RISK FACTORS CONTRIBUTING TO A POSTURAL BALANCE IMPAIRMENT IN COPD PATIENTS

A Thesis

by

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ABSTRACT

Falls are the fifth-leading cause of death, globally, and they also come with social and economic burdens. In the individual level, falls can result in increased mortality, increased morbidity rate, reduced functioning such as physical activity, and reduced quality of life. Therefore, it is needed to be considered the falls as a single disease. Due to the clinical and social impact of falls, numerous studies were completed on the risk of falls on the elderly population and the diseased population related to motor dysfunction such as Parkinson's or stroke. However, there are still unmentioned diseases which have a higher risk of falls. Chronic Obstructive Pulmonary Disease (COPD) is a disease that has airflow limitation during breathing. COPD patients experience not only lack of oxygen supplementation but also systemic impairment such as cardiovascular problems, impaired muscle function, and impaired cognitive function. Therefore, we assessed the postural balance function and other related variables which were suggested in previous studies. Comorbidities, lung function, body composition, skeletal muscle strength, exercise capacity, balance function, physical activity status, and cognitive function were measured in the Healthy control group and the COPD group. Lung function showed lower values in the COPD group (FEV1, $p<0.001$), and comorbidity index was higher in the COPD group (Charlson Comorbidity Index, $p<0.0001$). Muscle strength was lower in the COPD group (inspiratory muscle strength, $p=0.0007$; maximal leg extension force, $p=0.023$) and the cognitive function was lower in the COPD group ($p<0.0071$). Also, the postural balance function measured by the center of pressure showed higher sway velocity in the COPD group (anterior-posterior direction, $p<0.0081$). However, no difference was found between the groups in Berg Balance Scale and body composition. In the correlation analysis, the reduced balance in the COPD group

was significantly associated with increased weight, years of COPD related symptoms, usage of oxygen, comorbidity index (congestive heart failure and diabetes), fat mass, and reduced cognitive function ($p<0.05$). The aforementioned factors in the COPD can be considered as risk factors related to the reduced postural balance function.

DEDICATION

First of all, I dedicate this thesis to God who gives me power and strength. God has been my rock, my fortress, my source of inspiration, and knowledge. Next, I dedicate my thesis work to my beloved family, especially my wife, who has been patient during my research and course works. Also, if there was no encouragement from my family, including my adorable two little girls, Soeun and Sojung, I could not finish my research. I also dedicate this thesis to my parents and sister, especially my mom who is praying for me in the heaven. My dad have been encouraged me from the start of steps in academia and supported me as well. My sister also has been my mentor and supporter by praying during the program. I love you all, I bless you all, and I thank you all.

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NOMENCLATURE

5-HT	5-hydroxytryptamine
6MGS	6-Meter Gait Speed
ABC	Activities-specific Balance Confidence
AP	Anterior-posterior
ASMI	Appendicular Skeletal Muscle Index
BBS	Berg Balance Scale
BMI	Body Mass Index
CAT	COPD Assessment Test
CHF	Congestive Heart Failure
CoP	Center of Pressure
CoM	Center of Mass
COPD	Chronic Obstructive Pulmonary Disease
DXA	Dual-energy X-ray Absorptiometry
FEV	Forced Expiratory Volume
FFM	Fat Free Mass
FM	Fat Mass
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HbA1c	Glycated Hemoglobin
MEP	Maximum Expiratory Pressure
MIP	Maximum Inspiratory Pressure
ML	Mediolateral

mMRC	Modified Medical Research Council
NHLBI	National Heart, Lung, and Blood Institute
NS	Not Significant
PASE	Physical Activity Scale for the Elderly
PCA	Principal Component Analysis
QS	Quiet Standing
RMS	Root Mean Square
SE	Standard Error
SPPB	Short Physical Performance Battery
SR	Sway Range
SV	Sway Velocity
TMT	Trail Making Test
TUG	Timed Up and Go test
WHO	World Health Organization

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1. INTRODUCTION

1.1 Significance of falls

Falls are the fifth-leading cause of death in the older population, and they also come with a burden not only to the individual patient but also can result in social and economic consequences [1]. The World Health Organization (WHO) reported that each year globally, approximately 646,000 individuals experience fatal falls that might require hospitalizations due to severe injuries such as fractures [2]. In the United States, approximately one in four older adults aged ≥ 65 reported falling each year, and 3 million U.S. residents visit emergency departments due to fall related episodes [3]. Furthermore, the death rate from falls increased in the U.S. by an average of 3.0% per year during 2007 to 2016 [3]. Falls also result in an increased burden of medical support [4]. For example, in the single patient aspect, falls can result in increased mortality and morbidity rates, as well as reduced functioning, which causes a direct reduction in physical activity [5] [6]. Moreover, these factors come along with a reduced quality of life [1]. Considering all the negative factors mentioned above, falls are a critical issue to think about equally to single disease.

1.2 Factors of fall risk in general population

Due to the significance of falls, numerous studies were performed on the risk of falls. Approximately 400 different fall risk factors were reported [1] which shows that falls are not a simple issue. In healthy old populations, a number of studies reported that muscle weakness, balance deficit, number of medication, gait deficits, functional impairment, visual deficit, age, and cognitive impairment were intrinsic risk factors for falls [6] [4] [7] [8]. Also, environmental hazards and lifestyle factors such as cluttered surroundings were mentioned as extrinsic factors

[4]. Postural stability is also known to be affected by biomechanics, motor coordination, and sensory organization [9]. The findings of aforementioned research represent the fall risk factors of the healthy population. However, many diseases are associated with a significantly increased risk of falls which is not extensively researched. A number of studies show that an impaired balance function with increased fall risks was not only observed in motor-and neuro-related chronic diseases (e.g., Parkinson's, stroke, etc.) but also other systemic diseases (e.g., COPD).

1.3 Fall risk in the clinical population

Many researchers try to understand the underlying components of balance impairment — physiological, neuropsychological, and biomechanical mechanisms — and fall risk in the general and elderly populations [6] [4] [7] [8]. However, the dominant factors that are contributing to balance impairment might be different in every disease, and also it has not been clearly defined. Generally, these diseases have multiple negative effects on the risk of fall compared to a healthy population [10] [11]. In addition to the aforementioned studies, it is also not clearly known if COPD patients have the same risk factors for falls as a general elderly population or other diseases. Therefore, there is a critical need to identify the factors that contribute to impairment of balance function in COPD which increases risk of fall.

1.4 What is COPD

According to the National Heart, Lung, and Blood Institute/World Health Organization (NHLBI/WHO) Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is defined as "a disease state characterized by airflow limitation that is not fully reversible"[12]. The diagnosis of COPD considers the presence of related symptoms, such as a symptom of

cough, sputum production, or dyspnea. The confirmation of diagnosis for COPD is done by spirometry. Disease severity is classified by two component from spirometry such as Forced Expiratory Volume in the first one second (FEV1) and Forced Vital Capacity (FVC). With these values, FEV1/FVC ratio can be calculated that is also called the Tiffeneau-Pinelli index. To confirm the presence of airflow limitation that is not fully reversible, FEV1 < 80% of the predicted value and FEV1/FVC < 70% should be satisfied. Also, disease severity is classified with those factors [13]. In addition to GOLD staging, the COPD Assessment Test (CAT) and Modified British Medical Research Council (mMRC) questionnaire are used which are significantly related to physiological parameters of lung function [14] [15].

This airflow limitation of COPD is mainly caused by small airway disease and/or parenchymal destruction [16]. This structural change decreases the dimension of airway luminal area [17]. Chronic inflammation causes these structural changes, such as narrowing of the small airways and/or losing elasticity of recoil in alveolar [18]. Furthermore, this disease results in significant systemic disturbances along the whole body in organ function and biochemistry [19]. According to impairment in cardiovascular function, COPD patients have a 20% higher prevalence of heart failure [20] and vascular changes accompanied by arterial stiffness [21] and right ventricular failure [22]. Also, COPD can cause bone destruction by systemic inflammation [23] which results in a 60% higher prevalence of osteoporosis compared to people without COPD in the same age group. [24] [25]. In the muscular system, COPD subjects showed muscle atrophy, specifically reduced fat-free mass and cross-sectional area in type IIX fiber [26]. Also, weakness of skeletal muscle compared to healthy population was found in COPD [27].

1.5 What is known about balance impairment in COPD

Interestingly, COPD patients showed a high incidence rate of falls [28] and balance impairment by traditional balance measurements. Crisan et al. reported that COPD subjects with an exacerbation showed worse outcomes than COPD subjects without an exacerbation using the Berg Balance Scale (BBS), Single-leg stance (SLS), and Timed-Up and Go test (TUG) [29]. Furthermore, impaired balance function measured by TUG was related to global functioning assessment score in COPD [30]. A balance impairment in COPD measured by Short Physical Performance Battery Score (SPPB), 4-meter gait speed, and sit-to-stand time were associated with physical inactivity [31]. However, these traditional balance measurement methods in COPD were focused on a comprehensive and systemic balance function, but not on the independent balance function.

1.6 Limitations in previous studies

Some of the current studies and methods mentioned above have limitations as well as lack of evidence. Measurements using a scale type scoring system might be affected by the tester's bias. (e.g. inter-rater reliability) Also, these tests do not only have an insensitivity on mild balance impairment but also have a floor or ceiling effect [32]. In addition, these types of task-oriented tests mainly focused on the systemic function of the subject, but not specifically on the balance function [33, 34]. These limitations make it difficult for clinicians to detect balance impairment at diagnosis and to monitor the improvement during rehabilitation [35]. To manage this issue, a combination of multiple tests are recommended (e.g. ABC scale, FM-B, and PASS) [32]. Also, various methods were reported during the past few decades that enable measurement of balance function objectively: body accelerometer, motion capture system, force plate, etc.

Especially, center-of-pressure measurement by force plate was intensively applied with clinical populations. These postural measurements were widely applied on neurological disorders (e.g. Parkinson's disease, stroke) to quantify diagnostic balance function and to confirm improvement on balance function during rehabilitation [36]. These emerging technologies make clinically available to measure balance function and posture itself directly for other chronic diseases as well [37, 38]. Therefore, it is necessary to identify underlying causes of imbalance objectively by direct measurement of balance impairment.

1.7 Objective of the present study

The aims of the present study are 1) to investigate the presence of postural balance impairment in COPD patients determined by Center of Pressure (CoP) displacement measurement, and 2) to identify associating factors with postural balance impairment. To achieve our aims, we measured balance function by CoP trajectory and used calculations to convert it into quantifiable values. We hypothesized that a postural balance function is impaired in COPD due to dysfunction of skeletal muscle and cognition. Our research will contribute to identifying the high-risk fall patients prior to falls. Also, it will provide optimal and specific strategies for the prevention of falls in COPD population.

2. MATERIAL AND METHODS

2.1 Subjects

We recruited patients who were diagnosed with COPD by pulmonologists. 63 subjects were assessed for eligibility. 34 COPD and 22 Control subjects were included for data analysis who satisfies the inclusion criteria. Inclusion criteria for both groups were: age between 55 to 85 years old, and be able to walk, sit, and stand up independently (**Figure 1**). COPD subjects were classified as moderate to severe airflow obstruction (grade ll-lV), according to the established Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [39]. The control group consisted of 22 healthy participants matched with COPD for age, sex, and body-mass index (**Table 1**). Exclusion criteria were subjects who have: major neurological conditions that might affect postural balance (e.g., stroke history, Parkinson's disease, etc.), the presence of an acute illness, a metabolically unstable chronic illness, or fever within three days prior to the study day. Recruitment of COPD patients took place through local pulmonologist referral, whereas healthy subjects were recruited via advertisements in the local community. Medical history and medication use were assessed by research staff as part of the screening process according to Health Insurance Portability and Accountability Act (HIPAA) Authorization. All COPD patients were in a clinically stable condition and not suffering from a respiratory tract infection or exacerbation of their disease at least 4 weeks prior to the study. Transcutaneous oxygen saturation was measured using pulse oximetry. Exclusion criteria were pre-existent untreated metabolic or renal disease, malignancy, recent surgery, and use of systemic corticosteroids one month prior to the study. 66% of COPD patients was currently taking or took

bronchodilator medication, 16% inhalation corticosteroids, 44% were on long-term oxygen therapy and 22% were continuously on oxygen use. Written informed consent was obtained from all subjects, and the study was approved by the Institutional Review Board of Texas A&M University.

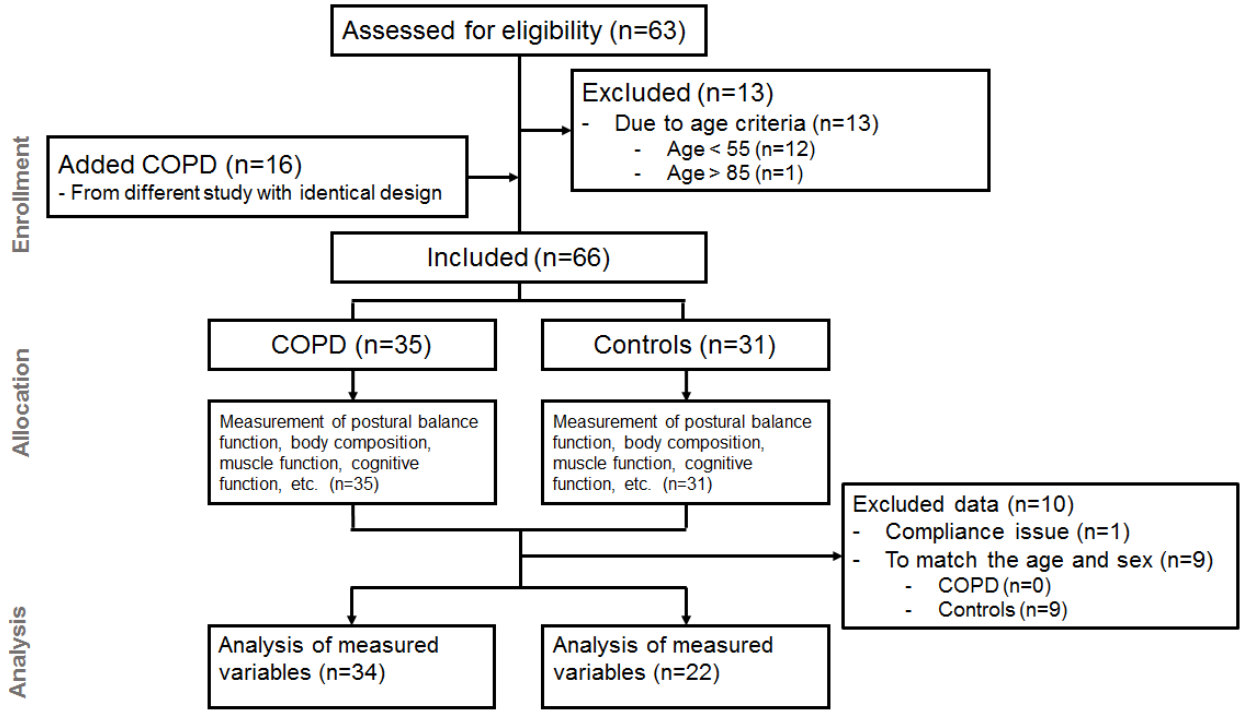


Figure 1: Consort flow diagram of the study.

2.2 Anthropometrics and body composition measurements

All study day procedure was performed at the Human Clinical Research Facility of the Center for Translational Research in Aging and Longevity at Texas A&M University. The study procedures were identical in both groups and the study day lasted approximately 4 hours. Body weight and height were measured by a digital beam scale and stadiometer, respectively. Furthermore, whole body, trunk and extremity (arms and legs) fat mass (FM) and fat-free mass

(FFM) were obtained from all subjects while in a supine position, by dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500 / Version 12.7.3.1 (Bedford, MA)). Anthropometric and body composition were measured to obtain body mass index (BMI, kg/m^2), FFM index (FFMI), FM index (FMI), and appendicular skeletal muscle index (ASMI). Also, lower limb length was measured, from Trochanter major to Medial malleolus, by an embed software in Hologic QDR 4500 [40] to obtain muscle mass in lower limb [41].

2.3 Lung function measurement

Spirometry measurement was performed with a hand-held device (Microloop Peak flow Meter, CareFusion, San Diego, CA). With spirometry, lung function was measured by parameters, such as FEV1, FVC, and FEV1/FVC ratio. Forced expiratory volume in 1 second was assessed with the highest value from ≥ 3 technically acceptable maneuvers [42]. Subjects were asked to sit up straight and to wear a nose clip to seal their nose, and then asked to have three normal breaths (tidal breath). After three breaths, subjects were instructed to inhale as deep as they can and exhale as fast and as much as possible. The software expresses percentage of predicted value according to a representative population with the subject's age and height information. Also, maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) were assessed by determining the maximal value of at least 3 reliable attempts using a hand-held mouth pressure device (Micro Respiratory Pressure Meter).

2.4 Muscle function and 6-meter gait speed (6MGS) measurement

Skeletal muscle function and exercise tolerance were assessed in all subjects. To measure skeletal muscle strength in the lower limb, following pre-test stretching and warm-up, the peak

leg torque during one leg reciprocal extensions (at 60 degrees/sec) were measured. Also, a peak handgrip force that the subject was able to generate out of 3 reproducible repetitions, with 1 minute of rest between each attempt, were used as a marker of maximum handgrip strength. Kin-Com isokinetic dynamometry (Isokinetic International, Chattanooga, TN) and Vernier dynamometry (Vernier Software and Technology, Beaverton, OR) were used respectively. 6-meter of usual and fast gait speed (6MGS) were measured to evaluate the tolerance of physical activity [43]. Time was measured over a distance of 6-meter after 1 trial of practice walk. Speed of usual and fast gait speed was calculated and expressed as meter/second. Subjects were allowed to use their walking aid and/or oxygen provided with a long tubing and movable cylinder [44].

2.5 Balance function measurement using Berg Balance Scale (BBS)

A performance-oriented and comprehensive balance function was evaluated by Berg Balance Scale in all subjects [45]. Berg Balance Scale (BBS) has been reported and used widely as a 'gold standard' for clinically assessing balance and postural control because of its documented reliability and validity [46-49]. BBS consists of 14 tasks that are common movements in everyday life that are scored by a 0 to 4 scale (items range from sit to stand and single leg stance) [45]. Research staff in our research facility had performed the test to maintain consistent inter and intra-rater reliability for the test as a whole (inter and intra- rater reliability reported as 0.98 and 0.99 respectively) [45]. The test was performed before the balance platform assessment. The maximum score of 56 indicates a good balance function.

2.6 Postural balance function measurement using center of pressure (CoP)

To obtain the measurable postural balance function, center of pressure (CoP) displacement data were collected. CoP displacement data were recorded by force plate (OR6-7-8000, Advanced Mechanical Technology, Inc., MA) during given 30 seconds. Three trials of quiet standing (QS) were performed according to standard instruction [50]. To control supported area which is defined by area of feet and the distance between two foot (Appendix A and B) [51], the distance between both feet was instructed according to designated markers on the surface of plate [51]. CoP is a bivariate distribution defined by anterior-posterior (AP) and mediolateral (ML) coordinates [52]. Sway range (SR), sway velocity (SV), root-mean-square distance (RMS distance), and 95% of ellipse area (Area) [53] were calculated to characterize individual balance function in each group. We used 100 Hz sampling frequency of CoP which is suggested as a reliable measurement in the static balance [54]. Subjects were asked to stand barefoot on the firm surface of the force plate and arms at the sides. Standardized instruction was given to subject to maintain the balance as still as possible during the measurement. After the given instruction, 5 seconds were given to adjust the posture, and 30 seconds were given for the measurement. A verbal cue sign for starting and ending were given by research staff with measuring time. Subjects were instructed to open their eyes and stare at the target which is located on a height of eye level and approximately 1.5 meters away. Three trials were given and resting time was allowed in between each trial as subjects requested. All the instruction to subjects was given according to standard instruction.

2.7 Cognitive function assessments

To assess cognitive impairment and, we used a Trail Making Test (TMT) which is simple and sensitive to detect neurological impairment and processes [55]. TMT consists of two parts, TMT-A and TMT-B. TMT-A is a task with drawing line sequentially 25 encircled numbers (e.g., 1 - 2 - 3 - 4, etc.). TMT-B is similar to TMT-A, but it is combined sequential numbers and alphabetical letters (e.g., 1 - A - 2 - B - 3 - C, etc.). Time for completion is measured during each part. The second test that we used to measure cognitive function was Stroop Color-Word Test [56]. Stroop test is a sensitive and reliable measurement method for neuropsychological response [55] [57]. According to the Stroop interference effect, an increased time is taken to name a color than to read out the name of a color [57]. There are possible theories to explain the Stroop effect, and the most common theories are regarding processing speed, selective attention function, and automaticity [58] [59]. Also, during the Stroop test, we can measure ability to selectively ignore the irrelevant stimuli and information [60]. We measured the time of completing Stroop reading tasks, and counted the number of errors. The Stroop test consists of three subtasks (l, ll, and lll). The materials for each subtask were shown on a white sheet of paper. The subjects were instructed to either read the name of the color or name of the ink color according to given subtasks. The first subtask shows color words in the random order that printed with black ink. The second subtask shows solid color patches among four colors. The third subtask shows color words printed in different ink color (e.g. the word “green” printed in “yellow” color) [61]. There was no time limit and completion time was measured for each task. Measured time was calculated for Stroop interference according to the equation below (1) [62].

$$\mathbf{Stroop_{interference}} = Time_{Stroop\mathrm{III}} - [(Time_{Stroop\mathrm{I}} + Time_{Stroop\mathrm{II}})/2] \quad (1)$$

2.8 Questionnaires

On the study day, habitual physical activity level was measured by the Physical Activity Scale for the Elderly questionnaire (PASE). The PASE was designed to assess activities commonly engaged by older people whose age is 65 or older [63]. The COPD Assessment Test (CAT) was used to assess the status of disease [64]. For the assessment of associated comorbidities, we used the Charlson Comorbidity Index [65]. Charlson Comorbidity Index (CCI) is known as most common tool for risk adjusted assessment. CCI gives a score of 0 to 6 for each comorbidity according to the seriousness of each comorbidity (e.g. myocardial infarction, chronic heart failure, peripheral vascular disease, etc. as 1; hemiplegia, moderate to severe renal disease, diabetes with end organ damage, any tumor, etc. as 2; moderate or severe liver disease as 3; and metastatic solid tumor and AIDS as 6) [66]. Self-reported CCI was cross-checked with medical history of individual subjects if it is fully available. However, self-reporting CCI proved the predictive power in clinical parameters (e.g. 1 year mortality) [67].

2.9 Data analysis

The CoP displacements were measured by the force platform. Three quiet standings were given to subjects, and data were recorded during the 30 seconds of displacement (sampling frequency: 100 Hz) [68, 69]. From the quiet standing CoP displacement data, we calculated 1) sway range (SR), 2) mean sway velocity (SV), 3) root mean square distance (RMS distance), and 4) sway area (95% confidence interval, SA).

Sway range (SR) was calculated as the distance of maximum value and minimum value on each coordinate respectively. Sway range (SR) in ML and AP were calculated with formula (2) and (3):

$$Swayrange_{ML} = \mid ML_{max} - ML_{min} \mid \quad (2)$$

$$Swayrange_{AP} = \mid AP_{max} - AP_{min} \mid \quad (3)$$

Sway velocity (SV) consists of three sub-analyses: those were the anterior-posterior (AP), mediolateral (ML), and combined coordinates (AP and ML). Sway velocity (SV) was calculated with this formula (4):

$$\mathbf{SwayVelocity} = Displacement\ Distance_{time}(cm)/time(sec) \quad (4)$$

The root-mean-square distance was calculated to quantify the amount of variation of CoP sway. Root mean square (RMS distance X) was calculated with the formula below:

$$\mathbf{RootMeanSquare_{distanceX}} = \sqrt{\left(X_1^2 + X_2^2 + ... + X_n^2\right)/n} \quad (5)$$

Principal component analysis (PCA) was used to measure the body sway area approximated by an ellipse. Sway area (SA) was calculated to characterize individual patterns represented by the accumulation of a trajectory of CoP. The PCA method quantifies the direction and the magnitude of the body sway [70]. 95% confidence ellipse was used for sway area calculation performed using Matlab code written by Marcos Duarte, available at the open-access public repository, Figshare (http://dx.doi.org/10.6084/m9.figshare.1126648) [71].

2.10 Statistical analysis

All results are expressed as means ± standard errors (SE). Normality test was performed by D'Agostino-Pearson omnibus normality test or for small group numbers with Shapiro-Wilk normality test. Unpaired Student's t-test was used to compare two groups at a time. If the normality test failed, unpaired Mann-Whitney test was performed instead. To test the association between postural balance function and all demographic variables, body composition related variables, comorbidity, cognitive function, and muscle strength. Pearson's correlation coefficient was used. The statistical packages within GraphPad Prism (GraphPad Software, La Jolla, CA, Version 8) and Matlab (The MathWorks, Inc., Natick, MA) were used for data analysis. The level of significance was set at $p<0.05$.

3. RESULTS

According to subject recruitment between 2017 and 2019, 66 subjects were included in the study: 22 control and 34 COPD subjects. Age, gender, and BMI were matched in both groups for analysis. In the Control group, the age range of 55 to 84 years and 50% were male. In the COPD group, the age range was 55 to 81 years and 41% were male (NS). There was no difference between the groups in age, gender, body weight, height, BMI, or physical activity level (NS). COPD subjects showed higher CCI score (0.31 vs 2.08, $p < 0.001$) (**Table 1**).

Table 1: General and clinical characteristics of the Control and COPD groups.

	Control, n=22 (SE)	**COPD, n=34 (SE)**	***P* value**
Age (years)	70.44 (1.72)	68.97 (1.36)	0.505
Gender (Male/Female)	11/11	14/20	0.588
Body Weight (kg)	82.36 (2.26)	83.32 (3.47)	0.838
Height (m)	1.67 (0.01)	1.65 (0.01)	0.326
Body mass index (kg/m^2)	29.50 (0.79)	30.53 (1.20)	0.528
Charlson comorbidity index (score)	0.31 (0.12)	2.08 (0.25)**	<0.0001
PASE (score)	122.0 (18.22)	106.4 (12.46)	0.507

Values are mean ± SE. Statistics are by unpaired t-test or Mann-Whitney test when normal distribution test failed. Categorical data were analyzed with Chi-square test. PASE: Physical Activity Scale for Elderly.

As we expected according to inclusion criteria on the diagnosis of COPD, the pulmonary related factors showed a lower lung function in the COPD group, and also average FEV1 predicted percentage showed 44.18% ($p < 0.0001$). Oxygen saturation was lower in the COPD group than the Control group (97.32% vs. 95.00%, $p = 0.014$). 20 subjects out of 34 were currently having oxygen therapy (including subjects who are using oxygen as needed, all day, and night only) (**Table 2**).

Table 2: Pulmonary functions of the Control and COPD group.

	Control, n=22 (SE)	**COPD, n=34 (SE)**	***P* value**
FEV_1 (% of predicted)	96.91 (2.96)	44.18 (3.13)**	<0.0001
FVC (% of predicted)	87.68 (2.79)	57.91 (2.38)**	<0.0001
FEV_1/FVC (ratio)	82.45 (1.27)	56.79 (2.70)**	<0.0001
Years of COPD related symptom (yr.)	-	10.82 (1.11)	-
Hospitalizations previous 12m. for exacerbation (No.)		0.26 (0.10)	-
Exacerbations in the past year (No.)	-	0.73 (0.24)	-
GOLD Stage	-	2.87 (0.13)	-
Dyspnea Scale	-	2.09 (0.18)	-
CAT (score)	-	21.00 (1.26)	-
O_2 use (yes/no)	0/22	20/14	-
Oxygen saturation (%)	97.32 (0.33)	95.00 (0.70)*	0.014

Values are mean ± SE. Statistics are by unpaired t-test or Mann-Whitney test when normal distribution test failed. Categorical data were analyzed with Chi-square test. GOLD: Global Initiative for Chronic Obstructive Lung Disease. FEV_1: Forced Expiratory Volume in one second. FVC: Forced Vital Capacity. CAT: COPD Assessment Test. No.: Number. m.: Months. Yr: Years. * = $p<0.05$; ** = $p<0.01$

In body composition, there was no difference between fat, lean, and muscle related variables. However, skeletal muscle function showed lower values in inspiratory muscle strength ($p = 0.0007$) and maximal leg extension force ($p = 0.023$). Leg extension force per kg fat-free mass also showed lower value in COPD group ($p = 0.026$) (**Table 3**).

Table 3: Body composition and muscle functions of the Control and the COPD group.

	Control, n=22 (SE)	**COPD, n=34 (SE)**	***P* value**
Body Composition			
Lean mass (kg)	49.00 (2.27)	48.51 (1.94)	0.871
Lean mass extremities (kg)	20.77 (0.91)	19.41 (0.90)	0.318
Fat mass (kg)	28.56 (1.65)	32.28 (1.91)	0.178
Fat mass trunk (kg)	15.22 (1.06)	17.03 (1.12)	0.275
Fat mass index (kg/m^2)	10.36 (0.68)	11.95 (0.78)	0.163
Fat-free mass (kg)	53.64 (1.89)	50.72 (2.19)	0.355
Fat-free mass index $(kg/m^2)^2$	19.09 (0.44)	18.46 (0.63)	0.478
Appendicular skeletal muscle mass (kg)	20.77 (0.91)	19.41 (0.90)	0.318
Appendicular skeletal muscle index $(kg/m^2)^3$	7.365 (0.22)	7.053 (0.25)	0.400
Android fat (%)[4]	37.54 (1.78)	38.53 (1.83)	0.715
Gynoid fat (%)[4]	35.10 (2.00)	37.91 (1.31)	0.226
Fat % android/gynoid (ratio)	1.101 (0.05)	1.015 (0.04)	0.205
Lower limb lean mass (kg)	15.67 (0.57)	14.53 (0.65)	0.223
Muscle function			
Inspiratory muscle strength (cmH2O)	83.50 (4.27)	60.97 (4.22)**	0.0007
Expiratory muscle strength (cmH2O)	100.90 (8.02)	82.71 (5.90)	0.068
Maximal handgrip strength (N)	235.80 (16.58)	203.40 (10.47)	0.087
Handgrip strength per kg fat-free mass (N/kg)	4.34 (0.21)	4.091 (0.17)	0.362
Maximal leg extension force (N)	257.70 (13.31)	210.50 (13.86)*	0.023
Maximal leg extension force per kg fat-free mass (N/kg)	4.82 (0.20)	4.15 (0.19)*	0.026
Maximal leg extension force per kg fat-free mass lower limb (N/kg)	33.49 (1.36)	28.63 (1.18)*	0.010

Values are mean ± SE. Statistics are by unpaired t-test. [2]Fat-free mass index = (muscle mass + bone mineral content)/$height^2$. [3]Appendecular skeletal muscle index = (lean mass legs + lean mass arms)/$height^2$. [4]Android fat and gynoid fat correspond to central and peripheral fat distribution, respectively. COPD: chronic obstructive pulmonary disease. * = $p<0.05$; ** = $p<0.01$

The traditional balance measurement, Berg Balance Scale, did not show a difference between the groups (NS). However, usual and fast gait speed measurements showed lower values in the COPD group (both $p < 0.0001$) (**Figure 2**).

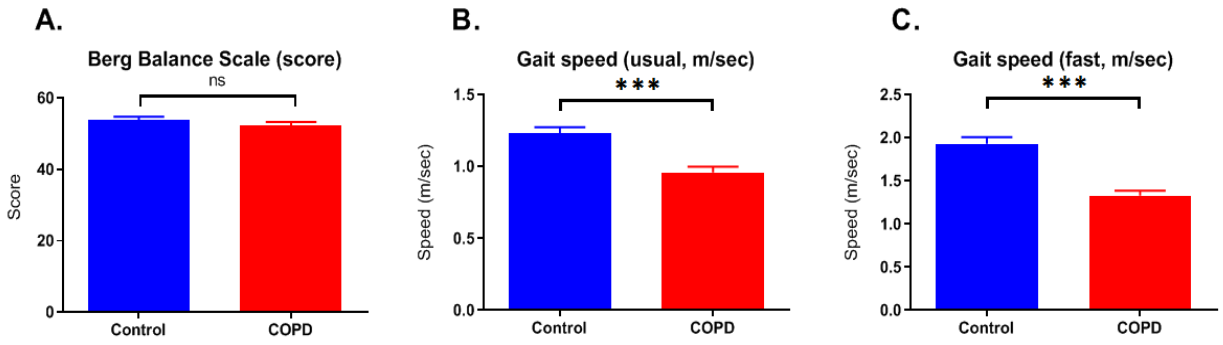


Figure 2: Berg Balance Scale (A), max score is 56; Gait speed for 6-meter distance walking (B: Usual speed; C: Fast speed).

The neurological test results showed that the COPD group needed more time to complete the given task in TMT (**Figure 3 - A**, $p < 0.0071$). The Stroop test did not show a statistical difference, but the COPD group tended to be significantly longer in the interference time (**Figure 3 - B**, $p < 0.061$).

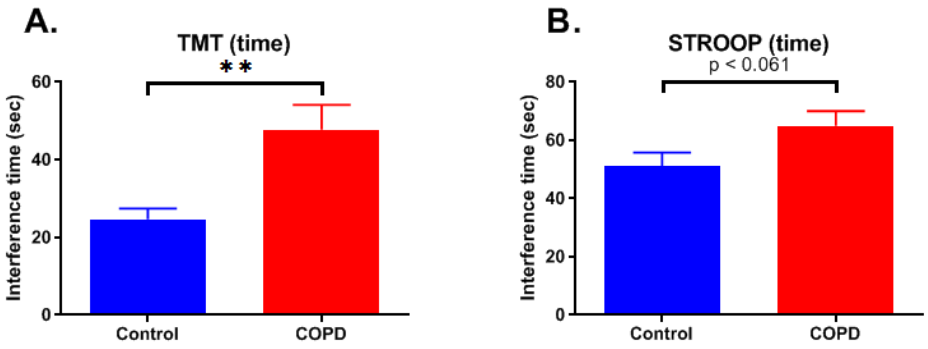


Figure 3: Cognitive function between the groups (A: TMT; B: Stroop).

In the CoP displacement, the COPD group had a significantly greater velocity than the Control group in AP and ML combined direction (**Figure 4 - A**, $p < 0.023$) and AP direction (**Figure 4 - B**, $p < 0.0081$). However, Sway area and Sway range did not show a difference between the groups (**Figure 4 - D, E, and F**).

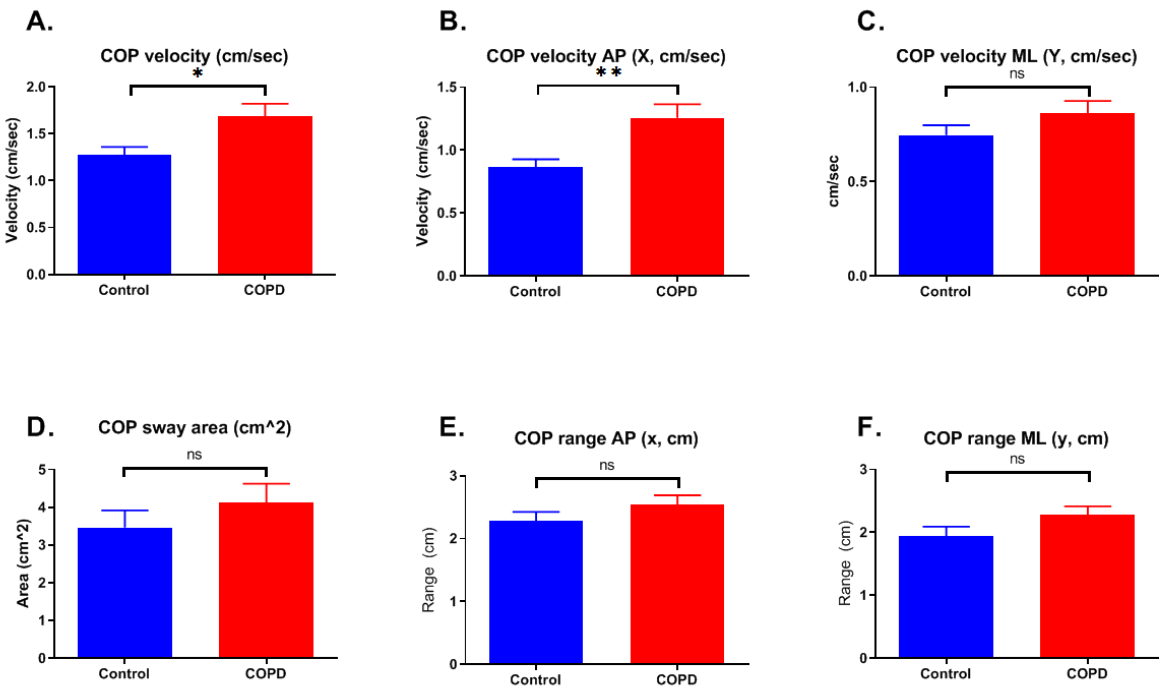


Figure 4: Postural balance function between the groups (A: Sway velocity of AP and ML combined direction; B: Velocity of AP direction; C: Velocity of ML direction, D: Sway area, 95% confidence interval; E: Sway range AP; F: Sway range ML).

In the Control and the COPD group, Pearson's correlation analysis was performed to identify association with postural balance function and other variables. Weight, age, systolic blood pressure, years of COPD related symptoms, and presence of oxygen therapy were positively correlated to AP sway velocity in the COPD group. Of the Charlson Comorbidity Index, the presence of diabetes was highly correlated with sway velocity ($r = 0.6635$, $p < 0.0001$) (**Table 4 and figure 5**). Also, in the variable of body composition, greater fat related variables (e.g., fat mass and fat percentage) were related to worse postural balance function. Interestingly, longer task time in the Stroop test was correlated to worse postural balance function ($r = 0.5927$, $p < 0.0002$).

Table 4: Correlation analysis between the AP sway velocity and other variables.

	Correlation	**Control**		**COPD**	
	AP sway velocity	**Pearson r**	**P value**	**Pearson r**	**P value**
Demog.	Weight	0.1071	0.6266	0.3725	**0.0300**
	Age	0.5977	**0.0026**	0.5089	**0.0021**
	Systolic BP	0.5555	**0.0059**	0.3945	**0.0209**
	COPD related symp. (yr.)			0.3787	**0.0298**
	Oxygen usage			0.3941	**0.0211**
CCI	CCI	0.0059	0.3138	0.6635	**<0.0001**
	Congestive heart failure			0.5241	**0.0015**
	Dia. w/o organ damage	-0.0050	0.9819	0.6361	**<0.0001**
	Dia. w/ organ damage			0.519	**0.0017**
Body comp.	Fat mass	0.1195	0.5869	0.3783	**0.0274**
	Fat mass extremities	0.0289	0.8958	0.4418	**0.0089**
	Fat percentage	-0.0077	0.9719	0.3563	**0.0386**
Cognitive	Stroop interference	0.7630	**<0.0001**	0.5927	**0.0002**
	Stroop part 3	0.6635	**0.0006**	0.4841	**0.0037**

Demog. = Demographics, CCI = Charlson Comorbidity Index, Dia. = diabetes, Comp. = composition

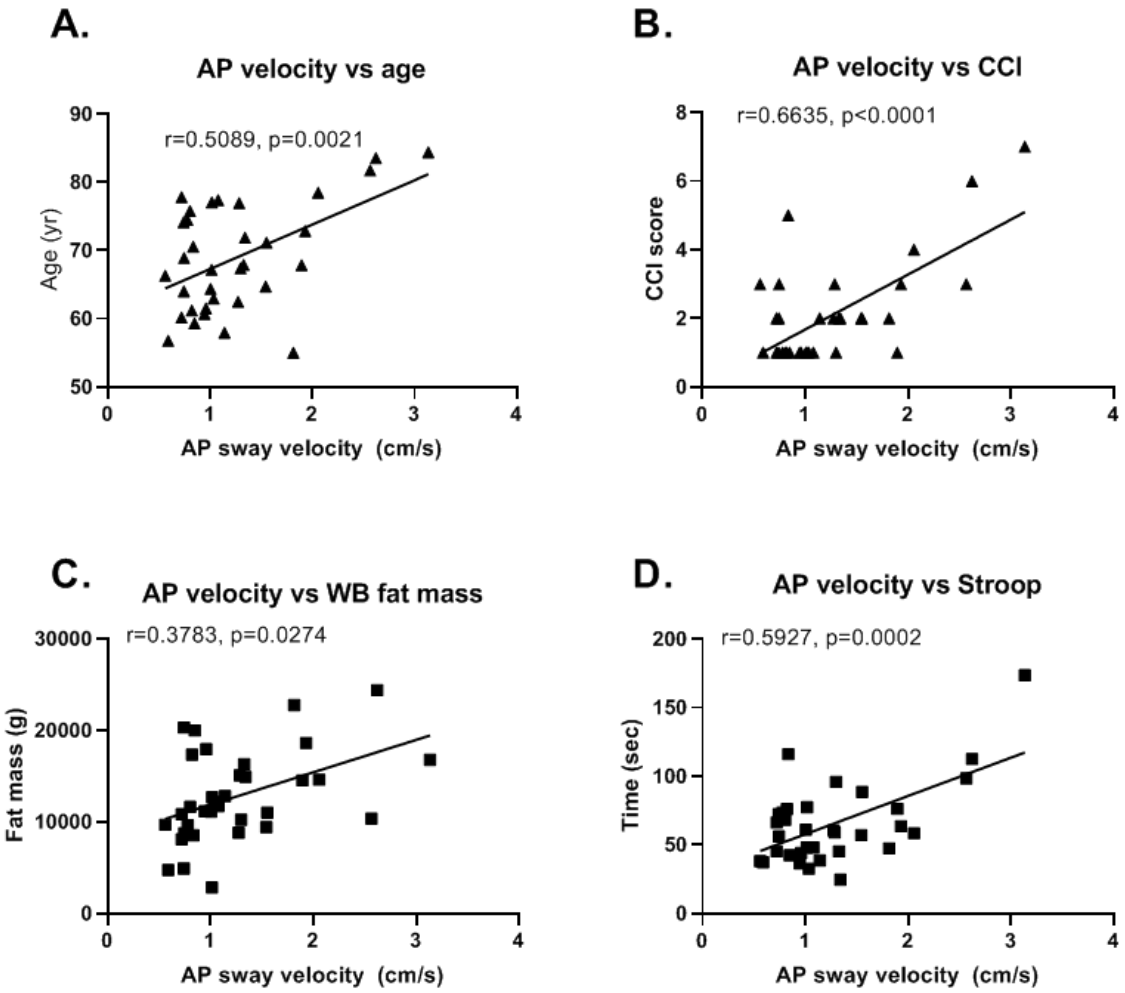


Figure 5: Correlation between AP velocity and variables in the COPD group.

In the Figure 6, cutoff analyses were done with the variable which was significantly correlated with AP sway velocity. This stratification figure, the presence of congestive heart failure ($p = 0.0015$), presence of any diabetes ($p < 0.0001$), COPD related symptoms more than 10 years ($p = 0.037$), usage of any oxygen therapy ($p = 0.021$), Charlson Comorbidity Index 2 or higher ($p = 0.009$), age over 75 years old ($p = 0.0143$), and over 130 seconds in Stroop subtask C ($p = 0.0163$) were identified for stratification on AP sway velocity (**Figure 6**).

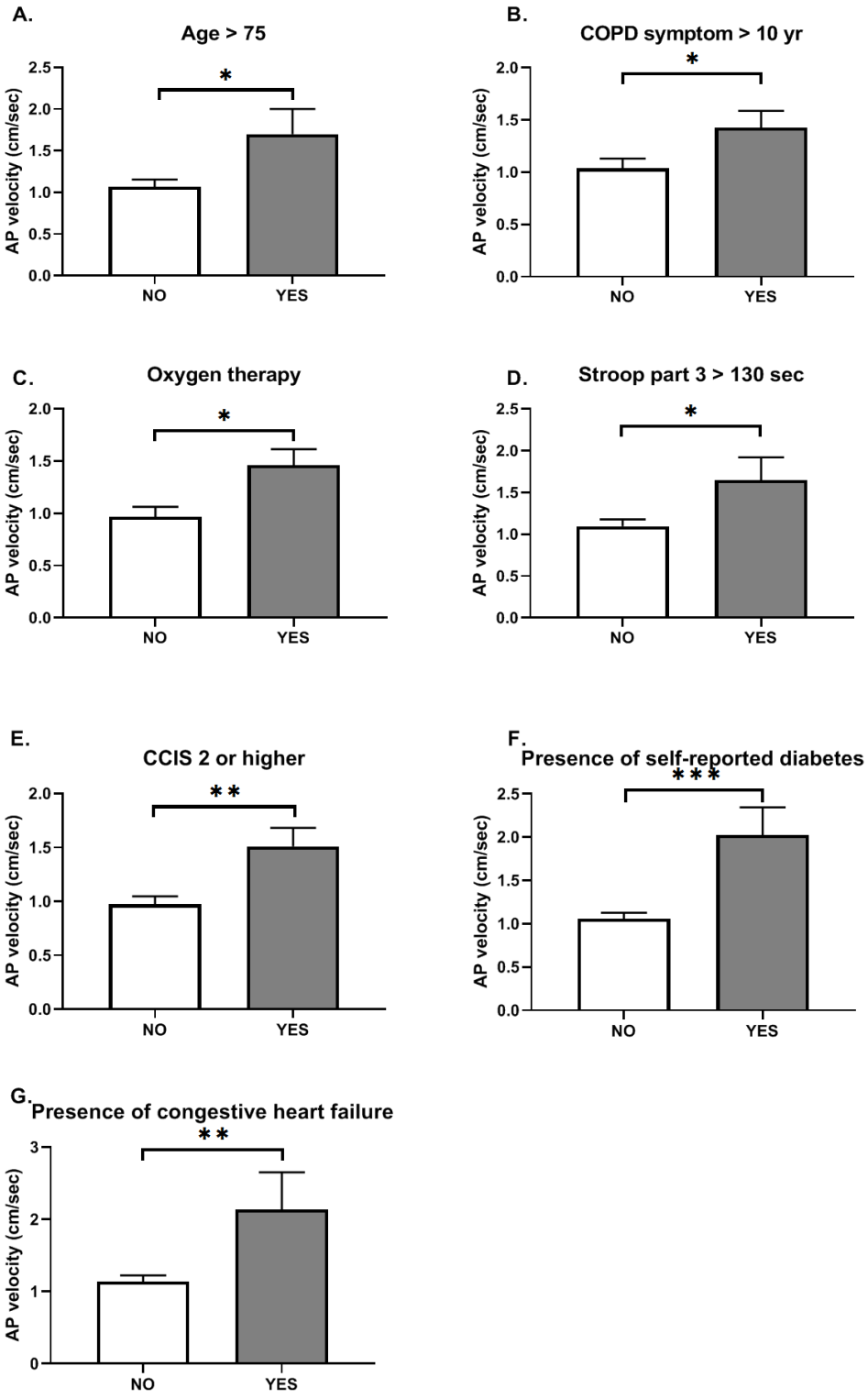


Figure 6: AP sway velocity stratifications by the variables.

4. DISCUSSION AND SUMMARY

Regarding impaired balance function in COPD, there is a need for identifying associated factors that could provide reliable detection for a potential risk of falls. In the present study, we used a postural balance function measurement which was impaired in the COPD group compared to the healthy group with the same age, gender, and BMI. We identified that velocity of CoP in AP direction is higher in the COPD group which is positively associated with CCI, fat-mass, and cognitive function.

4.1 Demographics

Despite no statistical difference found between the two groups according to age, gender, and BMI matching, the Control and COPD group showed a male-to-female ratio of 1.0 and 0.7, respectively. Expected factors that were possibly affected by the gender ratio are skeletal muscle function and body composition [72] [73]. According to our data, no gender difference on postural sway was found between the groups ($p=0.8799$). This finding is in contrast to other research [74].

4.2 Muscle functions and balance impairment in COPD

Our results indicated that balance function and skeletal muscle function is impaired in COPD patients. However, we could not find a relationship between skeletal muscle function and balance function, especially lower limb strength, and maximum handgrip strength. One possible explanation regarding the results of relationship is that protocol of muscle function measurement is not direct parameter for postural balance function. We used isokinetic extension and flexion of

the knee with a speed of 60 degrees/sec. This knee extension for maximal voluntary contraction represents recruitment of slow-twitch muscle fibers (type l) than fast-twitch fibers (type II) [75]. However, a knee is not only contributing factor in posture, but also combining ankle and hip strategy were reported previously [76]. Therefore, the muscle strength measurement that we used might not be able to explain the relationship between the muscle function and postural balance function.

4.3 Neurological function and balance impairment in COPD

We found that neurological function was lowered in COPD and also showed strong association between the greater postural sway velocity and cognitive dysfunction in COPD. Although, the COPD group showed lower cognitive function, both groups showed a similar degree of correlation between CoP AP velocity and Stroop time (Healthy vs. COPD, $p < 0.0001$ vs. $p = 0.0002$). Since the underlying mechanism of the Stroop test is not yet fully established, we can only assume possible explanations for the correlation between the postural impairment and a longer time in the Stroop test. One possible explanation is that COPD patients have a reduced attention due to exposure to chronic hypoxemia. The impaired attention might be contributed to a longer reaction time against a body sway because of latency of cognition. The other possible explanation is that impaired coordinating function in the posture is affected by dysfunction in sensory reception and integration that is caused by hypoxia related neuronal damage [77]. Furthermore, in a recent study, a structural change in the brain was reported among COPD subjects that might affect to sensory input and output processes [78].

4.4 Comorbidity, diabetes and balance impairment in COPD

Higher presence of diabetes in CCI and diabetes related risk factors were found in COPD. Also, strong correlations were found between greater sway velocity and CCI and diabetes related risk factors (fat mass, fat percentage, presence of CHF, and systolic BP). Therefore, we can assume that these factors might have contributed to the impairment in posture. Possible explanation is impairment in neurological pathway in diabetic patients, for example, diabetic neuropathy. Juster-Switlyk [79] reported that 50% of diabetic patient experience polyneuropathy during their lifetime which is supporting balance impairment in diabetic patients. Also, it is widely known that congestive heart failure (CHF) is common in diabetes patients. CHF was prevalent in over 11% of diabetic patients, and age, duration of disease, presence of hypertension, insulin usage were associated incidence of CHF [80]. These references are supporting our data showing that the presence of diabetes, the presence of congestive heart failure, and increased blood pressure are associated with postural balance impairment. Not only the comorbidity, but also the body composition showed a greater fat mass in the COPD group which is aligning to diabetic risk factor. Weight gain accompanied by an increased fat mass is commonly reported in diabetic patients [81]. However, we have a limited number of subject who has glucose concentration data which did not show meaningful correlation ($n = 17$, $p = 0.3927$). Analysis of HbA1c or serum leptin level will give us better understanding regarding correlation of diabetes [82].

4.5 Possible mechanisms of balance impairment in COPD

As we found in the sway velocity results, the greater postural velocity of the COPD group might be explained by: 1) a latency in sensory input of postural disturbance relating to three major system (vestibular, visual, somatosensory feedback)[83, 84] and/or 2) a higher number of posture adjustment [85] [86] with fine control of muscle which is relating to neuromuscular system. According to previous studies, Roig [87] reviewed articles to identify contributing factors on balance impairment and falls. Muscle weakness, gait deficit, nutritional depletion, impaired activities of daily living, and the number of medication were mentioned as risk factors for falls. However, the underlying mechanism for increased postural sway among the COPD subjects is still unknown. Possible mechanisms were found in other chronic diseases such as the cerebellar disorder [88] or somatosensory deficit [89]. For example, polyneuropathy with nerve conduction abnormalities showed a slower reaction time, worse static balance, and an increased number of falls [90] [91] [92]. Appenzeller et al suggested that long-lasting disturbance by COPD disease might lead to the breakdown of peripheral myelin [93]. Furthermore, the damage of myelin could be contributed to a reduced nerve conduction velocity [94]. This reduced nerve activity might contribute to a delayed response against perturbations. Also, polyneuropathy has shown to be related to a reduced single-leg stance, gait speed, lower limb muscle function, and an increased fall incidence. As we found a high association between sway velocity and oxygen usage and a presence of diabetes and fat mass and cognitive function in COPD, we suggest a systemic oxygen depletion and diabetes related factors as a risk factor in the balance impairment.

4.6 Limitations

Our research used the magnitude based postural sway as a balance function of the subjects that were calculated by the displacement of the center of pressure. However, a center of mass (CoM) is another key factor regarding human posture and balance [9, 95]. This motion of CoM is also closely related to the CoP [96, 97]. In general, the CoM can be detected by either a reaction board or a segmentation method [98]. Although we could not find a postural CoP difference between genders, the difference between genders was reported on relative height of the CoM [99]. Therefore, considering CoM with CoP together, this can provide more sensitive results [100, 101]. Furthermore, regarding estimating stability, CoM value can be calculated using the base of support that can be measured by distance of both feet and length of feet [101] and body weight [102]. To overcome these limitations of single method, CoP measurement by force plate, approaching with multiple methods would be needed.

4.7 Future research

Further research is necessary because approaching with multiple methods is needed to increase the sensitivity of detecting balance impairment instead of only using a CoP measurement. For example a motion capture system or accelerometer measurement can be applied to clearly characterize balance function in COPD. In this study, we found that there were various sub-characteristics of COPD in terms of comorbidities and/or related symptoms, oxygen therapy usage status, and etc. Therefore, it is necessary to increase the number of subjects to categorize/characterize subjects and analyze the purified data (e.g. COPD with Obstructive Sleep Apnea, COPD with diabetes, with or without oxygen therapy, and etc.) to better understand the underlying mechanism in the individual diseases. Regarding diabetic variable and cognitive

function assessment, it is also needed to collect a blood sample and analyze, such as serum leptin level, tryptophan and/or serotonin (5-HT) metabolism.

4.8 Summary

In summary, we have found general risk factors for postural balance impairment in COPD such as age, but we also identified COPD specific risk factors such as the use of oxygen, years of COPD related symptoms, comorbidities, and diabetes related factors. Future research is needed to clarify the given risk factor for postural balance impairment to prevent falls or improve a postural balance function in COPD patients.

REFERENCES

1. Czerwiński, E., et al., *Epidemiology, clinical significance, costs and fall prevention in elderly people.* Ortopedia, traumatologia, rehabilitacja, 2008. **10**(5): p. 419-428.

2. WHO. *Falls*. 2017 [cited 2018 16 January]; Available from: http://www.who.int/mediacentre/factsheets/fs344/en/.

3. Burns, E. and R. Kakara, *Deaths from falls among persons aged≥ 65 years—United States, 2007–2016.* Morbidity and Mortality Weekly Report, 2018. **67**(18): p. 509.

4. Paul, S., *Falls: Prevention and Management*, in *Geriatric Medicine: A Problem-Based Approach*, B.K.R. Nair, Editor. 2018, Springer Singapore: Singapore. p. 109-119.

5. Brown, A.P., *Reducing falls in elderly people: A review of exercise interventions.* Physiotherapy Theory and Practice, 1999. **15**(2): p. 59-68.

6. Robbins, A.S., et al., *Predictors of falls among elderly people: results of two population-based studies.* Archives of internal medicine, 1989. **149**(7): p. 1628-1633.

7. Rubenstein, L.Z., K.R. Josephson, and A.S. Robbins, *Falls in the nursing home.* Annals of internal medicine, 1994. **121**(6): p. 442-451.

8. Nevitt, M., *Falls in the elderly; risk factors and prevention.* Gait disorders of aging; falls and therapeutic strategies, 1997.

9. Horak, F.B., *Clinical assessment of balance disorders.* Gait & Posture, 1997. **6**(1): p. 76-84.

10. Ambrose, A.F., G. Paul, and J.M. Hausdorff, *Risk factors for falls among older adults: a review of the literature.* Maturitas, 2013. **75**(1): p. 51-61.

11. Agostini, J.V., L. Han, and M.E. Tinetti, *The relationship between number of medications and weight loss or impaired balance in older adults.* Journal of the American Geriatrics Society, 2004. **52**(10): p. 1719-1723.

12. Vogelmeier, C.F., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary.* American journal of respiratory and critical care medicine, 2017. **195**(5): p. 557-582.

13. Disease, G.I.f.C.O.L. *2019 GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD*. 2019 [cited 2019 3/3]; Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.

14. Kim, S., et al., *Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea scores: a cross-sectional analyses.* BMC pulmonary medicine, 2013. **13**(1): p. 35.

15. Mahler, D.A. and C.K. Wells, *Evaluation of clinical methods for rating dyspnea.* Chest, 1988. **93**(3): p. 580-586.

16. McDonough, J.E., et al., *Small-airway obstruction and emphysema in chronic obstructive pulmonary disease.* New England Journal of Medicine, 2011. **365**(17): p. 1567-1575.

17. Hasegawa, M., et al., *Airflow limitation and airway dimensions in chronic obstructive pulmonary disease.* American journal of respiratory and critical care medicine, 2006. **173**(12): p. 1309-1315.

18. Black, P.N., et al., *Changes in elastic fibres in the small airways and alveoli in COPD.* European Respiratory Journal, 2008. **31**(5): p. 998-1004.

19. Wouters, E.F., E.C. Creutzberg, and A.M. Schols, *Systemic effects in COPD.* Chest, 2002. **121**(5): p. 127S-130S.

20. Rutten, F.H., et al., *Heart failure and chronic obstructive pulmonary disease: an ignored combination?* European journal of heart failure, 2006. **8**(7): p. 706-711.

21. Sabit, R., et al., *Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease.* American journal of respiratory and critical care medicine, 2007. **175**(12): p. 1259-1265.

22. Haddad, F., et al., *Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle.* Circulation, 2008. **117**(11): p. 1436-1448.

23. Lehouck, A., et al., *COPD, bone metabolism, and osteoporosis.* Chest, 2011. **139**(3): p. 648-657.

24. Graat-Verboom, L., et al., *Current status of research on osteoporosis in COPD: a systematic review.* European Respiratory Journal, 2009. **34**(1): p. 209-218.

25. Silva, D.R., et al., *Osteoporosis prevalence and associated factors in patients with COPD: a cross-sectional study.* Respiratory care, 2011. **56**(7): p. 961-968.

26. Gosker, H.R., et al., *Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease.* The American journal of clinical nutrition, 2002. **76**(1): p. 113-119.

27. Engelen, M.P., et al., *Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease–.* The American journal of clinical nutrition, 2000. **71**(3): p. 733-738.

28. Roig, M., et al., *Falls in people with chronic obstructive pulmonary disease: an observational cohort study.* Respiratory medicine, 2011. **105**(3): p. 461-469.

29. Crişan, A.F., et al., *Balance impairment in patients with COPD.* PloS one, 2015. **10**(3): p. e0120573.

30. Cruz, J., et al., *Global functioning of COPD patients with and without functional balance impairment: an exploratory analysis based on the ICF framework.* COPD: Journal of Chronic Obstructive Pulmonary Disease, 2015. **12**(2): p. 207-216.

31. Iwakura, M., et al., *Relationship between balance and physical activity measured by an activity monitor in elderly COPD patients.* International journal of chronic obstructive pulmonary disease, 2016. **11**: p. 1505.

32. Blum, L. and N. Korner-Bitensky, *Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review.* Physical therapy, 2008. **88**(5): p. 559-566.

33. Dibble, L.E. and M. Lange, *Predicting falls in individuals with Parkinson disease: a reconsideration of clinical balance measures.* Journal of Neurologic Physical Therapy, 2006. **30**(2): p. 60-67.

34. Ebersbach, G., et al., *Scales in Parkinson's disease.* Journal of neurology, 2006. **253**(4): p. iv32-iv35.

35. Horak, F.B., D.M. Wrisley, and J. Frank, *The balance evaluation systems test (BESTest) to differentiate balance deficits.* Physical therapy, 2009. **89**(5): p. 484-498.

36. Paillex, R. and A. So, *Changes in the standing posture of stroke patients during rehabilitation.* Gait & posture, 2005. **21**(4): p. 403-409.

37. Rocchi, L., L. Chiari, and F. Horak, *Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease.* Journal of Neurology, Neurosurgery & Psychiatry, 2002. **73**(3): p. 267-274.

38. Frenklach, A., et al., *Excessive postural sway and the risk of falls at different stages of Parkinson's disease.* Movement Disorders, 2009. **24**(3): p. 377-385.

39. Vestbo, J., et al., *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary.* American journal of respiratory and critical care medicine, 2013. **187**(4): p. 347-365.

40. Chinappen-Horsley, U., et al., *A method for determining skeletal lengths from DXA images.* BMC musculoskeletal disorders, 2007. **8**(1): p. 113.

41. Lukaski, H.C., *Estimation of muscle mass.* Human body composition, 1996: p. 109-128.

42. Hankinson, J.L., J.R. Odencrantz, and K.B. Fedan, *Spirometric reference values from a sample of the general U.S. population.* Am J Respir Crit Care Med, 1999. **159**(1): p. 179-87.

43. Karpman, C. and R. Benzo, *Gait speed as a measure of functional status in COPD patients.* International journal of chronic obstructive pulmonary disease, 2014. **9**: p. 1315.

44. Kon, S.S., et al., *Reliability and validity of the four metre gait speed in COPD.* European Respiratory Journal, 2012: p. erj01627-2012.

45. Berg, K., et al., *Measuring balance in the elderly: preliminary development of an instrument.* Physiotherapy Canada, 1989. **41**(6): p. 304-311.

46. Berg, K.O., et al., *Measuring balance in the elderly: validation of an instrument.* Canadian journal of public health= Revue canadienne de sante publique, 1992. **83**: p. S7-11.

47. Harada, N., et al., *Screening for balance and mobility impairment in elderly individuals living in residential care facilities.* Physical therapy, 1995. **75**(6): p. 462-469.

48. Stevenson, T.J. and S.J. Garland, *Standing balance during internally produced perturbations in subjects with hemiplegia: validation of the balance scale.* Archives of physical medicine and rehabilitation, 1996. **77**(7): p. 656-662.

49. Shumway-Cook, A., et al., *Predicting the probability for falls in community-dwelling older adults.* Physical therapy, 1997. **77**(8): p. 812-819.

50. Winter, D.A., *Human balance and posture control during standing and walking.* Gait & Posture, 1995. **3**(4): p. 193-214.

51. Mochizuki, L., et al., *Changes in postural sway and its fractions in conditions of postural instability.* Journal of Applied Biomechanics, 2006. **22**(1): p. 51-60.

52. Prieto, T.E., et al., *Measures of postural steadiness: differences between healthy young and elderly adults.* IEEE Transactions on biomedical engineering, 1996. **43**(9): p. 956-966.

53. Schubert, P. and M. Kirchner, *Ellipse area calculations and their applicability in posturography.* Gait Posture, 2014. **39**(1): p. 518-22.

54. Panjan, A. and N. Sarabon, *Review of methods for the evaluation of human body balance.* Sport Science Review, 2010. **19**(5-6): p. 131-163.

55. Lezak, M.D., et al., *Neuropsychological assessment*. 2004: Oxford University Press, USA.

56. Stroop, J.R., *Studies of interference in serial verbal reactions.* Journal of experimental psychology, 1935. **18**(6): p. 643.

57. Golden, C.J. and S.M. Freshwater, *Stroop color and word test.* 1978.

58. Lamers, M.J., A. Roelofs, and I.M. Rabeling-Keus, *Selective attention and response set in the Stroop task.* Memory & Cognition, 2010. **38**(7): p. 893-904.

59. Logan, G.D., *Attention and automaticity in Stroop and priming tasks: Theory and data.* Cognitive psychology, 1980. **12**(4): p. 523-553.

60. Siegrist, M., *Test-retest reliability of different versions of the Stroop test.* The Journal of Psychology, 1997. **131**(3): p. 299-306.

61. Van der Elst, W., et al., *The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range.* Assessment, 2006. **13**(1): p. 62-79.

62. Valentijn, S.A., et al., *Change in sensory functioning predicts change in cognitive functioning: Results from a 6-year follow-up in the Maastricht Aging Study.* Journal of the American Geriatrics Society, 2005. **53**(3): p. 374-380.

63. Washburn, R.A., et al., *The Physical Activity Scale for the Elderly (PASE): development and evaluation.* Journal of clinical epidemiology, 1993. **46**(2): p. 153-162.

64. Jones, P., et al., *Development and first validation of the COPD Assessment Test.* European Respiratory Journal, 2009. **34**(3): p. 648-654.

65. Charlson, M., et al., *Validation of a combined comorbidity index.* Journal of clinical epidemiology, 1994. **47**(11): p. 1245-1251.

66. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* Journal of chronic diseases, 1987. **40**(5): p. 373-383.

67. Chaudhry, S., L. Jin, and D. Meltzer, *Use of a self-report-generated Charlson Comorbidity Index for predicting mortality.* Medical care, 2005: p. 607-615.

68. Nagano, A., et al., *Influence of vision and static stretch of the calf muscles on postural sway during quiet standing.* Human movement science, 2006. **25**(3): p. 422-434.

69. Scoppa, F., et al., *Clinical stabilometry standardization: basic definitions--acquisition interval--sampling frequency.* Gait & Posture, 2013. **37**(2): p. 290-292.

70. Wollseifen, T., *Different methods of calculating body sway area.* Pharmaceutical Programming, 2011. **4**(1-2): p. 91-106.

71. Apthorp, D., F. Nagle, and S. Palmisano, *Chaos in balance: Non-linear measures of postural control predict individual variations in visual illusions of motion.* PloS one, 2014. **9**(12): p. e113897.

72. Gallagher, D., et al., *Appendicular skeletal muscle mass: effects of age, gender, and ethnicity.* Journal of applied physiology, 1997. **83**(1): p. 229-239.

73. Lindle, R., et al., *Age and gender comparisons of muscle strength in 654 women and men aged 20–93 yr.* Journal of applied physiology, 1997. **83**(5): p. 1581-1587.

74. Faraldo-García, A., et al., *Influence of age and gender in the sensory analysis of balance control.* European Archives of Oto-Rhino-Laryngology, 2012. **269**(2): p. 673-677.

75. Froese, E.A. and M.E. Houston, *Torque-velocity characteristics and muscle fiber type in human vastus lateralis.* Journal of Applied Physiology, 1985. **59**(2): p. 309-314.

76. Kuo, A.D. and F.E. Zajac, *A biomechanical analysis of muscle strength as a limiting factor in standing posture.* Journal of Biomechanics, 1993. **26**: p. 137-150.

77. Dodd, J., S. Getov, and P.W. Jones, *Cognitive function in COPD.* European Respiratory Journal, 2010. **35**(4): p. 913-922.

78. Esser, R.W., et al., *Structural brain changes in patients with COPD.* Chest, 2016. **149**(2): p. 426-434.

79. Juster-Switlyk, K. and A.G. Smith, *Updates in diabetic peripheral neuropathy.* F1000Research, 2016. **5**: p. F1000 Faculty Rev-738.

80. Nichols, G.A., et al., *Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors.* Diabetes care, 2001. **24**(9): p. 1614-1619.

81. Chan, J.M., et al., *Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men.* Diabetes care, 1994. **17**(9): p. 961-969.

82. Fischer, S., et al., *Insulin-resistant patients with type 2 diabetes mellitus have higher serum leptin levels independently of body fat mass.* Acta diabetologica, 2002. **39**(3): p. 105-110.

83. Lord, S.R., H.B. Menz, and A. Tiedemann, *A physiological profile approach to falls risk assessment and prevention.* Physical therapy, 2003. **83**(3): p. 237-252.

84. Carter, N.D., P. Kannus, and K. Khan, *Exercise in the prevention of falls in older people.* Sports medicine, 2001. **31**(6): p. 427-438.

85. Santos, M.J., N. Kanekar, and A.S. Aruin, *The role of anticipatory postural adjustments in compensatory control of posture: 1. Electromyographic analysis.* Journal of Electromyography and Kinesiology, 2010. **20**(3): p. 388-397.

86. Massion, J., *Movement, posture and equilibrium: interaction and coordination.* Progress in neurobiology, 1992. **38**(1): p. 35-56.

87. Roig, M., et al., *Falls in patients with chronic obstructive pulmonary disease: a call for further research.* Respiratory medicine, 2009. **103**(9): p. 1257-1269.

88. Bronstein, A.M. and M. Pavlou, *Balance*, in *Handbook of clinical neurology*. 2013, Elsevier. p. 189-208.

89. Simmons, R.W., C. Richardson, and R. Pozos, *Postural stability of diabetic patients with and without cutaneous sensory deficit in the foot.* Diabetes research and clinical practice, 1997. **36**(3): p. 153-160.

90. Courtemanche, R., et al., *Gait problems in diabetic neuropathic patients.* Archives of physical medicine and rehabilitation, 1996. **77**(9): p. 849-855.

91. Palma, F.H., et al., *Static balance in patients presenting diabetes mellitus type 2 with and without diabetic polyneuropathy.* Arquivos Brasileiros de Endocrinologia & Metabologia, 2013. **57**(9): p. 722-726.

92. Kimura, J., T. Yamada, and N.P. Stevland, *Distal slowing of motor nerve conduction velocity in diabetic polyneuropathy.* Journal of the neurological sciences, 1979. **42**(2): p. 291-302.

93. Appenzeller, O., R.D. Parks, and J. MacGee, *Peripheral neuropathy in chronic disease of the respiratory tract.* The American journal of medicine, 1968. **44**(6): p. 873-880.

94. Waxman, S.G., *Determinants of conduction velocity in myelinated nerve fibers.* Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 1980. **3**(2): p. 141-150.

95. Schepers, H.M., et al., *Ambulatory estimation of center of mass displacement during walking.* IEEE Transactions on Biomedical Engineering, 2009. **56**(4): p. 1189-1195.

96. González, A., M. Hayashibe, and P. Fraisse. *Estimation of the Center of Mass with Kinect and Wii balance board*. in *2012 IEEE/RSJ International Conference on Intelligent Robots and Systems*. 2012. IEEE.

97. Morasso, P.G., G. Spada, and R. Capra, *Computing the COM from the COP in postural sway movements.* Human Movement Science, 1999. **18**(6): p. 759-767.

98. Clauser, C.E., J.T. McConville, and J.W. Young, *Weight, volume, and center of mass of segments of the human body*. 1969, Antioch Coll Yellow Springs OH.

99. Pawlowski, B. and M. Grabarczyk, *Center of body mass and the evolution of female body shape.* Am J Hum Biol, 2003. **15**(2): p. 144-50.

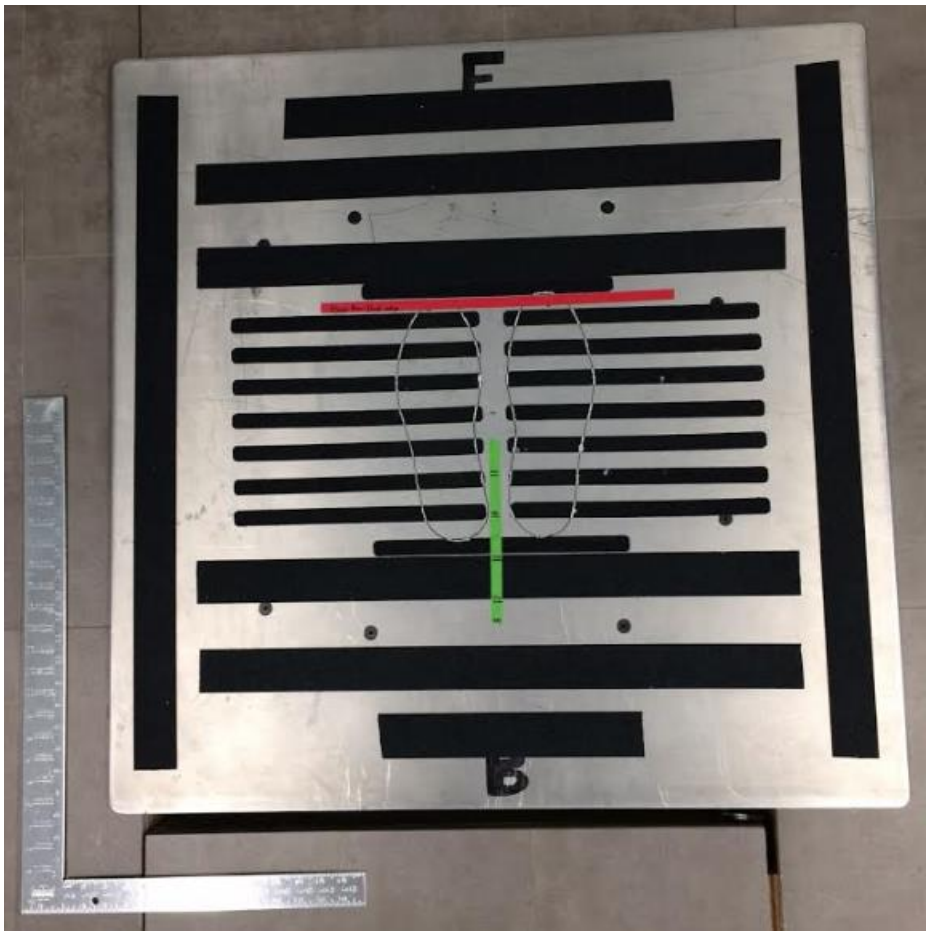
100. Corriveau, H., et al., *Evaluation of postural stability in elderly with diabetic neuropathy.* Diabetes care, 2000. **23**(8): p. 1187-1191.

101. B³aszczyk, J.W., *Sway ratio a new measure for quantifying postural stability.* Acta Neurobiol Exp, 2008. **68**: p. 51-57.

102. Hue, O., et al., *Body weight is a strong predictor of postural stability.* Gait & posture, 2007. **26**(1): p. 32-38.

APPENDIX A

THE PICTURE OF FORCE PLATE



APPENDIX B

THE MEASUREMENT OF POSUTRAL SWAY DURING QS