2}

1. CHU Lille, Department of Neurology and Movement Disorders, Lille University INSERM 1171, Lille, France
2. CHU Lille, Department of Medical Pharmacology, Lille University INSERM 1171, Lille, France
3. CHU Lille, Department of Allergy and Respiratory Medicine, Competence Center for rare lung diseases, Univ. Lille, CNRS, INSERM, Institut Pasteur de Lille, U1019 - UMR 8204 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille France
4. CHU Lille, Lung Function Department, Univ Lille, INSERM 1019, CNRS UMR 8204, Institut Pasteur de Lille, Center for Infection and Immunity of Lille, F-59000, Lille, France
5. Department of Biostatistics, Lille University, CHU Lille, EA2694, France

Corresponding author: Guillaume BAILLE, MD

Department of Neurology and Movement Disorders, Lille University Medical Center, Lille, France

Guillaume.baille@chru-lille.fr

Keywords: Parkinson's disease, pathophysiology, ventilatory function, dyspnea

Word Count: 2773/3000, Abstract: 248/250, Tables/Illustrations: 3/4, References: 30/30

Version en cours de relecture pour la revue Parkinsonism and Related Disorders.

ABSTRACT (248/250)

Introduction:

The clinical features, time course, and pathophysiology of ventilatory impairments in Parkinson's disease (PD) have not been characterized. The objectives of the present study 5-year follow-up study were to (i) measure changes over time in lung volumes and respiratory muscle strength in a cohort of patients with PD, and (ii) determine predictive factors of impaired lung function.

Method:

Twenty-seven patients with early-stage PD (mean \pm standard deviation age at inclusion: 67.3 ± 7.6 ; disease duration: 1.9 ± 1.6 years) were included. Neurologic assessments and pulmonary function tests (PFTs) were performed at inclusion and then 5 years later (V5). Twitch mouth pressure during magnetic stimulation of the cervical phrenic nerve was assessed in 21 patients at V5.

Results:

At V5, we observed decreases in forced vital capacity (median change: -5.43% predicted; $p=0.0091$), forced expiratory volume in 1 second (-3.74.2% predicted; $p=0.006010$) and total lung capacity (-129.4% predicted; $p=0.0008001$). Maximal inspiratory pressure, maximal expiratory pressure, sniff nasal inspiratory pressure, and cough peak flow did not change significantly. The decline in forced vital capacity decline was not correlated with the change in respiratory muscle strength or with twitch mouth pressure. The PFT results at V0 were not correlated with a worse motor outcome (UPDRS part III score) or a worse non-motor outcome (UPDRS part I, MoCA) at V5.

Conclusion:

After 5 years of PD progression, lung volumes (but not respiratory muscle strength) decreased in our cohort. This decline in lung volumes in PD might be due to a progressive decrease in chest wall compliance.

INTRODUCTION

At present, the diagnosis of Parkinson's disease (PD) is mainly based on the presence of motor symptoms [1]. However, many patients also report non-motor symptoms, the significance of which is subject to debate [2]. Some of these non-motor symptoms are said to be "axial" (e.g. gait, dysarthria, dysphagia, and postural instability), and are associated with a worse motor outcome and a higher mortality rate [3]. Although the precise mechanisms underlying dysphagia and dysarthria have not been characterized, lung volumes and respiratory muscle strength may have a key role in the pathophysiology of these symptoms [4]. Moreover, major respiratory comorbidities are frequent in patients with late-stage PD [5,6]. As in neuromuscular diseases [7], ventilatory dysfunction could potentially be classified as an axial symptom; therefore, its natural history and its prognostic value need to be determined.

A prospective study recently showed that inspiratory muscle weakness was common in a cohort of early-stage PD patients but did not change markedly over 2 years of follow-up [8]. The main objective of the present study was to prospectively assess lung function in 27 early-stage PD patients (from the same cohort) at inclusion and then 5 years later. We also determined whether the progression of motor symptoms in PD was associated with changes in pulmonary function, and whether the early occurrence of ventilatory disorder had prognostic value. With reference to Braak's model (in which neurodegeneration spreads to the pons, medulla oblongata and cerebral cortex [9]), we hypothesized that lung volumes and respiratory muscle strength would have significantly worsened after 5 years.

METHODS

In this prospective pilot study, all the participants came from the "Prospective Assessment of Dysarthria and Other Dopaminergic and Non Dopaminergic Axial Signs in PD" (PRODYGI-PARK)

cohort (ClinicalTrials.gov: NCT02627664). The main inclusion criteria were (i) a diagnosis of PD according to the Gibb and Lee criteria [10], (ii) a Hoehn and Yahr score below 3, and (iii) a disease duration of less than 5 years. The main exclusion criteria were (i) the presence of a cause of parkinsonism other than PD, (ii) modification of the dopaminergic drug regimen in the previous month, (iii) known cardiac or pulmonary disease, (iv) ear, nose or throat disease (tumors, infections, or functional disorders of the vocal cords), and (v) severe cognitive impairment (defined as a Mini-Mental State Examination score below 24 out of 30). The study was approved by the local investigational review board (*Comité de Protection des Personnes Nord Ouest IV*, Lille, France: reference 11/07 2010-A01391-38), and all participants gave their written, informed consent. With the exception of the neuropsychological assessment, all examinations were performed under “off-drug” conditions (i.e. at least 12 hours after the last administration of antiparkinsonian medication - typically overnight).

The Unified Parkinson's Disease Rating Scale (UPDRS) parts I (non-motor aspects of experiences of daily living), II (motor aspects of experiences of daily living), III (motor examination) and IV (motor complications) were scored. Antiparkinsonian medications were assessed, and expressed as the levodopa equivalent daily dose (LEDD).

Dyspnea was measured on the modified Medical Research Council (mMRC) scale [11], which ranges from 0 (“not troubled by breathlessness except with strenuous exercise”) to 4 (“too breathless to leave the house or breathless when dressing or undressing”). Spirometry, lung volumes (nitrogen washout), and respiratory muscle pressures were measured with a HypAir Compact+® system (Medisoft, Sorinnes, Belgium). We measured the total lung capacity (TLC), forced vital capacity (FVC), vital capacity (VC), functional residual capacity (FRC) and the forced expiratory volume in one second (FEV1). Respiratory muscle strength was assessed by measuring the maximal inspiratory pressure (P_Imax) at FRC, the sniff nasal inspiratory pressure (SNIP), the maximal expiratory pressure (P_Emax) at TLC, and the cough peak flow (CPF). The pulmonary function test (PFT) procedures complied with the European Respiratory Society (ERS)'s guidelines on defining obstructive, restrictive or mixed

patterns of respiratory impairment [12]. The lung volumes and FEV1 were expressed as a percentage of the predicted value (% pred), according to the ERS equations. Respiratory muscle strength was interpreted with regard to the predicted values published by Uldry et al. [13]. Inspiratory muscle weakness was defined as both P_{lmax} and SNIP values below the lower limit of normal (the 5th percentile). The PFTs were performed at inclusion (V0) and 5 years later (V5). At V5, non-volitional evaluation of diaphragm strength was performed by measuring mouth twitch pressure during magnetic stimulation of the cervical phrenic nerve (P_{mo,tw}[13]). A P_{mo,tw} value below 11 cm H₂O was indicative of diaphragmatic weakness [14].

The neuropsychological examination included the Montreal Cognitive Assessment (MoCA), the Lille Apathy Rating Scale (LARS [15]) and the Hamilton Depression Rating Scale (HDRS).

Quantitative variables were expressed as the mean \pm SD (range) and/or the median [interquartile range]. Qualitative variables were expressed as the number (percentage). The normality of distribution was assessed using histograms and the Shapiro-Wilk test. The 5-year changes in clinical and PFT parameters (all of which were quantitative variables) were assessed using Wilcoxon's signed-rank test. For PFT parameters, changes between V0 and V5 were calculated as a % pred or as an absolute value, depending on the guidelines [12]. We arbitrarily considered that a decrease in FVC of 10% or more between V0 and V5 corresponded to a significant change. McNemar's test was used to compare shortness of breath at V0 vs. V5. We used a nonparametric analysis of covariance (ANCOVA) on rank-transformed values [16] to compare the 5-year changes in clinical and PFT parameters for PD patients with vs. without inspiratory muscle weakness and for patients with vs. without a clinically significant decrease in FVC, after adjustment for values measured at inclusion. Pairwise correlations between 5-year changes in clinical and PFT parameters were assessed by calculating Spearman's rank correlation coefficient. Lastly, the correlations between values of VC and FVC at inclusion and the disease outcomes (i.e. the UPDRS scores) at 5 years were evaluated by calculating Spearman's partial correlation coefficients and adjusting for the UPDRS scores at inclusion. The threshold for statistical

significance in two-tailed tests was set to $p < 0.05$. All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

Twenty-seven PD patients (21 men and 6 women; mean \pm standard deviation (SD) age at V0: 67.3 ± 7.6 ; mean disease duration at V0: 1.9 ± 1.6 years) were included and assessed at V0 and V5. Four patients (14.8%) met the criteria for airway obstruction. None of the patients had restrictive lung disease. Fourteen patients (51.9%) displayed significant inspiratory muscle weakness (assessed via the SNIP and PImax) at inclusion. The patients' clinical characteristics and PFT results are summarized in Table 1.

Changes over time in lung volumes

The changes over time in lung volumes and flows between V0 and V5 are summarized in Table 2. The following lung volumes decreased significantly: VC % pred ($p=0.009$), FEV1 % pred ($p=0.010$), FRC % pred ($p=0.002$), and TLC % pred ($p=0.001$). The increase at V5 in the proportion of patients reporting shortness of breath (defined by an mMRC scale of 1 or more) was of borderline significance (25.9% at V0 vs. 48.2% at V5; $p=0.058$).

Changes over time in respiratory muscle strength

The changes over time in respiratory muscle strength are summarized in Table 2. PEmax and PImax remained stable after 5 years of follow-up ($p=0.98$ and $p=0.27$, respectively), as did CPF and SNIP ($p=0.09$ and $p = 0.07$, respectively).

Correlation between changes in VC and respiratory muscle strength

Nine participants displayed a decrease in FVC of more than 10% pred. In comparison with the 18 participants without a clinically significant decrease in FVC (% pred), there were no differences in muscle strength (P_Imax, SNIP, P_Emax and CPF: $p=0.60$, $p=0.63$, $p=0.92$, and $p=0.570$ for % pred values, respectively). In the population as a whole, the changes in FVC % pred were unrelated to the respiratory muscle parameters ($p=0.21$ for P_Imax; $p=0.82$ for SNIP, $p=0.26$ for P_Emax, and $p=0.36$ for CPF). The change in FVC as an absolute value (L) was also unrelated to those in SNIP (in cm H₂O) ($p=0.63$) and CPF (in L/sec) ($p=0.33$).

Twitch mouth pressure at V5

At V5, the mean \pm SD (range) P_{mo,tw} was 9.9 ± 2.7 cmH₂O (8.5–11), and 14 of the 21 patients had a value <11 cm H₂O. P_{mo,tw} was not correlated with P_Imax (cm H₂O) ($p=0.58$) or with SNIP (cm H₂O) ($p=0.29$). The change in FVC (% pred) was not correlated with P_{mo,tw} at V5 ($p=0.69$).

Association between disease progression and PFT data

There was no correlation between the changes in the severity of non-motor symptoms of PD (according to the UPDRS I score) and the PFT results. Concerning the severity of motor symptoms, an increase in the UPDRS III score was negatively correlated with the change in VC (% pred; $p=0.047$; $r=-0.38$) and the change in CPF (% pred; $p=0.025$; $r=-0.43$) but not with changes in SNIP or mouth pressures.

Effect of impaired lung function at inclusion on disease outcomes

When comparing PD patients with vs. without early inspiratory muscle weakness, there were no significant differences in the changes in motor symptoms ($p=0.30$ for the UPDRS part III score), non-motor symptoms ($p=0.54$ for the UPDRS part II score) or cognitive symptoms ($p=1.0$ for MoCA, and $p=0.64$ for the LARS). Further details are given in Table 3. The values of VC and FVC at inclusion were not associated with the disease outcome (UPDRS scores) at V5.

DISCUSSION

The present study's main findings were as follows: (i) 5 years of follow-up of lung function highlighted a slow, overall decrease in all lung volumes (-5% pred for VC and -12% pred for TLC); (ii) respiratory muscle strength did not change significantly; and (iii) neither early inspiratory muscle weakness nor VC at inclusion were correlated with the motor and non-motor outcomes of PD. To the best of our knowledge, this study included the longest yet follow-up period (5 years) for lung volumes and respiratory muscle strength in PD.

At V0, 25.9% of the patients in our cohort reported shortness of breath (defined by an mMRC scale score of 1 or more). In PD, other studies have reported a prevalence of dyspnea of between 11.5% and 40% [16,17].

At inclusion, all the lung volume values (expressed in % pred) were normal, and we did not observe any significant differences between these early-stage PD patients and age-matched healthy subjects [8]. After 5 years of follow-up, all the lung volumes had decreased. Cross-sectional studies of PD patients with the same mean disease duration as our participants have highlighted mixed ventilatory dysfunction in this population [18-19]. In contrast to the present study, the PFT in the literature was assessed under "on drug" conditions. The only longitudinal spirometry study in PD (with 4 years of follow-up [20]) did not find any changes in VC, FVC or FEV1 when these variables were expressed in % pred. This disparity might have been to the long disease duration in Tambasco et al.'s study (mean: 5.7 years, vs. 1.9 years in our study). The effect of antiparkinsonian drugs on spirometry values has not been determined [21]. Since our PFTs were performed under "off drug" conditions, the chronic administration of dopaminergic drugs did not appear to affect the patients' lung volumes. Given that the change of VC was correlated with the progression of motor symptoms (the UPDRS III score), the occurrence of lung restriction might have been due to axial hypertonia with impairment of the thoracic expansion, or to poor muscle coordination during the PFT protocol.

Only a few studies have assessed respiratory muscle function in PD [18], and none of them concerned early-stage PD. Furthermore, the present study is the first to have followed up inspiratory and expiratory muscle pressures in PD over a long period. At inclusion, half of the patients in our cohort displayed an impairment in inspiratory muscle strength. The impairments had not significantly worsened at V5. With regard to SNIP, our previous research had evidenced a trend towards an increase after 2 years of follow-up [8], although our earlier study may have lacked of statistical power. In PD, dopaminergic treatment (with an increase in LEDD in our population) might improve muscle coordination and thus help to counter a decline in P_Imax, P_Emax, SNIP and CPF [21]. Furthermore, physiotherapy or speech therapy might also have helped to stabilize respiratory muscle function over the 5 years of follow-up [22]. Unfortunately, there are no data on the minimal clinically important difference in expiratory and inspiratory muscle strength function, and so we could not stratify our patients as we have done for lung volumes. Furthermore, chronic treatment with dopaminergic medications may affect lung volumes and respiratory strength in different ways. Various studies of PD patients with a mean disease duration of between 3 and 9 years have highlighted inspiratory and expiratory muscle weakness, although P_Imax seemed to be more affected than P_Emax [18]. However, measuring P_Imax or P_Emax can be challenging in elderly patients; that is why we used SNIP and CPF measurements to better determine the presence or absence of respiratory muscle weakness in PD [23, 24]. The disparities between these studies might be due to methodological differences; the assessments of respiratory muscle in neuromuscular disease might not have complied with the ERS guidelines [25]. Furthermore, P_Imax is not impacted by chest compliance because it is measured at FRC. However, greater chest wall recoil at TLC might slightly increase P_Emax. These hypotheses require further investigation, and the use of non-volitional maneuvers might help to better determine the underlying mechanisms.

Diaphragmatic function was assessed with regard to P_{mo,tw} (measured in 21 of the 27 patients in the cohort); we did not observe significant correlations with P_Imax and SNIP. P_{mo,tw} is a relatively

specific marker of diaphragm strength [25]. Thus, a significant proportion of patients exhibited probable, moderate diaphragmatic weakness at the 5-year follow-up visit. However, the decline in FVC was not associated with overall inspiratory muscle weakness or with $P_{mo,tw}$. Therefore, PD does not seem to have the same impact on respiratory function as the main neuromuscular diseases do; the PFT data in our cohort and in other studies suggest that the results might rather be due to low chest wall compliance. The fact that the largest change in lung volumes in our patients involved the FRC (primarily corresponding to the balance between lung compliance and chest wall compliance) argues in favor of this hypothesis. Similarly, Sabaté et al. hypothesized that low chest wall compliance could explain the restrictive pattern observed in a cohort of PD patients [26]. In fact, ankylosing spondylitis might be a closer model of ventilatory dysfunction in PD than neuromuscular disease [27].

Our work had however some limitations. Firstly, the change in pulmonary function was not assessed in a control group. A study performed in 2003 compared early-stage PD patients with age-matched controls [9], there are no recent, precise data on changes in PFT results in older adults. The Global Lung Initiative equations are more recent than the ERS equations but only cover FEV1 and FVC. Healthy young adults and older adults did not differ with regard to year-to-year changes in P_Imax and SNIP [28, 29]. Only Enright et al. have highlighted a decrease in P_Imax (between 0.8 and 2.7 cm H₂O per year) in a cohort of 4443 healthy over-65 adults [30]. In our cohort, P_Imax had not changed at V5 and SNIP had significantly increased. We cannot rule out an effect of dopaminergic drugs or rehabilitation (i.e. physiotherapy and/or speech therapy) on the PFT results. Secondly, given that PFT involves voluntary maneuvers, the participants' level of commitment may have had an effect on the quality of the data. However, a training effect over a 5-year interval remains unlikely. Furthermore, our participants did not suffer from apathy. Our present results must be confirmed in a larger group of patients. A non-volitional test (such as magnetic stimulation of the cervical phrenic nerve) could potentially be used to assess diaphragm strength more specifically. Lastly, our follow-up period of five

years might nevertheless been too short to highlight an effect of ventilatory dysfunction on the course of PD (i.e. on gait, dysphagia or dysarthria).

CONCLUSION

In a 5-year follow-up study of a cohort of PD patients, we found that lung volumes decreased slowly and significantly, whereas respiratory muscle function was maintained. One can reasonably hypothesize that chest wall compliance is affected over the course of the disease; if so, ventilatory impairment could be classified as an axial manifestation of PD. Given that diaphragmatic function was impaired in half of our patients, PD might encompass various lung function phenotypes.

Our present results need to be confirmed in a larger population, in order to characterize the time course of diaphragmatic function in PD and establish whether respiratory dysfunction is a prognostic factor.

REFERENCES

1. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591-601.
2. Susan HF, & Lang AE Motor and nonmotor fluctuations. *Handbook of Clinical Neurology*. Elsevier 2007, Edinburgh-Toronto, pp. 159-184.
3. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525-35.
4. Dashtipour K, Tafreshi A, Lee J, Crawley B. Speech disorders in Parkinson's disease: pathophysiology, medical management and surgical approaches. *Neurodegener Dis Manag*. 2018;8(5):337-348.
5. Ebihara S, Saito H, Kanda A, Nakajoh M, Takahashi H, Arai H, & Sasaki H (2003) Impaired efficacy of cough in patients with Parkinson disease. *Chest*, 3, 1009-1015.
6. Fontana GA, Pantaleo T, Lavorini F, Maluccio NM, Mutolo D, & Pistolesi M (1998) Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med*, 2, 458-464.
7. Witting N, Andersen LK, Vissing J. Axial myopathy: an overlooked feature of muscle diseases. *Brain*. 2016;139(Pt 1):13-22.
8. Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C. Early occurrence of inspiratory muscle weakness in Parkinson's disease. *PLoS One*. 2018 Jan 12;13(1):e0190400. doi: 10.1371/journal.pone.0190400. eCollection 2018.
9. Braak H, Del Tredici K, RuÈb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003; 24(2):197-211.
10. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatr*. 1988;51(6):745-52.
11. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(7):581-6.
12. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-968.
13. Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. *Thorax*. 1995;50(4):371-5.
14. Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77(5):579-84.
15. Conover WJ, Iman RL: Analysis of covariance using the rank transformation. *Biometrics* 1982, 38:715-724.

16. Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatralo R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD; PRIAMO study group. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord*. 2009;24(11):1641-9.
17. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Chérif AA. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology*. 2002;59(3):408-13.*
18. Baille G, De Jesus AM, Perez T, Devos D, Dujardin K, Charley CM, Defebvre L, Moreau C. Ventilatory Dysfunction in Parkinson's Disease. *J Parkinsons Dis*. 2016 Jun 16;6(3):463-71.
19. Wang Y, Shao WB, Gao L, Lu J, Gu H, Sun LH, Tan Y, & Zhang YD (2014) 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*, 12, e116123.
20. Tambasco N, Murgia N, Nigro P, Paoletti FP, Romoli M, Brahim E, Filidei M, Simoni S, Muzi G, Calabresi P. Levodopa-responsive breathing discomfort in Parkinson's disease patients. *J Neural Transm (Vienna)*. 2018;125(7):1033-1036.
21. Reyes A, Castillo A, Castillo J, Cornejo I. The effects of respiratory muscle training on peak cough flow in patients with Parkinson's disease: a randomized controlled study. *Clin Rehabil*. 2018;32(10):1317-1327.
22. van Hooren MR, Baijens LW, Voskuilen S, Oosterloo M, Kremer B. Treatment effects for dysphagia in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord*. 2014;20(8):800-7.
23. Tilanus TBM, Groothuis JT, Ten Broek-Pastoor JMC, Doorduyn J, van Engelen BGM, Kampelmacher MJ, Raaphorst J. Respiratory Assessment of ALS Patients: A Nationwide Survey of Current Dutch Practice. *J Neuromuscul Dis*. 2018;5(4):431-438.
24. Terzi N, Corne F, Mouadil A, Lofaso F, Normand H. Mouth and nasal inspiratory pressure: learning effect and reproducibility in healthy adults. *Respiration*. 2010;80(5):379-86.
25. Laveneziana P, Albuquerque A, Aliverti A, Babb T, Barreiro E, Dres M, Dubé BP, Fauroux B, Gea J, Guenette JA, Hudson AL, Kabitz HJ, Laghi F, Langer D, Luo YM, Alberto Neder J, O'Donnell D, Polkey MI, Rabinovich RA, Rossi A, Series F, Similowski T, Spengler C, Vogiatzis I, Verges S. ERS Statement on Respiratory Muscle Testing at Rest and during Exercise. *Eur Respir J*. 2019 Apr 7.
26. Sabaté M, González I, Ruperez F, Rodríguez M. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci*. 1996;138(1-2):114-9.
27. Berdal G, Halvorsen S, van der Heijde D, Mowe M, Dagfinrud H. Restrictive pulmonary function is more prevalent in patients with ankylosing spondylitis than in matched population controls and is associated with impaired spinal mobility: a comparative study. *Arthritis Res Ther*. 2012;14(1):R19.
28. Barnes N, Agyapong-Badu S, Walsh B, Stokes M, Samuel D. Reliability and acceptability of measuring sniff nasal inspiratory pressure (SNIP) and peak inspiratory flow (PIF) to assess

respiratory muscle strength in older adults: a preliminary study. *Aging Clin Exp Res.* 2014;26(2):171-6.

29. Tolep K, Higgins N, Muza S, et al. Comparison of diaphragm strength between healthy adult elderly and young men. *Am J Respir Crit Care Med.* 1995;152(2):677–82.
30. Enright PL, Adams AB, Boyle PJ, Sherrill DL. Spirometry and maximal respiratory pressure references from healthy Minnesota 65- to 85-year-old women and men. *Chest.* 1995;108(3):663-9.

Age (years)	67.3 ± 7.6 66 (63 to 71)
Sex (M/F)	21/6
Disease duration (years)	1.9 ± 1.6 1 (1 to 3)
Tobacco use	2 (7.4%)
LEDD (mg)	260.8 ± 198.5 240 (100 to 475)
MoCA score (out of 30)	27.4 ± 1.9 27 (26 to 29)
LARS score (between -36 and 36)	-26.7 ± 5.7 -28 (-30 to -25)
HDRS score (out of 63)	5.7 ± 5.6 4 (0 to 11)
UPDRS part I score (out of 16)	5.8 ± 3.7 6 (3 to 8)
UPDRS part II score (out of 52)	5.9 ± 3.2 5 (3 to 8)
UPDRS part III score (out of 108)	18.3 ± 6.0 18 (13 to 22)
UPDRS part IV score (out of 23)	0.7 ± 1.4 0 (0 to 1)
Patients with dyspnea (mMRC ≥1) (n, %)	7 (25.9%)
mMRC dyspnea scale (out of 4), median (interquartile)	0 (0 to 1)

Table 1: Clinical and PFT characteristics of patients at V0 (mean ± SD, median (IQR)) M: male, F: female, LEDD: levodopa equivalent daily dose, MoCA: Montreal Cognitive Assessment, LARS: Lille Apathy Rating Scale, HDRS: Hamilton Depression Rating Scale, UPDRS: Unified Parkinson's Disease Rating Scale, mMRC: modified Medical Research Council;

	V0	V5	Change	p
UPDRS I (out of 16)	6 (3 to 8)	9 (7 to 12)	3 (2 to 8)	<0.0001
UPDRS II (out of 52)	5 (3 to 8)	19 (14 to 26)	12 (9 to 18)	<0.0001
UPDRS III (out of 108)	18 (13 to 22)	32 (26 to 48)	13 (9 to 23)	<0.0001
UPDRS IV (out of 23)	0 (0 to 1)	4 (2 to 5)	3 (2 to 4)	<0.0001
LEDD (mg)	240 (100 to 475)	733 (587 to 933)	480 (350 to 666)	<0.0001
MoCA (out of 30)	27 (26 to 29)	27 (21 to 28)	- 1 (- 4 to 0)	0.011
LARS (between -36 and 36)	- 28 (- 30 to - 25)	- 25 (- 30 to - 24)	2 (- 4 to 3)	0.42
HDRS (out of 63)	4 (0 to 11)	3 (2 to 6)	0 (- 5 to 2)	0.19
VC (% predicted)	111 (102 to 123)	109 (97 to 121.5)	- 3 (- 10 to 3)	0.009
FVC (L)	4.4 (3.9 to 4.9)	3.8 (3.1 to 4.4)	- 0.6 (- 0.8 to -0.4)	<0.0001
FVC (% predicted)	113 (101 to 122)	104.1 (96.0 to 118.8)	- 5.27 (- 11.4 to 3)	0.053
FEV1 (% predicted)	110 (98 to 119)	108.7 (95.0 to 116.9)	- 4.2 (- 8.2 to 2.9)	0.010
FEV1/FVC	0.77 (0.74 to 0.80)	0.81 (0.76 to 0.85)	0.03 (- 0.02 to 0.07)	0.099
FRC (% predicted)	123 (94 to 143)	105 (91.4 to 120.0)	- 17.6 (- 36.0 to 2.3)	0.002
TLC (% predicted)	110 (102 to 122)	96.8 (90 to 110)	- 9.4 (- 25.6 to 1.8)	0.001
PImax (cmH₂O)	62.4 (50.0 to 82.1)	77.0 (45.2 to 90.0)	7.4 (- 6.8 to 14.3)	0.16
PImax (% predicted)	72 (58 to 91)	74.3 (58 to 100.8)	0.30 (- 7.8 to 18.5)	0.27

SNIP (cmH₂O)	64.7 (47 to 81)	70.8 (57.5 to 83.8)	3 (- 4.8 to 21.6)	0.067
SNIP (% predicted)	64 (48 to 79)	73.4 (64.6 to 84.9)	6.9 (-0.3 to 26.8)	0.004
PEmax (% predicted)	71 (64 to 85)	73.3 (57.8 to 83.9)	- 0.2 (- 11.8 to 9.6)	0.98
CPF (L/sec)	7.5 (6.1 – 8.1)	8.0 (5.7 to 9.3)	- 0.5 (- 0.55 to 1.31)	0.098

Table 2. Changes over time in clinical and PFT parameters between V0 and V5. (median and interquartile range), UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: levodopa equivalent daily dose, MoCA: Montreal Cognitive Assessment, LARS: Lille Apathy Rating Scale, HDRS: Hamilton Depression Rating Scale, MRC: VC: vital capacity, FVC: forced vital capacity, FEV1: forced expiratory volume in one second, FRC: functional residual capacity, TLC: total lung capacity, PImax: maximal inspiratory pressure, SNIP: sniff nasal inspiratory pressure, PEmax: maximal expiratory pressure, CPF: cough peak flow.

	PD patients with inspiratory muscle weakness at V0 n=14	PD patients with normal inspiratory muscle strength at V0 n=13	p
Change in the UPDRS part I score	3 (2 to 7)	3 (2 to 10)	0.80
Change in the UPDRS part II score	11 (9 to 17)	14 (9 to 21)	0.54
Change in the UPDRS part III score	14.5 (9 to 27)	12 (3 to 16)	0.30
Change in the UPDRS part IV score	3 (2 to 6)	3 (2 to 4)	0.44
Change in the LEDD	480 (380 to 628)	405 (350 to 666)	0.77
Change in MoCA score	-1 (-2 to 0)	-1 (-4 to 0)	1
Change in LARS score	1 (-4 to 3)	3 (0 to 3)	0.64
Change in HDRS score	0 (-5 to 2)	0 (-3 to 1)	0.63

Table 3: Comparison (in an analysis of covariance) of clinical changes between V0 and V5 in PD patients with and without inspiratory muscle weakness. UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: levodopa equivalent daily dose, MoCA: Montréal Cognitive Assessment, LARS: Lille Apathy Rating Scale, HDRS: Hamilton Depression Rating Scale.

Discussion générale

1. Histoire naturelle des anomalies respiratoires dans la maladie de Parkinson

1-1-Données chez l'Homme

Afin de mieux déterminer la place de l'atteinte ventilatoire dans la MP, il convient, entre autres, de préciser à quel moment elle peut apparaître dans le cours évolutif de la maladie. Ainsi, la plupart des SNM sont rapportés par le patient dans la phase prodromale [5, 6, 9]. De même, de plus en plus d'études ont montré que les signes dits « axiaux » (instabilité posturale, dysarthrie ou dysphagie) sont présents peu d'années après l'apparition du syndrome parkinsonien [53]. Par ailleurs, l'histoire naturelle des troubles ventilatoires dans la MP pourrait nous aider à mieux comprendre certains aspects physiopathologiques de cette synucléinopathie.

Hormis notre cohorte Prodigy-Park, une seule étude a évalué les EFR dans une population plus importante (78 sujets) de patients parkinsoniens au début de la maladie [54]. Même si la durée d'évolution de la MP est plus hétérogène (extrêmes : 3 mois et 16 ans) que dans notre étude, Owolabi et al. ont également mis en évidence une diminution significative des volumes pulmonaires dès les stades précoces (médiane de la durée d'évolution : 2 ans). Récemment, à notre connaissance, une seule étude menée par une équipe chinoise a mesuré la force des muscles respiratoires à un stade aussi précoce que dans la cohorte Prodigy-Park ([55] durée d'évolution de $1,67 \pm 1,14$ ans vs $1,9 \pm 1,7$ ans). Zhang et al. ont retrouvé une baisse à la fois de la PEmax et de la PImax dans une cohorte de 43 patients parkinsoniens comparés à un groupe de témoins appariés. Les données des EFR au début de la MP restent donc contradictoires : y-a-t-il une atteinte des volumes respiratoires comme celle mise en évidence par Owolabi et al. [54] ou une faiblesse de la musculature inspiratoire comme nous l'avons

montré [56] ? De nouvelles cohortes de patients parkinsoniens devront être constituées afin de répondre à la question de la précocité et du type d'atteinte ventilatoire dans la MP.

Concernant le suivi longitudinal des données EFR dans la MP, 2 études ont été publiées. Dans la première, Hampson et al. ont vérifié la reproductibilité des données en spirométrie (à la fois en « on drug » et « off drug ») sur une durée de 4 semaines [57]. Cette durée est trop courte pour pouvoir mettre en évidence des variations liées à l'évolution de la maladie et empêche toute interprétation sur l'évolutivité à long terme. Ils ont cependant révélé que l'analyse morphologique des courbes est délicate dans la MP principalement à cause du phénomène de *flutter respiratoire* qui correspond à une oscillation de la courbe débit-volume (fréquence entre 4 et 8 Hz) [27 – illustration page 25 du manuscrit]. Dans une deuxième étude, Tambasco et al. ont réévalué au bout de 4 ans les EFR de 14 sujets parkinsoniens [58]. Ils ont montré, comme dans notre travail, une diminution significative du VEMS et de la CV lorsque les résultats sont exprimés en valeur absolue. Cependant, leurs résultats ne sont pas significatifs lorsqu'ils le sont en pourcentage de la valeur théorique. Cela montre combien il est important de suivre les recommandations des sociétés savantes de pneumologie et combien il est difficile de monter ce genre de projet de façon transdisciplinaire.

A des stades plus avancés de la MP, les données existantes de la littérature sont pour la plupart concordantes concernant la présence de troubles ventilatoires objectifs [27, 59]. L'atteinte restrictive semble la plus logique à analyser du fait d'un probable impact des troubles posturaux (tels que la camptocormie) [60]. En effet, lors de l'évaluation à 5 ans des sujets de la cohorte Prodigy-Park, la force musculaire inspiratoire ne diminuait pas significativement par rapport à l'inclusion, contrairement à l'ensemble des volumes pulmonaires. Florêncio et al. ont mis en évidence des anomalies fonctionnelles de la cage thoracique de patients parkinsoniens avec une asynchronie entre les sections thoracique et

abdominale qui la composent [61]. Ce genre d'anomalie est capable d'impacter la fonction inspiratoire sans altération directe de la musculature diaphragmatique [62, 63]. Ces troubles respiratoires dans la MP ne semblent donc pas être en lien avec un processus d'atteinte musculaire tels qu'ils sont observés dans les pathologies neuromusculaires. Sur le même modèle que la spondylarthrite ankylosante [64], il est possible d'imaginer que la rigidité de la paroi thoracique – possiblement présente dès les premières années de la MP – soit responsable en partie des anomalies objectivées en EFR. Cette hypothèse permettrait d'expliquer l'atteinte de la musculature respiratoire retrouvée dans de nombreuses études ayant inclus des sujets au stade évolué de la maladie [27]. De son côté, l'atteinte obstructive a fait l'objet de plusieurs hypothèses physiopathologiques comme un trouble de la coordination des fibres musculaires, une altération de la commande musculaire ou même une obstruction des voies aériennes supérieures [27, 65, 66, 67]. Dans cette thèse, nous n'avons malheureusement pas pu explorer ces pistes physiopathologiques, ni par ailleurs prendre en compte les possibles troubles ventilatoires nocturnes (syndrome d'apnées du sommeil obstructif ou central).

La cohorte Prodigy-Park a donc permis de progresser sur la connaissance de l'histoire naturelle de l'atteinte en EFR dans la MP, mais de nombreuses questions restent en suspens et la recherche translationnelle pourrait permettre de répondre à certaines d'entre elles. Le lien entre atteinte des volumes et musculature respiratoire doit donc encore être éclairci.

1-2-Données chez l'animal

L'apport des modèles animaux pour mieux comprendre l'atteinte ventilatoire dans la MP est assez récent. Bien que la complexité de la maladie rende incomplets les modèles existants [68, 69], les progrès des protocoles expérimentaux ont permis d'étudier la ventilation chez des souris « parkinsoniennes ».

Ainsi, de Campos et al. ont proposé le même modèle murin (injection de 6-OHDA dans le striatum droit) avec la modélisation des stades « précoces » [70] et « tardifs » [71] de la MP. La présence d'une atteinte ventilatoire dans le modèle précoce confirme nos données cliniques [56]. Les anomalies objectives mesurées ne semblent donc pas être la conséquence pure du syndrome akinéto-rigide. Cependant, il est extrêmement délicat, dans un modèle murin, de distinguer le syndrome parkinsonien axial de celui affectant le squelette appendiculaire. A ce niveau, les études cliniques sont indispensables. Dans ce même modèle, les auteurs interprètent les résultats comme témoignant d'une possible atteinte restrictive alors qu'au stade plus tardif, les données sont interprétées comme résultant d'une atteinte obstructive. Ces troubles ventilatoires apparaissent comme évolutif dans la MP et le phénotype à la fois potentiellement restrictif et obstructif serait le reflet des données parfois contradictoires de la littérature chez l'homme [27]. Néanmoins, la présence précoce d'anomalies évocatrices d'atteinte restrictive concorde davantage avec les données cliniques de la cohorte Prodigy-Park. Des progrès dans l'évaluation des volumes pulmonaires (par exemple des cabines de pléthysmographie adaptées) mais aussi de l'évaluation de la rigidité thoracique pourraient appuyer les données issues des observations cliniques.

Les données chez l'animal permettent cependant d'émettre des hypothèses physiopathologiques. En effet, avec un modèle murin similaire, l'équipe de Oliveira et al. a mis en évidence des lésions de neurodégénérescence dans les centres respiratoires du tronc cérébral, évoquant la combinaison possible d'une atteinte du système nerveux central, mais aussi d'une déficience du système sensoriel périphérique [72]. Ce postulat est étayé par des données anatomopathologiques chez l'homme qui ont révélé des dépôts d'alpha-synucléine dans les nerfs crâniens et les racines nerveuses [73], principalement le nerf glosso-pharyngien (IX) [74]. Ce dernier étant impliqué dans les afférences issues des glomus carotidien, au-delà

d'une atteinte purement « mécanistique » (volumes pulmonaires et/ou musculature respiratoire), la MP pourrait affecter d'autres aspects de la ventilation.

2. Réponse à l'hypoxie et à l'hypercapnie dans la MP.

Cet aspect d'EFR n'a pas été traité dans les articles publiés et regroupés dans cette thèse. Cependant, pour mieux comprendre les troubles ventilatoires dans la MP, il apparaît important de les appréhender dans leur globalité. Les résultats expérimentaux chez l'animal concernant la réponse à l'hypoxie et à l'hypercapnie sont plus fournis que les données cliniques.

Concernant l'hypercapnie, Andrzejewski et al. ont révélé que des rats « parkinsoniens » présentaient une réponse altérée aux variations gazeuses, principalement à l'hypercapnie [75]. En utilisant un modèle murin similaire, Oliveira et al. ont fait le même constat et cette mauvaise réponse à l'hypercapnie était corrélée à une dégénérescence des neurones orexigéniques [76]. Concernant la réponse à l'hypoxie, une étude a montré une exagération de la réponse à l'hypoxie, sans effet des modulateurs de la dopamine [77].

Les neuromédiateurs des noyaux du tronc cérébral qui pourraient être incriminés sont nombreux : dopamine [71] ?, sérotonine [71] ?, noradrénaline [35] ? De même, la responsabilité des structures du système nerveux périphérique et des mécanismes de détections périphériques est évoquée par certains auteurs [76] et cette hypothèse est appuyée par les résultats d'études réalisées chez des patients parkinsoniens.

En effet, la réponse à l'hypoxie et à l'hypercapnie était altérée dans 3 études [78, 79,80]. Une perte des neurones dopaminergiques dans les chémorécepteurs carotidiens dans la MP [81, 82]. Ce mécanisme associé à la perte neuronale dans les centres pontiques contrôlant la ventilation pourrait induire des conséquences sur l'homéostasie gazeuse. Chez l'Homme, une

seule étude a observé des épisodes d'hypoxémie asymptomatique chez des sujets parkinsoniens « de novo » non traités [83]. Cependant, une étude de cohorte est nécessaire pour confirmer ces résultats en comparant avec un groupe témoin.

Au total, la ventilation dans la MP est probablement affectée à différents niveaux : réduction des volumes respiratoires, troubles de la commande ventilatoire (avec une potentielle altération directe de la fonction musculaire respiratoire) et réponse altérée à l'hypercapnie/hypoxie.

3. Hypothèses physiopathologiques – corrélation anatomo-clinique.

L'histoire naturelle de ces troubles respiratoires est de mieux en mieux connue et nous permet d'émettre une hypothèse physiopathologique basée sur le modèle de Braak [4-figure3].

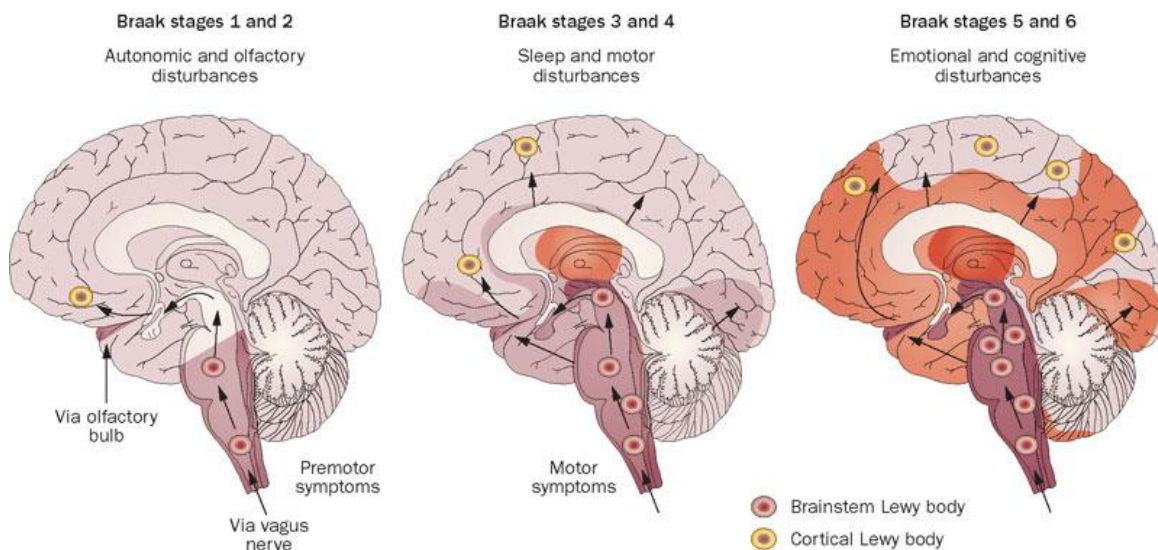


Figure 3 : les stades de la maladie de Parkinson selon Braak [4]. Source : Nature

De façon très précoce dans la MP, le bulbe rachidien est atteint par les dépôts d'alpha-synucléine et la neurodégénérescence. Le noyau du tractus solitaire est une des premières structures touchées [84, 85 – figure 4].

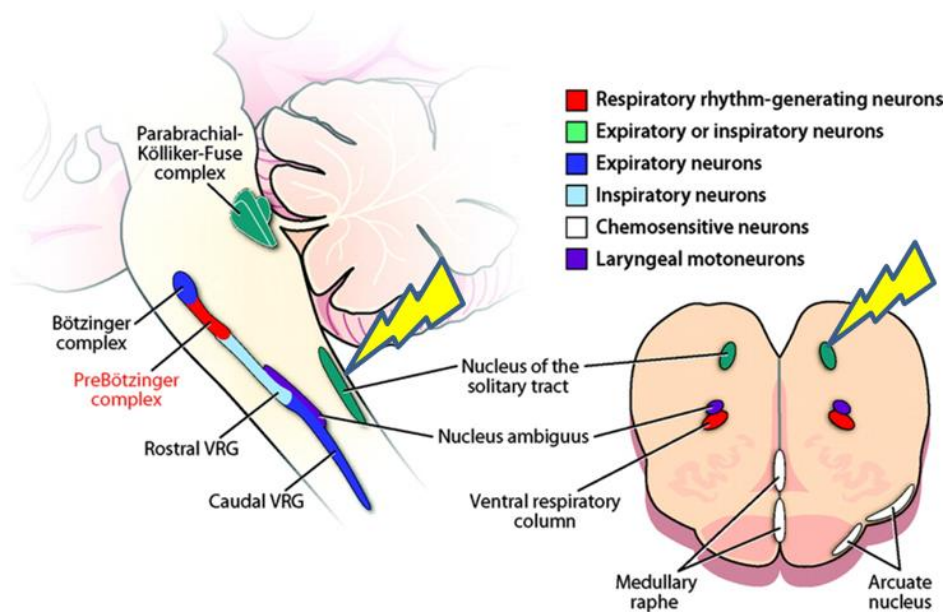


Figure 4 : zones du tronc cérébral impliquées dans le contrôle ventilatoire. VRG : ventral respiratory group. D'après E. Benarroch. Brainstem respiratory chemosensitivity: New insights and clinical implications Neurology, 2007; 68 (24)

Le noyau du tractus solitaire possède de nombreuses afférences, venant notamment des nerfs glosso-pharyngien et vague. Or, ces structures peuvent être impliquées dans la physiopathologie des troubles ventilatoires. D'une part, ils transmettent les informations venant des glomus carotidiens, dont la population de neurones dopaminergiques diminue fortement dès les premières années de la MP [82]. D'autre part, des dépôts d'alpha-synucléine ont été mis en évidence dans certains nerfs crâniens, principalement le nerf glosso-pharyngien, innervant les chémorecepteurs périphériques [73, 74].

Du fait de la progression caudo-rostrale des lésions de la MP [4], les structures de la protubérance sont également affectées par la perte neuronale. Le locus coeruleus qui, selon un modèle murin, joue un rôle dans le contrôle ventilatoire est donc touché [35]. De plus, l'une des structures clés dans la physiologie de la respiration se situe au niveau du pont (figure 4). Il s'agit du noyau de Kölliker-Fus qui est considéré comme le centre adaptatif de la ventilation [86, 87, 88]. Une dysfonction de ces neurones pourrait expliquer les troubles de la commande musculaire et participer à la réponse inadaptée à l'hypoxie ou à l'hypercapnie.

Parmi les efférences du noyau de Kölliker-Fus, on note le nerf phrénique et le nerf hypoglosse qui pourraient jouer un rôle dans l'atteinte ventilatoire. L'activation du nerf phrénique induit une contraction du diaphragme et il est donc possible d'évoquer une faiblesse de la commande diaphragmatique dans la MP. Ce point nous encourage à poursuivre les explorations qui concernent ce muscle par exemple par mesure de la pression buccale dès les stades précoces de la maladie.

Une altération de la commande du nerf hypoglosse (XII) pourrait également jouer un rôle dans la physiopathologie des troubles ventilatoires de la MP. En effet, la contraction de la langue est indispensable à la perméabilité des voies aériennes supérieures (figure 5). Le lien fonctionnel entre le noyau de Kölliker-Fus et celui du nerf hypoglosse a été confirmé récemment [89]. Même si ce nerf semble relativement épargné par les dépôts d'alpha-synucléine [73], sa dysfonction indirecte pourrait obstruer en partie les voies aériennes supérieures des patients parkinsoniens, et ce dès les stades précoces de la maladie. Par ailleurs, une bradykinésie de la langue a été observée dans la MP [90].

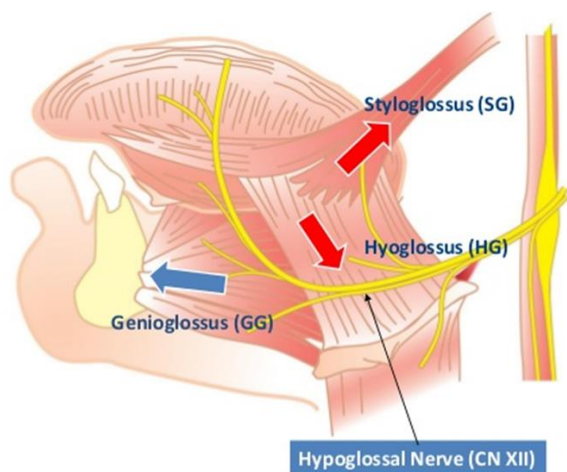


Figure 5 : Physiology of hypoglossal nerve stimulation D'après Mustafa Gerek,MD,MuratBinar,MD. Physiology of hypoglossal nerve stimulation. Operative Techniques in Otolaryngology (2015)26,105–107.

Les modèles animaux corroborent cette hypothèse avec un impact de l'injection de 6-OHDA sur l'activité à la fois du nerf phrénique et du nerf hypoglosse [91] et un possible rôle du système dopaminergique sur la commande motrice de la langue [92].

Chez l'homme, l'implication du nerf hypoglosse dans les apnées obstructives est reconnue et des équipes proposent même une stimulation de ce nerf en cas de syndrome d'apnées du sommeil obstructives sévères réfractaires à la pression positive continue [93, 94]. Il serait intéressant de voir si les apnées du sommeil des patients parkinsoniens ne répondent pas mieux à ce type de procédé.

S'il existe plusieurs arguments en faveur d'une atteinte obstructive dès le début de la MP, la question est de savoir pourquoi elle n'est pas mise en évidence sur les quelques études en EFR réalisées au stade précoce de la maladie. Au-delà de la nécessité de standardiser l'évaluation des volumes pulmonaires et de constituer une plus grande cohorte prospective, des mécanismes de compensation pourraient expliquer les données cliniques, mais aussi le fait que la dyspnée ne semble pas si fréquente à V0 dans l'étude Prodigy-Park. Les circuits végétatifs ou cognitifs seraient activés pour éviter les conséquences ventilatoires de l'obstruction des voies aériennes supérieures. Néanmoins, avec l'évolution de la maladie, les structures corticales sont également affectées par la diffusion de la neurodégénérescence [4]. Seccombe et al. ont mis en évidence une dysautonomie précoce à l'origine de la réponse inadaptée à l'hypercapnie/hypoxie [39]. Ce rôle central du système nerveux autonome dans la physiopathologie des troubles ventilatoires de la MP a été confirmé par une étude en *voxel-based morphometry* (VBM) [95]. Les auteurs évoquent une corrélation entre les paramètres obstructifs et l'altération des voies cortico-limbiques respiratoires [96, 97] et du réseau végétatif central [98, 99]. En effet, leurs résultats et les caractéristiques en EFR des anomalies ventilatoires dans la MP plaident pour une atteinte au-delà des centres respiratoires du tronc cérébral.

Toutefois, ce modèle ne parvient pas à expliquer l'ensemble des données de la cohorte Prodigy-Park qui mettent davantage en évidence une atteinte pulmonaire restrictive dans la maladie. Soulignons par ailleurs que la physiopathologie des signes axiaux, notamment des

troubles de la statique rachidienne, est encore méconnue mais certains auteurs évoquent une myosite focale de mode de révélation plus ou moins chronique [100, 101]. De façon intuitive, la camptocormie ou plus largement les troubles de la statique rachidienne (cypho-scoliose), qui sont fréquents dans la MP, semblent être les symptômes les plus à même d'induire des troubles ventilatoires restrictifs. Cette hypothèse pathophysiologique n'explique cependant pas à elle seule les troubles ventilatoires car ces derniers semblent toucher un pourcentage plus grand de patients que la camptocormie [102]. De plus, l'apparition relativement tardive des troubles statiques dans l'évolution de la maladie [101] va à l'encontre de nos données cliniques. Néanmoins, les anomalies radiographiques précoces du rachis [60] ou la limitation de la mobilité thoracique (l'expansion des côtes par exemple) ne sont pas évaluées en routine dans la MP (et ne l'ont pas été dans l'étude Prodigy) ; par conséquent, la fonction ventilatoire pourrait être affectée sans que le patient n'arrive au stade de camptocormie. Toutes ces données nous incitent de nouveau à classer l'atteinte ventilatoire de la MP parmi les signes axiaux.

Enfin, une altération de la fonction diaphragmatique peut être évoquée comme composante participant potentiellement à la dysfonction respiratoire. Des nouvelles mesures des pressions buccales devront être réalisées dès les stades précoces de la maladie, de façon prospective et sur des cohortes plus importantes que la nôtre pour avancer dans cette hypothèse physiopathologique. Si l'atteinte diaphragmatique est confirmée, deux questions seront à élucider. Premièrement, il faudra trancher entre une atteinte de la commande nerveuse (via le nerf phrénique) ou du muscle en lui-même (sur le modèle d'une myopathie focale axiale [101, 103]). Deuxièmement, l'effet des traitements dopaminergiques sera à étudier afin de vérifier si la coordination musculaire peut être améliorée, comme cela a été évoqué par De Bruin et al. [65].

Au total, l'existence d'une atteinte ventilatoire dans la MP est avérée. Au-delà de la nécessité de mieux comprendre les mécanismes sous-jacents, il semble indispensable de déterminer quels sont ses conséquences sur la maladie, que ce soit au niveau des processus neurodégénératifs (par le biais de l'hypoxie) ou de certains symptômes de la maladie (dysarthrie et dysphagie).

4. Impact des troubles ventilatoires sur le processus neurodégénératif.

La pathogénie de la MP est complexe et l'hypoxie a été identifiée comme un des facteurs participant à la mort cellulaire [104]. L'hypoxie intermittente chronique consécutive aux troubles ventilatoires pourrait aggraver le stress oxydatif et la cascade inflammatoire, deux processus en jeu au début de certaines maladies neurodégénératives comme la MP [105]. Les modèles animaux manquent encore pour étayer l'hypothèse d'une majoration des dépôts d'alpha-synucléine et de la perte neuronale en cas d'hypoxie chronique, phénomène qui pourrait se produire dès les stades précoces de la maladie. Chez l'homme, Gama et al. ont mis en évidence une corrélation entre les troubles ventilatoires nocturnes et l'atrophie cérébrale en IRM à la fois dans la MP et dans l'atrophie multi-systématisée [106].

Les données sont encore peu nombreuses dans la MP mais les résultats d'études menées dans des modèles animaux de maladie d'Alzheimer [107, 108, 109] ont retrouvé un effet aggravant de l'hypoxie sur les lésions anatomopathologiques. Une réduction du déclin cognitif a même été démontrée en cas de traitement par pression positive continue du syndrome d'apnées du sommeil de patients atteints de la maladie d'Alzheimer [110]. Cependant, cette pathologie n'est pas reconnue comme altérant la fonction ventilatoire.

S'intéresser aux maladies neuromusculaires permettrait de mieux comprendre l'impact de l'hypoxie dans le pronostic des maladies neurodégénératives, y compris de la MP. Les résultats

d'une étude sur un modèle murin de sclérose latérale amyotrophie, pathologie affectant la fonction diaphragmatique, donne des arguments supplémentaires pour une possible participation de l'hypoxie à la neurodégénérescence [111].

Toutefois, en plus d'une supposée aggravation du pronostic de la MP en cas de troubles ventilatoires, des nombreuses études cliniques ont incriminé ces mêmes troubles dans la physiopathologie de certains signes axiaux de la maladie.

5. Impact des troubles ventilatoires sur les autres signes axiaux de la MP

5-1-Sur la dysarthrie

La phonation est un processus complexe impliquant des circuits moteurs et non-moteurs (cognitifs et émotionnels). Dans la MP, le concept de dysarthro-pneumo-phonie a été proposé par Viallet et al. [112]. Dès les premières années de la maladie, une dysarthrie hypokinétique avec composante parfois importante d'hypophonie a été observée [53]. Les paramètres analysés en EFR influent logiquement sur la phonation. En effet, d'une part, une fonction musculaire expiratoire est indispensable pour générer le flux d'air suffisant pour faire vibrer les cordes vocales et, d'autre part, la réserve respiratoire (capacité pulmonaire totale et surtout capacité vitale [113]) joue un rôle important pour maintenir le flux pendant plusieurs secondes. Toutefois, peu d'études se sont intéressées à l'impact de la fonction ventilatoire sur la dysarthrie parkinsonienne. Récemment, Hegland et al. ont observé un lien plus complexe entre ventilation et dysarthrie avec un défaut de perception de la charge résistive respiratoire chez les patients parkinsoniens [114]. D'autres études seront nécessaires pour mieux déterminer la place des troubles ventilatoires (volumes pulmonaires ou fonction musculaire respiratoire) dans l'histoire naturelle de la dysarthrie dans la MP. Une meilleure compréhension de ces mécanismes aiderait à proposer une prise en charge adaptée,

notamment avec des exercices de respiration réalisés avec le kinésithérapeute ou l'orthophoniste.

5-2- Sur la dysphagie

Les données concernant la participation des troubles ventilatoires sur les troubles de déglutition dans la MP sont plus nombreuses. Afin d'assurer la protection des voies aériennes en dessous du carrefour aéro-digestif, une fermeture de l'épiglotte est indispensable au moment de la déglutition. Ce phénomène complexe nécessite une coordination fine entre la déglutition (phase pharyngée) et la respiration. Une étude non-invasive a confirmé que la qualité de la coordination entre les différents acteurs de la ventilation au cours de la déglutition pouvait être évaluée par un dispositif non-invasif comprenant un électromyogramme de surface posé sur le larynx associé à un capteur de flux nasal [115]. Le risque de fausse route semble accru si le sujet réalise une inspiration après la déglutition ou si l'apnée au cours de la déglutition est trop courte [116]. La capacité vitale intervient donc très probablement dans ce processus.

En plus de l'influence des volumes pulmonaires sur la dysphagie, la force musculaire expiratoire est un bon marqueur du risque de troubles de déglutition. La toux est un moyen de protection des voies aériennes en cas de fausse route et un défaut de la production de toux a été montré comme lié à la dysphagie dans la MP [117]. Partant de ce constat, Troche et al. ont mis en place une méthode rééducative de la musculature expiratoire avec des premiers résultats encourageant sur la déglutition [118].

6. Détection des troubles ventilatoires dans la MP

6-1- Dépistage de la dyspnée dans la MP

Jusqu'à présent, nous nous sommes focalisés sur l'atteinte ventilatoire objective dans la MP. Or, l'analyse clinique de la plainte fonctionnelle des patients, en l'occurrence la dyspnée, pourrait permettre de mieux dépister ces troubles. Malheureusement, les échelles utilisées en routine pour déterminer si un patient est dyspnéique ou non ne sont adaptées ni aux caractéristiques phénoménologiques de la dyspnée ni à la MP. En effet, si le mMRC n'est pas suffisamment sensible ou spécifique, l'utilisation de questions fermées simples, à l'image du NMSQuest [14], améliore la détection du symptôme [119]. La question est maintenant de savoir s'il faut inclure ou non un item portant sur la dyspnée dans les échelles de dépistage des SNM dans la MP. De notre côté, après l'étude des données des différents articles composants cette thèse, nous proposons qu'un item portant sur la dyspnée soit inclus dans les échelles de NMS Quest ou la partie I (expériences non-motrice de la vie quotidienne) de la MDS-UPDRS [120]. La fréquence de la plainte dyspnéique et son retentissement, tout comme l'éventuel diagnostic d'une pathologie cardiaque ou pulmonaire, plaident en faveur d'une meilleure prise en compte de ce symptôme chez les patients parkinsoniens.

Toutefois, la MP impactant la mobilité, le dépistage de l'atteinte ventilatoire à travers l'existence ou non d'une dyspnée n'est pas applicable à tous les patients. Cibler les patients susceptibles d'avoir des anomalies objectives en EFR permettrait de proposer une prise en charge spécifique des divers symptômes de la MP. Cependant, une évaluation systématique des EFR chez les parkinsoniens serait difficile à réaliser dans la pratique. En cas d'hypophonie ou de troubles de déglutition, la mise en évidence de troubles ventilatoires aiderait l'orthophoniste à travailler certains points précis (amélioration des capacités d'apnée, travail du souffle avec déplacement d'une balle à l'aide d'une paille...) pour améliorer la

dysarthrie ou la dysphagie. En cas de camptocormie ou de freezing, le diagnostic d'anomalies objectives inciterait le kinésithérapeute à réadapter certains patients à l'effort et le neurologue à les adresser un médecin rééducateur.

Au-delà d'un simple screening des patients dyspnéiques, la prise en charge spécifique de cette plainte fonctionnelle gênante et anxiogène est indispensable pour améliorer la qualité de vie des patients. Pour cela, l'échelle *multidimensionnal dyspnea profile* (MDP – [121]) représente un outil intéressant car il aide à la détermination des caractéristiques de la dyspnée propres à chaque individu.

6-2- Physiopathologie de la dyspnée dans la MP

Dans la cohorte DYS PARK, l'utilisation de cette échelle nous a permis de voir que la dyspnée dans la MP présente des caractéristiques propres, différentes de celles de pathologies respiratoires (BPCO [122]) ou neuromusculaires (SLA [123]). Concernant une population plus générale, Stevens et al. ont administré récemment l'échelle MDP à 156 patients présentant une dyspnée modérément intense dans les 24 heures suivant leur prise en charge dans un hôpital universitaire, quel que soit leur motif d'admission ou la pathologie sous-jacente [124]. Leurs résultats diffèrent également de ceux de notre cohorte de patients parkinsoniens avec le manque d'air comme sensation dominante mais surtout l'anxiété et la frustration comme réponses émotionnelles prédominantes. Mais au-delà de son caractère propre à la MP, la dyspnée reste une expérience individuelle, ce qui explique sa grande hétérogénéité de présentation clinique pour les aspects perceptifs et émotionnels.

Malgré tout, l'analyse purement anamnestique de la dyspnée dans notre cohorte de patients parkinsoniens peut aider à la formulation d'hypothèses physiopathologiques. D'une part, l'atteinte ventilatoire objective peut logiquement engendrer une plainte fonctionnelle. La sensation d'oppression thoracique pourrait être la conséquence du défaut de réponse à

l'hypoxie et/ou à l'hypercapnie. En cas d'existence d'un dysfonctionnement de la commande ventilatoire, le patient parkinsonien aurait tendance à rapporter un effort physique ou psychique pour respirer. Le lien entre les données perceptives de la MDP est le pattern restrictif possiblement lié à un manque de compliance thoracique reste à déterminer.

D'autre part, les symptômes anxieux (50%) et les troubles anxieux (34% selon les critères du DSM IV) sont extrêmement fréquents dans la MP [125]. Associés aux FNM, ils induisent des plaintes somatiques chez les patients, comme la dyspnée par exemple [126, 127]. Dans une étude en IRM fonctionnelle, von Leupoldt et al. ont montré que les voies liées à la réponse émotionnelle à la douleur et la dyspnée impliquaient les mêmes structures neuronales, notamment le cortex cingulaire antérieur, l'amygdale et l'insula [128]. Cette dernière structure cérébrale joue un rôle crucial dans le système nerveux autonome, et cela pourrait rapprocher la dyspnée des SNM végétatifs. Par ailleurs, au sein des FNM, la dyspnée est davantage rapportée par les patients en condition « off drug » [24, 119], ce qui pourrait correspondre à une recrudescence des troubles respiratoires en même temps que d'autres signes végétatifs associés à cet état moteur (comme la constipation, l'hypersialorrhée, la dysurie...). Néanmoins, certains patients (ou plutôt leur entourage) décrivent une ventilation plus marquée lors des épisodes de dyskinésies [47, 129]. Un dysfonctionnement des mêmes aires cérébrales (cortex cingulaire antérieur entre autres) pourrait expliquer en partie cette association [130, 131]. Le terme de dyskinésie respiratoire a été proposé par certains auteurs [129].

Au total, grâce à des questionnaires adaptés, les différents types de dyspnée dans la MP devraient être facilement discernables. Pour cela, des études s'intéressant à l'association entre données à la MDP et en EFR dans la MP pourraient être menées. Enfin, les progrès en imagerie fonctionnelle de la dyspnée mais aussi sur les connaissances de FNM permettraient de mieux prendre en charge ce symptôme gênant.

Perspectives

A l'avenir, afin de mieux déterminer les mécanismes physiopathologiques à l'origine des troubles ventilatoires dans la MP, l'apport des modèles animaux semble indispensable. Malheureusement, la dyspnée n'apparaît pas comme un marqueur clinique fiable chez la souris et l'interprétation des signes somatiques d'anxiété ou des éléments d'observation en faveur d'une détresse respiratoire ne semblent pas réalisables [132]. Les progrès doivent donc se focaliser sur les anomalies objectives en EFR. L'évaluation des volumes pulmonaires est bien reproductible mais il faudrait développer de nouveaux outils de mesure reflétant au mieux les troubles ventilatoires obstructifs et restrictifs, en utilisant par exemple la pléthysmographie [133]. De leur côté, les muscles inspiratoires semblent difficiles à analyser chez la souris ou le rat même si des techniques d'exploration du diaphragme sont de plus en plus fiables [134].

Au niveau de la recherche clinique, la constitution d'une plus grande cohorte de patients parkinsoniens permettrait de mieux déterminer le phénotype (moteur et non-moteur) des patients souffrant de troubles ventilatoires, et de répéter les mesures spécifiques concernant la fonction diaphragmatique. Le caractère pronostique de cette atteinte musculaire doit également être précisé avec un suivi clinique et EFR sur au moins 5 ans. Concernant la dyspnée, les prochaines études devront se focaliser sur le lien entre les caractéristiques de la dyspnée (via l'échelle DYSPARK) et les données en EFR. Pour cela, au-delà des volumes pulmonaires et de l'évaluation des muscles respiratoires, la réponse à l'hypoxie serait un marqueur intéressant. Cependant, afin d'étayer l'hypothèse d'un trouble de la commande ventilatoire, d'autres outils paraissent pertinents comme l'étude de la variabilité du mode ventilatoire [135], de l'IRMf, ou même des potentiels évoqués respiratoires [136, 137]. Cette dernière technique a déjà été utilisée chez des patients atteints de syndrome d'apnées du sommeil sévère [138], mais jamais dans des pathologies neurodégénératives. Combinées aux

scores perceptif et émotionnel de la MDP, ces données aideraient à mieux comprendre les mécanismes sous-jacents à la dyspnée mais aussi à d'autres SMN dans la MP comme l'anxiété ou la douleur.

Références bibliographiques

- 1- Lajugie D, Bertin N, Chantelou ML, Vallier N, Weill A, Fender P, Allemand H. Prévalence de la maladie de Parkinson et coût pour l'Assurance maladie en 2000 en France métropolitaine. *Rev Med Ass Maladie* 2005;(2):113-22.
- 2- Moisan F, Kab S, Moutengou E, Boussac-Zerebska M, Carcaillon-Bentata L, Elbaz A. Fréquence de la maladie de Parkinson en France. Données nationales et régionales 2010-2015. Saint-Maurice : Santé publique France, 2018. 69 p.
- 3- Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384-6.
- 4- Braak H, Del Tredici K, RuÈb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003; 24(2):197-211.
- 5- Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. *Mov Disord*. 2015;30(12):1600-11. doi: 10.1002/mds.26431.
- 6- Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591-601.
- 7- Storch A, Schneider CB, Wolz M, Stürwald Y, Nebe A, Odin P, Mahler A, Fuchs G, Jost WH, Chaudhuri KR, Koch R, Reichmann H, Ebersbach G. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology*. 2013;80(9):800-9.
- 8- Chou KL, Stacy M, Simuni T, Miyasaki J, Oertel WH, Sethi K, Fernandez HH, Stocchi F. The spectrum of "off" in Parkinson's disease: What have we learned over 40 years? *Parkinsonism Relat Disord*. 2018;51:9-16.
- 9- Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. *Parkinsonism Relat Disord*. 2016;22 Suppl 1:S41-6.
- 10- Banks SJ, Bayram E, Shan G, LaBelle DR, Bluett B. Non-motor predictors of freezing of gait in Parkinson's disease. *Gait Posture*. 2018 Dec 6;68:311-316.
- 11- Bugalho P, Lampreia T, Miguel R, Mendonça MD, Caetano A, Barbosa R. Non-Motor symptoms in Portuguese Parkinson's Disease patients: correlation and impact on Quality of Life and Activities of Daily Living. *Sci Rep*. 2016;6:32267.
- 12- Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry*. 2000;69(3):308-12.
- 13- Susan HF, Lang AE, Motor and nonmotor fluctuations, *Handbook of Clinical Neurology*, Elsevier, Edinburgh-Toronto, 2007, pp. 159–184.
- 14- Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, Mitra T, Frades-Payo B, Tluk S, Ruessmann A, Odin P, Macphee G, Stocchi F, Ondo W, Sethi K, Schapira AH, Martinez Castrillo JC, Martinez-Martin P. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord*. 2010;25(6):704-9.

- 15-Gallagher DA, Goetz CG, Stebbins G, Lees AJ, Schrag A. Validation of the MDS-UPDRS part I for nonmotor symptoms in Parkinson's disease. *Mov Disord* 2012; 27: 79–83.
- 16-Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord* 2007; 22: 1901–1911.
- 17-Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Mecco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatralo R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, P.D. DottoPRIAMO study group, The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease, *Mov. Disord.* 24 (11) (2009) 1641–1649.
- 18-Yust-Katz S, Shitrit D, Melamed E, Djaldetti R, Respiratory distress: an unrecognized non-motor phenomenon in patients with parkinsonism, *J. Neural.Transm.* 119 (1) (2012) 73–76.
- 19-Bonnet AM, Jutras MF, Czernecki V, Corvol JC, Vidailhet M. Nonmotor symptoms in Parkinson's disease in 2012: relevant clinical aspects. *Parkinsons Dis*;2012:198316.
- 20-Chaudhuri KR1, Odin P, Antonini A, Martinez-Martin P. Parkinson's disease: the non-motor issues. *Parkinsonism Relat Disord.* 2011;17(10):717-23.
- 21-Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, O'Donnell DE, American thoracic society committee on dyspnea. An official American thoracic society statement: update on the mechanisms, assessment, and management of dyspnea, *Am. J. Respir. Crit. Care Med.* 185 (4) (2012) 435–452.
- 22-Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III) *J Neurol Sci.* 1999;169(1-2):13-21.
- 23-Parkinson J (2002) An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci*, 2, 223-236.
- 24-Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Chérif AA, Nonmotor fluctuations in Parkinson's disease: frequent and disabling, *Neurology* 59 (3) (2002) 408–413.
- 25-Nejjari C, Tessier JF, Baldi I, Barberger-Gateau P, Dartigues JF, Salamon R. Epidemiologic aspects of respiratory aging: contribution of the PAQUID survey, *Rev. Epidemiol. Sante Publique* 45 (5) (1997) 417–428.
- 26-Ho SF, O'Mahony MS, Steward JA, Breay P, Buchalter M, Burr ML, Dyspnoea and quality of life in olderpeople at home, *Age Ageing* 2 (2001) 155–159.
- 27-Baille G, De Jesus AM, Perez T, Devos D, Dujardin K, Monaca C, Defebvre L, Moreau C. Ventilatory dysfunction in Parkinson's disease, *J Parkinson Dis.*;6(3):463-71.
- 28-Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol.* 2009;167(1):53-60.
- 29-Laveneziana P, Similowski T, Morélot-Panzini C. Multidimensional approach to dyspnea. *Curr Opin Pulm Med.* 2015;21(2):127-32.
- 30-Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER; National Heart, Lung, and Blood Institute's Severe Asthma

- Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181(4):315-23.
- 31- Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. *N Engl J Med.* 19;333(23):1547-53.
- 32- Nishino T. Dyspnoea: underlying mechanisms and treatment. *Br J Anaesth.* 2011;106(4):463-74.
- 33- Dutschmann M, Dick TE. Pontine mechanisms of respiratory control. *Compr Physiol.* 2012;2(4):2443-69.
- 34- Pyatigorskaya N, Mongin M, Valabregue R, Yahia-Cherif L, Ewencyk C, Poupon C, Debellemanniere E, Vidailhet M, Arnulf I, Lehericy S. Medulla oblongata damage and cardiac autonomic dysfunction in Parkinson disease. *Neurology.* 2016;87(24):2540-2545.
- 35- Oliveira LM, Tuppy M, Moreira TS, Takakura AC. Role of the locus coeruleus catecholaminergic neurons in the chemosensory control of breathing in a Parkinson's disease model. *Exp Neurol.* 2017;293:172-180.
- 36- McDonald DM. Role of glomus cells as dopaminergic interneurons in the chemoreceptive function of the carotid body. *Adv Biochem Psychopharmacol.* 1977;16:265-74.
- 37- Toledo-Aral JJ, Méndez-Ferrer S, Pardal R, López-Barneo J. Dopaminergic cells of the carotid body: physiological significance and possible therapeutic applications in Parkinson's disease. *Brain Res Bull.* 2002 Apr;57(6):847-53.
- 38- Serebrovskaya T, Karaban I, Mankovskaya I, Bernardi L, Passino C, & Appenzeller O (1998) Hypoxic ventilatory responses and gas exchange in patients with Parkinson's disease. *Respiration*, 1, 28-33.
- 39- Seccombe LM, Rogers PG, Hayes MW, Farah CS, Veitch EM, & Peters MJ (2013) Reduced hypoxic sympathetic response in mild Parkinson's disease: Further evidence of early autonomic dysfunction. *Parkinsonism Relat Disord*, 11, 1066-1068.
- 40- von Leupoldt A, Dahme B. Cortical substrates for the perception of dyspnea. *Chest.* 2005;128(1):345-54.
- 41- von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, Büchel C. Dyspnea and pain share emotion-related brain network. *Neuroimage.* 2009;48(1):200-6.
- 42- Borg GA. *Med Sci Sports Exerc.* 1982;14(5):377-81. Psychophysical bases of perceived exertion.
- 43- Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax.* 1999;54(7):581-6.
- 44- Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J.* 2005;26(3):511-22.
- 45- Green M, Road J, Sieck GC, Similovski T. Tests of respiratory muscle strength. *Am J Respir Crit Care Med* 2002; 166 : 528-47.
- 46- EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)-revised report of an EFNS task force. *Eur J Neurol.* 2012;19:360-75.
- 47- Mehanna R, Jankovic J. Respiratory problems in neurologic movement disorders. *Parkinsonism Relat Disord.* 2010;16(10):628-38.
- 48- Torsney KM, Forsyth D. Respiratory dysfunction in Parkinson's disease. *J R Coll Physicians Edinb.* 2017;47(1):35-39.
- 49- Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief

- screening tool for mild cognitive impairment, *J. Am. Geriatr. Soc.* 53 (4) (2005) 695–699.
- 50- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatr.* 1988;51(6):745–52.
- 51- Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;17(5):427–42.
- 52- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189–98.
- 53- Moreau C, Devos D, Baille G, Delval A, Tard C, Perez T, Danel-Buhl N, Seguy D, Labreuche J, Duhamel A, Delliaux M, Dujardin K, Defebvre L. Are Upper-Body Axial Symptoms a Feature of Early Parkinson's Disease? *PLoS One.* 2016 Sep 21;11(9):e0162904. doi: 10.1371/journal.pone.0162904. eCollection 2016.
- 54- Owolabi LF, Nagoda M, Babashani M. Pulmonary function tests in patients with Parkinson's disease: A case-control study. *Niger J Clin Pract.* 2016;19(1):66-70.53
- 55- Zhang W, Zhang L, Zhou N, Huang E, Li Q, Wang T, Ma C, Li B, Li C, Du Y, Zhang J, Lei X, Ross A, Sun H and Zhu X (2019) Dysregulation of Respiratory Center Drive (P0.1) and Muscle Strength in Patients With Early Stage Idiopathic Parkinson's Disease. *Front. Neurol.* 10:724. doi: 10.3389/fneur.2019.00724
- 56- Baille G, Perez T, Devos D, Deken V, Defebvre L, Moreau C. Early occurrence of inspiratory muscle weakness in Parkinson's disease. *PLoS One.* 2018 Jan 12;13(1):e0190400. doi: 10.1371/journal.pone.0190400. eCollection 2018.
- 57- Hampson NB, Kiebertz KD, LeWitt PA, Leinonen M, Freed MI. Prospective evaluation of pulmonary function in Parkinson's disease patients with motor fluctuations. *Int J Neurosci.* 2017;127(3):276-284.
- 58- Tambasco N, Murgia N, Nigro P, Paoletti FP, Romoli M, Brahimi E, Filidei M, Simoni S, Muzi G, Calabresi P. Levodopa-responsive breathing discomfort in Parkinson's disease patients. *J Neural Transm (Vienna).* 2018;125(7):1033-1036.
- 59- Torsney KM, Forsyth D. Respiratory dysfunction in Parkinson's disease. *J R Coll Physicians Edinb.* 2017;47(1):35-39.
- 60- Sabaté M, González I, Ruperez F, Rodríguez M. Obstructive and restrictive pulmonary dysfunctions in Parkinson's disease. *J Neurol Sci.* 1996;138(1-2):114-9.
- 61- Florêncio RB1, da Nobrega AJS, Lima ÍNDF, Gualdi LP, Cabral EE, Fagundes MLLC, Aliverti A, Resqueti VR, Fregonezi GAF. Chest wall volume and asynchrony in stroke and Parkinson's disease subjects: A case-control study. *PLoS One.* 2019 May 16;14(5):e0216641.
- 62- Berdal G, Halvorsen S, van der Heijde D, Mowe M, Dagfinrud H. Restrictive pulmonary function is more prevalent in patients with ankylosing spondylitis than in matched population controls and is associated with impaired spinal mobility: a comparative study. *Arthritis Res Ther.* 2012;14(1):R19.
- 63- Layachi L, Georges M, Gonzalez-Bermejo J, Brun AL, Similowski T, Morélot-Panzini C Diaphragm pacing failure secondary to deteriorated chest wall mechanics: When a good diaphragm does not suffice to take a good breath in. *Respir Med Case Rep.* 2015;15:20-3.
- 64- Tzelepis GE. Chest Wall Diseases: Respiratory Pathophysiology. *Clin Chest Med.* 2018;39(2):281-296.
- 65- de Bruin PF, de Bruin VM, Lees AJ, Pride NB. Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis.* 1993;148(6 Pt 1):1576-80.

- 66- Izquierdo-Alonso JL, Jiménez-Jiménez FJ, Cabrera-Valdivia F, Mansilla-Lesmes M. Airway dysfunction in patients with Parkinson's disease. *Lung*. 1994;172(1):47-55.
- 67- Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med*. 1984 Aug 16;311(7):438-42.
- 68- Dawson TM, Golde TE, Lagier-Tourenne C. Animal models of neurodegenerative diseases. *Nat Neurosci*. 2018;21(10):1370-1379.
- 69- Konnova EA, Swanberg M. Animal Models of Parkinson's Disease. Editors In: Stoker TB, Greenland JC, editors. *Source Parkinson's Disease: Pathogenesis and Clinical Aspects* [Internet]. Brisbane (AU): Codon Publications; 2018. Chapter 5.
- 70- De Campos PS, Hasegawa K, Kumei Y, Zeredo JL. Cineradiographic analysis of respiratory movements in a mouse model for early Parkinson's disease. *Respir Physiol Neurobiol*. 2015;218:40-5.
- 71- De Campos PS, Kawamura LRS, Hasegawa K, Kumei Y, Zeredo JL. Analysis of respiratory movements in a mouse model of late Parkinson's disease submitted to stress. *Respir Physiol Neurobiol*. 2018;251:50-56.
- 72- Oliveira LM, Oliveira MA, Moriya HT, Moreira TS, Takakura AC. Respiratory disturbances in a mouse model of Parkinson's disease. *Exp Physiol*. 2019 Feb 13. doi: 10.1113/EP087507. [Epub ahead of print]
- 73- Nakamura K, Mori F, Tanji K, Miki Y, Toyoshima Y, Kakita A, Takahashi H, Yamada M, Wakabayashi K. α -Synuclein pathology in the cranial and spinal nerves in Lewy body disease. *Neuropathology*. 2016;36(3):262-9.
- 74- Mu L, Sobotka S, Chen J, Su H, Sanders I, Adler CH, Shill HA, Caviness JN, Samanta JE, Beach TG; Arizona Parkinson's Disease Consortium. Alpha-synuclein pathology and axonal degeneration of the peripheral motor nerves innervating pharyngeal muscles in Parkinson disease. *J Neuropathol Exp Neurol*. 2013;72(2):119-29.
- 75- Andrzejewski K, Budzińska K, Kaczyńska K. Effect of 6-OHDA on hypercapnic ventilatory response in the rat model of Parkinson's disease. *Physiol Res*. 2019 Jan 10. [Epub ahead of print].
- 76- Oliveira LM, Falchetto B, Moreira TS, Takakura AC. Orexinergic neurons are involved in the chemosensory control of breathing during the dark phase in a Parkinson's disease model. *Exp Neurol*. 2018;309:107-118.
- 77- Andrzejewski K, Budzińska K, Zaremba M, Kaczyńska K. Hypoxic ventilatory response after dopamine D2 receptor blockade in unilateral rat model of Parkinson's disease. *Neuroscience*. 2016;316:192-200.
- 78- Secombe LM, Giddings HL, Rogers PG, Corbett AJ, Hayes MW, Peters MJ, Veitch EM. Abnormal ventilatory control in Parkinson's disease--further evidence for non-motor dysfunction. *Respir Physiol Neurobiol*. 2011 Dec;179(2-3):300-4.
- 79- Onodera H, Okabe S, Kikuchi Y, Tsuda T, Itoyama Y. Impaired chemosensitivity and perception of dyspnoea in Parkinson's disease. *Lancet*. 2000;356(9231):739-40.
- 80- Serebrovs'ka TV, Kolesnikova IeE, Karaban' IM. Respiratory regulation during adaptation to intermittent hypoxia in patients with Parkinson disease. *Fiziol Zh*. 2003;49(3):95-103.
- 81- Wakai J, Takayama A, Yokoyama T, Nakamuta N, Kusakabe T, Yamamoto Y. Immunohistochemical localization of dopamine D2 receptor in the rat carotid body. *Acta Histochem*. 2015;117(8):784-9.
- 82- Orimo S, Suzuki M, Inaba A, Mizusawa H. 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 2012;18:494-500.

- 83-Joy SP, Sinha S, Pal PK, Panda S, Philip M, Taly AB. Alterations in Polysomnographic (PSG) profile in drug-naïve Parkinson's disease. *Ann Indian Acad Neurol.* 2014;17(3):287-91.
- 84-Pyatigorskaya N, Mongin M, Valabregue R, Yahia-Cherif L, Ewencyk C, Poupon C, Debellemanniere E, Vidailhet M, Arnulf I, Lehericy S. Medulla oblongata damage and cardiac autonomic dysfunction in Parkinson disease. *Neurology.* 2016;87(24):2540-2545.
- 85-Seidel K, Mahlke J, Siswanto S, Krüger R, Heinsen H, Auburger G, Bouzrou M, Grinberg LT, Wicht H, Korf HW, den Dunnen W, Rüb U. The brainstem pathologies of Parkinson's disease and dementia with Lewy bodies. *Brain Pathol.* 2015;25(2):121-35.
- 86-Dutschmann M, Dick TE. Pontine mechanisms of respiratory control. *Compr Physiol.* 2012;2(4):2443-69.
- 87-Anderson TM, Garcia AJ, Baertsch NA, Pollak J, Bloom JC, Wei AD, Rai KG, Ramirez JM. A novel excitatory network for the control of breathing. *Nature.* 2016;536(7614):76-80.
- 88-Barnett WH, Jenkin SEM, Milsom WK, Paton JFR, Abdala AP, Molkov YI, Zoccal DB. The Kölliker-Fuse nucleus orchestrates the timing of expiratory abdominal nerve bursting. *J Neurophysiol.* 2018;119(2):401-412.
- 89-Yokota S, Niu JG, Tsumori T, Oka T, Yasui Y. Glutamatergic Kölliker-Fuse nucleus neurons innervate hypoglossal motoneurons whose axons form the medial (protruder) branch of the hypoglossal nerve in the rat. *Brain Res.* 2011;1404:10-20.
- 90-Wang CM, Shieh WY, Ho CS, Hu YW, Wu YR. Home-Based Orolingual Exercise Improves the Coordination of Swallowing and Respiration in Early Parkinson Disease: A Quasi-Experimental Before-and-After Exercise Program Study. *Front Neurol.* 2018;9:624.
- 91-Andrzejewski K, Budzińska K, Kaczyńska K. Phrenic and hypoglossal nerve activity during respiratory response to hypoxia in 6-OHDA unilateral model of Parkinson's disease. *Life Sci.* 2017;180:143-150.
- 92-Zhou L, Wang ZY, Lian H, Song HY, Zhang YM, Zhang XL, Fan RF, Zheng LF, Zhu JX. Altered expression of dopamine receptors in cholinergic motoneurons of the hypoglossal nucleus in a 6-OHDA-induced Parkinson's disease rat model. *Biochem Biophys Res Commun.* 2014;452(3):560-6.
- 93-Kompelli AR, Ni JS, Nguyen SA, Lentsch EJ, Neskey DM, Meyer TA. The outcomes of hypoglossal nerve stimulation in the management of OSA: A systematic review and meta-analysis. *World J Otorhinolaryngol Head Neck Surg.* 2018;5(1):41-48.
- 94-Schwartz AR, Thut DC, Russ B, Seelagy M, Yuan X, Brower RG, Permutt S, Wise RA, Smith PL. Effect of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis.* 1993;147(5):1144-50.
- 95-Lee SY, Chen MH, Chiang PL, Chen HL, Chou KH, Chen YC, Yu CC, Tsai NW, Li SH, Lu CH, Lin WC. Reduced gray matter volume and respiratory dysfunction in Parkinson's disease: a voxel-based morphometry study. *BMC Neurol.* 2018;18(1):73.
- 96-Evans KC. Cortico-limbic circuitry and the airways: insights from functional neuroimaging of respiratory afferents and efferents. *Biol Psychol.* 2010;84(1):13-25.
- 97-Lacuey N, Hampson JP, Harper RM, Miller JP, Lhatoo S. Limbic and paralimbic structures driving ictal central apnea. *Neurology.* 2019;92(7):e655-e669.
- 98-Benarroch EE. The central autonomic network: functional organization, dysfunction, and perspective. *Mayo Clin Proc.* 1993;68(10):988-1001.

- 99-Beissner F, Meissner K, Bär KJ, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J Neurosci.* 2013;33(25):10503-11.
- 100- Margraf NG, Wrede A, Deuschl G, Schulz-Schaeffer WJ. Pathophysiological Concepts and Treatment of Camptocormia. *J Parkinsons Dis.* 2016; 6(3): 485–501.
- 101- Margraf NG, Wrede A, Rohr A, Schulz-Schaeffer WJ, Raethjen J, Eymess A, Volkmann J, Mehdorn MH, Jansen O, Deuschl G. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. *Mov Disord.* 2010;25(5):542-51.
- 102- Srivannitchapoom P, Hallett M. Camptocormia in Parkinson's disease: definition, epidemiology, pathogenesis and treatment modalities. *J Neurol Neurosurg Psychiatry.* 2016;87(1):75-85.
- 103- Witting N, Andersen LK, Vissing J. Axial myopathy: an overlooked feature of muscle diseases. *Brain.* 2016;139(Pt 1):13-22.
- 104- Olanow CW. The pathogenesis of cell death in Parkinson's disease. *Mov Disord.* 2007 Sep;22 Suppl 17:S335-42.
- 105- Snyder B, Shell B, Cunningham JT, Cunningham RL. Chronic intermittent hypoxia induces oxidative stress and inflammation in brain regions associated with early-stage neurodegeneration. *Physiol Rep.* 2017;5(9).
- 106- Gama RL, Távora DG, Bomfim RC, Silva CE, de Bruin VM, de Bruin PF. Sleep disturbances and brain MRI morphometry in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy - a comparative study. *Parkinsonism Relat Disord.* 2010;16(4):275-9.
- 107- Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y, Takahashi F, Hattori N, Tabira T, Mochizuki H, Takahashi K. Chronic intermittent hypoxia/reoxygenation facilitate amyloid- β generation in mice. *J Alzheimers Dis.* 2013;37(2):325-33.
- 108- Liu H, Qiu H, Yang J, Ni J, Le W. Chronic hypoxia facilitates Alzheimer's disease through demethylation of γ -secretase by downregulating DNA methyltransferase 3b. *Alzheimers Dement.* 2016;12(2):130-143.
- 109- Menal MJ, Jorba I, Torres M, Montserrat JM, Gozal D, Colell A, Piñol-Ripoll G, Navajas D, Almendros I, Farré R. Alzheimer's Disease Mutant Mice Exhibit Reduced Brain Tissue Stiffness Compared to Wild-type Mice in both Normoxia and following Intermittent Hypoxia Mimicking Sleep Apnea. *Front Neurol.* 2018;9:1.
- 110- Troussière AC, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, Pasquier F, Bombois S. Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2014;85(12):1405-8.
- 111- Kim SM, Kim H, Lee JS, Park KS, Jeon GS, Shon J, Ahn SW, Kim SH, Lee KM, Sung JJ, Lee KW. Intermittent hypoxia can aggravate motor neuronal loss and cognitive dysfunction in ALS mice. *PLoS One.* 2013;8(11):e81808.
- 112- Viallet F, Teston B. La dysarthrie dans la maladie de Parkinson. P. Auzou. *Les Dysarthries, SOLAL*, pp.169-174, 2007.
- 113- Hammer MJ. Aerodynamic assessment of phonatory onset in Parkinson's disease: evidence of decreased scaling of laryngeal and respiratory control. *J Parkinsons Dis.* 2013;3(2):173-9.
- 114- Hegland KW, Troche M, Brandimore A. Relationship Between Respiratory Sensory Perception, Speech, and Swallow in Parkinson's Disease. *Mov Disord Clin Pract.* 2019;6(3):243-249.

- 115- Wang CM, Shieh WY, Weng YH, Hsu YH, Wu YR. Non-invasive assessment determine the swallowing and respiration dysfunction in early Parkinson's disease. *Parkinsonism Relat Disord.* 2017;42:22-27.
- 116- Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease. *Dysphagia.* 2011;26(3):218-24.
- 117- Pitts T, Bolser D, Rosenbek J, Troche M, Sapienza C. Voluntary cough production and swallow dysfunction in Parkinson's disease. *Dysphagia.* 2008;23(3):297-301.
- 118- Troche MS, Okun MS, Rosenbek JC, Musson N, Fernandez HH, Rodriguez R, Romrell J, Pitts T, Wheeler-Hegland KM, Sapienza CM. Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: a randomized trial. *Neurology.* 2010;75(21):1912-9.
- 119- Baille G, Chenivresse C, Perez T, Machuron F, Dujardin K, Devos D, Defebvre L, Moreau C. Dyspnea: An underestimated symptom in Parkinson's disease. *Parkinsonism Relat Disord.* 2019;60:162-166.
- 120- Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, Poewe X, Sampaio C, Stern MB, Dodel R, Dubois B, Holloway R, Jankovic J, Kulisevsky J, Lang AE, Lees A, Leurgans S, LeWitt PA, Nyenhuis D, Olanow CW, Rascol O, Schrag A, Teresi JA, van Hilten JJ, LaPelle N. Movement disorder society UPDRS revision task force. Movement disorder society sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, *Mov. Disord.* 23 (15) (2008) 2129–2170.
- 121- Banzett RB, O'Donnell CR, Guilfoyle TE, Parshall MB, Schwartzstein RM, Meek PM, Gracely RH, Lansing RW. Multidimensional Dyspnea Profile: an instrument for clinical and laboratory research. *Eur Respir J.* 2015 ;45(6):1681-91.
- 122- Morélot-Panzini C, Gilet H, Aguilaniu B, Devillier P, Didier A, Perez T, Pignier C, Arnould B, Similowski T. Real-life assessment of the multidimensional nature of dyspnoea in COPD outpatients. *Eur Respir J.* 2016 Jun;47(6):1668-79.
- 123- Morélot-Panzini C, Perez T, Sedkaoui K, de Bock E, Aguilaniu B, Devillier P, Pignier C, Arnould B, Bruneteau G, Similowski T. The multidimensional nature of dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: Air hunger, anxiety and fear. *Respir Med.* 2018;145:1-7.
- 124- Stevens JP, Sheridan A, Bernstein H, Baker K, Lansing R, Schwartzstein RM, Banzett RB. A Multidimensional Profile of Dyspnea in Hospitalized Patients. *Chest.* 2019 May 22.
- 125- Leentjens AFG, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, & Starkstein SE (2012) Anxiety and motor fluctuations in Parkinson's disease: A cross-sectional observational study. *Parkinsonism Relat Disord,* 10, 1084–1088.
- 126- Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. *Mov Disord.* 2011;26(3):484-92.
- 127- Leander M, Lampa E, Rask-Andersen A, Franklin K, Gislason T, Oudin A, Svanes C, Torén K, Janson C. Impact of anxiety and depression on respiratory symptoms. *Respir Med.* 2014;108(11):1594-600.
- 128- von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, Büchel C. Dyspnea and pain share emotion-related brain network. *Neuroimage.* 2009;48(1):200-6.
- 129- Rice JE, Antic R, & Thompson PD (2002) Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease. *Mov Disord,* 3, 524-527.

- 130- Stoeckel MC, Esser RW, Gamer M1, Büchel C, von Leupoldt A. Dyspnea catastrophizing and neural activations during the anticipation and perception of dyspnea. *Psychophysiology*. 2018;55(4).
- 131- Palermo S, Lopiano L, Morese R, Zibetti M, Romagnolo A, Stanziano M, Rizzone MG, Geminiani GC, Valentini MC, Amanzio M. Role of the Cingulate Cortex in Dyskinesias-Reduced-Self-Awareness: An fMRI Study on Parkinson's Disease Patients. *Front Psychol*. 2018;9:1765.
- 132- Burki NK, Lee LY. Mechanisms of dyspnea. *Chest*. 2010 Nov;138(5):1196-201.
- 133- Mailhot-Larouche S, Deschênes L, Lortie K, Gazzola M, Marsolais D, Brunet D, Robichaud A, Bossé Y. Assessment of Respiratory Function in Conscious Mice by Double-chamber Plethysmography. *J Vis Exp*. 2018; (137): 57778.
- 134- Martin M, Li K, Wright MC, Lepore AC. Functional and morphological assessment of diaphragm innervation by phrenic motor neurons. *J Vis Exp*. 2015;(99):e52605.
- 135- Jaworski J, Bates JHT. Sources of breathing pattern variability in the respiratory feedback control loop. *J Theor Biol*. 2019;469:148-162.
- 136- Chan PY, Davenport PW. Respiratory related evoked potential measures of cerebral cortical respiratory information processing. *Biol Psychol*. 2010;84(1):4-12.
- 137- von Leupoldt A, Chan PY, Esser RW, Davenport PW. Emotions and neural processing of respiratory sensations investigated with respiratory-related evoked potentials. *Psychosom Med*. 2013;75(3):244-52.
- 138- Donzel-Raynaud C, Redolfi S, Arnulf I, Similowski T, Straus C. Abnormal respiratory-related evoked potentials in untreated awake patients with severe obstructive sleep apnoea syndrome. *Clin Physiol Funct Imaging*. 2009;29(1):10-7.

AUTEUR : Nom : Baille

Prénom : Guillaume

Date de soutenance : 14 octobre 2019

Titre de la thèse : Atteinte ventilatoire dans la maladie de Parkinson : du symptôme à l'atteinte objective

Mots-clés : maladie de Parkinson, troubles ventilatoires, dyspnée, explorations fonctionnelles respiratoires, signes axiaux, signes non-moteurs.

La maladie de Parkinson (MP) est la deuxième maladie neurodégénérative la plus fréquente. Parmi les nombreux signes cliniques rapportés par les patients et observés par les médecins, les manifestations respiratoires sont encore très peu étudiées.

Premièrement, la dyspnée, signe fonctionnel invalidant et altérant la qualité de vie, semble fréquente dans la MP mais sa prévalence et ses caractéristiques (dimension perceptive et réponse émotionnelle notamment) doivent être précisées. L'objectif de l'étude DYSPARK était de mieux définir le profil des patients dyspnéiques, le retentissement de la plainte respiratoire et de corrélérer ses caractéristiques avec des éléments cliniques de la MP afin de mieux appréhender sa physiopathologie.

Deuxièmement, les anomalies ventilatoires objectives (explorations fonctionnelles respiratoires - EFR) sont encore mal connues dans la MP, de même que leur évolution. Une altération des volumes pulmonaires ou une atteinte de la musculature respiratoire pourraient avoir un retentissement sur le cours évolutif de la maladie. L'objectif de l'analyse d'une sous-population de la cohorte PRODIGY-PARK était de déterminer de façon prospective, sur 5 ans, le cours évolutif des données en EFR et leur impact pronostique potentiel.

Composition du jury :

Présidente : Madame le Professeur Cécile Chenivresse

Rapporteurs : Madame le Professeur Capucine Morélot-Panzini, Monsieur le Professeur David Maltete

Examineur : Madame le Docteur Christine Brefel-Courbon

Directeurs de recherche : Monsieur le Professeur Luc Defebvre, Madame le Professeur Caroline Moreau