Autonomic (dys)function in patients with chronic obstructive pulmonary disease

Evidence and non-pharmacological interventions

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Table of content

"What really counts are good endings not flawed beginnings"

Ibn Taymiyyah

Abbreviations

A

Ach	Acetylcholine
AET	Aerobic exercise training
ANS	Autonomic nervous system
ApEn	Approximate entropy
ASP	Autonomic symptom profile
ATS	American thoracic society

B

BMI	Body mass index
BODE	BMI, airflow obstruction, dyspnea and exercise capacity
BRS	Baroreceptor sensitivity

C

CASS	Composite autonomic scoring scale
CIS	Checklist individual strength
CL	Cycle length
CNS	Central nervous system
cPNA	Cardiac parasympathetic nerve activity
cSNA	Cardiac sympathetic nerve activity
CO	Cardiac output
COMPASS	Composite autonomic symptoms score
CON	Control group
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CVRR	Coefficient of variation of R-R

D

DB	Deep breathing
DBP	Diastolic blood pressure

E

ERS	European respiratory society
ECG	Electro cardiograph

F

FEV_1	Forced expiratory volume in first second
FEF	Forced expiratory flow
FEV_1/FVC	Tiffeneau index
FFM	Fat free mass
FIF	Forced inspiratory flow
FVC	Forced vital capacity
FRC	Functional residual capacity

G

GI	Gastro intestinal
GOLD	Global initiative for obstructive lung disease
GRADE	Grading of recommendations, assessment development and evaluation

H

HADS	Hospital anxiety and depression scale
MeSH	Medical subject heading
HF	High frequency power (0.15-0.4Hz)
HFnu	High frequency normalized units
HR_{DB}	Heart rate during deep breathing
HRmax	Maximum heart rate
HRR	Heart rate recovery
HRV	Heart rate variability

I

ICS	Inhaled corticosteroids
IL-6	Inter-Lukens 6

L

LABA	Long acting beta agonists
LAMA	Long acting muscarinic antagonist
LF	Low frequency power (0.04-0.15Hz)
LFnu	Low frequency power normalized units
LOI	Line of identity

M

MCS	Mental component summary (of SF-36)
MEP	Maximal expiratory pressure
MIBG	Metaiodobenzylguanidine
MIP	Maximal inspiratory pressure
mMRC	Modified medical research council
MSNA	Muscle sympathetic nerve activity

N

NE	Norepinephrine
NIMV	Non-invasive mechanical ventilation
NN50	Low frequency normalized units

O

OH	Orthostatic hypotension

P

PaO_2	Arterial oxygen tension
$PaCO_2$	Arterial carbon dioxide tension
PCS	Physical component summary (of SF-36)
PEF	Peak expiratory flow rate
pNN50	Portion of N-N, differing more than 50 milliseconds
POTS	Postural orthostatic tachycardia syndrome
PP Drop	Pulse pressure drop
PRISMA	Preferred reporting items for systematic reviews and meta analyses
PRT	Pressure recovery time
PSD	Power spectral density

Q

QoL	Quality of life

R

R- SAM	Respiratory sinus arrhythmia maneuver
RCT	Randomized control trial
RMSSD	Root mean square successive differences
RRI	Heart rate interval
RTF	Range to fault calibration
RV	Residual volume

S

SAD	Small airway disease
SampEn	Sample entropy
SBP	Systolic blood pressure
SD1	Dispersion of points (standard deviation) perpendicular to the axis of line-of-identity
SD2	Dispersion of points (standard deviation) along the axis of line-of-identity
SDANN	Standard deviation of the averages of N-N
SDNN	Standard deviation of NN intervals
SDNNi	Standard deviation of NN intervals for 5 minutes segments
SF-36	36-Item short form questionnaire
SI3	Sympathetic index
sNN50	Sum of N-N, differing more than 50 milliseconds
SSR	Sympathetic skin response
SV	Stroke volume

T

TINN	Triangular interpolation of NN interval
TLC	Total lung capacity
TNF	Tumor necrosis factor

U

ULF	Ultra low frequency

V

VC	Vital capacity
VO_2-peak	Peak oxygen consumption
VLF	Power in very low frequency range, ≤0.04Hz

W

WHO	World health organization
Wmax	Maximum work rate

Outline and scope of the dissertation

This dissertation comprises 7 chapters divided in 3 parts, and a general discussion. Part I is the general introduction, which consists of 3 chapters. The first chapter offers a general overview (definition, burden, features, pathogenesis, assessment, classification and management options) of COPD (Chapter 1). This chapter is written to show COPD as a complicated, under-diagnosed and under-recognized disorder that affects a significant proportion of the global population. The second chapter is dedicated to the autonomic nervous system (ANS). The introducing aspects presented a physiological overview of the ANS: divisions, structure and function. Thereafter, a detailed account of various means of assessing the integrity and/or anomalies in the ANS was presented (Chapter 2). These assessment techniques included both subjective (symptoms assessment) and objective measures (autonomic function test parameters) that are capable of evaluating autonomic dysfunction or dysautonomia. The third and concluding chapter of the general introduction describes the link between autonomic function and the disease of COPD by means of a systematic review (Chapter 3). The major aim of this chapter is to establish the evidence to support the impairment of the autonomic function, and it's major influencing factors, in patients with COPD in the existing literature.

PART II presents the original research studies in this dissertation. These studies were aimed at assesses dysautonomia in COPD using different means with the objective of answering two research questions:

(i) what is the profile of autonomic symptoms that are present in patients with stable COPD, and what are the contributing factors?

(ii) are autonomic function and autonomic reactivity test parameters impaired among physically active patients with COPD?

To answer these questions, two separate studies were conducted. The first study reports on autonomic symptoms in COPD. In this study, the 31-item composite autonomic symptoms score (COMPASS-31) questionnaire along with other important patient outcomes were examined to provide an overview of autonomic symptoms in COPD (Chapter 4). The second original research is a laboratory study that reports on the autonomic function and autonomic reactivity tests in a subgroup of COPD patients in rehabilitation (Chapter 5).

In the third and final part of this dissertation (Part III), we sought to answer the question, "is there evidence to support the effect of non-pharmacological interventions on the autonomic function in COPD?". To achieve this, we systematically reviewed the available studies in literature that have reported on diverse non-pharmacological interventions for autonomic function modulation in COPD. Here, two systematic reviews were conducted. The first systematic review focused on the effect of respiratory rehabilitation techniques such as oxygen therapy,

noninvasive ventilation (NIV) and controlled breathing on the autonomic function in COPD (Chapter 6). The second systematic review investigated the efficacy of aerobic exercise training in modulating autonomic function indices in COPD (Chapter 7).

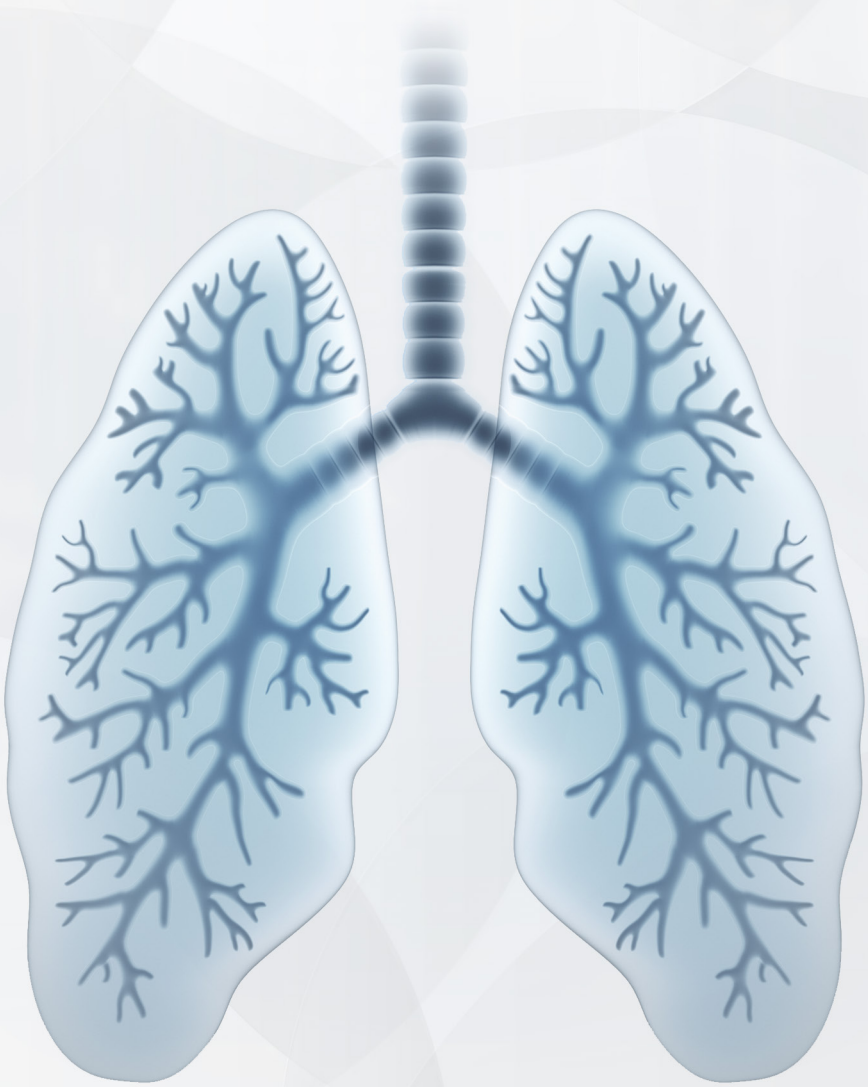
In the concluding segments of this dissertation, a general discussion comprising the main findings, validation of the Dutch COMPASS-31 in COPD, clinical implications, strengths and limitations, directions for future research, is provided. Thereafter, a general conclusion based on the results of the entire research ensued.

"The complexities of life situations are really not as complicated as we tend to experience them"

Chogyam Trungpa

Part I

General Introduction



Chapter 1

Overview of chronic obstructive pulmonary disease (COPD)

1. Definition and description

Chronic obstructive pulmonary disease (COPD) refers to a diverse clinical disorder of the pulmonary system that ranges from chronic bronchitis to lung emphysema (1, 2). The disease is mainly characterized by an airflow limitation that is usually progressive, and associated with abnormal chronic airway inflammatory responses of the lungs to noxious particles or gases (3-5). COPD is complex, heterogeneous, and it is a significant contributor to the morbidity and mortality rates in the world (6, 7).

A recent definition of COPD describes it as a preventable and treatable disease that is characterized by persistent respiratory symptoms such as dyspnea, chronic cough and excessive sputum production, as well as an airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (8). COPD also has a multi-component aspect that is characterized by structural and functional changes, both within and outside the lungs. These components operate in a complex and interdependent manner that has been described as a 'vicious cycle', typically involving factors such as mucus hypersecretion and accumulation in the airways, bacterial colonization, ciliary damage, neutrophil activation, release of inflammatory mediators, tissue damage and systemic effects [Figure 1] (9).

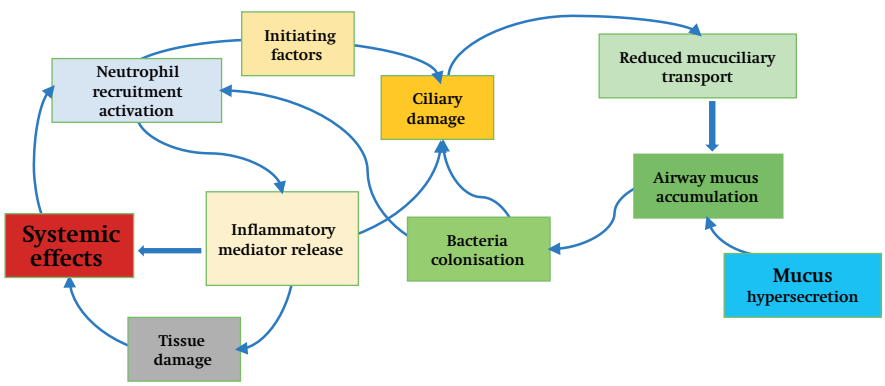


Figure 1 A schematic representation of the multi-component aspects of COPD (9).

2. Burden

COPD continually induce a substantial economic and social burden worldwide. The prevalence, morbidity and mortality of COPD is also known to vary across countries and even across different groups within countries (8). The data regarding

the prevalence of COPD has a wide variation due to differences in survey methods. Nevertheless, the lowest estimates from these surveys (spirometry alone) puts the prevalence rate of COPD among adults at about <6%. However, higher prevalence (up to 11.6 %) are often reported among older adults that are 55 years and above (10). With over 3 million deaths per year, COPD is currently the third leading cause of death worldwide, and it remains a significant global health problem (11-13).

COPD is projected to cause over 4.5 million deaths per year by the year 2030, partly due to the increasing prevalence of cigarette smoking, and also the high proportion of an ageing population across the world (8, 14). Currently, COPD accounts for about 10% of all hospitalizations, thereby causing a significant socioeconomic burden to individuals and health systems (15). The progression of COPD is further complicated by individual variation from patient-to-patient, which makes identification and treatment challenging (16, 17). Consequently, there are no accurate data for some aspects of COPD such as incidence and mortality, as current estimates are mainly based upon administrative health data or hospital records (18).

According to the 2017 report of the global strategy for the diagnosis, management, and prevention of COPD, the total direct costs associated with COPD in the European Union (EU) is estimated to be around 38.6 billion Euros. This represents about 6% of the total health care budget of the EU (8). More importantly, these costs were mainly incurred from hospitalizations following COPD exacerbations, and the use of devices such as ambulatory oxygen (8). In addition, the management of coexisting COPD comorbidities such as hypertension and diabetes mellitus equally accounts for a significant proportion of these costs.

3. Common features and risk factors

Most COPD patients are elderly (19) and those with severe COPD have low quality of life (QoL), and a limited life expectancy compared to their healthy counterparts (20). Consequently, it is not unusual to find COPD patients presenting with high rates of depression (21-23), anxiety (21-23), fatigue (24, 25), dyspnea (26) and a largely poor health status. COPD patients have poor muscle function especially in the lower limbs, which is also implicated in the exercise intolerance and poor exercise capacity in these patients (27). In the majority of COPD patients, there is a decrease in muscle strength of about 20-30% and a concomitant decrease in muscle mass in some patients, due to disuse-related muscle atrophy (27).

The major risk factors for COPD are cigarette (tobacco) smoking, outdoor and indoor pollution and physical inactivity (28). Cigarette (tobacco) smoking is primarily an important etiological factor in COPD because it constitutes over 90% of COPD etiology (8, 29). Tobacco smoking is associated with the decline of the

pulmonary function, and it is implicated in the majority of the inflammatory changes that occur in the airways of patients with COPD (30). Smoking is also associated with an increase in sympathetic activity through its action in (i) reducing the baseline levels of the vagal-cardiac nerve activity, and (ii) altering the vagally mediated arterial baroreceptor-cardiac reflex responses (31). Adequate understanding of the functioning of the ANS in COPD may help to further predict and identify important aspects to COPD prognostication and management. Presently, a host of diverse factors such as disease severity (32), exacerbations (33), lung function and respiratory parameters (34-38), physical activity levels (39) and presence or absence of disease comorbidities have been documented to influence important patient outcomes in COPD.

4. Pathophysiology

COPD is a consequence of a complex interplay of several factors including genetic features (α_1- antitrypsin deficiency), environmental predisposition and impaired lung development. Several genetic predisposing factors have been identified to play an important role in the pathogenesis of COPD (40). The best investigated among these are the genetic variants in the alpha-1 antitrypsin (AAT) gene serpin peptidase inhibitor, clade A, member 1 (*SERPINA1*), which is responsible for about 1-2% of COPD prevalence (40, 41).

Systemic inflammation and chronic airway hyper inflammation are the most important aspects to the pathogenesis of COPD. Inflammation persists throughout the course of COPD, is also associated with the level of airway obstruction and prognosis to therapy (42). COPD is referred to as a, "chronic systemic inflammatory syndrome" because of the numerous inflammatory biomarkers that have been found to be prevalent in persons with the disease (43). Some of the circulating inflammatory biomarkers that are often increased and frequently used for establishing a diagnosis of COPD include white blood cells, fibrinogen, C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (44, 45). The amount of these inflammatory biomarkers is affected during exacerbations, exercise training and use of medication (46).

Abnormal inflammatory responses in COPD are a consequence of the interplay between several mechanisms that occur during the pathogenesis of the disease. Fabbri *et al.,* (2008) described how these inflammatory markers are associated with the severity of COPD and are a major contributor in the development of disease comorbidities such as cardiovascular diseases, diabetes mellitus, muscular dysfunction and osteoporosis (43, 47) [Figure 2].

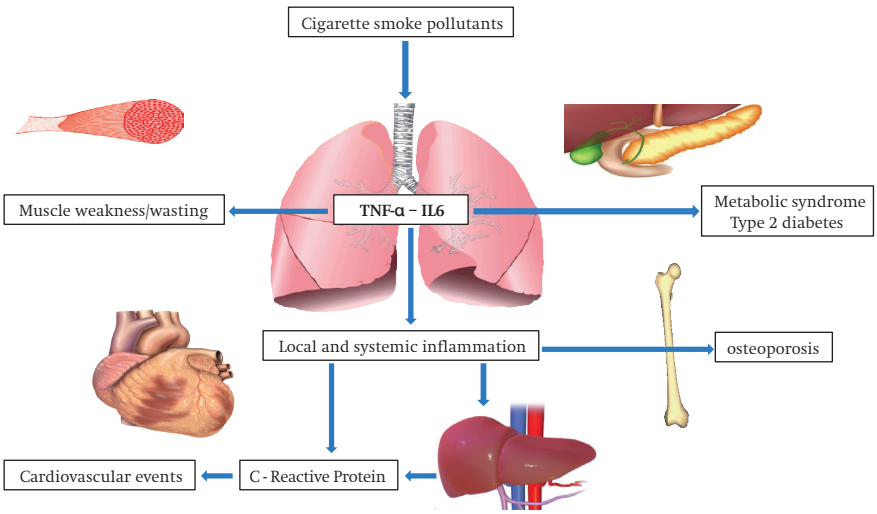


Figure 2 A schematic representation of the inflammatory processes in COPD and how it relates to other organs (43).

Table 1 Inflammatory markers in COPD and non-COPD individuals. Adapted from (29).

	CD45	CD3	Neutr	EOS	Mast	CD25	CD68	ELAM-1
Severe COPD	_	↓	↑	→	→	_	↑	_
Mild/ moderate COPD	↑	↑→	↑	→	→	↑→	↑→	↑
Control smokers	→	→↑	→	→	→	→	→	→
Control non-smokers	→	→	→	→	→	→	→	→

Notes: ↑, significantly increased values in comparison with that indicated by →; →, basal values or values non-significantly changed; ↓, significantly decreased values in comparison with that indicated by →. Similar numbers indicate results from the same study comparisons. ELAM-1, endothelial adhesion molecule-1; NK, natural killer; NF-κB, nuclear factor-kappa B; STAT-4, signal transducer and activators of transcription; MPO, myeloperoxidase; NT, nitro tyrosine.

4.1 Cellular and molecular aspects

A number of cells (both inflammatory and structural) play a significant role as inflammatory agents or mediators in COPD pathogenesis (48). They include macrophages, epithelial cells, dendritic cells, neutrophils, eosinophils and T and B lymphocytes. Precisely, these cells along with other genetic and epigenetic factors contribute to the amplification of inflammation in COPD.

Furthermore, they are also implicated in the marked proliferation in oxidant and antioxidant imbalance in patients with COPD, consequently leading to oxidative stress (49, 50). Oxidative stress in turn causes DNA damage and generation of antibodies, which often results in an increased ageing process, formation of cancerous cells, steroid resistance, emphysema and fibrosis in addition to the amplified inflammation in COPD (48).

In a review, Di Stefano *et al.* in 2005 provided a profile of inflammatory cells in the submucosa of three different COPD stages (mild, moderate & severe) and two control groups (smokers and non-smokers) [Table 1]. They found COPD to be associated with an increase in several inflammatory cells in the blood.

4.2 Pathogenesis

The pathogenesis of COPD usually starts from exposure to noxious substances such as tobacco smoke. The inhalation of these noxious particles causes inflammation, which results in the release of chemical mediators like TNF-alpha, interleukin 8, and leukotriene B_4. The continuous release of these mediators (abnormal inflammatory response) leads to a damage of the airways, pulmonary vasculature and lung

CD8	TGF-b	NK	CD4	CCR5-CD3	NF-kB (P65)	IFN-y	STAT-4	MPO	NT
↓	_	↑	→	↓	_	_	_	↑	↑
↑→	↑	→	→	→	↑	↑	↑	→	→
↑→	↑	→	→	→	↑	→	→	→	→
→	→	-	→	-	→	→	→	→	→

parenchyma (emphysema). The progression of COPD is also accelerated by the presence of underlying genetic or age-related decline in lung function (17).

The pathology of COPD can be broadly classified into two parts; (i) a structural damage to the small airways, also known as small airway disease, and (ii) a damage to the lung parenchyma including the alveolar (especially the ducts). Irrespective of whether the disease is characterized by either small airway disease or damage to the lung parenchyma, chronic inflammation remains a key factor in the progression of COPD. Additionally, other conditions such as the development of oxidative stress as mentioned earlier, and proteases/anti-proteases imbalance are also known to play a role in confounding COPD through an exaggeration of the inflammatory response to elements such as cigarette smoke, environmental pollutants, or bacterial infections (50, 51). Lastly, bacterial infections in the respiratory mucosa is another factor contributing to the pathogenesis of COPD. Specifically, bacterial colonization of the lower airway is associated with the rate of COPD inflammation and exacerbations (52).

5. Diagnosis and assessment

COPD is associated with several systemic manifestations such as muscle dysfunction, systemic inflammation and metabolic dysfunction. Consequently, making a single disease diagnosis somewhat rare. According to the 2017 global strategy for the diagnosis, management and prevention of COPD, assessment is carried out to determine the level of airflow limitation, health status, risk of undesirable events such as exacerbation, hospitalization and to support treatment prognosis. To achieve this goal, a set of assessment techniques including spirometry, anamnesis, and several forms of examination techniques are used. Nevertheless, COPD is primarily diagnosed by spirometry (1). However, with more understanding of the disease as a multifactorial entity, current assessment and classification techniques are based on several assessment variables that take into account symptoms, arterial oxygen and carbon dioxide tension, the degree of spirometric abnormality, the exacerbation risk, and the presence of comorbidities.

5.1 Pulmonary function tests (spirometry)

Pulmonary function tests or spirometry is one of the most useful techniques for diagnosing and monitoring the progression of COPD. Spirometry comprises several parameters that provide different information regarding the lung function status of individuals with respiratory diseases. The forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and the Tiffeneau index (FEV_1/FVC) are three important parameters of spirometry that are utilized for assessing and

diagnosing COPD in the clinic. The FEV_1 in particular is highly reproducible and it forms a major part of the COPD classification system (Table 2) (53). The FEV_1 has been used and is capable of predicting an age-related decline in the lung function that may even predict future COPD disease, as presented in Figure 3.

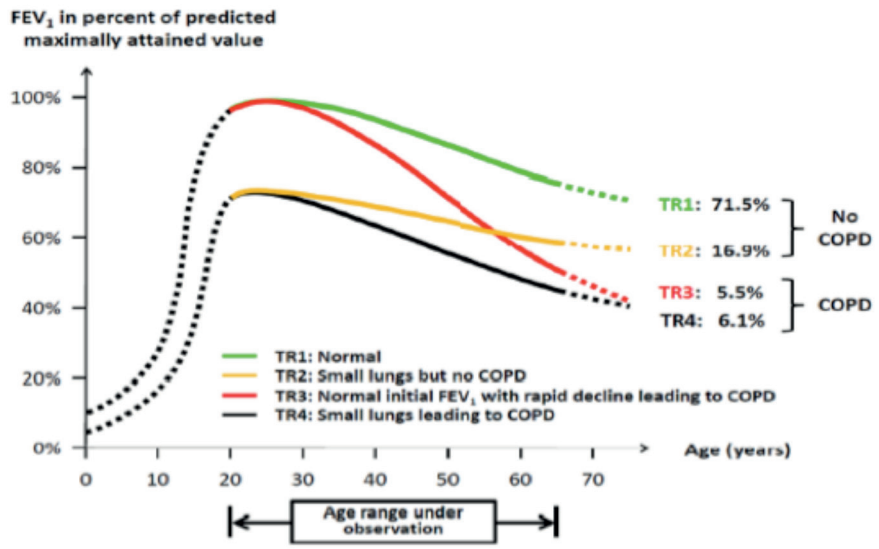


Figure 3 Progression of the FEV1 in four different trajectories and how two leads to COPD, while the other two did not lead to COPD (17).

Other parameters of pulmonary function tests (lung function and volumes), that are useful in COPD assessment and monitoring, include peak expiratory flow rate (PEF), forced inspiratory flow (FIF), force expiratory flow (FEF), vital capacity (VC), residual volume (RV), functional residual capacity (FRC) and total lung capacity (TLC) [Figure 4].

Clinically, a diagnosis of COPD is made after the administration of at least one short acting inhaled bronchodilator, which does not lead to a reversal of airway obstruction. Specific spirometric cut-off points are utilized in staging the disease as shown in Table 2. In the past, COPD was graded using a single measurement such as FEV_1, but improvements in the identification of the disease has led to better staging systems that are able to monitor disease progression and predict morbidity and mortality. This is achieved through the incorporation of variables such as age, arterial blood gases, dyspnea, body mass index (BMI), and distance walked during a six minute walk test in addition to assessing the FEV_1 (55).

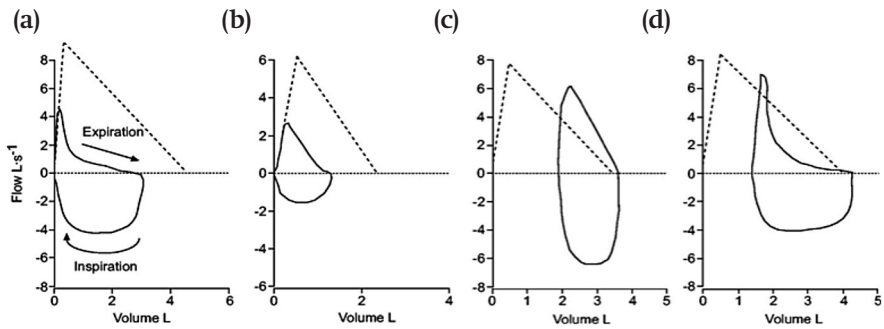


Figure 4 Flow volumes of different disease scenarios. Adapted from (54).

– – –: predicted flow–volume curves; ––––: observed inspiratory and expiratory flow–volume curves.

(a) Obstructive defects with a low FEV_1, 38%; FEV1/VC, 46%; PEF, 48%; TLC, 101% or normal

(b) Obstructive defects with a FEV_1, 57%; FEV_1/VC, 73%; PEF, 43%; TLC, 96% ratio of FEV1/VC. In both (a) and (b), TLC is normal, and flows are less than expected over the entire volume range.

(c) Example of a typical restrictive defect (FEV_1 66%; FEV_1/VC 80%; PEF 79%; TLC 62%). The TLC is low and flow is higher than expected at a given lung volume.

(d) Example of a typical mixed defect characterized by a low TLC and a low FEV_1/VC ratio (FEV_1 64%; FEV_1/VC 64%; PEF 82%; TLC 72%).

Table 2 Spirometric GOLD grading system

Severity	Post-bronchodilator FEV_1/FVC	FEV_1 % Predicted
Mild COPD	≤0.7	≥80
Moderate COPD	≤0.7	50-80
Severe COPD	≤0.7	30-50
Very severe COPD	≤0.7	<30

5.2 Symptoms assessment in COPD

The most common COPD symptoms include chronic cough, sputum production and dyspnea. While symptoms such as chronic cough and excessive sputum production are usually asked during the initial (or subsequent) hospital visit, the other symptoms such as dyspnea can be measured using questionnaires. The Modified British Medical Research Council (mMRC) dyspnea scale is a questionnaire that has been proven to be useful in assessing the dyspnea symptoms in patients with COPD (56). This 5-item scale accurately measures the perceived respiratory distress, which is also a frequently occurring feature of patients with COPD.

5.3 Health status of patients with COPD

Psychological issues, particularly anxiety and depression, are among the important variables affecting the quality of life (QoL) in patients with COPD (57). The hospital anxiety and depression scale (HADS) has been often used for this purpose. The COPD assessment test (CAT) questionnaire is another instrument that can be utilized to assess the QoL of patients with COPD (58, 59). These questionnaires along with other instruments are an important part of assessing the health status of patients with COPD. In general the health status of patients with COPD is affected by several parameters including disease symptoms, depression, fatigue, especially during exacerbation (60). While, the clinical control of COPD symptoms is measureable with the clinical COPD questionnaire (CCQ) (59), the rates of exacerbation in COPD, which provides valuable insight to the progression and prognosis of COPD may requires hospitalization especially in severe cases. Burge and Wedzicha recently defined exacerbation as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations that is acute in onset and may warrant additional treatment in a patient with underlying COPD (61). Patients with COPD often present with a high rate of fatigue, which is associated with the severity of the disease (62). Fatigue in COPD has been measured in the past using subjective instruments like the CRQ (fatigue subscale), multidimensional fatigue inventory (MFI), the identity-consequences fatigue scale (ICFS), functional assessment of chronic Illness therapy-fatigue scale (FACIT-Fatigue) and the checklist individual strength (CIS) scale (63-66).

5.4 The BODE index

The BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index is a multidimensional grading system that was developed to enhance the prognosis of several outcomes in patients with COPD such as hospitalization, morbidity and mortality (67). The BODE index is currently summarized as a 10-point scale, in which higher scores indicate an increased severity of the disease and higher risk of mortality of the individual patient (12) [Table 3]. Moreover, the use of the BODE index has helped decision makers to allocate scarce health resources such as diagnostic or therapeutic interventions in a more systematic and efficacious way to patients in need.

5.5 The ABCD classification system of patients with COPD

The **ABCD** system of COPD classification was initially developed in 2011 as a form of revision of the global obstructive lung disease (GOLD) strategy document with the aim of increasing the understanding of the impact of COPD on an individual patient level (68). This system of grading combines the symptoms burden, exacerbation in the last year along with the spirometric scores [Figure 5].

Table 3 BODE index

BODE score	0	1	2	3
FEV1	≥65%	50–64%	36–49%	≤35%
6 min walk test	>350meters	250–349 meters	150–249 meters	<149 meters
Dyspnea scale	0–1	2	3	4
BMI	>21kg/m^2	<21 kg/m^2		

Mild COPD (0 – 2), Moderate COPD (3 – 5), Severe COPD (≥ 6).

5.6 Phenotypic heterogeneity

Generally, the goal of phenotyping is to recognize various sub-groups with distinctive prognostic or therapeutic features. In COPD, a number of studies have attempted to provide different forms of classification with the aim of optimizing therapy in patient care (clinical use) as well as for research purposes (improving the quality of clinical trials). For example, about 20% to 35% of COPD patients have been reported to have nutritional depletion that predisposes them to metabolic problems manifesting as disease phenotypes (69).

(A) **Low risk,** **Less symptoms** *(exacerbation = not leading to hospital admission; symptoms = CAT< 10; breathlessness= mMRC 0-1)*	**(B)** **Low risk,** **More symptoms** *(exacerbation = not leading to hospital admission; symptoms= CAT≥ 10; breathlessness= mMRC ≥ 2)*
(C) **High risk,** **Less symptoms** *(exacerbation = 2 or 1 leading to hospital admission; symptoms= CAT< 10; breathlessness= mMRC 0-1)*	**(D)** **High risk,** **More symptoms** *(exacerbation = 2 or 1 leading to hospital admission; symptoms = CAT≥ 10; breathlessness= mMRC ≥ 2)*

Figure 5 The ABCD system of COPD classification. Adapted from (8).

Metabolic phenotypes range from cachexia, which refers to unintentional weight loss of >5% in 6 months and fat free mass index (FFMI) ≤16 kg/m^2 (males) and ≤15 kg/m^2 (females) (70, 71), to sarcopenia (skeletal muscle index <2; BMI >21 kg/m^2 and FFMI ≤16 kg/m^2 (men) or ≤15 kg/m^2 (women) (71), to obesity (BMI of 30-35 kg/m^2)

[Figure 6]. Other classifications include additional subdivisions of morbid obesity, sarcopenia obesity and pre-cachexia (72). These phenotypes are often associated with increased cardiovascular and mortality risk and/or impaired physical performance. There is also a loss of skeletal muscle mass combined with muscle fiber atrophy that is characterized by a shift of type I to type II fibers, thereby leading to a decrease in the skeletal muscle mass and function (72). Other characteristics include osteoporosis and low-fat mass. Cachexia is usually associated with emphysema and hyper-inflation, and muscle wasting (72). Cachexia in COPD has been attributed to factors such as energy imbalance, disuse atrophy, tissue hypoxia from arterial hypoxemia, systemic inflammation and anabolic hormonal insufficiency (73).

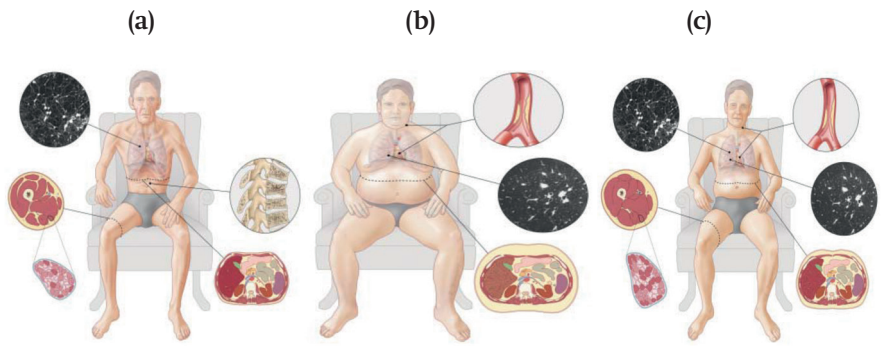


Figure 6 Abnormal metabolic phenotypes in COPD: (**a**) Cachexia, (**b**) Obesity, and (**c**) Sarcopenia. Adapted from (72).

The obesity phenotype is usually associated with chronic bronchitis, increased subcutaneous and visceral adipose tissue, decreased thoracic compliance, increased airway resistance, increased work of breathing, worsened dyspnea and wheezing and arterial stiffness (72, 74). Patients with COPD who are obese or overweight have decreased QoL, increased physical limitations, increased dyspnea, reduced functional capacity, poor prognosis and reduced health status(75). The sarcopenia is mainly characterized by loss of skeletal muscle mass and muscle fiber atrophy, which then leads to reduced exercise performance, decreased muscle strength and poor health status (75-77). Here, there is preservation of fat mass, but it is redistributed in favor of increased visceral adipose tissue.

6. Management of stable patients

6.1 Smoking cessation

Cigarette smokers have a higher prevalence of symptoms and problems with lung function (FEV_1 decline), and a greater COPD mortality than nonsmokers (78). Unfortunately, a significant proportion of COPD patients have been reported to have not only smoked for a long time, but still smoke during the course of the disease (79). Smoking cessation has been reported to be the single most effective and sensible way to reduce exposure to COPD risk factors (8). Ideally, all COPD smokers should be offered the most intensive smoking cessation intervention feasible, and a smoking cessation plan should be first line of approach for managing these patients (8).

Presently, smoking cessation programmes have been reported to be an effective intervention for stopping the progression of COPD and reducing morbidity (78). The major component of a smoking cessation plan is counselling (no matter how brief), in addition, a number of agents or interventions like varenicline and bupropion SR or nicotine replacement therapy (NRT) can be added to help counselling (80). Long term NRT-use has been reported to be efficacious for cessation among the general population of COPD smokers, regardless of daily cigarette consumption (81). Several other options have been proposed in addition to those earlier mentioned with successful results: counter nicotine gum, transdermal patches, lozenges, and electronic cigarettes. The use of electronic cigarettes in particular, has been reported to ameliorate subjective and objective disease-related outcomes and exacerbation rates as well as improving success in abstaining from smoking in the long term (82). However, the evidence to support these claims are scanty. Moreover, the European Respiratory Society (ERS) recently (14th Feb. 2018) reacted strongly to an article citing beneficial uses of electronic cigarettes, “Human lungs are made to breath clean air and any substance inhaled long term may be detrimental”.

6.2 Pharmacological options

Generally, the most commonly used pharmacological options for COPD symptoms/events are bronchodilators, glucocorticoids and antibiotics. However, because of the complexity in the pathogenesis of COPD, current therapies are not only challenging, but remain inadequate and have numerous adverse effects (13, 83). Consequently, a host of other medications are consumed on a case by case basis as the need arises.

6.2.1 Bronchodilators

Inhaled bronchodilators are prescribed to treat symptomatic COPD. Bronchodilators (84) are either short-acting or long-acting. Long acting bronchodilators such as long acting beta agonists (LABA) and Long acting muscarinic antagonists (LAMAs) have been referred to as the cornerstone of pharmacotherapy for patients with COPD who are stable (85). More recently, novel approaches that are aimed at improving adherence, compliance and the overall clinical outcomes in COPD have been reported (86). Adherence to bronchodilators such as SAMAs (ipratropium) and SABAs (salbutamol) and theophylline (using different administration forms) have been associated with a reduced risk of death and admission to hospital due to exacerbations in COPD (87). The focus of new therapies involving the administration of bronchodilator medications, is to increase adherence and treatment efficacy either through reduction of dose frequency and/or a combination of several classes of bronchodilators. Specifically, the use of long acting bronchodilators is associated with improvement of QoL, exercise tolerance, and exacerbation in COPD patients (88).

6.2.2 Glucocorticoids

The use of glucocorticoids offers an effective therapy means for treating inflammation in patients with COPD. Glucocorticoids are administered either orally (89) or by inhalation (8). The administration of glucocorticoids by inhalation (inhaled corticosteroids [ICS]), especially when used in combination with other inhalation therapies have been reported to be highly efficacious (90). Glucocorticoids are indicated in COPD patients with an FEV_1 of <50% or a history of severe and frequent exacerbations (91, 92). On the one hand, the use of ICS in COPD is associated with optimal improvement of QoL and, in some patients, reduce exacerbation rate. In addition, ICS has been associated with slowing down the rate of lung function decline in COPD when used over a long duration of ≥2 years (93). On the contrary, there are also reports of poor/absent responses, resistance, insensitivity and even adverse reactions with ICS use in some patients, and withdrawal of ICS use is also associated with lung function (significant dose- and time-dependent FEV_1) decline (92, 94) and poor health status (92).

6.2.3 Antibiotics

About 50% (or less) of COPD exacerbations are caused by bacterial infections (52). This phenomenon warrants the use of antibiotics in order to improve the patient's condition and reduce symptoms. Antibiotics are also prescribed in patients who cough, have dyspnea and produce purulent sputum (95). In addition, a variety of antibiotic medication such as macrolides (azithromycin) (8) may be administered for COPD patients, even though the use of these antibiotic therapy in acute

exacerbations of COPD still remains controversial (resistant organisms) (96). For example, azithromycin administered over 1 year in COPD patients who are at an increased risk of acute exacerbations, but have no hearing impairment, resting tachycardia, or apparent risk of QTc prolongation, have been found to have a decreased frequency of acute exacerbations and an improved QoL (97).

6.2.4 Other medication options

A number of medications are prescribed for COPD patients on a case by case bases depending on the diagnosis and presentation: (i) alpha-1 antitrypsin augmentation therapy can be given in patients with severe hereditary alpha-1 antitrypsin with an associated decline in FEV_1, (ii) anti-oxidant mucolytics are also given to selected patients especially those who respond less well to inhaled steroids (low reversibility and heavy smoking) (98), (iii) theophylline may be given in the absence of LABA due to its anti-inflammatory effects (side effects) (99), and (iv) low dose long acting opioids can be used for severe COPD patients with dyspnea. The medication compositions for COPD can also be based on the ABCD classification system and staging as described earlier. Generally, polypharmacy is common due to the complex nature of the disease. Unfortunately, combining different groups of medications comes with significant risks (8). Figure 7 highlights the medication pattern using this classification system.

Generally, COPD is associated with a wide variety of systemic consequences, most notably is systemic inflammation. Therefore, there is need for a better understanding of its origin, consequences and most importantly, the potential therapy to enhance care (43). Another method of pharmacological intervention for COPD according to clinical phenotypes based on the ABCD classification system is available and popular [Figure 8]. Here, it can be seen that bronchodilators are the basis of treatment of COPD irrespective of the clinical phenotype, while glucocorticoids such as inhaled corticosteroids (ICS) are only indicated when there are frequent exacerbations or in case of COPD-asthma overlap. Miravitlles *et al.* reported that in the event of a severe case of chronic bronchitis and frequent exacerbation in spite of optimal therapy, a treatment with long-term antibiotics under close follow-up should be utilized (5).

Another important medication that has been used for a long time with beneficial outcomes in patients with COPD is phosphodiesterase-4 (PDE4) inhibitors (100). PDE4 is associated with a modest improvements of the lung function, while maintaining exacerbation rate and health status, as well as considerably reducing the sputum neutrophil and eosinophil concentration (100, 101).

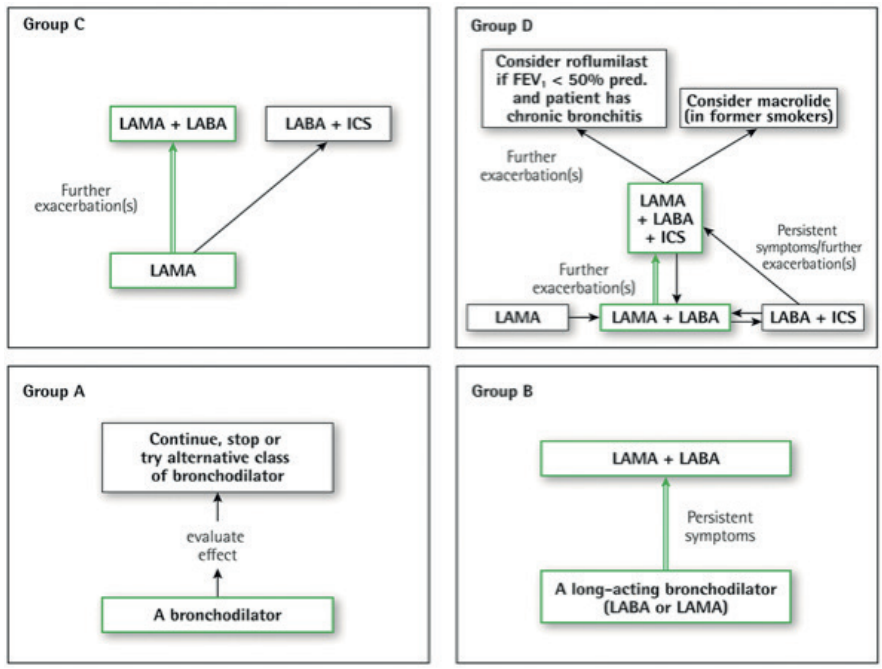


Figure 7 Pharmacologic treatment algorithms by Global Initiative for Chronic Obstructive Lung Disease (GOLD)/ABCD grading system (8).

Green boxes and arrows indicate preferred treatment pathways. ICS=inhaled corticosteroid; LABA=long-acting β-agonist; LAMA=long-acting muscarinic antagonist.

6.3 Non-pharmacological options

Pulmonary rehabilitation (PR) is one of the main non-pharmacological options in the management of COPD. PR has become an important component in the management of COPD because it has demonstrated physiological, symptom-reducing, psychosocial, and health economic benefits for patients with chronic respiratory diseases. One of the most comprehensive description of PR is provided in the joint official statement of the American Thoracic Society/ European Respiratory Society (ATS/ERS) in 2013. Here, PR is defined as a, "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (102) [Figure 9].

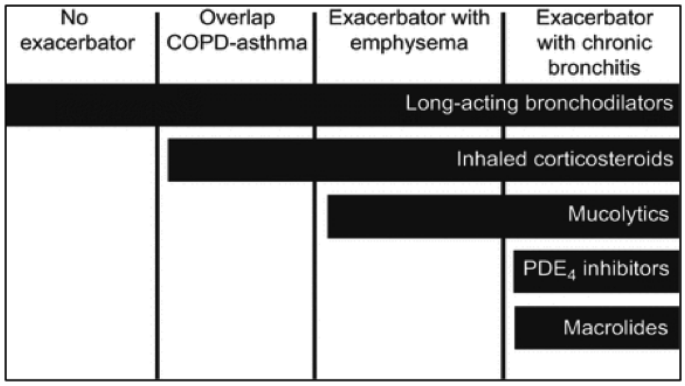


Figure 8 An example of pharmacological intervention in accordance to clinical phenotypes PDE4: phosphodiesterase-4 (5).

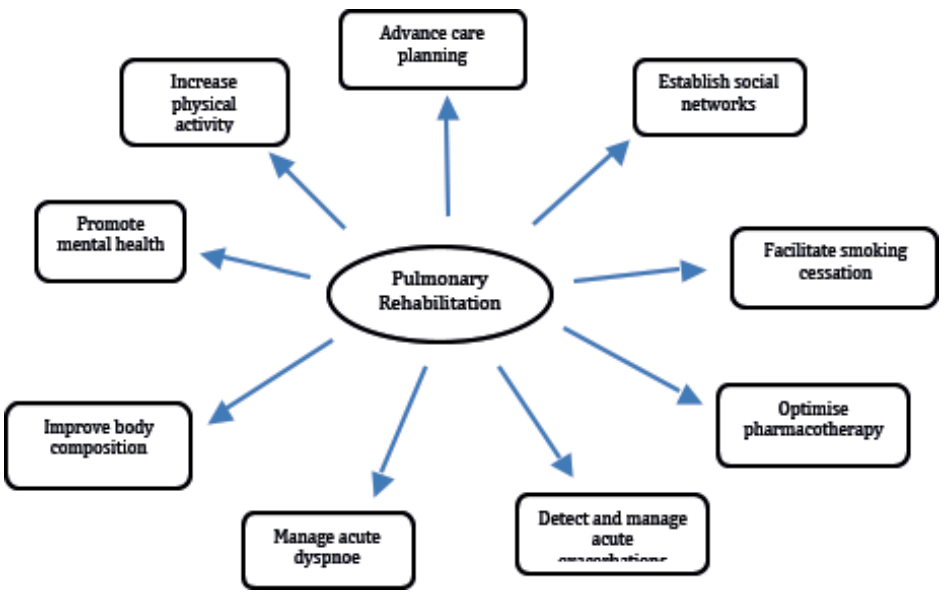


Figure 9 Components and goals of pulmonary rehabilitation. Adapted from (103).

The first ATS/ERS joint official statement on the use of PR for chronic respiratory diseases was in the year 2006 (104). Ever since, there has been a significant growth in our knowledge of its effectiveness and scope of PR. Moreover, this can be seen in recent Cochrane reviews and high quality randomized controlled trials (RCT) studies that have provided evidence for large and clinically significant improvements in dyspnea, fatigue, emotional function and sense of control in COPD patients following PR (105, 106). Consequently, comprehensive PR is an important component in the clinical management of patients with COPD (103), providing both short and long term treatment benefits even among patients with severe stage disease (106-108).

6.3.1 Exercise training

Exercise training can be defined as an activity lasting at least 20 minutes in which the heart rate is elevated above 60% of the maximal heart rate (MHR). Exercise training has been shown to reverse functional impairments (109), improve exercise capacity, muscle function and QoL. Exercise training interventions also have a positive effect on the ANS control of the heart, by increasing the parasympathetic nervous activity influence over the heart, and concurrently lowering the sympathetic nervous activity (110). The use of supervised and structured exercise (endurance/aerobic) training is considered to be a cornerstone of effective PR.

Exercise training is the main component of PR that leads to the significant improvements for several parameters such as in maximal exercise capacity, walking distance and endurance capacity (111). The general recommendation for exercise training in COPD is that it should take the form of constant load or interval training combined with strength training (8). It is important to note that COPD patients vary from one another, whilst some respond well to exercise training, others do not (112). Therefore, exercise training parameters should be chosen with care depending on treatment goals. Exercise training parameters vary depending on whether a include sub-maximal (113) or maximal (37, 113) training intensity is desired. Exercise training can also be applied in a continuous or interval training modes. Interval training refers to repeated short periods of exercise alternated with rest or high vs low intensity, which is variable and depends on the duration of the work phase (114). Lastly, the use of exercise training, protocols such as one legged (partitioning) exercise training which uses less amount of active muscle mass and equally less demand on the cardiorespiratory system offers a different approach to COPD rehabilitation (115).

6.3.2 Resistance training

In clinical practice, most COPD patients may not be able to perform high intensity aerobic or endurance exercises due to cardiopulmonary limitations or disease

symptoms such as dyspnea and leg fatigue (116). Therefore, other means of exercises, such as resistance training, that can generate high muscle force becomes a treatment option. Resistance training uses a principle of loading whereby selected muscles are engaged in repetitive lifting of weights. Resistance training improves peripheral muscle force and endurance (109), functional capacity, and other outcomes (117). Resistance exercises can offer help in carrying out simple tasks such as pulling, pushing, and lifting (which require skeletal muscle mass and the strength of both upper and lower limbs).

Additionally, an improved muscular function from resistance training allows patients to perform submaximal physical tasks at a lower percentage of maximal voluntary contraction, which in turn results in a lower cardiovascular load (118). Also, the poor muscle function in COPD patients is implicated in the lowered autonomic function indices (119).

6.3.3 Inspiratory muscle training

Inspiratory muscle training (IMT) is an intervention that is designed to increase strength and/or endurance of inspiratory muscles(120). COPD patients are known to have a diminished maximal inspiratory pressure (MIP) as well as a diminished maximal expiratory pressure (MEP). Consequently, IMTs have been utilized to offer improvement in both strength and endurance of the respiratory muscles in COPD. The use of IMT also has a significant effect on important COPD parameters such as dyspnea at rest and during exercise, functional exercise capacity, adaptive changes in the structure of external intercostal muscles and the overall muscle function (121-123). Moreover, respiratory muscle dysfunction in COPD is associated with a number of negative consequences such as comorbid conditions, hypoxia, hypercapnia, nutritional status, medication, inflammation, and oxidative stress (116, 124, 125) .

6.3.4 Nutritional intervention

Nutritional supplementation is recommended for patients with COPD because of the negative impact of the disease on the overall nutritional status of some patients (obesity or cachexia) (72). The main parameters of interest are body weight, fat mass and fat free mass. Patients who received nutritional supplementation have been reported to show significantly improve clinical, physiological and functional outcomes (8). However, there is only limited evidence to support this claim.

6.3.5 Education and self-management

According to the 2017 report of the global strategy for the management and prevention of COPD, self-management and education (i.e. coaching by healthcare professionals) are major components of chronic care in the non-pharmacological

approaches to improve COPD management (8). Patients with COPD often present with high rates of depression, anxiety and cognitive disorders (psychiatric morbidities) (21, 23). The use of a self-management programme is reported to improve the health status and reduce hospital admission in COPD (126).

Generally, the goal of self-management is to stimulate and engage COPD patients into adapting their lifestyles and health behavior in order to be able to manage and cope with the disease. Education and self-management takes into account individual patient's needs, preferences and goals to form a self-management education plan (126, 127). Some of the features of self-management include education on smoking cessation, nutrition, sleep, how to deal with breathlessness, energy conservation techniques, stress management, avoiding triggers/aggravating factors, social interaction, disease monitoring and advanced care strategies depending on the COPD stage (8, 128).

6.3.6 Oxygen therapy

Hypoxemia at rest is an important complication in patients with COPD, and it is often associated with premature death. Therefore, oxygen therapy (supplementation) is generally recommended for patients with low oxygen tension (PaO_2) at or below 7.3kPa/55mmHg or oxygen saturation (SaO_2) at or below 88% with or without hypercapnia (39). The use of oxygen therapy in combination with other non-pharmacological options such as noninvasive ventilation (NIV) is also common. Oxygen therapy is associated with improved admission free survival rates following life threatening COPD exacerbations (129). Long term oxygen therapy is usually given for at least 16 hours/day in chronic hypoxemic patients. Hypoxemia should be re-evaluated after every 3 months (8). Oxygen therapy has been associated with improved patient outcomes including pulmonary hypertension (130) and autonomic function (131-134).

6.3.7 Mobile health (mHealth) or tele monitoring

More recently, there has been a focus on new possibilities that mHealth offers in view of the latest advances in mobile communications and technologies (135). Generally, mHealth involves an integration of mobile computing, medical sensor, and communications technologies for mobile health-care applications that can be used as wearables or electrodes to provide feedback for monitoring (for example in a remote control center) (136). Mobile health (mobile technology) can help to recognize early symptoms of disease deterioration, support patients in self-management, and it has the potential to increase adherence, reach a wider audience, and even increase quality of life, patient satisfaction outcomes and compliance to rehabilitation intervention (137, 138).

6.3.8 Mechanical ventilation

The use of assisted mechanical ventilation, in the form of either NIV or invasive mechanical ventilation (IMV), to improve gas-exchange and reduce symptoms in COPD patients with unstable condition is common and effective (129, 139). Specifically, NIV is a supportive technique that is applied in the event of severe respiratory failure in COPD, that is either due to mechanical disturbances, central depression or respiratory muscle fatigue in COPD (140, 141). The use of long term NIV as a complementary therapy (such as positive pressure ventilation), has been reported to improve the survival rates of hypercapnic stable COPD patients (142). NIMV is delivered using a nasal or full face mask for which different pressure parameters have been used (143, 144). NIV is effective for improving several patient outcomes (141). Even though IMV is usually utilized upon NIV failure, which is common in high risk COPD patients that are admitted in the intensive care unit (ICU), or those with respiratory failure associated with acute exacerbation of COPD (AECOPD), it has become an intervention of choice during exacerbations (15).

Although a small group of stable COPD may benefit from NIV, the current evidence only supports its use for COPD exacerbation and patients with unstable condition. Hence, it is not usually administered as a long term maintenance therapy. Nevertheless, some studies have even reported that NIV enhances autonomic function of patients with COPD (145, 146).

Table 4 Definitions of COPD exacerbations. Adapted from (95).

Type	Symptoms	Additional minor symptoms
1	An increase in sputum volume	
	An increase in sputum purulence	
2	Any two from	
	An increase in sputum volume	
	An increase in sputum purulence	
	An increase in sputum dyspnea	
3	A single symptom from	
	An increase in sputum volume	Sore throat or nasal discharge within last 5 days
	An increase in sputum purulence	Fever without cause
	An increase in sputum dyspnea	Increased wheezing
	Plus at least one minor symptom	Increased respiratory rate (>20% above baseline) Increased heart rate (>20% above baseline)

7. Exacerbation

Exacerbations are a significant cause of morbidity and mortality in COPD (147). It refers to a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and may warrant additional treatment in a patient with underlying COPD (95). It is also defined as worsening of respiratory symptoms requiring treatment with oral or parenteral corticosteroids or antibiotic or both. It is reported to be more common in those patients with moderate-to-severe disease. Table 4 presents the 3 types of COPD exacerbation.

The etiology of COPD exacerbations include bacterial and viral infections, cold weather, pollution, and interruption of regular treatment (95).

8. Comorbidities

A significant proportion of COPD patients often suffer from extra pulmonary abnormalities that include nutritional-body composition abnormalities, skeletal muscle dysfunction, osteoporosis, psychiatric morbidity, gastro-esophageal reflux disease, metabolic syndrome, obstructive sleep apnea, renal dysfunction, and hormonal dysregulation (8, 23, 46, 148). Cardiovascular diseases (CVDs) are the most frequently occurring comorbidities that are associated with high morbidity and hospitalization rates in COPD. Five separate disease entities within have been reported in COPD: heart failure, ischemic heart diseases, arrhythmias, peripheral vascular diseases and hypertension (8). The onset and progression of CVD in COPD involve the affectation of many organs and tissues. For example, in the arteries, there is unusual thickening, stiffening, remodeling and endothelial dysfunction, while in the veins thromboembolism may occur [Figure 10] (83). Other manifestations of COPD that can put an individual at risk of CVDs include increased arterial carbon dioxide tension ($PaCO_2$), decreased oxygen tension (PaO_2) and increased respiratory rates (149).

The TOward a Revolution in the treatment of CHronic obstruction (TORCH) trial also attributed about 26% of COPD deaths to cardiovascular causes, 21% to cancer and only 35% to COPD (150). Consequently, cases of cardiovascular mortality, including sudden cardiac death is often reported among individuals with COPD (151). In the existing literature, a number of studies have reported an unusually heightened presence of CVD risk factors in COPD (1, 6, 34, 35, 152-156). Patients with COPD also have higher prevalence of cerebral cortical dysfunction as a result of an increased cortical inhibition levels compared to their healthy counterparts (157).

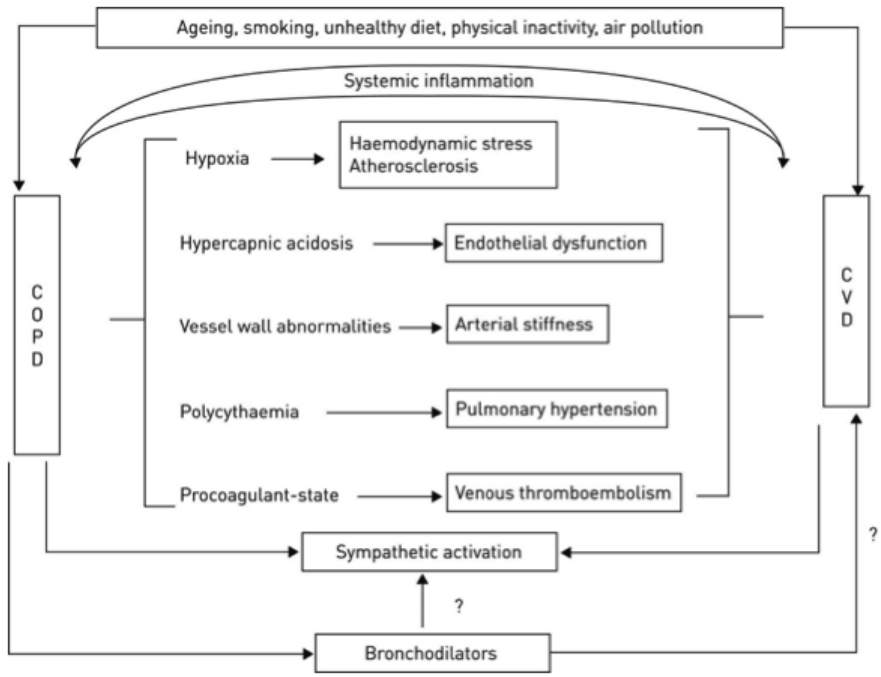


Figure 10 The interaction between COPD and the pathogenesis of CVD (83).

Occasionally, COPD coexists with other chronic diseases such as asthma, namely asthma-COPD overlap syndrome (ACOS), which is a condition in which an individual has clinical features of both asthma and COPD (158) [Figure 10]. Heart failure and left ventricular systolic dysfunction (LVSD) also coexist with COPD especially among the elderly dyspneic COPD types (159). These complexities often present a therapeutic challenge because COPD medications are also associated with some adverse and deleterious effect on a coexisting condition.

Another aspect to the cardiovascular-related morbidity and mortality in COPD is the impairment in the autonomic nervous system (ANS) (160). Patients with COPD have been reported to have cardiac sympathetic activation, systemic neurohumoral activation and peripheral sympathetic activation as a result of impaired autonomic control (161). Cardiac sympathetic activation is reflected by a significantly reduced heart rate variability (HRV) and baroreceptor reflex sensitivity (BRS) indices, also demonstrating poor cardiac autonomic control.

Neurohumoral activation is represented as an abnormally increased concentration of organic chemicals such as plasma norepinephrine and plasma renin or aldosterone

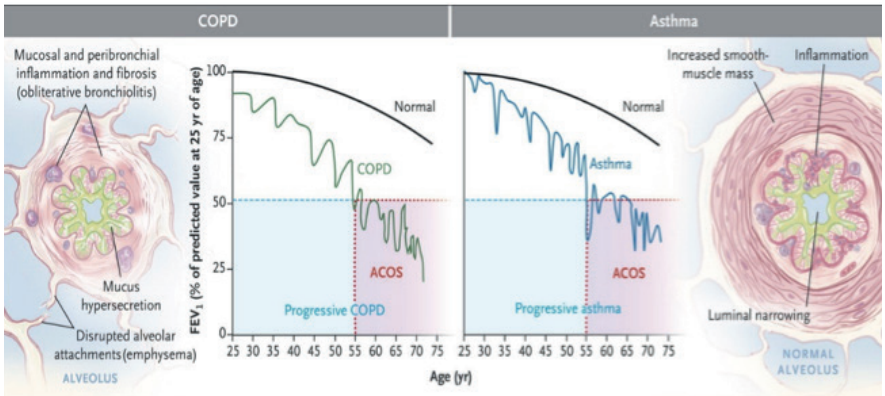


Figure 11 Hypothetical Course of lung function in COPD and asthma (158).

activities, all of which in the long run augment the sympathetic nerve traffic, have been widely reported in COPD (161-163). Similarly, peripheral sympathetic activation has been reported in a number of studies assessing the muscle sympathetic nerve activity (MSNA) in COPD compared to healthy controls (164-166). Other measures of the ANS integrity in COPD such as heart rate recovery (HRR) following exercise training and sympathetic skin response test have also revealed similar outcome (167-169). More information regarding these autonomic function parameters and more are described in detail in Chapter 2.

The use of certain classes of COPD medication have been reported to have an effect on the HRV values in COPD (170). More specifically, the following two classes of drugs have been associated with adverse effects on the cardiovascular autonomic system: (i) long acting β_2 agonists, which are typically administered to improve lung function and health status in symptomatic COPD, and (ii) inhaled corticosteroids (ICS), which are given to reduce the frequency of acute episodes of symptoms exacerbation and also delay deterioration of the health status (171). Moreover, polypharmacy, which is common in COPD, has a negative influence on the autonomic function.

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Chapter 2

Autonomic nervous system (ANS): physiological overview and assessment means

1. General description of the autonomic nervous system (ANS)

The autonomic nervous system (ANS) consists of a set of nerves (cells and axons) that provides innervation to several organs of the body such as blood vessels, glands, smooth muscles of viscera, heart, lungs (airways) and urogenital organs (1, 2). The ANS represents a crossing point between the central nervous system (CNS) and the body (3). It is responsible for regulating and coordinating certain bodily functions mainly comprising secretory activity of glands, contraction and relaxation of smooth muscles, cardiovascular adaptation and functioning relating to the body physiology, responses to stimulus and homeostasis (4-6). The ANS relays impulses that are initiated in visceral receptors via the afferent autonomic pathways to the CNS for processing. Subsequently, the CNS transmits responses to the target organs via efferent pathways to the respective visceral effectors (7).

The ANS is responsible for the continuous adaptation of the human body to both internal and external changes by regulating bodily functions such as blood pressure, respiratory rate, blood circulation, body temperature and digestion, without a conscious effort. The ANS also regulates the caliber of the airways, secretion production, modulates the inflammatory response and modulates airway responses to inflammation (8). The ANS is referred to as the visceral nervous system or the vegetative nervous system. Combined with the somatic nervous system, it forms the efferent (i.e. outgoing) division of the peripheral nervous system [Figure 1]. The a regulates

The ANS consists of a central and a peripheral part. The central part of the ANS is located in the brain, brainstem and spinal cord, while the peripheral part comprises nerve axons that originate from the spinal cord to various target organs or glands. Generally, the ANS is made up of two major divisions: sympathetic and parasympathetic. However, a third division, known as the enteric nervous systems, encompasses a complex set of neurons (both parasympathetic and sympathetic) lining the wall of the gut especially the small and large intestines (4, 9). Our focus in this section of the dissertation is to provide a general description, anatomical structure, functions and interactions of the ANS.

1.1 Sympathetic nervous system

The sympathetic nervous system originates from the preganglionic neurons located in the inter-medio-lateral cell column (lateral horn) of the thoracic and upper lumbar (thoracolumbar) region, specifically, between T1 and L3 segments of the spinal column [Figure 2] (4, 10). The preganglionic cells of the neurons of the sympathetic nervous system receive inputs from the vasomotor center in the brain stem. The preganglionic neurons leave the spinal column via the ventral root, and

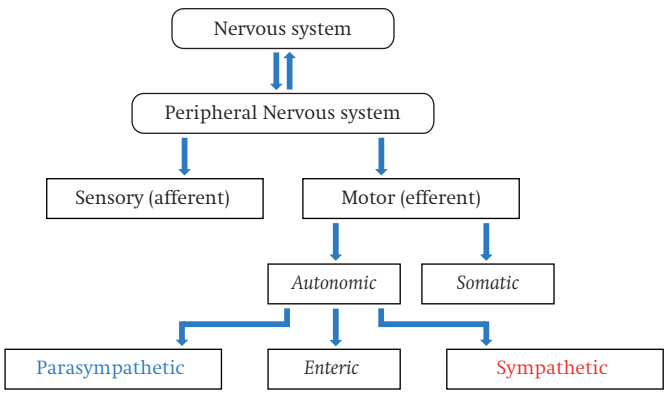

Figure 1 An illustration of the functional division of the nervous system.

then through the white rami, in a segmentally organized manner to pass through the para-vertebral sympathetic chain ganglia. Thereafter, a different subgroup of neurons arising from the sympathetic chain ganglia further converge to form the celiac, mesenteric (superior and inferior) and cervical (superior sympathetic) ganglia [Figure 2]. The sympathetic ganglia allows for mass activation of the sympathetic chain as a large unit through a phenomenon known as 'divergence', which results when a preganglionic fiber synapses with many post ganglionic neurons. Divergence is useful in situations that require a more global response such as during danger, exercise hypoglycemia, dehydration and exposure to extreme temperature conditions (11). The sympathetic nervous system is also capable of acting in a localized fashion to create selective regional effects in organs, a phenomenon known as 'convergence'.

The sympathetic effects in the ANS last longer compared to the parasympathetic effect due to the nature of the neurotransmitter released at the post ganglionic fibers, the norepinephrine (NE) (Table 6). The NE is activated slowly and its action lasts for several minutes before it is finally metabolized by the liver (11). During sympathetic stimulation, there is an increase in the firing rate of the pacemaker cells in the SA node, which in turn increases the heart rate (12). Physiologically, this occurs as a result of a positive inotropic effect of NE on heart muscle, when it is binding to beta-1 adrenergic receptors of the heart, resulting in an increased cardiac output. NE also decreases the basal pulmonary vascular tone and elevates the pulmonary blood flow through the activation of α2-adrenoceptors and NE release, also causing a pulmonary vasodilator response (13). Peripheral circulatory effects of NE include increasing blood flow to the skeletal muscles and reducing blood flow to the gastrointestinal system.

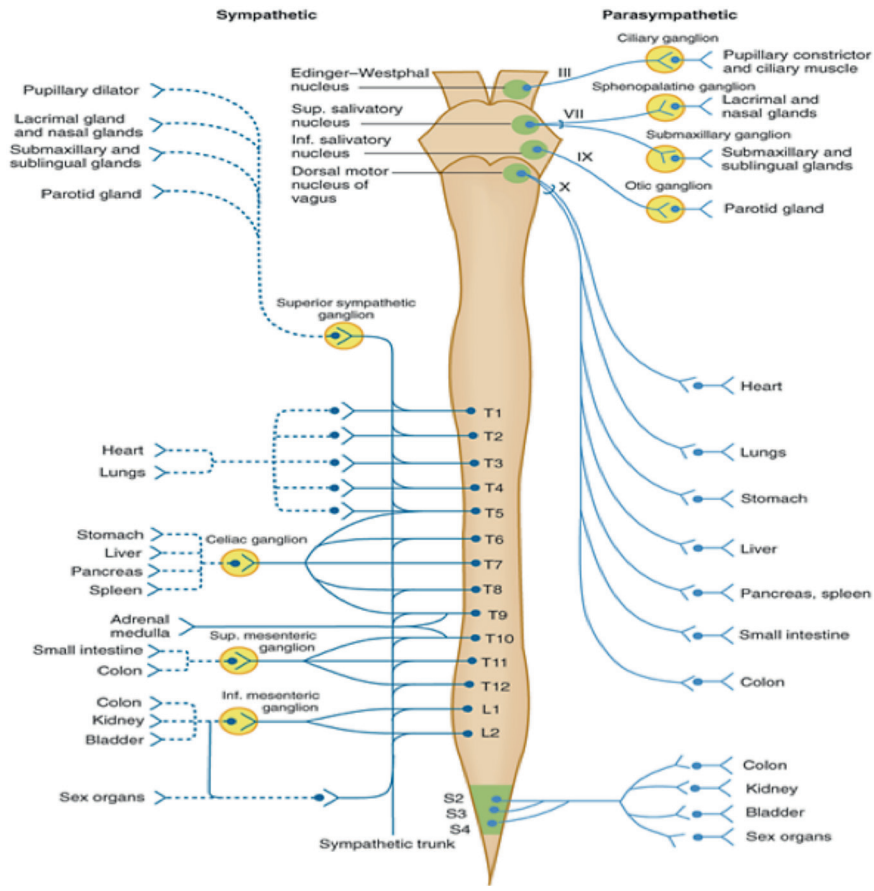

Figure 2 Differences and functions of the sympathetic and parasympathetic systems (18).

The role of the sympathetic nervous system on the heart and peripheral circulation is mainly coordinated by intrinsic mechanisms comprising cardiopulmonary mechanoreceptors, baroreceptors in the carotid sinus and aortic arch, cardiovascular low threshold poly-modal receptors, and arterial chemoreceptors (14).

1.2 Parasympathetic nervous system

The parasympathetic nervous system is part of the efferent neurons that originate from the brain stem and sacral regions of the spinal cord. Their pre-ganglionic fibers, which originate from medial medullary sites (nucleus ambiguous, nucleus

tractus solitarius, and dorsal motor nucleus) of the spinal cord, travel over a long distance to reach a ganglion that is located near or inside a target organ. Consequently, only short post-ganglionic axons make a connection with the target organ or gland. The neurotransmission in the parasympathetic nervous system is mainly modulated by nicotinic and muscarinic receptors (10, 15). The parasympathetic nervous system is controlled by the hypothalamus in the brain stem, and majority of its preganglionic innervation comes from the vagus nerve, which is one of the major cranial nerves.

The parasympathetic nervous system functions in a very localized manner and its effects are mostly for a short-term and often localized because of the ratio of pre-to-post-ganglionic neurons [Figure 2]. Furthermore, the neurotransmitter released by the post ganglionic neurons in the parasympathetic nervous system is acetylcholine (Ach), which is metabolized quickly by circulating acetylcholinesterase thereby reducing the effect of parasympathetic stimulation. The parasympathetic branch acts mainly by decreasing the firing rate of the pacemaker cells in the SA node (12). Examples of the effects of parasympathetic stimulation include inhibition of the heart, constriction of the bronchi, constriction of the pupils and stimulation of the salivary gland.

1.3 Enteric nervous system

The enteric nervous system is the third division of the ANS that is mainly associated with the gastrointestinal system (7, 16). Unlike the sympathetic and parasympathetic nervous systems, the enteric nervous system performs many of its functions independent of CNS contribution. It comprises two main ganglionated plexuses (the myenteric and submucosa), and the nerve fibers which arise from the plexuses and supply the muscle, blood vessels and mucosa of the gastrointestinal (GI) tract. The enteric nervous system contains a large number of neurons, approximately 10^7 to 10^8 (17). Its major functions are GI peristalsis and secretion.

1.4 Parasympathetic vs sympathetic interactions

Even though the role of the sympathetic and parasympathetic divisions of the ANS tend to be antagonistic to one another, especially when they innervate the same organ. However, the two branches do not oppose one another per se. Instead, both systems interact in a complex and dynamic manner that includes either co-activation or reciprocal activation with a view to maintaining a desirable autonomic tone in the nervous system (3). Generally, there is a predominance of vagal "tone" (parasympathetic activation) over sympathetic tone (sympathetic activation) at rest. Additionally, unexpected parasympathetic stimulation (accentuated antagonism) occurs in order to inhibit tonic sympathetic activation during rest and strenuous conditions through a strong vagus nerve discharge.

1.5 Chemical divisions of the autonomic nervous system

The chemical division of the ANS, also referred to as neurotransmitter division, is based on the chemical mediators that are released to enable the ANS function (7). Neurotransmitters are synthesized and stored in the axons before they are released. The major neurotransmitters that are released by neurons of the ANS are Ach and NE, representing the cholinergic and noradrenergic divisions, respectively (19). The cholinergic nerve fibers include all preganglionic fibers of the ANS in both sympathetic and parasympathetic nervous systems, all postganglionic fibers of the parasympathetic system, and the sympathetic postganglionic fibers innervating sweat glands. On the other hand, all other sympathetic postganglionic fibers release NE and are adrenergic fibers. Table 1 describes the respective receptors, location and effect of binding of the chemical divisions of the ANS.

2. Indicators of altered ANS functioning

A diagnosis of autonomic failure is sometimes an indication of a problem in the CNS function. However, for this to be established, isolated peripheral autonomic nerve disorders have to be ruled out (20). In many autonomic laboratories, the assessment of altered ANS function assessment is only possible in a systematic and segmental fashion. This is because of the absence of a distinctive test or assessment protocol that assesses all the components of the nervous system at once. Besides, it is still practically impossible to assess the function of deeply sited unmyelinated nerve axons accurately.

Consequently, a number of studies have proposed several means of assessing the integrity of the ANS. Several parameters are now being used to identify abnormal or altered ANS functioning. In the past, the use of plasma and urinary catecholamine levels provided one of the few ways to assess the level of sympathetic activity (3, 21, 22). However, several parameters now exist that reflect ANS functioning accurately, with an added advantage of being non-invasive (23).

The analysis of the autonomic control of the heart, by means of indirect markers, represents a valuable approach for identifying patients at higher risk for sudden cardiovascular events (24). Several stimuli (internal and external) continuously act by balancing the tone between the two branches of the ANS (25). Problems with the ANS can be screened subjectively, by means of questionnaires collecting information regarding autonomic symptoms (26), in addition to objective autonomic function tests in the laboratory (27, 28).

Table 1 Effect of acetylcholine and (nor)epinephrine. Adapted from (19).

Neuro transmitter	Receptor	Location	Effect of binding
Acetylcholine	*Cholinergic*		
	Nicotinic	All ganglionic neurons	Excitation
		Adrenal medulla	
		Neuromuscular junctions of skeletal muscle	
	Muscarinic	All parasympathetic targets	Excitation in most cases Inhibition in cardiac muscles
		Some sympathetic targets (sweat glands and blood vessels in skeletal muscle)	Activation (sweating) Inhibition (vasodilation)
Norepinephrine Epinephrine	*Adrenergic*		
	β_1	Heart	Increases heart rate and contraction strength
		Coronary blood vessels	Dilates coronary arteries
		Kidneys	Stimulates renin released by the kidneys
	β_2	Lungs.	Dilatation of the bronchioles
		Blood vessels serving the heart	Dilatation
		Digestive organs.	Relaxes smooth muscle wall of digestive organs
		Urinary tract.	Relaxes smooth muscle walls of urinary visceral organs, relaxes pregnant uterus
	β_3	Adipose tissue.	Stimulates lipolysis by fat cells
	α_1	Blood vessels to the skin mucosa abdominal viscera kidneys and salivary glands.	Constricts blood vessels and visceral organs sphincters
		Most sympathetic target organs except the heart.	Dilates pupils of the eyes
	α_2	Membrane of adrenergic axon terminals; blood platelets.	Mediates inhibition of NE release from adrenergic terminal, promotes blood clotting

2.1 Subjective assessment of the ANS

Subjective assessment of the signs of ANS dysfunction takes the form of questionnaire administration or anamnesis that are usually performed in clinical settings. The subjective assessment of the ANS to determine the level of autonomic symptoms has been simplified for various purposes. The autonomic symptoms profile (ASP), which is valid and reliable (29) has been used for various patient populations (30, 31). The most recent and simplified version of the ASP is the composite autonomic symptoms scores (COMPASS-31), which delineate the severity and distribution of autonomic symptoms across six domains; orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, urinary and pupillomotor function (26). The psychometric properties of the most recent COMPASS-31 including the Cronbach α coefficient values range from moderate to good (0.40 to 0.90), and with 4 domains (orthostatic intolerance, vasomotor, gastrointestinal and pupillomotor) reaching a Cronbach α coefficient greater than 0.70 (32). Additionally, the total score COMPASS-31 score has a moderately good rank correlation (r= 0.67) with the composite autonomic symptom scale (CASS), indicating a good criterion validity (29). In addition to being valid and reliable, this instrument is easy to use and it has a good diagnostic accuracy (33).

For autonomic symptom assessment using the COMPASS-31 questionnaire, a score between 0 and 100 is achievable. The higher the score, the unhealthier the subject or patient is. For the six COMPASS-31 domains (orthostatic intolerance, gastro intestinal, vasomotor, secretomotor, urinary and pupillomotor) different sympathovagal interpretations can be suggested. For example, higher orthostatic intolerance score is a reflection of increased sympathetic activity (34), while higher gastro-intestinal score (especially the constipation subgroup) indicates problems with parasympathetic function (35). The vasomotor scores are reflective of sympathetic dysfunction (36). For secretomotor symptoms, tears and sweat formation, and dryness of the mouth indicate parasympathetic dysfunction (37), while problems with sweating have to do with sympathetic function (38). Lastly, low scores for bladder and pupillomotor domains are associated with impairments in the parasympathetic function (37, 39).

2.2 Objective assessment tests of autonomic function

The objective assessment of the ANS uses indirect recordings of parameters such as the heart rate variability (HRV), which has gained acceptance. Conversely, direct tests of sympathetic post ganglionic nerves in the tests of muscle sympathetic nerve activity (MSNA) and skin sympathetic response (SSR) are limited by lack of generalizability. As a result, current efforts and guidelines have increasingly recommended that several autonomic function tests should be performed in order to gain insight into the overall autonomic activity of organs of individual subject (40).

Thereafter, all this information can be combined in a complementary manner to provide information about the state of the ANS.

3. Selected autonomic function parameters

3.1 Heart rate variability analyses

The HRV is a sensitive and noninvasive electrocardiographic method of measuring the functioning of the autonomic input to the heart (41, 42). It reflects the beat-to-beat changes of the heart known as R-R intervals [Figure 3], which is related to the ongoing interplay between the sympathetic and parasympathetic systems of the ANS, and the ability of the cardiovascular system to adapt to both external and internal changes (25, 43). According to the report of the Task Force of the European Society of Cardiology (1996), the HRV is one of the recognized parameters for the estimation of cardiac autonomic modulations(33). The HRV has been extensively used for the autonomic modulation of the sinus node due to its improved standards of measurements, physiological interpretation and clinical implications (40, 44, 45). The HRV is particularly useful when evaluating the balance between sympathetic and parasympathetic activities (46). The HRV is an analysis of the fluctuations in the heart rate, which are mediated by the sympatho-vagal activities. Furthermore, the HRV index is a widely accepted and frequently reported physiological marker of autonomic function in COPD (23, 47, 48).

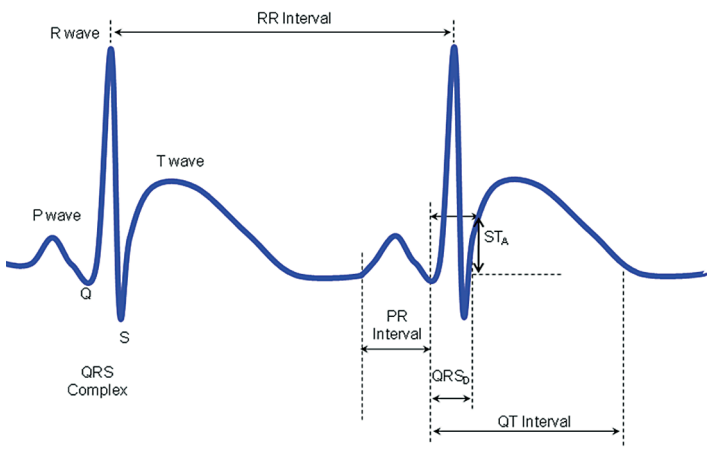

Figure 3 Representation of the normal sinus rhythm of the heart and R to R wave interval (RRi) (49).

Presently, the HRV has become an important tool for assessing, prognosticating and detecting autonomic impairments in several neurological and even in non-neurological disorders. It remains an invaluable tool for both clinical practice and physiological research (50). The HRV responses can indicate alterations and abnormalities in cardiac autonomic control as earlier stated (51). A decrease in the overall index of HRV analyses is in turn associated with the development of several cardiovascular disorders including myocardial infarction, alcoholic cardiomyopathy, chronic heart failure and ventricular arrhythmia (43).

The HRV analysis consist of several individual parameters categorized as either linear or nonlinear HRV analyses. The linear HRV analysis is further subdivided into time and frequency domain. In general, the linear analyses are measured in terms of inter-beat intervals of normal beats, while the nonlinear analyses is based on interpretations of the degree of the HRV in less stable circumstances.

3.1.1 Time domain linear HRV analyses

The time domain analysis refers to measures and quantification of the HRV in terms of heart rate at the intervals between successive beats (R-R intervals), measured in units of time (milliseconds) (40). These inter-beat intervals of the heart rate time series vary (shorter or longer) over a course of time. The indices derived from the time domain HRV analysis largely depend on vagal modulation, and a reduction in the values of these indices is interpreted as a sign of heightened sympathetic modulation of the sinus node (45). One of the major indices of time domain HRV is the standard deviation of the N-N interval (SDNN), which depicts variability of the heart beats in a particular time series. The SDNN also depends on the length of the time series, making it unsuitable to use for comparison, if different time series lengths are used. The standard deviation of the average NN interval (SDANN), is another index of time domain parameters that is computed over short periods (typically 5 mins), and is used for estimating the changes in heart rate over longer periods of time (Table 2).

The next three important indices of HRV analysis follows computations that are based on the variations in successive NN intervals. These measures include the square root of the mean squared differences of successive NN intervals (RMSSD) (52), the number of interval differences of successive NN intervals greater than 50ms (NN50), and (iii) the proportion derived by dividing NN50 by the total number of NN intervals (pNN50). All these parameters show variations in the high frequency band of the power and they are mainly reflective of parasympathetic activity.

3.1.2 Frequency domain analyses of HRV

The frequency domain HRV analysis measures the index of the variability in the fluctuations at various frequencies in a specified R-R time series with a correlation to neural discharge (45). The frequency domain analysis of HRV also provides significant assessment of the cardiac autonomic control (53)W. The frequency-domain analyses approach is based on a spectral technique, which analyzes the RR interval series as a complex sum of waveforms. Thereafter, it is decomposed with either fast Fourier transformation (FFT) or autoregressive approach (AR) algorithms (54), each having its advantage and disadvantages (55). The power spectrum of a time series refers to the frequency content within a time series (and the power contained in every frequency). For example, if a set of R-R series has a significantly high variability, there would be a greater contribution at higher frequencies, while RR series with low variability are associated with lower frequencies. Usually, the R-R interval data are converted to power spectral density (PSD), which enables the determination of the amount of variance or power as a function of frequency ranges.

The frequency domain comprises different indices (Table 6), which are classified according to their frequency bands. The indices include high frequency (HF) band (.15 and .4 Hz), low frequency (LF) band (.04 to .15Hz), very low frequency (VLF) band (.0033 and .04Hz) and the ultra-low frequency band (ULF) (.0000115 and .0033Hz) as illustrated in Figure 11 (56). A minimum period of at least 1 min, 2 min, 5 min and 24 h recording is required to assess the HF, LF, VLF and ULF band, respectively (57).

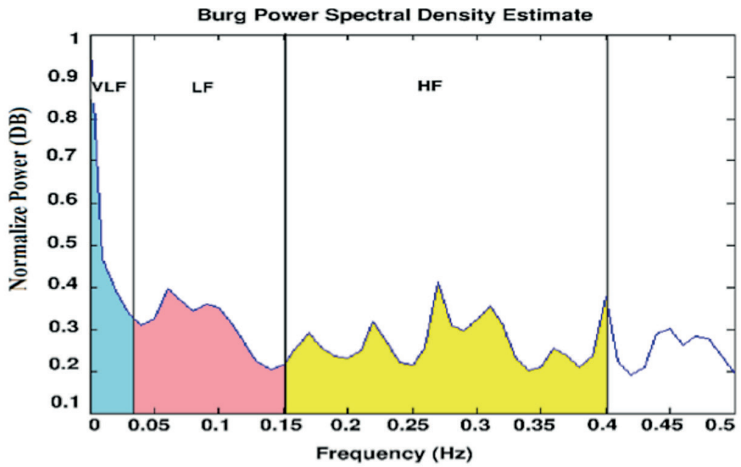

Figure 4 Power spectral density of the HRV signal indicating the difference frequency bands. Adapted from (58).

The HF power, also called respiratory band, indicative of the changes in the heart rate that is primarily prompted during respiratory cycle, mainly comprise activation during expiration and inhibition during inspiration. For this reason, most frequency domain analyses reflect parasympathetic activity. This effect of respiration on heart rate is a phenomenon that is referred to as, 'respiratory sinus arrhythmia (RSA)'(53). The LF band has been reported to also characterize both sympathetic and parasympathetic activities (43). The LF has been earlier referred to as the baroreceptor range because it mainly reflects activity during resting conditions (57). In addition, its sympathetic tone feature is thought to be more dominant (59). This interpretation forms the basis of using the LF as an index to estimate sympathovagal balance. For example, during Orthostatic tilt, there is an increase in LF and a decrease in HF fluctuations, which corresponds to activation of sympathetic and withdrawal of vagal activity as a response to tilting. Moreover, the LF represents oscillations related to regulation of blood pressure and vasomotor tone (53).

Past studies have even proposed the use of the ratio of LF to HF (LF/HF) for quantifying the changing relationship between sympathetic and parasympathetic activities. The use of LF/HF ratio has gained wide acceptance mainly because it is easy to interpret. An increased ratio of LF/HF is interpreted to represent a shift towards a "sympathetic dominance" (>2), while the opposite corresponds to a "parasympathetic dominance"(15). This was based on the postulation that HF and LF represents cardiac parasympathetic tone and sympathetic outflow, respectively (53, 60). The LF and HF indices are also expressed in normalized values, which is a second step measure after the initial estimation of the power in the LF and HF bands. The normalized units (nu) indices are based on the following formula (61).

$$LFnu = LF/(LF + HF)$$
$$HFnu = HF/(LF + HF)$$

The normalization of the spectral HRV measures of LF and HF makes it easier to understand the proportion of the quantities expressed, and even exchange values across different laboratories. Normalization also ensures removal of within and across subject variability in the total HRV spectral power (61). The VLF is generally believed to be a factor that is related to thermoregulation and kidney function. However, it occurs less frequently during short term recording just like the ULF. Their effects on the ANS are computed mainly during long term HRV recordings (24hours).

In summary, the parameters of the HRV analyses expressed in ms^2 have clinical application unlike those expressed in hertz. All HRV analysis parameters (Table 2) give information about the sympathetic and parasympathetic tone to the

Table 2 Heart rate variability parameters. Adopted and modified from (25, 62, 63).

Variable	Units	Description
Time domain analysis		
Statistical measures		
SDNN	ms	Standard deviation of all normal R-R intervals (same as SDRR)
SDANN	ms	Standard deviation of the mean of all 5-min segment of normal R-R intervals
RMSSD	ms	The root mean square of differences of successive RR intervals
NN50(count)		Number of consecutive RR intervals that differ more than 50 ms
pNN50	%	The percentage value of consecutive RR intervals that differ more than 50 ms
Mean-RR	ms	
Geometric measures		
RR triangular index		The integral of the RR interval histogram divided by the maximum of the histogram
TINN	ms	Baseline width of the RR interval histogram
Differential index		Difference between the widths of the histogram of differences between adjacent NN intervals (in heights)
Logarithmic index		Coefficient of the negative exponential curve which is the best approximation of the histogram of absolute differences between adjacent NN intervals
Frequency domain analysis		
Spectra measures (parametric and non-parametric)		
Total power	ms^2	Peak frequencies of the power spectral density estimate for VLF, LF, and HF frequency bands (Hz)
ULF	ms^2	The powers for ultra-low frequency bands in ms^2 and in percentage value.
VLF	ms^2	The powers for very low frequency bands in ms^2 and in percentage value.
LF [LFnu]	ms^2	The power in the low frequency bands in ms^2 , in percentage value [and also represented in normalized units (n.u)].
HF [HFnu]	ms^2	The power in the High frequency bands in ms^2 , in percentage value and [also represented in normalized units (n.u)].
LF/HF	ratio	Ratio of LF and HF frequency band powers

heart (64). The VLF power is only applicable to long terms (typically 24 hrs.) and cannot be interpreted from short-term measurements. The LF power reflects both sympathetic and parasympathetic changes in heart rate largely due to the effect of the baroreflex system. Therefore, higher LF scores indicate optimum functioning of the autonomic control of the heart. The HF power reflects parasympathetic influence - changes in heart rate largely caused by breathing (vagus control), while the LF / HF ratio reflects balance between sympathetic and parasympathetic (43). The higher the ratio, the more sympathetic dominance.

3.1.3 Nonlinear analyses of the HRV

The nonlinear analysis of the HRV offers a robust interpretation of the HRV in less stable conditions. It uses a symbolic analysis of 3-beats sequences to distinguish between both branches of the ANS (3). Due to the likelihood that the neural modulation of cycle length (CL) of the SA node is not linear, hence, the complete reliance on the use of linear HRV analysis may be limited in its interpretation or scope (45). The nonlinear HRV analysis fills this gap by providing us with innovative indices that are capable of increasing the understanding of the correlation properties and even characteristics of heart rate behavior (Table 3).

Poincaré plots

The Poincaré plots (also called return map) of HRV is one of the recent means of HRV analysis that presents the nonlinear dynamics of both randomness of heart rate and autonomic modulation (50, 65), and it shows the nature of fluctuations in the heart rate (66). The plot itself is a graph of every RR interval plotted against the prior interval, thereby creating a scatter plot (57). More importantly, Poincaré plot is a quantitative-visual tool that shows the shape of the plot as well as the summary of the beat-to-beat information on the behavior of the heart that can be categorized into functional classes that reflect the degree of problems in the heart function (Figure 5) . Poincaré analysis allows researchers to visually observe patterns buried within a time series.

Additionally, the 'width' of the Poincaré plot is reported to be a measure of parasympathetic nervous system activity (67). Generally, the shape of the plot is quantified by fitting an ellipse into the data points oriented along the line-of-identity (LOI). The width and length of the ellipse are determined by the standard deviations of the points perpendicular to and along the LOI and they are denoted by SD1 and SD2, respectively. The SD1 index measures short-term HRV variability, whereas SD2 index measures the long-term HRV variability (68) [Figure 5].

Table 3 Nonlinear heart rate variability parameters.

Variable	Units	Description
Poincare plot		
SD1	ms	The standard deviation of the Poincaré plot perpendicular to the line-of-identity
SD2	ms	The standard deviation of the Poincaré plot along the line-of-identity
Recurrence plot		
Lmean	beats	Mean line length
Lmax	beats	Max line length
REC	%	Recurrence rate
DET	%	Determinism
ShanEn		Shannon entropy
Other		
ApEn		Approximate entropy
SampEn		Sample entropy
DFA:α1		Detrended fluctuations
DFA:α2		Detrended fluctuations

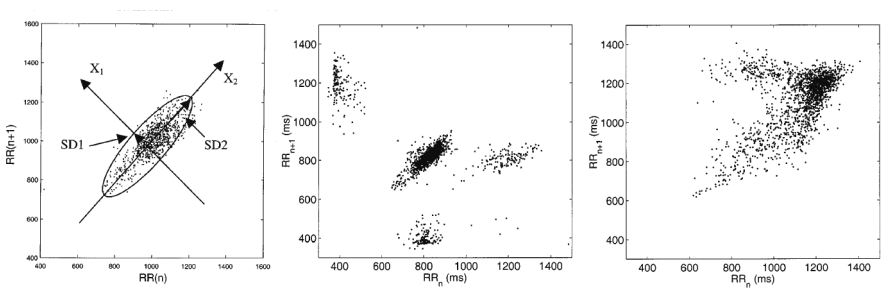

Figure 5 Poincaré plots (66).

The figure on the left shows the ellipse fitting process in a normal plot. The coordinate system x1 and x2 is established at 45° to the normal axis. The standard deviation of the distance of the points from each axis determines the width (SD1) and length (SD2) of the ellipse.
The figure in the middle is that of a subject who has intermittent ventricular premature contractions. The Poincaré plot clearly separates the activity caused by the ectopic and the activity caused by sinus rhythm.
The figure on the right is that of a subject with prominent RSA. The oscillation caused by respiration causes a gradual increase in heart rate during inspiration, followed by a rapid decrease during expiration. This causes the plot to appear asymmetrical.

Recurrence plot

Several parameters including mean line length (Lmean), maximum line length (Lmax), recurrence rate (REC), determinism (DET) and Shannon entropy of line length distribution (ShanEn) comprise the recurrence plot, which helps in analyzing the complexity of the nonlinear HRV data. The recurrence plot uses variables such as the embedding dimension (*m*) and threshold (*r*) values as such as the D_2 (the minimum number of dynamic variables needed to model the underlying system) to produce a binary square matrix consisting of values of either 0 and 1 point (68). Higher D_2 values indicate greater degree of complexity.

Other nonlinear HRV analyses variables

Other nonlinear parameters include the sample entropy (SampEn), which provides a reliable measure signal regularity and complexity especially for data from short time series. The approximate entropy (ApEn) also measures the complexity or irregularity of the HRV based on two parameters; the embedding dimension (m) and tolerance (r). ApEn values indicate low predictability of fluctuations in successive RR intervals, and small ApEn values is indicative of a regular and predictable signal, i.e. the smaller the ApEn values, the better the cardiovascular autonomic functioning of the heart (57). Other nonlinear HRV analysis are: (i) detrended fluctuations analyses (DFA), which is the extracts of the correlations between successive RR intervals over different time scales. These DFA correlation results in two slopes; (i) α1, which describes brief fluctuations and also reflects the baroreceptor reflex, while (ii) the α2 describes the long-term fluctuations and that reflects the regulatory mechanisms that limit fluctuations in a beat cycle. The DFA is decreased in cardiovascular disorders such as myocardial infarction (57, 69); and (ii)) the D_2, which refers to the minimum number of dynamic variables needed to model the underlying system (68). Higher D_2 values indicate greater complexity, and hence better cardiac autonomic functioning (57).

3.2 Baroreceptor sensitivity

The baroreceptor system comprises a cardiovascular and a CNS aspect. It is one of the most important systems responsible for cardiovascular autonomic control (70), as well as a significant prognostic variable in cardiovascular medicine (71). The baroreflex system adjusts the heart rate and sympathetic output to blood vessel intermittently, thereby, preventing wide fluctuations in the blood pressure at the same time maintaining blood flow to the brain (72). The baroreceptor functions in a linear relationship (between the systolic blood pressure and R-R interval) model that is referred to as the sigmoidal stimulus (73).

Baroreceptors are located in the aortic arch and carotid sinus anatomically, making them well positioned to relay information regarding blood pressure changes to the CNS [Figure 6].

Even though the BRS remains continuously active both in rest by inhibiting sympathetic activity, it mainly functions upon external or internal stimulation such as valsalva maneuver, exercise, stress and food intake. Expectedly, the impairments in the functioning of the baroreflex are associated with cardiovascular disease.

In the laboratory or clinical setting, the BRS can be assessed with the aid of devices that monitors the fluctuations in the heart rate per unit blood pressure changes (expressed in ms/mmHg). Two major techniques have been widely used in the assessment of BRS; (i) the first technique measures the reflex response to external stimuli such as Valsalva maneuver (VM) and head up tilt (HUT) when the focus is on sympathetic stimulation (75), (ii) the second and more advanced technique with clinical relevance and does not require external intervention even by subject. Here the resting cardiovascular parameters are continuously evaluated for the fluctuations in heart rate and blood pressure correlation (regression) in mostly a standard laboratory (71, 76). The second method provides a more accurate and reliable estimate of the BRS (71) compared to the first, which has some limitations (76). Figure 7 illustrates both normal and abnormal BRS and cardiovascular responses to VM. Finally, the BRS index is a parameter that reflects the rate of parasympathetic function. Higher BRS values reflects better function of the autonomic functioning of the heart.

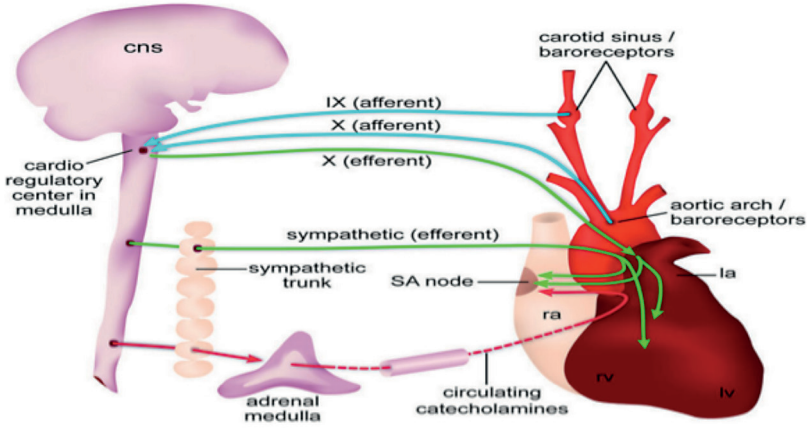

Figure 6 Baroreceptor reflex innervation (sympathetic and parasympathetic). Adapted from (74).

3.3 Muscle/skin sympathetic nerve activity (MSNA/SSNA)

The MSNA and SSNA represents the measure of the peripheral sympathetic activation that is generally increased in COPD. The MSNA can be determined in using microneurography, a process whereby the nerve activity is recorded directly from intraneural microelectrodes inserted percutaneously into a peripheral nerve. Presently, the quantification of the MSNA is limited to measures of burst frequency (bursts/minute) and burst incidence (bursts/100 heart beats) (77). Another major constraint is the difficultly in applying microneurography in routine clinical settings is that it is invasive, assesses only a localized segment of the nervous system (sympathetic tone in the peripheral nerves), and requires a high level of expertise and is time consuming.

3.4 Heart rate recovery

The heart rate recovery (HRR) is a simple-to-measure vagal mediated recovery of the heart to pre-exercise levels following an exercise training. Specifically, HRR, which is measured in beats per minute, refers to the fall in the heart rate during

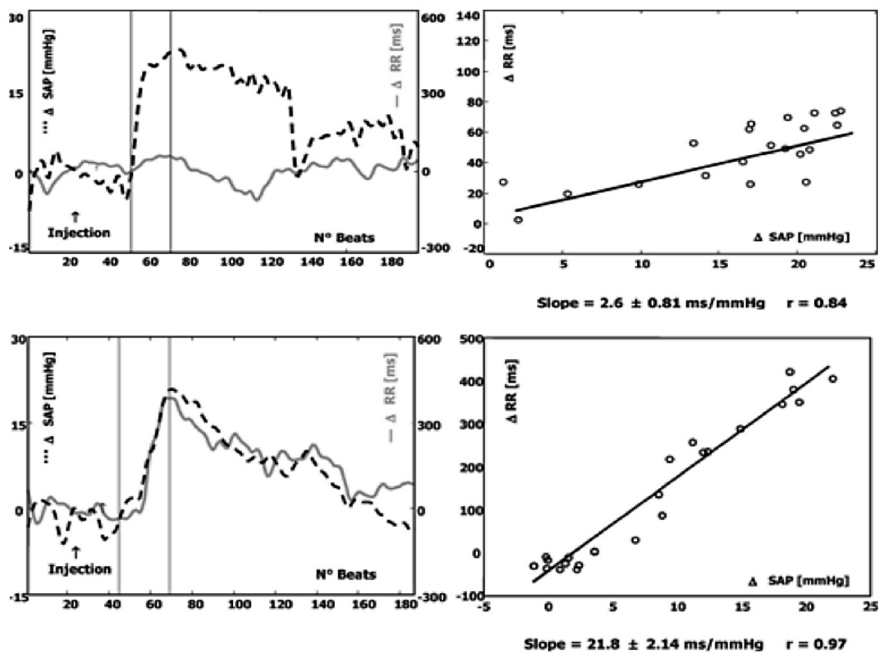

Figure 7 Examples of a normal (top) and abnormal (bottom) BRS response (82).

Note the beat-to-beat changes in systolic arterial pressure (SAP) (dotted line) and in RR intervals (solid line) in both figures.

the first minute after peak exercise (HRR = heart rate $_{peak}$ – heart rate$_{1\ minute\ recovery}$) (78, 79). Abnormal HRR after symptom-limited exercise predicts mortality (78, 79). The HRR has been used as an outcome for assessing the effect of exercise intervention on the autonomic control even in COPD patients populations (80, 81).

3.5 Metaiodobenzylguanidine (MIBG) scintigraphy/imaging

The MIBG imaging is a direct, noninvasive and quantitative method of assessing cardiac (adrenergic) autonomic dysfunction. The test is based on the principle that impaired MIGB uptake by the myocardial muscle is associated with sympathetic denervation (83), specifically impairments in the NE reuptake function (84). The test is performed by injecting iodine-123 (I-123) MIBG, a norepinephrine analog that shares the same uptake-I mechanism into sympathetic nerve terminals, and scintigraphically assessing MIBG uptake and release measurements on the planar images obtained at different time intervals (prior and after injection) (84).

The MIBG test has a long-term prognostic capacity to predict cardiac death, and for identifying threshold levels for patients at risk of cardiovascular diseases (85, 86). Currently, it is more utilized in cardiology for conditions such as cardiomyopathy, myocardial infarction, heart failure and long QT syndrome (83, 85). Nevertheless, a few studies have adopted the test for other patient populations especially those with established autonomic neuropathy (87, 88).

4. Assessment of the ANS function using autonomic reactivity tests

In the past, a group of tests reflecting either cardiac parasympathetic or sympathetic damage was developed for assessing diabetic autonomic neuropathy (27). These tests, mainly comprise an evaluation of abnormal responses of the heart rate to VM, HUT or standing, and the heart rate variation during deep breathing, to assess parasympathetic damage. The other two tests are blood pressure response to standing and hand grip tests to assess sympathetic damage. All these tests are popular in assessing the ANS integrity. And have been utilized commonly to provide clinically important information regarding the distribution, location and even severity of the ANS deficits. For this reason, the autonomic reflex test battery, which assesses the reaction of the ANS to stimuli such as deep breathing, VM and HUT, is considered as a standard measure (40, 89-91).

Several other tests including evaluation of resting values of HRV and the baroreflex receptor sensitivity, which connotes the rate of fluctuations in blood pressure, have also been used in several patient and non- patient populations (92-95). The subsequent sections will provide a detailed description of the 3 notable

autonomic reactivity tests, namely heart rate during deep breathing HR_{DB}, VM and HUT tests.

4.1 Deep breathing

The deep breathing is a widely utilized and popular test (89, 96, 97) that is based on the principle of respiratory sinus arrhythmia (RSA) maneuver. The RSA connotes the modulation of cardiac vagal efferent activity by the central respiratory drive (98) via the premotor cardio inhibitory parasympathetic neuron activity and the lung inflation reflex. With healthy individuals, the heart rate increases during inspiration and decreases during expiration (99). The deep breathing test is conducted by performing 8 consecutive breathing cycles at a rate of 6 breaths/minute. The average value of the differences between the maximum and minimum heart rate of 5 consecutive and largest responses is then calculated as the heart rate during deep breathing (HR_{DB}) (28). The HR_{DB}, which is also referred to as expiratory-inspiratory ratio [IE ratio], is a parasympathetic parameter. Higher values represent better autonomic control of the heart. The normative/reference values are presented in Table 4.

4.2 Valsalva maneuver

The VM represents a natural challenge for the baroreceptors (82). It is a test with both respiratory and circulatory implications. When VM is evoked, it incites a sequence of rapid changes in preload and afterload stress on the cardiovascular system. During the strain, venous return to the heart is decreased and peripheral venous pressures become increased (100). Thereafter, systolic and pulse pressures begin to fall, while mean arterial pressure remains stable. In the laboratory, the test is evoked by blowing at a pressure of between 40 and 50 mmHg through a mouthpiece + plastic tube (with a small air leak) connected to a manometer usually in a supine position except conditions warrant some degree of tilting (101).

Under normal conditions and under continuous recording of beat-to-beat finger plethysmography and blood pressure monitoring, the blood pressure goes through 4 phases during VM. The first phase (I) is when the test is initiated, and it is characterized by intra-thoracic and intra-abdominal pressure surges causing mechanical compression of the aorta, which leads to an increase in blood pressure. The early second phase (II_E) of the VM kicks in when the cardiac output and blood pressure starts to drop due to the effect of the already increased intra-thoraco-abdominal pressure on the venous return (venous preload), thereby prompting a sympathetic response (vasoconstriction in the extremities thereby increasing peripheral resistance). The late second phase (II_L) occurs as a consequence of sympathetic activation aimed at restoring blood pressure back to normal levels. The next phase (third) launches after the VM is stopped. Here, the intrathoracic

pressure drops suddenly causing the blood pressure to fall quickly. A mild sympathetic activation occurs for about 1 or 2 seconds to restore the blood pressure back to normal levels again. Finally, the fourth phase(IV) comprises a rise in the blood pressure rises again leading to an overshooting above the resting levels due to a persisting vasoconstriction in the extremities even after CO and venous return are back to normal levels (102).

The response to VM depends on the integrity of the BRS pathway. Blunting of the HR is an indication of impairment in vagal component of the BRS, while adrenergic failure is manifested as loss of normal phase II_L and phase IV pattern. Both the function of the sympathetic and parasympathetic components of the ANS can be assessed using the responses of the blood pressure (103) and heart rate(104) to VM, respectively. Figure 8 illustrates a normal and abnormal cardiovascular responses to VM.

A number of parameters can be derived from the VM test (28). These include: (i) Vasalva ratio (VR), which is a parasympathetic variable that is calculated as the ratio of the maximum HR (HRmax) during VM and the maximum HR within 30 seconds from the HRmax; (ii) Valsalva index (VI) is calculated as the ratio between the longest RRi during VM recovery (phase 4) and the shortest RRi during the peak of VM. A VI of less than 1.4 is considered abnormal (104); (iii) blood pressure drop is a sympathetic nervous system variable that is expressed as the value of the BP during the phase II minus baseline value (negative values are referred to as BP drops, while positive values are blood pressure rise); (iv) insufficient recovery is when the blood pressure parameters fail to rise up to baseline in phase II L; (v) pressure recovery time (PRT) is the time (in seconds) between the lowest point of phase III and the return of the blood pressure to the baseline. the longer this time, the more abnormal and it is reflective of sympathetic abnormality; (vi)

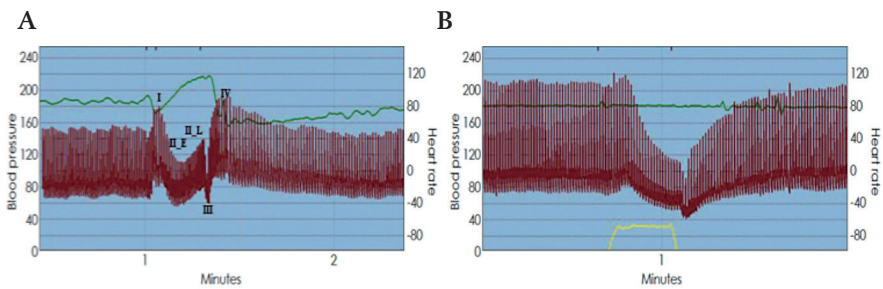

Figure 8 Cardiovascular (heart rate and beat to beat blood pressure) responses to VM test (103). (**A**) normal subject, and (**B**) subject with diabetic autonomic neuropathy. All the VM phases are also indicated (I, ll_E, II_L, lll, IV). HR is the line in green.

pulse pressure (pp) drop during VM is the difference between the baseline pulse pressure and the pulse pressure during the VM. The deeper the PP falls during valsalva, the more this indicates sympathetic failure. The normative/reference values of some VM indices are presented in Table 4.

A number of parameters are also calculated from the VM parameters. They include the adrenergic BRS (BRS_a), which is a sympathetic measure. Lower BRS_a values are indicative of abnormal sympathetic functioning. The next is the vagal BRS (BRS_v), which is a parasympathetic measure. Here, lower, values reflect abnormal parasympathetic functioning. The last is the global BRS (BRS_g), which is a product of BRS_a and BRS_v. Lower BRS_g values are abnormal.

4.3 Head up (passive) tilt

The HUT is a passive tilt of at least 60° angle from a supine position on a tilt table or couch. The test has been used for detecting vasovagal syncope and other orthostatic symptoms (105, 106). Head-up tilt is utilized for as a valuable research tool by physiologists and/or physicians to study the hemodynamic and endocrine adaptation to changes in position. During tilting, there is activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system activity (67). These lead to changes in the body, which include blood redistribution from thorax to the extremities, significant fall in stroke volume and blood pressure (107).

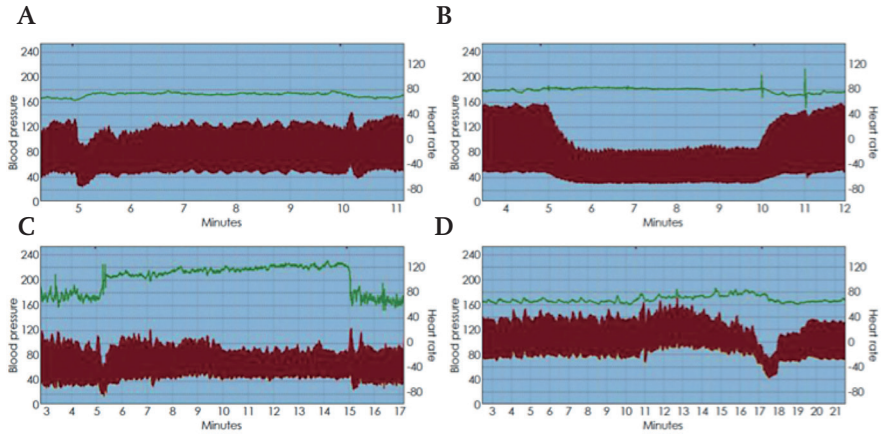

Figure 9 Cardiovascular (heart rate and beat to beat blood pressure) responses to HUT test in normal subject (**A**), neurogenic OH patient indicated by a pronounced fall in blood pressure (**B**), POTS indicated as an increased HR without OH (**C**), and syncope which is characterized by and abrupt fall in blood pressure (**D**). Adapted from (103).

However, these changes are minimized in healthy subjects through a number of compensatory mechanisms involving the ANS (early phases), renal system and through the action of hormones (later phases). Furthermore, the baroreceptors (initiating a decrease in the parasympathetic outflow and a corresponding increase in sympathetic outflow), veno-arteriolar reflex (by constricting arterioles in the muscles fat and skin), respiration and muscle pumps are also known to contribute to mitigate the impact of tilting on the various body systems (108).

Individuals with compromise to either ANS or any of the above-mentioned systems usually exhibit abnormal responses to HUT. These abnormal responses may include; (i) initial orthostatic hypotension, defined as a transient drop in blood pressure amounting to >40 of SBP mmHg and >20mmHG of DBP within the first 15 seconds of head up tilt, (ii) orthostatic hypotension, defined as a drop in blood pressure that is >40 of SBP mmHg and >20mmHG of DBP within 3 minutes of head up tilt either as a result of hypovolemia or neurogenic cause, (iii) delayed orthostatic hypotension is the fall blood pressure that occurs after 3 minutes of tilting, (iv) postural orthostatic tachycardia syndrome refers to the sustained and excessive increases in the heart rate of at least 30 bpm or reaching a heart rate of 120 bpm or higher during a 10 minutes tilt, (v) vasovagal syncope (reflex syncope) is the loss of consciousness that follows a large and abrupt decrease in the systemic blood pressure, and (vi) orthostatic hypertension, which refers to an increase in the SBP or 20 mmHg or more. Table 4 presents selected HUT parameters reference values.

5. Autonomic reflex screening (battery) tests for grading of autonomic failure

More recent advancement in the field of autonomic function testing has led to the development of a number of laboratory tests that can be used to assess the level of autonomic failure. In this dissertation, we will focus on the composite autonomic scoring scale (CASS) and the quantitative autonomic reflex and small fibers tests (QASAT) methods for grading autonomic failure.

5.1 Composite autonomic scoring scale (CASS)

The CASS comprises three subscales: an adrenergic, sudomotor and a cardiovagal. The adrenergic and cardio-vagal subscales represent cardiovascular reflex tests, while the sudomotor test is assessed by quantitative sudomotor axonal reflex test (QSART). The CASS is slightly weighted to recognize the importance of adrenergic function, by allocating 4 points to it, while only 3 points are assigned to postganglionic sudomotor and cardiovagal functions. Grading autonomic failure

Table 4 Normative values for Derp breathing, Valsalva and HUT tests. Adapted from (109) and (110).

Test	Normative value
Deep breathing	
Respiratory sinus arrhythmia	50-59 years (≥9 beats per minute)
	60-69 years (≥7 beats per minute)
Valsalva maneuver	
Valsalva ratio [VR]	50-59 years (female, 1.47; male, 1.36) 60-69 years (female, 1.39; male, 1.29)
Maximal drop of the MBP during the early phase 2	≥20 mm Hg
MBP at phase IV (recovery)	≥ baseline (mmHg)
MBP at phase IV (overshoot)	> baseline (mmHg)
Maximal pulse pressure drop	>50% of baseline
Systolic pressure recovery time	<4 seconds
HUT	
First 15 seconds of HUT	Systolic BP, <40 mmHg; diastolic BP <20 mmHg of baseline
Within 3 minutes of HUT	Systolic BP, <20 mmHg; diastolic BP <10 mmHg of baseline
After 3 minutes of HUT	≥ baseline <20 mmHg
Throughout test	HR increases should be < 30 beats per minute or should remain <120 beats per minute

is possible using this scores (Table 5) (109). To calculate the cardiovagal score, both deep breathing and Valsalva ratio are required. Adrenergic score requires both Valsalva maneuver and tilt test results, while sudomotor score can be calculated from QSART results or from the thermoregulatory sweat test (109).
The CASS provides a quantitative estimation of autonomic failure in cardiovagal (score 0-3), adrenergic (score 0-4), and sudomotor (score 0-3) domains as well as total score (0-10). Generally, a total CASS score of 0 represents no autonomic failure, 1-3 indicates no or mild autonomic failure, scores from 4 to 6 indicate moderate autonomic failure, while scores from 7 to 10 indicate severe autonomic failure (Table 6).

The original developers of CASS have identified a number of limitations with the scale (111). Firstly, the CASS does not take into account the baseline heart rate and other mechanisms underlying changes in heart rate variability during the subscale of cardiovascular heart rate index also known as the HR_{DB} test (111). Secondly, the adrenergic subscale, which is only defined as a combination of abnormal blood pressure responses to VM and the presence of orthostatic

Table 5 Laboratory grading of autonomic failure. Adapted from (109).

CASS Indices	Interpretations
Sudomotor index	
0	Normal (≥ normative value)
1	Single site abnormal on quantitative sudomotor axon reflex test *or* Length-dependent pattern (distal sweat volume < 1/3 of proximal value) *or* Persistent sweat activity at foot (on thermoregulatory sweat test, anhidrosis present but <25%).
2	Single site <50% of lower limit on quantitative sudomotor axon reflex test
3	Two or more sites <50% of lower limit on quantitative sudomotor axon reflex test (on thermoregulatory sweat test, anhidrosis present >50%)
Adrenergic	
0	Normal (≥ normative value)
1	Phase II, decrease of <40 but >20 mm Hg mean BP *or* Phase II, does not return to baseline *or* Decrease in pulse pressure to ≤50% of baseline
2	Phase II, decrease of <40 but >20 mm Hg mean BP + phase II, or IV absent
3	Phase II, decrease of <40 but >20 mm Hg mean BP + absent phases II and IV
4	Criterion for 3+ orthostatic hypotension (systolic BP decrease of ≥30 mm Hg; mean BP decrease of ≥20 mm Hg
Cardio-vagal	
0	Normal (≥ normative value)
1	HR_{DB} or VR mildly decreased (≥50% of minimal normal value)
2	HR_{DB} or VR decreased to <50% of minimal normal value
3	Both HR_{DB} and VR decreased to <50% of minimal normal value

Table 6 Laboratory grading of autonomic failure based on the CASS. Adapted from (28).

Composite autonomic scoring scale	Degree of autonomic failure
0	No
1-3	Mild
4-6	Moderate
7-10	Severe

Table 7 Cardiovascular component of QASAT. Adapted from (111).

Heart rate			
1. Bradycardia – Supine and/or during tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	HR ≥ 50 BPM
Abnormal		1	HR < 50 BPM
*HR = heart rate, BPM = beats per minute, at least 10 minutes of the rest should be obtained			
2. Tachycardia- supine			
Results	***Grading***	***Value***	***Definition***
Normal		0	HR ≥ 100 BPM
Abnormal	Mild	1	HR < 100 BPM
3. Increased heart rate response to tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	HR increment ≥ 10 BPM and < 30 BPM during tilt and HR ≤ 110 during tilt
Abnormal	Mild	1	HR > 110 but ≤ 120 BPM during tilt only or HR increment during tilt >30 BPM and HR ≤ 120 BPM during tilt
	Moderate	2	HR > 120 BPM and < 150 BPM and HR increment during tilt > 30 BPM or HR > 150 BPM and HR increment during tilt < 30 BPM
	Severe	3	HR > 150 BPM and HR increment during tilt > 30 BPM
At least 10 minutes of tilt should be obtained			
4. Reduced heart rate response to tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	HR increment ≥ 10 BPM and < 30 BPM during tilt
Abnormal		1	HR increment during tilt <10 BPM
5. Heart rate variability			
Results	***Grading***	***Value***	***Definition***
Normal		0	*Heart rate variations to deep breathing test
Abnormal	Mild	1	abnormal but ≥ 50% of normal value*
	Moderate	2	< 50% but ≥ 35% of normal value
	Severe	3	< 35 % of normal value
Blood pressure			
6. Supine hypotension			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal		1	SBP < 90 or DBP < 60

Table 7 Continued.

7. Orthostatic hypotension during tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	*Abnormal result is defined as a systolic BP ≤ 80% of baseline or a mean BP ≤85% of baseline. Baseline is defined as the BP in supine position just before the tilt test
Abnormal	Mild	1,2	
	Moderate	3,4	
	Severe	5,6	
	Marked	>6	
8. Valsalva maneuver-blood pressure			
Results	***Grading***	***Value***	***Definition***
Normal		0	End of phase 2 returns to or exceeds the baseline
	End of phase 2 fails to return to baseline, the reduction is:		
Abnormal	Mild	1	≥ 90% of baseline
	Moderate	2	< 90% but ≥ 60% of baseline
	Severe	3	< 60 % of baseline
9. Supine hypertension			
Results	***Grading***	***Value***	***Definition***
Normal		0	SBP < 140 or DBP < 90
Abnormal	Mild	1	(SBP ≥ 140 or DBP ≥ 90) and (SBP < 160 or DBP < 100)
	Moderate	2	(SBP ≥ 160 or DBP ≥ 100) and (SBP < 180 or DBP < 110)
	Severe	3	SBP ≥ 180 or DBP ≥ 110
10. Orthostatic hypertension during tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	SBP ≤ 120% of baseline
Abnormal		1	SBP > 120% of baseline

hypotension. The CASS lacks other components/factors like the supine hypo-/hypertension or excessive heart rate increment to tilt which are also based on adrenergic functions (111). Lastly, the sudomotor component of the CASS is based upon the QSART which grades only the postganglionic sudomotor deficit (111).

5.2 Quantitative autonomic reflex and small fibers tests (QASAT)

The QASAT represents the most recent improvement in the measurement of autonomic function across the major components of the ANS. Unlike the CASS that is based upon cardiovascular tests, and QSART, the QASAT also assesses small fiber densities obtained from skin biopsies and cerebral blood flow. The QASAT has

Table 8 Cerebral blood flow component of QASAT. Adapted from (111).

11. Valsalva maneuver – cerebral blood flow			
Results	***Grading***	***Value***	***Definition***
Normal		0	≥ 85 % of baseline*
Abnormal	Mild	1	≥ 80 and < 85 % of baseline
	Moderate	2	≥ 65 and < 80 % of baseline
	Severe	3	< 65 % of baseline
12. Cerebral autoregulation			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal		1	Systolic CBFV > 160 cm/s during phase 4 and (Systolic CBFV-Diastolic CBFV) phase 4/ (Systolic CBFV − Diastolic CBFV)baseline) > 140 %
13. Supine cerebral blood flow low			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal		1	< upper normal limit
14. Supine cerebral blood flow high			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal		1	> upper normal limit
15. Cerebral blood flow response to tilt			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal	Mild	1,2	
	Moderate	3,4	
	Severe	5,6	

Using mean CBFV. CBFV should be measured at baseline, and at 1,5 and 10 minutes of tilt. *At each measurement, assign the value 0 for normal results. Abnormal results are defined as CBFV less than normal limit. Normal limit is defined as follows: At 1.minute: normal drop of CBFV ≥ 90%. Assign 1 for CBFV 80 − 89% of baseline, 2 for 70 - 79% of baseline and 3 for < 70% of baseline. AT 5. minute: normal drop of CBFV ≥ 89%. Assign 1 for CBFV 79 − 88% of baseline, 2 for 69 -78% of baselines and 3 for < 69% of baseline. At 10. minute: normal drop of CBFV ≥ 86%. Assign 1 for CBFV 77 − 85% of baseline, 2 for 67 - 76% of baseline and 3 for < 67% of baseline. Total score is obtained by sum of all scores. For tilt, longer than10 minutes, additional measurements should be obtained every 5 minutes with the same grading as used at 10th minute.

Table 9 Small fiber Neuropathy component of QASAT. Adapted from (111).

Sudomotor			
16. QSART			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal	Mild	1	Single site ≥ 50 % and < 100 % or Length-dependent pattern* or Persistent sweat activity
	Moderate	2	Single site < 50% or Two or more sites < 100 % and ≥ 50 %
	Severe	3	Two or more sites < 50%
*100% = normal limit. At least 3 sites should be studied. *Length dependent pattern is defined as a reduction of the distal sweat volume more than 1/3 of proximal value.			
17. Sweat gland nerve fiber density			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal	Mild	1	Single site < 100% and ≥ 85 % of lower limit
	Moderate	2	Single site < 85% and ≥ 65 % or two sites < 100 % and ≥ 85 %
	Severe	3	One site < 65% or two or more sites <85% and ≥ 65 %
	Marked	4	One site < 50% or two or more sites < 65%
*100% = normal limit. At least 1biopsy should be done at the distal leg (10 cm above the lateral malleolus), with a second site at the thigh (20 cm distal to the iliac spine).			
18. Epidermal nerve fiber density			
Results	***Grading***	***Value***	***Definition***
Normal		0	
Abnormal	Mild	1	Single site < 100%* and ≥ 70 %
	Moderate	2	Single site < 70% and ≥ 40 % or two sites < 100% and ≥ 70 %
	Severe	3	One site < 40% or two or more sites < 70% and ≥ 40 %
	Marked	4	One site < 20% or two or more sites < 40%
100% = normal limit. At least 1biopsy should be done at the distal leg (10 cm above the lateral malleolus) , with a second site at the thigh (20 cm distal to the iliac spine).			

Table 10 Laboratory grading of autonomic failure based on the QASAT. Adapted from (111).

Total of 18-item QASAT scores	Degree of autonomic failure
0	Normal
1-5	Mild
6-12	Moderate
>12	Severe

been validated recently in a large study sample and has been found to be of a greater advantage over the CASS. The final QASAT sections are grouped in 3 main categories: Cardiovascular (sections 1-10), Cerebral blood flow (sections 11-15) and Small fiber neuropathy (sections 16-18) as illustrated in Tables 7, 8 and 9, respectively (111). The total QASAT item-grade score is presented as Table 10.

6. Application of ANS measures in disease populations

Generally, the clinical assessment of the ANS is conducted with a view to predict or stratify patients that are at risk of cardiac events or sudden death after acute myocardial infarction and non-cardiac events such as diabetic neuropathy (25, 62). Current measures of the ANS either for physiological or clinical uses appear to differ depending on the protocol or purpose. Patients with COPD also present with many disease comorbidities (especially cardiovascular related), each with its potential influence on the autonomic function. Therefore, autonomic function test results ought to be interpreted carefully and viewed within specific contexts. For now, the overall HRV, which connotes vagal activity is able to give a clue regarding the sympathovagal influence of the ANS on the sinus node. A decreased HRV analyses is interpreted as an increase in the sympathetic dominance or a reduction in the vagal modulation of the sinus node.

Time domain HRV analysis has been reported to negatively correlate with the ejection fraction (45). Different cutoff points have been suggested for a number of autonomic function parameters (82). For example, the SDNN cut-off point of <70 milliseconds has been reported to be able to identify patients at risk of deaths due to ventricular fibrillation or heart pump failure(82). Furthermore, the frequency domain HRV analysis such as the LF/HF ratio recorded in the short term is utilized extensively to provide an index of the sympathovagal balance that can be useful for identifying disorders in early stages of myocardial infarction and even heart

failure. The nonlinear HRV analysis, which offers an outlook regarding the integrity of the ANS through the nonlinear behavior of the heart, also provides interesting results that are still being explored. Lastly, the BRS and the other measures of the autonomic function are potentially useful for prognostication and predicting cardiac related mortality various patient populations especially when impaired vagal reflexes are identified (82).

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Chapter 3

Autonomic function and its influencing factors in subjects with chronic obstructive pulmonary disease: a systematic review

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Abstract

Cardiovascular autonomic neuropathy is one of the factors implicated in the high morbidity and mortality rate in patients with COPD. Thus, several studies and nonsystematic reviews have increasingly reported autonomic function impairment in these patients. For a better understanding, this systematic review was performed to evaluate not only the evidence for autonomic function impairment, but also factors influencing it. The results of the studies reviewed revealed a strong level evidence to support the impairment of heart rate variability in the time domain. A similar evidence level was found to support the impairment in baroreceptor sensitivity (BRS) and muscle sympathetic nerve activity (MSNA). Furthermore, this review identified physical activity level, muscle function and circadian rhythm were identified as the major influencing factors (strong evidence) of autonomic function in subjects with COPD. However, no definite conclusion could be reached for factors such as dyspnea, anxiety, body composition, pulmonary function, age, respiratory rate, ventilatory effort, quality of life and disease severity due to limited, conflicting or lack of existing evidence. The results of this review highlight relevant clinical messages for clinicians and other health-care providers regarding the role autonomic function can play as an important physiological marker for prognostication and stratification. Hence, autonomic function outcomes should be identified and considered during management of patients with COPD. Moreover, this review can serve as basis for future research aimed at assessing the interventions for autonomic function abnormalities in these patients.

Keywords: *Nervous system disease, autonomic, sympathetic, parasympathetic, chronic obstructive, pulmonary disease, review.*

Introduction

COPD is a highly prevalent cause of disability and mortality characterized by airflow limitation that is not fully reversible (1). Patients with COPD have features that encompass several body systems such as inflammation of the airways, cachexia or obesity, structural and functional changes in the respiratory and peripheral muscles, arrhythmias, fatigue, dyspnea, poor quality of life (QOL), reduced exercise capacity, depression, anxiety and sleep disturbances (1-8).

More recently, COPD is reported to adversely affect the autonomic nervous system (2, 5, 6) Consequently, the autonomic function in patients with COPD has received a considerable amount of attention in literature (2-7, 9-11). The autonomic nervous system controls and regulates the internal physiology of the body and plays a very important role in the pathophysiology of COPD. It consists of 2 branches (sympathetic and parasympathetic), both of which exert antagonistic effects on most bodily functions and also contribute to homeostasis in the body (12). Moreover, the autonomic nervous system is also responsible for maintaining involuntary vital parameters like blood pressure, heart rate, respiration, gastro intestinal secretions and temperature control.

Autonomic function can be directly assessed by monitoring and testing certain specific markers of the neurophysiologic condition of the autonomic nervous system. These include parameters like heart rate variability in time and/or frequency domain analysis, baroreceptor sensitivity, muscle sympathetic nerve activity, and sympathetic skin response. The heart rate variability, which is the variability in time and/or frequency of successive R waves of the heartbeats, reflects the integration between the cardiovascular system and the mechanisms it regulates. Moreover, the heart rate variability has been recognized as a parameter for assessing autonomic function and quantifying sympathovagal balance for many decades (1, 13). Additionally, baro-receptor sensitivity (which reflects the short-term regulation of the cardio-vascular system), muscle sympathetic nerve activity (which shows the degree of sympathetic activity in muscle nerves) and sympathetic skin response (which reflects the sudomotor function of the unmyelinated sympathetic nerves) are reported to be reliable measures of autonomic function (14-16).

The available data in literature suggest that autonomic function parameters of patients with COPD may be severely impaired (17-20). Nevertheless, for a better understanding, a systematic evaluation of the existing literature is necessary. Also, there is a need to evaluate the factors associated with autonomic function in patients with COPD, because this has not been clearly elucidated in literature. Therefore, this systematic review evaluated (1) evaluate the evidence on the autonomic function of subjects with COPD and (2) the factors associated with a possible altered autonomic function.

Methods

This systematic review is reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (21).

Eligibility criteria

To be included in this systematic review, studies had to report on either the autonomic function (outcomes) of patients with COPD (population) versus healthy participants (comparator) and/or the relationship between autonomic function and influencing factors. Only randomized control trials or patient control or cohort studies were retained.

Information sources and search strategy

To identify relevant articles, the databases of PubMed, Embase, and Web of Science were searched. Only articles published between January 2004 and May 2014 were included. The search strategy was based on a combination of the following key words: autonomic function OR autonomic dysfunction OR heart rate variability OR baroreceptor sensitivity OR muscle sympathetic nerve activity OR sympathetic skin response AND chronic obstructive pulmonary disease OR COPD. For the PubMed database, key words were also converted to possible MeSH terms. The search strategy for the Web of Science was done in the topic field using the key words autonomic function AND COPD. For the Embase database, the search terms were: autonomic AND function AND COPD. The search strategy for all databases was also filtered based on article type (clinical trial), language (English), and species (human). Additionally, a secondary search of the reference list of the included studies was undertaken to make the review as complete as possible.

Study selection

To be included in the review, the following inclusion criteria had to be fulfilled for each article. (1) Subjects had to be clinically diagnosed with COPD (explicitly stated). (2) The autonomic function parameters should comprise of at least one the following parameters for studies comparing subjects with COPD and healthy controls and/or reporting relationship between any of the parameters with influencing factors; (a) the heart rate variability in a time and/or frequency domain. The time domain may consist of (i) the square root of the mean of the sum of the squares of differences (RMSSD), (ii) RR interval (RRi), (iii) the SD of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN), (iv) SDs of all NN intervals (SDNN), (v) the total number of differences between adjacent RRi above 50ms (sNN_{50}), (vi) the percentage of RRi that differ from each other by >50 ms (vii) the ratio between the shortest RRi around the 15th beat and longest

RRi around the 30th beat (30:15 ratio), (viii) the difference in heart rate during inspiration and expiration (ΔIE), (ix) triangular interpolation of RRi, (x) the SD of instantaneous beat-to-beat variability (SD_1), (xi) standard deviation in long term of the RRi (SD_2) and (xii) the Valsalva ratio (the ratio of the longest RRi after release from the maneuver to the shortest RRi during the maneuver), (xiii) the ratio of the longest RRi during the 5 beats before lying down to the shortest RRi during 10 beats after lying down (S/L ratio), (xiv) SD of RRi (SDRR), (xv) the variability triangular index, (xvi) the average NN interval, and (xvii) the coefficient of variation of RRi (CVRR). The frequency (the density of beat-to-beat oscillation in the RRi) domain were recorded either in the high (0.15 - 0.4 Hz), low (0.04 - 0.15 Hz) and very low (0.00 – 0.04Hz) frequency bands, and may be described using parameters such as; (i) total power (TP), (ii) high frequency (HF), (iii) very low frequency (VLF), (iv) low frequency (LF) and (v) low-high frequency ratio (LF/HF). Additionally, the spectral components may be expressed as normalized units (nu), which is the absolute power/total power-VLF power × 100 (depicted as LFnu or HFnu); (b) the baroreceptor sensitivity expressed as ms/mm Hg; (c) the muscle sympathetic nerve activity expressed in burst frequency (burst/min) and/or burst incidence (burst/100 heartbeats); and (d) the sympathetic skin response expressed in terms of latency, area and amplitude in s, mV/s, and mV, respectively. (3) The article had to be published in English, and (4) it had to be a full-text original research report.

Initially, all search results were screened based on title and abstract. Thereafter, the full-text articles of studies that were considered potentially eligible and relevant were retrieved. All full-text articles were evaluated to ascertain whether they fulfilled the inclusion criteria. If an article did not fulfill all 4 criteria, it was excluded from the review.

Qualification of searchers

Literature was searched and screened by JM and PC (who has published systematic reviews) (12, 22-24).

Data items and collection

Information extracted from each of the included studies are presented in Table 1. This table provides: (1) author and year, (2) sample size and characteristics of participants, (3) inclusion and exclusion criteria, (4) results of autonomic function parameter comparison with controls, and (5) results of influencing factors.

Risk of bias in individual studies

To establish the validity of the selected articles, the risk of bias (methodological quality) in the articles was determined using specific checklists per design provided by the Dutch Cochrane Centre. The methodological quality was determined by

asking 7, 9 and 10 questions for the patients control, cohort and RCT studies, respectively, from the checklists as shown in Table 2. Methodological quality was assessed by 2 researchers (JM and HDS) who were not acquainted with each other's evaluation at first. We scored each question as either + (for informative description of the issue and study meets the criterion), or - (the study does not meet the criterion).

After rating the selected articles, the results of both researchers were compared, and the differences were analyzed. In case of disagreement, the reviewers screened the manuscript a second time, and each point of differences were discussed. Both reviewers also had the opportunity to argue and to convince one another to obtain a consensus. When consensus could not be reached a third and final opinion was provided by PC. Each study received a total method score, which was the sum of all positive (+) ratings from the checklists questions. For uniformity across different designs, the overall method score was converted to percentages. A study was considered to be high quality if the methodological quality ≥60% and low-quality if the methodological quality was <60% (25).

The evidence listing for the outcomes were classified according to the methods used by Barker et al (25). The possible evidence levels are: strong, moderate, limited, conflicting evidence and no evidence. Strong evidence represents consistent findings in at least 2 high- quality studies. Moderate evidence connotes consistent findings in one high and one low quality study or at least 2 independent studies of low quality. Limited evidence suggests that only one study is available. Conflicting evidence connotes inconsistent findings in the available studies (5).

No evidence refers to when no study that reported any autonomic function outcomes was found. Additionally, findings were considered consistent only if at least 75% of the available studies reported the same conclusion for the outcome in question.

Table 1 Evidence table of included studies.

Reference	Sample	Inclusion criteria	Results of autonomic function: COPD versus CON	Influencing factors (COPD): significant (*) relationship/association exist between;
Aggarwal et al., 2011	90 ♂COPD: 30 ♂CON:	COPD: Already diagnosed with COPD and attending clinic. No further details provided. CON: Healthy	30:15 ratio < S/L ratio< Valsalva ratio<	
Antonelli Incalzi et al., 2009	54 COPD (46♂, 8♀) 69.1±7.7yr 95 CON (80♂, 15♀): 68.8±9.0yr	COPD & CON: diagnosis of COPD according to ATS, undergoing in hospital rehabilitation following nonsmokers. COPD and CON: Randomly assigned		LF/HFnu* and disease severity, $PaCO_2$, FEV_1, loss of IADL, functional status Circadian rhythm and VLFP, LFnu, HFnu and LF/HFnu*
Bartels et al., 2012	14 ♀COPD:62±8yr 14 ♀CON:59±6yr	COPD: COPD, on b agonist medication CON: Healthy, No medication. COPD and CON matched: post- menopausal, ex-smokers Nil cardiac disease	BRS <	
Bernadi et al., 2008	15 COPD: (10♂, 5♀) 62±8yr 28 CON: (13♂,15♀) 59±6yr	COPD: Mild (GOLD), on medication CON: Healthy . COPD and CON matched: , smokers, non/never-smokers	BRS<	
Bedard et al., 2010	41 COPD: (28♂, 13♀) 67±7yr 19 CON: (14♂,5♀) 68±7yr	COPD: Clinically stable (GOLD), on medication. CON: Healthy . COPD and CON matched: Age sex and smoking	NN= PNN50= RMSSD = SDANN= SDNN = LF= HF= LF/HF <	LF/HF ratio and FEV_1* (r=0.342) and Age* (r=0.342)

Table 1 Continued.

Reference	Sample	Inclusion criteria	Results of autonomic function: COPD versus CON	Influencing factors (COPD): significant (*) relationship/association exist between;
Bir et al., 2005	30 COPD: (21♂, 9♀) 60.9±9.5yr 21 CON: (15♂, 6♀) 57.3±7.9yr	COPD: Mild to severe (GOLD), no medication, ex-smoker. CON: Healthy, Non-smokers. COPD and CON matched	SSR <	SSR* and FEV_1/FVC and % FEV_1/FVC
Borghi-Silva et al., 2008	19♂ COPD69±8yr 8♂ CON 68±5yr	COPD: FEV_1 <50% predicted, no medication, ex-smoker. CON: Healthy, Non-smokers. COPD and CON matched: Sedentary, Nil other chronic diseases	RMSSD < SDNN < LF< HF= LF/HF < LFnu< HFnu>	
Camillo et al., 2008	31 COPD(16♂, 15♀) 66±8yr	COPD: COPD(GOLD), no medication		SDNN* and ADL, total daily energy expenditure, BMI, FFM, triceps and quadriceps muscle force, daily expenditure and number of steps >3METs, time spent in ADL >3METs and LCADL SDNN index* and energy expenditure LF/HF ratio* and total daily expenditure, FFM, triceps and quadriceps muscle force R-R interval*time spent walking and standing, BMI, QOL No relationship between PFT, Fat mass and HRV No relationship between QOL and SDNN, LF/HF
Camillo et al., 2011	40 COPD (21♂,19♀) COPD:67±7yr CON: 65±10yr	COPD: GOLD 2-3; CON: GOLD 2-3 COPD and CON matched: regular PA, no unstable cardiac dx, no comorbidity, randomly assigned		Time spent walking and HRV* Biceps and triceps muscle force and SDNN* No relationship between QOL and HRV No relationship between smoking status and RMSSD Dyspnea and RMSSD*

Carvalho et al., 2011	15 COPD(9♂, 6♀) 73.9±6.6yr: 15 CON (8♂, 7♀) 68.7±7.3yr	COPD: Diagnosis of COPD (GOLD), excluded smokers, recent exacerbation, no medication. CON: Healthy (normal lung function). COPD and CON matched: Age	RMSSD< SDNN< LF< HF <	
Chang et al., 2011	9 COPD (not stated)	COPD: GOLD 2-3 Bronchodilators stop before testing, excluded unstable cardiac /musculoskeletal dx and patients on active phase pulmonary rehab ilitation		Respiratory rate and LF and HF* Ventilatory effort and LF and HF*
Chen, Chen & Kuo, 2006	30 COPD:(25♂, 5♀) 69.6±8.5yr 18 CON: (15♂, 3♀) 64.6±9.0yr	COPD: Moderate to severe (GOLD) Bronchodilators stop before testing CON: Healthy Excluded those with unstable cardiac. COPD and CON matched: Age	SDRR< CVRR< TP< LF< HF< LF/HF= LFnu= HFnu=	No relationship between FEV_1 % Predicted and FEV1/FVC ratio vs HFnu and LF/HF ratio PaO_2 and LF, HF and LF/HF*
Chhabra & De, 2005	56♂COPD: 57.96±9.81yr 11♂CON: 50.82±9.82yr	COPD: diagnosis of COPD by BTS, history of >20 pack-years of cigarette smoking, no recent exacerbation, no metabolic dx CON: Healthy, non- smokers. COPD and CON: Age matched.	Valsalva ratio:.< ΔIE: < 30:15 ratio:<	Disease severity and% FEV_1* $PaO_2$and valsalva ratio and 30:15 ratio* No relationship between PaO_2 and $PaCO_2$ and HRV $TLCO_2$ and 30:15 ratio* MPAP and valsalva ratio*
Costes et al., 2004	21 COPD: (♂, ♀): 62±9yr18 CON: (♂, ♀): 66±1yr	COPD: GOLD 1-2, on medication CON: Healthy COPD and CON matched: Age	BRS< LF= HF= LFnu= HFnu= (p>0.05)	No relationship between FEV_1 , % FEV_1, FVC, %FVC, RV, FEV_1/ FVC , PaO_2 with BRS
Dias de Carvalho et al., 2011	17 COPD(10♂, 7♀): 73.1±5.6yr 17 CON: (8♂, 9♀): 68.8±8.6yr	COPD: diagnosis of COPD by LF (GOLD 2-3), excluded smokers, recent exacerbation, no medication/metabolic dx CON: Healthy (normal LF). COPD and CON: matched	SD1 < SD2 < TINN < RRTri <	

Table 1 Continued.

Reference	Sample	Inclusion criteria	Results of autonomic function: COPD versus CON	Influencing factors (COPD): significant (*) relationship/association exist between;
Fatouleh, Vaughan & Macefield, 2011	15 COPD: (8♂, 7♀): 71±2yr 12 CON_1: (8♂, 4♀): 29±2yr 13 HTN: (10♂, 3♀): 53±2yr 10 CON_2: (5♂, 5♀): 50±3yr	COPD: diagnosis of COPD, on medication12 CON_1: Healthy13 HTN: on their regular medication10 CON_2: Healthy	MSNA> (burst frequencies and burst incidence)	
Gunduz et al., 2011	25 COPD:(22♂, 3♀): 63±7yr 25 CON: (19♂, 6♀): 60±8yr	COPD: stable, ambulatory, GOLD 2-3 CON: Healthy; COPD and CON matched: Age	sNN50 pNN50 < SDNN < SDNNi < SDANN< RMSSD <	
Haidar et al., 2009	18 COPD(10♂, 8♀): 51.7±2.4yr 14 CON: (5♂, 9♀): 47.7±2.8yr	COPD: GOLD 1-2, no medication, ex-smoker Placebo: GOLD 1-2, no medication, ex-smoker CON: Healthy, Non-smokers. COPD, Placebo and CON matched: Age	BRS< RRi<	FEV_1 and FEV_1/FVC and BRS* FEV_1 and FEV_1/FVC and R-R interval*
Lewis, Annadale & Lewis, 2009	10 COPD: (7♂, 3♀): 73.9±7.2yr	COPD: STAGE 3-4 (GOLD), Excluded patients on beta blockers and other drugs affecting ANS		Circadian rhythm (morning time)vs HRV (QT multi-fractal, R-R & QTV index)*
Ramos et al., 2009	16 COPD(12♂,4♀): 64±11yr	COPD: COPD(GOLD 1-3), mean FEV1 60±25% of predicted, no medication, no ANS associated diseases		No correlation was found between severity and RMSSD
Raupach et al., 2008	15 COPD(11♂, 4♀): 60.9±1.4yr 15 CON:(11♂, 4♀): 60.7±1.4yr	COPD: FEV1 ≤60% predicted (GOLD), no diuretic medication Between 30-80 years CON: Healthy COPD and CON matched: Nonsmoking, age, weight & sex	BRS< MSNA<	Respiratory rate and BRS * and MSNA*

Raupach et al., 2011	15 COPD(11♂, 4♀): 60.9±1.4yr 15 CON:(11♂, 4♀): 60.7±1.4yr	COPD: FEV_1 ≤60% predicted (GOLD), no diuretic medication Between 30-80 years. CON: Healthy COPD and CON matched: Nonsmoking, age, weight & sex.	MSNA< (burst incidence)	
Reis et al., 2010	10 ♂ COPD69±9yr 9 ♂ CON:64±5yr	COPD: FEV_1 ≤60% predicted (GOLD), FEV/FVC <0.7 stable clinically, on normal medication, nonsmoker CON: Healthy, no cardiac & metabolic dx COPD and CON matched: LFT, FC.	LF< HF= SDNN= RMSSD=	MIP and ΔIE *
Reis et al., 2010	10 ♂ COPD: 69±9yr 9 ♂CON:64±5yr	COPD: FEV_1 ≤60% predicted (GOLD), FEV/FVC <0.7 stable clinically, on normal medication, nonsmoker CON: Healthy, no cardiac & metabolic dx COPD and CON matched: LFT, FC.	RRi = SDNN;< RMSSD;< LF< HF< LFnu= HFnu= LF/HF =	
Rossi et al., 2014	17 ♂ COPD: 67.3±6.9yr 15 ♂CON:63.2±8yr	COPD: GOLD II (5), GOLD III (9) and GOLD IV (3). Excluded smokers, those who consume recent exacerbation (<2 months), those using medication that might affect cardiac modulation, metabolic/ cardiac disease comorbidity CON: Healthy	SDNN< RMSSD< LF< HF< LF/HF>	
Sin et al., 2001	21COPD (10♂,11♀) COPD: 64.1±9.7yr CON: 66.6±10.6yr	COPD and CON: clinical diagnosis of COPD,≥10 pack/yr. smoking history, FEV1 <70% predicted, excluded cardiac dx coexisting disorder, cognitive impairment, poor prognosis.		Circadian rhythm (Night time)and SDNN* and SDANN*
Suh et al., 2013	30 COPD(15♂, 15♀): 59.1±11.2yr 30 CON (15♂, 15♀): 59.2±11.3yr	COPD: FEV_1 ≤60% predicted (GOLD), FEV/FVC <0.7 anxious and non-anxious. CON: Healthy, anxious and non-anxious COPD and CON matched: age, sex.		Anxiety and SDNN and HF*

Table 1 Continued.

Reference	Sample	Inclusion criteria	Results of autonomic function: COPD versus CON	Influencing factors (COPD): significant (*) relationship/association exist between;
Tug et al., 2005	35 COPD(15♂, 15♀): 65.2±7.29yr 15♂CON 56.24±7.69yr	COPD: According to GOLD criteria, excluded those on drugs affecting the ANS, other chronic comorbidities CON: Healthy, COPD and CON matched: Age		No correlation was found between severity age, smoking status, PaO_2 , SaO_2 age of illness and SSR (p>0.05) No correlation was found between severity age, smoking status, PaO_2 , SaO_2 age of illness and RRi (p>0.05)
van Gestel et al., 2011	60 COPD (23♂, 37♀): 65.2±7.7yr	COPD: diagnosed GOLD I-IV, clinically stable, 40-75years, FEV_1 <80% predicted, normal BMI , excluded; CVD dx cancer, other respiratory dx, history of lung surgery, unable to ambulate, receiving corticosteroids other vasoactive medication		HRQOL and RMSSD, HF, LF/HF ratio*
van Gestel et al., 2012	154 COPD (67♂,87♀): 62.5±10.7yr	COPD: diagnosed based on GOLD guidelines. clinically stable, 40-75years, patients on long term corticosteroids or morphine medications, mental or physical disability, acute or recent exacerbation (6 weeks)		Exercise capacity (6MWT) and physical activity with HRV (NNmean)*
Yazici et al., 2007	28COPD(♂,♀): 64±10yr	COPD: clinical diagnosis COPD (ATS/ERS) with HRF and excluded those with cardiovascular diseases, diabetes, disease, hemodynamic instability, systemic disorders that can affect ANS		No significant relationship between PaO_2 , PH and $PaCO_2$and HRV
Zamarron et al., 2014	23 ♂ COPD 69.6±7.3yr 8 ♂ CON: 68.6±4.9yr	COPD: According to GOLD criteria, BMI: 28.7±5.4kg/m2, treated with b-agonists and anticholinergic, sever but stable condition, CON: Healthy, BMI: 28.2±3.8kg/m2	HF> LF> LF/HF ratio = TP=	HRV(POW) and peak flow * Acute exacerbations and LF, HF and POW *

Zupanic et al., 2014	31 COPD (13♂ ,18♀): 61±7yrs 31 COPD (13♂,18♀): 60±8yrs	COPD: The patients were clinically stable. And they had an average %FEV_1 predicted of 37±20% (GOLD III-IV). The patients had a mean BMI of 25.8±6.7kg/m^2. However, some patients with other co morbidities like hypertension were not excluded. Also, all patients were allowed to continue their medications. COPD and CON matched: age, sex.	AVNN< SDNN< RMSSD< pNN50< HF< LF< TP< LFnu= HFnu= LF/HF= QTc=	Significant relationship between QOL and autonomic function*

Notes; COPD: chronic obstructive pulmonary disease, CON: control, *: significant relationship,<: significantly lowered in COPD, > significantly increased in COPD, =: No significant difference; p : alpha probability level, ♂: male, ♀: female, vs: versus, GOLD: Global initiative for obstructive lung disease, LF: lung function, FEV_1 : forced expiratory volume in one second, FVC: forced vital capacity, MET: metabolic equivalence, BRS: baroreceptor sensitivity, MSNA muscle sympathetic nerve activity, SSR: sympathetic skin response, HRV: heart rate variability, rMSSD: square root of the mean of the sum of the squares of differences, RRi: RR waves interval, SDANN: standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording, SDNN: standard deviations of all NN intervals, sNN50: total number of differences between adjacent RR intervals that were greater than 50ms, 30:15 ratio: the ratio between the shortest R-R interval around the 15th beat and longest R-R interval around the 30th beat, I–E difference/ ΔIE: difference of heart rate during inspiration and expiration, RRtri: variability triangular index, TINN: triangular interpolation of RR interval, SD1: standard deviation of instantaneous beat-to-beat variability, SD2: standard deviation in long term of the RR interval, SDRR: standard deviation of RR interval, CVRR: coefficient of variation of RR interval, TP: total power, HF: high frequency, VLF: very low frequency, LF: low frequency LF/HF: low-high frequency ratio. ADL: activity of daily living, nu: normalized, ab: absolute, ATS: American thoracic society, TP: total HRV power.

Results

Study selection

A total of 154 studies were identified from the database and reference search. After the first and second screening 33 articles were included in the review for quality synthesis as shown in Figure1.

Risk of bias and level of evidence

The risk of bias and the level of evidence showed that, in most cases (263 out of 277 items), the two researchers (JM and HDS) agreed in the quality assessment. After a second review, the researchers reached a consensus for 11 out of the14 items of which they initially disagreed. The remaining 3 questions were scored by PC. The evaluation criteria and final scores for the studies are presented in Table 2. After converting to percentages, 82% of the studies were scored as high methodological quality (i.e. > 60% from the checklist percent) because only 6 studies were of low methodological quality scores (10, 26-30).

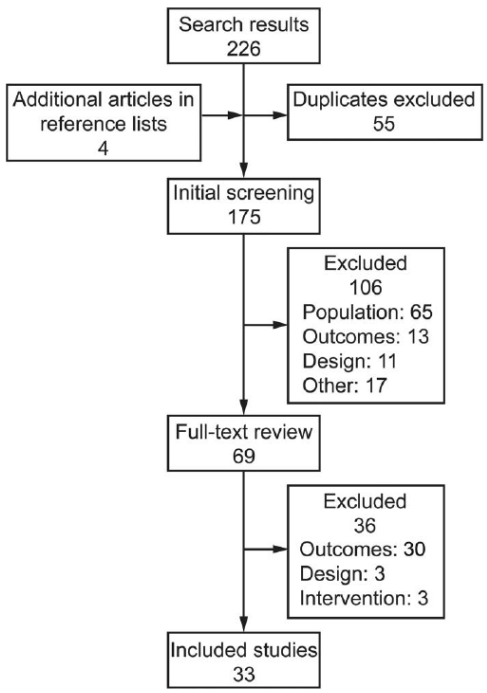

Figure 1 Flow chart.

Study characteristics and outcome measures

The characteristics (study size, participants, inclusion criteria, autonomic function parameters and influencing factors) are presented in Table 1. Of the 20 studies that compared the autonomic function between patients with COPD and healthy controls, 15 studies reported heart rate variability as outcome, whereas baroreceptor sensitivity (10, 11, 19, 27, 31) and muscle sympathetic nerve activity (31-33) were the reported outcomes in 5 and 3 studies, respectively. Only one study assessed the sympathetic skin response (17). Accordingly, heart rate variability was expressed in ms or ms^2, muscle sympathetic nerve activity was expressed as bursts/min and/or bursts/100 heart beats, and baroreceptor sensitivity was expressed as ms/mmHg. Furthermore, an overview (trend) of the autonomic function outcomes for the and frequency domain heart rate variability, baroreceptor sensitivity and muscle sympathetic nerve activity of subjects with COPD in the included studies is illustrated in Figure 2.

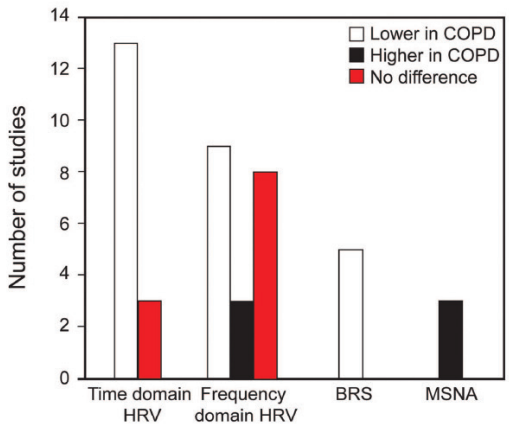

Figure 2 Trend of the autonomic function results in the reviewed studies.

Table 2 Table of evidence synthesis.

S/no	Author and year	1	2	3	4	5	6	7	Total (P-C)	Method-ological Quality (%)	Evidence grade
1	Aggarwal et al., 2011	+	+	-	+	-	+	+	5/7	71	
2	Bartels et al., 2012	+	+	+	+	-	+	+	6/7	71	B
3	Bedard et al., 2010	+	+	+	+	-	+	+	6/7	86	B
4	Bernadi et al., 2008	+	+	-	+	-	-	+	4/7	57	B
5	Bir et al., 2005	+	+	+	+	-	+	+	6/7	86	B
6	Borghi-Silva et al., 2008	+	+	+	+	-	+	+	6/7	86	B
7	Carvalho et al., 2011	+	+	-	+	-	+	+	5/7	71	B
8	Dias de Carvalho et al., 2011	+	+	+	+	-	+	+	6/7	86	B
9	Chen, Chen & Kuo, 2006	+	+	-	+	-	+	+	5/7	71	B
10	Chhabra & De, 2005	+	+	-	+	-	+	+	5/7	71	B
11	Costes et al., 2004	+	+	-	+	-	-	+	4/7	57	B
12	Fatouleh, Vaughan & Macefield, 2011	+	+	-	+	-	+	+	5/7	71	B
13	van Gestel et al., 2012	+	+	+	+	-	+	+	6/7	86	B
14	Gunduz et al., 2009	+	+	-	+	-	+	+	5/7	71	B
15	Raupach et al., 2008	+	+	+	+	-	+	+	6/7	86	B
16	Raupach et al., 2010	+	+	+	+	-	+	+	6/7	86	B
17	Reis et al., 2010	+	+	-	+	-	+	+	5/7	71	B
18	Reis et al., 2010	+	+	-	+	-	+	+	5/7	71	B
19	Suh et al., 2013	+	+	+	+	-	+	+	6/7	86	B
20	Rossi et al., 2014	+	+	+	+	-	+	+	6/7	86	B
21	Tug, Terzi & Yoldas, 2005	+	+	+	+	-	+	+	6/7	86	B
22	Zamarron et al., 2014	+	+	+	+	-	+	+	6/7	86	B
23	Zupanic et al., 2014	+	+	+	+	-	+	+	6/7	86	B

	Author and year	1	2	3	4	5	6	7	8	9	Cohort			
24	Camillo et al., 2008	+	+	+	+	-	+	-	+	+	7/9		78	B
25	Camillo et al., 2011	+	+	+	+	-	+	+	-	+	7/9		78	B
26	Chang et al., 2011	+	-	+	+	-	+	-	-	+	5/9		56	B
27	Lewis, Annandale and Lewis, 2009	+	+	-	+	-	+	-	+	+	6/9		67	B
28	Ramos et al., 2009	-	-	+	+	-	+	-	-	+	4/9		45	B
29	van Gestel et al., 2011	+	+	+	+	-	+	-	-	+	6/9		67	B
30	Yazici et al., 2007	+	+	+	+	-	+	-	+	+	5/9		56	B
	Author and year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**RCT**		
31	Antonelli Incalzi et al., 2009	+	-	-	-	-	+	+	+	-	-	4/10	40	A2
32	Haidar et al, 2009	+	+	+	+	-	+	+	+	-	+	8/10	80	A2
33	Sin et al., 2007	+	+	-	+	-	+	+	+	+	+	8/10	80	A2

Notes: + : Agree and -: disagree, ***For the patient controlled studies***, 1: clear description of the patient group, 2: clear description of the control group, 3: well defined in/exclusion criteria, 4:clearly defined and appropriate intervention, 5 blinding, 6 identification of confounders in the design and analysis and 7: whether we considered the results valid and applicable. ***For the cohort studies***, 1:description of the patient groups, 2:selection bias excluded, 3: description of exposure and adequate evaluation, 4: description of outcome and adequate evaluation, 5:blinding, 6: Sufficiently long follow up (including drop-outs and loss on follow-up), 7:selective loss to follow up sufficiently excluded, 8: identification of confounders and 9: whether we considered the results valid and applicable. ***While For the RCTs***, 1: randomization, blinding of randomization, 3: patients blinded to treatment, 4: health care professionals blinded to treatment 5 Outcome assessors blinded to treatment, 6: groups comparable at baseline, 7 sufficient amount of the patients were available at follow up, 8 intention to treat analysis, 9: Comparability of treatment and 10: whether we considered the results valid and applicable.

Evidence for autonomic function in Subjects with COPD

Heart rate variability

Fifteen studies of high methodological quality investigated the differences in heart rate variability values between Subjects with COPD and healthy controls (3, 10, 13, 19, 34-44). Most of these studies reported significantly lower heart rate variability in subjects with COPD. Specifically, the time domain parameters in most of the studies (12 of 15) showed that patients with COPD had lower heart rate variability compared to healthy controls. The studies reported that parameters such as sNN_{50} (35), average NN interval (44), pNN_{50} (35, 44), SDANN (35), SDNN (3, 35, 38, 43, 44) SDNN index and RMSSD (3, 35, 38, 43, 44), RRi (19), SD_1(13, 43), SD_2 (13, 43), SD_1/SD_2(43) , triangular interpolation of RRi, and the variability of triangular index (13)wÿ, were all reduced (or negatively altered) in patients with COPD compared with healthy controls ($p<0.05$). Furthermore, other time domain values reported to be impaired in patients with COPD include SD of the RRi (34), coefficient of variation of RRi (34), Valsalva ratio (37, 42), 30:15 ratio (37), S/L ratio (42) and ΔIE (37). However, 3 studies reported comparable time-domain parameters between patients with COPD and healthy controls (36, 39, 41).

The frequency domain values for heart rate variability showed more variation across the studies. Lower domain values were reported in some studies for LF (3, 34, 36, 38, 39, 43, 44), HF (3, 34, 38, 43, 44) LF/HF ratio (39, 41), LFnu (39, 44) and TP (34, 40, 44), whereas other investigators reported comparable findings for the LF(10, 41), HF (10, 36, 39, 41), LF/HF (34, 38, 40, 44), LFnu (10, 34, 38, 44) and HFnu in subjects with COPD compared with their healthy counterparts (10, 34, 38, 44). Additionally, higher values were reported in a few studies for LF (40), HF (40), LF/HF(43) and HFnu (39) in subjects with COPD compared with healthy controls.

Based on the quality and level of evidence and the results from majority of the studies reviewed, there is a strong evidence to support impairment of time domain heart rate variability in subjects with COPD. For frequency domain heart rate variability, the evidence is inconsistent.

Baroreceptor sensitivity

Five studies of low (10, 27) and high (11, 19, 31) methodological qualities reported that baroreceptor sensitivity was significantly depressed among subjects with COPD in compared with healthy controls. Across all of the studies, the baroreceptor sensitivity of subjects with COPD ranged from 1.9 ± 2.92 to 8.9 ± 1.70 ms/mmHg, whereas that of the healthy control ranged from 6.2 ± 2.26 to 14.3 ± 2.00 ms/mmHg. Raupach et al (31) reported that baroreceptor sensitivity among subjects with mild COPD was significantly lower compared to control (5.0+0.60 vs 9.3 ± 1.10 ms/mmHg). Similarly, significantly lower values were also reported for subjects with

different stages (moderate to severe) of COPD in studies by Costes et al (10) (2.7 ± 1.50 vs 7.8 ± 4.90 ms/mmHg; p<0.01), Bartels et al (11) (1.9 ± 2.92 vs 6.2 ± 2.26 ms/mmHg; p<0.01), and Haidar et al (19) (6.2 ± 1.05 vs. 10.7± 1.65 ms/ mmHg; p=0.03). Another study on subjects with mild COPD also showed baroreceptor sensitivity depression compared to healthy age-matched controls (8.9 ± 1.70 vs 14.3 ± 2.00 ms/mmHg) (27). Based on the quality and level of evidence, there is a strong evidence to support baroreceptor sensitivity depression in subjects with COPD.

Muscle sympathetic nerve activity

Three studies of high methodological qualities compared the muscle sympathetic nerve activity between subjects with COPD and healthy controls, and all concluded that muscle sympathetic nerve activity was impaired in subjects with COPD (31-33). The values in bursts/100 heartbeats ranged between 55 ± 4.7 to 86.9 ± 2.0 for COPD and 33 ± 6.0 to 49 ± 6.0 for healthy controls, respectively. In one study, subjects with COPD were reported to present with significantly elevated muscle sympathetic nerve activity compared to the healthy controls (burst frequency of 62 ± 2.0 vs 29 ± 3.0 bursts/min, which corresponds to a burst incidence of 86 ± 2.0 vs 49 ± 6.0 bursts/100 heartbeats) (32). Furthermore, similar findings were reported in 2 other studies that reported baseline muscle sympathetic nerve activity to be significantly elevated among patients with COPD compared to healthy controls (p<0.05) (31, 33). Based on the quality and level of evidence, there is a strong evidence to support elevation of muscle sympathetic nerve activity in subjects with COPD.

Sympathetic skin response

Only one study of high methodological quality reported the sympathetic skin response of subjects with COPD (17). The outcome demonstrated that the sympathetic skin response was impaired in subjects with COPD compared with healthy controls. The evidence supporting the impairment of the sympathetic skin response in subject with COPD is limited

Factors influencing autonomic function in subjects with COPD

Disease severity (stage), duration and acute exacerbation

Four studies of low (26, 29) and high (37, 45) methodological quality evaluated the influence of disease severity on autonomic function in subjects with COPD. Two of the studies concluded that disease severity had a significant effect on the autonomic function (26, 37). Chabbra and De (37) revealed that autonomic neuropathy was

observed more often in subjects with moderate and severe COPD compared to patients with mild COPD ($p<0.05$). Antonelli Incalzi et al (26) also reported significant correlations between LF/HFnu ratio with the indices of disease severity. Conversely, the other 2 studies reported that disease severity did not influence AF. Tug et al (45) found no significant difference between mild and moderate-severe COPD groups either for the isolated parasympathetic, sympathetic or mixed form ($p>0.05$). Similarly, Ramos et al (29) reported that different stages of COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages I-III) had no influence on RMSSD.

Two studies (17, 45) of high methodological quality assessed the influence of disease duration on autonomic function in subjects with COPD, and both studies concluded that it had none ($p>0.05$). Furthermore, one study with high methodological quality indicated that COPD exacerbation was associated with a significant increase in LF, HF, LF/HF and TP ($p<0.05$) compared with subjects with stable COPD and/or healthy controls (40).

The evidence supporting the effect of disease severity on autonomic function is inconsistent. However, there is a strong evidence to support that disease duration has no influence on autonomic function, and there is limited evidence to support that exacerbation influences autonomic function in subjects with COPD.

Pulmonary function and respiratory parameters

Eight studies of low(10, 26) and high (1, 17, 19, 34, 37, 41) methodological qualities reported a relationship between spirometric indices (FEV_1, percent-of-predicted FEV_1, FEV_1/FVC ratio) and autonomic function in subjects with COPD. Three of these studies reported that there were no significant correlations between pulmonary function variables and autonomic function (1, 10, 34). In contrast, the remaining 5 studies reported significant correlations between the lung function variables and autonomic function parameters (17, 19, 26, 37, 41). Weak correlations were found between percent-of-predicted FEV_1 and Valsalva ratio (0.39) (37) and 30:15 ratio ($r=0.31$) (37), between FEV_1 and LF/HF ($r=0.34$) (41) and LF/HFnu ($r=0.32$) (26), and also between baroreceptor sensitivity and FEV_1/FVC ($r=0.38$)(19). Haidar et al (19) reported a more moderate correlation between baroreceptor sensitivity and FEV_1 ($r=0.46$; $p<0.01$) and also between RRi and FEV_1 ($r=0.56$; $p<0.01$) and FEV_1/FVC ($r=0.53$; $p<0.01$). Similarly, Bir et al (17) revealed a moderately strong relationship was between FEV_1/FVC and latency ($r=-0.468$), amplitude ($r=0.408$) and area ($r=0.401$), as well as between %FEV_1/FVC and latency ($r=-0.640$), amplitude ($r=0.523$) and area ($r=0.519$) ($p<0.05$).

Only one study with a low methodological quality reported the influence of respiratory rate on the autonomic function in subjects with COPD (28). The study results showed that both LF and HF were significantly correlated with breathing

frequency (r=-0.76; r=-0.70, respectively) and ventilatory effort(r=-0.52; r=-0.49, respectively) in subjects with COPD.

Seven studies of low (10, 26, 30) and high (17, 34, 37, 45) methodological qualities investigated the relationship between arterial blood gas parameters (PaO_2, $PaCO_2$, pH, SaO_2) and autonomic function parameters in subjects with COPD. Most of these studies demonstrated that arterial blood gas parameters did not significantly correlate with autonomic function. Tug et al (45) reported that both PaO_2 and $PaCO_2$ did not significantly correlate with SSR and RRi ($p>0.05$). Antonelli Incalzi et al (26) also reported that there was no significant correlation between PaO_2 and LF/HFnu (except for a weak but significant relationship with $PaCO_2$ at night time; r = -0.29). Furthermore, no significant relationship was reported between skin sympathetic response and $PaCO_2$, PaO_2 , O_2 saturation and pH values (17), between baroreceptor sensitivity and PaO_2 (10), and between HRV (tri index, pNN_{50} and HF) and $PaCO_2$, PaO_2 and pH (37). However, 2 studies of high methodological quality reported significant correlations between PaO_2 and HFnu (r = -0.60)(34), LFnu (r = 0.44) (34) , LF/HF ratio (r=0.37) (34), Valsalva ratio (r = 0.27) (37) and 30:15 (r= 0.29)(37). Moreover, significant correlations were reported between alveolar volume transfer factor ($TLCO_2$) and 30:15(r = 0.36) (37), and also between mean pulmonary artery pressure and Valsalva ratio (r = -0.33) (37).

Two studies assessed the influence of dyspnea on autonomic function in subjects with COPD. One study (high methodological quality) significant relationship between all the domains of dyspnea and RMSSD ($-0.45 < r < -0.48$; $p<0.05$) (2). However, the other study (low methodological quality) was unable to demonstrate any significant correlation between dyspnea and LF/HFnu ratio ($p>0.05$) (26). Based on the quality and level of evidence of the studies, the evidence supporting the influence of pulmonary function, arterial blood gas and dyspnea on autonomic function in subjects with COPD is inconsistent.

Physical activity, physical fitness and body composition

Five studies of low (26) and high (1, 2, 8, 45) methodological quality reported the relationship between autonomic function and physical activity, physical fitness and exercise capacity level in subjects with COPD. Camillo et al (2008) (1) concluded that total daily energy expenditure, daily energy expenditure in activities requiring >3 metabolic equivalents, number of steps per day and time spent daily in activities demanding >3 metabolic equivalents significantly affected the SDNN index ($0.36 < r < 0.60$; $p < 0.05$). The energy expenditure also correlated with SDNN index ($r = 0.60$; $p = 0.003$) and the LF/HF ratio ($r = 0.36$; $p<0.05$). Furthermore, they found also significant correlations between RRi and time spent walking (r = 0.46) and standing (r = 0.41), and between SDNN index and total score of activities of daily living (r = -0.44).

van Gestel et al (8) reported that there was a significant correlation between mean NN intervals and 6- min walk distance (r= 0.43) and physical activity levels (r=0.42). However, no correlation was reported between mean NN intervals and peak oxygen uptake and maximal workload (p>0.05). Similarly, the time spent walking per day was significantly correlated with heart rate variability (r=0.47; p < 0.05) (2). In another study, loss of activities of daily living was significantly correlated with LF/HFnu ratio (r=-0.41; p=0.003), in addition to a weak relationship that was reported between the functional status and LF/HFnu analysis over 24 h (r = 0.29) and in the daytime (r = 0.29) (45). Conversely, a study of low methodological quality reported that there was no significant relationship between exercise capacity and LF/HFnu ratio in patients with COPD (26).

The influence of muscle force and muscle strength on the autonomic function in COPD was reported in 3 studies with high methodological quality (1, 2, 36). SDNN significantly correlated with biceps brachii (r=0.61) (2) and triceps brachii (r=0.56) muscle force (2), and the quadriceps and triceps muscle force also correlated with SDNN and LF/HF (0.37 > r < 0.44, p <0.05) in another study (1). Furthermore, inspiratory muscle weakness was also significantly associated with ΔIE (r = 0.60) (36).

Only one study reported on the relationship between body composition and autonomic function (1). The results revealed that there was a significant relationship between body mass index and SDNN (r=0.44) and RRi (r = 0.37) and also between fat-free mass and SDNN (r = 0.49) and LF/HF (r = 0.40). However, no significant correlation was reported between heart rate variability and total fat mass (p > 0.05). Based on the quality and level of evidence of the studies, there is strong evidence to support the influence of physical activity level and muscle function (force and strength) on autonomic function in subjects with COPD, but only a limited evidence to support the influence of body composition.

Socio-demographic variables

Four studies of high methodological quality reported on the relationship between QOL and autonomic function (1, 2, 5, 44). The results showed inconsistent findings. Significant relationships were reported between QOL and RMSSD (r = 0.34, *P*= 0.012) (5), SDNN (r=5.4, *P* =0.02), RRi (r=-0.38, *P* <0.05) and HF (r = 0.35, *P* = 0.01) (5), and LF/HF ratio (r= -0.40, *P* <0.05) (5). However, in 2 studies, there were no significant correlations (p>0.05) between QOL and several heart rate variability parameters (1, 2). In a similar trend, the relationship between age and autonomic function in subjects with COPD was reported in 3 studies with high methodological quality (32, 41, 45). In one of the studies, the results indicated that there was a significant correlation between age and LF/HF ratio (r=-317; p=0.044) (41), whereas the other 2 studies reported that age was not significantly associated with LF/HFnu values (p>0.05)(32) and autonomic function (p>0.05) (45).

The influence of cigarette smoking on autonomic function in COPD patients was investigated in 3 studies with low (27) and high (1) (45), methodological quality. Despite this, no correlation was found between smoking and RMSSD (1), baroreceptor sensitivity (27), skin sympathetic response (45) and RRi (45). Also, one study of high methodological quality reported on the influence of anxiety on autonomic function revealed that anxious subjects with COPD had impaired SDNN and HF values compared to non-anxious subjects ($p<0.05$) (6). Based on the quality and level of evidence of the studies, the evidence supporting the influence of QOL and age on autonomic function is inconsistent. Furthermore, there is a strong evidence to support that smoking does not influence autonomic function, and limited evidence to support the influence of anxiety on autonomic function in subjects with COPD.

Time of day (circadian rhythm)

Four studies with low (26) and high (4, 41, 46) methodological quality reported on the influence of circadian rhythm on autonomic function in subjects with COPD. The results from Bedard et al (41) showed that patients with COPD have a reduced LF/HF ratios (median and interquartile range) compared with healthy controls during daytime (2.6 [1.5–3.8] vs. 3.5 [2.9–5.6]), nighttime (1.8 [1.1–4.3] vs. 4.2 [2.7–6.9]) as well as during the entire 24-hour (1.9 [1.5–3.4] vs. 3.9 [3.2–5.6]) recordings ($p< 0.005$). In another study, SDNN ($p= 0.021$) and SDANN ($P = 0.02$) values measured at night time were significantly higher compared with daytime values in subjects with COPD (46). Similarly, time-dependent fluctuations in HRV parameters were reported among patients with COPD, which were significantly reduced during morning periods compared to night periods ($p<0.001$) (4). Antonelli Incalzi et al (26) also reported that patients with COPD showed fluctuations in VLF during 24-h and daytime periods, and also lower LFnu, higher HFnu and lower LF/HFnu during the daytime period compared to night time (all, $P<0.05$). Based on the quality and level of evidence of the studies, there is strong evidence to support that circadian rhythm influences the autonomic function in subjects with COPD.

Discussion

The objective of this systematic review was to determine the level of evidence for the autonomic function and its influencing factors in subjects with COPD. This was the first attempt to provide concise information and a systematic review evidence on autonomic function in subjects with COPD. Our review included 33 studies comprising about 1, 000 subjects with COPD. Additionally, the results of this review provided a more global representation of the several parameters that make up autonomic function in these studies.

The results of this review showed that the heart rate variability time-domain parameters were significantly lowered among patients with COPD in most of the studies. In general, it would appear that this reduction in heart rate variability timing may be an indication of a problem with time-series of normal RRi in subjects with COPD. This may also imply that these subjects have a lower autonomic activity level when compared with healthy controls. Consequently, the time domain could readily serve as a yardstick for ascertaining autonomic function. Moreover, time-domain indices of heart rate variability have been reported to be of independent prognostic significance (47).

On the other hand, frequency-domain heart rate variability parameters revealed a more conflicting outcome. The results ranged from lower to comparable and even higher values for LF, HF, LFnu, HFnu, LF/HF and TP variables in subjects with COPD compared with healthy controls. Consequently, evidence supporting impaired frequency domain parameters could not be ascertained. The results obtained with the frequency-domain parameters tend to suggest, for these variations and inconsistencies, that they are random and may not provide the best measure for stratification. However, there appears to be a preponderance of lower LF presentations in subjects with COPD. This may be an indication of sympathetic tone dominance, as earlier reported in chronic diseases that are closely linked with cardiovascular death (48, 49). Therefore, in view of our results, time domain analyses may provide a better interpretation and prognostic value compared to frequency domain for patients with COPD. Moreover, Lanza et al (50) demonstrated that there is a strong association between low time-domain heart rate variability and mortality. They further stated that little data are available regarding the prognostic value of frequency-domain heart rate variability analysis.

In this review, we also found strong evidence in support of baroreceptor sensitivity depression in subjects with COPD. The baroreflex mechanism plays a key role in cardiovascular function, especially in the short-term regulation of blood pressure during normal and pathological conditions (51, 52). The possible contributors to the depression in for baroreceptor sensitivity include intra-thoracic pressure changes, hypoxia and oxidative stress (5). Moreover, these are regular features of COPD. Therefore, it is not surprising that for baroreceptor sensitivity was impaired even in subjects with mild COPD (10, 19, 27). Our review has shown that even during the early stages of COPD, baroreceptor sensitivity is impaired. Hence, it can be utilized as a reliable marker by clinicians who are presented with patients with COPD for a more comprehensive intervention.

The results from 3 studies showed that muscle sympathetic nerve activity was considerably higher (reflection of increased sympathetic excitation) in subjects with COPD compared with their healthy counterparts (31-33). Furthermore, like baroreceptor sensitivity, muscle sympathetic nerve activity is significantly

associated with some features of COPD such as decreased oxygen concentration, impairment in BRS (through the inhibitory afferent systems), high oxidative stress and systemic inflammation (5, 53-55). Moreover, our review also found elevated muscle sympathetic nerve activity in normoxic subjects and subjects with mild COPD (5).

Generally, this review has shown that heart rate variability was impaired mainly in the time-domain parameters in subjects with COPD. Similarly, the same outcome was found for baroreceptor sensitivity and muscle sympathetic nerve activity, thereby enhancing the inference that can be drawn from our results. Our review also found that fewer studies have reported variables (baroreceptor sensitivity and muscle sympathetic nerve activity) other than the heart rate variability (see Figure 2). Moreover, only one study reported on the sympathetic skin response parameter (17). However, it is very likely that sympathetic skin response is impaired in patients with COPD, despite the limited evidence. Unlike heart rate variability, baroreceptor sensitivity and muscle sympathetic nerve activity, sympathetic skin response assesses the sudomotor function of unmyelinated sympathetic fibers through electromyography. It is non-invasive, requires less equipment, and can be easily be performed (less expertise) (56, 57), and it may provide an alternative to assess autonomic function (sympathetic). This review has shown that a strong level evidence in support of autonomic function impairment in patients with COPD. Subsequent research can focus on providing evidence for intervention modes for enhancing autonomic function in these population.

This review also focused on the influencing factors of autonomic function in subjects with COPD. For these, we categorized the influencing factors from the studies into 5 groups: disease severity features, pulmonary function and respiratory parameters, physical activity and body composition, socio-demographic variables and circadian rhythm. This categorization made analyzing the evidence easier. The results suggests that the physical activity level (energy expenditure, duration of activities of daily living , duration of walking/day, and number of steps taken/day) is the major factor that may be useful in enhancing autonomic function (heart rate variability). Additionally, this may be a useful intervention strategy due to the high level of deconditioning that is a common feature in these patients. Moreover, physical activity is known to modulate the autonomic nervous system (10, 58). A similar level of evidence was also reported in support of the positive association of muscle function and autonomic function. However, further studies are needed to help to determine the optimal mode for incorporating these parameters as key components of COPD rehabilitation.

The results from the studies in our review showed strong evidence that cigarette smoking does not influence autonomic function in subjects with COPD.

This finding is at variance with earlier reports that have linked smoking with reductions in the baseline levels of vagal-cardiac nerve activity through its effect on the arterial baroreceptor-cardiac reflex response and increasing sympathetic activity through arterial pressure reductions (59). Moreover, smoking is one of the major causes of COPD, and most patients with COPD are required to stop smoking. The evidence for other socio-demographic circumstances was mostly conflicting, limited or non-existence. For example, inconsistent evidence was reported for age and QOL. No explicit reason could be deduced except for the normal physiological aging process because subjects with COPD are generally older (60-62). Our review did not find any study that reported on the influence factors such as sleep quality, fatigue, depression and sex. Hence, further studies are needed to explore the potential links between these variables and autonomic function in subjects with COPD.

In most of the studies, the use of medication that can influence the autonomic function in patients with COPD such as systemic sympathomimetic drugs, calcium channel blockers, beta (β) blockers, other cardiac medications, caffeine/tea, smoking and alcohol, were suspended before and/or during autonomic function assessment. However, in some studies the patients were not stopped from using their regular medications such as anticholinergic, β_2-agonists, corticosteroids, aminophylline and bronchodilators (4, 11, 27, 32, 36, 38, 40). Still, in other studies, medication use was completely withdrawn for a period of between 6-24 h before autonomic function assessment (17, 29, 34, 39). Nevertheless, these variations in medication use are not likely going to affect our result since none of the studies included medications that could have had any significant effect on the autonomic nervous system. We also noticed also noticed differences in the heart rate variability assessment across the studies. The differences were mostly in terms of number of RRi points utilized in the heart rate variability analysis. In some studies, a detailed description of the setting was given, while in others, this was not the case. On a general note, however, the analyses were reliable to draw conclusions for both time- and frequency domain heart rate variability analysis because all of the procedures were standardized and reproducible. For baroreceptor sensitivity assessment, a more uniform procedure was also observed across the studies. Electrocardiogram monitoring was done in a rested and recumbent position, systolic blood pressure was continuously measured using cuff technique, and the limb lead with the greatest R waves was used for assessment (10, 11, 27). The muscle sympathetic nerve activity assessment also utilized the same modalities and protocol (31-33).

The results of our review had some demographic variations. Slightly more than half of the participants (except for 3 studies that did not provide information on the sex (10, 28, 30)) were males (524 of 100). Moreover, COPD is traditionally

known to be higher in males compared to females (63). Also, few studies subjects who were not clinically stable and/or free from comorbidities that may have had an effect on the autonomic function. Moreover, the subjects also presented with diverse COPD disease stages in the studies. However, the checklist that was used to grade the study quality took these points into consideration. Additionally, the majority of the studies included mainly patients with moderate COPD; only a few included subjects with mild (10, 19, 27), severe (1, 2, 28, 40, 46) and a mixed stage (5, 13, 17, 29, 37) COPD. Consequently, our results could be a global reflection of the general autonomic function trend in subjects with COPD.

The major limitation of this review is the general lack of blinding across the studies, perhaps due to the technical and cumbersome nature of assessing autonomic function in a laboratory setting. However, we use a standardized methodological quality rating approach (>60% for high quality), which showed that most of the studies had high scores, thus providing a firm base for our results. In addition, a few of the studies had low sample sizes. Also, the quality assessment criteria used in arriving at the results in this review did not take the sample size of the studies into account. However, the results of the heart rate variability parameters are likely to be reliable because of the large number of studies (some with large sample sizes) that were reviewed. For muscle sympathetic nerve activity and baroreceptor sensitivity, the sample sizes were relatively smaller. However, this this would not likely change the results due to the feasibility of recording a larger sample because the study procedures are not only technical, but also invasive, as in the case of muscle sympathetic nerve activity.

The findings of this systematic review are important to clinicians and other health-care providers given the high evidence backing our conclusion and the more concise information we presented. Moreover, this review has highlighted specific and important physiological markers that should be taken into consideration for prognostication, stratification and management of patients with COPD. Additionally, our review can serve as a basis for future studies and reviews that will provide information on the effect of various intervention modes on autonomic function in these patients.

Conclusion

There is a strong level evidence supports the impairment of autonomic function parameters in subjects with COPD. A similar evidence level also suggests that physical activity level, muscle function and circadian rhythm significantly influence autonomic function and may play a role in autonomic function modulation during COPD rehabilitation.

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"If the heart becomes hardened, the eye becomes dry"

Ibn Qayyim

Part II

Dysautonomia in chronic obstructive pulmonary disease

Chapter 4

Autonomic symptoms in patients with moderate and severe chronic obstructive pulmonary disease

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Abstract

Objectives: A synoptic description of the autonomic symptoms profile (ASP) of patients with COPD is not available. Therefore, we aimed to provide an overview of autonomic symptoms and its associates in COPD.

Methods: We evaluated 89 subjects with COPD (65±7.3 years; 66 males; GOLD II-IV) with an equal number of age and sex matched control subjects by means of the composite autonomic symptom score (COMPASS-31) questionnaire, which assesses autonomic symptoms across six domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, urinary and pupillomotor). Lung function, medication use, and health status variables (quality of life: physical/mental component summary [PCS/MCS], fatigue, anxiety, depression & dyspnea levels) were also assessed.

Results: Compared to controls, all subjects with COPD reported significantly higher orthostatic intolerance, secretomotor and total autonomic symptom scores ($p<.05$). Additionally, subjects with moderate COPD also reported significantly higher scores for vasomotor, gastrointestinal, urinary and pupillomotor symptoms compared to controls ($p<.05$). Nevertheless, these symptoms were comparable between the moderate and severe COPD sub-groups ($p>.05$). The COPD subjects had poorer health status compared to controls as exhibited by significantly higher scores for depression, anxiety, fatigue and dyspnea, and lower scores for PCS and MCS ($p<.05$). These health status variables were mildly associated with autonomic symptoms ($0.214\leq r \geq 0.421$; $p<.05$), but not with demographic and lung function ($p>.05$). The MCS was the only significant predictor of total autonomic symptoms score in COPD ($p=0.001$; beta=-0.430).

Conclusion: Autonomic symptoms are present in all domains of the COMPASS-31 in COPD, irrespective of disease severity and demographic variables. Autonomic symptoms in COPD were mainly influenced by poor mental health.

Keywords: *Autonomic nervous system, chronic obstructive, pulmonary disease, symptoms, health status*

Introduction

Cardiovascular and autonomic nervous system (ANS) abnormalities have been reported in patients with COPD (1-3). Previous studies that have focused on the ANS abnormalities in COPD have highlighted profound impairments of autonomic function indices. Some of these indices include heart rate variability (3, 4), heart rate recovery following exercise testing (5), baroreceptor reflex sensitivity (4, 6), sympathetic skin response (4, 7) and muscle sympathetic nerve activity (4, 8).The results from these studies also indicated that these impairments, mostly in the form of increased sympathetic tone/activity, are important factors contributing to the morbidity and mortality rates in patients with COPD.

The ANS is an important system in the assessment and treatment of a number of pathophysiological conditions involving the cardiovascular system (9), and for identifying problems in the cardiac autonomic control (10). Assessing autonomic symptoms is a simple and easy means of assessing signs of ANS dysfunction (11). Since autonomic symptoms occur in events of sympathovagal imbalance or hormonal disturbances (12), it is utilized as a valuable means of clinical evaluation. The autonomic symptoms can be categorized into more pure physical symptoms and into more mixed psychosomatic symptoms. A few examples of autonomic symptoms that are indicative of ANS abnormalities include deficiency in sweating, tear formation and salivation, orthostatic intolerance, poor pupil reflex, gastro-intestinal complaints, poor sexual and bladder function, and cardiac rhythm disturbances (13).

The prevalence of autonomic symptoms has been reported in several chronic diseases (13-16). Autonomic symptom severity is also associated with frequently occurring COPD comorbidities like depression, anxiety, dyspnea, cognitive dysfunction, psychiatric complications and sleep disturbances (17-20). However, a comprehensive and synoptic evaluation of autonomic symptoms is not available for patients with COPD. The information in the literature regarding autonomic symptoms for patients with COPD are sparse and often limited to specific symptoms such as problems with gastro-intestinal (21, 22) orthostatic (22, 23), visual(23) and urinary(22, 23) functioning. A comprehensive assessment of autonomic symptoms in a large COPD cohort is necessary to provide relevant and easy means of understanding the extent of ANS affectation from the symptomatic point of view among patients with COPD.

Therefore, the main objective of the present study is to examine the autonomic symptoms profile in COPD based on disease severity (GOLD classification) in comparison to age-matched controls. A secondary objective of this study is to evaluate the association between autonomic symptoms with clinical and demographic characteristics.

Methods

Study population

Eighty-nine subjects with COPD (predicted FEV_1 <70%; GOLD II-IV) who attended the Department of Respiratory Medicine of Ghent University Hospital between April, 2015 and December, 2016 participated in this study. A list of potential participants who fulfilled the following criteria was retrieved from the hospital database; (i) have a stable condition (no recent exacerbation or hospitalization within the last 3 months), (ii) have no chronic co-morbidities such as chronic heart diseases, hormonal dysfunction that can significantly impair the ANS like hyper- or hypothyroidism and/or mental disorders, and (iii) hove no history of any recent major surgical operation. The eligible subjects were thereafter contacted to participate in the study either during scheduled hospital visitations or by post.

A healthy control group consisting mainly of persons without a diagnosis of COPD, or who have no known systemic medical condition that can significantly impair the ANS such as chronic heart diseases, congenital disorders and hormonal dysfunction, were also recruited. The control group participants were matched by age and sex (ratio 1:1). The age matching was done using a three age-bracket classification method (50-60 years; 61-70 years; and above 70 years). The control group participants were contacted via personal contacts, social media and/or by post.

All participants had to understand and speak the Dutch language. A study information form and a consent form was also made available to the participants along with the study instruments. The study was reviewed and approved by the ethical committee at the Ghent University Hospital, Belgium (registration number: B670201422863) (Figure 1).

Assessment

General characteristics

Characteristics of the participants such as age, sex, civil state, educational attainment, occupational status, smoking history, alcohol use, weight and height were collected using a general questionnaire.

Autonomic symptom profile

Autonomic symptoms were assessed using the composite autonomic symptoms score (COMPAS-31). The COMPASS-31 is the shortest and the most recent questionnaire for assessing autonomic symptoms profile (ASP). The psychometric properties of the questionnaire have been previously established (16, 24). The COMPASS delineates the severity, distribution and frequency of autonomic symptoms, and it also evaluates the autonomous capacity across six domains;

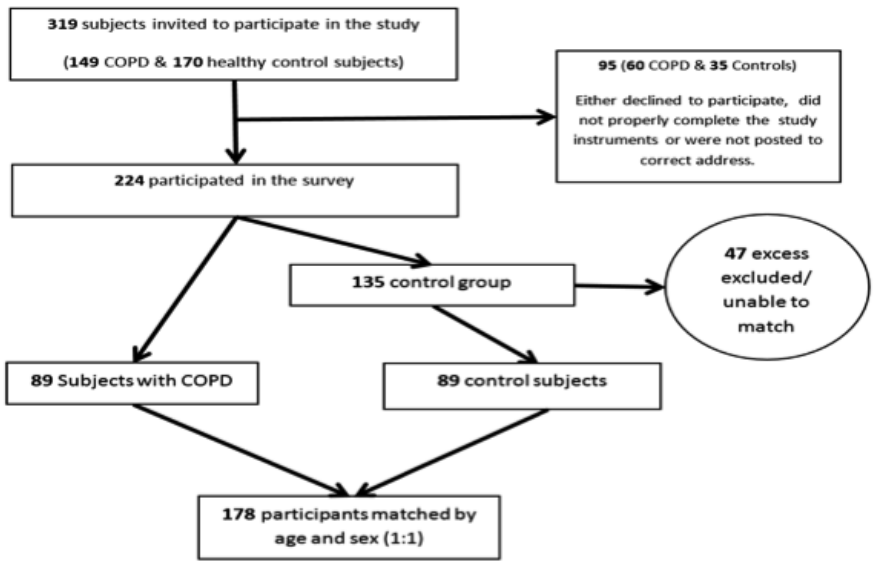

Figure 1 Flowchart of the recruitment process of study participants.

orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, urinary and pupillomotor function. An electronic version of the COMPASS-31 (in Dutch) is available via https://goo.gl/forms/0MUSGANc1J8lFVtH2. In the end, each domain has an assigned weight factor that is based on a predetermined formula. Upon analyses, a possible minimal score of 0 (best) to 100 (worst), indicating more autonomic symptoms, was reached for each participant.

Pulmonary function

The pulmonary function tests of patients with COPD were collected from the hospital records of the participating COPD patients. These parameters included forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) and the Tiffeneau index (FEV_1/FVC). The parameters were utilized in grading the disease severity in COPD. Mild (FEV_1/FVC < 70% but FEV_1 ≥ 80% predicted), moderate (30% ≤ FEV_1 < 80% predicted) and severe (FEV_1<30% predicted) GOLD stages served as the means for classifying the disease severity in subjects with COPD in this study (25).

Health status

Four different instruments, also validated in Dutch language, were used to ascertain the general health status of the patients with COPD. These instruments

were the hospital anxiety and depression scale (HADS), checklist individual strength (CIS), the medical research council dyspnea scale and the short form 36 (SF-36). The score from each instrument was converted to percentage scores for the purpose of analyses (0-100).

- ***HADS***: The HADS is an instrument consisting of 14 items, which comprises depression and anxiety sub-scales (7 items each). The HADS is a widely used instrument with good psychometric properties(26). Each question item is scored using a scale of 0–3 to achieve a minimum score of 0 and a maximum score of 21 points for the sub-scales (anxiety & depression). Higher scores are interpreted as indicating more depressive or anxiety symptoms.
- ***CIS:*** The CIS scale is an instrument used to measure the subjective fatigue and behavior related to fatigue of an individual over the last two-week period. The questionnaire comprises 20 questions on a 7-point likert scale (27). On the CIS, a higher score indicates worsened symptoms or more feelings of fatigue.
- ***MRC dyspnea scale***: The medical research council (MRC) dyspnea scale has been proven to be useful in assessing disability in COPD (28). This is a 5-item scale that is used for measuring perceived respiratory distress. The question items were graded from "1 - 5". Higher scores here indicated worsened perceived level of respiratory distress.
- ***SF-36***: The SF-36 questionnaire assesses quality of life of the individuals. The questionnaire comprises 36 questions structured across eight different domains. The domains are reported in two components, physical and mental components summaries. The physical component summary (PCS) comprises four domains namely, general health, physical functioning, limitation due to physical health and body pain, whereas the mental component summary (MCS) comprises the domains of vitality (energy/fatigue), emotional wellbeing, limitation due to emotional health and social functioning domains (29). The questionnaire is reported in a scale of 0 to 100. Lower the scores in either the PCS or MCS indicates lower quality of life.

Medication use

The participants were asked about their medication use. Information regarding brand or generic name, dosage and intake frequency of medication were collected using a tabular form. Grouping of medications was subsequently carried out based on the pharmaceutical compendium.

Statistics

Statistical analysis was performed using Social Packages Social Sciences version_22 (SPSS Inc., Chicago, IL, USA). Normality of the data was evaluated using Shapiro-Wilk test and also by manual inspection of histograms and QQ plots.. Demographic and

other clinical characteristics were summarized using descriptive statistics. Differences in the study variables between moderate and severe COPD and the control group participants were compared using Chi square test for categorical variables, and independent samples t-test for normally distributed continuous variables. On the other hand, Mann-Whitney U and/or Kruskal-Wallis H non-parametric tests were performed to analyze differences in variables that were not normally distributed. Spearman rho correlation coefficient was utilized to assess correlations between variables. A multiple stepwise regression analyses was performed to identify predictors of autonomic symptoms from the study variables. Significance was set at P<0,05.

Results

General characteristics

Table 1 summarizes the general characteristics of the participants. Overall, the patients with COPD were similar to the control participants with respect to weight, BMI and civil state (p> 0.05). Subjects with COPD presented with significantly higher prevalent rates of comorbidities/risk factors such as diabetes mellitus and gastrointestinal complaints, arthritis and headaches compared to the control group participants. Hypercholesterolemia was more prevalent among the control group participants (21 vs 12%). The healthy control group participants had a significantly higher educational attainment qualification, and a significant proportion of them were employed fulltime.

Autonomic symptoms profile scores

The participants in our study reported autonomic symptoms across all the domains assessed. Significant differences were seen across the autonomic symptoms domain scores for subjects with COPD (moderate and severe) as well as the control group participants (p<0.05). Specifically, orthostatic intolerance domain symptoms score was significantly higher for the moderate (7.0±9.44) and severe COPD (7.3±11.42) subjects compared to controls (2.3±6.38). Similarly, the secretomotor domain symptoms score was significantly higher for moderate (4.6±3.37) and severe COPD (4.2±3.17) compared to that of the control subjects (1.5±2.01). The results further showed that only subjects in the moderate severity COPD subgroup reported significantly higher vasomotor (0.5 vs 0.18), gastrointestinal (4.65 vs 2.92) , urinary (1.28 vs 0.8) and pupillomotor (1.46 vs 1.09) domain symptoms score compared to the control group(p<0.05). The results for the total autonomic symptoms score also indicated that both moderate (19.5±13.66) and severe (17.7±15.58) COPD subjects reported significantly higher scores compared to the

Table 1 Baseline characteristics of study participants.

Variables	COPD (n=89; 66 males)	Healthy controls (n=89; 66 males)	p-value
Height (cm)	168.7±7.75	172.8±9.37	**0.002** [a]
Weight (kg)	75.1±17.84	76.9±12.99	0.457 [a]
BMI (kg/m^2)	26.4±6.02	25.7±3.39	0.321 [a]
Educational attainment			
Elementary school	22(24.7%)	10(11.2%)	**0.031** [b]
Secondary and high school	46(51.6%)	36(40.4%)	0.176 [b]
College/university	21(23.5%)	43(48.4%)	**0.001** [b]
Civil state			
Living alone/divorced	18(20%)	13(11.8%)	0.43 [b]
Cohabitant/married	65(73.9%)	73(83.5%)	0.208 [b]
Widow/widower	5(5.6%)	3(3.5%)	0.72 [b]
Employment status			
Employed fulltime	2(2.4%)	22(24.7%)	**0.000** [b]
Part time	5(5.6%)	5(5.6%)	1 [b]
Disability/sick leave	14(15.7%)	1(1.2%)	**0.001** [b]
Pension	65(72.9%)	61(68.5%)	0.621 [b]
Comorbidities/risk factors			
High blood pressure	21(23.5%)	20(22.4%)	1 [b]
Diabetes mellitus	9(10.1%)	3(3.5%)	0.132 [b]
High cholesterol	11(12.4%)	19(21.3%)	0.16 [b]
Others (e.g. arthritis, rhinitis, headaches)	18(20%)	2(2.4%)	**0.000** [b]
Lung function			
FEV_1 *(% FEV_1 predicted)*	1.2±0.46 (41.7%)	-	
FVC *(% FVC predicted)*	2.9±0.87 (82%)	-	
Tiffeneau index	40.5±12.63 (75.8%)	-	
PEF(*% PEF predicted)*	3.8±1.33 (51.9%)	-	

Notes: Data are expressed as mean ± standard deviation for continuous variables and as absolute frequency and percentages for categorical variables.
Key: cm, centimeter; kg, kilogram, m, meters; n, number; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; PEF, peak expiratory flow rate; %, percent; BMI, body mass index, GI, gastro-intestinal. Tiffeneau index= FEV_1/FVC.
*Significance level for comparison between COPD and control groups.
[a] Students t-test for independent samples: comparison of continuous variables between COPD and control.
[b] Chi square test: comparison of categorical variables between COPD and control group participants.

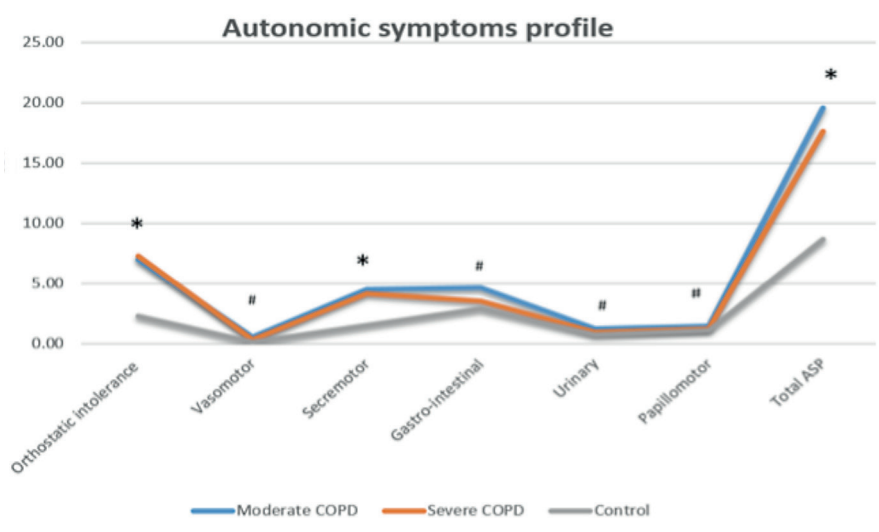

Figure 2 Line graph showing the distribution of autonomic symptoms (domain scores and total ASP score).

Notes: *= Significant difference between both COPD stages and the control group (Kruskal-Wallis); # = significant difference between moderate COPD and control group (Mann-Whitney U); p, significant at 0.05 alpha probability level.

subjects in the control group (8.7±9.91) as illustrated in figure 2. Additionally, no significant differences were found in the autonomic symptoms domain scores between the moderate and severe COPD group (p> 0.05).

Health status of patients with COPD

As illustrated in Figure 3, subjects with COPD reported significantly lower quality of life scores based on the PCS and MCS outcomes compared to the control group ($p<0.05$). Higher values in the rates of fatigue, anxiety, depression and dyspnea were recorded in COPD compared to the control group($p<0.05$). No differences were found in the values of these variables between the moderate and severe COPD subgroups ($p>0.05$), except for the dyspnea scores, which was significant higher among the severe COPD subgroup($p<0.05$).

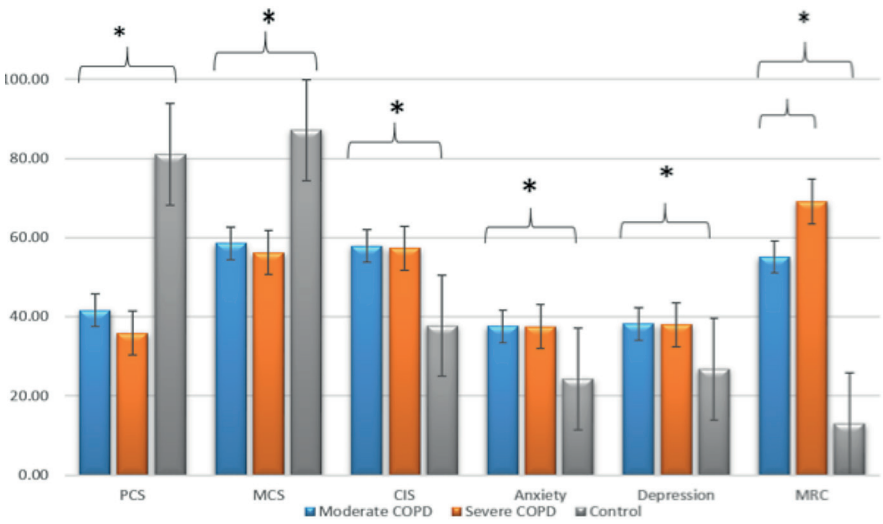

Figure 3 Health status of the participants using various parameters.

Notes: PCS, physical component summary; MCS, mental component summary; CIS, checklist individual strength, MRC, medical research council dyspnea scale; *= significant differences between COPD and control group (Kruskal-Wallis H test); # = significant differences between COPD stages (Mann-Whitney U); p, significant at 0.05 alpha probability level.

Correlation between autonomic symptoms and health status

The correlation matrix (Table 2) generated from the results of the Spearman rho correlation coefficient analyses showed that the demographic (age, height & weight) and lung functions variables did not significantly correlate with autonomic symptom scores ($p > 0.05$). Only the parameters the comprising the health status (anxiety, depression, fatigue, and the physical & mental health) scores indicated a mild to moderate correlation with autonomic symptoms scores ($p < 0.05$).

Multiple regression analyses

The multiple regression (stepwise) analyses revealed that only the MCS (mental health) score was a significant covariate (predictor) of total autonomic symptoms score in patients with COPD ($p = 0.000$; beta = -.430; adjusted $R^2 = .175$). Here, for every unit increase in the MCS score, the total autonomic symptoms burden is reduced by 0.4 unit (Figure 4). All other variables entered into the stepwise regression model did not show any potential significant influence ($p > 0.05$).

Table 2 Correlation matrix of the autonomic symptoms and other variables of subjects with COPD.

Domains /variables	Orthostatic intolerance	Vasomotor	Secremotor	Gastro intestinal	Bladder	Pupillo-motor	Total ASP score
Age							
Height							
Weight							
BMI							
FEV_1							
FVC							
PEF							
Tiffeneau index							
Anxiety	0.253		0.406		0.214		0.361
Depression		0.223	0.347		0.231		0.334
Fatigue			0.313		0.304	0.279	0.379
PCS	-0.244	-0.265		-0.292			-0.351
MCS	-0.298	-0.228	-0.332	-0.307			-0.421

Notes: Only significance correlation (r) values levels are shown in the matrix ($p < .05$). PCS, physical component score on SF-36; MCS, mental component score on SF-36; BMI, body mass index; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; PEF, peak expiratory flow rate.

Medication use

The majority of patients with COPD (94.3%) and a significant proportion of the control subjects (24.6%) reported using various medications. Table 3 shows the breakdown of the medication use. Subjects with COPD reported a significantly higher use of pulmonary, cardiovascular, gastro intestinal, analgesic/anti-inflammatory, neuropsychiatric, antibiotic, diabetic mellitus, antidepressants and lipid lowering medications compared to the control groups subjects ($p<0.05$). Within the COPD group, those with sever COPD reported significantly higher intake of inhaled corticosteroids and significantly less intake of cardiovascular diabetic, gastro intestinal medications($p<0.05$). None of the control group subjects reported using any pulmonary medications.

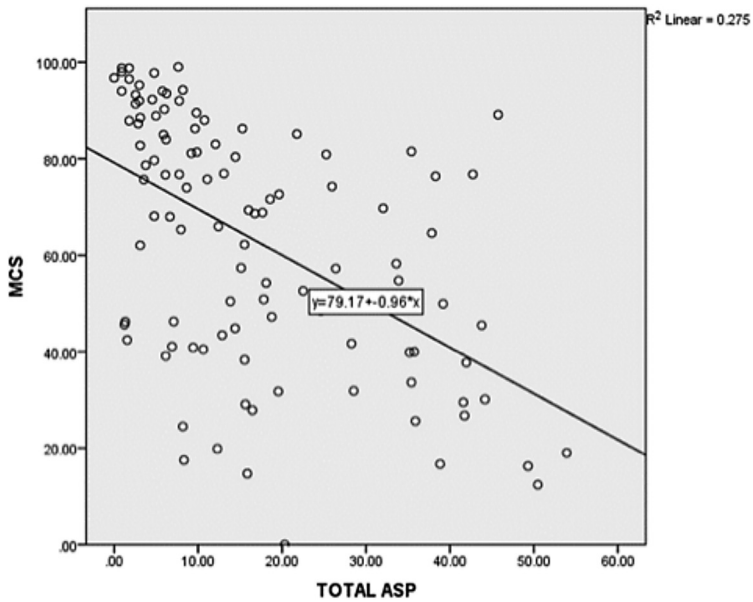

Figure 4 Regression (correlation) coefficient between the MCS and the total autonomic symptoms scores.

Discussion

This study aimed to examine the profile of autonomic symptoms among patients with COPD. Our results indicated that autonomic symptoms were significantly higher in subjects with COPD compared to the control group participants. In general, autonomic symptoms were more prevalent in the orthostatic intolerance and secretomotor function domains in subjects with COPD. Additionally, higher symptoms were also recorded for autonomic symptoms relating to the gastrointestinal and vasomotor domains in the moderate COPD subgroup in comparison with control. Subjects with COPD also reported higher levels of anxiety, depression, fatigue symptoms as well as the lower quality of life (physical and mental component summary) scores compared to the control group, indicating poorer health status. Despite matching the participants by age and gender to eliminate potential baseline differences, slight demographic differences were still observed (Table 1).

A major finding of our study that is was the high rate of orthostatic intolerance and secretomotor symptoms reported in subjects with COPD. This finding is supported by an earlier report, which describes both orthostatic intolerance and

secretomotor disorders as the best predictors of autonomic failure in both healthy and diseased populations (11). This finding is clinically important for a few reasons; orthostatic intolerance is linked to sudden tachycardia and cerebral vasoconstriction (30) and orthostatic intolerance symptoms is a major clinical test that is capable of ascertaining symptoms of cerebral hypo-perfusion (following an upright position) that is secondary to inadequate hemodynamic regulation by the ANS (13, 31, 32). It is not surprising that subjects with COPD in our study reported high rates of orthostatic symptoms. Orthostatic intolerance can appear in many forms such as fatigue, diminished concentration, a feeling of absence, brain fog, chest pain, shortness of breath, palpitations, coat-hanger headache, and vision disturbances (31). Moreover, COPD patients who have shortness of breath due to reduced ventilatory capacity, hypercapnia and/or lowered oxygen saturation have been reported to be at more risks of orthostatic symptoms compared to those without these symptoms (33).

Our results also showed a significant presence of a possible secretomotor disorder in COPD. The COMPASS-31 questionnaire used in this study assessed secretomotor domain function using questions centered around tear formation, salivary gland secretion and sweating. In general, secretomotor disorders also include conditions that are characteristic of thermoregulatory dysfunction that include heat intolerance, impaired body sweating and dryness of the eyes and mouth (13, 34). Problems with the secretomotor function are important to patients because of its correlation with quality of life and perceived mental health status (35). By the way, the COPD subjects in this study did not only report a significantly higher secretomotor symptoms compared to controls, but these symptoms were also associated with the levels of anxiety, depression, fatigue and mental health, suggesting a negative influence of health status on the ANS. The presence of secretomotor symptoms in COPD may explain the results of poor performance in sympathetic skin response, a measure of sudomotor function (36) and acetylcholine sweat test (7, 37) among patients with COPD in earlier reports. However, further studies are needed to prove this.

Only the moderate COPD group in our study reported higher rates of vasomotor, gastrointestinal urinary and pupillomotor symptoms compared to the control group participants. Although rather unexpected, nevertheless, we can attribute this present finding to the relatively low number of participants that make up the severe COPD sub-group. It is likely that a future similar survey with larger sample sizes of severe COPD cohort will report similar findings. For the gastro intestinal symptoms reported, there is also a possibility that the high rate of gastrointestinal medications use might have influenced these results. Moreover, both COPD groups reported a significantly higher use of gastrointestinal medication. The link between autonomic symptoms and the presence of ANS (in both para-

Table 3 Profile of the medication use reported by the study participants.

Variables	Control group subjects (n=89)	Moderate COPD (GOLD II; n=66)	Severe COPD (GOLD III-IV; n=23)	p value
Reported medication use	22(24.6%)	63(95.4%)	21 (91.3%)	
Analgesic/anti-inflammatory drugs (paracetamol, NSAIDs & opiates)	0(0%)	8(12.1%)	1(4.3%)	**0.003*** 0.353
Antibiotics	0(0%)	12(18.2%)	7(30.4%)	**0.001*** 0.269
Anticoagulants	6(6.7%)	34(51.5%)	5(21.7%)	**0.001*** **0.003#**
Antihistamines	0(0%)	2(3%)	0(0%)	0.180 0.472
Antidepressants/sedatives (Benzodiazepines & SSRIs)	3(3.4%)	18(27.3%)	7(30.4%)	**0.001*** 0.531
Cardiovascular medications (ACE inhibitors, beta blockers, calcium channel blockers, diuretics & anti-arrhythmic)	19(21.3%)	38(57.6%)	9(39.1%)	**0.001*** **0.035#**
Neuropsychiatric medications	0(0%)	4(6.1%)	0(0%)	**0.031*** 0.256
Diabetes mellitus medications (metformin, sulfonylureas, thiazolidinedione & insulin therapy)	3(3.4%)	14(21.2%)	0(0%)	**0.001*** **0.023#**
Gastrointestinal medications (anti-peptic agents, laxatives & proton pump inhibitors)	1(1.1%)	18(27.3%)	5(21.7%)	**0.001*** 0.429
Lipid lowering medications (statins & fibrates)	15(16.9%)	25(37.9%)	4(17.4%)	**0.008*** 0.051
Other Medications (calcium supplements, vitamins, hormone therapy, cancer [prostate] therapy & uric acid)	3(3.4%)	21(33.8%)	9(39.1%)	**0.001*** 0.526

Table 3 Continued.

Variables	Control group subjects (n=89)	Moderate COPD (GOLD II; n=66)	Severe COPD (GOLD III-IV; n=23)	p value
Pulmonary medications				
LABA/LAMA, LABA+LAMA, SABA/SAMA	0(0%)	63(95.5%)	21(91.3%)	**0.001*** 0.943
Mucolytic(s) and nasal decongestants	0(0%)	19(28.8%)	8(34.8%)	**0.001*** 0.296
LABA+LAMA+ICS, ICS	0(0%)	12(18.2%)	9(39.1%)	**0.001*** **0.016#**

Notes: P, significant at 0.05 alpha probability level, *= significant difference between both COPD and control groups derived from Kruskal-Wallis H test, # = significant difference between only the moderate and severe COPD groups based on Mann-Whitney U test. n= number, %=percentages and frequency of drugs comparison is based upon groups (moderate & severe COPD) and for those who reported medication use, GOLD= global initiative for obstructive lung disease, SSRI= selective serotonin reuptake inhibitor, NSAIDS= non-steroidal anti-inflammatory drugs, ACE= angiotensin converting enzyme. SABA= Short acting beta agonists, LABA= long acting beta agonists, SAMA = short acting anti-muscarinic antagonists, LAMA = long acting anti-muscarinic antagonists, ICS= inhaled corticosteroids.

sympathetic and sympathetic branches)) disorders may have been recently explained (22). Here, the having parasympathetic nervous system disorder was reported to be linked with the prevalence of secretomotor, bladder and gastrointestinal symptoms. On the other hand, sympathetic involvement was identified as a major variable for reported orthostatic symptoms, impaired sweating and vasomotor dysfunction. To further elaborate on this result, our next study will be to investigate the correlations between autonomic symptoms and objective autonomic function tests such as autonomic reactivity tests in COPD.

Another interesting finding from this study was that the components that make up the health status (anxiety, depression, fatigue, physical & mental health) of subjects with COPD significantly correlated with autonomic symptoms. It is equally surprising that demographic variables and lung functions did not correlate with autonomic symptoms in COPD. It can only mean that these findings represents the importance of patient subjective outcomes (38). Moreover, previous studies have linked subjective symptoms with several patient important health outcomes with clinical implication (17-20). For example, the COPD patients in this study also exhibited high rate of depression as earlier observed other similar studies (39).

A significant medication use was recorded in our study. It is also very plausible that the reported medication use had influence on the autonomic symptoms reported in the results of this study. Even though no statistical analyses were carried out to reveal if any relationship exist between medication use and autonomic symptoms in this study, the presence of significant variation in the pattern and profile of medication use between COPD and control group subjects (Table 3), is suggestive of a potential medication influence on the autonomic symptoms. A recent review attributed significant increases in the sympathetic nervous activity and heart rate activity, as well as poor heart rate variability in COPD patients to the use of sympathomimetic drugs (40). Although there are differences in the reported medication use (especially vasoactive drugs) between the moderate and severe COPD and also between COPD and controls, we cannot explain at present whether this had any effect on the autonomic symptoms profile (Figure 2). Moreover, a few studies have even suggested the COPD medication does not significantly contribute to the impairments in autonomic function (7, 36, 40).

Our results must be viewed within the limitations of the study. Using a self-report method for symptom and health status questioning may not provide a real prevalence of symptoms since symptoms that are not intensely present or frequently experienced by the patient may not have been reported. However, we are convinced that this method accurately identifies patient important health outcomes, hence, a significant treatment goal. Another limitation of this study is the cross-sectional design. Follow-up studies may be warranted in order to accurately evaluate the course of autonomic symptom in these patients.

The present study also recorded a few areas of strengths. Firstly, this is the first study to focus on autonomic symptoms in COPD, and to assess the impact of those symptoms by evaluating the relationship with measures of quality of life and mood. Secondly, our study also recorded a response rate of about 59.7% of the population that was contacted for the survey. Therefore, the findings from specifically, our study sample adequately represents the autonomic profile of patients with moderate and severe COPD. Lastly, our results only presented a profile of autonomic symptoms in COPD. More studies are still needed in order to provide better clinical awareness and proper identification of the underlying mechanisms of the autonomic symptoms, and its evolution in COPD.

Conclusion

This study demonstrates that patients with moderate and severe COPD have autonomic symptoms in the orthostatic, secretomotor, vasomotor, gastrointestinal urinary and pupillomotor systems that is independent of COPD severity. The

presence of these symptoms was somewhat associated with high levels of depression, anxiety, fatigue and poor quality of life in COPD. Our study also revealed that only mental health status considerably influences the total autonomic symptoms score in COPD.

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Chapter 5

Cardiac autonomic function and reactivity tests in physically active moderately severe subjects with chronic obstructive pulmonary disease

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Abstract

Patients with chronic obstructive pulmonary disease (COPD) show impairments in the autonomic nervous systems (ANS) function, which is responsible for cardiac autonomic regulation. This study assessed the autonomic function and cardio-vagal reactivity in conveniently sampled subjects with COPD participating in a pulmonary rehabilitation (PR) program. 26 subjects with COPD and 22 age and gender matched control subjects were evaluated. R-R intervals were collected at rest in supine position. Thereafter, resting autonomic function parameters comprising linear and nonlinear analyses of heart rate variability (HRV) and baroreceptor sensitivity (BRS) were calculated. Autonomic reactivity tests comprising deep breathing (DB), Valsalva maneuver (VM) and head up tilt (HUT) were also performed. The results of this study indicated that resting autonomic function variables were generally reduced in COPD compared to controls. However, this difference was only statistically significant for a few HRV parameters: mean RR intervals, low frequency (LF), standard deviation of dispersion of points perpendicular to the line-of-identity (SD1) and approximate entropy (ApEn) ($p<0.05$). The results also indicated that all cardio-vagal indices following the autonomic reactivity tests were comparable between COPD and controls ($p>0.05$). It was concluded that subtle autonomic impairments exist in physically active COPD patients, and these autonomic function deficits were mainly recognized by resting HRV indices and not autonomic reactivity tests.

Keywords: *autonomic reactivity, chronic obstructive, pulmonary disease, autonomic function, physically active, COPD.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a pulmonary disease mainly characterized by airflow limitation in the lungs and also multi-systemic manifestations on a number of extra-pulmonary systems especially the cardio-vascular and autonomic nervous systems (ANS) (1-3). These manifestations are associated with COPD comorbidities, most of which contribute to poor prognosis, risks of arrhythmias, and COPD related mortality rates (1, 4). Specifically, patients with COPD present with functional alterations and dysfunction of the cardiac autonomic modulation, which is primarily reflected in the form of an elevation in the resting heart rate and/or reduction in heart rate variability (HRV) indices (2, 3, 5).

Therefore, the assessment of various ANS parameters have been the focal point in understanding the autonomic function, and its clinical implications in COPD (3). Current reports have also shown that ANS parameters (physiological biomarkers) such as heart rate variability (HRV) (1, 6, 7), heart rate response (HRR) to exercise (1), muscle sympathetic nerve activity (MSNA) and baroreceptor sensitivity (BRS) (8) are significantly impaired in patients with COPD. The HRV in particular is an autonomic function parameter that represents a powerful research tool for quantifying the state of the ANS, with reliable clinical applications (9). Moreover, autonomic function parameters are utilized for calculating the sympathetic tone, vagal modulation of the sinus node and the sympatho-vagal balance with a view to optimizing treatment (10). A number of limitations have been observed in the existing studies over the years. For example, in our recent systematic review, we found that most of the available studies often do not take into account variables such as differences in disease stage (global obstructive lung disease [GOLD] criteria) or presence of variable COPD comorbidities and no evidence exist for a number of autonomic function variables (11). Additionally, autonomic function has been found to be influenced by several factors such as circadian rhythm (12), clinical and even demographic variables and physical activity status (11).

Furthermore, several important autonomic function parameters like the nonlinear HRV analyses (including entropy changes), which has recently become more useful in assessing the ANS function remain under-reported in patients with COPD (2, 13-15). Specifically, the nonlinear HRV values have the capacity to reflect important nonlinear heart dynamics or patterns in the ECG data. Moreover, no systematic evidence is presently available to support a severely impaired nonlinear HRV indices in COPD (11). Additionally, conflicting results have been reported among different subgroups of COPD. Cardiac autonomic control is a complex mechanism that require careful interpretation and application in clinical settings (4). Nevertheless, since autonomic function is widely reported in COPD, it is largely

assumed to be impaired in these patients. We hypothesize that there will be a diminished or impaired ANS function (e.g. lower LF or impaired baroreflex activation) among a subgroup of individuals with COPD who are physically active and fairly homogenous. Furthermore, the use of the widely used autonomic reactivity tests (comprising validated test battery for assessing autonomic failure) of cardio-vagal autonomic function indices has been inadequately reported for patients with COPD (16).

To address these gaps, this study was conducted to evaluate both parameters of resting autonomic function and cardio-vagal responses to validated autonomic reactivity tests among non-sedentary individuals with COPD.

Methods

Subjects

The population of this study comprised twenty-six patients with severe COPD (23 males & 3 females; %predictedFEV_1 of 39.5%) aged between 50 and 80 years. All COPD subjects were non-sedentary, and this was defined as participating in a pulmonary rehabilitation (PR) program continuously for at least two months. COPD subjects fulfilling the following inclusion criteria were eligible for participation in the study: (i) a stable condition (no acute exacerbation or change in therapeutic treatment plan in the past three months), (ii) no severe co-morbidity such as chronic heart diseases, uncontrolled diabetes mellitus, neurological problems, cancer, mental disorder and complex cardiac arrhythmias, and (iii) no recent surgery (<6 months).

A control group comprising 22 age and sex- matched healthy individuals (19 males and 3 females) without COPD or any other chronic disease was recruited from the general population. The participants in the control group were screen using the Baecke physical activity questionnaire (17), and only those with a moderate or high physical activity level participated in the study.

All participants signed an informed consent form prior to commencement of study measurements. The research protocol was approved by the ethical committee of Ghent University Hospital.

Procedure

The measurements were conducted in a room with constant temperature between 21-23° Celsius. All measurements were carried out in the morning hours between 8 and 11 am to avoid the influence of circadian rhythm. The participants were also instructed to refrain from coffee and nicotine use prior to the test moment on the scheduled day. Prior to the measurements, the participants were questioned

regrading age, gender, smoking status, alcohol use was measured, and their body mass index (BMI) was also calculated. Information regarding medical history, and medication use of subjects with COPD was retrieved from their hospital based medical records. The ECG and beat-to-beat blood pressure recordings were conducted via 3-lead electrodes (placed on the chest) and bicep/finger (plethysmography) cuffs attached to a Finometer PRO® ECG machine (Finapres Medical Systems, The Netherlands). The finger volume pulse waveform measured by Finometer device has been recently confirmed to be a reliable source for analysis of HRV (18).

Autonomic function tests

Data acquisition and analysis

The data files were retrieved from the Finometer PRO machine. The files were then transformed into a readable (Excel) format in order to extract stable signals corresponding to the middle 5 minutes of resting autonomic function recordings. The pulse interval (RRi) in TXT format was then imported into Kubios (software package version 2.2, University of Eastern Finland, Kuopio) (19) for further analyses. Artefact correction was set at 'very strong' in all cases.

Resting heart rate variability analysis

The resting HRV was assessed by linear as well as by nonlinear analyses. For linear HRV analyses, this was done for both time and frequency domain parameters. The time domain HRV analyses included; mean of RR (mean RR) intervals, the standard deviation of the mean of all RR intervals (SDRR or SDNN), the square root of the mean squared differences of successive RR intervals (RMSSD), mean heart rate (HR), number of pairs of adjacent NN intervals differing by more than 50ms in the entire recording (NN50), NN50 count divided by the total number of all NN intervals (pNN50), the triangular index (RRi tri) and triangular interpolation of NN interval histogram (TINN). In general, higher values in the time domain HRV analyses reflects vagal influence over the heart control.

The frequency domain HRV analyses, which were based on the Fast Fourier Transformation (Welsh periodogram estimates) included the very low frequency (VLF), low frequency (LF) and high frequency (HF), were expressed in milliseconds squared (ms^2). Higher values of the HF index represent parasympathetic activity, while the LF characterizes both sympathetic and parasympathetic outflows. The normalized units (nu) of the LF and HF, as well as the LF/HF ratio, which represents the sympathovagal balance were also calculated.

The indices of the nonlinear HRV analysis, which provide a more robust information relating to the behavior of the cardiac control were also retrieved. These included the standard deviation measuring the dispersion of points in the plot perpendicular to the line of identity (SD_1) and the standard deviation measuring

the dispersion of points along the line of identity (SD_2). The SD1 measures short term HRV in ms, while the SD2 represents both the short and long term HRV in milliseconds (ms). Other nonlinear parameters included the (i) approximate entropy (ApEn), which measures the complexity or irregularity or randomness within the HRV data (series). Small ApEn values is indicative of a regular and predictable signal (20) (ii) Shannon entropy (ShannEn), is also a measure of short term HRV that reflects the degree of complexity of the signal similar to ApEn, and (iii) mean line length (Lmean) and max line length (Lmax) of the data series. Furthermore, we also reported on the sample entropy (SampEn), which is a measure of signal regularity and complexity, and small values also represent regular signals. The detrended fluctuation analysis (DFA) measures the rate of fluctuation in the data series, and it is described in terms of both brief (1) and long term (2) fluctuations that represents baroreceptor reflex and regulatory mechanisms that limit fluctuation of the beat cycle was also assessed (20, 21). DFA is decreased in cardiovascular disorders such as myocardial infarction . And lastly, we calculated the correlation dimension (D_2) which estimates the minimum number of variables required to construct a model of system dynamics. Here, higher values indicate greater complexity (20).

Resting baroreceptor reflex sensitivity

The resting BRS reported in this study was the time domain cross-correlation BRS (xBRS), which was computed according to the method of Westerhof (22). Other xBRS parameters such as interval (in milliseconds), delay time (in seconds) and the regression coefficient of determination (R^2) were also extracted.

Autonomic reactivity tests

The autonomic reactivity tests of cardio-vagal indices were conducted by means of continuous ECG and cardiovascular monitoring during three test moments based on a validated and standardized protocol (23). They include heart rate response to deep breathing (HR_{DB}), Valsalva maneuver (VM) and head up tilt (HUT).

heart rate response to deep breathing

For the HR_{DB}, the participants were asked to perform 8 cycles of deep inspirations (via the nose) and expirations (via the mouth) at a breathing rate corresponding to 6 breaths/minute. They were provided with a visual biofeedback on a computer screen. The maneuver was repeated twice with a resting time interval of five minutes. The best trial comprising at least 5 cycles good of breaths was retrieved. The average of the range of maximum HR achieved during inspiration and the minimum HR during expiration for each cycle of breath was calculated. This parameter assesses the vagal control of the heart, a measure of parasympathetic

reactivity (normal: >15 beat/minute, borderline: 11-14 beats/minute, and abnormal: <11 beats/minute) (24).

Valsalva maneuver

The VM was evoked by asking the subjects to continuously blow for 15 seconds, through a mouthpiece attached onto a sphygmomanometer at pressure between 40 and 50 mmHg. A visual feedback was provided on a computer screen to aid the maneuver. This maneuver was repeated three times with a resting interval time of 3 minutes between the maneuvers. For each subject, only the best of the 3 trials showing adequate pressure, duration and normal mean arterial pressure response that reflects the 4 phases of VM(23, 25) was selected for analyses. This decision was taken after a careful inspection of the maneuver (excel graph plot) was made.

Several parameters were calculated from the data of subjects who completed at least one adequate VM trial. They include: Valsalva ratio (VR), which represents vagal activity, was calculated as the ratio of the maximum HR (HRmax) during Valsalva maneuver and the maximum HR within 30 seconds from the HRmax. The Valsalva index (VI), which is also an indirect measure of the ANS integrity, was calculated as the ratio between the longest RRi during VM recovery (phase 4) and the shortest RRi during the peak of VM. A VI of less than 1.4 is considered abnormal. Three BRS parameters comprising adrenergic baroreceptor sensitivity (BRS_a), vagal baroreceptor sensitivity (BRS_v) and global baroreceptor sensitivity (BRS_g) indices were also calculated using an existing protocol (26).

Head up tilt

After a 5-minute period of continuous recording in a supine position, the table was slowly tilted up to 60° angle and maintained for 10 minutes. The participants were asked to report any symptoms of light headedness, feelings of dizziness, discomfort or pain throughout the duration of the tilt. The HUT test was terminated only if severe orthostatic intolerance complaints or signs of vasovagal syncope were suspected (27).

Statistical analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences vaersion_22 (SPSS Inc. Chicago IL, USA). Demographic and other clinical characteristics were mainly summarized using descriptive statistics. All the variables were subjected to the Shapiro-Wilk's test and manual inspection of both QQ plots and histograms to ascertain whether or not they were normality distributed. To evaluate the significance of differences of variables between COPD and controls, we used independent samples t-test or Mann-Whitney U-test, where appropriate. For non-parametric variable comparison, we used Chi square test.

Lastly, to assess the cardiovascular responses during the HUT, two-way repeated measure ANOVA was utilized. Alpha probability value was considered significant at < 0.05 level in all cases.

Results

Demographic characteristics

The demographic and baseline clinical characteristics are presented in Table 1. These results show that the majority of the study variables such as age, body weight, BMI, systolic and diastolic blood pressures as well as mean arterial pressure (MAP) variables were all comparable between patients with COPD and healthy control subjects ($p>0.05$). However, the control subjects were significantly taller ($p=0.008$). The Table further shows that subjects with COPD had a significantly higher resting HR, and they reported significantly higher use of two vasoactive medications (beta blockers and ACE inhibitors) compared to controls ($p<0.05$).

Resting autonomic function

Table 2 shows the results for resting autonomic function indices between subjects with COPD and the healthy controls. Subjects with COPD were found to consequently have lower values for almost all the time domain HRV analyses compared to controls. However, only the differences for mean RR was statistically significant ($p=0.011$). This is suggestive of a decreased vagal activity of subjects with COPD compared to controls. Similarly, frequency domain indices with the exception of HF (nu) were decreased in COPD compared to controls, however, only the LF(ms^2) power was of significance ($p=0.035$).

For the nonlinear HRV analyses, all reported variables were comparable between subjects with COPD and control subjects except for SD_1, which was significantly decreased in COPD ($p=0.041$). The ApEn was also found to be significantly increased in COPD compared to the controls ($p=0.02$), suggesting a higher complexity and lower signal predictability. Lastly, the results of this study revealed that subjects with COPD had lower resting BRS parameters compared to the control group (5.5 vs 8.0, ms.mmHg). However, these differences did not reach statistical significance ($p>0.05$).

Cardio vagal autonomic reactivity

The results from the autonomic reactivity tests are presented in Table 3. The HR_{DB} were comparable between subjects with COPD and controls ($p=0.869$). All parameters derived from the VM including the VR, VI, BRS_a, BRS_v, BRS_g, PRT and PP drop were comparable between subjects with COPD and controls ($p>0.05$). For HUT, even

Table 1 Baseline characteristics.

Variables	COPD (n, 26)	Controls (n,22)	p-value
Age *(years)*	65.8±8.99	64.2±8.5	.538[t]
Sex, male(%)	23 (88.5%)	19 (86.4%)	.582[X]
Height *(m)*	1.70±0.06	1.76±0.08	**.008*[t]**
Weight *(kg)*	75.3±10.22	76.0±10.57	.807[t]
BMI *(Kg/m²)*	26.2±3.47	24.6±2.82	.102[t]
HR *(bpm)*	72.9±11.48	61.3±7.82	**.001*[t]**
Systolic BP	139.7±23.48	136.8±17.67	.642[t]
Diastolic BP	75.5±11.7	71.7±7.50	.191[t]
MAP	99.1±15.69	95.2±9.64	.313[t]
Lung function			
FEV_1 *(% FEV_1 predicted)*	1.17±0.53 (39.5%)	-	
FVC *(% FVC predicted)*	2.97±0.79 (79.6%)	-	
Tiffeneau index	36.4±14.83%	-	
PEF *(% PEF predicted)*	6.0±9.65 (52.9%)	-	
~6MWD			
Meters	471±124.1		
% of reference value	70±14.8		
Medication (vasoactive) use			
Opiates	1(3.8%)	0(0%)	.364[X]
Antidepressants (tricyclic)	2(11.5%)	0(0%)	.194[X]
Diuretics	2(7.7%)	0(0%)	.194[X]
Beta-blockers	7(26.9%)	0(0%)	**.010*[X]**
Calcium channel blockers	2(7.7%)	0(0%)	.194[X]
ACE inhibitors	8(30.8%)	1(4.5%)	**.044*[X]**
Sedatives	1(3.8%)	0(0%)	.364[X]
Anticonvulsants	1(3.8%)	0(0%)	.364 [X]

Notes: bpm, beats per minute; m, meters; kg, kilogram; ms, milliseconds; %, percentage; mmHg, millimeter of mercury; MAP, mean arterial pressure; BP, blood pressure; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; PEF, peak expiratory flowrate; ACE, angiotensin converting enzyme; HR, heart rate; BMI, body mass index; MAP, mean arterial pressure. ~ not available in published version.
*, significant difference at p<0.05 alpha probability level; [t], results based upon independent samples T-test statistics; [X], results based on Chi^2 tests.

Table 2 Comparison of resting autonomic function parameters between COPD and controls.

Variables	COPD (n, 26)	Controls (n, 22)	p-value
Time domain HRV analyses			
SDNN (ms)	31.0±13.18	40.38±17.64	.067[m]
RMSSD(ms)	18.5±5.78	22.9±10.13	.065[t]
NN50(count)	6.9±8.89	7.5±7.18	.359[m]
pNN50(%)	2.3±3.09	2.6±2.34	.263[m]
RR tri	6.8±2.13	8.4±3.46	.055[t]
TINN	113.5±58.43	116.1±88.03	.917[m]
Mean RR (ms)	865.6±185.75	991.8±133.43	**.011*[t]**
Frequency domain HRV analyses			
LF (ms^2)	219.9±158.56	351.9±256.66	**.035*[t]**
HF (ms^2)	144.9±93.62	189.8±277.65	.442[t]
LF (n.u.)	56.8±18.96	65.5±17.96	.113[t]
HF (n.u.)	43.1±18.95	34.4±17.92	.113[t]
LF/HF ratio	2.2±2.29	2.9±2.37	.104[m]
Nonlinear HRV analyses			
SD_1(ms)	13.1±4.09	19.4±14.63	**.041*[t]**
SD_2(ms)	41.7±18.53	54.2±25.15	.056[m]
Lmean (beats)	12.3±5.30	14.8±6.25	.104[m]
Lmax (beats)	241.6±112.92	227.3±97.11	.645[t]
Detrended fluctuations (DFA): α1	1.1±0.21	1.2±0.28	.437[t]
Detrended fluctuations (DFA): α2	1.0±0.18	1.0±0.29	.646[m]
Shannon entropy (ShannEn)	3.2±0.36	3.4±0.38	.158[t]
Approximate entropy (ApEn)	1.1±0.12	0.98±0.14	**.02*[t]**
Sample entropy (SampEn)	1.6±0.38	1.4±0.51	.170[t]
Correlation dimension (D2)	0.9±0.84	1.3±1.13	.242[m]
BRS			
xBRS (ms.mmHg)	5.4±3.18	8.0±5.99	.138[m]
Mean tau (s)	1.7±0.94	2.2±0.68	.051[m]
R^2	0.70±0.04	0.70±0.03	.918[t]
Interval (ms)	120.2±97.99	122.3±80.97	.650[m]

Notes: SDNN, standard deviation of all normal R-R intervals; RMSSD, the root mean square of differences of successive RR intervals; NN50, number of consecutive RR intervals that differ more than 50 ms; pNN50, the percentage of NN50, SD_1, the standard deviation of the Poincaré plot perpendicular to the line-of-identity ; SD_2, the standard deviation of the Poincaré plot along the line-of-identity; RR tri, the integral of the RR interval histogram divided by the maximum of the histogram; LF, low frequency; HF, high frequency; LF/HF, ratio of LF and HF frequency band powers; ms= milliseconds, nu= normalized units; xBRS, cross-correlational baroreceptor sensitivity; %, percentage;

*, significant difference at p<0.05 alpha probability level; [t] , results based upon independent samples T-test; [m], results based on Mann-Whitney U-Test.

Table 3 Results of cardio-vagal reactivity indices for COPD and control subjects.

	COPD	Healthy controls	p-value
Deep breathing			
HR_{DB} (bpm)	12.1±6.87	12.3±7.09	.869[m]
Valsalva maneuver			
VR	1.66±0.44	1.41±0.25	.076[m]
VI	1.55±0.44	1.44±0.3	.488[m]
BRS_a (mmHg/sec)	5.4±2.55	5.4±3.84	.972[t]
BRS_v (sec/mmHg)	2.8±2.34	2.2±1.6	.547[m]
BRS_g	12.4±7.68	15.6±20.42	.399[m]
PRT (sec)	5.5±3.78	4.6±2.58	.374[t]
PP drop	6.1±4.74	7.9±7.81	.419[t]
Inadequate VM (loss of any phase)	11(42%)	4(18%)	.121[X]
Tilting			
Initial OH	5(19.2%)	1(4.5%)	.139[X]
OH	7(26.9%)	2(9%)	.132[X]
Delayed OH	7(26.9%)	3(13%)	.293[X]
POTS	1(3.8%)	0(0%)	.364[X]
Early stop due to other reasons	1(3.8%)	0(0%)	.364[X]

Notes: data expressed as mean ± standard deviation for continuous variables and as absolute frequency and percentages for categorical variables. Bpm, beats per minute; mmHg, millimeter of mercury; OH, orthostatic intolerance; POTS, postural orthostatic tachycardia syndrome; HR_{DB}, heart rate response to deep breathing; BRS_a, adrenergic baroreceptor sensitivity; BRS_v, vagal baroreceptor sensitivity; BRS_g, global baroreceptor sensitivity; PP drop, pulse pressure drops; PRT, Pressure recovery time; VI, valsalva index, VR, valsalva ratio; VM, Valsalva maneuver.
[*]= significant difference at $p<0.05$ alpha probability level, [X]=results based upon Chi^2 tests, [m] =results based on Mann-Whitney U-Test.

though subjects with COPD reported more orthostatic symptoms compared with controls, these were not statistically significant ($p>0.05$). Further analyses of the HUT results revealed that the subjects with COPD also recorded a slightly higher drop in both systolic and diastolic blood pressures, as well as a slightly increased heart rate during the HUT. The results from the 2 way repeated measures ANOVA analyses indicated that these variations were no statistically significant interaction (between subject's effects) in the systolic blood pressure (F, 2.302; p=137), diastolic blood pressure (F, 0.034; p=0.855), and heart rate (F, 0.975; p=0.330) of both COPD and control groups. These results are illustrated in a graphical manner in Figure 1.

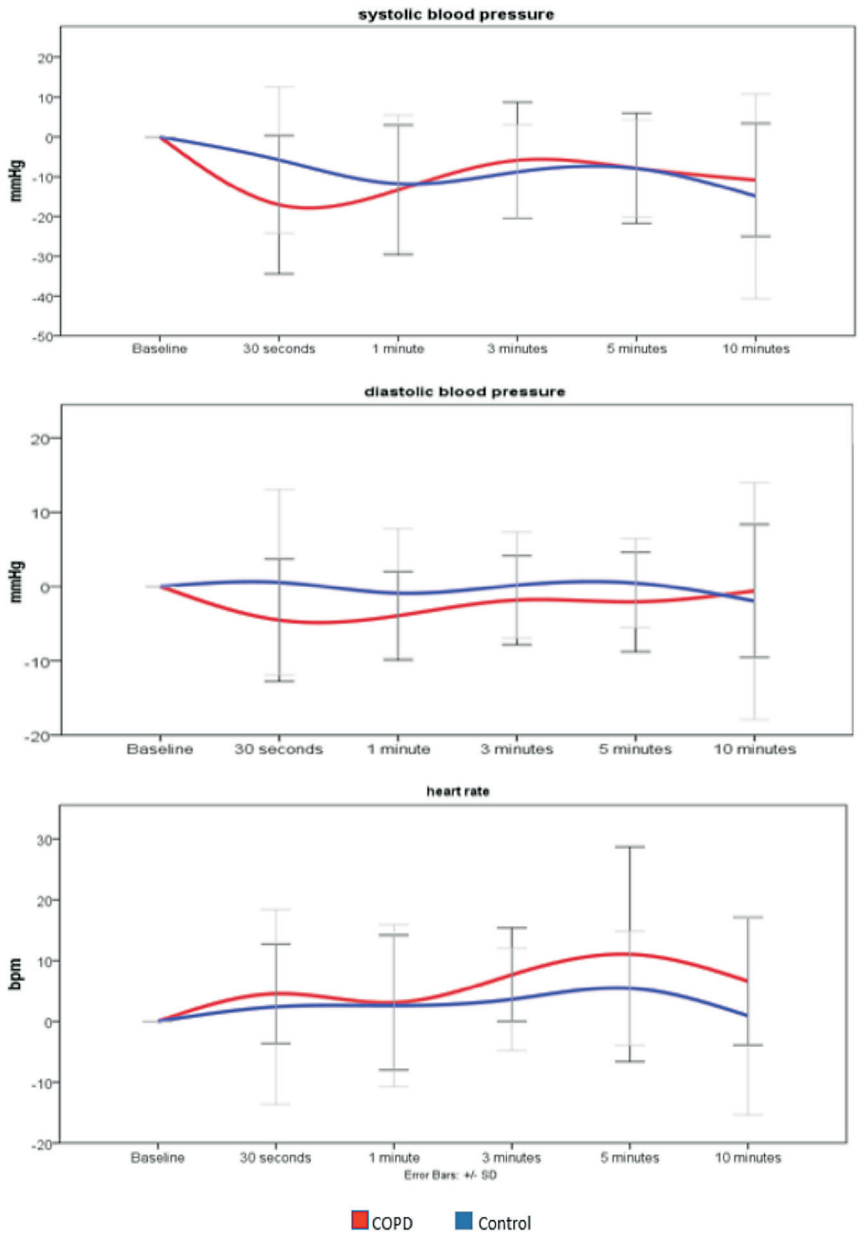

Figure 1 Cardiovascular responses to head up tilt (HUT).

Graphs are plotted as a function the relevant time (categorical) intervals of HUT parameter. The standard deviation (SD) of each time point is represented by the error bars.

Discussion

This study was aimed at providing additional extensive assessment of the ANS or autonomic function in COPD. We limited our study population to a specific cohort of COPD-patients that were non-sedentary or were 'physically active' due to the heterogeneous and complex nature of COPD, and also because of the feasibility of testing in this specific population. Consequently, it is important that our results should be understood in this context. We also included a control group so that our results can be viewed in perspective of the prevailing autonomic function health status of their counterparts in the general population. More importantly, our study reported several autonomic function parameters some of which are not frequently reported in COPD in existing studies. Also, including autonomic reactivity tests represents a first attempt in the area of autonomic function research in COPD.

The major results of our study are as follows: (i) subjects with COPD have a significantly lowered RR intervals compared to controls, (ii) most HRV and BRS indices were lower in subjects with COPD compared to the control group, however only a few of these indices were of statistical significance, (iii) the autonomic responses to the three autonomic reactivity tests of (deep breathing, valsalva maneuver and tilting) were largely normal and similar between COPD and controls, and (iv) further analyses of tilting revealed that subjects with COPD have a slightly poorer cardiovascular response to tilting in comparison to controls. The significant decrease in LF among the COPD and marginal reduced the baroreflex control (measured by resting BRS) in COPD are important results that is in line with past trend. There is evidence –at least in cardiovascular diseases – that the baroreflex control and LF power in HRV are associated (28). Additionally, we found that the ApEn, which is a measure of signal regularity and complexity was significantly increased in COPD. The ApEn has been reported to be a very useful tool for predicting individual risk of cardiovascular disease (29). All of these results put together are suggestive of residual autonomic function deficits in COPD, thereby lending credence to earlier reports that have stated that ANS is impaired in COPD (3, 30). Nevertheless, our results for resting HRV parameters including mean RR, SDNN, RMSSD, LF(ms^2) LF(n.u.), HF(ms^2) HF (n.u) and LF/HF ratio, were largely comparable with the normative value reported among heathy adults during short term HRV measurements in a systematic review by Nunan et al (31).

We understand that several factors may have influenced the results of our study. The use of COPD subjects participating in a rehabilitation program may have explained the similarity in the results in most of the autonomic function variables that were assessed, and also the non-statistical difference for the cardio-vagal indices following the autonomic reactivity tests. A number of studies including our recent systematic review has demonstrated that participating in an aerobic exercise

training program, which forms the core of pulmonary rehabilitation or a maintenance program affects the autonomic function in COPD (2, 7, 32-34). For example, a 4-week rehabilitation have been shown to significant increase HRV indices, which were also associated with health related quality of life in COPD (35). Furthermore, pulmonary rehabilitation programs may comprise interventions that have been proven to influence the autonomic function in COPD such as controlled breathing techniques and noninvasive mechanical ventilation (36). The LF/HF ratio, which is an index of sympathovagal balance was found to be higher among the controls, albeit not statistically significant. Nevertheless, this results is indicative of a generally higher sympathetic functioning among the controls over the COPD group (37). In addition, the results could mean that autonomic function, represented by both sympathetic and parasympathetic branches in COPD is deficient. Comparing the results in this study with existing studies demonstrate that the subjects in our study had a higher average resting HRV (2, 38-40) and BRS (41) parameters. However, the resting BRS was found to be similar to the values reported in COPD patients who were much younger (51 years) (42). Again, the use of beta blockers and ACE inhibitors by subjects with COPD may have also contributed to the largely comparable results, since these medications are known to affect HRV in the direction of normalization.

Even though the cardio-vagal response indices (HR_{DB}, BRS_a, BRS_v, BRS_g, VI and VR) and the HUT parameters were comparable between COPD and controls, further analyses may provide extra information. For example, both groups had a HR_{DB} value that has been is classified to be a borderline parasympathetic response (24), suggesting a possible influence of ageing. We also discovered that the average VI and VR in COPD recorded in our study was just above the normal reference cut-offs reported for healthy adults (4, 24, 26), which may indicate that both groups have normal parasympathetic responses. Moreover, the HRV during deep breathing in the context of autonomic function testing has been successfully used for detecting parasympathetic disorders or rates of parasympathetic activity (43). Nevertheless, more studies are needed for other COPD populations.

We used a number of VM parameters to describe the autonomic reaction to the maneuver all of which showed a normal trend, and even higher values for COPD. The higher VR results of subjects with COPD in our study can be explained by a more rapid HR increase during second phase of VM, which is as a result of vagal activity withdrawal over the sinus node that is only reactivated after the Valsalva strain is removed (44). The average value of the adrenergic, vagal and global BRS indices and even the VR of the participants (COPD and control) of this study were comparable to the values obtained for subjects with orthostatic hypotension, but lower than those of the healthy controls in the study of Schrezenmaier et al (26). However, the participants of our study were much older compared to those in the latter study (65 vs 51 years).

After further analyzing the cardiovascular responses to tilting (Figure 1), a few differences were observed. Even though these differences were not statistically significant, they still represent signs of residual autonomic function impairments in subjects with COPD. During HUT, the ensuing orthostatic change triggers an increased sympathetic nervous system outflow (45), which produces a shift in spectral power from HF bands to LF bands (or increased LF/HF ratio). This is reflected in the cardiovascular system in the form of peripheral vasoconstriction in order to maintain hemodynamic functioning. The marginal lowering of the systolic and diastolic blood pressures as well as the increased baseline HR we found in our results could be suggestive of a diminishing sympathovagal response to orthostatic stimuli, as is already known (6, 8, 46).

As mentioned earlier, the non-sedentary nature of the subjects with COPD in this study may be an important factor that influenced the non-significant differences between COPD patients and healthy controls in the majority of the autonomic function indices. We also must take into account that the COPD patients used more vasoactive medications (beta agonists and ACE inhibitors) that are known to influence autonomic test results (47, 48). which are to allow us assess the subjects autonomic function in their current (day-to-day) conditions, and for ethical concerns that might be related to withdrawal of prescribed medications. Therefore, the extent by which any of these factors in addition to certain lifestyle circumstances may have affected the results is presently not clear. This study has highlighted the need for more focus on reporting tests of physiological biomarkers in various COPD phenotypes in. Our study has provided new and noteworthy results that could form the basis for further autonomic function analyses in COPD. Notably, our study has shown that the cardiovascular response to tilting offers a more discriminatory ability of autonomic reactivity tests in COPD even when other cardio-vagal variables appear to be within normal range. All these findings can assist clinicians in defining the presence of autonomic failure and even their response to treatment (49).

The results of this study must be viewed within the limitations of the study. A significant proportion of the participants were males and we did not carry out any gender based analyses. However, this was taken into account by the gender/age matching (maximum 5-year interval) that was used during subject recruitment. Cardio-vagal index represents only 2 of 3 aspects of the composite autonomic scoring scale (CASS) (50), which is a validated test protocol for assessing autonomic failure. Future studies assessing these tests in addition to sudomotor function which can be evaluated with the quantitative sudomotor axon reflex test and the thermoregulatory sweat test, also impaired in COPD(51, 52), may be necessary. Lastly, the study utilized a cross-sectional case-control design. We recommend study designs with either larger number of participants and /or follow-up analyses in order to accurately evaluate the course of these indices (autonomic function and cardio-vagal) over time.

Conclusion

To summarize, our results in this study suggest that autonomic impairment exists in COPD. However, COPD patients who are non-sedentary or physically active may show several comparable autonomic function indices with their healthy counterparts. Autonomic reactivity tests are not of any discriminatory value over resting autonomic function indices in the COPD cohort in this study.

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"The good physician treats the disease. The great physician treats the patient with the disease"

William Osler

Part III

Non-pharmacological aspects to autonomic function modulation in COPD

Chapter 6

Effects of respiratory rehabilitation techniques on the autonomic function in patients with chronic obstructive pulmonary disease: a systematic review

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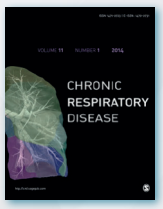

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Impact Factor $_{(2016)}$ = **1.82**
Ranking (JCR$_{2016}$) = **Q3** (43/59-Respiratory System)

Abstract

Patients with chronic obstructive pulmonary disease (COPD) show several extra-pulmonary abnormalities such as impairment in the autonomic function. Similarly, the use of respiratory training techniques such as controlled breathing techniques, non-invasive mechanical ventilation (NIMV) and oxygen supplementation for autonomic function modulation in patients with COPD is popular in existing literature. However, the evidence supporting their use is non-existent. A systematic search of studies reporting on the effect of controlled breathing techniques, NIMV, and/or oxygen supplementation techniques on autonomic function outcome parameters was conducted in three databases: PubMed, Embase and Web of Science. Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, relevant studies were retained for evidence synthesis. The methodological quality in these studies was evaluated using the evidence based guideline development (EBRO) check-lists per designs provided by the Dutch Cochrane Centre. Eighteen studies met the inclusion criteria of the review and were included and discussed. The evidence synthesis revealed that a strong and moderate level evidence supported the significant effect of oxygen supplementation and slow breathing techniques, respectively in significantly enhancing the baroreceptor sensitivity (BRS) values in patients with COPD. The effect of the examined techniques on heart rate variability (HRV) and muscle sympathetic nerve activity (MSNA) was of a limited or inconsistent evidence. The findings from this review suggest that oxygen supplementation and controlled breathing techniques have profound positive influence on the BRS in patients with COPD. However, it is not fully known if the effects of these influence translate to any therapeutic benefit on the general autonomic function of patients with COPD in the long term.

Keywords: *COPD, sympathetic, parasympathetic, review, autonomic nervous system, respiratory training techniques.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex, heterogeneous, and highly prevalent clinical syndrome, which is associated with high morbidity and mortality (1-3). The scourge of COPD, which is mainly as a result of ageing and tobacco use, is on the increase and it is presently projected to be among the top three leading causes of mortality by the year 2020 (4). COPD is mainly characterized by a progressive and nonreversible airflow obstruction, and patients with the disease present with other numerous extra-pulmonary abnormalities (5, 6). For example, conditions like chronic fatigue syndrome, arrhythmias, reduced exercise capacity and impaired autonomic functions have been repeatedly reported in patients with COPD (7, 8).

The autonomic function in patients with COPD has been widely reported in literature due to its prognostic value in determining the cardiovascular health status of these patients. Unfortunately, the trends reflected in the results in most of these studies have shown that autonomic function parameters like heart rate variability (HRV) (1, 6), baroreceptor sensitivity (BRS) (9, 10), heart rate recovery (HRR) (11), chemoreflex sensitivity (12), skin sympathetic responses (SSR) (13), and the muscle sympathetic nerve activity (MSNA) (10, 14, 15) are significantly impaired. Similarly, There is also an increasing report on the use of non-pharmacological approaches for the management of patients with COPD These approaches range from smoking cessation programs to, nutritional intervention, psychosocial support and in some cases surgical interventions (16). A group of respiratory rehabilitation techniques such as hypoxic training/oxygen supplementation (17-20), non-invasive mechanical ventilation (NIMV) (5, 21-23), aerobic exercises (24, 25), and controlled breathing techniques (8, 26-28) are also employed for a variety of important outcomes for patients with COPD. While the effect of these respiratory rehabilitation techniques on most COPD symptoms is clear, the evidence to support their effects on the autonomic function outcomes is non-existent. Therefore, a clear overview of the existing evidence regarding the effects of these techniques on autonomic function is warranted. Also, it is necessary to make a distinction between various autonomic function parameters with a view to highlighting possible clinical implications.

The aim of this systematic review is to provide a grade 2 evidence to support the effects of three distinct respiratory rehabilitation techniques; namely, controlled breathing, NIMV application and oxygen supplementation on the autonomic function parameters in patients with COPD. Conclusions regarding the evidence generated from the existing can shape the direction of future studies, and also aid clinicians in making an informed choice regarding the use of respiratory rehabilitation techniques in the management of patients with COPD.

Materials and methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (29).

Information sources and search strategy

To identify relevant articles, the online databases of PubMed (1966 to August 23, 2015), Embase (1966 to August 23, 2015) and Web of Science (1955 to August 23, 2015) were searched for published articles. For PubMed, the search strategy was conducted using a combination of Medical Subject Headings (MeSH) terms in the following order: "(pulmonary disease, chronic obstructive [MeSH Terms]) AND autonomic function OR heart rate variability OR baroreceptor sensitivity OR muscle sympathetic nerve activity AND breathing exercises OR rehabilitation". For the Embase and Web of Science databases, two free-text keywords ("COPD AND autonomic function") were utilized for the search strategy. Search filters were applied to restrict search outputs in all three databases for article type (clinical trials), species (humans) and language (English). In addition, the reference list of the potentially relevant studies were screened to make the review as complete as possible.

Eligibility criteria

To be included in this systematic review, studies had to report on the effect of controlled breathing, NIMV and/or oxygen supplementation (I) on autonomic function outcomes (O) in patients with COPD (P).

Study selection

After de-duplication, the search results (articles) were screened based on title and abstract (for fulfillment of the review eligibility criteria). Thereafter, the full-text reports of articles that were considered potentially eligible and relevant were retrieved for further evaluation. The second round of evaluation of the studies was based upon six clearly stated predetermined inclusion criteria before any study was included in the review:

i. Study participants were clinically diagnosed with COPD using standardized measures (%FEV_1 predicted, global initiative for obstructive lung disease (GOLD), American Thoracic Society);
ii. Study design ranging from randomized controlled trials (RCTs), case-control, cohort, crossover, and cross-sectional studies, expert opinions, reviews, and letters were excluded;
iii. A respiratory rehabilitation technique was used for intervention, and this was delimited to controlled breathing techniques, NIMV application and oxygen supplementation;

iv. Reported any autonomic function outcome measures,
v. article was published in English language; and
vi. Full-text original research report, short communications such as congress proceedings and abstracts were excluded.

Qualification of searchers

Literature search and screening were conducted by two authors; JM (Master of Science in Physiotherapy) and PC (who has obtained the degree of PhD). Both authors have experience with publishing systematic reviews (30-34).

Data items and collection

Data regarding author information and year of publication, sample size and characteristics of participants, inclusion and exclusion criteria, respiratory training intervention, reported autonomic function outcomes, main results and conclusions were extracted from the included studies (Table 1).

Assessment of methodological quality

The Checklists of the EBRO platform (an evidence-based guideline development in the Netherlands) present on the website of the Dutch Cochrane Centre [http://dcc.cochrane.org/]) were used to assess methodological quality of the included studies. The appropriate checklist related to each study design was applied accordingly. All question items criteria used for the methodological quality evaluation are presented in Table 2.

The methodological quality was evaluated by two assessors (authors; JM and HDS) who were initially blinded from each other's evaluation. Author HDS is (Master of Science in Rehabilitation Sciences and Physiotherapy) a PhD candidate working on the "autonomic function in patients with heart failure".

The assessors rated each question item with either a positive (+) or a negative (-) score. A positive score was obtained for each question item when questions items if adequate information when provided regarding: (i) the definition of the study population (both patients or control) reported in terms of place and time of recruitment, mean age and sample size, (ii) selection bias sufficiently excluded stated in terms of the study population concerned or when a random sample of the source population with a participation rate at baseline of at least 70% was adopted, (iii) clearly defined exposure and assessment fulfilled if appropriately described in terms of duration, dosage and frequency, (iv)clearly defined outcomes that are reproducible in terms of internationally accepted values, (v) outcome-assessment method clearly defined and adequate if they were presented in terms standardized autonomic function outcome measures , (vi) blinding, if this was implemented during outcome assessment, (vii) follow-up period, if reported and

Table 1

Reference	Sample	Inclusion criteria
Bartels et al.[35]	51 COPD *Gender distribution not reported 63.18±7.92 years	COPD: Medically diagnosed (severe), no any other active respiratory disease, maintain their normal daily routine and medications. All patients refrained from short-acting bronchodilators during assessment.
Bartels et al.[36]	70 COPD (35♂, 35♀) 62.8±8.5 years	COPD: %FEV_1: 30.4, %FVC: <70% (of predicted. All patients were medically diagnosed as moderate-severe, and they maintained daily routine and medications.
Barnerdi et al.[8]	15 COPD (10♂, 5♀) 52.2±2.6 years 28 CON (13♂,15♀) 47.2±1.7 years	COPD: Mild (GOLD: I-II), smoking status (mixed), on medication such as B-agonists, anticholinergic, cortisone and theophylline.
Borghi-Silva et al. [37]	19 COPD (19♂) 69±8 years 8 CON (8♂) 68±5 years	COPD: FEV_1 <50%, FVC<70% of predicted, (moderate-severe), clinically stable, ex-smokers, sedentary, no other chronic diseases, B2-agonists, xanthene derivatives and steroid treatments were suspended for 24 hours to measurement time.
Haidar et al.[20]	18 COPD (10♂,8♀) 51.7±2.4 years 14 CON (5♂, 9♀) 47.7±2.8 years	COPD: Mild (GOLD: I-II), normoxic, those on COPD were allowed to continue with their medications. Smokers and ex-smokers were allowed to participate.

Intervention	Outcome	Results	Conclusion
Oxygen supplementation: Acute administration of 31% SuppO_2 and CA; both treatments were randomized (double blind) by turns and patient's breath at 12 breaths/minute.	BRS HRV	BRS↑ HF↑ LF/HF↓ LF=	SuppO2 in COPD patients significantly and favorably alters autonomic modulation.
Oxygen supplementation: Acute administration of 31% SuppO_2 and CA. The intervention was delivered in a counter balanced randomized double-blind cross over design.	BRS	BRS↑	Oxygen supplementation ameliorates BRS by changes in vasomotor activity.
Controlled breathing and oxygen supplementation: Acute administration of a 2-minute controlled breathing at 15 breaths/minute (spontaneous breathing, and 2 minutes of controlled breathing at 6 breaths/minute (slow breathing. The treatments were randomly done by turns. Intervention also included progressive hypercapnic hyperoxia, isocapnic hypoxia and oxygen administration were also done.	BRS	BRS↑	Slow breathing and oxygen administration improved BRS in patients with COPD.
NIMV Acute administration of BIPAP (1 minute) comprising of; IPAP, which was initially set at 6 cmH_2O (increased gradually at 2 cmH_2O per minute to a maximum of 14 cmH_2O), and EPAP, which was set at 3 cmH_2O (and increased gradually at 1 cmH_2O per minute to a maximum of 6 cmH_2O). The CG received only spontaneous breathing.	HRV	RMSSD= SDNN= HF= LF↑ LF(nu) ↑ HF(nu) ↓ LF/HF ratio↑	Ventilation improved but autonomic function decreased as HF was significantly reduced while LF was significantly increased during BIPAP in patients with COPD.
Oxygen supplementation: 3 weeks (15 sessions) of passive interval hypoxic training for the TG for 3-5 times at 15% down to 12% of oxygen was administered progressively, meanwhile the placebo group received a constant normoxic air at 21% oxygen.	BRS/ HRV	BRS ↑ RRi ↑	Patients with mild COPD with signs of cardiovascular autonomic abnormalities at baseline normalized (similar to healthy individuals) to following 3 weeks of hypoxic training.

Table 1 Continued.

Reference	Sample	Inclusion criteria
Jaju et al.[6]	11 COPD (7♂,4♀) 43.9±20.6 years 6 CON (4♂, 2♀) 43.5±14.6 years	COPD: FEV_1 <60% predicted, No diabetes, CCF or hypertension. The patients were allowed to continue medications. Patients had normal BMI (21.9±5.52kg/km^2).
Lewis et al. [19]	10 COPD (7♂, 3♀) 73.9±7.2 years	COPD: Severe (GOLD III- IV). All patients were hypoxic but stable. Patients on drugs affecting ANS were excluded and they had other comorbidities like hypertension (pulmonary) and ischemic heart disease. Patients had normal BMI (24.8±4.2kg/km^2).
Ramos et al[27]	16 COPD (12♂,4♀) 64±11 years	COPD: COPD (GOLD 1-3), mean FEV_1 was 60±25% of predicted. The mean weight was 66±14kg and BMI 24±4kg/m^2. No medication was taken 12 hours prior to trials, non ANS associated diseases or comorbidities. They were asked to abstain from stimulating substances such as coffee, and alcohol.
Raupach et al. [10]	15 COPD (11♂, 4♀) 60.9±1.4 years 15 CON (11♂, 4♀) 60.7±1.4 years	COPD: FEV1 ≤60% predicted (GOLD), and the mean BMI was 27±1.1kg/m^2. All were between 30-80 years No diuretic medication was taken. The patients were also normoxic, had stable sinus rhythm and nonsmoking. All those with comorbidities and those on sympathomimetic drugs were excluded.
Raupach et al. [15]	15 COPD (11♂, 4♀) 60.9±1.4 years 15 CON (11♂, 4♀) 60.7±1.4 years	COPD: FEV1 ≤60% predicted (GOLD), and the mean BMI was 27±1.1kg/m^2. All were between 30-80 years No diuretic medication was taken. The patients were also normoxic, had stable sinus rhythm and nonsmoking. All those with comorbidities and those on sympathomimetic drugs were excluded.

Intervention	Outcome	Results	Conclusion
Controlled breathing 3 months of PBE was administered once, which comprise the closing of one nostril with the thumb, and inhale slowly over (6 seconds), afterwards, both nostrils are close for another count of 6 seconds. The second nostril was then open for slow exhalation over 6 seconds. Thereafter, inhalation with the same nostril slowly over 6 seconds is done. This constituted a single sequence, which was repeated for a duration of 30/min/ day for at least 5 days/week.	HRV	HF= LF= LF(nu)= HF(nu)= LF/HF =	Vago-sympathetic balance shifted towards the sympathetic in both patients with COPD, but it was not significant.
Oxygen supplementation: 3 sessions of LTOT was prescribed to be taken for 16 hours per 24-hour period at home. The sessions were at least 2 weeks apart.	HRV	RMSSDNN↑ SDNN↑ TP=	An increase in HRV multi-fractal properties following LTOT were observed. However, the beneficial effects was mainly expressed during the morning hours.
Controlled breathing Initial spontaneous breathing for ten minutes (Rest), then PLB for 8 continuous minutes and rest for another ten minutes breathing spontaneously (recovery).	HRV	RMSSD↑ LF(nu)= HF(nu)= LF/HF ratio=	Analysis of only the RMSSD index showed that PLB promoted increased parasympathetic activity.
Controlled breathing 15 breaths/min-1 for 4 min, followed by another 4 min respiration at 6 breaths/ minute (3 seconds inspiration, 7 s expiration. Breathing at a rate of 6 breaths/minute was done using visual feedback.	MSNA/BRS	BRS↑ MSNA↓	Slow breathing significantly enhanced BRS and MSNA in patients with COPD.
Controlled breathing IRL was performed while patients were breathing through a spirometer. Work of breathing was increased (tension-time index) by roughly 110% (from 0 to 10 hPa/l/s).	MSNA	MSNA=	Short term doubling the work of breathing does not affect sympathetic activation in COPD patients.

Table 1 Continued.

Reference	Sample	Inclusion criteria
Reis et al. [26]	10♂ COPD 69±9 years 9♂ CON 64±5 years	COPD: FEV_1 ≤60% predicted (GOLD: II), FEV/FVC: <0.7 and the mean BMI was 23±3.3kg/m^2. The patients were stable clinically and were taking their normal medication (nonsmokers). CON: Healthy and none of them had cardiac or metabolic diseases. COPD and CON matched by several parameters.
Reis et al. [22]	10♂ COPD 69±9 years 8♂ CHF 62±8 years 10♂ CON 64±5 years	COPD: FEV_1 <60% (GOLD: II), FVC<0.7 predicted and the mean BMI was 23±3.3kg/m^2. Patients were clinically stable, non-alcoholics, sedentary and they took their normal medication (bronchodilators). They were also nonsmokers, free from cardiac and metabolic diseases, patients avoided B2-agonists, xanthene derivatives and steroids for 24 hours before the experimental test.
Rossi et al. [38]	17 ♂ COPD 67.29±6.87 years 15♂ CON 63.2±7.96 years	COPD: GOLD II-IV and their mean BMI was 25.54±4.44kg/m^2. All smokers, alcoholics and those with <2 months exacerbation, metabolic/cardiac disease, cannot perform procedure were excluded. Those with other chronic comorbidities and those on ANS influencing medications were also excluded.
Scalvini et al.[39]	11 COPD (8♂,3♀) 65±8 years 13♂ CON 51±7 years	COPD: ATS criteria with chronic hypercapnia, FEV_1: 28±9%, FVC: 42±13 % predicted, excluded patients with other co morbidities such as cancer and those who cannot perform the procedure.

Intervention	Outcome	Results	Conclusion
Controlled breathing Patients underwent 2 minutes of spontaneous breathing at rest, then 4 minutes of R-SAM, which is a series of deep/slow inspirations and expirations to provide a pulmonary volume that varied from the TLC to RV. Each respiratory cycle was performed for 10 second (5 each for inspiration and expiration) corresponding to a breathing rate of 6 cycles/minute.	HRV	RMSSD= SDNN= LF= HF= LF(nu)= HF(nu)= LF/HF-ratio=	COPD patients demonstrated impaired cardiac autonomic, which remained unchanged both at rest and during RSA-M when compared with healthy subjects who had improved HRV values.
NIMV I. Spontaneous breathing II: Randomly treated with three different levels of CPAP on the same day: sham ventilation, 5 cmH_2O (CPAP5) and 10 cmH_2O (CPAP10) for 10 minutes. (randomized double blind/ cross sectional)	HRV	RMSSD↓ SDNN= LF= HF= LF(nu) ↑ HF(nu) ↓ LF/HF ratio= TP=	The results indicated that acute treatment NIMV led to altered HRV parameters, also significant negative effects occurred during CPAP10 patients with stable COPD.
Controlled breathing Comprised of three 20-minute phases – The first (rest) and third being spontaneous breathing while the second phased is PLB. Protocol between 8 am and 12 pm in a room with temperature between 21 and 23°C and relative humidity between 40 and 60%.	HRV	SD_1↑ SD_2↑ SD_1/SD_2= SDNN↑ RMSSD↑ LF↑ HF↑ LF/HF=	PLB led to improvements in booth linear and non-linear HRV parameters as well as in vagal activity.in patients with COPD.
Oxygen supplementation: Two groups of patients had an alternate application of both; (a) control breathing while breathing room air in a tilted position and (b) control breathing with oxygen supplementation in a tilted position. (intervention randomized in a AB-BA scheme)	HRV	SDRR= LF↑ HF=	Oxygen supplementation (therapy) only partially reversed ANS derangements in hypoxemic patients with COPD.

Table 1 Continued.

Reference	Sample	Inclusion criteria
Sin et al. [23]	21 COPD (10♂,11♀): 64.1±9.7 years	COPD: All patients had clinical diagnosis of COPD, and a ≥10 pack/year smoking history. The FEV_1 was <70% predicted. Patients were excluded if they had cardiac disease (coexisting), cognitive impairment or a poor prognosis.
Skyba et al. [40]	23 COPD (18♂,5♀) 68.2±1.7 years	COPD: FEV_1: 45.5±3.9% predicted; FVC: 66.1±3.8 % predicted (ATS/ERS), with acute exacerbation on beta agonist and anticholinergics. Exclusion criteria were respiratory arrest, decreased level of consciousness, severe exacerbation of COPD requiring intubation.
Van Gestel et al.[28]	40 COPD (23♂, 37♀) 66.1 ± 6.4 years	COPD: all patients were clinically diagnosed (GOLD), FEV1: 45.9 + 17.4% predicted. Patients had no clinical signs or symptoms of acute exacerbations, hospital admissions preceding 6 weeks. And, they all had normal BMI. 20 patients randomly assigned to TG and CG.
Yazici et al.[5]	28 COPD 64 ± 10 years	COPD: the patients were clinically diagnosed using the ATS/ERS criteria. All patients had HRF. However, those with cardiovascular diseases, diabetes, hemodynamic instability, systemic disorders that can affect ANS were excluded. The HRF was defined by arterial blood gas criteria (partial pressure of CO2: PaCO2 >45 mmHg (6kPa), and pH< 7.35).

Notes: CON: control; #: significantly lower; ": significantly higher; (¼): no significant difference; _: male; \: female; vs: versus; GOLD: global initiative for obstructive lung disease; LF: lung function; %FEV1: percent forced expiratory volume in 1 s; FVC: forced vital capacity; BIPAP: bi-level positive airway pressure; BRS: baroreceptor sensitivity; CPAP; continuous positive air way pressure; HRV: heart rate variability; IPAP: inspiratory positive airway pressure; MSNA: muscle sympathetic nerve activity; EPAP: inspiratory positive airway pressure; TLC: total lung capacity; RV: residual volume; SuppO2: supplemental oxygen; CA: compressed air; PBE: pranayama breathing exercise; HRF: hypercapnic respiratory failure; BMI: body mass index; RFT: respiratory feedback training; ATS: American Thoracic Society; ERS: European Respiratory Society; ANS: autonomic nervous system; R-SAM: respiratory sinusoidal arrhythmia maneuver; IRL: inspiratory resistive loading; PLB: pursed lip breathing; cmH2O: centimeter

Intervention	Outcome	Results	Conclusion
NIMV I: Training group (TG): 3 months of standard medical therapy plus nocturnal NIMV (4 cm H_2O of EPAP and 8 cm H_2O of IPAP). II: Control group (CG): 3 months of standard medical therapy plus sham NIMV (CPAP set at 4 cmH_2O).	HRV	*24 hours:* TINN↑ SDNN↑ HRVI↑ *Night time:* HRVI↑ RMSSD= SDSD= SDNN index = SDANN↑	NIMV applied nocturnally over 3 months may improve HRV parameters in patients with COPD.
NIMV Acute NIMV using BIPAP technique for 60 minutes at a level of 4 cmH_2O of EPAP and 8 cmH_2O of IPAP in a spontaneous mode.	HRV	LF↑ HF↑ VLF=	BIPAP may potentially cause sustained improvements in the autonomic control of heart rate. The LF also significantly increased only during post BIPAP phase.
Controlled breathing I: TG; 4-week conventional PR + RFT, 30-min/ sessions of controlled breathing using techniques of biofeedback with rapid shallow breathing, breath-to-breath irregularity in rate and depth and predominant thoracic breathing. II: CG; 4-week of conventional PR.	HRV	NN mean= SDNN= RMSSD= LF/HF= LF= HF=	Adding RFT to conventional PR intervention did not have additional effect on cardiac autonomic function in patients with COPD.
NIMV BIPAP was administered at a level of 5 cmH2O of EPAP and 15 cmH2O of IPAP in a spontaneous/time mode as indicated for patients with HRF.	HRV	RMSSD= SDNN index= SDNN= SDANN= pNN50↑ HRVi↑ LF= HF↑ LF/HF=	The NIMV may improve HRV indices of parasympathetic modulation of heart rate in COPD cases with HRF and decrease arrhythmic potential.

of water (pressure); RRi: R-R waves interval; RMSSD: square root of the mean of the sum of the squares of differences between adjacent normal RRi within a given time minus one; pNN50: percentage of RRi that differs each other more than 50 ms; SDNN: standard deviations of all NN intervals; SDANN: standard deviation of the averages of NN intervals in all 5-min segments of the entire recording; TINN: triangular interpolation of RRi; NIMV: noninvasive mechanical ventilation; NNmean: average RRi; RMSSDNN: RMSSD between adjacent RRi; SDSD: standard deviations between adjacent NN intervals; SDRR: standard deviation of RRi for time domain analyses. For frequency domain analyses, these included TP (total power), HF (high-frequency power), VLF (very low-frequency power), LF (low-frequency power), and LF/HF (low frequency/high frequency ratio).

was sufficiently long, (viii) selective loss-to-follow-up was excluded at analysis also represented as the total number of drop-outs or loss to follow-up >20%, and (ix) identification and consideration of confounders if and differences in medication use and patients characteristics were reported and accounted for.

A negative score (-) was allotted when noninformative description was provided to answer any of the question item or when the provided information was insufficient. After evaluating the included studies individually, the assessors met to compare their evaluation and to discuss areas of differences to obtain a consensus. Each study received a total methodological quality score by collating the number of positive item scores (+) over the number of question items. The scores were then converted into percentages (100%) in order to facilitate comparability across different study designs (Table 2). Only studies with high methodological quality (≥60%) were included for evidence synthesis.

Assessment of evidence synthesis

For each respiratory training technique, the evidence synthesis was based on specific autonomic function outcome. In total, five possible evidence levels; strong, moderate, limited, inconsistent and no evidence could be reached. A strong evidence signifies consistent findings reported in at least three studies. Moderate evidence connotes consistent findings reported in two studies. A limited evidence was when results were found in only one study. Inconsistent evidence indicates conflicting findings in the available studies, while no evidence is when no study was available. Findings in two or more studies were considered to be consistent only when similar results formed at least 75% of the results in the studies evaluated.

Results

Study selection

As shown in Figure 1, a total of 724 hits were identified from the database search. After de-duplication, 633 articles remained. Of these, 613 articles were excluded for not fulfilling the eligibility criteria (during title and abstract screening). Six potential articles were also added following a search of the reference lists of the articles that fulfilled the eligibility criteria. Altogether, the full-text reports of 26 articles were retrieved and evaluated based on the inclusion and exclusion criteria. Eight articles were further excluded for failure to meet all the inclusion criteria. In the end, 18 studies comprising eleven case-controlled (6, 8, 10, 15, 35-39, 41) four cohort (5, 19, 27, 40) and three RCT(20, 23, 28) studies were included for evidence synthesis.

Table 2 Risk of bias and study quality.

Author and year	Design	1	2	3	4	5	6	7	8	9	Total	MQ 100%	LOE
Bartels et al, 2000	CC	+	+	+	+	+	-				5/6	83	B
Bartels et al, 2004	CC	+	+	+	+	+	+				6/6	100	B
Bernadi et al, 2008	CC	+	+	+	+	-	+				5/6	83	B
Borghi-Silva et al, 2008	CC	+	+	+	+	-	+				5/6	83	B
Haidar et al, 2009	RCT	+	+	+	+	-	+	+	+	+	8/9	89	A2
Jaju et al, 2011	CC	+	+	-	+	-	+				5/6	83	B
Lewis, Annandale & Lewis, 2009	Cohort	+	+	+	+	-	-	+	+		6/8	75	B
Ramos et al, 2009	Cohort	+	+	+	+	-	-	-	+		5/8	63	B
Raupach et al, 2008	CC	+	+	+	+	-	+				5/6	83	B
Raupach et al, 2010	CC	+	+	+	+	-	+				5/6	83	B
Reis et al , 2010	CC	+	+	+	+	-	+				5/6	83	B
Reis et al, 2010	CC	+	+	+	+	-	-				4/6	66	B
Rossi et al, 2014	CC	+	+	+	+	-	+				5/6	83	B
Scalvini et al, 1999	CC	+	+	+	+	-	+				5/6	83	B
Sin et al, 2007	RCT	+	+	+	+	-	+	+	+	+	8/9	89	A2
Skyba et al, 2007	Cohort	+	-	+	+	-	-	+	+		6/8	75	B
van Gestel et al, 2012	RCT	+	+	+	-	-	+	+	+	+	7/9	77	A2
Yazici et al, 2007	Cohort	+	+	+	+	-	-	+	+		6/8	75	B

Notes: + : positive, -: negative, or no adequate information, CC: case control study, RCT: randomized control trial, LOE: level of evidence, MQ: Methodological quality. **For Cohort studies; (1)** Was the study population clearly defined? **(2)** Could selection bias be sufficiently excluded? **(3)** Was the exposure clearly defined and was the exposure-assessment method adequate? **(4)** Was the outcome clearly defined and outcome-assessment method adequate? **(5)** Was the outcome assessed blinded for the exposure status? **(6)** Was the follow-up period sufficiently long? **(7)** Could selective loss-to-follow-up be excluded? **(8)** Were the most important confounders or prognostic variables identified and adequately considered in the study design and analysis? **For case-control; (1):** Was the study population clearly defined? **(2)** Was the control group clearly defined? **(3)** Well defined in/exclusion criteria? **(4)** Clearly defined and appropriate intervention? **(5)** Was the exposure (treatment) assessed blinded? **(6)** Identification of confounders in the design and analysis? **For RCTs; (1)** Was patient selection to group randomized? **(2)** Was randomization blinded (single or double blinded)? **(3)** Were patients blinded to treatment? **(4)** Were the health care professionals blinded to treatment? **(5)** Were the outcome assessors blinded to the treatment? **(6)** Were the groups comparable at baseline? **(7)** Could selective loss-to-follow-up be excluded? **(8)** Presence of intention to treat analysis, if all enrolled patients were analyzed in their randomized group? **(9)** Are the groups, with the exception of the intervention, treated in the same?

Study characteristics and outcome measures

A total of 322 (197 males) patients with COPD participated across the studies. However, two studies did not provide information on gender distribution (5, 35). The FEV_1 among the participants was generally <70% of predicted value (indicating a sign of obstructive lung disease). The participants across the reviewed studies varied from mild COPD (GOLD I-II) (8, 20, 22, 41), to moderate-severe COPD (GOLD II-III) (27, 36, 37) to severe COPD (GOLD III-IV) (19, 35), and a mixture of all stages (GOLD II-IV) in one study (38). Generally, most study participants were clinically stable since, those with chronic comorbidities and/or other active respiratory diseases were largely excluded.

The respiratory rehabilitation techniques reported on in the studies included are oxygen supplementation (six studies) (8, 19, 20, 35, 36, 39), NIMV (five studies) (5, 22, 23, 37, 40) and controlled breathing techniques (eight studies) in form of; slow breathing (8, 10), purse lip breathing (27, 38), resistive loading (15) and breathing maneuvers (6, 28, 41). Only three autonomic function outcomes were reported in the included studies. Majority of the studies (14 of 18) reported on the HRV indices (5, 6, 19, 20, 22, 23, 27, 28, 35, 37-41) followed by the BRS (8, 20, 35, 36)

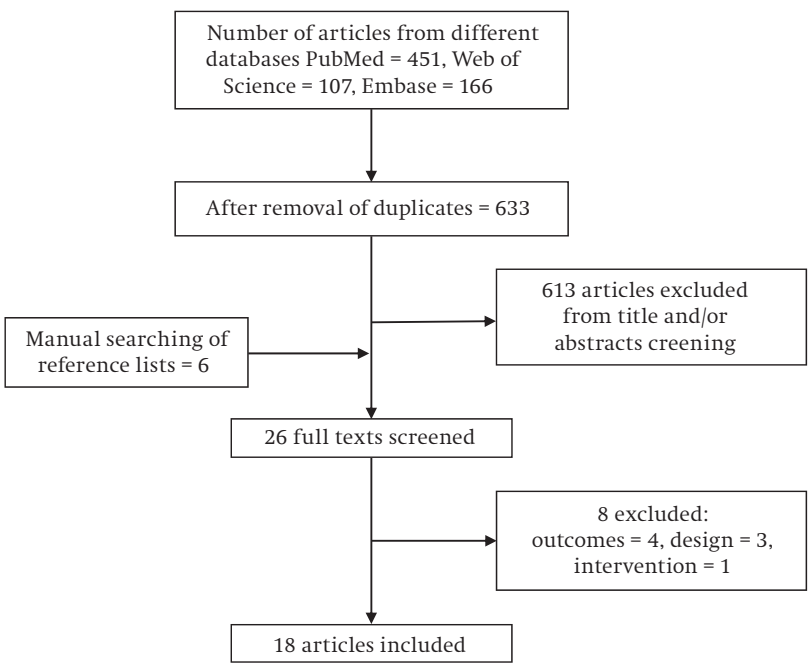

Figure 1 A flowchart of literature search used in the review.

in four studies and then the MSNA in two studies (10, 15). Furthermore, the HRV parameters were represented in terms of time and frequency domain analyses. The time analyses of HRV reported in the included studies are; R-R waves interval (RRi), square root of the mean of the sum of the squares of differences between adjacent normal RRi within a given time minus one (RMSSD), the percentage of RRi that differ each other more than 50 ms (pNN50), standard deviations of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN), triangular interpolation of RRi (TINN) average RRi (NNmean), RMSSD between adjacent RRi (RMSSDNN), standard deviation 1 (SD1), standard deviation 2 (SD2) from the Poincare plots, standard deviations between adjacent NN intervals (SDSD) and standard deviation of RRi for time domain analyses (SDRR). For frequency domain analyses, these included; total power (TP), high frequency power (HF), very low frequency power (VLF), low frequency power (LF), and low-high frequency ratio (LF/HF). The frequency parameters were also expressed either in terms of absolute or normalized units (nu).

Methodological Quality Assessment

Initially, the assessors were in agreement regarding the evaluation of 116 out of 125 question items. A consensus was only reached for the remaining nine question items after both assessors met to discuss initial points of disagreement. Table 2 shows the results of the methodological assessment. Generally, none of the studies fulfilled the criteria for blinding. However, the other question items (criteria) were mostly fulfilled. The overall methodological quality score in terms of percentages ranged from 63 to 83% across all the reviewed studies.

Synthesis of Results

Controlled breathing techniques

Eight studies (6, 8, 10, 15, 27, 28, 38, 41) reported on the effect of different controlled breathing techniques on three autonomic function outcome parameters in the reviewed studies. The results from two of these studies that investigated the effect of pursed lip breathing (PLB) indicated that significant increases were recorded for some HRV indices including RMSSD (27, 38), SDNN (38), SD_1 (38), SD_2 (38) , LF (38) and HF (38). Simultaneously, no significant changes were reported for other HRV indices such as SD_1/SD_2 ratio (38), LFnu (27), HFnu (27) and LF/HF ratio (27, 38).

The results from the studies that utilized other fairly known controlled breathing maneuvers (pranayama breathing exercise, respiratory sinus arrhythmia maneuver and resistance breathing) all reported that there were no significant changes for the HRV indices such as NNmean (28), SDNN (28, 41), RMSSD (28, 41), LF (6, 28, 41), HF (6, 28, 41), LFnu (6, 41), HFnu (6, 41) and LF/HF (6, 28, 41). Similarly, inspiratory resistive loading did not have any significant effect on the MSNA of

patients with COPD (15). On the other hand, however, slow breathing techniques (6 breaths/minute) was reported to positively influence both MSNA (10) and BRS (8, 10) in patients with COPD in two studies.

Based on the results of these studies, the evidence to support the effects of controlled breathing techniques on the HRV and MSNA parameters of autonomic function is inconsistent. A moderate level evidence seems to support the effect of slow breathing on the BRS.

Noninvasive mechanical ventilation

Five studies (5, 22, 23, 37, 40) reported on the effect of NIMV application on the HRV indices in both time and frequency domain analyses in patients with COPD. Both significant and non-significant changes were reported in the results of the reviewed studies. Specifically, the results across the studies showed that just as no significant changes occurred for RMSSD(5, 23, 37), SDNN(5, 22, 23, 37), SDNN index (5, 23), SDSD (23), LF (5, 22), HF(22, 37), LFnu (22), HFnu (22), TP (22), LF/HF (5, 22) and VLF (40), significant increases were seen for pNN50(5) SDNN(23), TINN(23), SDANN(23), HRVi(5, 23), RMSSD(22), LF(22, 37, 40), HF(5, 40) LFnu(22, 37) and LF/HF(37) indices. Furthermore, a significant decrease was also reported for HFnu (22, 37).

Based on the reviewed studies, the evidence to support the effect of NIMV application on the HRV indices is inconsistent.

Oxygen supplementation

Five studies (19, 20, 35, 36, 39) examined the effects of oxygen supplementation on the HRV and BRS parameters in patients with COPD. Of these, the results from four studies that reported on the effect of oxygen supplementation led to significant increase in the value of HRV indices like RRi(20), RMSSDNN(19), SDNN(19) and HF. (35) A significant decrease was also seen in for LF/HF in one study (35). However, another results across three studies reported that HRV indices like SDRR (39), HF (39), TP (19) and LF (35) were not significantly influenced by oxygen supplementation.

Four studies assessing the effect of oxygen supplementation on the BRS of patients with COPD reported significant increases in the results of all four studies ($p<0.05$) (8, 20, 35, 36).

Based on the results of the reviewed studies, the evidence to support the effect of oxygen supplementation on HRV indices in patients with COPD is inconsistent. Second, a strong evidence was found to support the effect of oxygen supplementation on the BRS in these patients.

Discussion

This systematic review evaluated the existing evidence to support the effect of three respiratory rehabilitation techniques (controlled breathing, NIMV and oxygen supplementation) on the autonomic function indices in patients with COPD. The inclusion of different study designs provided an opportunity to include as much studies as possible with a view to answering our review objectives. Additionally, all the included studies had high methodological quality, despite the lack of blinding and follow-up in most of the studies.

The results of this review indicated that most of the evidence profile for the effect of respiratory rehabilitation techniques on the autonomic function in patients with COPD was inconsistent, except for the evidence found to support the effect of controlled breathing and oxygen supplementation on the BRS values. This widespread inconsistency in the evidence validates the importance of our review. Hence, careful interpretation of autonomic function parameters is warranted. Presently, it is known that lower values for BRS and time domain analyses of the HRV such as RMSSD, SDNN and RRi is a sign of poor autonomic functioning. On the other hand, a high value for the MSNA variables signifies sympathetic activation, which is causes an imbalance in the autonomic function. Furthermore, the values for frequency domain parameters such as the LF HF and LF/HF ratio have variable interpretations, and they present robust information that can be utilized for monitoring patient's prognosis. In a few occasions, however, differences may arise as a result of different laboratory assessment protocols or human error. However, the general output is reliable and indicative of the patients' autonomic status.

The positive effects of controlled breathing on the BRS has a potential for future application in clinical settings in addition to its current application for risk stratification. Moreover, the BRS is known for its protective role in regulating the blood pressure changes through its impact on the heart rate in individuals, as well as its role in monitoring the prognosis of patients with chronic diseases (42). With these results, the mechanism by which BRS in particular responded to controlled breathing can be further brought to spotlight with a view to increasing it use for different purposes. Currently, it is known that this significant and consistent findings for the BRS values may have been as a result of increased oxygenation of the blood in the tissues independent of changing minute ventilation (43). This implies that control breathing techniques may be of significant benefit for patients with COPD. Besides, reduced peripheral chemoreflex has been demonstrated in normal individuals who are instructed to slow down their ventilatory patterns (44).

The HRV indices were mostly reported in the studies included in this review. However, the inconsistent evidence that were recorded for the HRV indices in both time and frequency domain analyses following respiratory rehabilitation

techniques poses a challenge in postulating the actual effects of these techniques on the HRV, as well as their potential use for HRV modulation. Unfortunately, HRV indices provides a better and more robust information of the cardiovascular health, and it also acts as a powerful independent prognostic factor for risks stratification (45). Nonetheless, there is need for more studies focusing on separate control breathing techniques so as to re-enforce our findings. For instance, PLB showed a slight beneficial effect on a few important HRV indices (27, 38). However, the presence of other controlled breathing maneuvers like pranayama, respiratory sinus arrhythmia maneuver, respiratory feedback training and inspiratory resistance exercises(6, 15, 28, 41), all of which had no significant effect on the HRV in patients with COPD contributed to the inconsistent evidence.

Another result of this review revealed that an inconsistent evidence also supported the effect of NIMV application on the HRV (5, 22, 37, 40). This results is also corroborated by the findings of an earlier study that reported that NIMV has opposing influence on the HRV (46). Three studies also reported significant increases in the values of LF HRV indices (22, 37, 40). This is an indication of sympathetic activation, which is undesirable for patients with COPD. Second, a significant decrease in the HF indices, which is reflective of parasympathetic deactivation was also recorded in two studies following NIMV application (22, 37). From this finding, it can be inferred that NIMV as a technique may have no potentially beneficial therapeutic effect on the autonomic function of patients with COPD. However, this does not underestimate the role of NIMV in enhancing other clinical variables such as oxygen perfusion and breathing pattern that have been widely established for patients with COPD (22, 23, 37).

One of the most important findings of our review was the strong evidence in support of oxygen supplementation on the BRS in patients with COPD. Oxygen supplementation showed a more potent and consistent effect on the BRS compared to other outcomes. This evidence clearly shows that oxygen supplementation has an unambiguous influence on the cardiovascular health of patients with in COPD as represented by the BRS indices (8, 9, 20, 47). It is also known that oxygen supplementation could have enhanced the BRS through its action in reducing the levels of the pulmonary arterial tension and vasoconstriction, reduced right ventricular wall stress and also in improving the central venous oxygen saturation levels, all of which in turn causes a reduction in sympathetic tone (35). Moreover, oxygen supplementation leads to an increase of the resting oxygen saturation and ventilation/perfusion (PO_2), which in turn causes a reduction in the sensation of dyspnea thereby activating the chemoreflex sensitivity (42).

This review had a few limitations. First, the autonomic function outcome parameters were mostly reported for the HRV indices. Fewer studies reported for BRS and MSNA, and there were no studies were available for parameters like the

heart rate recovery, chemoreflex sensitivity and sympathetic skin responses, all of which are known to be significant markers of autonomic function. Second, we observed the heterogeneity in some of the clinical characteristics of the study participants: stage of COPD disease, BMI, degree of $\%FEV_1$ predicted values, age and medication use across the included studies. Nevertheless, our findings remain relevant due to the multiplicity of studies and the need to shape the focus of future research in the topic area.

This review has showed that a variety of respiratory rehabilitation techniques may have a beneficial influence that can be clinically applied for the management of impairments of the sympathetic and parasympathetic systems, hence, making important modifications in the cardiovascular health possible among patients with COPD. Finally, the findings from our systematic review will help draw the attention of researchers in the field of rehabilitation of chronic respiratory disease to the impact of conservative treatment approaches on the extra-pulmonary system.

Conclusion

It was concluded that oxygen supplementation and controlled breathing techniques had profound influence on the autonomic function of patients with COPD, albeit mainly on the BRS indices. However, it is not yet clear whether this influence is of any therapeutic value in the long term. Hence, future studies may focus on specific long-term effects of these techniques on patients' important autonomic markers.

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Chapter 7

Evidence for aerobic exercise training on the autonomic function in patients with chronic obstructive pulmonary disease: a systematic review

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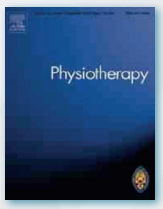

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Ranking (JCR_{2016}) = **Q1** (7/65 - Rehabilitation)

Abstract

Objective: To assess evidence for the effectiveness of exercise training on autonomic function outcomes in patients with chronic obstructive pulmonary disease (COPD). **Data sources**: Online databases of PubMed, CINAHL and Web of Science were systematically searched for all years till 26th of January, 2017 using a combination of predefined keywords; COPD/exercise/autonomic function outcomes. **Study selection**: Research studies assessing any measure of autonomic function following exercise training in patients with COPD were included. **Data extraction and synthesis**: Data were extracted from studies with high methodological quality for evidence synthesis. The review was reported in accordance with the PRISMA statement, while rating of evidence quality was determined GRADE guidelines. **Results**: Majority of the included studies utilized continuous exercise training mode with a vigorous level of intensity. Each exercise training session lasted between 30-40 minutes, and the frequency of intervention was ≥3 times/week. Evidence synthesis of the studies with high methodological quality per outcome revealed that a high quality evidence supported significant increases in time-domain heart rate variability (HRV) analyses and the heart rate recovery (HRR). However, the frequency domain HRV analyses were not significantly enhanced following exercise training. The evidence to support the effect of exercise training on baroreceptor sensitivity (BRS) in patients with COPD is very low. **Conclusion**: Exercise training demonstrated beneficial but limited effects on the autonomic function in COPD. Presently, it is not clear whether these effects are sustained in the long term. Only a limited number of RCTs were available indicating a significant gap in the literature.

Keywords: *Pulmonary disease; chronic obstructive; autonomic function; exercise training; systematic review.*

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent systemic disease that is caused by both environmental determinants and genetic risk factors (1). Although COPD is primarily associated with airflow obstruction that is not fully reversible, it is also known to negatively affect other systems such as cardiovascular, muscular and autonomic functions (2, 3). Moreover, impairments in autonomic function has been reported in patients with COPD. In a recent systematic review of our group (Mohammed *et al.* [2015])(4), a strong level of evidence was reported supporting impairments as altered heart rate variability (HRV), baroreceptor sensitivity (BRS) and muscle sympathetic nerve activity (MSNA), all reflecting a potential dominance of the sympathetic activity in COPD (2, 5).

The HRV is a sensitive, noninvasive measurement tool that is utilized for assessing the autonomic input to the heart. It reflects the beat-to-beat changes of the heart known as R-R intervals, which relates to the interplay between the sympathetic and parasympathetic nervous systems (6). The HRV is widely recognized as a parameter for the estimation of cardiac autonomic modulations (of sinus node). Owing to a continuous improvements in its standards of measurements, physiological interpretation and clinical applications (7), the indices of the HRV are able reflect cardiac mortality related arrhythmia, identify early stages of disorders like of myocardial infarction, heart failure (ejection fraction) and the overall integrity of the ANS (8, 9). Other autonomic function parameters that have shown clinical applicability are the BRS and the MSNA, both of which are significant correlates of the HRV indices (10). Additionally, the heart rate recovery (HRR), a vagal mediated recovery of the heart to pre-exercise levels has been equally used as an outcome for assessing the effect of exercise intervention on the autonomic control in both healthy and diseased populations.

An effective COPD management plan includes four components: (i) disease assessment and monitoring; (ii) risk factors reduction; (iii) achieving a stable condition; and (iv) treatment of exacerbations. Pulmonary rehabilitation (PR) and physiotherapy is a cornerstone in this management plan (3, 11, 12). In this review, we focused on the effect of exercise training in patients with COPD, which is a major part of PR and physiotherapy, on autonomic function indices. Exercise training has been shown to significantly improve exercise capacity, dyspnea, medical consumption, self-confidence and quality of life (2, 13-16).

Effects of exercise training on autonomic function have been reported and discussed in other chronic disease such as chronic heart failure (17), spinal cord injury (18), chronic kidney disease (19), all of them reporting an amelioration of the autonomic dysfunction. In COPD, several studies have investigated the effect of exercise training on sympatho-vagal balance. However, their conclusions seems to

not be concordant (3, 5, 20-24). Consequently, this systematic review has the aim to provide summative and more reliable information on the role and effects of exercise training on autonomic function modulation in patients with COPD.

Methods

This systematic review was reported in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (25) statement.

Eligibility criteria

To be included in this systematic review, (RCTs and non RCTs) articles had to report the effect of exercise training on autonomic function parameters in patients with COPD.

Information sources and search strategy

To identify relevant articles, the online databases of PubMed (from inception to 26th January , 2017), Web of Science (1955 – 26th January, 2017) and CINAHL (1983 – 26th January, 2017) were searched. The search was conducted using a combination of free text words and subject headings as search terms (Table 1). Furthermore, search filters were applied to restrict search outputs for the type of article (clinical trial), species (humans) and language (English).

Study selection

The studies included in the review fulfilled the following inclusion criteria:

i. study participants were clinically diagnosed with COPD (GOLD criteria/FEV_1);
ii. RCTs or non-RCTs;
iii. exercise training parameters was clearly described (with parameters);
iv. autonomic function parameters such as (i) HRV, interpreted as the variability of time between successive R waves of the heart beats in time and/or frequency domains outcomes, (ii) BRS, expressed in millisecond per millimeter of mercury, and (iii) heart rate recovery (HRR) expressed in beats per minutes were the main outcomes;
v. article was published in English; and
vi. full-text original research report.

Initially, the titles and abstracts of all search results were screened for fulfillment of the inclusion criteria. The reference lists of articles that were included from the title and abstract screening was manually searched to identify potentially relevant articles. Thereafter, articles which did not fulfill all of the criteria were excluded from the review (Figure 1).

Table 1 Search strategy utilized in the database search.

S/no	Database	Search builder	Hits
1	PubMed	((“Pulmonary Disease, Chronic Obstructive”[Mesh] OR COPD) AND (“Heart Rate”[Mesh] OR autonomic function OR baroreflex OR HRV) AND (“Exercise”[Mesh] OR exercise OR physical training))	75
2	CINAHL	(((MH “Heart Rate Variability”) OR “heart rate variability” OR “baroreflex” OR “heart rate recovery” OR “autonomic function”) AND ((MH “Exercise”) OR “exercise”) AND ((MH “Pulmonary Disease, Chronic Obstructive”) OR “COPD”)))	43
3	Web of Science	TS=(COPD AND exercise* AND (HRV OR autonomic*))	9

Data items and collection

Relevant information such as name of author(s) and year of publication, sample size and clinical characteristics of the participants, inclusion and exclusion criteria, intervention, outcomes, main results and conclusion were retrieved from the included studies (Table 2).

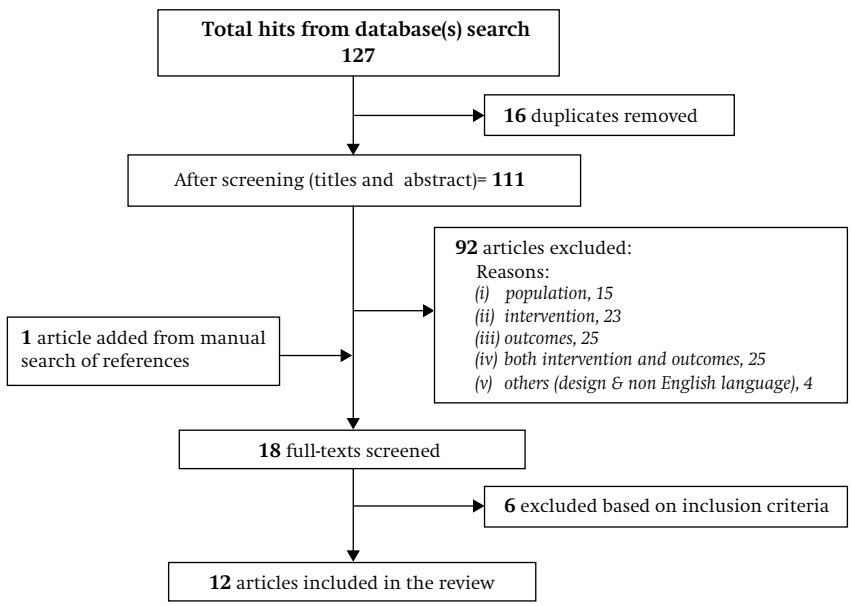

Figure 1 Flowchart of the methodology used in the review.

Table 2 Table of evidence synthesis and study characteristics.

Reference	Sample	Inclusion criteria/ characteristics	Design
Borghi-Silva et al, 2009	40 COPD: (25♂,15♀) 67±10 yrs	The COPD patients had %FEV_1 predicted of 40%, had normal BMI values and were sedentary individuals. Those with orthopedic conditions and other comorbidities were excluded. In addition, all patients were allowed to continue their regular medications.	RCT
Borghi-Silva et al, 2015	20 COPD: (12♂, 8♀) TG:67±7yrs CG:66±10yrs	COPD: Moderate to severe (GOLD II-IV) with a %FEV_1 predicted of 32±11% and 35±12% for TG and CG, respectively. All patients were sedentary and had no other chronic diseases.	RCT
Camillo et al, 2011	40 COPD (21♂,19♀) TG:67±7yr CG:65±10yr	COPD: The %FEV_1 predicted for the TG and CG were 40±13% and 39±14%, respectively (GOLD II-III). All patients performed physical activity regularly in the past. However, none of them had unstable cardiac disease or other co-morbidities.	RCT
Cheng et al, 2014	64 COPD (55♂,9♀) 70.1±8.7yr	COPD: Diagnosis of COPD was based on a %FEV_1/FVC predicted of 45.8±10.4%. All patients were stable, free from exacerbations and had no serious co-morbidities. The patients were also ambulant with an average BMI of 22.9±3.6 kg/m^2 . Those who use systemic drugs were excluded.	Non- RCT
Costes et al 2004	21♂ COPD: 62±9yrs	COPD: Mild and moderate (GOLD II-III). The average %FEV_1 predicted of the patients was 43.6±18.1%. And the patients had only mild hypoxemia. Those with other co-morbidities were excluded. All patients were also allowed to continue their medications (beta agonist, anticholinergic and steroids).	Non- RCT
Geogiopoulou et al, 2012	45 COPD: (35♂, 10♀) 66.5±7.6yrs	COPD: Patients were clinically stable. And had a %FEV_1 predicted of 45.7±18.7% (GOLD II-IV). All patients were ex-smokers and slightly overweight (BMI: 27.1±4.1 kg/m^2). The patients were allowed to continue their optimal medications. However, those with co-morbidities were excluded.	Non- RCT
Gimeno Santos et al, 2014	73 COPD: (67♂, 6♀) 66±8yrs	COPD: Patients were clinically stable (moderate-to-severe COPD). The %FEV_1 predicted was approximately 39% of normal values. None of the patients had COPD exacerbations. The average BMI was 27.9±5 kg/m^2. Moreover, those with severe chronic diseases, cancer and those who participated in rehabilitation programs < 12 months prior to study were excluded.	Non- RCT

Intervention	Results	Conclusion
The TG underwent a 6-week of 30 minutes treadmill training (ambulation) 3 times/week + stretching exercises for upper and lower limbs. The training intensity was set at 70% of the maximal speed achieved during the symptom-limited exercise test. The CG received only usual care.	RMSSD ↑ RMSM↑ LF(nu)= HF(nu)= LF/HF ↓	Aerobic exercise training positively altered the neural control of heart rate in patients with COPD.
The TG received 6 and 12 weeks of 30 minutes treadmill training at 70% the maximal speed (achieved during the symptom-limited exercise test). All stable and optimized medication was also continued. The CG received only normal medication.	RMSSD↑ SDNN= SD1↑ SD2↑	Improvement in cardiac autonomic modulation occur after six weeks of physical training.
The TG received 12 week of high intensity exercise such as ergometry at 60% of maximum work rate, treadmill training at 75% walking speed and also strength training at 70% of 1RM. CG: 12 weeks of low intensity exercises including breathing exercises and calisthenics.	RMSSD↑ SDNN↑ LF(nu)= HF(nu)= LF/HF =	Significant improvement in HRV indices occurred only after the high-intensity protocol in patients with COPD.
All patients received 12-week at 2 sessions/week outpatient-based PR comprising education (self-management and breathing retraining). Exercise training consisted 40 minutes of cycle ergometer training performed at the best ability of each patient (60-100% of VO_2 max).	RMSSD ↑ SDNN ↑ LF(nu) ↓ HF(nu) ↑ LF/HF ↑	Pulmonary rehabilitation provides significant improvement in HRV indices.
The participants underwent 8 weeks outpatient PR program comprising 30-40 minutes on a cycle ergometer for 3 time/week at 60%, which was progressively increased to 75% of exercise capacity.	BRS↑ LF= HF= LF(nu)= HF(nu)= LF/HF= TP↓	Exercise training is associated with a gain in spontaneous BRS in patients with COPD.
Patients received 36 sessions exercise-based cardiopulmonary rehabilitation program comprising of breathing control and relaxation techniques, clearance of secretions psychological support and exercise training of 40 minutes daily between 60% to 80% of maximum work load at 3 times/week.	HRR↑	Exercise-based rehabilitation modestly improves HRR in patient with COPD.
The patients received 8 weeks of interval training consisting on a cycle ergometer for 3 times/week for a duration of 40 minutes using a combination of 2-minute at high work rate (70−100% Wpeak) and 3-minute at (40−50% Wpeak).	HRR↑	Endurance training enhances HRR in patients with COPD.

*cycling was maintained at 60-70 rotations per minute.

Table 2 Continued.

Reference	Sample	Inclusion criteria/ characteristics	Design
Leite et al, 2015	16 COPD	COPD: Patients were clinically stable (no exacerbation in the last 30 days) ex-smokers (> 1 year). Not performed any physical training program prior to the study, not on oxygen therapy. No sever comorbidities. Participants were allocated to TG and CG, the data was analyzed for 10 and 6, respectively.	Non-RCT
Marquis et al, 2008	16 COPD: (8♂, 8♀) A: 67±7yrs B: 72±5yrs	COPD: The patients were clinically stable (moderate-to-severe). The %FEV_1 predicted for the two groups was 50±19% and 39±9%, respectively. None of the patients had COPD exacerbation at time of recruitment. Those on systemic medications, severe chronic and musculoskeletal diseases were excluded.	Non- RCT
Ramponi et al, 2013	27 COPD: (18♂, 9♀) 69±8yrs	COPD: The patients had a %FEV_1 predicted was 50±14%. The patients had moderate-to-severe (GOLD) airflow obstruction. Patients with a clinical history of concomitant cardiac heart failure, anemia and/or inability to perform a symptom-limited cycle ergometry cardiopulmonary test were excluded. The patients were allowed to take only regular medications.	Non- RCT
Rodriguez et al, 2014	29 COPD: (27♂,2♀) 68±8yrs	COPD: Patients were clinically stable with a %FEV_1 predicted of 42±13%. Patients had no exacerbation and were not on steroid medications. Those with chronic comorbidities and those who participated in a previous PR or long term oxygen therapy were excluded.	Non- RCT
Zupanic et al, 2014	31 COPD: (13♂,18♀) 61±7yrs	COPD: The patients were clinically stable. And they had an average %FEV_1 predicted of 37±20% (GOLD III-IV). The patients had a mean BMI of 25.8±6.7kg/m^2. However, some patients with other co morbidities like hypertension were not excluded. Also, all patients were allowed to continue their medications.	Non- RCT

Notes: ↑= significantly increased, ↓= significantly decreased, (=) = no significant difference, ♂= Male, ♀= female, yrs=years RCT=randomized control trial, , GOLD=global initiative for obstructive lung disease, HRR= heart rate recovery, HRV=heart rate variability, BRS, baroreceptor sensitivity, nu=normalized values;

Intervention	Results	Conclusion
12-week aerobic training protocol with continuous and interval sessions.	SDNN= RMSSD= LF= HF↑ LF(nu)= HF(nu)= LF/HF=	Twelve weeks of aerobic training (continuous and interval sessions) positively influenced the autonomic modulation.
Both patient groups received 12 weeks of exercise training on a calibrated ergo cycle for 30 minutes at 3 times/week. The exercise intensity was set at 80% of the maximal power output (VO_2). *One group received irbesatan medication (drug) while the other group received placebo.	*Both groups* SDNN= pNN50= RMSSD= VLF= LF= HF= LF/HF=	12-week aerobic exercise training program was not associated with significant enhancement of HRV parameters.
The patients received 9 weeks of PR of 3 hours per session at 3 times/week (minimum of 21 sessions) for a duration of 10-30 minutes of consecutive incremental exercise on a cycle ergometer at 70-80% of maximum load. The intervention consisted of strength training, education, nutritional, psychosocial counseling and exercise training.	HRR↑	The PR training program improved the cardio-vascular response during exercise at submaximal exercise independent of the external workload
Two groups:8 weeks of cycle ergometry, 3 times/week for 24 sessions: One group received interval training comprising; warm up at 30% of work rate; interval training of 40 minutes comprising 2 minutes of high work rate (Wpeak) at 70–100%, with 3 minutes at moderate intensity (40–50%). The other group received continuous training comprising warm-up (20%), exercise training at 60% work rate and a cool down for 3 minutes (20%). *cycling was maintained at 60-70 rpm	HRR↑	Both interval and continuous exercise training improved HRR in patients with COPD
The patients received a 4 week rehabilitation program at 5 days/week. The program comprises; inspiratory and expiratory training exercises, cycle ergometry training of 20–35 minutes twice daily + occasional stair climbing exercises, treadmill workout for 10–25 minutes daily, electro stimulation of the quadriceps and muscle flexibility and strength training exercises for the upper extremities and thoracic muscles. *exercise training intensity 60-70% of Peak work rate.	SDNN↑ AVNN= pNN50= RMSSD= QTc= LF= HF= TP↑ LFnu= HFnu= LF/HF=	Some reduced parameters of HRV were improved in patients with COPD after the rehabilitation program.

$\%FEV_1$= percent forced expiratory volume in one second, RM=repetition maximum, PR= pulmonary rehabilitation, TG=training group, CG=control group, INT=Intervention, PA=physical activity LTOT=long time oxygen therapy.

Evidence synthesis

The evidence synthesis for this review was conducted in accordance with the grading recommendations assessment, development, and evaluation (GRADE) guidelines. For a clear assessment of evidence profiling, the results for each autonomic function outcome was analyzed only after a judgment had been made regarding the study design and the exercise training parameters utilized. Additionally, the exercise training intensity in each study was determined based on the information provided by the exercise and sports association (Australia) that categorized it into four categories; high, vigorous, moderate and light (26).

Table 3 Evidence level assessment criteria across studies.

Study design	Quality of evidence	Scale down if	Scale up if
RCT	High	Risk of bias 0 No serious limitation -1 Serious limitation -2 Very serious limitation	Large effect +1 large +2 very large
	Moderate	Inconsistency 0 No serious inconsistency -1 Serious inconsistency -2 Very serious inconsistencies	Dose response +1 Evidence of a gradient
Non RCT	Low	Imprecision 0 No imprecision -1 Serious imprecision -2 Very serious imprecision	All plausible residual confounding
	Very low	Publication bias 0 Unlikely -1 Likely -2 Very likely	+1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed

Evidence grading was reached for RCT and non RCT (if applicable) studies separately. Non- RCT studies were only used for evidence grading in the absence of RCT studies. Results derived from RCT studies were initially ranked high quality (4 points) evidence, whereas those from Non- RCT studies were designated low quality (2 points) evidence level. Thereafter, evidence quality was scaled down using five assessment criteria: assessment of risk of bias (27); presence of publication bias, which was determined by assessing whether the sample size was representative of the

population or if signs of negative trends could be identified (28); presence of imprecision in the study results, which was determined by observing the margin of 95% confidence interval (CI) range around the mean difference and the effect sizes between the treatment and control groups (29); inconsistency in the different outcome results that could not be attributed to heterogeneity in population or end points (30) and the presence of indirectness determined through reported differences in population, intervention, outcomes and indirect comparisons, that could limit the generalizability of the results (31). Scaling up of evidence was conducted using three assessment criteria when there is a: large effect, dose-response gradient and plausible confounders explaining the results were reported (32) (Table 3). The eventual cumulative points reached for each of the autonomic function outcomes per intervention based on the evidence quality levels were labeled as high (≥4 points), moderate (3 points), low (2 points) and very low (≤1 point), accordingly.

Results

Study selection

As shown in Figure 1, a total of 127 hits were identified from database search. After 16 duplicates were removed, 111 articles remained. These articles were then screened based on the eligibility criteria (title and abstract), which resulted in the exclusion of 92 articles. One article was added manually. In total, the full-text of 18 articles were retrieved and evaluated based on the inclusion and exclusion criteria. Finally, 12 publications comprising three RCTs and nine non RCT studies were included in the review.

Study characteristics

A total of 422 patients with COPD across twelve studies. Three autonomic function parameters were analyzed. The HRV was analyzed in both time and frequency domain analyses (2, 5, 11, 22, 23, 33, 34). The BRS expressed in ms/mmHg was the outcome in one study (11), whereas the HRR (beats/minutes) was reported in four non RCT studies (12, 24, 35, 36).

Evidence quality

As shown in Table 4, study limitations were mostly in the area of low sample sizes (22, 23, 37), and substantial drop out (30-50%) of participants at the point of final analysis (2, 5, 22, 23, 37). Three RCTs with methodological quality were used for grading the evidence for the HRV indices, while four non RCT studies were used to reach the conclusions for HRR. Table 5 shows the details of evidence grading for each outcome.

Table 4 Assessment of risk of bias in the studies used for evidence synthesis.

RCT studies	Outcome	Randomization	Allocation concealment
Borghi-Silva et al, 2009	HRV	Adequate	Unclear, randomly assigned
Borghi-Silva et al, 2015	HRV	Adequate	Through draws of shuffled, opaque, coded envelopes
Camillo et al, 2011	HRV	Adequate	Using concealed envelop procedure

Non RCTs	Outcome	Appropriate eligibility criteria	Flawed measurement in both exposure and outcome
Costes et al, 2004	BRS	Adequate (well described)	Unlikely all measurements were adequately described
Geogiopoulou et al, 2012	HRR	Adequate, (but no control group)	Unlikely all measurements were adequately described
Gimeno Santos et al, 2014	HRR	Adequate (large sample size)	Unlikely, as HRR is a simple measurement. Moreover, this were adequately described
Ramponi et al, 2013	HRR	Adequate, (but no control group)	Unlikely, as HRR is a simple measurement. Moreover, this were adequately described

Exercise training parameters

The exercise training in all the included studies had a frequency of at least three times/week and a duration of 4 to 12 weeks. Continuous exercise training was proposed in nine of the studies, interval training accounted for two studies and one study combine both interventions (38). Majority of the included studies utilized vigorous intensity for exercise training and each exercise session lasted between 30 to 40 minutes.

Two RCT studies and one non RCT study used an intensity corresponding to 60 - 75% of maximal speed/VO_2 for a duration 30 minutes/session on a treadmill modality (2, 22). One RCT and one non RCT study combined both treadmill and cycle ergometer modalities with a combined intensity of 60-75% of maximal speed/

Blinding	Loss to follow up	Selective outcome reporting bias	Other
Unclear, it was not stated whether the caregiver, patients and data collectors were blinded	30% loss in control group. However, these were accounted for in the analyses	None detected. All autonomic function outcome of concern were reported	Not Applicable
Patients were not blinded. However, the investigators (caregiver and data collector) were blinded.	40% loss in both treatment and control groups. However, these were accounted for in the analyses	Unlikely. All autonomic function outcome of concern were reported	Small sample size
Unclear, it was not stated whether the caregiver, patients and data collectors were blinded	30% loss in each of treatment and control groups. However, these were accounted for in the analyses	Unlikely	Sample size adequate
Inadequate control of confounders	**Incomplete follow up**	**Other**	
Unlikely	No loss at follow up	N/A	
Unlikely	87% completed the testing	N/A	
Unlikely, patients were also free from co morbidities	Likely, as a significant as about 35% did not complete the test at analysis	N/A	
Likely, 67% of the patients developed arterial hypertension and were administered medication during the course of the study	No loss at follow up	N/A	

peak work rate as exercise training intervention (5, 34). Five studies reported using only cycle ergometer training. In two of these studies, cycle ergometer was used exclusively (11, 23). The remaining three studies combined cycle ergometer training with other pulmonary rehabilitation intervention such as, self-management, education, respiratory muscle strength training, peripheral muscle strength training, functional electrical stimulation, psychosocial support, nutritional counseling, and chest physiotherapy (3, 12, 36). The exercise intensities corresponded to an intensity of between 60% and 80% of VO_2 max, except in one study (3) where participants voluntarily exercised at the highest level of intensity possible (60-100% of VO_2 max).

Only two studies used interval training exercise exclusively (24, 35). Interestingly, both studies have similar exercise training parameters; duration (40 minutes), frequency (3 times/week), and length of intervention (8 weeks). Furthermore, both studies similar exercise intensities; two minutes of cycling of high work rate (70% to 100% of HRmax) combined with three minutes of moderate work rate (40% to 50% of exercise capacity).

Outcome Measures

The results from the majority of included studies revealed that exercise training had variable effects on HRV parameters of patients with COPD. Results from five studies reported significant increases for time domain HRV analysis like RMSSD (2, 5, 22), SDNN (3, 5, 34), RMSM(2), SD_1 (22), and SD_2 (22). Similarly, results across four studies showed that exercise had no significant effect on some time domain HRV analysis including RMSSD (23, 34, 38), SDNN(22, 23, 38), AVNN (34), and pNN50 (23, 34) indices. Nevertheless, evidence synthesis of the RCT studies shows that exercise training leads to a significant increase in parameters of time domain HRV analyses (2, 5, 22).

Table 5 GRADE evidence profile: different exercise training on AF in patients with COPD (quality assessment).

Outcome	Subjects	Risk of bias	inconsistency	indirectness	imprecision
Time domain HRV analyses	100 (3 studies)	No serious limitation	No serious inconsistency	No Serious indirectness	No Serious imprecision
Frequency domain HRV analyses	80 (2 studies)	No serious limitation	No serious inconsistency	No Serious indirectness	No Serious imprecision
BRS	21 (1 study)	Serious limitation (-1)[a]	N/A	N/A	No serious imprecision
HRR	146 (4 studies)	No serious limitation	Not serious	Not serious	Not serious

Abbreviation: N/A= not applicable; [a] a point reduced for presence of study limitations; [b] a dose response was demonstrated in the results of the outcome measure following aerobic exercise training.

Six studies investigated the effects of exercise training on frequency domain HRV parameters. The results from most of these studies indicated that exercise training had no significant effect on the frequency domain analyses of HRV such as LF (11, 23, 34, 38), HF (11, 23, 34), VLF (23), LF(nu) (2, 5, 11, 34, 38), HF(nu) (2, 5, 11, 34, 38), and LF/HF (5, 11, 23, 34, 38). However, a few significant changes were reported. These included significant increases for HF(38), HF(nu) (3), LF/HF(3), and TP(34) parameters, and significant decreases were reported for LF(nu) (3) and TP(11) values. Interestingly, evidence synthesis of the two RCT studies (2, 5) shows that exercise training does not significantly influence frequency domain HRV parameters.

Four non RCT studies reported on the effect of exercise training on HRR of patients with COPD (12, 24, 35, 36). The results from these studies revealed the exercise training had a significant positive effect on the HRR indices ($p<0.05$). All four non RCT studies were used for evidence grading. In the end, a high quality evidence was found to support the influence of exercise training on HRR in patients with COPD. Lastly, one non RCT study reported the effect of cycle ergometer training on BRS values in patients with COPD. The results from this study also showed significant improvement in BRS values following exercise training ($p<0.05$).

Publication bias	Effect	Dose response	Con-founding	Total points	Remarks	Quality level
Unlikely	N/A	N/A	-	4	Significant improvements occurred in most time domain parameters.	High
Unlikely	N/A	N/A	-	4	No significant improvement were recorded in the frequency domain HRV parameters in the two RCT studies.	High
Unlikely	N/A	N/A	-	1	Evidence is limited because to only one study was available.	Very low
Unlikely	N/A	+1[b]	-	4	Two of the studies used interval training.	High

Reported adverse events

Adverse events that can be attributed to exercise training were reported in 32 patients (5.6%) in seven studies. These events included cardiac arrhythmias (24, 34), exacerbation of symptoms (2, 5, 36), arterial hypertension (12), atrial fibrillation (34), and non-specified abnormal cardiovascular responses (22). In the other four studies, no adverse events were reported (3, 11, 23, 35).

Discussion

This systematic review evaluated the evidence for the effect of exercise training on autonomic function parameters in patients with COPD. Generally, the results indicated that exercise training has beneficial effects on only the time domain analyses of HRV and the HRR parameters. The results also indicated exercise training may have a significant effect on the BRS values in patients with COPD. More importantly, no evidence is in support of the effects of exercise training on the frequency domain analyses of HRV.

Exercise training interventions for patients with COPD are usually well structured. This is obvious from the largely similar exercise training parameters recorded from the studies in this review. Nevertheless, to provide reliable evidence, the RCT studies formed the basis our evidence synthesis, and were given preference over results of non RCT studies. Each study was also appraised on its methodological strength before the results in it were extracted. For example, one originally designated RCT study by Marquis *et al.* (2008) (23), was considered to be non RCT in design because medication use was the outcome of interest, and all the participants received exercise training.

Heart rate variability is a major predictor of cardiovascular health with a significant clinical relevance (39, 40). The HRV is also an outcome of choice in studies focused on cardiovascular health and autonomic functioning. The significant changes that were reported in the studies for time domain parameters of HRV following exercise training was consistent in the studies used for evidence synthesis in our review (2, 5, 22). Even though, the time domain HRV analysis represents important aspects of HRV markers with clinical benefits (41), these benefits appears to be limited because the frequency domain analysis, which provides a more robust index of heart rate function in across both sympathetic and parasympathetic branches was not significantly enhanced by exercise. The frequency domain analyses of HRV is also a more sensitive index for evaluating changes underlying the heart function rhythms compared to time domain analysis (39). Moreover, the frequency domain analyses has been recommended as the gold standard for short term measurements of HRV analyses (7). Hence, the

positive results reported for time domain analysis in this review maybe inadequate to arrive at a firm conclusion on the effect of exercise training on HRV.

On the other hand, the results of this review showed substantial increases for HRR indices following both continuous and interval training. This finding is further corroborated by the results of previous studies that reported improvements in HRR in both healthy and diseased populations (42-44) following exercise. Clinically, the HRR is relevant because an immediate recovery of the heart rate after exercise signifies a function of vagal reactivation. Moreover, severely decreased vagal activity is known to be a risk factor for death. Interestingly, the exercise training intensity in the studies that reported on the HRR were also within the recommended guidelines for patients with chronic diseases(14, 45). Consequently, we assumed that there is sufficient evidence indicating that aerobic exercise training lasting for at six weeks at an intensity of between 60% to 80% of maximal work capacity has positive impact on the HRR in COPD.

This review also highlighted several benefits of exercise training for patients with COPD. For example, exercise training is known to improve muscle function, which is a strong determinant of autonomic function (4). Besides exercise training provides other benefits that may be directly linked to the overall wellbeing of patients (12, 46-48). Furthermore, the review has highlighted the need for the use of important cardiovascular markers as HRR for monitoring during exercise training intervention. Incidentally, the HRR can easily assessed by practitioners, and it does not require complex procedures (12, 24, 36).

Our results must be viewed within the limitations of the review. Firstly, no study reported on the effect of exercise training on autonomic function parameters like MSNA, chemoreflex sensitivity and sympathetic skin response indices, and only one non RCT study assessed the effect of exercise training on BRS (11). As a result, our conclusions are limited to HRV and HRR indices. Nevertheless, these indices captures a clinically relevant and significant areas of autonomic function that reflects the sympathovagal and cardiovascular health profile. Secondly, about half of the included studies recorded high drop-out rates among patients with COPD (2, 5, 22, 24, 36). Furthermore, a relatively low sample size (sparse data) were used on some of the included studies (3, 11, 23, 37). We assumed that most patients with COPD are elderly, and they may be uncooperative of intimidated by the prospects participating in exercise training programmes (49). Lastly, a few heterogeneity in clinical characteristics of patients with COPD, medication use and exercise training parameters were observed. For example, supplemental oxygen was administered to some participants (50-52). However, using only RCTs for evidence synthesis appears to have limited these concerns.

Our review has shown that the HRR can be used for the determination of the heart's capacity to adapt to induced stressors such as exercise training, and also

to evaluate the long term benefits of exercise-based interventions. At this stage, it is difficult to recommend whether the HRV can be effectively useful as physiotherapy treatment outcomes for prognostication and goal setting during COPD rehabilitation. Lastly, conducting this review using GRADE guidelines has provided an insight into the methodological inadequacies in the existing studies, as well as the paucity of data on this topic.

Conclusion

Long-term exercise training with vigorous intensity provides beneficial effects on selected autonomic function indices in patients with COPD. Presently, only a limited number of high quality studies have reported on the effect of exercise training on autonomic function in COPD, indicating a significant gap in the literature. Therefore, future studies focusing on other relevant measures of autonomic function indices are still necessary.

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"After climbing a great hill, one only finds that there are many more hills to climb"

Nelson Mandela

General Discussion

1. Summary of main results

The aim of this dissertation was to provide a better understanding about the state of the autonomic nervous system (ANS) in chronic obstructive pulmonary disease (COPD) while focusing on both the existing literature and filling up well identified gaps in this area of expertise. The results described in the chapter 3, systematic review, revealed that a strong level of evidence supported the impairment of autonomic function in COPD patients expressed by time domain heart rate variability (HRV) analyses, baroreceptor sensitivity (BRS) and muscle sympathetic nerve activity (MSNA). This systematic review further identified physical activity level, muscle function and variation in time of day (circadian rhythm) as major influencing factors of the autonomic function in COPD.

Besides, two original studies were conducted to assess a possible dysautonomia among subjects with COPD. The results from the first study revealed that autonomic symptoms were present in all domains of the COMPASS-31 questionnaire in COPD (Chapter 4). These autonomic symptoms were slightly associated with mental health status, but not with severity and lung function outcomes in COPD patients. Furthermore, poor mental health status was found to be the most important predictor of autonomic symptoms. The aim of the second original study was to assess autonomic function through a standardized validated autonomic reactivity test (Chapter 5). The results of this study revealed a slightly impaired autonomic function among COPD subjects who were undergoing a pulmonary rehabilitation program, compared to their healthy counterparts.

The purpose of the third and final part was to examine non-pharmacological interventions for autonomic function in COPD through a systematic review. In the latter, there was a strong proof of concept supporting the acute positive effects of controlled breathing techniques and oxygen supplementation on the BRS of patients with COPD (Chapter 6). Similarly, a high-level of evidence was found to support the influence of aerobic exercise training on the autonomic function in COPD (Chapter 7).

2. Validation of the Dutch COMPASS-31 in a sub-group of patients with COPD

The COMPASS-31 is a validated, comprehensive instrument that is used to both evaluate autonomic symptoms (1-3) and effectively identify autonomic dysfunction in a wide variety of conditions (1, 2, 4-9). This instrument contains questions about both problems with the ANS and detection of psychosomatic indices. As such, this self-report questionnaire is designed to provide an index for autonomic symptom

severity (3, 10). The questionnaire consists of 31 items, evaluating six domains of autonomic symptoms: orthostatic intolerance (4 items), secretomotor (3 items), vasomotor (4 items), gastrointestinal (12 items), urinary (3 items) and pupillomotor (5 items) complaints. The current COMPASS-31 is a shorter and simplified version, developed from an earlier 72-item COMPASS questionnaire, which was in turn derived from the original 169-item ASP questionnaire, developed by Suarez et al., in 1999 (3). Each domain of the COMPASS-31 is scored using a predetermined formula. The total scores are calculated by adding all six autonomic domains a weighted score with a possible maximum score of 100. Higher scores indicate more autonomic symptoms.

Apart from the English version that has been validated in different diseases (4, 11, 12), an Italian, Spanish, Swedish, and Serbian/Croatian versions of the COMPASS-31 questionnaire are available (1, 4, 13, 14). In this study, a COMPASS-31, already translated into Dutch language (Appendix A) using the IQOLA project approach was used (15). Thereafter, we aimed to validate and determine the cut-off score for screening of autonomic dysfunction in COPD on the Dutch COMPASS-31. For the validation of the COMPASS-31, the adrenergic and cardio vagal function were calculated as earlier explained (Chapter 2, sub-section 5.1, Table 5). Since sudomotor function data were not available for these subjects, the total CASS was not reported. However, specific adrenergic and cardiovagal functions were mainly utilized because resting HRV indices only provides information about sympathetic and vagal activity to the heart. Moreover, the COMPASS-31 assesses the autonomic contribution across many organs of the body.

Statistical analyses were conducted using the statistical package for social sciences (SPSS) version 24 (Inc., Chicago, IL). In general, all data were subjected to the Shapiro-Wilk's test to check whether the variables were normally distributed or not. To determine the discriminative power of the Dutch COMPASS-31, a Man-Whitney U test was used for domain and total scores comparison between COPD patients with normal autonomic function and COPD patients with mild dysfunction. The internal validity (consistency) was assessed by Cronbach's α value. For rating the level of internal consistency, a Cronbach score of between 0.50 and 0.60 was considered poor, between 0.60 and 0.70 acceptable, between 0.70 and 0.90 good, and higher than 0.90 was considered excellent. Spearman rho correlation coefficient between the COMPASS-31 scores and adrenergic/cardiovagal scores were performed to determine the criterion validity. Lastly, a receiver operating characteristic (ROC) analysis was tested on the adrenergic and cardiovagal function, HRV index (16) and the Valsalva index (17) in order to determine the best cut off for screening autonomic dysfunction in subjects with COPD.

The results of this study indicated that a majority (57.6%) of the COPD patients suffered from mild adrenergic dysfunction, while 8 (30.7%) patients had normal

function. For cardiovagal function, 57.6% of the COPD patients were normal, while 38.5% reported mild dysfunction. Moderate and severe dysfunction were represented by very few patients. Consequently, discriminative power of the questionnaire was based upon the normal and mild dysfunction groups only (Table 1).

Table 1 Discriminatory power of the Dutch COMPASS-31 questionnaire among COPD patient with normal and mild adrenergic/cardiovagal dysfunction.

COMPASS 31 weighted scores	Adrenergic dysfunction					Cardiovagal dysfunction			
	Normal (n, 8)	Mild (n, 15)	Moderate (n, 1)	Severe (n, 2)	P value	Normal (n, 15)	Mild (n,10)	Moderate (n, 1)	P value
Total score	23.1±14.96	15.1±13.98	12.86	23.0±22.83	.237	16±13.45	19±16.06	33.61	.799
OI	13.7±13.04	4.5±8.67	0.00	14.0±19.8	.162	6.9±11.36	8.8±12.04	8.00	.666
Vasomotor	0.47±1.25	0.55±1.07	0.00	0.00	.731	.42±0.96	.25±0.79	3.32	.666
Secretomotor	3.6±3.14	3.9±3.26	6.3	2.1±2.96	.837	3.5±2.92	4.0±3.49	6.30	.625
GI	3.1±2.66	3.9±3.36	6.23	4.9±3.89	.535	3.2±2.17	3.65±2.58	13.35	.796
Urinary	0.95±1.35	0.96±1.1	0.00	0.56±0.79	.891	0.87±1.08	1.0±.1.22	0.00	.886
Pupillomotor	1.3±0.54	1.3±1.06	0.33	1.49±1.17	.945	1.1±.94	1.35±0.83	2.64	.508

Mann-Whitney U tests statistic of the COMPASS-31 between mild and normal COMPASS-31 scores $P<0.05$; OI, orthostatic intolerance; GI, gastrointestinal.

The results of the discriminative power analyses of the COMPASS-31 indicated that all 6 domains and total scores of the Dutch COMPASS-31 were comparable across all domains, indicating a poor discriminative power for mild autonomic dysfunction in this COPD population (Table 1). The internal consistency (validity) of the Dutch COMPASS-31 in COPD was acceptable (Cronbach's alpha, 0.669; 95%-CI, 0.424 - 0.834, P= 0.001). For the criterion validity, all aspects of the Dutch COMPASS-31 in COPD did not significantly correlate with adrenergic and cardiovagal function tests ($P> 0.05$), as illustrated in Table 2.

The results of this validation study indicated that the adrenergic, cardiovagal and Valsalva indices were not significant upon ROC analyses ($p> 0.05$). Hence, the HRV index was the only significant parameter to predict mild autonomic failure on the Dutch COMPASS-31 with an area under the curve of 0.825 (CI = 0.659- 0.991; P=0.027), as illustrated in Figure 1. A cut off point of 34.5 on the Dutch COMPASS-31 was capable of screening for poor HRV index (with a sensitivity 60% and specificity of 85%).

Table 2 Correlation coefficients of COMPASS 31 and autonomic tests.

COMPASS 31 controls weighted scores	Adrenergic	Cardiovagal
Total score	-.100	.051
Orthostatic intolerance	-.206	.152
Vasomotor	-.037	.065
Secretomotor	.005	.178
Gastro-intestinal	.264	.187
Urinary	-.064	-.037
Pupillomotor	-.21	-.24

*, significant at p< .05

To summarize, the Dutch COMPASS-31 has been found to have poor discriminative power and criterion validity for screening of mild autonomic dysfunction in this COPD population. However, the internal consistency was acceptable, and a cut off score to screen for poor HRV index was achievable.

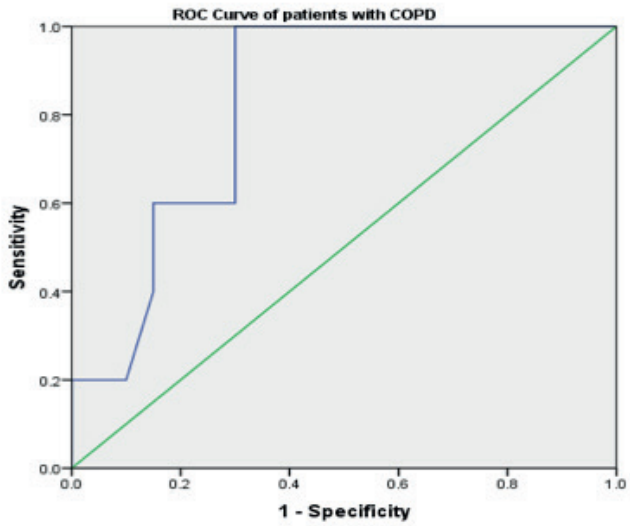

Figure 1 The ROC curve indicating effectiveness of the Dutch COMPASS 31 total score for detecting problems with autonomic dysfunction in COPD patients.

3. Is autonomic function impaired in COPD?

This part of the general discussion will focus on the autonomic function parameters that were found to be frequently reported in COPD, i.e. HRV analyses (time and frequency domains), BRS, MSNA and heart rate recovery (HRR).

3.1 Heart rate variability

In our systematic review (Chapter 1), we reported a general reduction in HRV among individuals with COPD (18). This is not surprising as HRV indices reflecting vagal modulation sympathetic tone are known to be affected in COPD (19). In addition, HRV is well known to be reduced in an elderly, inactive population as well as in a number of diseases (20). Therefore, it is not surprising that we found similar results in most of the chapters dealing with autonomic function in this dissertation (18, 21, 22). Furthermore, a reduced HRV may imply an increase in resting HR and/or a lowered cardiac parasympathetic nerve activity (cPNA) (23). In addition, patients with COPD have respiratory mechanical abnormalities (hyperinflation) that may contribute to the impairment of cardio dynamic responses and reduced heart rate kinetics (HRV) (24).

The HRV is a reliable and robust outcome measure, capable of monitoring treatment prognosis in individuals with various disorders. In COPD, a reduced HRV could be the result of multi-systemic manifestations of the disease on several extra-pulmonary systems such as the cardiovascular system. Moreover, COPD is known to be associated with features that could have potential deleterious effects on the HRV such as hypoxemia, hyperventilation, anxiety and depression (25, 26). In chapter 5 of this dissertation, we have found that individuals with COPD had a significantly higher baseline heart rate (HR) compared to a healthy control population. This higher baseline HR could be a possible explanation for the relatively lower HRV indices among subjects with COPD.

The HRV method is capable of reflecting both chronotropic and inotropic influences on the SA node in the heart (27). This HRV parameter, which is primarily a measure of sinus node cycle length (CL), is based on a physiological concept stating that ANS controls the pacemaker activity of the SA-node (28). Nevertheless, it is important to note that the HRV mainly assesses the end-organ response from the dual control of the periodic sympathovagal neural activity over the Sino-atrial (SA) node. Additionally, other factors have been documented to influence the value of the SA node including the sympatho-adrenal activity, mechanical/hemodynamic elements and local reflexes that cannot be reflected by the HRV test (28).

Despite software advances for HRV analyses (18), a number of challenges keep on persisting. For example, a large number of reported HRV indices (Table 6) in the literature are very often contradictory (18). The frequency domain HRV analysis in

particular, shows variable results in COPD patients, suggesting a complex and heterogonous patient population (as described in the first section of the general introduction). Overall, from the results of the chapters in this dissertation, we can conclude that the HRV is reduced in COPD. This reduction can be interpreted as a reduced vagal activity or an increased sympathetic nerve activity.

In chapter 5 of this dissertation (29), we reported a number of HRV indices in COPD that have not been adequately reported earlier (30-32). Autonomic reactivity tests were also performed in a fairly homogenous subgroup of COPD, who were attending a pulmonary rehabilitation program. Surprisingly, our results seemed to indicate that resting HRV indices were largely comparable to autonomic reactivity tests. This result is in contrast with the findings of Scalvini *et al*., (1999), who reported that stable COPD patients without chronic respiratory insufficiency exhibit a quite normal HRV in the resting condition, and an abnormal response to autonomic reactivity tests (vagal and sympathetic stimuli) (33). We think that the differences in the physical activity status of the COPD population in both studies may explain the discrepancy in these results.

3.2 Baroreflex receptor sensitivity

The short term regulation of the arterial blood pressure through the ANS principally involves the arterial baroreflex (34). Physiologically, the BRS plays a significant role in the maintenance of circulatory homeostasis by providing a continuous stream of information to the CNS via the stretch receptors, which results into either an increase or decrease in the discharge of vagal-cardio-inhibitory neurons or sympathetic neurons to the heart and blood vessels, respectively (35). The BRS is also subject to the cycle length of the SA-node (28). In chapters 3 and 5 of this dissertation, we reported significant impairments in the values of the BRS in COPD (18, 29), suggesting a possible underlying autonomic dysfunction in these patients. Moreover, the baroreflex system is known to be a strong predictor of COPD-comorbidities such as heart failure and arterial hypertension (36).

In general, the baroreflex system functions by either increasing or decreasing the HR and peripheral vascular resistance (sympathetic output to vessels) instigated by blood pressure changes (37). The BRS is also responsible for maintaining a stable blood pressure in the body during possible changes in body position. This stability in blood pressure is achieved either through the vagal part (adjusting the HR) or the sympathetic adrenergic part (adjusting the total peripheral resistance) (17). The results of poor BRS values are indicators to a possible future baroreflex failure, and can be an onset for chronic conditions such as autonomic failure and autonomic neuropathies. Due to the overall depression in the BRS index values, reported in multiple studies (18, 38, 39), there may be a need to screen COPD patients for autonomic imbalances during the course of initial assessment.

3.3 Muscle sympathetic nerve activity

Efferent muscle sympathetic nerve activity (MSNA) has been used to assess the sympathetic activation in COPD (40). The MSNA test is highly reproducible, and it adequately reflects the short-term changes in the sympathetic outflow (activity) in the peripheral nerves. The acute hypoxemia, hypercapnia and apnea which is present in COPD pathology, will result in a stimulation of the arterial chemoreceptors subsequently causing an increase of sympathetic outflow in the peripheral nerves (41, 42). Specifically, when peripheral chemoreceptor activation occurs, there is a release of exogenous adenosine, which is the chemical mediator leading to an increase in the MSNA. Peripheral chemoreceptor activation is also associated with increased cardiovascular parameters (blood pressure and heart rate) and hyperventilation (42, 43).

Even though we did not assess the MSNA in our original studies, we found evidence to support the significantly increased MSNA in patients with COPD by means of a systematic review (Chapter 3) (18). Presently, we can conclude that MSNA is indeed increased in COPD. Moreover, MSNA is associated with several sympathetic nervous system indicators such as increased cardiac and plasma norepinephrine and epinephrine levels (40, 44, 45).

3.4 Heart rate recovery

The HRR is a cardiac marker for parasympathetic activity. Its reduction is a sign of impaired parasympathetic activity (46). The HRR is simple and easy to determine, and can be quickly used for assessing the autonomic function in exercising patients. The ability of the heart to recover from a stressful event like exercise training is subject to central command control. When exercise training is initiated, a concurrent sympathetic activation and parasympathetic withdrawal occurs continuously (47). The reverse mechanism occurs upon exercise cessation and is principally mediated by vagal reactivation (causing a rapid decrease in HR). A delayed HRR is thus indicative for abnormalities in the functioning of the nervous system.

Poor HRR has been reported to be an independent risk factor for predicting the occurrence and risk of mortality after cardiac diseases such as coronary artery disease, myocardial infarction and cardiac arrhythmia (48, 49). In chapter 7 of this dissertation, we revealed that aerobic exercise training was very effective in improving HRR in COPD. This means that HRR can serve as a tool for centers with limited resources to monitor treatment outcomes during exercise training intervention for individuals with COPD.

4. Are autonomic symptoms prevalent in COPD?

To answer this research question, we assessed a profile of autonomic symptoms in COPD based on our hypotheses that individuals with COPD will have a higher prevalence of autonomic symptoms compared to their healthy counterparts. This hypothesis formed the core objective of Chapter 4 of this dissertation. In line with our expectations, autonomic symptoms were found to be more present in patients with COPD compared to a healthy control population. Additionally, COPD patients who had poorer health status reported higher autonomic symptoms. Specifically, the mental health status component from the SF-36 instrument was a found to be a significant predictor of total autonomic symptoms score, suggesting a possible impact of psychosocial issues in the autonomic function in COPD.

Autonomic symptoms including orthostatic intolerance, upper gastrointestinal (GI) tract symptoms, bladder dysfunction, and secretomotor dysfunction are known to be associated with autonomic dysfunction in patients with postural orthostatic tachycardia syndrome (POTS) (50). In chapter 5, COPD patients also showed early signs of POTS. Hence, this discussion will focus on the 6 domains of autonomic symptoms that were reported in Chapter 4: orthostatic intolerance, secretomotor, vasomotor, gastrointestinal, urinary and pupillomotor.

4.1 Orthostatic intolerance

Symptoms of orthostatic intolerance were reported among COPD (Chapter 4) (51). This was mainly expected because COPD patients are known to frequently have cerebral hypo-perfusion (52) (i.e. a form of orthostatic stress that can be expressed as orthostatic symptoms (53)). Individuals with orthostatic intolerance usually express feelings of dizziness (of variable severity) and light headedness, which may lead to (pre) syncope (54). Orthostatic intolerance has been associated with common COPD features such as shortness of breath, reduced ventilatory capacity, hypercapnia and lowered oxygen saturation (55). Physiologically, orthostatic intolerance is associated with norepinephrine transporter deficiency, especially when an individual changes from supine to an upright position (56). However, it is not yet clear whether the high rate of orthostatic symptoms is indicative of any underlying ANS deficits in patients with COPD. A head up tilt test study in a large cohort of subjects with COPD may be necessary to confirm this link.

4.2 Secretomotor complaints

After orthostatic symptoms, secretomotor dysfunction complaints were the most prevalent autonomic symptoms in COPD (Chapter 4) (51). The COMPASS-31 delimits secretomotor symptoms to questions regarding impaired sweating and dryness of the eyes and mouth. Secretomotor disorders are characteristic for thermoregulatory

dysfunction such as heat tolerance, impaired body sweating, parasympathetic affectation, and dryness of the eyes and mouth (8).

Dryness of the mouth is common in the elderly, and is also associated with the use of many medications (57). A number of COPD medications, when ingested or inhaled, are known to have dryness of the mucus membranes as side effects. Therefore, it is difficult to state that these symptoms are solely caused by COPD pathology. This result may be explained by a recent study that concluded that autonomic symptoms are strongly associated with burden of co-morbid chronic diseases, and also associated with ANS-relevant medication use (58). In addition, the rapid and shallow breaths that is common in COPD, may also be a contributing factor to the secretomotor complaints reported in our study.

4.3 Vasomotor problems

Vasomotor problems were identified to be slightly more present in COPD than their healthy counterparts. Vasomotor symptoms are associated with poor quality of life and are more prevalent in females and elderly (59). These symptoms can induce a loss in temperature control (especially in the extremities) or 'night sweats' and color changes in the hands and/or feet. All of these symptoms can be assessed by means of self-report. The ANS is also implicated in the control of vasomotor activity. For example, problems such as hypothermia and heat strokes are generally common in the elderly due to dysfunction in the sweat response and autonomic vasomotor (60). Therefore, it was not surprising that these vasomotor problems were reported in both COPD and healthy controls in our study (51). Loss of vasomotor function is a potentially dangerous phenomenon and for that reason, it may be important to incorporate adequate means of identifying and treating vasomotor symptoms for eligible COPD patients (especially females and the elderly).

4.4 Gastro intestinal problems

Gastrointestinal disorders form one of the six major common comorbidities in elderly patients (61, 62). Therefore, is was not surprising that gastrointestinal symptom(s) were recorded in both subjects with COPD and healthy controls in this study. However, COPD patients reported more gastrointestinal symptoms compared to both healthy controls in our study and previous scientific reports (63). Considering the lack of clear and specific age related explanations (60), it is not surprising that patients with chronic respiratory diseases have high prevalence ratios of gastro intestinal symptoms. Again, there is a close and complex anatomical and physiological relationship/interaction between the upper-airway tract and the esophagus, which has been linked to the high prevalence of gastro-esophageal reflux disease (GERD) in COPD (64), and even asthmatic patients (65). These mechanisms may explain why we failed to find a

link between the presence of autonomic dysfunction and gastrointestinal symptoms in COPD.

Additionally, gastrointestinal symptoms are also known to affect QoL, and even contribute to mortality. The results in chapter 4 recorded a high (about >21% of COPD) use of gastrointestinal medications among the COPD patients (51). This finding implies that either there is a high prevalence of gastrointestinal problems or the use of COPD medications such as PDE4, corticosteroids or may have been responsible for these symptoms. Despite the high use of gastrointestinal medications, subjects with COPD still reported gastrointestinal symptoms, suggesting that these symptoms could have been under-estimated in these results.

4.5 Bladder dysfunction symptoms

We also reported a higher prevalence of urinary tract complaints in COPD compared to age and gender matched controls. The ANS is one of the major systems controlling the optimal functioning of the urinary system via the micturition reflex (60). Therefore, it is very likely that autonomic dysfunction COPD extends to the higher centers responsible for various micturition (66). Patients with other forms of neurological and rheumatic disorders have been reported to suffer from urinary complaints as a result of unexplained autonomic affectation. This is particularly the case among patients with multiple sclerosis (67), Sjögren's syndrome and systemic lupus erythematosus (68). In patients with Parkinson's disease, urinary symptoms are also associated with problems in the higher centers (69). For now, we can assume a poor health status as a contributing factor to the susceptibility for bladder dysfunction symptoms in these COPD patients.

4.6 Pupillomotor complaints

The pupillomotor domain of the COMPASS-31 question items measures the symptoms associated with problems with the neural control of the pupils in the eye. These questions specifically interrogated about focusing, blurred vision and photophobia (66). The significantly higher results reported in the COPD population suggest a possible neurological deficit. However, from the results of our studies, we cannot explain the link between these symptoms and autonomic function deficits. Presently, hypersensitivity to bright light and difficulty in focusing complaints have been linked to the use of ICS medication. Daily use of ICS medication, which are widely prescribed for COPD patients (70), has been associated with a number of adverse effects including ocular symptoms.

5. What is the role of non-pharmacological interventions on the autonomic function in COPD?

Pulmonary rehabilitation remains an indispensable non-pharmacologic intervention in a significant proportion of patients with COPD (71). Nevertheless, pulmonary rehabilitation is still grossly underutilized worldwide due to both inadequate access to transportation and poor perception regarding the benefits of pulmonary rehabilitation and disease comorbidities like depression (72). In this section of the discussion, we focus on the effects of control breathing, oxygen supplementation and exercise training interventions on the autonomic function in COPD.

5.1 Controlled breathing and oxygen supplementation

In COPD, exercise training (endurance or aerobic) is often limited due to ventilation, cardiorespiratory constraints and peripheral muscle weakness (73, 74). Therefore, alternative or supplementary interventions are administered in these patients. This study found that both oxygen supplementation and controlled breathing positively affected autonomic function variables in COPD. These beneficial effects of oxygen supplementation are induced by counteracting the hyper-adrenergic state which is associated with hypoxia in COPD. In addition, parasympathetic autonomic dysfunction has been associated with arterial oxygen tension (PaO_2) in COPD (75), since reduced oxygen tension can cause structural and functional abnormalities in the peripheral nerves (76). Therefore, it is not surprising that oxygen supplementation had a positive influence on the autonomic function indices.

On the other hand, controlled breathing techniques such as slow breathing and pursed lip breathing influences the lung inflation reflex through the action of the pulmonary vagal afferent mediation, which alters the baroreflex. Controlled breathing increases both the tidal volume and attenuated sympatho-inhibitory effect of the lung inflation reflex (40). Controlled breathing is also associated with enhanced central inhibitory rhythms, and a reduction in the chemoreceptor activity, which can result in an attenuation of the autonomic function indices such as the baroreflex function (77, 78).

5.2 Exercise training

Chapter 7 indicated that exercise training positively influenced the autonomic function in COPD (22). This can be explained by the cardiovascular adjustments that take place in order to meet the metabolic (muscles) and thermoregulatory (skin) demands without compromising other structures (79). In general, when exercise training is initiated, the chemoreceptors/mechanoreceptors in the exercising skeletal muscles are activated. This activation leads to a withdrawal of the cardiac parasympathetic nerve activity (cPNA), resulting in an increased HR.

When exercise intensity remains above the aerobic threshold, arterial baroreceptors will reset as a consequence of both an increased concentration of the metabolites and sympatho-adrenergic activity. Also, an activation of the cardiac sympathetic nerve activity (cSNA) will take place, resulting in a preservation of the HR at maximal levels (Figure 2).

The cardiovascular autonomic control during exercise training is described as a process that involves an initial input (feed forward mechanism) from the higher brain centers (central command) into the medullary cardiovascular center, thereby resetting the arterial baroreflex to a higher operating point (27, 80). This process leads to a reduction in parasympathetic activity which subsequently leads to a rapid increase in HR (23). As exercise intensity increases, progressive baroreflex resetting (without concurrent change in sensitivity) and afferent muscle metaboreceptors trigger a continuous cardiac parasympathetic withdrawal and sympathetic activation (via the excitatory afferents) (27). In the extremities (muscles), the production of oxygen free radicals following ischemic metabolism that occur during skeletal muscle contraction is also reported to contribute to the ANS adaptation during exercise (36). The process of continuous activation of the cardiovascular center in the medulla during rhythmic exercise by mechanical and chemical peripheral input is called "exercise pressor reflex"

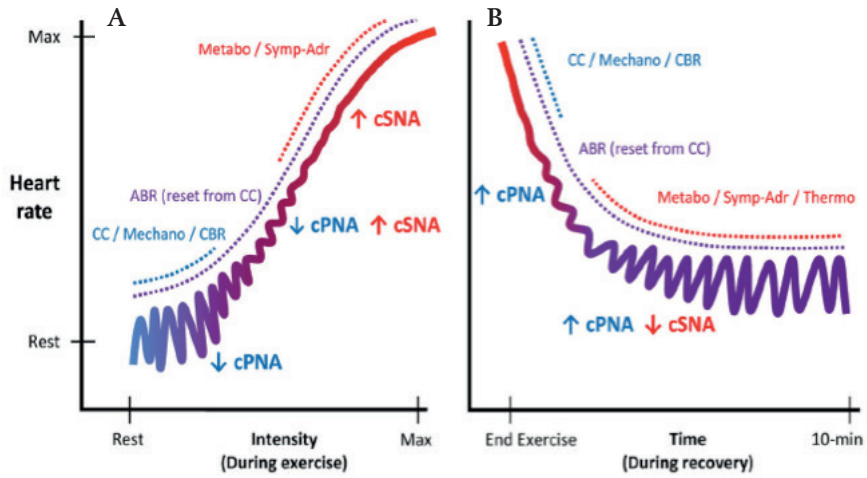

Figure 2 Cardiovascular autonomic regulation during exercise and recovery (27).

In the long run, exercise training has been associated with lowering resting HR and a reduction in the concentration of plasma catecholamine, norepinephrine and epinephrine (81-83). Moreover, muscle function is significantly correlated with autonomic function in COPD (84).

6. Issues associated with the assessment of autonomic function in COPD

During the course of this study, we identified a number of issues that can significantly affect the results of autonomic function testing in COPD. These issues include (i) variation in autonomic function testing protocol, (ii) heterogeneity and clinical differences among the individuals with COPD such as GOLD stage, medication use, demographic characteristics and physical activity level, and (iii) analysis and interpretation of the results.

6.1 Influence of the protocol used in reporting autonomic function

The earliest assessment of autonomic function in COPD mainly used invasive methods to determine whether there was an imbalance in the ANS function. Currently, a number of non-invasive assessment have been proposed. Hence, existing studies have relied on a variety of tests (85), depending on their objectives. In chapter 5 of this dissertation, we reported on the cardio-vagal indices following standardized autonomic reactivity tests comprising heart rate during deep breathing (HR_{DB}), Valsalva maneuver (VM) (Figure 3) and passive tilting or head up tilt (HUT) (Figure 4).

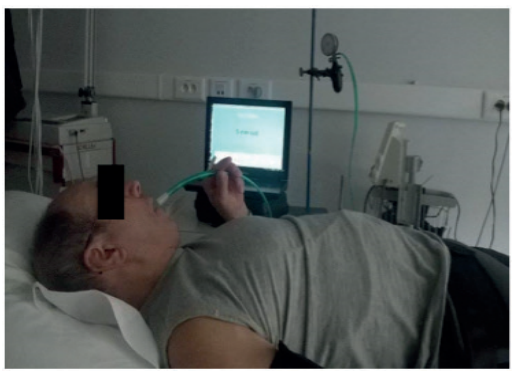

Figure 3 Subject with COPD performing VM test in supine position with the aid of a visual feedback.

Other autonomic function parameters such as the BRS can be analyzed by means of either autoregressive spectral analysis or the alpha-angle method (40) or by intravenous injection of a pressor agent (e.g. phenylephrine) (86). Research performed in this dissertation (Chapter 5) showed different and novel BRS parameters for patients with COPD.

From the results of the studies in this dissertation, we also identified a number of autonomic function parameters that can be assessed for various purposes. The HRR and time domain HRV analyses offers simple and straight forward possibilities to interpret, and assess autonomic function in clinical practice. Additionally, due to continuous advancements in technology and technical devices, new noninvasive means for assessing the HRV are introduced. A good example of these novel techniques is the use of photo-plethysmography (an optical pulse sensor), which can be used to assess the HRV either during exercise surveillance or in a clinical setting (87, 88). This method may be utilized in subsequent studies to validate the results of the existing autonomic function studies.

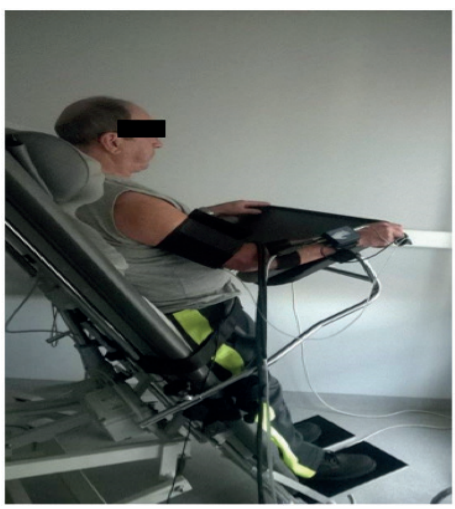

Figure 4 A subject with COPD during HUT test with continuous ECG recording.

6.2 Effects of disease heterogeneity and clinical differences on the autonomic function in COPD

Since most COPD patients are elderly, it is expected that they already started to show or experience a decline in autonomic function. Therefore, it was important to interpret the results from our sample, with a majority of elderly COPD patients,

with caution. In our chapters two and three, the control subjects also reported some autonomic symptoms and had a number of comparable autonomic function indices with COPD patients (51). Hence, we cannot completely rule out the effect of age in these results.

Studies have identified age and gender related differences to account for significant changes in autonomic function, even among healthy individuals. With advancing age, there is an increased basal and stimulated plasma noradrenaline concentration, adrenoceptor dysfunction and unresponsiveness to adrenergic agonists and antagonists agents (89). Increasing age is also associated with a reduction in maximal HR, an augmented resting HR and SBP and a decrease in beta adrenergic modulation. Age related changes are also reported to affect cardiovascular parameters like cardiac output (i.e. determinants such as preload, afterload, coronary flow and myocardial cell performance), peripheral vascular resistance and ejection fraction (90).

A number of studies have reported gender differences in the ANS modulation. Specifically, the cardiopulmonary reflex inhibition of sympathetic nerve activity was found to be greater in females. Furthermore, females showed a decreased sensitivity to adrenergic nerve stimulation (but not to noradrenaline), attenuated stress-induced increases in plasma catecholamine (less sensitive and less responsive) and less sensitive pathways regulating the sympathetic nerve activity (91). Nevertheless, gender differences in autonomic function appear to be more pronounced among a younger population. Specifically, the influence of hormones (both estrogen and progesterone having a vagal effect) has been associated with these differences (90). Based on these factors, we can presume that gender variation may not have significantly influenced the results presented in this dissertation.

Intrathoracic pressure swings is common in COPD (92), and has been associated with autonomic dysfunction and more specific with the activity of the sympathetic nerves due to airway obstruction. COPD patients have a number of comorbidities as well such as coronary artery disease (CAD) and pulmonary arterial hypertension (PAH) that may affect autonomic function. CAD is the most common cardiovascular morbidity in COPD, accounting for a significant proportion of CVD comorbidities in COPD (93), partly due to common risk factors (cigarette smoking, airborne pollution) (94, 95). Secondly, impaired autonomic function parameters such as increasing resting heart rate and orthostatic intolerance have been reported to predict both COPD and CAD, independent of one another (96-98). There may be a future need to compare the severity of autonomic function deficits among COPD patients with or without CAD co-morbidity in order to clearly answer these questions. Similarly, PAH has been associated with increased sympathetic nervous system (SNS) activation, decreased heart rate variability and presence of cardiac arrhythmias in COPD (99).

Additionally, severe autonomic dysfunction and dysautonomia is frequently reported in patients with metabolic disorders such as diabetes mellitus, obesity and among severely malnourished individuals. Since these descriptions fit phenotypical description of most COPD patients (100), it is likely that disease phenotype may be an important factor in the autonomic function in COPD (100).

6.3 Influence of medication use on the autonomic function in COPD

Medication use remains an unavoidable confounder in the assessment of autonomic function in COPD. Even though the role of medication use in the impaired autonomic function in COPD has been frequently ruled out (101), a number of studies have assessed the autonomic function in COPD both with and without medication withdrawal (102, 103). Of course, there are both ethical concerns and potential deleterious effects of COPD or vasoactive medication withdrawal in some COPD patients explaining why medications are not withdrawn in some studies.

The major classes of drugs and how they can affect the two branches of the ANS (sympathetic and parasympathetic) is well established (104). Therefore, it is conceivable that the use of any of these drugs would have a significant influence on the autonomic function test results. These medications typically include the adrenergic (agonists and antagonists) and cholinergic drugs. Moreover, medications such as opiates, ACE inhibitors and beta-adrenergic blockers which are often used to frequently manage COPD comorbidities, are known for their autonomic properties (44, 105, 106). Other medications that could be administered to be used by COPD patients include macrolides and other broad-spectrum antibiotics. The use of a broad-spectrum macrolide such as azithromycin have been reported to cause a prolongation of the QT interval, cardiac arrhythmias and even an increased risk of cardiac death (107, 108). Additionally, when assessing autonomic symptoms (COMPASS-31), there is a possibility that medication such as PDE4 inhibitors will cause gastrointestinal disturbances.

In order to assess the influence of beta blockers medication use on autonomic function in our COPD sample, an additional sensitivity analysis was performed. As such, 7 patients who reported to use beta adrenergic blockers, were excluded from the dataset. Afterwards, the analyses were repeated based on the remaining 19 COPD patients versus controls. Interestingly, the results indicated that resting HRV results were still largely similar (means, standard deviation and P values). The results from these second analyses are presented in Table 4 below (refer to Chapter 5 Table 2 for the initial comparison analyses).

Table 4 Comparison of resting autonomic function parameters between COPD (excluding beta blocker users) and controls.

Variables	COPD (n,19)	Controls (n, 22)	p-value
Time domain HRV analyses			
SDNN (ms)	29.8±11.72	40.38±17.64	.055[m]
RMSSD(ms)	18.5±6.05	22.9±10.13	.102[t]
NN50(count)	6.8±9.58	7.5±7.18	.263[m]
pNN50(%)	2.3±3.32	2.6±2.34	.190[m]
RR tri	6.9±2.01	8.4±3.46	.097[t]
TINN	111.1±52.11	116.1±88.03	.979[m]
Mean RR (ms)	854.4±203.54	991.8±133.43	**.013*t**
Frequency domain HRV analyses			
LF (ms^2)	204.7±143.28	351.9±256.66	**.033*t**
HF (ms^2)	140.0±101.18	189.8±277.65	.465[t]
LF (n.u.)	56.8±20.7	65.5±17.96	.157[t]
HF (n.u.)	43.2±20.74	34.4±17.92	.156[t]
LF/HF ratio	2.4±2.6	2.9±2.37	.196[m]
Nonlinear HRV analyses			
SD_1(ms)	13.1±4.29	19.4±14.63	.078[t]
SD_2(ms)	40±16.32	54.2±25.15	**.045*m**
Lmean (beats)	11.3±3.14	14.8±6.25	**.048*m**
Lmax (beats)	248.2±116.93	227.3±97.11	.536[t]
Detrended fluctuations (DFA): α1	1.1±0.23	1.2±0.28	.516[t]
Detrended fluctuations (DFA): α2	0.98±0.17	1.0±0.29	.610[m]
Shannon entropy (ShannEn)	3.2±0.28	3.4±0.38	.054[t]
Approximate entropy (ApEn)	1.6±0.35	0.98±0.14	**.006*t**
Sample entropy (SampEn)	1.1±0.97	1.4±0.51	.095[t]
Correlation dimension (D2)	0.9±0.87	1.3±1.13	.266[m]
BRS			
xBRS (ms.mmHg)	5.4±3.18	8.0±5.99	.138[m]
Mean tau (s)	1.7±1.05	2.2±0.68	.062[m]
R^2	0.71±0.05	0.70±0.03	.806[t]
Interval (ms)	104.2±88.51	122.3±80.97	.334[m]

Notes: SDNN, standard deviation of all normal R-R intervals; RMSSD, the root mean square of differences of successive RR intervals; NN50, number of consecutive RR intervals that differ more than 50 ms; pNN50, the percentage of NN50, SD_1, the standard deviation of the Poincaré plot perpendicular to the line-of-identity ; SD_2, the standard deviation of the Poincaré plot along the line-of-identity; RR tri, the integral of the RR interval histogram divided by the maximum of the histogram; LF, low frequency; HF, high frequency; LF/HF, ratio of LF and HF frequency band powers; ms= milliseconds, nu= normalized units; xBRS, cross-correlational baroreceptor sensitivity; %, percentage; *, significant difference at $p<0.05$ alpha probability level; [t], results based upon independent samples T-test; [m], results based on Mann-Whitney U-Test.

7. Clinical implications

The findings from our results have a number of clinical implications. Firstly, we have shown that a significant proportion of the COPD patients (7.7% to 76.9% respectively) suffer from impaired autonomic function indices (Table 5). These results largely suggest a persistent predominance of sympathetic activity among COPD patients who participated in our study. Since an imbalance (e.g. persistent sympathetic activation) in ANS functioning could lead to a number of consequences, these results imply the recommendation and importance of assessing autonomic function in COPD. A few examples of these consequences include sodium-sodium retention, rhythm disorders, hypertrophy of both the ventricles and arterial walls, coagulation and lymphadenopathy, which could lead to cardio- vascular events (109). Furthermore, autonomic imbalance can cause abnormal blood pressure and heart rate regulation, increased myocardial remodeling and impaired myocardial oxygen consumption, dysregulation of glucose concentrations in the blood, myocardial ischemia, lack of adaptation to stress situation, abnormal cardiovascular homeostasis and poor treatment prognosis (110-114).

A decreased HRV index is a reflection of poor cardiac autonomic control, which represents a risk factor for future cardiovascular events even among healthy individuals (19). Specific HRV parameters that are often impaired in COPD such as the LF index and an increased LF/HF ratio represent a higher sympathetic tone possibly predicting severe cardiovascular disorders (115, 116). Hence, there may be a need to focus COPD treatment interventions to counteract sympathetic dominance in patients who fit to this description. It is important to keep in mind whatsoever, that a number of COPD features including systemic inflammation, hypoxia, oxidative stress, physical inactivity, and changes in the vascular connective tissue also contribute to the impairment of the ANS function (Figure 5) (117). One of the key outcomes of this dissertation is that BRS index, which is an independent risk factor for mortality after cardiovascular events (118), was generally reduced in patients with COPD.

For the purpose of clinical practice, it is important to identify these COPD patients with impaired autonomic indices or autonomic dysfunction in an early stage to be able to monitor their disease prognosis and possibly prevent future cardiovascular events. These patients can be identified by an initial screening using the autonomic symptom profile questionnaires, after which simple tests such as the HRR and possibly HRV recording can be obtained among those with a higher number and intensity of autonomic symptoms based on the questionnaire. After these patients are identified, specific non-pharmacological interventions could be initiated. In this dissertation, it was reported that patients with COPD who were participating in pulmonary rehabilitation or maintenance programs

Table 5 Comparison of the selected autonomic function test variables of COPD patients in this research with established reference norms.

Variable	Number and % of COPD patients with abnormal autonomic function values compared to normative value	Reference
Time domain HRV analyses		Nunan et al., 2010 (119)
SDNN (ms)	15/26 (57.7%)	
RMSSD(ms)	16/26 (61.5%)	
Mean RR (ms)	9/26 (34.6%)	
Frequency domain HRV analyses		Nunan et al., 2010 (119)
LF (ms^2)	14/26 (53.8%)	
HF (ms^2)	10/26 (38.5%)	
LF (n.u.)	2/26 (7.7%)	
HF (n.u.)	4/26 (15.4%)	
LF/HF ratio	11/26 (42.3%)	
Deep breathing		Novak et al., 2011 (120)
HR_{DB} (bpm)		
Normal	20/26 (76.9%)	
Borderline	17/26 (65.4%)	
Abnormal	15/26 (57.7%)	
Valsalva maneuver		Schrezenmaier et al., 2007 (17)
Valsalva index		
Normal	12/26 (46.2%)	
Abnormal	14/26 (53.8%)	

Notes: SDNN, standard deviation of all normal R-R intervals; RMSSD, the root mean square of differences of successive RR intervals; LF, low frequency; HF, high frequency; LF/HF, ratio of LF and HF frequency band powers; ms= milliseconds, nu= normalized units; HR_{DB}, heart rate during deep breathing; bpm, beats per minute.

did not have severely diminished autonomic function quality. As such, this can be interpreted as evidence to support the current pulmonary rehabilitation guidelines in COPD as reported in chapter 1. However, a few COPD patients were found to have moderate/severe adrenergic and vagal dysfunction as presented in Table 1. For these patients we have proposed two case studies (Appendix B). Furthermore, as an alternative in case aerobic training could not be achieved, interval training, also provides a non-pharmacological option for modulating the autonomic function indices in COPD (Chapter 7).

For now, exercise training appears to be a better and effective approach compared to oxygen supplementation in enhancing the autonomic function in COPD patients who have impaired autonomic function indices. Exercise training is known to enhance the ANS function by increasing the vagal modulation of the heart, as indicated by greater post exercise HRV and BRS values (121). Other benefits of exercise training include a cardiovascular adaption encompassing several neuro-muscular structures like the central command, baroreceptor reflex and the neural reflex feedback from the muscles. Additionally, fitness levels in both athletes and non-athletes are associated with vagal-HRV (122).

Even though the role of aerobic exercise training in modulating autonomic function in COPD is barely reported in literature, using three high quality RCT studies (22). Nevertheless, we have identified high evidence to support aerobic exercise training at an intensity of 60 - 80% of the maximal work range for 30-40 minutes at a frequency of ≥3 times/week in order to be effective in enhancing HRV time domain analysis and HRR (Chapter 7).

Furthermore, we reported a strong association between skeletal muscle function and autonomic function for COPD patients in chapter 3. Skeletal muscles dysfunction in diaphragm and quadriceps muscles is common in COPD and associated with poor health status, health care utilization, exercise capacity and mortality (123, 124). Therefore, skeletal muscle function should be monitored in clinical COPD rehabilitation by physiotherapists as an indirect mean of

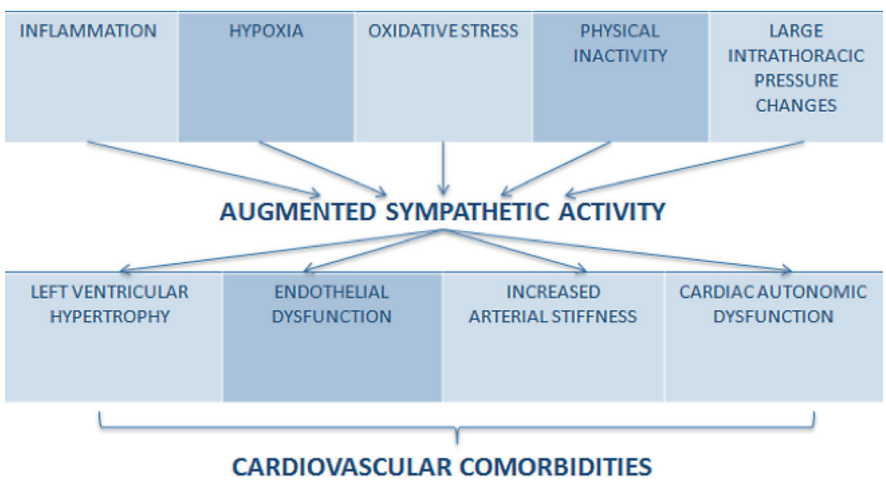

Figure 5 A postulated mechanism for sympathetic over activity in COPD. Adopted from (117).

ascertaining the possible state of the autonomic function. Typical interventions for muscle dysfunction may include exercise training, neuromuscular stimulation and resistance exercises.

The use of respiratory rehabilitation techniques in the context of pulmonary rehabilitation are equally important results in this dissertation. Specifically, the positive results recorded in the included studies in our review on the effect of controlled breathing (125, 126) and oxygen supplementation (21, 127, 128), remain a potential asset to exercise training in COPD patients suffering from autonomic dysfunction during rehabilitation. Slow breathing in particular has been found to have a training effect on heart rate fluctuations (20). COPD patients who presented decreased autonomic function indices or autonomic dysfunction could be treated in the clinic using different combinations of respiratory rehabilitation techniques. For example, patients who are not able to perform endurance training could be administered controlled breathing. Also, improving physical activity status of these patients can offer a vital alternative intervention for autonomic dysfunction.

In conclusion, since COPD subjects have autonomic symptoms that could be linked to poor mental health status (4, 11, 12). And these results suggest a possible psychosocial aspect manipulating the autonomic symptoms in COPD patients. Therefore, there may be a need to further assess and explore the need for possible psychological support or intervention for patients who report high autonomic symptoms.

8. Strengths and limitations

The first limitation of this research is that the obtained results in the original studies do not reflect all the COPD stages. For example, only moderate and severe COPD patients responded to our survey while no information was collected from patients with mild COPD (GOLD I). Similarly, in chapter 5 of this dissertation, only severe stage COPD patients (GOLD III-IV) who are clinically stable were included in the study. While this may not be the best approach to evaluate autonomic dysfunction in COPD, we tried to recruit a more homogenous sample.

Secondly, the etiology of autonomic dysfunction in different chronic disorders is multifactorial, and this includes ageing also. There is also a possibility that molecular/cellular changes such as inflammatory mediators, in many of these disorders can affect the results of autonomic function tests. Therefore, quantifying the actual impact of autonomic dysfunction and ascertaining a specific means of rehabilitation is difficult.

Thirdly, a significant proportion of the study participants were males. Although the general prevalence of COPD is slightly more common in males than

in females [55 vs 45%] (129), the results of the original research in this dissertation were based on a higher male-female proportion as presented in chapter 4 (74% vs 26%) and chapter 5 (88.5 vs 11.5%). Nevertheless, a one-on-one gender matching of the COPD patients with heathy control subjects was performed to provide a balance in the study results. Hence, the results have to be viewed within this perspective.

The fourth limitation is that a number of objective autonomic function screening tests such as the MSNA and sudomotor function were not assessed in this research due to practical issues. Also, it is possible that some of these tests could have provided more information, larger input and another perspective to our results as they examine other aspects of the ANS. Nonetheless, the inclusion of systematic reviews of existing research provided a reference to compare our results with existing results. Moreover, the MSNA, which reflects the rate of sympathetic discharge to the vascular bed of skeletal muscles (44), is an invasive test and may not be tolerated by all patients as stated earlier in this dissertation. The sudomotor test also requires a high level of expertise and the margin of error is high. At present, the sudomotor test alone does not offer the gold standard any longer to measure sudomotor function (16), since the recent autonomic function test protocol, QASAT utilizes both QSART and small fibers (intra-epidermal sensory and sweat glands) densities from skin biopsies. Still, the results in this dissertation remains valid and reliable as we have reported on other important autonomic tests that can be used in simple practical situations.

The fifth limitation of this research is that we could not adequately validate the Dutch COMPASS-31 questionnaire for COPD patients in this research. The validation study was based on a relatively low sample of COPD patients who were recruited from an ongoing rehabilitation program (Chapter 5). The majority of these COPD patients had only mild adrenergic or cardiovagal dysfunction (General discussion, Table 1), partly due to the homogeneity of the study sample used in the laboratory study. For example, all COPD patients were clinically stable, and the majority suffered from stage III COPD based on the GOLD classification. Therefore, it was expected that the COMPASS-31 questionnaire was not able to discriminate and screen for autonomic dysfunction in this COPD population.

The sixth limitation is the relatively low sample sizes utilized in the laboratory study (chapter 5). Larger and adequately powered study designs are needed to confirm our results. An additional power analysis indicated that a larger sample comprising 44 to 77 subjects per group, is needed to achieve a conclusion on the question of autonomic function in COPD. Nevertheless, the results of this dissertation provide a current platform for future studies.

Lastly, since COPD remains a complex clinical syndrome that varies between individuals, comorbidities and other variables becomes an issue. As expected, a number of confounding factors that are known to influence the autonomic

function, could not be controlled. These variables include age, undiagnosed comorbidities, other sub-clinical disorders and use of medications such as beta-adrenergic blockers, sympathomimetic, inhaled corticosteroids. Despite these challenges, we believe our results are valid because we followed a validated autonomic function testing protocol (2011). Additionally, the sensitivity analyses performed after excluding patients who use beta blockers revealed that our results were not substantially influenced by these medications. However, similar sensitivity analyses could not have been performed for the COPD medications due to lack of statistical power to perform the analyses.

Notwithstanding these limitations, this work offers valuable insights. The use of three systematic reviews provides us with a high level of evidence for future clinical practice guide. More importantly, several autonomic function parameters that could be assessed and monitored as outcome measures during COPD rehabilitation have been highlighted in this research.

9. Directions for future research

A large number of parameters are available to assess autonomic function and the integrity of the ANS in general. However, only the resting HRV and BRS indices, as well as adrenergic and cardio vagal function of patients with COPD were reported in this dissertation. Therefore, future studies in this area should focus on more recent autonomic function test protocols. The QASAT (Chapter 2, Tables 6, 7 & 8) and the MIBG provide two robust options for answering this question. Also, it will be interesting to consider whether the QASAT results will correlate with autonomic symptoms (in order to validate the COMPASS-31) and other COPD outcomes.

The results of this research showed a significantly higher prevalence of autonomic symptoms in COPD, which may suggest the presence of underlying ANS deficits. However, this link was not established in the present dissertation. Also, our attempt to validate the COMPASS-31 was not successful. Therefore, there is a need to identify a population of COPD patients who already have established autonomic imbalance or dysfunction (mild, moderate and severe) in order to validate this instrument in the future. One possibility would be to conduct a large questionnaire study (survey), and screen those who reported very high and low scores on the COMPASS-31 for further autonomic function testing.

Going forward, future studies need to go beyond pilot observations in order to state some rigorous conclusions on this topic. Following a power analysis, conducted (presented above) to estimate the effect sizes of each outcome, we recommend that clinical trials should comprise, in each disease and control group, about 42 subjects for time domain HRV analyses, 77 subjects for nonlinear HRV

analyses, and 45 subjects for BRS indices. Also, there is a need to use more robust assessment means to determine autonomic function, e.g. the QASAT and/or more reliable tests like MIBG.

Additionally, future interventional studies could aim at reporting the effect of pulmonary rehabilitation in patients with COPD who have an established autonomic failure or dysautonomia. RCT designs should be used in these studies, and the assessment of autonomic function should be performed using comprehensive test protocols like the QASAT. Lastly, there is a need to also focus on the long-term effects (using follow up studies) of exercise training and other non-pharmacological interventions on the autonomic function in COPD. For example, an integrated pulmonary rehabilitation program comprising controlled breathing techniques, inspiratory muscle training, other forms of exercise training, physical activity participation and strength training could be tested in COPD populations.

10. General conclusion

This dissertation formulated three research questions bothering around three main themes: (i) is autonomic function impaired in COPD? (ii) 'are autonomic symptoms prevalent in COPD, and what are the contributing factors? and (iii) what is the role of non-pharmacological interventions for possible autonomic dysfunction in COPD? Therefore, the results of this dissertation are important for understanding the impact of COPD on the ANS integrity.

Presently, it can be concluded that there is evidence to support impairments of autonomic function indices in COPD. These indices include HRV in time domain, BRS and MSNA. More importantly, physical activity levels and muscle function were found to be the major factors that negatively contribute to the autonomic function indices in these patients.

The results of our research also indicated that a sub-population of COPD patients who are participating in a rehabilitation or maintenance program have autonomic function parameters that are largely similar with their healthy counterparts. The autonomic reactivity tests of sympathetic/vagal indices revealed even more parallel values between these patients and controls. Moreover, the vast majority of these COPD sub-population had normal or mild adrenergic and cardio-vagal dysfunction. This finding is suggesting that current pulmonary rehabilitation or maintenance programmes inadvertently provides beneficial influence on the autonomic health in COPD patients.

For the question regarding autonomic symptoms, it was concluded that patients with COPD have a high prevalence of autonomic symptoms present across multiple domains compared to healthy individuals. Poor mental health status

considerably contributed to the rates of autonomic symptoms in these patients. Other COPD outcomes such as disease severity, fatigue levels, anxiety and depression status and demographic characteristics were not associated with total autonomic symptoms score in COPD. For now, the possible role medication use or unreported disease comorbidities is clearly identified. Presently the Dutch COMPASS-31 is capable of providing a profile of autonomic symptoms, as its validity and reliability for the overall COPD population was not ascertained at this moment.

Lastly, non-pharmacological interventions mainly aerobic exercise training, and oxygen supplementation, and possibly controlled breathing techniques offer important non-pharmacological options, with marginal beneficial effects, on the autonomic function indices of patients with COPD.

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"You are unique in your own disease (COPD)"

Janet Plank

Appendices

Appendix A

31-item Dutch composite autonomic symptoms scale (COMPASS-31)

Domein hart en bloedvaten

1. Hebt u zich in het voorbije jaar ooit flauw, duizelig of verdwaasd gevoeld, of hebt u moeite gehad met nadenken, kort na het rechtop komen uit zittende of liggende positie?
   - o Nee (ga naar vraag 5)
   - o Ja
2. Hoe vaak hebt u deze gewaarwordingen of klachten bij het rechtop komen? Markeer slechts één alternatief.
   - o Zelden
   - o Af en toe
   - o Vaak
   - o Bijna altijd
3. Hoe ernstig zijn deze gewaarwordingen of klachten? Markeer slechts één alternatief.
   - o Mild
   - o Matig
   - o Ernstig
4. Deze gewaarwordingen of klachten zijn in het voorbije jaar: Markeer slechts één alternatief.
   - o Veel erger geworden
   - o een beetje erger geworden
   - o ongeveer gelijk gebleven
   - o een beetje verbeterd
   - o veel verbeterd
   - o volledig verdwenen
5. Hebt u in het voorbije jaar ooit opgemerkt dat de kleur van uw huid veranderde? Werd uw huid bijvoorbeeld rood, wit of paars? Markeer slechts een alternatief.
   - o Nee (ga naar vraag 8)
   - o Ja
6. Welke delen van uw lichaam worden getroffen door deze kleurveranderingen? Kruis ALLE passend antwoorden aub.
   - o Mijn handen
   - o Mijn voeten
7. Deze kleurveranderingen zijn: Markeer slechts één alternatief.
   - o Veel erger aan het worden
   - o een beetje erger aan het worden
   - o ongeveer hetzelfde gebleven
   - o een beetje aan het verbeteren
   - o veel aan het verbeteren
   - o volledig verdwenen

Zweetreactie

8. Zijn er in de voorbije 5 jaar veranderingen opgetreden in uw algemeen zweetpatroon?
   Markeer slechts één alternatief.
   - o Ik zweet veel meer dan vroeger
   - o Ik zweet een beetje meer dan vroeger
   - o Ik zweet een beetje minder dan vroeger
   - o Ik zweet veel minder dan vroeger
   - o Ik heb geen veranderingen gemerkt
9. Voelen uw ogen abnormaal droog aan?
   - o Nee
   - o Ja
10. Voelt uw mond abnormaal droog aan?
    - o Nee
    - o Ja
11. Hoe evolueert de klacht waarvan u langst last had? Deze klacht is....
    Markeer slechts één alternatief.
    - o veel erger aan het worden
    - o een beetje erger aan het worden
    - o ongeveer hetzelfde gebleven
    - o een beetje aan het verbeteren
    - o volledig verdwenen

Spijsvertering

12. Hebt u in het voorbije jaar verandering gemerkt in hoe snel u zich voldaan voelt bij een maaltijd?
    Markeer slechts één alternatief.
    - o Ik ben nu veel sneller voldaan dan vroeger
    - o Ik ben nu sneller voldaan dan vroeger
    - o Ik heb geen verandering gemerkt
    - o Ik ben nu minder snel voldaan dan vroeger
    - o Ik ben nu veel minder snel voldaan dan vroeger
13. Hebt u zich in het voorbije jaar na een maaltijd overmatig vol gevoeld of aanhoudend vol gevoeld (opgeblazen gevoel)?
    Aanhoudend = gedurende een groot deel van de dag of langer
    Markeer slechts één alternatief.
    - o Nooit
    - o Soms
    - o Vaak
14. Hebt u in het voorbije jaar gebraakt na een maaltijd?
    Markeer slechts één alternatief.
    - o Nooit
    - o Soms
    - o Vaak
15. Hebt u in het voorbije jaar buikkrampen of koliekachtige buikpijn gehad?
    Kolieken = hevige krampachtige buikpijn
    Markeer slechts één alternatief.
    - o Nooit
    - o Soms
    - o Vaak

16. Hebt u in het voorbije jaar een periode van diarree gehad?
    Markeer slechts één alternatief.
    - o Nee (Ga naar vraag 20)
    - o Ja
17. Hoe vaak komt dit voor?
    Markeer slechts één alternatief.
    - o Zelden
    - o Af en toe
    - o Vaak, hoeveel keer per maand? beschrijf hieronder
    - o Voortdurend

Hoeveel keer per maand hebt u last van diarree?

_____

18. Hoe ernstig zijn deze episodes van diarree?
    Markeer slechts één alternatief.
    - o Mild
    - o Matig
    - o Ernstig
19. De periodes van diarree zijn: (Markeer slechts één alternatief.)
    - o veel erger aan het worden
    - o een beetje erger aan het worden
    - o hetzelfde gebleven
    - o een beetje aan het verbeteren
    - o veel aan het verbeteren
    - o volledig verdwenen
20. Hebt u in het voorbije jaar last gehad van constipatie (moeilijke stoelgang, opstopping)?
    - o Nee (Ga naar vraag 24).
    - o Ja
21. Hoe vaak hebt u constipatie?
    Markeer slechts één alternatief.
    - o Zelden
    - o Af en toe
    - o Vaak
    - o Voortdurend

Hoeveel keer per maand hebt u last van constipatie?

_____

22. Hoe ernstig zijn deze periodes van constipatie?
    Markeer slechts één alternatief.
    - o Mild
    - o Matig
    - o Ernstig
23. Deze constipatie is:
    Markeer slechts één alternatief.
    - o Veel erger aan het worden
    - o een beetje erger aan het worden
    - o hetzelfde gebleven
    - o een beetje aan het verbeteren
    - o veel aan het verbeteren
    - o volledig verdwenen

Urogynaecologisch

24. Hebt u in het voorbije jaar ooit last gehad van urineverlies of bent u in het voorbije jaar ooit de controle over uw blaas verloren?
    Markeer slechts één alternatief.
    - o Nooit (Ga naar vraag 27)
    - o Af en toe
    - o Vaak
    - o Voortdurend
25. Had u in het voorbije jaar ooit moeite om te kunnen plassen? *
    Markeer slechts één alternatief.
    - o Nooit
    - o Af en toe
    - o Vaak
    - o Voortdurend
26. Had u in het voorbije jaar ooit moeite om uw blaas volledig te ledigen?
    Markeer slechts één alternatief.
    - o Nooit
    - o Af en toe
    - o Vaak
    - o Voortdurend

Pupilreflex

27. Hebt u het voorbije jaar last ondervonden van uw ogen van fel licht, als u geen zonnebril of donkere bril droeg?
    Markeer slechts één alternatief.
    - o Nooit (Ga naar SF-36 vragenlijst)
    - o Af en toe
    - o Vaak
    - o Voortdurend
28. Hoe ernstig is deze gevoeligheid voor fel licht?
    Markeer slechts één alternatief.
    - o Mild
    - o Matig
    - o Ernstig
29. Hebt u in het voorbije jaar moeite gehad om uw ogen te focussen (scherp te stellen)? *
    Markeer slechts één alternatief.
    - o Nooit (Ga naar SF-36 vragenlijst)
    - o Af en toe
    - o Vaak
    - o Voortdurend
30. Hoe ernstig is dit probleem?
    Markeer slechts één alternatief.
    - o Mild
    - o Matig
    - o Ernstig

31. Deze hinderlijkste oogklacht is:
    Markeer slechts één alternatief.
    - o veel erger aan het worden
    - o een beetje erger aan het worden
    - o hetzelfde gebleven
    - o een beetje aan het verbeteren
    - o volledig verdwenen

Appendix B

Case studies presentation

Case 1: a 72-year-old man with moderate cardiovagal dysfunction

Patient RVH (race, Caucasian; occupation, retired; height, 163cm; weight, 81 kilograms; BMI, 30.5 kg/m^2) was diagnosed with COPD in 2010. RVH was actively smoking for several years before stopping in 2009. At the time of recruitment into the autonomic function study. He had a moderate stage COPD based on the global obstructive lung disease (GOLD) classification system. His lung function parameters are as follows: forced expiratory volume in first second (FEV_1), 1.49 (60% of predicted); forced vital capacity (FVC), 2.29 (71% of predicted); and peak expiratory flow (PEF), 5.46 (77% of predicted). RVH walked a distance of 370 meters (62% of predicted reference) during the six-minute walk test (6MWT). At the time of testing, his blood pressure and heart rate were 149/58 mmHg and 62 bpm, respectively. RVH was participating in a pulmonary rehabilitation program at the time of autonomic function testing. RVH reported using cardiovascular (Coruno® [molsidomine], Belsar plus® [olmesartan-hydrochlorothiazide]), cholesterol (Zocor® [simvastatin]), diabetes and gastro intestinal (Pantomed® [pantoprazole], Asaflow® [acetylsalicylic acid]) medications. For COPD medication, He reported using long acting muscarinic antagonists (Spiriva® [tiotropium]) and a combination of inhaled corticosteroids and long acting beta agonists (ICS/LABA) (Seretide® (fluticasone propionate/salmeterol xinafoate).

RVH reported a poor quality of life (mainly physical component), but anxiety and depression scores were fairly normal. He also reported no fatigue symptoms (using CIS), or dyspnea on the modified medical research council dyspnea scale (mMRC= 1/5).

The results of the autonomic symptoms score, from the COMPASS-31 questionnaire, revealed that RVH reported problems with all domains of the Dutch COMPASS-31 version, with the exception of urinary tract complaints. Gastro intestinal symptoms were more intense, suggesting both parasympathetic (constipation) and sympathetic (diarrhea) nervous system problems. The total autonomic symptoms score was 33.61 (out of 100). The autonomic function parameters for RVH are presented in Table 1 below. Lastly, Hiscardio-vagal dysfunction (moderate) level was determined based on the heart rate during deep breathing and valsalva maneuver (parameters) values.

Implication for rehabilitation experts: Based on the data presented above and in Table 1, pulmonary rehabilitation intervention for patient RVH should be slightly modified to also target the cardio-vagal dysfunction. **Firstly,** and more importantly, exercise training should be emphasized This can be in the form of a combined exercise training program, since low 6MWD test can be caused by low aerobic capacity and/or low quadriceps strength. Aerobic exercise training session

should last between 30-40 minutes, at a frequency of ≥3 times/week. An intensity of 60-70% of peak work rate (Wpeak) should be maintained. Interval training program is also an option for RVH because of its huge impact on mitochondrial function in peripheral muscles. Interval training should be performed on a cycle ergometer for 3 times/week for a duration of 40 minutes using a combination of 2-minute at high work rate (70–100% Wpeak) and 3-minute low work rate at (40–50% Wpeak). **Secondly**, there is a need to carefully inspect the medication use of RVH. Since RVH used number of medications that have side effects that could have presented as autonomic symptoms reported in COMPASS-31, especially gastro intestinal symptoms. Specifically, the use of Spiriva® has been known to cause dryness of the mouth, constipation, upset stomach and vomiting. If possible these medications should be replaced by other agents. **Thirdly**, other non-pharmacological options aimed at stimulating the parasympathetic nerve activity should be incorporated in the management of RVH. One example can be the use of controlled breathing exercise such as deep breathing, based on the respiratory sinus arrhythmia (RSA) technique.

Case 2: a 72-year-old woman with severe adrenergic dysfunction

Patient IIR (race, Caucasian; occupation, retired; height, 159 cm; weight, 66 kilograms; BMI, 26.1 kg/m^2) was diagnosed with COPD since 2004. IIR has a history of cigarette smoking which she quitted in 1997). Her blood pressure and heart rate on the test day was 200/90 mmHg and 65 bpm, respectively. IIR reported occasional alcohol consumption at the time of study testing. IIR has a severe staged (GOLD III) COPD, and was only able to walk 352 meters (67% predicted) during 6MWT. Her pulmonary function parameters are as follows: forced expiratory volume in first second (FEV_1), 0.50 (27% of predicted); forced vital capacity (FVC), 2.11 (93% of predicted); and peak expiratory flow (PEF), 2.58 (47% of predicted). During the period of the study testing, IIR reported using cardiovascular (Belsar plus® [olmesartan-hydrochlorothiazide]), anti-rhinitis (Flixonase® [fluticasone]), anti-biotics (Augmentin® [amoxicillin/clavulanate]); and anti-inflammatory (Medrol® [methylprednisolone]) medications. For COPD medications, short acting muscarinic antagonists (Atrovent® [ipratropium]), long acting muscarinic antagonists (Spiriva® [tiotropium]) and a combination of inhaled corticosteroids and long acting beta agonists (Seretide® [fluticasone propionate/salmeterol xinafoate]), were used by IIR. Despite participating in an ongoing maintenance program (*longclub*), IIR was highly dyspneic (mMRC= 4/5). For other health outcomes, IIR reported having a moderately impaired quality of life (physical and mental) and also a moderate fatigue, anxiety and depression levels.

IIR reported, by means of the Dutch COMPASS-31, a very intense orthostatic intolerance symptoms (peak), mild secretomotor, gastro intestinal, and urinary and pupillomotor complaints. Her total autonomic symptoms score at the time of

Table 1 Autonomic function test results for patient RVH and IIR.

Autonomic function indices	Patient RVH	Patient IIR
Time domain HRV analyses		
SDNN (ms)	17.8	32.6
RMSSD(ms)	12.1	27.7
NN50(count)	1	24
pNN50(%)	.31	6.9
RR tri	4.47	8.97
TINN	75	150
Mean RR (ms)	930.1	830.4
Frequency domain HRV analyses		
LF (ms^2)	79.5	132
HF (ms^2)	48.6	209.9
LF (n.u.)	61.98	38.55
HF (n.u.)	37.9	61.44
LF/HF ratio	1.64	.63
Deep breathing		
HR_{DB} (bpm)	3.2	11.4
Valsalva maneuver		
Valsalva ratio	1.55	1.33
Valsalva index	2.01	1.96
BRS_a (mmHg/sec)	10.73	1.64
BRS_v (sec/mmHg)	.56	2.33
BRS_g	6.01	3.83
PRT (sec)	0	3
PP drop (mmHg)	31	23
Inadequate VM (loss of any phase)	No	Loss of phase 2 L
Tilt test		
Initial orthostatic hypotension (OH)	Yes	Yes
OH	Yes	Yes
Delayed OH	No	No
Postural orthostatic tachycardia syndrome (POTS)	No	No
Early stop due to other reasons	No	No

autonomic function testing was 39.2 points. Autonomic function parameters for RVH are also presented in Table 1 above. The adrenergic dysfunction for IIR was determined using the valsalva maneuver and tilt test values.

Implication for rehabilitation experts: Based on the data presented for IIR, she will likely benefit from a patient-tailored-education-program that specifically targets her orthostatic intolerance. Information which explains the underlying mechanisms for orthostatic symptoms need to be well explained in the form of

education. IIR needs to know that these physical symptoms are relatively harmless, in order to reduce Her anxiety levels. Moreover, patient education has been shown to promote self-management. In the same vein, advice should be given to avoid large meals, alcohol consumption, prolonged mental activity, prolonged sitting and standing. Also, some instructions to deal with acute orthostatic intolerance symptoms can be provided. These include rapid ingestion of water (500 ml) and contraction of large muscle groups (especially the calf and quadriceps through squatting) in order to aide venous return. IIR can also benefit from an augmentation of cardiac vagal tone through an exercise training program (typically at 60 – 80% of maximum work rate). Endurance training has been shown to have beneficial effects on the cardiovascular regulation by four means: (i) increasing in blood volume, (ii) increase in muscle tone, (iii) decrease in cardiac sympathetic activity, and (iv) increase in vagal activity. Endurance exercises for IIR can be in form of cycling, hopping, stair climbing. The work rate for IIR should be gradually increased from 0 minutes to 20 minutes of aerobic exercise 3 times per week. Another possible intervention for IIR is tilt training (repeated orthostatic stress), which is thought to increase vascular tone. A typical tilt training session consists of standing upright for 30 minutes, once or twice daily. Furthermore, IIR should be thought techniques that reduces stress such as deep breathing exercises and mindfulness training in order to increase parasympathetic activity in favor of a better balance in the ANS. Several medication options could be explored to address the severe adrenergic dysfunction. The role of medications such as fludrocortisone (to increase blood volume), beta blockers, alpha-adrenergic (either alone or in combination with fludrocortisone), either or both of serotonin reuptake inhibitors and norepinephrine reuptake inhibitors (to prevent neuro-cardiogenic syncope), and sympatholytic agents are useful options that can be considered.

Summary | Samenvatting

Summary

Chronic obstructive pulmonary disease (COPD) is a chronic and slowly progressive lung disease which results in more and more difficulty in breathing as a result of an obstruction or narrowing of the airways. Abnormal functioning of the autonomic nervous system (ANS) is one of the most important systemic consequences of COPD. The ANS controls involuntary body functions such as the excretion of urine and sweat, heart rate, respiration, blood pressure and digestion. In general, the aim of this dissertation was to further improve our understanding about ANS deficits in COPD, and possible non-pharmacological interventions. Although previous studies have unanimously reported that autonomic function deficits are present in COPD, the assessment techniques used in these studies appear to be inadequate. Similarly, a number of studies have shown that non-pharmacological interventions could reverse the autonomic function deficits in COPD, however the evidence to support these claims is scanty. Therefore, this dissertation was based upon three key themes; (i) describing the evidence to support the link between autonomic function and COPD, (ii) assessment of possible dysautonomia in COPD, and (iii) non-pharmacological interventions for autonomic function modulation in COPD.

The organization of the present dissertation is based on seven chapters, divided in three parts:

- In **Part I**, an extensive overview of COPD **(Chapter 1)** and the ANS **(Chapter 2)** was provided. The objective of this part was to present a detailed description of all relevant topics regarding COPD and ANS. A secondary objective of this part was to introduce the link between COPD and the ANS by means of a systematic review, which assessed the evidence for autonomic dysfunction (and the influencing factors) in COPD **(Chapter 3).**
- The second objective in this dissertation, presented in **Part II,** was to assess dysautonomia in COPD with two distinct original studies. The first study focused on autonomic symptoms and its possible controlling variables, whereas the second original study concentrated on wide-ranging autonomic function parameters as well as cardiovagal reactivity in a subgroup of COPD. These studies are respectively presented as **Chapters 4** and **5**.
- **Part III** aimed to investigate the effects of selected non-pharmacological interventions on the autonomic function in COPD. This part included two systematic reviews evaluating current evidence of the latter: (i) the effect of respiratory rehabilitation techniques such as noninvasive ventilation (NIV), oxygen therapy and controlled breathing techniques on autonomic function in COPD **(Chapter 6)**, and (ii) the influence of aerobic exercise training (AET) on the autonomic function modulation in COPD **(Chapters 7)**.

Part I of this dissertation, which is partly based on the results of a systematic review, showed that autonomic function parameters are more impaired in COPD than in healthy control subjects. The parameters that were reviewed included the time domain heart rate variability, baroreceptor sensitivity and muscle sympathetic nerve activity in COPD (strong evidence). Additionally, physical activity level, muscle function and day-night circadian rhythm were identified as influencing factors for the autonomic function in COPD (strong evidence). For other factors such as dyspnea, body composition, respiratory rate, pulmonary function outcomes, age, disease severity and quality of life, there was only weak to no evidence. These results demonstrate that autonomic function is compromised in patients with COPD, especially those with low physical activity status and impaired muscle function.

Because previous studies have reported autonomic function deficits in COPD, Part II of this dissertation included two original studies which aimed to further evaluate dysautonomia in COPD. The first study, which focused on autonomic symptoms in COPD, revealed higher rates of autonomic symptoms in the patient population compared to healthy individuals. These symptoms were reported across the domains of orthostatic intolerance, secretomotor, vasomotor, gastrointestinal, urinary and pupillomotor symptoms, possibly indicating the presence of underlying ANS deficits. However, further analyses in a subgroup of COPD patients with mild autonomic dysfunction revealed that these autonomic symptoms were insufficient to screen for autonomic dysfunction. Also, medication use, age and participation in a rehabilitation programs were found to possibly confound the rates of autonomic symptoms. Nevertheless, mental health status was found to predict total autonomic symptoms score. This finding further highlights the importance of the psychological aspect in COPD.

The findings from the second study revealed that the resting autonomic function were only slightly reduced in a subgroup of COPD, who were recruited from a pulmonary rehabilitation program. From these results, two conclusions could be drawn: (i) the persistence of mild ANS deficits in COPD, and (ii) a possible amelioration of autonomic dysfunction among COPD patients in pulmonary rehabilitation. Furthermore, the adrenergic and cardio-vagal autonomic function tests showed similar results for both the COPD population and heathy controls, thereby indicating that none of these tests may have additional advantages compared to the resting autonomic function tests.

To appraise evidence in support of non-pharmacological aspects to autonomic function modulation in COPD, two separate systematic reviews were conducted. The first systematic review indicated that a moderate to strong level of evidence supports the effect of oxygen supplementation and slow breathing techniques in increasing baroreceptor sensitivity. These results demonstrate that these

techniques could serve as potential treatment options or adjuncts in COPD rehabilitation. The second systematic review revealed that a high level of evidence supports the role of aerobic exercise training programs in enhancing time-domain HRV analyses and heart rate recovery (HRR) parameters in COPD. However, most of these results are based on a low number of randomized control trials. In addition, there was only a limited number of studies reporting on autonomic function parameters (resting heart rate variability and baroreceptor sensitivity) were. Hence, future assessment studies are necessary.

Due to the large number of available parameters for the assessment of autonomic function, future studies should focus on reporting homogenous subgroups of COPD that have not been included in the existing literature. Also, future interventional studies with both sufficient power and high quality designs are needed to reveal the effect of other non-pharmacological approaches on autonomic dysfunction in COPD. It would be interesting to see the effect of interventions like inspiratory muscle training, partitioning exercises, physical activity participation and strength training.

To conclude, the research in this dissertation has provided evidence to show that several ANS parameters are impaired in COPD. Autonomic symptoms are also present across several domains (body systems) in COPD. Medication use and other patient characteristics such as age muscle function and physical activity levels largely influenced autonomic function in these patients. Last but not least, non-pharmacological interventions such as aerobic exercise training and oxygen therapy have demonstrated a capability to enhance the autonomic function indices in COPD.

Nederlandse samenvatting

Chronisch obstructieve longlijden (Engels afkorting, COPD) is een chronisch en langzaam progressieve longaandoening die net zoals astma, ontstaat ten gevolge van een obstructie of vernauwing van de luchtwegen. Hierdoor wordt het ademen steeds moeilijker. COPD heeft verschillende systemische consequenties. Het autonome zenuwstelsel (AZS) is het systeem dat onze onvrijwillige lichaamsfuncties controleert zoals het afscheiden van urine en zweet, de hartslag, de ademhaling, de bloeddruk en de spijsvertering. Het algemene doel van deze thesis is het verder uitdiepen van de kennis omtrent het functioneren van het AZS bij patiënten met COPD. Vroegere studies hebben reeds uitgebreid gerapporteerd dat de autonome functie bij deze patiënten een dysbalans vertoond tot effectief faalt in COPD, maar het bepalen en karakteriseren van de defecten is nooit uitgebreid gebeurd. Bovendien is het interessant om na te gaan in welke mate niet-farmacologische interventies het autonome functie falen in COPD kan verhelpen. Dit doctoraatsproefschrift is gebaseerd op drie belangrijke thema's; (i) autonoom functie falen in COPD aan de hand van een systematisch literatuuronderzoek en het bevragen van specifieke autonome klachten in deze populatie; (ii) onderzoek naar dysautonomie in een zeer specifieke subgroep van patiënten met COPD, en (iii) niet-farmacologische interventies voor autonome functies in COPD aan de hand van een systematisch literatuuronderzoek.

De inhoud van deze thesis bestaat uit zeven hoofdstukken verdeeld over drie delen:

- In **Deel I** van dit werk, wordt een uitgebreid overzicht van COPD **(Hoofdstuk 1)** en het AZS **(Hoofdstuk 2)** gegeven. Het doel van dit deel is om in detail alle relevante informatie over deze onderwerpen te beschrijven alsook om de evidentie te onderzoeken over het voorkomen van autonome dysbalans/dysfunctie (en zijn beïnvloedende factoren) in COPD **(Hoofdstuk 3).**
- Het tweede doel van deze thesis, dat wordt voorgesteld in **Deel II,** onderzoekt dysautonomie in COPD. Dit heeft geleid tot twee originele studies. De eerste studie behandelt autonome symptomen in COPD en welke factoren hier een belangrijke correlatie mee vertonen, terwijl de tweede studie een rapport omvat over de autonome functie in rust en in stress (cardiovasculaire reactiviteit) in een subgroep van COPD. Beide studies worden voorgesteld in **Hoofdstuk 4** en **5**, respectievelijk.
- **Deel III** heeft tot doel om het effect van geselecteerde niet-farmacologische interventies na te gaan op de autonome functies in COPD. Dit deel omvat twee systematische reviews die de huidige evidentie evalueren binnen studies die; (i) het effect van respiratoire revalidatietechnieken zoals niet-invasieve ventilatie (NIV), zuurstoftherapie en gecontroleerde ademhalingstechnieken onderzoeken

op de autonome functies in COPD **(Hoofdstuk 6)**, en (ii) de invloed van een aerobe training (Engelse afkorting AET) op de autonome functie modulatie in COPD **(Hoofdstuk 7)**.

Deel I dat gedeeltelijk op de resultaten van een systematische review is gebaseerd, toont aan de autonome functie aangetast is bij patiënten met COPD wanneer ze worden vergeleken met gezonde individuen. Deze onderzochte parameters omvatten de *time domain heart rate variability* (HRV), baroreceptor sensitiviteit (BRS) en de musculaire sympathetische zenuwactiviteit (Engelse afkorting MSNA) in COPD (bescheiden evidentie). Fysieke activiteit, spierfunctie en dag-nacht circadische ritmes werden geïdentificeerd als beïnvloedende factoren voor de autonome functie in COPD (bescheiden evidentie). Voor andere factoren zoals ademnood, lichaamssamenstelling, longfunctie, leeftijd, ziektestatus en levenskwaliteit, was de evidentie niet bestaande, gelimiteerd of conflicterend.

Omdat de aantasting van de autonome functie reeds beschreven is in de vorige studies, bevat Deel II van deze verhandeling twee originele studies die een verdere evaluatie omvatten van dysautonomie in COPD. De eerste studie, die als doel had om autonome symptomen in COPD in kaart te brengen resulteerde in de bevinding dat, vergeleken met gezonde individuen, de COPD patiënten een hoger aantal autonome symptomen vertoonden, met name orthostatische intolerantie, secretomotor, vasomotor, gastro-intestinale, urinaire en pupillomotor symptomen. Deze resultaten tonen aan dat COPD patiënten symptomen vertonen die indicatief zijn voor het onderliggende AZS falen. Deze autonome symptomen correleerden ook met de gezondheidstoestand, waarbij vooral de mentale toestand een goede voorspeller bleek te zijn van deze symptomen. Dit doet vermoeden dat psychosociale interventies mee moeten genomen worden in de behandeling van dysautonomie in COPD.

De bevindingen van de tweede studie toonden aan dat de rust-autonome functie verminderd was in een COPD cohort die een longrevalidatieprogramma doorliepen. Dit resultaat is misschien indicatief voor een persistent AZS falen in COPD. De cardio-vagale autonome reactiviteitstesten gaven geen bijkomende informatie, benevens de resultaten van de Tilt-test. Dit kan een indicatie zijn van vroege signalen van een mogelijke orthostatische hypotensie en posturele tachycardie syndroom (POTS).

In deel III werd ingegaan op mogelijke niet-farmacologische interventies om autonoom falen te verbeteren. Een systematische review gaf een gematigd en sterk niveau van evidentie aan voor een verhoogde baroreflex sensitiviteit (BRS) als gevolg van zuurstofsupplementatie respectievelijk specifieke ademhalingstechnieken. Deze resultaten demonstreren dat deze technieken potentie bevatten als behandeling tijdens COPD revalidatie. Een laatste systematische review toonde

een hoge mate van evidentie voor een verhoogde time-domain HRV analyse en een hartslag herstel als gevolg van een aerobe trainingsinterventie in COPD. Echter, de meeste van deze resultaten waren gebaseerd op lage aantallen RCTs, met een gelimiteerd aantal gerapporteerde autonome functieparameters waardoor verder studies noodzakelijk blijven.

Door het grote aantal mogelijke parameters bij het onderzoek naar autonome functies zullen toekomstige studies zich moeten toespitsen op het rapporteren van homogene subgroepen bij COPD patiënten die niet zijn opgenomen in de bestaande literatuur. Bovendien, zouden toekomstige interventies de effecten van niet-farmacologische technieken op de autonome functies in COPD moeten onderzoeken. Hierbij is aandacht voor inspiratoire spierkrachttraining en algemene krachttraining noodzakelijk.

Tot besluit, deze thesis geeft een bewijs voor de aanwezigheid van ANS falen in COPD. Dit autonome functie falen kon gecorreleerd worden aan het fysieke activiteitsniveau en met spierfuncties van de patiënten. Zoals verwacht, autonome symptomen zijn wijdverbreid in deze patiënten, en vooral bij deze met een lage mentale gezondheid. Tenslotte, niet-farmacologische interventies zoals aerobe training en zuurstoftherapie zorgen voor een potentiële mogelijkheid om AZS verstoring te kunnen verhelpen/reduceren in COPD.


الحمد لله رب العالمين

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"If you want to go fast, go alone. If you want to go far, go together"

African proverbs

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"Acquire knowledge and teach it to people"

Umar Bn Khattab

Curriculum Vitae

Curriculum Vitae

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Awards

2014–2017	PhD Study Fellowship, awarded by the Tertiary Education Trust Fund (TETFund), Nigeria.

Teaching experience

2016-present ***Department of Rehabilitation Sciences and Physiotherapy,*** Ghent University, Belgium: Masters Thesis Supervision (1é and 2é Master).

2010-2014 ***Department of Physiotherapy,*** Bayero University Kano, Nigeria: Teaching of Undergraduate Program Courses (Cardiopulmonary and Metabolic Disorders; Introduction to Kinesiology); and Undergraduate Project Supervision.

Research Experience

2014 to 2018 **PhD thesis:** Autonomic Function in Patients with Chronic Obstructive Pulmonary disease: Evidence and Non-Pharmacological Interventions.

2008-2010 **Master thesis:** Influence of Socioeconomic Status on the Lung Function of Children in Ile-Ife, Nigeria.

Memberships

2016-present Member of the European Respiratory Society

Peer-reviewed Publications (National & International)

Da Silva H, **Mohammed J,** Calders P, De Backer T, Rambaut L, De Wandele I, (2018). Validation of the 31-item Dutch composite autonomic symptoms scale (COMPASS-31) in patients with chronic diseases. *Acta Neurologica Belgica.* (Under Preparation).

Mohammed J, Derom E, De Backer T, De Wandele I, Calders P (2017). Cardiac autonomic function and reactivity tests in subjects with COPD attending a pulmonary rehabilitation program. *Journal of Chronic Obstructive Pulmonary Disease.* (Article in Press).

Mohammed J, Derom E, De Wandele I, Rambaut L, Calders P. Autonomic Symptoms in Subjects with Moderate and Severe chronic obstructive pulmonary disease. *Acta Clinica Belgica.* (Article in Press).

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evidence for aerobic exercise training on the autonomic function in patients with chronic obstructive pulmonary disease: a systematic review. *Physiotherapy.* (Article in Press).

Mohammed J, Da Silva H, Van Oosterwijck J, Calders P. Effect of respiratory rehabilitation techniques on the autonomic function in patients with chronic obstructive pulmonary disease: a systematic review. *Chronic Respiratory Disease* 2017; 14(3): 217-230.

Mohammed J, Meeus M, Derom E, Da Silva H, Calders P. Evidence for Autonomic Function and its influencing factors in Subjects with Chronic Obstructive Pulmonary Disease: A Systematic Review. *Respiratory Care 2015;* 60 (12), 1841-1851.

Sumaila FG, Omotara ZG, **Mohammed J**. Knowledge of the role of physiotherapy in prevention and treatment of soccer injuries among managers of amateur soccer teams. *African Journal of Physiotherapy and Rehabilitation Sciences* 2015; 7 (1-2), 19-24.

Sumaila FG, Okafor P, **Mohammed J,** Badaru UM. Assessment of functional and musculoskeletal problems, and barriers to obtaining physiotherapy services among elderly individuals in a rural community in Kano State, Nigeria. *African Journal of Physiotherapy and Rehabilitation Sciences 2015;* 7 (1-2), 1-6.

Mohammed J, Maiwada SA, Sumaila FG. Relationship between anthropometric variables and lung functions parameters among primary school children. *Annals of Nigerian Medicine* 2014; 8(2): 19-24.

Nuhu JM, **Mohammed J,** Mohammed M. Ultraviolet Therapy: Physiotherapists Perception and barriers to usage. *Hong Kong Physiotherapy Journal* 2014; 32; 44-48.

Kodzo E.K., **Mohammed J,** Kodzo P. Gender and postural differences in cardiovascular response to hand grip exercise among elderly normotensives. *African Journal of Physiotherapy and Rehabilitation Sciences 2013; 5 5(1/2): 45-49.*

Arogundade IO, **Mohammed J**. Cardiovascular disease risk factors among retirees and non-retirees in Ile Ife: a comparative study. *Nigeria Medical Journal* 2013; 54(3): 168-172.

Mohammed J, Adedoyin RA, Awotidebe TO, Onigbinde TA. Influence of Parental socioeconomic status on lung functions among children In Ile-Ife, Nigeria. *Journal of Nigeria Society of Physiotherapy* 2012; 20; 67-72.

Referee Work

2017-present **Reviewer** for International Journals (indexed in the Web of Science): European Respiratory Journal; International Journal of COPD; Croatia Medical Journal; Journal of COPD; Journal of Back and Musculoskeletal Disorders.

Published Abstracts and International Presentations

Mohammed J, Derom E, De Backer T, De Wandele I, Calders P. Cardiac autonomic function and reactivity in non-sedentary subjects with COPD. **Podium *Presentation*** *at the the the European Respiratory Society Research Seminar, "Systems Medicine in Respiratory Disease", Germany* ***(Berlin, 2017)***

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evidence for exercise training in autonomic function modulation in patients with chronic obstructive pulmonary disease (COPD): a systematic review. *European Respiratory Journal 49 (Suppl. 61), PA..*). **Thematic Poster** *presented at the 27th International Congress of the European Respiratory Society, Italy* ***(Milan, 2017).***

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evidence for exercise training in autonomic function modulation in patients with chronic obstructive pulmonary disease (COPD): a systematic review. *European Journal of Physiotherapy*). **Podium Presentation** *at the International Congress of the World Confederation of Physical Therapists (WCPT), South Africa* ***(Cape Town, 2017).***

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evaluation of autonomic function in patients with COPD. **Podium presentation** *at the Research Day - Students Research Symposium, Ghent University, Belgium* ***(Ghent, 2017).***

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evidence for exercise training in autonomic function modulation in patients with chronic obstructive pulmonary disease (COPD): a systematic review. *Physiotherapy 102, e107*). **Poster presentation** *at the 4th International Congress of the European Region of the World Confederation of Physical Therapist (ER-WCPT), United Kingdom* ***(Liverpool, 2016).***

Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Prevalence and clinical correlates of patient-reported autonomic symptoms among subjects with COPD. *European Respiratory Journal 48 (Suppl. 60), PA4618*. **Poster discussion** *at the 26th International Congress of the European Respiratory Society, United Kingdom* ***(London, 2016).***

Mohammed J, Calders P. Autonomic function in patients with COPD: a systematic review. **Bullet presentation** *at the Faculty Research Day of the Faculty of Medicine and Health Sciences, Ghent University, Belgium* ***(Ghent, 2015).***

Mohammed J, Kodzo E.K., Kodzo P. Gender and postural differences in cardiovascular response to upper extremity isometric exercise among elderly normotensives in Shahuci Kano. **Podium presentation** at t*he 52nd Annual Scientific Conference of The Nigeria Society of Physiotherapy, Edo State, Nigeria* ***(Benin, 2012).***

Mohammed J. The role of Physiotherapy in Cardiac Rehabilitation. **Podium presentation** at *the 51st Annual Scientific Conference of the Nigeria Society of Physiotherapy, Jigawa State, Nigeria* ***(Dutse, 2011)****.*

Mohammed J. Knowledge of and attitude to cardiovascular disease risk factors among members of the Nigerian armed forces. **Podium presentation** at *the 51st Annual Scientific Conference of the Nigeria Society of Physiotherapy, Jigawa State, Nigeria* ***(Dutse, 2011)****.*

Courses and Certificates

Exercise is Medicine: One day symposium organized by the Transplantoux in Leuven, Belgium on the 23rd of February 2018.

Translational research data handling and analyses Workshop organized by the European Respiratory Society in Berlin, Germany on the 26 to 28th of October 2017.

Targeting the locomotor and respiratory muscles in chronic obstructive pulmonary disease: novel interventional tools and rehabilitation strategies. Post graduate course organized by the European Respiratory Society in Milan, Italy, on the 9th of September 2017.

Two-day workshop on mobile health organized by the Flanders training network life sciences (f-TALES) at Diepenbeek Campus, Hasselt University, Belgium between 27th and 28th of April 2017.

Seminars in transferable skills course (cluster-leadership and personal efficacy): Two-day course on Meeting skills organized by the Ghent University Doctoral School at Ghent University, Belgium between 24th and 25th of November 2016.

Advanced Academic English: Conference Skills Course (Life Sciences & Medicine), organized by the Ghent University Doctoral School at Ghent University, Belgium between 7th October until 23rd of December 2016.

New frontiers in exercise training in patients with chronic obstructive pulmonary disease course organized by the European Respiratory Society (ERS) in London, the United Kingdom on the 5th of September 2016.

Clinical studies, study designs, implementation and reporting organized by the Ghent University Doctoral School of Life Sciences and Medicine at Ghent University, Belgium between 17th and 18th of September 2015.

Advanced Academic Writing Skills Course (Life Sciences & Medicine), organized by the Ghent University Doctoral School at Ghent University, Belgium between 21st February and 22nd of May 2015.

Seminars in transferable skills course (cluster-career management): Two-day course on Creative thinking organized by the Ghent University Doctoral School at Ghent University, Belgium between 21st and 22nd of January 2015.

Flames Summer School on Research Methodology (5 Modules; research methodology, basic statistical principles and their applications, hands on research methodology, focus groups; theory and practice, and narrative analysis) at Ghent University, Belgium between 8th and 19th of September 2014.

Statistical parametric mapping (SPM): Two-day basic course organized by the Ghent University Doctoral School of Life Sciences and Medicine at Ghent University, Belgium between 7th and 8th of June 2014.

Two-day workshop on systematic review and qualitative approach to evidence synthesis organized by the KU Leuven continuing education at Utrecht, The Netherlands, between 26th and 27th of May 2014.

Hobbies

Playing football
Travelling
Reading