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Increased risk of atrial fibrillation in patients with acute exacerbation of chronic obstructive pulmonary disease and sinus rhythm

Dissertation

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Für meine Eltern

Zusammenfassung

Vorhofflimmern ist bekannt als eine relevante Komorbidität in Patienten mit chronisch obstruktiver Lungenerkrankung (COPD). Die Auswertung der Gesamtvorhofleitungszeit mittels Gewebe Doppler (PA-TDI Intervall) kann benutzt werden, um das Risiko von neuem Vorhofflimmern (VHF) in Patienten zu stratifizieren. Ein verlängertes PA-TDI Intervall ist mit einem erhöhten Risiko für VHF verbunden. Unsere Hypothese war, dass das PA-TDI Intervall länger bei Patienten mit akut- exazerbierter COPD (AECOPD) als bei Patienten mit stabiler COPD ausfallen würde. Zudem haben wir auch das autonome Nervensystem in Patienten mit stabiler und AECOPD untersucht. Unsere Annahme war, dass Patienten mit AECOPD einen höheren Grad der autonomen Dysfunktion aufweisen würden und daher ein höheres Risiko für VHF hätten. Für diesen Zweck haben wir 32 Patienten rekrutiert, 16 mit stabiler COPD und 16 mit AECOPD. Alle Patienten erhielten eine Lungenfunktionstestung, Blutgasanalyse, laborchemische Untersuchung des Blutes, eine Echokardiographie mit Messung des PA-TDI Intervall und eine autonome Funktionstestung. Die verschiedenen Variablen der autonomen Funktionstestung waren die Baroreflex Sensibilität, Chemoreflex Sensibilität, Kälteapplikation im Gesicht sowie an der Hand, Herzfrequenzvariabilität und der Ewing Test. Unsere Ergebnisse zeigten, dass Patienten mit AECOPD ein signifikant längeres PA-TDI Intervall aufwiesen als Patienten mit stabiler COPD. Das Alter der Patienten, der Body-Mass-Index sowie die Fläche des linken Vorhofs korrelierten positiv mit der Länge des PA-TDI Intervalls. Eine Korrelation zwischen des prozentualen Messwertes zum Sollwert des forcierten exspiratorischen Volumen der ersten Sekunde, dem Residualvolumen, dem Sauerstoffpartialdruck, dem Kohlendioxidpartialdruck, NT-proBNP und dem PA-TDI konnte nicht gefunden werden. Es zeigte sich auch ein verlängertes korrigiertes QT-Intervall in Patienten mit AECOPD. Ein verlängertes QTc Intervall kann Ausdruck von elektrophysiologischen Alterationen sein und wird unter anderem bei Patienten mit Vorhofflimmern beschrieben. Die Ergebnisse der autonomen Testung zeigten keine statistisch signifikanten Unterschiede unter den Variablen der autonomen Funktionstestung zwischen Patienten mit stabiler COPD und AECOPD. Es zeigte sich lediglich eine Tendenz für eine verringerte Baroreflex Sensibilität und Chemoreflex Sensibilität in Patienten mit AECOPD. Daraus kann man schließen, dass Patienten mit AECOPD eine Tendenz für eine verringerte parasympathische Aktivität haben. In Zusammenschau der Ergebnisse konnten wir zeigen, dass Patienten mit AECOPD ein höheres Risiko für Vorhofflimmern als Patienten mit stabiler COPD aufwiesen, weil Patienten mit AECOPD ein längeres PA-TDI Intervall hatten. Ein erhöhtes Alter der Patienten, der Body-Mass-Index sowie die Fläche des linken Vorhofs korrelierten positiv mit der Länge des PA-TDI Intervalls. Der Grad der autonomen Dysfunktion zwischen Patienten mit AECOPD und stabiler COPD war vergleichbar, jedoch zeigte sich eine Tendenz für weniger parasympathische Aktivität in Patienten mit AECOPD.

Summary

Atrial fibrillation has been suggested as a relevant comorbidity in patients with chronic obstructive pulmonary disease (COPD). The assessment of the total atrial conduction time via tissue Doppler imaging (PA-TDI interval) can be used to find patients with an increased risk of new onset atrial fibrillation. A prolonged PA-TDI interval is associated with an increased risk of atrial fibrillation. We hypothesized that the PA-TDI interval is more increased in acute exacerbation of COPD (AECOPD) when compared with stable COPD. Our secondary objective was to assess the autonomic nervous system in patients with stable COPD and AECOPD. Our assumption was that patients with AECOPD had a higher degree of autonomic dysfunction and therefore longer PA-TDI interval and greater risk of new onset atrial fibrillation. For this purpose, we recruited 32 patients, 16 with stable COPD and another 16 with AECOPD. All patients underwent a lung function test, blood gas analysis, laboratory tests, electrocardiogram (ECG), echocardiography including measurement of the PA-TDI interval and autonomic function test. The variables of the autonomic nervous system included the baroreflex sensitivity, deep breathing test, chemoreflex sensitivity, cold pressure test, cold face test, heart rate variability and the Ewing test. Our results showed that patients with AECOPD had a significant longer PA-TDI interval than patients with stable COPD. A higher age, a higher body mass index (BMI) and a greater left atrial area positively correlated with a longer PA-TDI interval. No correlation was found between FEV1 (percentage of the predicted forced expiratory volume in one second), residual volume, partial pressure of carbon dioxide (pO2), partial pressure of carbon dioxide (pCO2), NT-proBNP and the PA-TDI interval. It was also shown that patients with AECOPD had a prolonged corrected QT-interval (QTc) as opposed to patients with stable COPD. A prolonged QTc can be interpreted as an electrophysiological alteration, which is often described in patients with atrial fibrillation. Results from the autonomic function tests did not reveal a statistically significant difference among the various variables of the autonomic nervous system between patients with stable COPD and AECOPD. However, we did see a tendency for a decreased baroreflex sensitivity and chemoreflex sensitivity in patients with AECOPD and thus a tendency for decreased parasympathetic activity. In conclusion, we demonstrated that patients with AECOPD had an increased PA-TDI interval which has been noted to increase the risk of atrial fibrillation. A higher age, a higher BMI and a greater left atrial area positively correlated with the PA-TDI interval. The degree of autonomic dysfunction in patients with AECOPD and stable COPD was similar though there was a tendency for less parasympathetic activity in patients with AECOPD.

Abbreviations

ACI	acceleration index
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ARIC	atherosclerosis risk in communities
BE	base excess
BMI	body mass index
BPdia(T0)	diastolic blood pressure before the cold pressure test/cold face test
BPdia45s	diastolic blood pressure whilst the hand was emerged in ice water for 45 seconds/ diastolic blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds
BPdia-Diff	difference between BPdia(T0) and BPdia45s
BPm(T0)	mean blood pressure before the cold pressure test/cold face test
BPm45s	mean blood pressure whilst the hand was emerged in ice water for 45 seconds/ mean blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds
BPm-Diff	difference between BPm(T0) and BPm45s
BPsys(T0)	systolic blood pressure before the cold pressure test/cold face test
BPsys45s	systolic blood pressure whilst the hand was emerged in ice water for 45 seconds/ systolic blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds
BPsys-Diff	difference between BPsys(T0) and BPsys45s
BRS	baroreflex sensitivity
CAT	chronic obstructive pulmonary disease assessment test
CI	cardiac index
CPAP	continuous positive airway pressure
CO	cardiac output

COPD	chronic obstructive pulmonary disease
dBP	diastolic blood pressure
DECAF score	The Dyspnea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation score
DLCO-SB	single-breath diffusing capacity for carbon monoxide
DLCO-VA	diffusing capacity for carbon monoxide corrected for alveolar volume
E	expiration
ECG	electrocardiogram
EDI	end diastolic index
EHRA	European Heart Rhythm Association
FEV1	percentage of the predicted forced expiratory volume in one second
FVC	forced vital capacity
HF0	heart rate before the cold pressure test/ cold face test
HF 45 sec	heart rate whilst the hand is emerged in ice water for 45 seconds/ heart rate before the cold face test, HF 45 sec=heart rate whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds
HF	high frequency
HR	heart rate
HRV	heart rate variability
I	Inspiration
IC	contractility index
LF	low frequency
LVET	left ventricular ejection time
LVWI	left ventricular work index
LTOT	long term oxygen therapy
mBP	mean blood pressure
MESA	Multi-Ethnic Study of Atherosclerosis

mMRC	modified medical research council dyspnoea scale
NIV	non-invasive ventilation
pCO2	partial pressure of carbon dioxide
pO2	partial pressure of oxygen
NT-proBNP	N- terminal pro hormone B-type natriuretic peptide
QTc	corrected QT interval
RMSSD	the root mean square of successive differences between normal heartbeats
RRI	RR interval
RV	residual volume
sBP	systolic blood pressure
SCD	sudden cardiac death
SDNN	the standard deviation of the normal to normal sinus-initiated interbeat interval
SDNN index	the mean of the standard deviations of all the NN intervals for each 5-minute segment
SI	stroke index
SO2	oxygen saturation
SV	stroke volume
TAPSE	tricuspid annular plane systolic excursion
TACT	total atrial conduction time
TDI	tissue Doppler imaging
TFC	total chest fluid content
TPR/ TPRI	total peripheral resistance
VC	vital capacity
VHF	Vorhofflimmern
VLF	very low frequency

Contents

1 Introduction

COPD is a pulmonary disease which is characterized by progressive obstruction and poor airflow. The term COPD came first into existence in the year 1965 (Pretty, 2006). An acute exacerbation of COPD is a sudden worsening of COPD symptoms such as shortness of breath or cough. These symptoms last typically for a few days. Moreover, COPD is known as a systemic disease which negatively influences the autonomic and cardiovascular nervous system. The autonomic nervous system is characterized as subgroup of the peripheral nervous system that innervates smooth muscle and glands and therefore affects the function of internal organs. This function of internal organs includes respiratory rate, heart rate, digestion, pupillary response, urination and sexual arousal (LeBouef & Whited, 2019). The negative impact of COPD on the autonomic nervous system may cause autonomic dysfunction, where the pathways of autonomic nervous system do not work adequately. The degree of autonomic dysfunction that is caused by COPD remains to be elucidated. Hypoxemia, hypercapnia, increased intrathoracic pressure swings due to airway obstruction, increased respiratory effort and systemic inflammation are hypothesized to be potential pathways in which COPD may cause autonomic dysfunction (van Gestel & Steier, 2010).

Likewise, atrial fibrillation has been suggested as a relevant cardiac comorbidity in patients with chronic obstructive pulmonary disease (COPD). Atrial fibrillation is a type of heart rhythm disorder which is characterized by irregular und rapid beating of the atria. It was first described in the year 1874 by Edme Felix Alfred Vulpian in dog hearts (Schweizer & Keller, 2002). It is thought that cardiac autonomic dysfunction frequently antecedes the onset of atrial fibrillation. Such autonomic dysfunction could be due to abnormal function at a chronotropic, bathmotropic, dromotropic, isotropic or lusitropic level. The purpose of this thesis is to examine a possible link between COPD and atrial fibrillation via autonomic dysfunction.

1.1 Definition of COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD Guideline, 2019) defines COPD the following way:” COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (GOLD Guideline, 2019). The respiratory symptoms include chronic and progressive dyspnoea, cough and sputum production (GOLD Guideline, 2019; Kessler et al., 2011). These symptoms may vary between days. Upon exertion, patients with COPD may complain about chest tightness. On auscultation of the lung fields widespread inspiratory and expiratory wheezing may present.

1.2 Epidemiology of COPD

COPD is regarded as a leading cause of morbidity and mortality worldwide (GOLD Guideline, 2019). COPD as disease is often a tremendous economic and social burden (Lozano et al., 2012). Prevalence of COPD correlates to the prevalence of tobacco smoking though in many countries occupational and indoor air pollution such as burning of wood or biomass fuel also contribute to COPD (Orozco-Levi et al., 2006). In the coming years the prevalence and burden of COPD will increase due to greater exposure of people to risk factors such as smoking that contribute to COPD and an aging world population (Lopez et al., 2006). Studies carried out in 28 countries between 1990 and 2004 showed that the prevalence of COPD is greater in smokers and ex-smokers as opposed to non-smokers, in those ≥ 40 years of age as opposed to those < 40 years, and in men as opposed to women (Halbert et al., 2006). The burden of obstructive lung diseases is assessed by a standardized methodology of questionnaires as well as pre- and post-bronchodilator spirometry in 29 countries in people aged 40 and over (BOLD, 2019). Based on this data, it is suggested that 384 million people suffered from COPD in the year 2010 (Adeloye et al., 2015) and that three million people die from COPD around the globe (GBD, 2015). People with COPD also suffer from comorbidities, even at an early age (Divo et al. 2018, GOLD Guideline, 2019). Such comorbidities include cardiovascular disease, musculoskeletal impairment, diabetes mellitus and others (Chen et al., 2015). These chronic comorbidities in people suffering from COPD further worsens their health status and elevates the cost of managing COPD patients (Maninno et al., 2015).

1.3 Pathophysiology of COPD

The airflow limitation is the result of structural changes caused by chronic inflammation in the lung which is often associated with chronic irritants such as cigarette smoke (Barnes, 2016; Ofir et al., 2008). The exact mechanism of this kind of chronic inflammation has not been fully elucidated. The structural changes induced by chronic inflammation are brought in by small airway disease such as obstructive bronchiolitis and parenchymal destruction like emphysema. Likewise, such structural changes can cause gas exchange abnormalities resulting in hypoxemia and hypercapnia. This abnormality can be explained by increased dead space ventilation and reduced ventilatory drive (Elbehairy et al., 2015). Moreover, airflow limitation leads to a hyperinflating lung causing exertional dyspnoea (Ofir et al., 2008). A further result of these structural changes is the loss of alveolar attachment to the small airways leading to a decreased ability of airways to stay open during expiration and subsequent air trapping as well as mucociliary dysfunction. Mucociliary dysfunction can cause a chronic productive cough. Chronic airway irritation leads to enlarged submucosal glands and thus this exemplifies the effect of mucus hypersecretion and thus chronic productive cough. Additionally, during the late

course of COPD, patients may develop pulmonary hypertension. This is mainly caused by hypoxic vasocontriction of the pulmonary arteries (Sakao et al., 2014). Respiratory infections with bacteria or viruses, unknown factors or environmental pollutants are associated with increased inflammation in patients with COPD. This can cause an acute exacerbation of COPD (AECOPD) and therefore an exacerbation of the respiratory symptoms. As a result, patients often complain about a sudden increase in dyspnoea as AECOPD is associated with increased hyperinflation, gas trapping and reduced expiratory flow (Parker et al., 2005).

1.4 Diagnosis of COPD

The airflow limitation is measured by spirometry as it is the most widely available non-invasive method to evaluate lung function. In the spirometry the total amount of air is exhaled from the point of maximal inspiration which is defined as forced vital capacity (FVC). The amount of air exhaled in the first second is termed as the FEV1. COPD is associated with a reduction in the FEV1 and the ratio FEV1/FVC (Hogg et al., 2004). A fixed ratio of FEV1/FVC<0.7 is expected for the presence of airflow limitation after treatment with bronchodilators. The severity of airflow limitation is classed according to spirometric cut-points based on post-bronchodilator FEV1 whilst the letters (groups A to D) reflects symptom burden and risk of exacerbation as shown in the table below (Table 1 & Figure 1). Both classifications are important in optimizing therapy. The symptom burden can be classified by the Modified British Medical Research Council (mMRC) questionnaire or by the COPD assessment test (CAT) (Table 2 & Table 3).

GOLD 1	Mild	FEV1≥80% predicted
GOLD 2	Moderate	50%≤FEV1<80% predicted
GOLD 3	Severe	30%≤FEV1<50% predicted
GOLD 4	Very severe	FEV1<30% predicted

Table 1: ***Severity of airflow limitation in COPD.*** *COPD is grouped into spirometric cut-off points based on post-bronchodilator FEV1. FEV1= percentage of the predicted forced expiratory volume in one second (Table taken from COPD GOLD guideline 2019 with permission)*

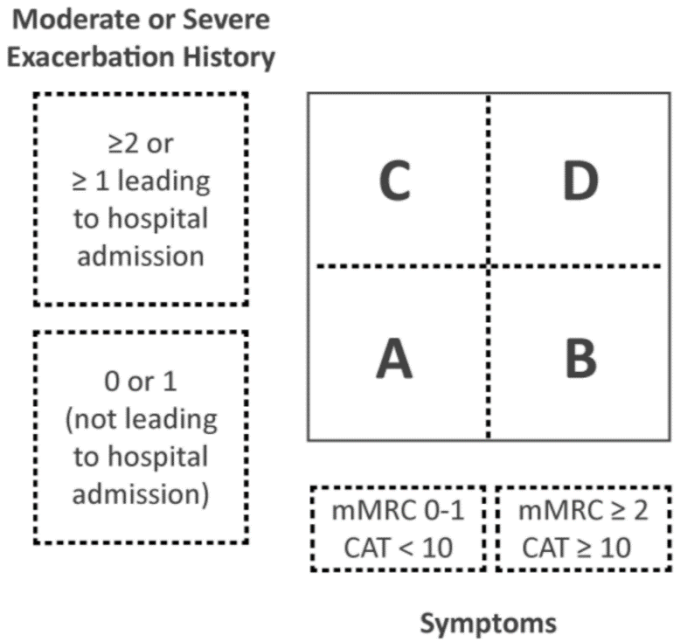

Figure 1: ***Assessment of symptom/risk of exacerbations.*** *The letters (groups A to D) reflects symptom burden and risk of exacerbation. The grouping is done according to the number of hospital admissions due to exacerbations, the mMRC as well as the CAT assessment. CAT= COPD assessment test, mMRC= modified medical research council dyspnoea scale (Table taken from COPD GOLD guideline 2019 with permission)*

Dyspnea only with strenuous exercise	0
Dyspnea when hurrying or walking up a slight hill	+1
Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace	+2
Stops for breath after walking 100 meters or after a few minutes	+3
Too dyspneic to leave house or breathless when dressing	+4

Table 2: ***Modified MRC dyspnoe scale.*** *The questionnaire is used to assess symptom burden in patients with COPD. (Table taken from COPD GOLD guideline 2019 with permission)*

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	☐
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	☐
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	☐
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	☐
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	☐
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	☐
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	☐
I have lots of energy	0 1 2 3 4 5	I have no energy at all	☐
		SCORE	☐☐

*Table 3: **The CAT Assessment**. The questionnaire is based on a scoring ranging from 0-40 to quantify the symptoms in patients with COPD. (Table taken from Jones et al., 2009 with permission)*

1.5 Management of COPD

So far, no cure for COPD has been known. The primary management of COPD is aimed at treating symptoms. For this purpose, inhaled bronchodilators are used. These are classed into beta-agonists and anticholinergics (Kew et al., 2014). Both aim at reducing or preventing symptoms such as dyspnoea, wheezing or cough resulting in a better quality of life (Liesker et al., 2002). The way bronchodilators work is by increasing airway smooth muscle tone. This results in an improvement of expiratory flow and thus increase in the FEV1. Also, inhaled corticosteroids may be used (Decramer et al., 2012). The administration of oral glucocorticoids has a system anti-inflammatory effect which plays an important role in treating patients with AECOPD whilst chronic administration of oral glucocorticoids has no role in stable COPD due to the high rate of systemic complications (Renkema et al., 1996; Rice et al., 2000). Reduction

of mortality in patients with COPD can be achieved by smoking cessation and the long-term administration of oxygen (Cranston et al., 2005; van Eerd et al., 2016). Other measures are vaccination such as influenza or pneumococcal vaccination (Walters et al., 2017; Wongsurakiat et al., 2004).

1.6 COPD and cardiac arrhythmias

The prognosis of COPD is often affected by other diseases or comorbidities (Barnes & Celli, 2009). Cardiovascular diseases play an important role as comorbidity in COPD (Soriano et al., 2005). Important cardiovascular diseases are the following: heart failure, ischemic heart disease, arrhythmias, peripheral vascular disease and arterial hypertension, metabolic syndrome as well as cerebrovascular disease.

One example for cardiac arrythmias is atrial fibrillation where a link has been found between atrial fibrillation and FEV1 (Buch et al., 2003). This link was shown in a prospective study where data from 13430 males and females was analysed with no previous history of myocardial infarction. The risk of atrial fibrillation was re-examined after five years. Here, the onset of new atrial fibrillation was 1.8 times higher for patients with a FEV1 between 60 to 80% of predicted as opposed to FEV1 greater or equal to 80% after modification for sex, smoking, age, blood pressure, diabetes and BMI. The final conclusion was that reduced lung function is an independent risk factor for atrial fibrillation (Buch et al., 2003).

Atrial fibrillation also plays an important role in predicting the mortality of patients with COPD. In one study, the Dyspnea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation (DECAF) score was used as a predictor of mortality in patients with ACOPD. The DECAF score has the 5 strongest predictors of mortality i.e. MRC Dyspnea Score, eosinopenia, consolidation, acidemia, and atrial fibrillation (Steer et al., 2012).

In the therapy of COPD, inhaled beta-2 adrenergic agonists play an important role. It is known that inhaled beta-2 adrenergic agonists increase the heart rate and may thus contribute to cardiac arrhythmias due to beta adrenergic effects (GOLD Guideline, 2019). Nevertheless, a number of studies have come to the conclusion that inhaled beta-2 adrenergic agonists are overall safe. Two trials looked at the effect of LABAs on the heart rate and demonstrated a slight increase in atrial tachycardias. Both trials did not find an increase in the mean heart rate or an increased risk of serious arrhythmias (Hanrahan et al., 2008; Donohue et al., 2008).

Moreover, patients with AECOPD often experience atrial fibrillation as a consequence of AECOPD (Terzano et al., 2014). In one study, 193 patients were hospitalized for AECOPD. Among those, 35 patients had COPD and atrial fibrillation. The probability of new onset atrial fibrillation was higher in patients with lower FEV1, hypoxemia, respiratory acidosis and higher

pulmonary hypertension (acquired via transthoracic echocardiography). There are several possible explanations for this higher probability of new onset atrial fibrillation. For instance, hypercapnic and hypoxemic patients with COPD in hospital with fluid retention and peripheral oedema were observed to have elevated norepinephrine levels (Anand et al., 1992). This may be due to low arterial blood pressure triggered by hypercapnia leading to an elevation of norepinephrine. The elevation of norepinephrine may then cause arrythmias such as atrial fibrillation. In a cohort study of 1013 patients with AECOPD, it was found that arrythmias increases the risk of death (odds ratio 2.70, 95% CI 1.40–5.22) (Ongel et al., 2014). Therefore, it is clinically important to optimize COPD management in patients with AECOPD in order to reduce the risk of arrythmias and thus the risk of mortality.

1.7 Definition of atrial fibrillation

Atrial fibrillation is observed on an ECG when an irregular heartbeat is assumed. On the ECG, atrial fibrillation presents itself with absent P waves, irregular R-R intervals and narrow QRS complexes (Fuster et al., 2007). Risk factors for atrial fibrillation include age, hypertension, heart failure, myocardial infarction, thyroid dysfunction, diabetes mellitus, COPD, obstructive sleep apnoea and smoking (Schnabel et al., 2015; Selmer et al., 2012). There are five types of atrial fibrillation: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (Kirchhoff et al., 2016). Patients with no known history of atrial fibrillation and new onset of atrial fibrillation have a first diagnosed atrial fibrillation. Paroxysmal atrial fibrillation is self-terminating within 7 days even when cardioverted by direct current or with drugs. Persistent atrial fibrillation is defined as atrial fibrillation that lasts longer than 7 days even when cardioverted by direct current or with drugs. Long-standing persistent atrial fibrillation is continuous atrial fibrillation lasting for equal to or more than 1 year, after a rhythm control strategy has been decided. If no rhythm control strategy is followed, then atrial fibrillation is defined as permanent atrial fibrillation.

Patients with atrial fibrillation might have a poor quality of life due to various symptoms such as lethargy, palpitations, dyspnoea or chest tightness (Dorian et al., 2000). To quantify the severity of symptoms in atrial fibrillation, the European Heart Rhythm Association (EHRA) has suggested the EHRA symptom scale (I-IV) (Wynn et al., 2014). Patients with atrial fibrillation that are asymptomatic have an EHRA Score I whilst patients with mild symptoms that do not affect daily activities have an EHRA score of 2a. When the daily activities of patients are not affected by the symptoms of atrial fibrillation, but patients are concerned about their symptoms then this is scored as EHRA 2b. When symptoms of atrial fibrillation start affecting the normal daily activities of patients then they have an EHRA score of 3. An EHRA score of 4 is achieved when no normal activity can be carried out by the patients.

1.8 Epidemiology of atrial fibrillation

Currently, the prevalence for atrial fibrillation is estimated to be 3% in adults aged 20 years or older, but the prevalence is higher in older people and in patients with hypertension, coronary artery disease, heart failure, valvular heart disease, obesity, diabetes mellitus, chronic kidney and chronic obstructive pulmonary disease (Zoni-Berisso et al., 2014; Björck et al., 2013; Colilla et al., 2013). The risk of all-cause mortality in women is two-fold whilst in men it is 1.5-fold (Benjamin et al., 1998). Increased morbidity is also observed in atrial fibrillation. Examples for increased morbidity include heart failure or stroke (Stewart et al., 2002).

1.9 Pathophysiology of atrial fibrillation

Some patients, especially those with early-onset atrial fibrillation have a genetic predisposition for atrial fibrillation (Fox et al., 2004). These patients suffer from inherited cardiomyopathy or channelopathy which are caused by disease causing mutations. Other mechanisms leading to atrial fibrillation include atrial remodeling. Structural heart disease, hypertension and perhaps diabetes can trigger a slowly progressive structural remodeling of the atria. This process is characterized by activation of fibroblasts, increased deposition of connective tissue and the formation of fibrotic tissue (Anne et al., 2005; Nguyen et al., 2009). Structural remodeling causes an electrical disconnection between muscle bundles causing arrythmia before the onset of atrial fibrillation (Allessie et al., 2010; Anne et al., 2005). Apoptosis and necrosis induced by coronary artery disease and heart failure can also create fibrotic tissue (Aime-Sempe et al., 1999). Myocyte hypertrophy triggered by atrial dilatation can lead to conduction disturbances of electrical impulses (Schotten et al., 2001). Another important pathway for explaining the mechanism of atrial fibrillation is autonomic nervous system dysfunction. Sympathetic hyperinnervation induced by heart failure or hypertension can enhance propensity to ectopy (Nguyen et al., 2009; Chen et al., 2014). Histopathological specimen showed that the density of sympathetic nerve twigs in patients with atrial fibrillation was greater as opposed to other nerves.

1.10 The PA-TDI interval

In 2009 a new transthoracic echocardiographic tool emerged to assess the risk of atrial fibrillation (De Vos et al., 2009). This echocardiographic tool is a predictor of atrial fibrillation in patients with no previous history of atrial fibrillation or with paroxysmal atrial fibrillation. It measures the total atrial conduction time (TACT) via tissue Doppler imaging (TDI) during sinus rhythm. This measured interval is termed the PA-TDI interval and is defined as the time from the beginning of the P wave on the ECG in lead II to the A´ wave on the left lateral mitral valve annulus. In one study, 249 patients with no previous history of atrial fibrillation underwent echocardiographic measurement of the PA-TDI interval (De Vos et al., 2009). It was found that 6% of these had a new-onset of atrial fibrillation. At the same time, they had a prolonged PA-TDI interval as opposed to the patients who remained in sinus rhythm (172 (25) ms vs 150 (20)

ms, p = 0.001). Another study showed similar results (Weijs et al., 2011). The PA-TDI interval was determined in 427 patients and it was found that patients with a previous history of atrial fibrillation, hypertension, valve disease, higher age and a higher BMI had a prolonged PA-TDI interval. Similarly, it was shown that patients with newly diagnosed obstructive sleep apnoea undergoing continuous positive airway pressure (CPAP) therapy had after 30 days a shorter PA-TDI interval and a lower NT-proBNP level possibly due to decreased atrial pressure or volume overload (Müller et al., 2016). This proposes that the PA-TDI interval may serve an indirect surrogate marker of atrial remodelling.

1.11 The autonomic nervous system

The autonomic nervous system also known as the vegetative nervous system is a subgroup of the peripheral nervous system. It innervates the smooth muscles and the glands and therefore affects the function of the internal organs (Furness, 2006). The autonomic nervous system unconsciously controls the heart rate, digestion, respiratory rate, urination, sexual arousal as well as pupillary response. The control centre of the autonomic nervous system lies in the hypothalamus and the medulla oblongata in the brainstem. The autonomic nervous system is further divided into the sympathetic nervous system and the parasympathetic nervous system. Both systems have opposite effects. Whilst one system activates a physiological action, the other system inhibits the physiological action. The sympathetic nervous system is regarded as the “flight or fight” system whilst the parasympathetic nervous system is termed the “rest and digest” system. The sympathetic nervous system originates from the spinal cord in the thoracic and lumbar region and ends around L2-3 whilst the parasympathetic nervous system emerges at the cranial nerves and the sacral spinal cord (S2-S4) (Kapa et al., 2010, Smith, 1970). The electrical impulse of the autonomic nervous system travels via a two-neuron efferent pathway (preganglionic and postganglionic neuron) to reach the target organ. The electrical impulse begins at the preganglionic neuron and subsequently synapses onto the postganglionic neuron before ending at the target organ. Both groups of the autonomous nervous system use acetylcholine as preganglionic neurotransmitter. Likewise, acetylcholine is used as postganglionic neurotransmitter in the parasympathetic nervous system in order to stimulate muscarinic receptors. On the other hand, postganglionic neurotransmitters of the sympathetic nervous system employ noradrenalin to act upon alpha- and beta-adrenoreceptors (McCorry, 2007).

1.12 The autonomic function of the heart

Heart rate and heart rhythm are modulated by the autonomic nervous system (Berger et al., 1989). The sinoatrial node can be found in the wall of the right atrium of the heart. The sinoatrial node has the function of rhythmically stimulating the heart rate. At the same time, sympathetic and parasympathetic factors affect the heart rate. The sympathetic input is supported by the accelerans nerve which discharges noradrenalin on the sinoatrial node. Similarly, the

parasympathetic is denoted by the vagus nerve and it discharges acetylcholine onto the sinoatrial node cells as well as atrioventricular node (Schmidt & Lang, 2007). Thus, activation of the accelerans nerve triggers a rise of the heart rate exhibiting a positive chronotropic effect whilst vagus nerve stimulation lowers the heart rate which is termed a negative chronotropic effect. Normal resting heart rate lies in the range between 60 to 100 beats per minute (Spodick, 2009). This range is defined as the autonomic tone which is supported by simultaneous stimulation of both the parasympathetic and sympathetic input to the sinoatrial node. The cardioinhibitory and cardioaccelerator areas are located in the medulla oblongata of the brainstem. The visceral receptors provide important information for the regulation of the heart rate via the sensory fibres in the vagus and sympathetic nerve. Examples of these receptors include baroreceptors and chemoreceptors (Schmidt & Lang, 2007).

The modulation of the autonomic nervous system is reflected by the heart rate variability (Task Force of the European Society of Cardiology, 1996). The heart rate variability measures the rhythm fluctuation by quantifying the time interval between heartbeats. In other words, it quantifies the variation in the beat-to-beat interval or the RR interval (R corresponds to the peak of the QRS complex in the ECG wave). Various statistical analysis gave rise to indicators for the autonomic nervous system from the heart rate variability (Malik & Camm, 1993; Task Force of the European Society of Cardiology, 1996). The heart rate variability also has a certain clinical significance. For instance, it was shown that reduced heart rate variability is linked with higher mortality after myocardial infarction (Bigger et al., 1992).

1.13 Baroreflex sensitivity

The baroreceptors are defined as stretch receptors and can be found in the aortic sinus, carotid bodies, vena cavae and pulmonary vessels. The baroreflex serves to uphold a constant mean arterial blood pressure (Persson, 1996). An increase in the blood pressure or stretch of those baroreceptors enhances the parasympathetic nervous system. This results in a decrease of the heart rate and the total peripheral resistance (Pang, 2001). On the contrary, heart rate and total peripheral resistance rise when the arterial blood pressure falls. This mechanism allows the baroreflex to maintain a constant blood pressure in the human body. The Ewing test plays a crucial role in testing the baroreceptor reflex (Ewing et al., 1980). The Ewing test involves a person suddenly standing up from a lying position. In the initial phase of standing, this causes a drop of blood pressure as the blood pools in the blood vessels of the legs. As blood pressure falls, the baroreceptors are less stimulated causing an increased sympathetic activity and decreased parasympathetic activity. As a result, heart rate and blood pressure increase. After around 30 seconds, the blood pressure normalizes and reaches its earlier state (Wieling et al., 1997). The sensitivity of the baroreceptor reflex regarding changes in blood pressure is defined as the baroreflex sensitivity. Thus, the baroreflex sensitivity can be used to judge the function of the autonomic nervous system (Hilz & Dutch, 2006).

1.14 Chemoreflex sensitivity

Another type of receptor is called the chemoreceptor (Seals et al., 1991). Chemoreceptors are innervated by the vagus and glossopharyngeal nerve. Increased metabolic activity in the body such as high-intensity exercise creates an increased levels of carbon dioxide, lactic acid or falling levels of oxygen. These dynamic changes of metabolic products are then detected by chemoreceptors and the information is conveyed to the cardiovascular centres in the medulla oblongata. In the cardiovascular centres the parasympathetic nervous system is inhibited causing a rise in the heart rate and thus the increased demand for oxygen is met with an increased blood flow (Lahiri et al., 1981). The response of chemoreceptors in regard to the level of partial pressure of oxygen in the blood is called the chemoreflex sensitivity.

1.15 Respiratory arrythmia

During inspiration, the heart rate is accelerated whilst expiration leads to a reduced heart rate (Pfeifer et al., 1993). There are many explanations for this mechanism. The central neuronal circuitry plays an important role in inspiration and it most likely inhibits the cardiovagal neurons. Secondly, respiration causes fluctuations in the central venous blood volume and thus the heart rate via activation of the brainbridge reflex (Hilz & Dutch, 2006). Moreover, there are stretch receptors in the lungs that are controlled by medulla oblongata which inhibit parasympathetitc neurons causing an increase in the heart rate (Schelegle & Green, 2001). The deep breathing test serves to stimulate respiratory arrhythmia (Hilz & Dutch, 2006). In the deep breathing test the participant must forcefully breath in and out for one minute (Blumenthal et al., 2005). This causes the greatest variation of heart rate.

1.16 Sympathetic activation via the cold pressure test

Submerging one´s hand in cold in ice water triggers a rise in the heart rate and blood pressure (Mourot et al., 2009). So called nociceptive receptors and temperature receptors on the skin are activated when encountering cold. Once activated, an enhanced sympathetic outflow is induced which triggers peripheral vasoconstriction and a rise in the heart rate (Hilz et al., 2002; Mourot et al., 2009). This mechanism was shown by direct measurement of sympathetic activity in muscles (Tulppo et al., 2005). For that purpose, one`s hand is submerged in ice water (0-1°C). This test is called the cold pressure test and used as an autonomic function test for the sympathetic nervous system.

1.17 Sympathetic and parasympathetic nervous system activation via the cold face test

Applying cold stimulus to the face can cause bradycardia and peripheral vasoconstriction (Heath & Downey; 1990). The cold stimulus activates temperature and nociceptive receptors at the skin of the face causing a peripheral vasoconstriction and increase in the blood pressure (Heistad et al., 1968). At the same time, afferent pathways of the trigeminal nerves cause an activation of the parasympathetic nervous system and thus a fall in the heart rate. In summary, the cold face test activates both the sympathetic and parasympathetic nervous system. For the cold face test, gel-filled pads are applied on the forehead and the maxillary region of the face. Bradycardia is observed before the increase of blood pressure. In one study, bradycardia was on average observed six seconds after the application of a cold stimulus to the face whilst the increase in blood pressure followed after 15 seconds (Khurana, 2007).

1.18 Autonomic dysfunction as the potential trigger of atrial fibrillation in AECOPD

Several studies have shown that patients with COPD may have an increased risk of arrythmias due to autonomic dysfunction (Andreas et al., 2005; Camillo et al., 2011; van Gestel et al., 2011; Suh et al., 2013). Patients with COPD have a higher resting heart rate, elevated heart rate variability and a reduced baroreflex sensitivity (Volterrani et al., 1994; Steward et al., 1986; Heindl et al., 2001; Velez-Roa et al., 2004). This may indicate a higher sympathetic activity in patients with COPD and therefore higher risk of new onset atrial fibrillation. Patients with AECOPD have a higher degree of hypercapnia and hypoxemia and thus a higher sympathetic activity (Somers et al., 1989). This may be due to higher levels of norepinephrine in patients with AECOPD due to lower blood pressure caused by hypercapnia (Anand et al., 1992). Furthermore, it was shown that patients with hypoxemic COPD have a prolonged corrected QT (QTc)-interval (Stewart et al., 1995). A prolonged QTc was shown to be associated with a higher risk of atrial fibrillation (Mandyam et al., 2013). The relationship between the prolonged QTc and COPD may be due to circadian heart rate variability disturbances like the lack of absence of the normal nocturnal decrease in sympathetic tone and overall sympatho-vagal imbalance preferring increased sympathetic activity (Tükek et al., 2003).

2 Aim of the study

COPD is associated with a great mortality and morbidity. It is expected in the year 2020 that COPD will be the third leading cause of death (GOLD Guideline, 2019). Cardiac comorbidities are often seen in patients with COPD. Among those cardiac comorbidities are coronary heart disease as well as arrhythmias such as atrial fibrillation. Atrial fibrillation is observed in around 2% of patients with stable COPD whilst atrial fibrillation is detected in 8-13% of patients with AECOPD (Laratta & Eeden, 2014). A possible explanation for this difference could be autonomic dysfunction. The autonomic nervous system modulates various functions in the human body so that the human body can adapt to external and internal stimuli. This includes also regulation of the heart rate and heart rhythm. Current literature suggests that COPD can cause changes in the autonomic nervous system (Andreas et al., 2005; Camillo et al., 2011; van Gestel et al., 2011; Suh et al., 2013). These changes include a reduction in the heart rate viability, a reduction in the chemoreflex sensitivity as well as a reduction in the baroreflex sensitivity (Volterrani et al., 1994; Steward et al., 1986; Heindl et al., 2001; Velez-Roa et al., 2004). One of the aims of this study was to compare the probabilities of new onset atrial fibrillation in patients with stable COPD and AECOPD using the PA-TDI interval as an echocardiographic predictor of atrial fibrillation. Furthermore, a special monitoring system (Task Force ® Monitor) was used to explain if autonomic dysfunction could be a possible pathophysiological pathway for an increased likelihood of atrial fibrillation. For this purpose, the degree of autonomic dysfunction was compared between patients with AECOPD and stable COPD. If patients with AECOPD had a higher risk of atrial fibrillation, then the expectations would be to see a greater degree of autonomic dysfunction in patients with AECOPD. A systemic characterization of the autonomic function and the prediction of atrial fibrillation in patients with AECOPD would allow the development of new therapeutic intervention.

3 Materials and methods

3.1 Study population

In this study, 32 patients with stable or exacerbated COPD were included. The patients were grouped into 16 patients with stable COPD and 16 patients with exacerbated COPD. The study was conducted once written informed consent was gained from all patients. The inclusion criteria for both groups were COPD with Grade I, II, III and IV according to the GOLD criteria (GOLD Guideline, 2019). Additionally, all patients had to show a sinus rhythm in the ECG and were between the ages of 40 and 80 years. The cohort of the stable COPD patients did not have an exacerbation of the COPD in the last 6 months. Patients with ST-elevated myocardial infarction, severe left ventricular dysfunction, low blood pressure (lower than 100 mmHg), atrial fibrillation or severe valvular pathology were excluded from this study. Moreover, patients were exempted with acute or chronic kidney disease when creatine levels were greater than 1,5 mg/dl and if they had an active rheumatic disease or an active malignancy.

3.2 Study Design

The patients for this prospective study were recruited via our out- and inpatient department for respiratory medicine at the university hospital of Duesseldorf. For every patient, the entire procedure of this study was explained in detail by a doctor and written consent was gained. The protocol of this study was approved by the ethics committee of the Heinrich Heine university of Duesseldorf (Aktenzeichen 5698). All the examinations and tests for the purpose of evaluating COPD, cardiac structure and function, risk for atrial fibrillation and autonomic function lasted for approximately half a day for each patient. An overview of the examinations and tests is provided in the figure below (Figure 2).

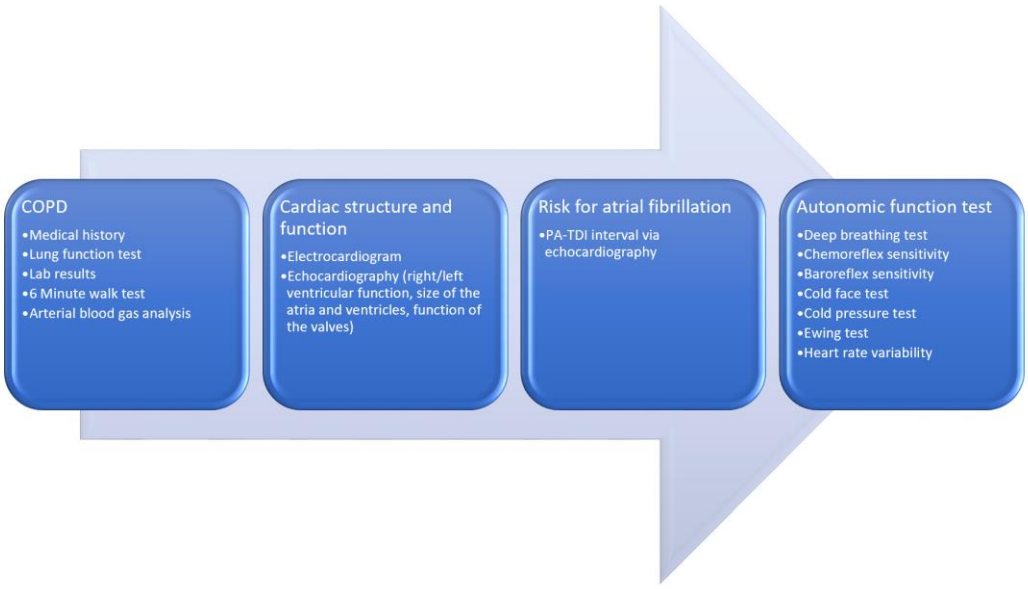

Figure 2: ***Overview of all tests and examinations****. This figure represents an overview of all the tests and examinations that patients undertook for the evaluation of COPD, cardiac structure and function, risk for atrial fibrillation and autonomic function test. Overall, the tests and examinations lasted half a day.*

3.3 History and medical examination

The patients´ history were taken by a doctor and written down on a standardized questionnaire. In this questionnaire the patients' symptoms, disease history of their COPD, comorbidities, medication as well as smoking history in pack years was documented. After that the patients were thoroughly examined by the same doctor and the findings were documented on a standardized sheet for medical examination.

3.4 Lung function test

A lung function test (JAEGER, Master Screen Body) was used to assess pulmonary obstructive disease. The lung function test included body plethysmography and the measurement of CO diffusion capacity. If patients with stable COPD had a lung function test performed within the last four weeks, then a current lung function test was discarded.

3.5 Blood test

Blood gas analysis was performed with arterialized blood samples using the ABL800 Flex. One of the ear lobes of the patient was embedded in Finalgon® (Nonivamid und Nicoboxil crème) and after approximately 10 minutes arterialized blood was retrieved from the ear lobe. A full blood test (25ml of blood) via venipuncture (blood count, renal and liver function, C-reactive protein, TSH, NTpro-BNP) was performed on all patients.

3.6 Transthoracic echocardiogram

In our study, all patients received a full transthoracic echocardiogram by experienced echocardiographers. All transthoracic imaging including pulsed wave, continuous wave, colour

flow, tissue doppler imaging, M-Mode and 2-D were finalized using the model General Electric, Vivid S60. Transthoracic imaging was performed in the left lateral decubitus position in all patients. Moreover, all images were acquired in the parasternal long- and short axis views and the apical 4-, 3-, and 2- chamber views. The left and right atrial volumes were measured during the end-systolic phase whilst the diameter of the right ventricle was determined at the end-diastolic phase. The left ventricular ejection fraction was estimated visually in the apical 4-chamber view. Pulsed wave doppler was used to measure the parameters of the mitral valve inflow which included E wave, A wave, E wave deceleration time and the E/A ratio. To assess right ventricular function, the tricuspid annular plane systolic excursion (TAPSE) was measured in the four chamber view by placing the M-Mode at the tricuspid lateral annulus.

Additionally, the total atrial conduction time (PA-TDI interval) was measured via transthoracic echocardiogram in order to quantify atrial conduction time (De Vos et al., 2009). A sample volume was positioned on the lateral wall of the left atrium just adjacent to the mitral valve. Here, the duration from the beginning of the p-wave on lead II of the electrocardiogram to the peak of the A' wave on the tissue doppler image (see Figure 3 & Figure 4). Another lead in the electrocardiogram was chosen if the p-wave was not adequately displayed in lead II. Changes in the PA-TDI interval may serve as a surrogate marker of atrial remodelling. In one study, it was shown that reverse atrial remodelling may occur when patients with obstructive sleep apnoea are treated with continuous positive airway pressure (CPAP) therapy (Müller et al., 2013; Müller et al., 2014). This may lead to decreased atrial pressure or volume overload and thus a reduced PA-TDI interval. Likewise, in our study we tested the hypothesis if atrial remodelling may occur in patients with exacerbated COPD.

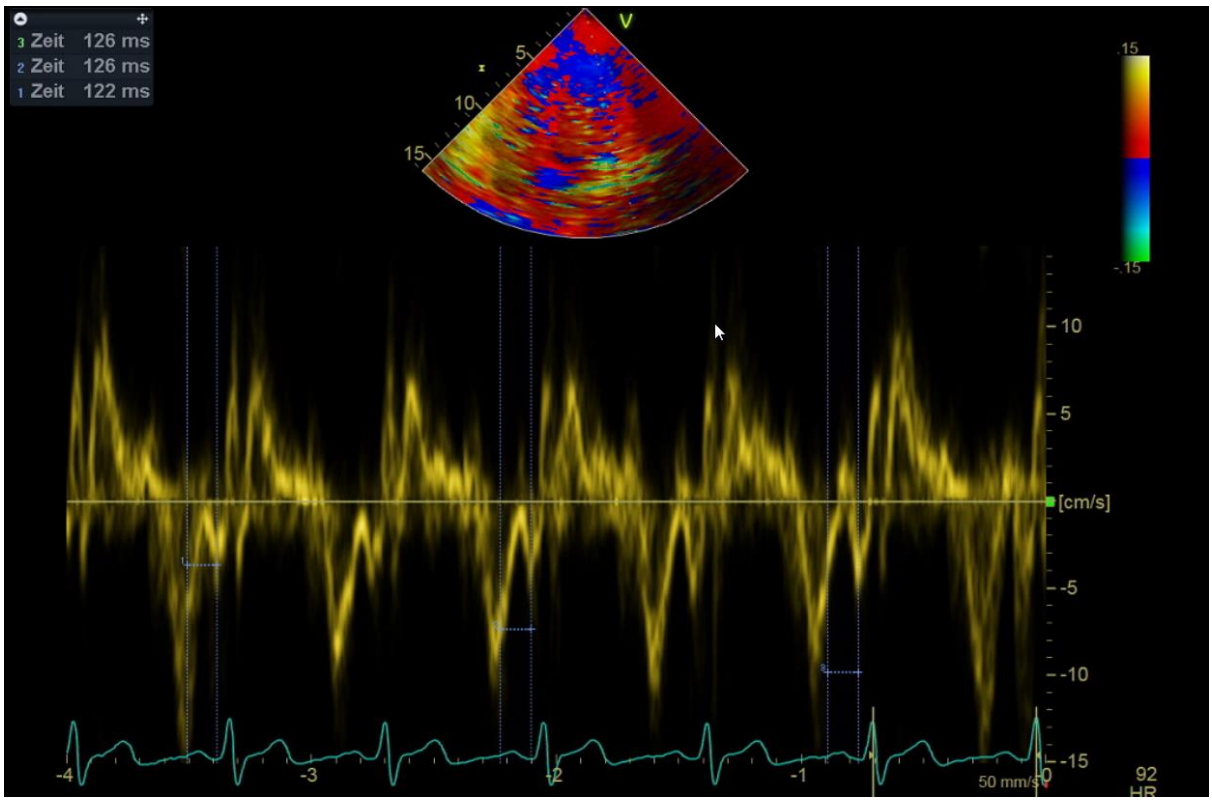

Figure 3: ***Transthoracic echocardiogram showing the PA-TDI interval.*** *This figure is an echocardiographic example the measurement of the total atrial conduction. The total atrial conduction time is represented by the PA-TDI interval. The PA-TDI interval is the distance between peak A of the tissue doppler Image of the lateral mitral valve anulus and the beginning of the p-wave in lead II.*

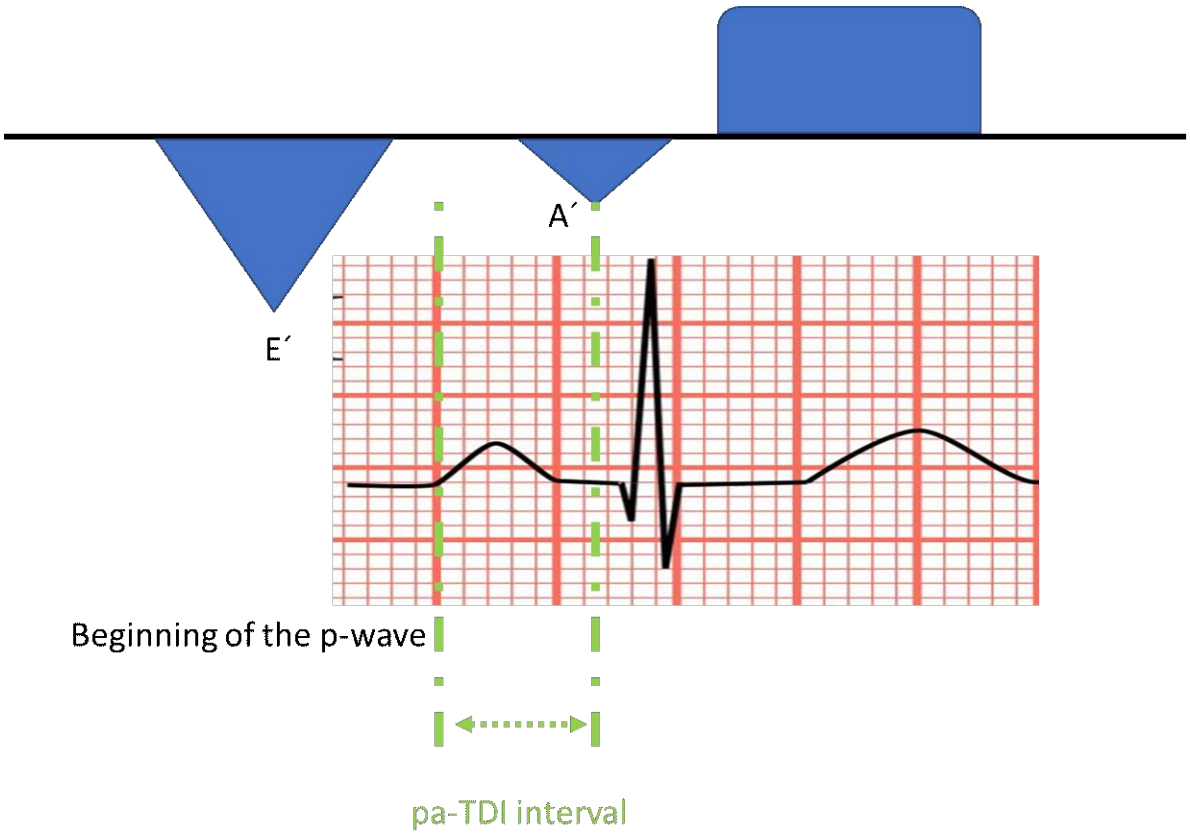

Figure 4: ***Schematic representation of the PA-TDI interval.*** *This figure represents a schematic presentation of how the PA-TDI interval is measured. The PA-TDI interval is the distance between peak A of the tissue doppler Image of the lateral mitral valve anulus and the beginning of the p-wave in lead II.*

3.7 6-minute walk test

To assess cardiorespiratory function, all patients took part in the 6-minute walk test. In this test, the patients walked over a hallway of 50 meters for 6 minutes. No exercise equipment was needed for this purpose. This test is a simple and cost-efficient cardiopulmonary exercise testing as it provides information relating to a broad range of cardiorespiratory conditions and functional capacity (Enright, 2003).

3.8 Autonomic function test

The autonomic function test was conducted in a quiet environment with a room temperature of 20 to 22 °C. No food, cigarettes or alcohol were allowed four hours prior to the start of the autonomic function test. The parameters of the autonomic function tests were measured via a special monitoring system (Task Force ® Monitor, CNSYSTEM CE0408) that allowed continuous non-invasive hemodynamic and autonomic assessment. This special monitoring system acquired information about the patient's autonomic nervous system through electrodes that were connected to the patient. An overview of the individual autonomic parameters is provided in the following table (Table 4).

Abbreviation	Hemodynamic parameter	Unit
RRI	RR-interval	[ms]
HR	Heart rate	[min^{-1}]
sBP	Systolic blood pressure	[mmHg]
dBP	Diastolic blood pressure	[mmHg]
mBP	Mean blood pressure	[mmHg]
SV	Stroke volume	[ml]
CO	Cardiac output	[l/min]
TPR	Total peripheral resistance	[dyne*s/cm^5]
BRS	Baroreflex sensitivity	[ms/mmHg]

Table 4: ***Continuous non-invasive measurement of parameters via the Task Force® Monitor.*** *These hemodynamic parameters are measured continuously via the Task Force® Monitor.*

Before initiating the autonomic function test, the patients had an adaption phase lasting five minutes. During this phase continuous non-invasive measurement of the parameters listed in table 1 was performed (Tulppo et al., 2005; Meyer et al., 2010; Meyer et al., 2011). The adaption phase was followed by a resting phase to get baseline values and measure baroreceptor sensitivity. After that, individual autonomic function tests were performed. The individual autonomic function tests were divided into the following: chemoreflex sensitivity test, Ewing test, cold pressure test and the cold face test. Between each of the autonomic function test, a resting phase of five minutes was given to the patients allowing the parameters to return to baseline (Task Force of the European Society of Cardiology, 1996). An overview of the individual phases and meaning of the autonomic function test can be seen in the figures below (Figure 5 & Figure 6).

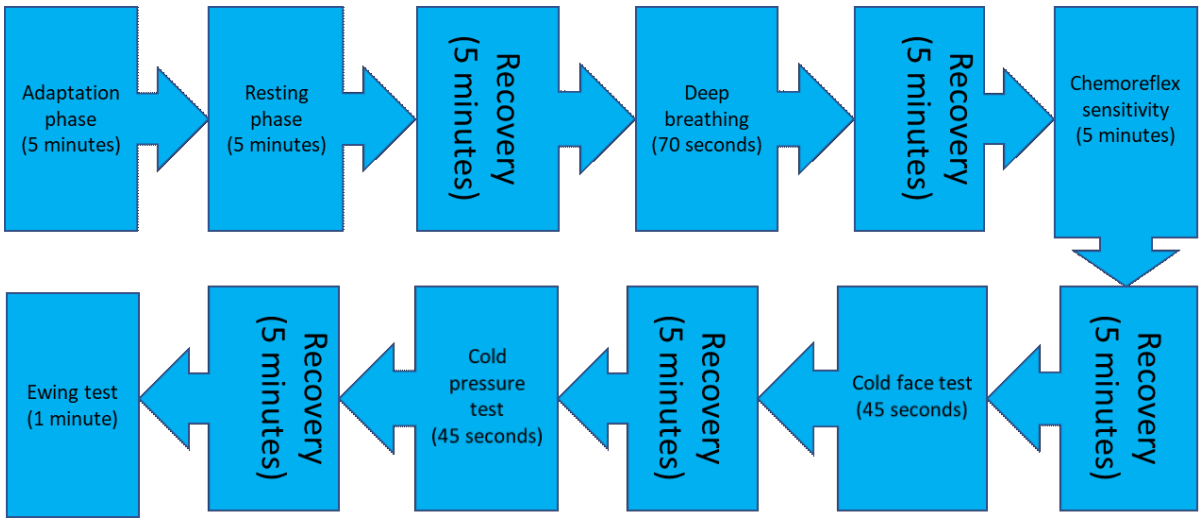

Figure 5: ***Overview of the timing in the autonomic function test.*** *This figure shows the individual phases and its corresponding time interval in testing the autonomic function of the patients.*

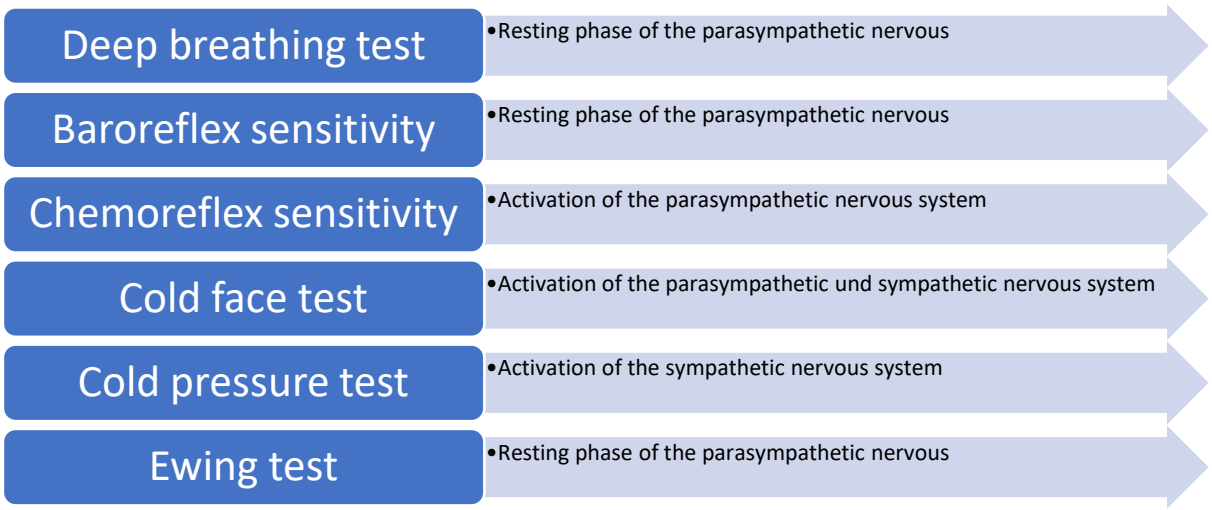

Figure 6: ***Testing phases in the autonomic function test.*** *The autonomic function test is composed of various testing phases. This figure displays the purpose of each testing phase*

3.9 Baroreflex sensitivity

For the resting phase, the patients had to lie down on a medical couch for 5 minutes. During that time, the baroreflex sensitivity was measured with the help of the Task Force® Monitor software. The baroreflex sensitivity assesses the resting phase of the parasympathetic nervous system by measuring the degree of sinus arrythmia in relation to the parasympathetic nervous system (Agelink et al., 2001). The TFM employs the sequence method for determining the spontaneous activity of the baroreceptors. The sequence method looks at changes in the

heart rate in relation to changes in blood pressure (Fritsch et al., 1986; La Rovere et al., 2008; Parati et al., 2000). Raising sequences are analysed and displayed via raising systolic blood pressure and prolonged RR- interval whilst falling sequences with falling systolic blood pressure and shortened RR- interval. The slope of the sequence depends on the minimum threshold of the heart rate (RR-interval of at least six milliseconds) and the blood pressure (change of at least one mmHg). Thus, an upslope is defined as the simultaneous raise of blood pressure and heart rate whilst a downslope marks a simultaneous fall in blood pressure and the heart rate. The values of all intervals give the final value of the BRS. The values of the BRS varies according to age and the time of the day (Parati et al., 1988; Parati et al., 1995). High values of the BRS represent a high parasympathetic activity (Parlow et al., 1995). A normal value of the BRS is said to be around 9,3 ms/mmHg (Agelink et al., 2001).

3.9.1 Deep breathing test

The next test was the deep breathing test. Here, the patients had to forcefully inhale for five seconds followed by a forceful expiration phase for five seconds (Blumenthal et al., 2005; Agelink et al., 2001; Shields, 2009). This breathing pattern was repeated seven times for 70 seconds whilst the heart rate at both inspiration and expiration was recorded. This variation in breathing causes a variation in the heart rate. Forceful inhalation accelerates the heart rate while forceful exhalation reduces the heart rate (Pfeifer et al., 1993). This mechanism can be explained by changes in the central venous pressure and the activation of the stretch receptors of the lung and the chest wall during inhalation inhibiting the parasympathetic neurons of the heart (Schelegle and Green, 2001; Richter et al., 1992). For the purpose of quantifying the association between breathing and heart rate, the Task Force® Monitor software calculates the average difference between the highest heart rate at inspiration and the lowest heart rate at expiration. Once this is done, the expiration/inspiration (E/I) ratio is determined by the Task Force® Monitor software (Hilz & Dutsch, 2006). The difference in the heart rate between expiration and inhalation should not be more than five beats per minute (Hilz & Dutsch, 2006, O'Brien et al., 1986). An E/I ratio less than 1.10 is said to be pathological (Sundkvist et al., 1979).

3.9.2 Chemoreflex sensitivity

The third test was the chemoreflex sensitivity test. Here patients were given five litres of 100% Oxygen via a face mask for five minutes and for patients with long term oxygen therapy five litres were added to the already existing oxygen therapy (Rassaf et al., 2012). The rationale behind this test is to assess the cardiac parasympathetic nervous system because oxygen inhibits peripheral chemoreceptors (Seals et al., 1991). This inhibition causes an increased

parasympathetic cardiac activity and a subsequent fall in the heart rate (Lahiri et al., 1981, O´Regan, 1977). Throughout this test, the high-resolution ECG of the Task Force® Monitor software recorded the difference of the average length of the ten subsequent RR intervals meaning the time interval between each successive normal QRS complex before and after the application of oxygen. Blood gas analysis was performed on all patients before and after applying oxygen and the Task Force® Monitor software calculated the difference between the pO2 before and after applying oxygen. Finally, the difference of the average RR-intervals was divided by difference of the pO2 interval and this ratio represented the chemoreflex sensitivity. A value below 3.0 ms/mmHg is regarded as pathological (Meyer et al., 2010; Rassaf et al., 2010; Hennersdorf et al., 2002).

3.9.3 Cold pressure test

After that, the cold pressure test was performed. For this purpose, the patient had to immerse the right hand into an ice water (0-1°C) container for 45 seconds whilst changes in blood pressure and heart rate were measured. When pain due to contact of the hand with ice water was present then the cold pressure test was aborted. The aim of the cold pressure test is to assess the function of the sympathetic nervous system (Weimer, 2010, Mourot et al., 2009). Cold causes an increase in the sympathetic nervous system and a subsequent rise in the heart rate and blood pressure via vasoconstriction (Heistad et al., 1968, Hines Jr. and Brown, 1936, Hilz et al., 2002). Thus, the blood pressure and the heart rate were recorded during the cold pressure test.

3.9.4 Cold face test

For the cold face test, cold stimulus (0-1°C) was applied through gel filled compresses on the forehead and cheeks of the patient for 45 seconds (Tulppo et al., 2005). This kind of stimulation causes an activation of the peripheral sympathetic and parasympatehthic nervous system (Hilz et al., 1999, Hilz and Dutsch, 2006). This causes a fall in the heart rate and a rise in the blood pressure via peripheral vasoconstriction (Finley et al., 1979, Khurana and Wu, 2006). Like in the cold pressure test, changes in blood pressure and heart rate were recorded.

3.9.5 Ewing test

Lastly, the Ewing test was carried out by allowing the patient to stand for over a minute with blood pressure and heart rate being measured (Stamboulis et al., 2006). This test aims to assess the cardiac function of the parasympathetic nervous system by looking at changes in the heart rate. (Neurology, 1996, Stamboulis et al., 2006). Gravity induced venous blood

pooling in the lower extremities a reduced blood flow to upper part of the body. This is detected by the baroreceptors which cause an immediate vasoconstriction, allowing the blood to be pushed to the upper part of the body. At the same time, the parasympathetic activity is reduced and the heart rate is increased. After 30 seconds of standing, heart rate and blood pressure have returned to baseline (Ewing et al., 1980, Wieling and van Lieshout, 1993). The Task Force® Monitor software measures this phenomenon by the 30/15 ratio. This ratio assesses the parasympathetic activity of the heart by deriving the ratio of the longest RR interval after 30 seconds and the shortest RR interval after 15 seconds. The 30/15 ratio should be 1,09 or more (Agelink et al., 2001).

3.10 Description of the tools and software

The Task Force Monitor (CNSystems, Graz, Austria) was used a tool for measuring the autonomic nervous system of the probands in this study. This tool allows non-invasive and painless hemodynamic assessment of the cardiovascular system. This hemodynamic assessment was done by high resolution 6-channel ECG, continuous non-invasive arterial blood pressure, total peripheral resistance, continuous non-invasive cardiac output and oscillatory blood pressure monitoring. Once full hemodynamic assessment was completed, the assessment of autonomic function was carried out by calculating the heart rate variability, blood pressure variability and baroreceptor sensitivity. All values were recorded in an MS Excel® file by the Task Force Monitor® software.

3.10.1 Electrocardiogram

The electrocardiogram (ECG) was conducted in a bipolar manner according to the principle of Einthoven. For this purpose, two channels were considered: Einthoven I and Einthoven II. Four electrodes were applied on the patient's chest wall. Via those electrodes at 1000 Hz, the ECG signal was conducted and subsequently the RR-intervals counted. From this the HRV and BRS were calculated.

3.10.2 Continuous measurement of the blood pressure

The continuous measurement of the blood pressure (beat to beat) occurred by using a vascular unloading technique with a finger cuff around the index- and middle finger (Drexel et al., 2013). This measures the pressure in the finger arteries without interruption and is registered in mmHg (Penaz et al., 1976). The mechanism works by concentrically interlocking control loops for the correct measurement of the blood pressure (Fortin et al., 2006b). At the same time, oscillometric blood pressure was measured on the contralateral arm to correct the blood pressure measured by the vascular unloading technique. It has been shown that the vascular

unloading technique correlates with the oscillometric blood pressure measurement (Fortin et al., 2006b).

3.10.3 Impedance cardiography

Impedance cardiography (ICG) serves as a non-invasive measuring tool to measure the total electrical conductivity of the thorax in relation to time via electrodes placed on the outside. This allows continuous monitoring for various cardiodynamic parameters: stroke volume (SV), heart rate (HR), left ventricular ejection time (LVET) and cardiac output (CO). The gold standard is invasive thermodilution but ICG achieves similar results to thermodilution and is at the same time a non-invasive technique (Fortin et al., 2006a).

3.10.4 Heart rate variability

The autonomous nervous system consists of descending (efferent) and ascending (afferent) activity. These two branches are affected by mechanical, hormonal and other physiological mechanisms aimed at keeping the cardiovascular system in its optimal range. In the resting state, both the parasympathetic and the sympathetic nerves are tonically active. This balance between the sympathetic and parasympathetic nervous system is called the autonomic balance. The autonomic balance is represented by the heart rate. The sympathetic nervous system accelerates the heart rate whilst the parasympathetic nervous system decelerates heart rate. This dynamic change of the heart rate is best represented by the heart rate variability (HRV). Complex signal processing in the 1960s and 1970s lead to the study of the heart rate rhythm or HRV (Singer et al., 1988). Irregularities in the pattern of the heartbeat are visible when the heart rate is analysed on a beat-to- beat or RR interval. An increase in the heart rate causes less variability between the heartbeats so HRV decreases whilst a decrease in the heart rate means that there is more time between the heartbeat allowing more room for variability to occur and thus an increase in the HRV. Elderly patients with cardiac disease often have less HRV as HR decreases so that the link between heart rate and HRV is ultimately lost (Jandackova et al., 2016). HRV can be analysed via frequency domain (power spectral density) analysis and time domain analysis (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For both methods, the time interval between each successive RR-interval is determined. These changes in the time interval are typically shown in a heart rate tachogram (Figure 7).

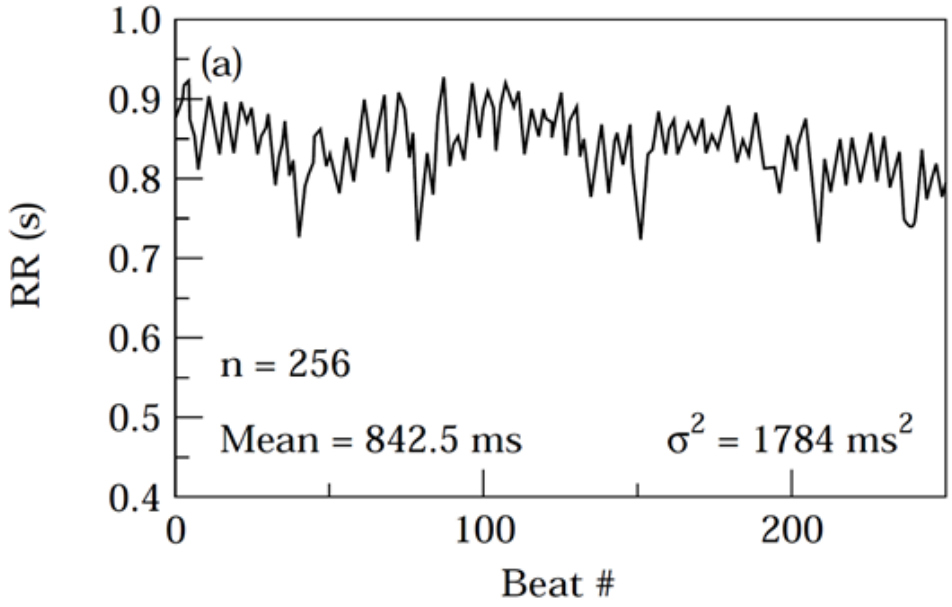

Figure 7: Heart rate tachogram at rest. *Heart rate tachogram consisting of 256 consecutive RR values at supine rest (diagram taken from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996 with permission)*

Power spectral analysis serves to dissect the complex HRV waveform into its component rhythms (Akselrod et al., 1981). This gives an overview of the distribution of power (the variance and the amplitude of a given rhythm) in relation to frequency (the time period of a given rhythm). Power spectral analysis has the advantage of giving both frequency and amplitude information when being compared to time domain analysis. The height of the peak at any given frequency shows the consistency of the rhythm whilst the frequency denotes the time interval over which the rhythm occurs (Figure 8). For instance, a period of ten seconds is shown by 0,1 hertz frequency. The power spectrum is divided into three main frequency ranges: high-frequency (HF), low-frequency (LF)- and very low-frequency band (VLF).

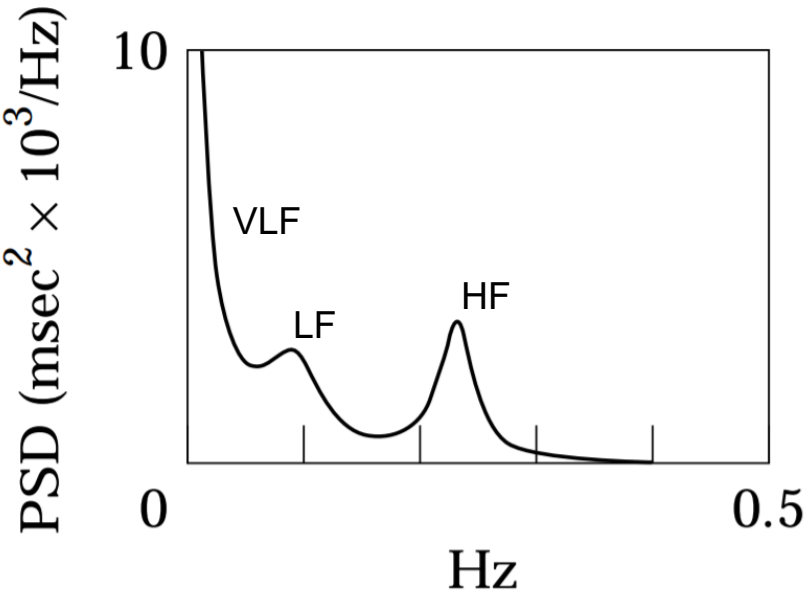

Figure 8: ***HRV in healthy subjects at rest using power spectral analysis.*** *At rest the graph is divided via filtering techniques into three main components: very low-frequency (VLF), low-frequency (LF) and high-frequency (HF). (diagram adapted from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996 with permission)*

The HF band is defined as the power in the range of 0.15 to 0.4 hertz. In other words, at the high-frequency spectrum rhythms are shown that have a period between 2.5 and 7 seconds. Physiologically, this band correlates to the parasympathetic nervous system or vagal activity (Gratze et al., 2005, Bettoni & Zimmermann, 2002, Task Force of the European Society of Cardiology, 1996). This was shown in studies involving blocking the muscarinic receptor and vagotomy (Malliani et al., 1991; Akselrod et al., 1981). It is also often called the respiratory band as it is linked to heart rate variations connected to the respiratory cycle as explained previously (see section deep breathing test).

The LF band is defined in the range between 0.04 and 0.15 hertz. This means that it displays rhythms with a period between 7 and 25 seconds. This period is also often termed baroreceptor range as it represents baroreceptor activity during rest (see section baroreceptor sensitivity). LF is said to represent the sympathetic and parasympathetic activity (Pagani et al., 1986). The LF/HF ratio is used to weigh the relationship between the sympathetic and parasympathetic nervous system. The correlation of sympathetic modulation with the LF band comes from 24-hour HRV recordings of healthy probands. Here a predominant sympathetic activity was observed during the day whilst main activity observed during the night was parasympathetic (Alexrod et al., 1987). A disequilibrium of the LF/HF ratio can be observed in many pathologies such as early myocardial infarction where an increase in the LF was evident (Malliani et al., 1994).

The VLF band lies in the power spectrum range between 0.0033 and 0.04 hertz meaning a period between 25 and 300 seconds. In comparison to the LF and HF bands, the VLF is frequently linked to all-cause mortality than LF and HF bands (Hadase et al., 2004; Tsuji et al., 1994). A physiological correlation for the VLF band is still in discussion. Thermoregulation, the renin-angiotensin system and other hormonal factors may play an important role in forming this band (Cohen et al., 1999). Furthermore, experiments suggest that the VLF rhythm is created by via an intrinsic mechanism by the heart itself (Kember et al., 2001; Kember et al., 2000). It was shown that a blockade of the sympathetic nervous system did not affect the power of the VLF rhythm and the VLF activity still persisted after disruption of the sympathetic nervous system in the tetraplegics (Berntson et al., 1997).

3.11 Statistical analysis

For the statistical analysis we used the software SPSS® (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). The mean and the standard deviation of all values was calculated. After that the values were tested for standard distribution. The two-tailed T-test was employed when the standard distribution was given. For variables with no given standard distribution, the Mann-Whitney-U-Test was used. The correlation between the PA-TDI and all other values was performed with the Pearson correlation test. The rationale of the statistical analysis was to find statistically significant differences with an error probability of less than 5%. For the Pearson correlation test, the corresponding correlation coefficient ´r´ was calculated and was defined in the following manner: an ´r´ value equal to zero was an indication for no correlation, an ´r´ value with less than 0,4 showed little correlation, an ´r´ value between 0,4 and 0,7 showed intermediate correlation and ´r´ values between 0,7 and 1 showed a strong correlation. An ´r´ value equal to 1 had a complete correlation (Mukaka, 2012).

4 Results

4.1 Clinical parameters

In the period between March 2017 and March 2018, a total of 32 patients with COPD were recruited. A total of 16 patients had stable COPD whereas 16 were exacerbated. Both patient groups consisted of 25 men and 7 women. The age of both groups ranged from 50 years to 83 years. The mean age of the stable COPD patients was 65.813 ± 7.626 years whilst the AECOPD patients had a mean age of 68.188 ± 7.574 years (p=0.384) (Table 6). Patients with AECOPD had similar symptoms as stable COPD patients (Table 7). Moreover, patients with AECOPD were characterized by a higher incidence of hypertension, and chronic kidney disease than patients with stable COPD, but no statistical difference was found except for hyperlipoproteinemia (Table 8). Other cardiovascular comorbidities were similar. The laboratory test results demonstrate that c-reactive protein was higher in the group of patients with AECOPD than stable COPD (0.73 ± 1.08 vs 3.06 ± 3.68; p=0.023) (Table 9). Thus, patients with AECOPD had a higher degree of inflammation than stable COPD patients. The number of leucocytes was not different between stable and AECOPD patients. Furthermore, the oral medication and inhaler therapy of patients with AECOPD and stable COPD was similar (Table 10). The only difference was that patients with AECOPD underwent high dose (40 mg or 50 mg) corticosteroid therapy for five days.

		stable COPD			exacerbated COPD			***p***
Total number of patients		16			16			
Age	*[years]*	65.81	±	7.63	68.19	±	7.57	0.38
Male sex	*n*	13.00			12.00			0.35
Height	*[cm]*	171.38	±	7.30	170.19	±	8.57	0.68
Weight	*[kg]*	67.56	±	12.82	72.19	±	20.88	0.46
Body Mass Index	*[kg/m2]*	22.92	±	3.67	24.41	±	6.63	0.81

*Table 6**: **Basic characteristics.** The basic characteristics of both patient groups were similar. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease*

		stable COPD	exacerbated COPD	***p***
Dyspnoe	*n*	15	16	0.50
Cough	*n*	12	9	0.50
Sputum	*n*	12	11	0.23
Chest pain	*n*	5	2	0.20
Palpitation	*n*	0	1	0.50
Peripheral edema	*n*	0	2	0.24

*Table 7: **The symptoms of the patients.** Both patient groups had similar symptoms. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease*

		stable COPD	exacerbated COPD	*p*
Arterial hypertension	*n*	9	13	0.13
Diabetes mellitus type II	*n*	1	4	0.17
Hyperlipoproteinemia	*n*	5	12	0.02
Coronary heart disease	*n*	3	5	0.34
Cerebrovascular disease	*n*	1	2	0.50
Peripheral vascular disease	*n*	2	0	0.24
Aortic valve pathology light/moderate/severe	*n*	4/0/0	2/0/0	0.33
Mitral valve pathology light/moderate/severe	*n*	1/0/0	1/0/0	0.76
Tricuspid insufficiency Grade I/II/III	*n*	2/0/0	0/0/0	0.24
Chronic kidney disease Stage 1/2/3/4/5	*n*	8/7/1/0/0	5/9/2/0/0	0.14
Active malignancy	*n*	0	0	0.50
Arrythmia other than AF	*n*	0	0	0.00
Cardiac pacemaker/implantable cardioverter defibrillator	*n*	0	0	0.00

Table 8: ***Cardiovascular comorbidities.*** *Overall, the cardiovascular comorbidities between both groups were similar. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease*

		stable COPD	exacerbated COPD	*p*
Leucocytes	*x1000/µl*	8.52 ± 3.79	10.33 ± 3.86	0.19
Thyroid stimulating hormone	*µlU /ml*	1.47 ± 0.66	1.77 ± 1.44	0.96
Thyroxine T4	*pg/ml*	13.59 ± 1.65	14.34 ± 3.47	0.55
Sodium	*mmol/l*	139.07 ± 3.65	140.38 ± 3.65	0.33
Potassium	*mmol/l*	4.43 ± 0.28	4.29 ± 0.55	0.38
Creatinine	*mg/dl*	0.93 ± 0.25	0.93 ± 0.17	0.94
Glomular filtration rate	*ml/min*	82.63 ± 17.72	78.75 ± 12.95	0.49
Urea	*mg/dl*	32.69 ± 13.70	32.88 ± 11.03	0.97
Lactate dehydrogenase	*U/l*	200.38 ± 53.40	236.94 ± 68.14	0.21
Aspartate transaminase	*U/l*	24.86 ± 11.80	27.75 ± 11.13	0.38
Alanine transaminase	*U/l*	22.43 ± 9.70	28.50 ± 14.07	0.28
Gamma glutayml transpeptidase	*U/l*	23.92 ± 11.82	61.00 ± 118.98	0.56
Erythrocytes	*mio/ µl*	4.86 ± 0.58	4.50 ± 0.63	0.11
Hemoglobin	*g/dl*	14.34 ± 1.92	13.40 ± 1.97	0.18
Hematocrit	*%*	43.54 ± 5.18	41.50 ± 5.74	0.30
Mean corpuscular volume	*fl*	89.49 ± 6.36	92.24 ± 5.80	0.21
Mean corpuscular hemoglobin	*pg*	29.41 ± 3.11	30.06 ± 2.35	0.51
Mean corpuscular hemoglobin concentration	*g Hb/dl*	32.70 ± 1.57	32.49 ± 0.99	0.66
Platelets	*x1000/ µl*	252.25 ± 59.97	298.44 ± 119.60	0.67
Mean platelet volume	*fl*	10.09 ± 1.00	11.06 ± 1.15	0.02
Hemoglobin A1c	*mmol/mol*	35.21 ± 12.13	41.89 ± 11.20	0.56
C-reactive protein	*mg/dl*	0.73 ± 1.08	3.06 ± 3.68	0.02

Table 9: ***Laboratory test results.*** *C-reactive protein was higher in exacerbated COPD patients than in stable COPD patients. The remaining laboratory test results were similar. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease*

		stable COPD	exacerbated COPD	*p*
Long-acting beta-adrenoceptor agonist	*n*	15	16	0.50
Long-acting muscarinic antagonist	*n*	15	14	0.50
Inhaled corticosteroids	*n*	9	10	0.50
Permanent glucocorticoid therapy	*n*	1	2	0.50
Roflumilast	*n*	2	0	0.24
Beta blocker	*n*	2	7	0.06
Calcium channel blocker	*n*	2	3	0.50
Aspirin	*n*	5	7	0.36
Anticoagulation DOAK/Phenprocoumon	*n*	0/2	1/2.0	0.5/0.23
Diuretics	*n*	6	9	0.01
Renin angiotensin system inhibtor	*n*	2	9	0.24

*Table 10: **Patient medication.** Both groups used similar oral medication and inhaler therapy. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease*

4.2 Lung function parameters

The lung function parameters of patients with AECOPD were much worse than patients with stable COPD. The forced expiratory volume in one second (FEV1) was lower in the AECOPD patient group than in stable COPD (FEV1 in liter: 1.24 ± 0.55 vs 0.75 ± 0.36; p=0.002; FEV1 in %: 41.64 ± 15.48 vs 28.53 ± 17.12; p=0.004). Due to the exacerbation the cardiorespiratory capacity of the patients was compromised as shown by the 6-minute walk test. Here the patients with AECOPD achieved worse results as opposed to patients with stable COPD (325.21 ± 116.86 vs 221.17 ± 110.26; p=0.029). Partial pressure of oxygen (PO2) and of carbon dioxide (PCO2) were similar across both groups (PO2: 63.38 ± 6.38 vs 63.06 ± 11.41; p=0.925; PCO2: 38.88 ± 8.93 vs 42.13 ± 6.36; p=0.25). The base excess in the blood gas analysis was higher in the patient group with AECOPD (1.04 ± 3.36 vs 3.89 ± 2.97; p=0.02). A summary of the lung function parameters can be seen in the following table (Table 11).

COPD Stage 1/2/3/4		stable COPD 0/5/8/3	exacerbated COPD 1/1/1/13	*p*
Active smoker	*n*	5	1	0.09
Pack years	*[py]*	51.56 ± 30.82	48.63 ± 25.84	0.09
NIV	*n*	2.00	3.00	0.50
LTOT	*n*	4.00	7.00	0.23
6 Minute Walk test	*[meters]*	325.21 ± 116.86	221.17 ± 110.26	0.03
FEV1	*[liter]*	1.24 ± 0.55	0.75 ± 0.36	0.01
FEV1	*[%]*	41.64 ± 15.48	28.53 ± 17.12	0.01
FEV/VC	*[%]*	44.45 ± 11.69	44.19 ± 15.29	0.96
RV	*[%]*	228.56 ± 79.31	241.31 ± 65.50	0.62
DLCO-SB	*[%]*	40.67 ± 17.90	31.77 ± 23.35	0.16
DLCO-VA	*[%]*	50.36 ± 28.02	48.22 ± 31.53	0.86
PO2	*[mmHg]*	63.38 ± 6.38	63.06 ± 11.41	0.93
pCO2	*[mmHg]*	38.88 ± 8.93	42.13 ± 6.36	0.25
pH		7.42 ± 0.04	7.44 ± 0.04	0.07
SO2	*[%]*	93.13 ± 2.75	92.87 ± 3.40	0.82
BE	*[mEq/L]*	1.04 ± 3.36	3.89 ± 2.96	0.02

*Table 11: **Lung function parameters**. Patients with exacerbated COPD achieved much less in the 6-minute walk test, had a lower FEV1 and a higher base excess (BE) than stable COPD patients. The remaining values were similar across both groups. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease; NIV=non-invasive ventilation; LTOT=long term oxygen therapy; FEV1= percentage of the predicted forced expiratory volume in one second; VC=vital capacity; RV=residual volume; DLCO-SB=single-breath diffusing capacity for carbon monoxide; DLCO-VA= diffusing capacity for carbon monoxide corrected for alveolar volume, PO2=partial pressure of oxygen;PCO2=partial pressure of carbon dioxide, SO2=oxygen saturation; BE=base excess*

4.3 Cardiovascular parameters

Looking at the cardiovascular parameters, it was demonstrated that patients with AECOPD had a higher heart rate and systolic blood pressure than patients with stable COPD (heart rate: 79.75 ± 11.84 vs 107.13 ± 19.52; p=0.001; systolic blood pressure: 111 ± 12 vs 138 ± 31; p=0.004). It should be noted that the heart rate measured in patients with AECOPD was the first heart rate recorded when they presented in the accident and emergency department. Likewise, the QTc was prolonged in patients with AECOPD (428.75 ± 34.11 vs 463.69 ± 51.35; p=0.021). NT-proBNP was similar in both groups (354.38 ± 515.36 vs 404.063 ± 311.403; p=0.102). Equally, important echocardiographic parameters like the left area of the atrium, left ventricular dysfunction or systolic pulmonary artery pressure were comparable in both groups. The following table shows a summary of the cardiovascular parameters (Table 12).

		stable COPD	exacerbated COPD	*p*
Blood pressure	*[mmHg]*	111/ 71 ± 12.0/ 10	138/ 77 ± 31/ 13.0	0.004/0.1
NT-proBNP	*[ng/l]*	354.38 ± 515.36	404.06 ± 311.40	0.10
Heart rate	*[bpm]*	79.75 ± 11.83	107.13 ± 19.52	0.00
Reduced ejection fraction (<55%)	*n*	1	1	0.76
Right atrial area	*[cm2]*	15.00 ± 3.88	12.95 ± 4.89	0.20
Mid-right ventricular diameter	*[mm]*	33.81 ± 8.04	31.06 ± 6.90	0.31
Intraventricular septum thickness	*[mm]*	11.94 ± 3.11	12.25 ± 7.93	0.12
Vena cava inferior diameter	*[mm]*	14.95 ± 4.94	14.38 ± 4.53	0.81
Left atrial area	*[cm2]*	14.21 ± 5.95	14.14 ± 4.14	0.87
E/A ratio		0.87 ± 0.17	0.91 ± 0.18	0.43
Systolic pulmonary artery pressure	*[mmHg]*	19.70 ± 27.35	12.08 ± 15.96	0.69
Tricuspid annular plane systolic excursion (TAPSE)	*[mm]*	17.71 ± 8.30	22.38 ± 4.00	0.05
PA-TDI Interval	*[ms]*	123.70 ± 12.97	136.28 ± 11.40	0.01
P-pulmonale	*n*	0	1	0.50
QRS interval	*[ms]*	88.63 ± 15.23	87.00 ± 18.85	0.31
PQ interval	*[ms]*	143.88 ± 18.41	133.75 ± 9.52	0.06
corrected QT interval	*[ms]*	428.75 ± 34.11	463.69 ± 51.35	0.02

*Table 12: **Cardiovascular parameters.** The systolic blood pressure, heart rate and the PA-TDI interval were elevated in the patient group with exacerbated COPD as opposed to stable COPD patients. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease; PA-TDI interval= total atrial conduction time*

4.4 The PA-TDI interval

Similarly, the PA-TDI interval was significantly longer in the patient group with AECOPD than patients with stable COPD (123.70 ± 12.97 vs. 136.28 ± 11.40 ms; p=0.007; Figure 9). This implies that exacerbation of COPD may be associated with an increased risk of atrial fibrillation. Higher age as a cardiovascular risk factor also positively correlated with an increased length of the PA-TDI interval (r=0.377; p=0.034; Figure 10). There was also a positive correlation between a higher BMI and a longer PA-TDI interval (r=0.412; p=0.019; Figure 11). Likewise, there was a link between NT-proBNP as a marker for heart failure and the PA-TDI interval (r=0.3710; p=0.037; Figure 12), but the correlation showed that a higher NT-proBNP correlated with a shorter PA-TDI interval. We expected a correlation between a higher NT-proBNP and a longer PA-TDI interval. There was no reasonable explanation for this correlation. Other cardiac parameters such as the left atrial area were also found to correlate with a prolonged PA-TDI interval (left atrial area: r=0.398; p=0.024, Figure 13). Lung function parameters did not correlate with the PA-TDI interval (Figure 14, Figure 15,Figure 16, Figure 17).

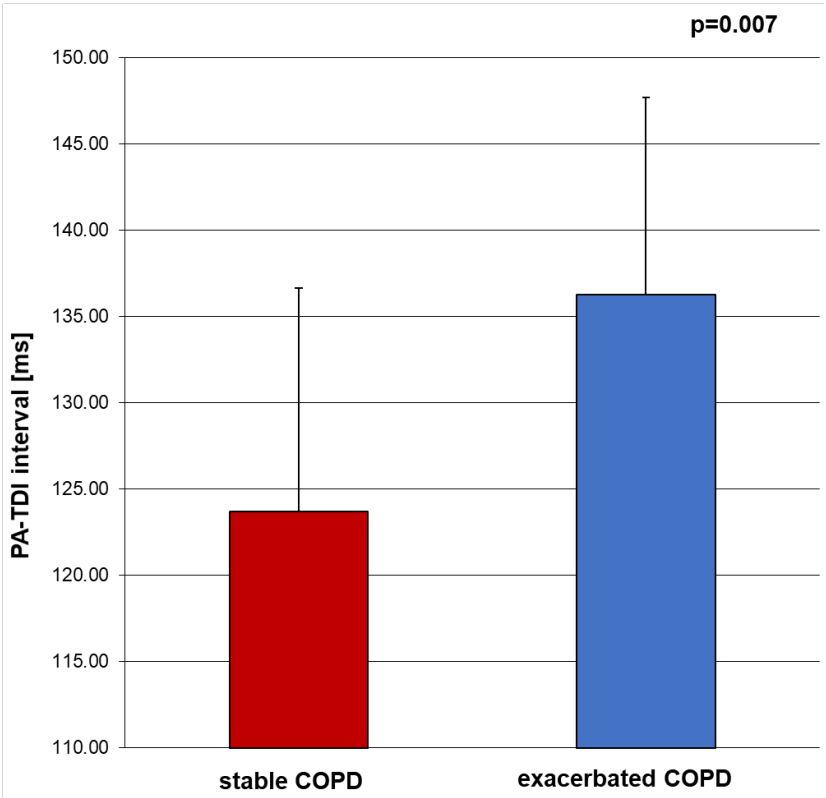

Figure 9: ***The PA-TDI interval in patients with stable COPD and exacerbated COPD****. The PA-TDI interval representing atrial conduction time was increased in patients with AECOPD reflecting a higher risk for atrial fibrillation. COPD=chronic obstructive pulmonary disease.*

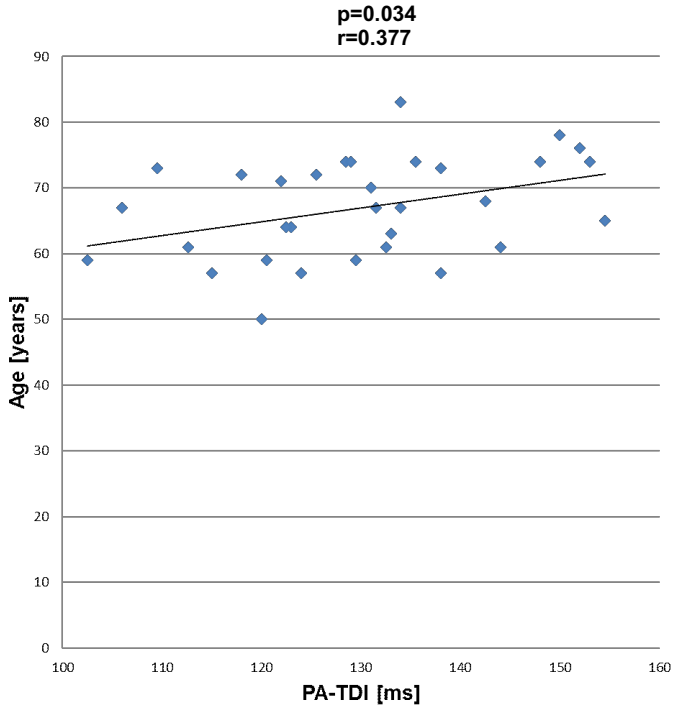

Figure 10: ***The PA-TDI interval in relation to age****. Older patients had a longer PA-TDI interval.*

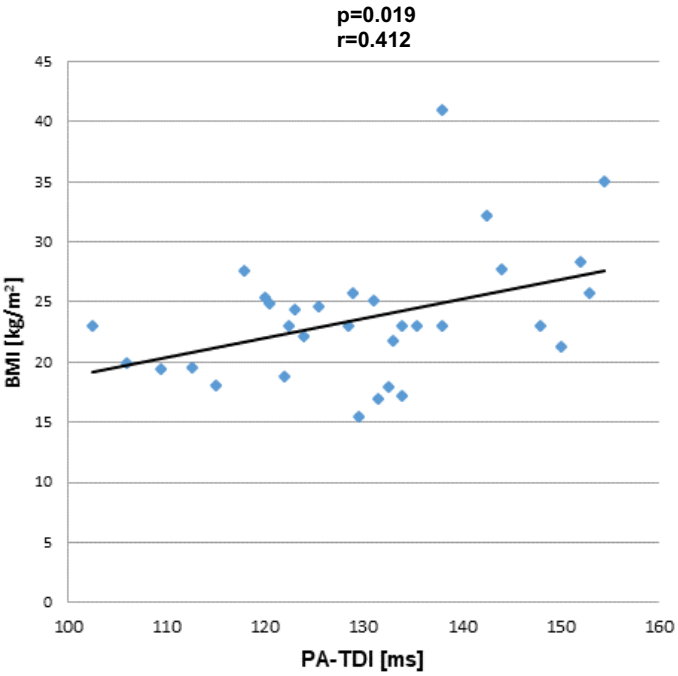

Figure 11: ***The PA-TDI interval in relation to the BMI****. Patients with a higher BMI had a longer PA-TDI interval.*

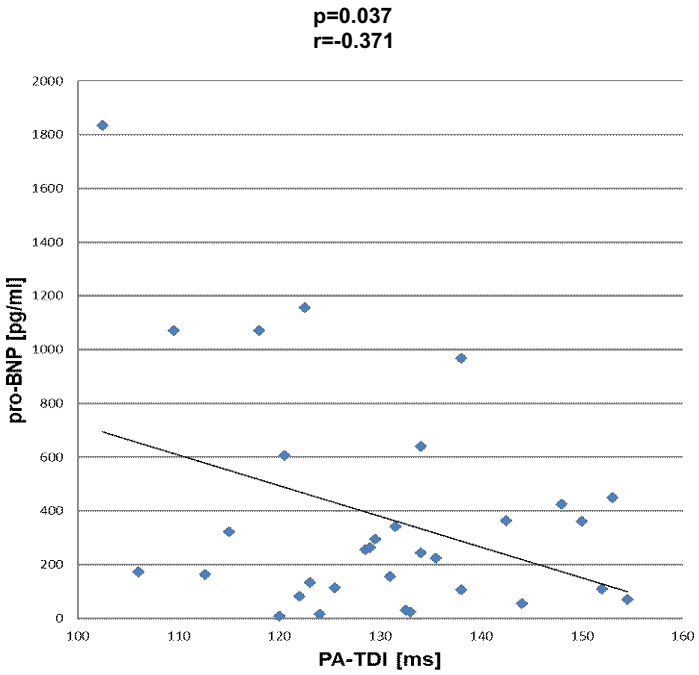

Figure 12: ***The PA-TDI interval in relation to NT-proBNP****. There was a significant association between NT-proBNP and the PA-TDI interval.*

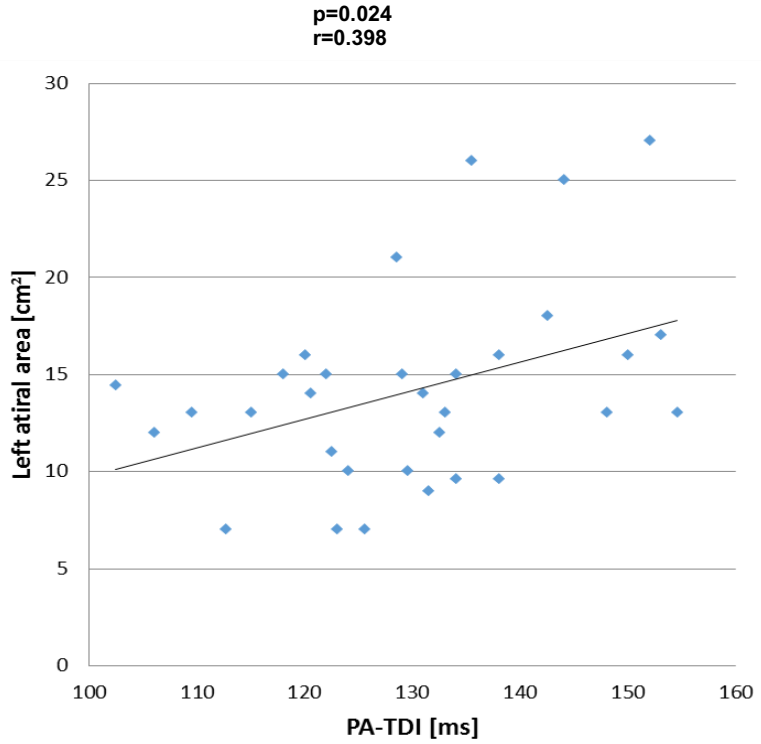

Figure 13: ***The PA-TDI interval in relation to left atrial area.*** *There was significant association between the left atrial area and the PA-TDI interval.*

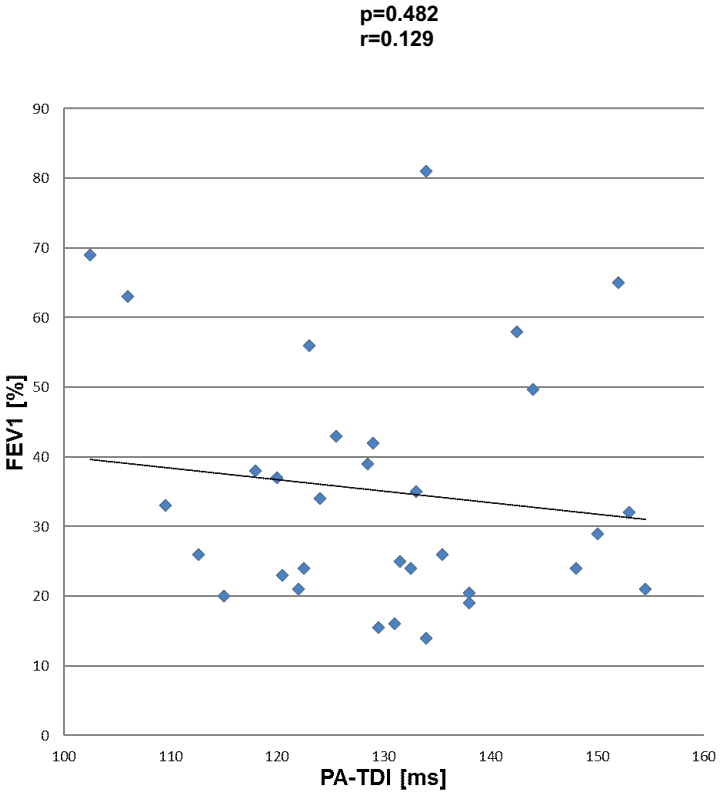

Figure 14: ***The PA-TDI interval in relation to FEV1 [%].*** *The PA-TDI interval did not correlate with the FEV1 [%]. FEV1= percentage of the predicted forced expiratory volume in one second*

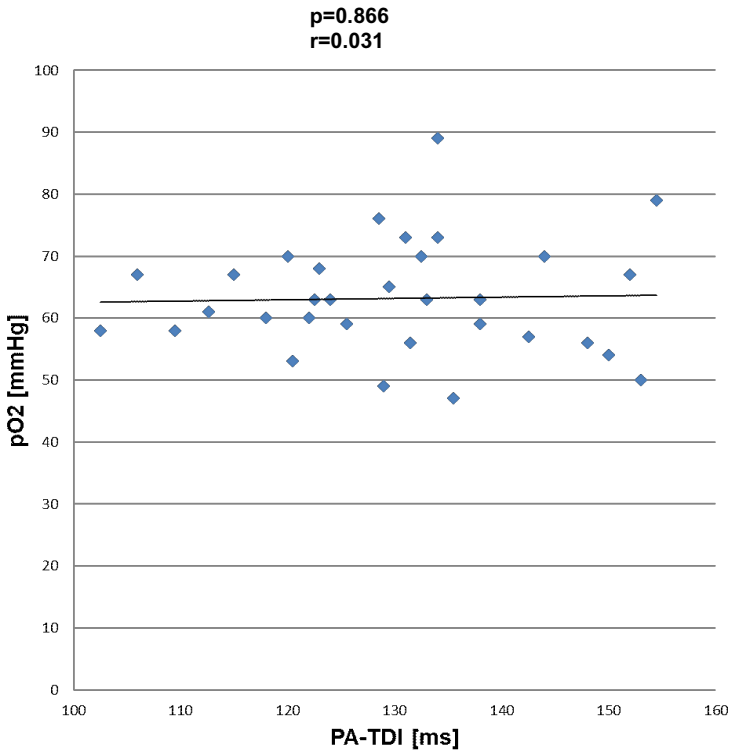

Figure 15: ***The PA-TDI interval in relation to pO2.*** *There was no association found between the PA-TDI interval and the pO2. pO2=partial pressure of oxygen*

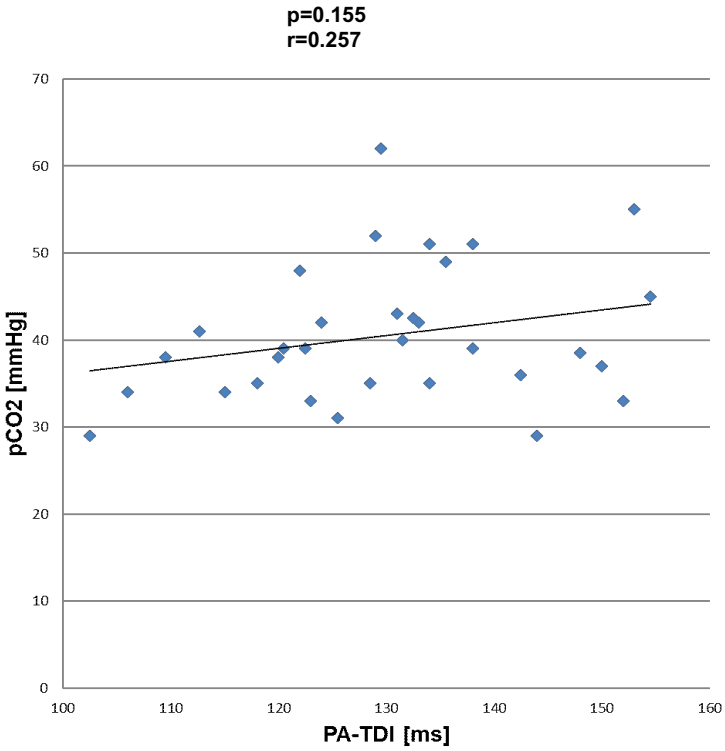

Figure 16: ***The PA-TDI interval in relation to pCO2.*** *There was no correlation between the pCO2 and the PA-TDI interval. pCO2=partial pressure of carbon dioxide*

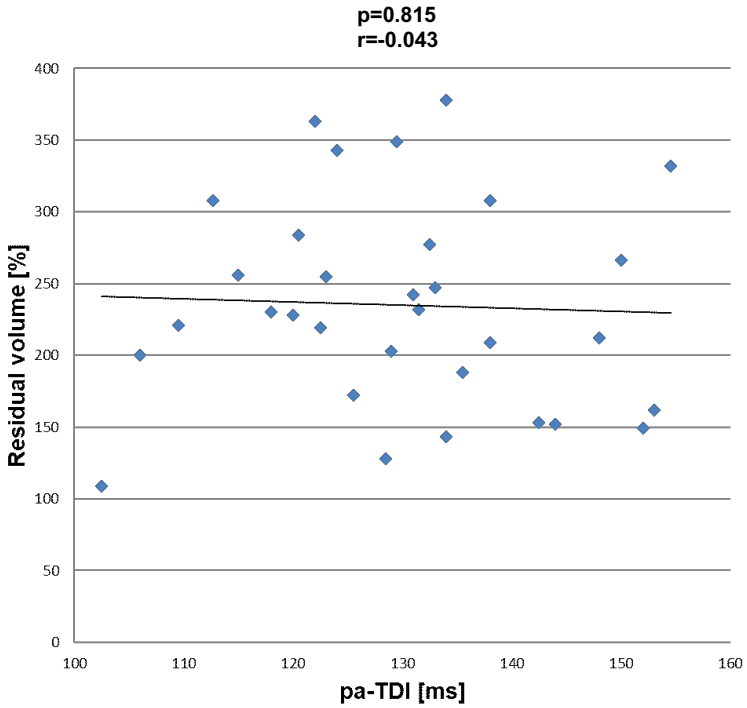

Figure 17: ***The PA-TDI interval in relation to residual volume.*** *There was no correlation between the residual volume and the PA-TDI interval.*

4.5 The QTc

The QTc was prolonged in patients with AECOPD as opposed to patients with stable COPD (418.75 ± 34.12 vs. 463.69 ± 51.35 ms; p=0.021). The patients with AECOPD had a higher C-reactive protein and therefore higher degree of inflammation. A similar observation was made between the QTc and the C-reactive protein. Patients with a higher C-reactive protein also had a higher QTc (r=0.427; p=0.0150; Figure 18) which shows that a higher degree of inflammation is associated with a longer QTc. A positive correlation between the QTc and various hemodynamic variables (cardiac index, end diastolic index, contractility index, total peripheral resistance and left ventricular work index) was also found (r=0.443; p=0.0130; Figure 19 r=0.372; p=0.039; Figure 20; r=0.363; p=0.0450; Figure 21; r=0.395; p=0.0280; Figure 22 r=0.442; p=0.0130; Figure 23). These hemodynamic values reflect that a worse cardiac output is associated with a longer QTc.

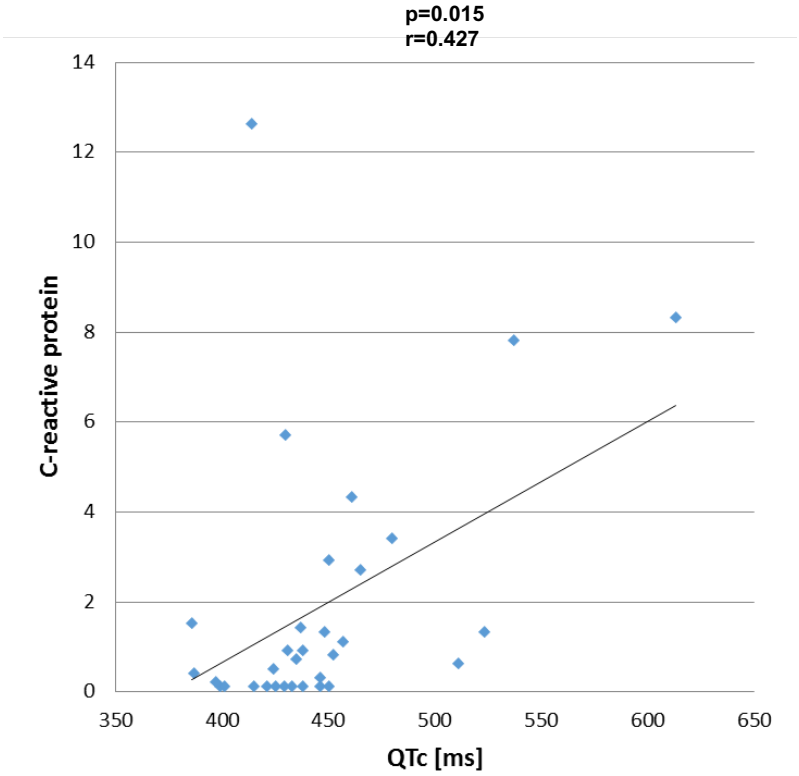

Figure 18: ***The QTc in relation to the C-reactive protein****. There was a significant association between the QTc and the C-reactive protein.*

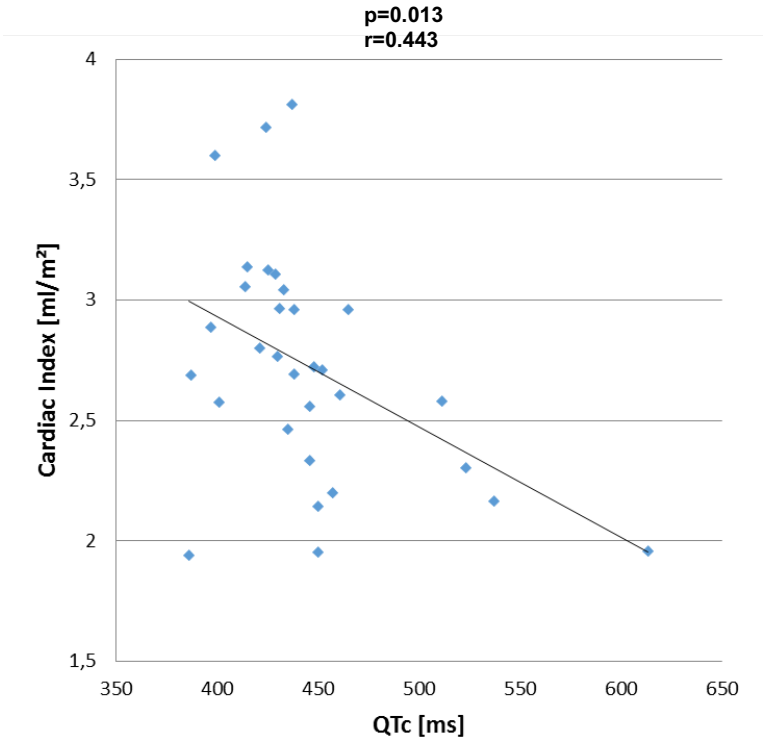

Figure 19: ***The QTc in relation to the cardiac index*** *There was a significant association between the QTc and the cardiac index.*

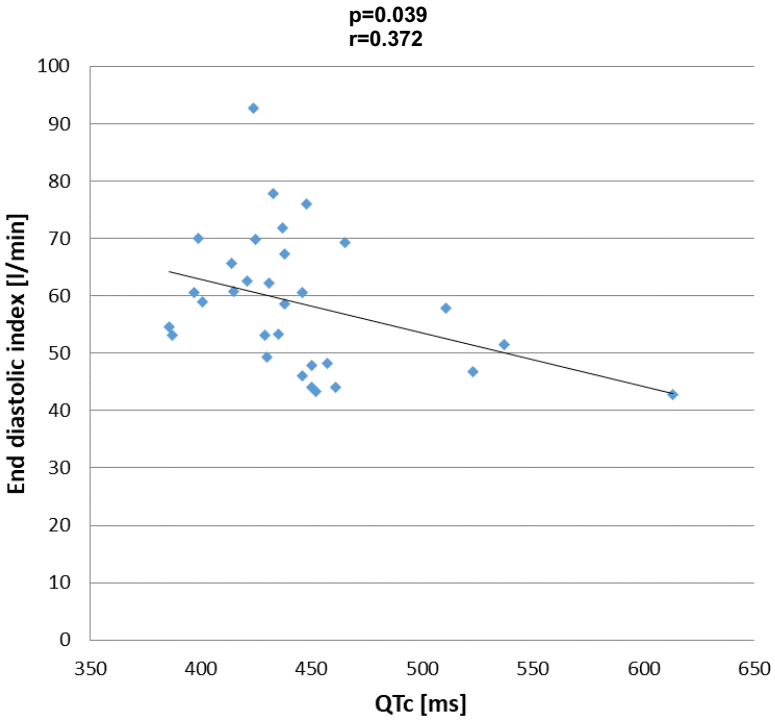

Figure 20: ***The QTc in relation to the end diastolic index****. There was a significant association between the QTc and the end diastolic index.*

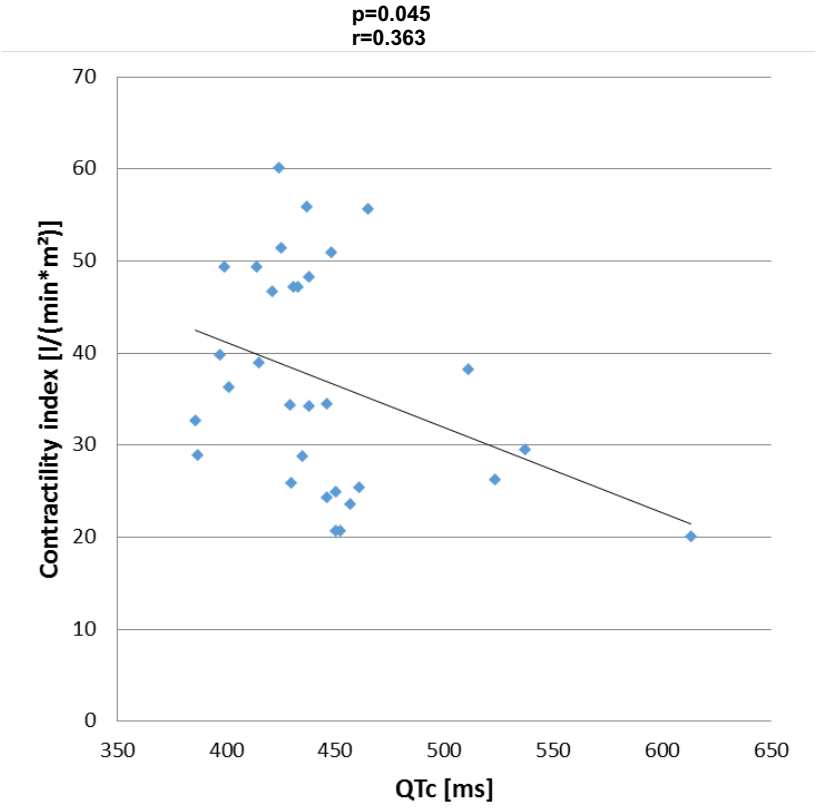

Figure 21: ***The QTc in relation to the contractility index****. There was a significant association between the QTc and the contractility index.*

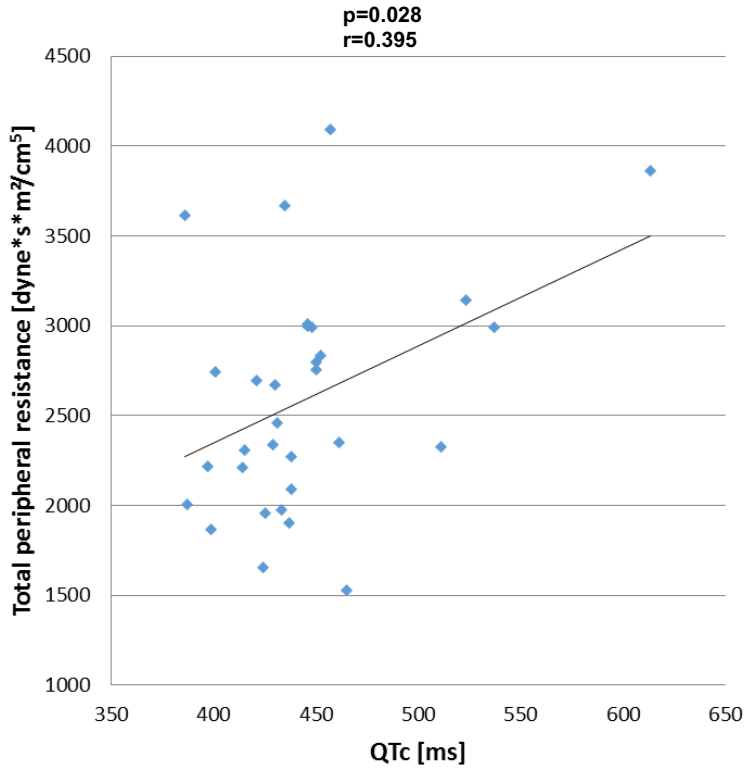

Figure 22: ***The QTc in relation to the total peripheral resistance****. There was a significant association between the QTc and the total peripheral resistance.*

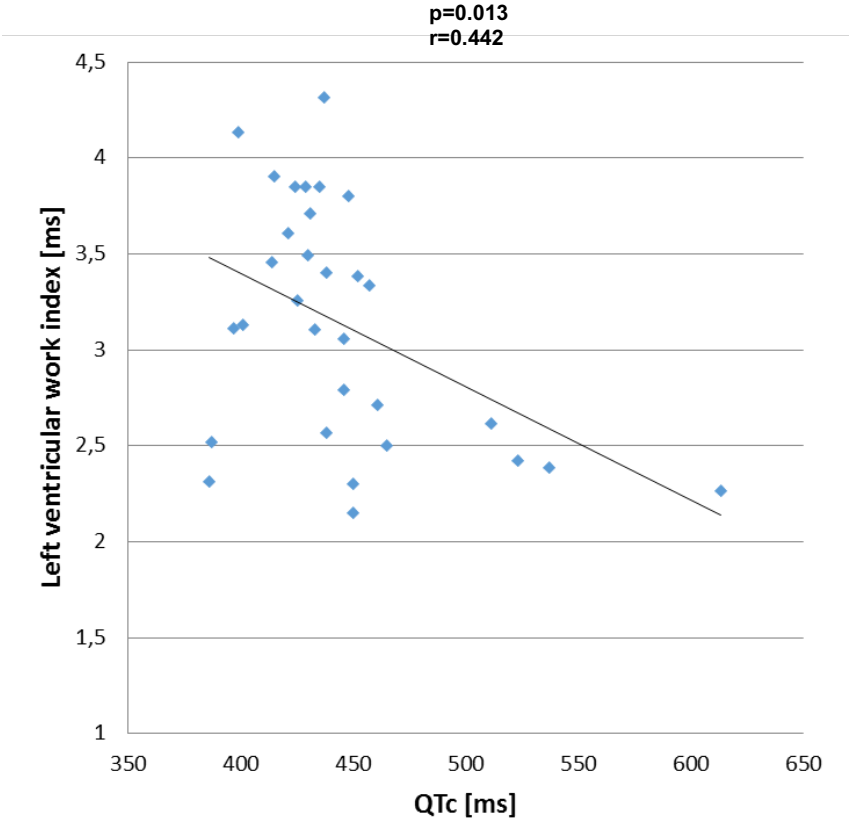

Figure 23: ***The QTc in relation to the left ventricular work index****. There was a significant association between the QTc and the left ventricular work index.*

4.6 Hemodynamic parameters during the resting phase

The hemodynamic parameters during the resting phase were recorded in patients with AECOPD and stable COPD (Table 13). There was no difference visible in comparing the hemodynamic parameters during the resting phase between both groups. It is important to note that the hemodynamic parameters during the resting phase were recorded in patients with AECOPD several days after they presented in the accident and emergency department. Thus, there was a difference in the heart rate at the accident and emergency department and when the patients underwent autonomic function testing several days after.

		stable COPD	exacerbated COPD	***p***
HR	*[bpm]*	82.50 ± 14.33	75.15 ± 9.81	0.11
sBP	*[mmHg]*	111.37 ± 11.69	109.92 ± 17.95	0.79
dBP	*[mmHg]*	71.66 ± 10.23	66.83 ± 12.64	0.25
mBP	*[mmHg]*	88.74 ± 10.09	85.04 ± 13.84	0.40
SI	*[ml]*	34.85 ± 6.49	35.60 ± 8.84	0.79
CI	*[ml/m²]*	2.82 ± 0.46	2.62 ± 0.50	0.25
EDI	*[l/min]*	58.65 ± 9.91	58.78 ± 14.01	0.98
IC	*[l/(min*m²)]*	37.03 ± 10.09	36.96 ± 14.07	0.99
ACI	*[dyne*s/cm^5]*	52.74 ± 14.82	54.27 ± 25.71	0.92
TPRI	*[dyne*s*m²/cm^5]*	2558.31 ± 573.24	2625.08 ± 722.18	0.78
LVWI	*[ms]*	3.30 ± 0.62	2.96 ± 0.61	0.14
LVET	*[1000/s]*	294.89 ± 22.19	299.58 ± 20.67	0.55
TFC	*[100/s²]*	27.69 ± 3.40	26.33 ± 4.86	0.37

Table 13: ***Hemodynamic parameters during the resting phase between patients with stable and exacerbated COPD.*** *There was no difference noted between the hemodynamic parameters in both groups. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease, sBP=systolic blood pressure, dBP=diastolic blood pressure, mBP=mean blood pressure; SI=stroke index, CI=cardiac index; EDI=end diastolic index, IC=contractility index, ACI=acceleration index, TPRI=total peripheral resistance, LVWI=left ventricular work index; LVET=left ventricular ejection time; TFC=total chest fluid content*

4.7 Heart rate variability during the resting phase

During the resting phase, the heart rate variability of both patient groups was recorded. The high frequency representing the parasympathetic activity did not differ between the patients with stable COPD and patients with AECOPD. Likewise, the low frequency expressing sympathetic and parasympathetic activity, was also not different between both groups. The LF/HF ratio displaying the relationship between sympathetic and parasympathetic nerve activities also did not show any change between both groups (Table 14).

		stable COPD	exacerbated COPD	*p*
LF/HF Ratio		2.07 ± 2.14	1.54 ± 1.93	0.42
LFnu-RRI-Baseline Ende	*[%]*	51.28 ± 25.77	45.02 ± 20.76	0.51
HFnu-RRI-Baseline Ende	*[%]*	48.72 ± 25.77	54.98 ± 20.76	0.51
LF-RRI-Baseline-Ende	*[ms²]*	139.72 ± 194.52	234.68 ± 424.01	0.74
HF-RRI-Baseline-Ende	*[ms²]*	9907.79 ± 38356.96	351.73 ± 909.74	0.77

Table 14: ***Heart rate variability during the resting phase in patients with stable and exacerbated COPD.*** *Overall, there was no difference noted across both groups. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease; LF=low frequency; HF=high frequency.*

4.8 Resting phase of the parasympathetic nervous system

Looking at the deep breathing test (E/I- difference and E/I ratio), the Ewing test (30/15 ratio) and the spontaneous baroreflex sensitivity in patients with AECOPD and stable COPD, one could see that there was no difference between both groups (Table 15). Thus, the resting phase of the parasympathetic nervous system was unchanged in the stable and AECOPD patients, though there was a tendency for the BRS and chemoreflex sensitivity to be reduced in the patient group with AECOPD, suggesting lower parasympathetic activity. The hemodynamic parameters before applying 5 Liters of oxygen were similar in both patient groups (Table 16). Likewise, there was no difference in the hemodynamic parameters after applying 5 liters of oxygen (Table 17).

		stable COPD	exacerbated COPD	*p*
E/I- Differenz (normal value ≥5)	*[min $^{-1}$]*	11.43 ± 10.56	9.19 ± 5.93	0.98
E/I Ratio (normal value: ≥ 1,10)		1.22 ± 0.29	1.12 ± 0.09	0.83
30/15 ratio (normal value: ≥ 1,09)		1.22 ± 0.29	1.12 ± 0.09	0.71
BRS (normal value: ≥ 9,3)	*[ms/ mmHG]*	8.59 ± 3.79	6.38 ± 3.86	0.09
Chemoreflexsensitivity	*[ms/ mmHG]*	0.98 ± 1.44	0.41 ± 0.41	0.09

Table 15: **Resting phase of the parasympathetic nervous system.** Overall, there was no difference noted across both groups. Values are calculated as mean values ± standard deviation. COPD=chronic obstructive pulmonary disease; E=expiration, I=inspiration, BRS=baroreflex sensitivity.

		stable COPD	exacerbated COPD	*p*
RRI-O2 onset	*[ms]*	790.84 ± 135.61	840.56 ± 121.12	0.29
HR-O2 onset	*[bpm]*	78.76 ± 13.47	73.15 ± 10.76	0.21
sBP-O2 onset	*[mmHg]*	114.02 ± 9.11	112.78 ± 19.37	0.82
dBP-O2 onset	*[mmHg]*	73.50 ± 10.75	70.16 ± 10.61	0.39
mBP-O2 onset	*[mmHg]*	91.19 ± 9.81	88.34 ± 12.66	0.49
SV-O2 onset	*[ml]*	64.53 ± 16.68	63.53 ± 13.43	0.86
SI-O2 onset	*[ml/m²]*	35.79 ± 6.95	35.33 ± 7.82	0.86
HZV-O2 onset	*[l/min]*	4.93 ± 0.91	4.55 ± 0.78	0.22
CI-O2 onset	*[l/(min*m²)]*	2.76 ± 0.41	2.53 ± 0.43	0.14
TPR-O2 onset	*[dyne*s/cm^5]*	1518.35 ± 427.31	1552.63 ± 301.38	0.80
TPRI-O2 onset	*[dyne*s*m²/cm^5]*	2669.50 ± 618.68	2820.96 ± 730.43	0.54

Table 16: ***Hemodynamic parameters before activation of the parasympathetic nervous system (before applying 5 Liter O2).*** *Overall, there was no difference noted across both groups. Values are calculated as mean values ± standard deviation. RRI=RR-interval, HR=heart rate, sBP=systolic blood pressure, dBP=diastolic blood pressure, mBP=mean blood pressure, SV=stroke volume, HZV= heart rate variability, TPR=total peripheral resistance, BRS=baroreflex sensitivity.*

		stable COPD	exacerbated COPD	*p*
RRI-O2 after	*[ms]*	787.89 ± 119.95	829.36 ± 111.78	0.33
HR-O2 after	*[bpm]*	79.33 ± 11.15	74.90 ± 10.13	0.26
sBP-O2 after	*[mmHg]*	113.92 ± 8.40	112.45 ± 23.87	0.82
dBP-O2 after	*[mmHg]*	74.98 ± 9.40	68.40 ± 13.52	0.12
mBP-O2 after	*[mmHg]*	92.23 ± 8.27	87.44 ± 16.99	0.32
SV-O2 after	*[ml]*	64.61 ± 15.83	64.95 ± 13.80	0.95
SI-O2 after	*[ml/m²]*	35.95 ± 6.98	35.99 ± 7.38	0.99
HZV-O2 after	*[l/min]*	5.00 ± 0.95	4.74 ± 0.76	0.41
CI-O2 after	*[l/(min*m²)]*	2.80 ± 0.46	2.62 ± 0.32	0.24
TPR-O2 after	*[dyne*s/cm^5]*	1583.08 ± 492.99	1488.84 ± 312.43	0.53
TPRI-O2 after	*[dyne*s*m²/cm^5]*	2796.11 ± 825.85	2713.72 ± 693.53	0.77

Table 17: ***Hemodynamic parameters after activation of the parasympathetic nervous system (after applying 5 Liter O2).*** *Overall, there was no difference noted across both groups. Values are calculated as mean values ± standard deviation. RRI=RR-interval, HR=heart rate, sBP=systolic blood pressure, dBP=diastolic blood pressure, mBP=mean blood pressure, SV=stroke volume, HZV= heart rate variability, TPR=total peripheral resistance, BRS=baroreflex sensitivity.*

4.9 Activation of the sympathetic nervous system via the cold pressure test

Patients with stable COPD and AECOPD both had similar hemodynamic values (heart rate and blood pressure) before the cold pressure test (Table 18). After 45 seconds of embedding the hand in ice water, the heart rate rose in both groups but the difference in the rise of the heart rate was not different across both groups. Likewise, both patient groups had similar systolic and diastolic blood pressure before the cold pressure test. A slight rise in the systolic and diastolic blood pressure was noted in both groups. However, there was no statistically

significant difference in the rise of the blood pressure between both groups. So, the degree of the sympathetic activation in the cold pressure test was similar in patients with stable COPD and AECOPD.

		stable COPD	exacerbated COPD	*p*
HF T0	*[bpm]*	83.28 ± 12.26	75.69 ± 12.05	0.10
HF 45 sec	*[bpm]*	88.69 ± 19.86	77.90 ± 10.67	0.08
HF-Diff	*[bpm]*	5.07 ± 14.50	2.21 ± 6.55	0.50
BPsys (T0)	*[mmHg]*	109.85 ± 11.23	119.47 ± 19.32	0.13
Bpsys 45s	*[mmHg]*	116.57 ± 17.66	122.20 ± 21.14	0.47
BPsys-Diff	*[mmHg]*	6.24 ± 11.94	2.73 ± 6.33	0.35
BPdia (T0)	*[mmHg]*	72.85 ± 11.17	72.28 ± 15.56	0.91
BPdia 45s	*[mmHg]*	74.50 ± 9.07	73.91 ± 14.40	0.90
BPdia-Diff	*[mmHg]*	1.53 ± 7.67	1.63 ± 7.58	0.97
BPm (T0)	*[mmHg]*	88.17 ± 10.72	93.38 ± 14.52	0.31
BPm 45s	*[mmHg]*	91.81 ± 9.22	94.76 ± 15.32	0.56
BPm-Diff	*[mmHg]*	3.38 ± 10.35	1.38 ± 7.53	0.57

Table 18: ***Heart rate and blood pressure before and after cold pressure test.*** *Values are calculated as mean values ± standard deviation. HF0=heart rate before the cold pressure test, HF 45 sec=heart rate whilst the hand is emerged in ice water for 45 seconds, BPsys(T0)=systolic blood pressure before the cold pressure test, BPsys45s=systolic blood pressure whilst the hand was emerged in ice water for 45 seconds, BPsys-Diff=difference between BPsys(T0) and BPsys45s, BPdia(T0)= diastolic blood pressure before the cold pressure test, BPdia45s= diastolic blood pressure whilst the hand was emerged in ice water for 45 seconds, BPdia-Diff= difference between BPdia(T0) and BPdia45s, BPm(T0)= mean arterial blood pressure before the cold pressure test, BPm45s= mean arterial blood pressure whilst the hand was emerged in ice water for 45 seconds, BPm-Diff= difference between BPm(T0) and BPm45s.*

4.10 Sympathetic and parasympathetic activation via the cold face test

Both patient groups had similar heart rates before the cold face test (Table 19). After gel filled compresses on the forehead and cheeks were applied for 45 seconds, the heart rate was recorded again. The difference between the first reading of the heart rate before the cold face test and 45 seconds after the cold face test in the group of patients with stable COPD was not statistically different from the group of patients with AECOPD. Likewise, the difference in the first reading of the diastolic and mean arterial blood pressure before the cold face test and 45 seconds after the cold face test did not differ across both patient groups. There was a slight tendency for a greater rise in systolic blood pressure in the patients with stable COPD as opposed to patients with AECOPD. This tendency for a greater rise in the systolic blood pressure in the stable COPD patients could imply that there is impaired sympathetic activation in patients with AECOPD than in patients with stable COPD.

		stable COPD	exacerbated COPD	*p*
HF T0	*[bpm]*	83.02 ± 21.05	74.07 ± 11.83	0.16
HF 45 sec	*[bpm]*	78.44 ± 11.79	74.25 ± 10.46	0.31
HF-Diff	*[bpm]*	-4.58 ± 20.66	0.17 ± 5.78	0.40
BPsys (T0)	*[mmHg]*	115.44 ± 11.85	117.05 ± 21.47	0.81
BPsys 45s	*[mmHg]*	122.16 ± 13.78	116.52 ± 17.87	0.36
BPsys-Diff	*[mmHg]*	6.71 ± 9.78	-0.53 ± 12.77	0.10
BPdia (T0)	*[mmHg]*	73.52 ± 11.12	70.91 ± 13.40	0.58
Bpdia 45s	*[mmHg]*	78.30 ± 11.11	73.22 ± 13.45	0.29
BPdia-Diff	*[mmHg]*	4.78 ± 6.74	2.31 ± 5.82	0.31
BPm (T0)	*[mmHg]*	92.94 ± 11.41	90.29 ± 14.89	0.60
BPm 45s	*[mmHg]*	97.98 ± 10.97	91.55 ± 13.96	0.19
BPm-Diff	*[mmHg]*	5.04 ± 7.50	1.26 ± 8.93	0.24

Table 19: ***Heart rate and blood pressure before and after cold face test.*** *Values are calculated as mean values ± standard deviation. HF0=heart rate before the cold face test, HF 45 sec=heart rate whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds, BPsys(T0)=systolic blood pressure before the cold face test, BPsys45s=systolic blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds, BPsys-Diff=difference between BPsys(T0) and BPsys45s, BPdia(T0)= diastolic blood pressure before the cold face test, BPdia45s= diastolic blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds, BPdia-Diff= difference between BPdia(T0) and BPdia45s, BPm(T0)= mean arterial blood pressure before the cold face test, BPm45s= mean arterial blood pressure whilst gel filled compresses on the forehead and cheeks were applied for 45 seconds, BPm-Diff= difference between BPm(T0) and BPm45s.*

5 Discussion

5.1 Increased PA-TDI in AECOPD

On the TDI echocardiography the PA-TDI interval is measured and represents the total atrial conduction time (De Vos et al., 2009). The PA-TDI interval is thought to be a noninvasive surrogate marker for atrial fibrosis (Müller et al., 2013). It was shown that patients after cardiac surgery with more atrial fibrosis on biopsy specimen and a prolonged PA-TDI interval had a greater risk of developing new onset atrial fibrillation (Müller et al., 2013). Likewise, it was shown that the PA-TDI interval is related to left atrial enlargement, reduction in left atrial voltage and prolongation of the left atrial total activation time (Chao et al., 2011; de Vos et al., 2009; Müller et al., 2014). The enlargement of the left atrium is an elementary process of left atrial remodeling and increased dimensions have been seen in patients with increased PA-TDI in previous studies (de Vos, Müller 2014).

Our results demonstrate that patients with AECOPD have a prolonged PA-TDI interval when compared to patients with stable COPD suggesting an increased risk of atrial fibrillation in AECOPD patients. Likewise, there was a positive correlation between a prolonged PA-TDI interval and the left atrial area. Although the FEV1 was significantly reduced in patients with AECOPD, no correlations between the PA-TDI interval and the FEV1 was found. Likewise, the PA-TDI interval did not correlate with other parameters of pulmonary function including residual volume, pO2 or pCO2. Caglar et al. measured the total atrial conduction in patients with COPD as well as in patients without COPD, who were the control subjects. This study found a weak correlation between the total atrial conduction time of the right atrium and the FEV1 (Cagler et al., 2012). However, previous studies have not elaborated the total atrial conduction time in patients with AECOPD.

Concerning cardiac characteristics both patient groups (stable and exacerbated COPD) had a similar level of NT-proBNP. This means that cardiac function as assessed by a biomarker seems to be comparable between study groups. From this it can be postulated that the increased PA-TDI interval and the increased risk of AF were not related to an obvious cardiac decompensation during exacerbation. Perhaps the higher heart rate of patients with AECOPD may lead to a greater formation of atrial fibrosis and thus prolonged PA-TDI interval. For example, rapid atrial pacing in a canine model resulted in a fourfold release of collagen-I and fibronectin-I from atrial myocytes causing atrial remodeling (Burstein et al., 2007). Also, no differences were found in left ventricular function, left atrial dimensions or severity of pulmonary hypertension between patients with stable and exacerbated COPD.

Three other parameters were identified as a major determinant of an increased PA-TDI interval in our study. These parameters were age, BMI as well as cardiac structure and function. The relationship between an increase in age and atrial fibrillation was also found in the ATRIA study

(Go et al., 2001). This cross-sectional study with around 1.9 million probands found that the prevalence of atrial fibrillation increases with more age. This link could possibly be explained by the greater degree of atrial fibrosis in older people (Akoum et al., 2018). Abou et al. measured the PA-TDI interval in 386 patients aged between 16 and 91 years without structural heart disease. In this study it was found that a greater age was independently associated with prolonged a PA-TDI possibly due to age-related fibrosis (Abou et al., 2017).

Also, obesity according to the BMI is considered as a risk factor of AF (Murphy et al., 2006; Huxley et al., 2014). The pathways of obesity contributing to atrial fibrillation are multifactorial. Studies have shown that obese patients have a greater degree of left ventricular diastolic dysfunction, increased sympathetic activity, more inflammation and increased fatty infiltration of the atria (Karason et al., 1999; Russo et al., 2011; Visser et al., 1999). Weight reduction in obese patients led to fewer recurrences of atrial fibrillation and (Pathak et al., 2015). Increased fatty infiltration of the atria has been shown to give rise to an enlargement of the left atria and reduced compliance of the left atria (Aurigemma et al., 2013). This pathway may be a possible explanation for the positive correlation between the PA-TDI interval and the BMI.

Further evidence suggests the role of inflammation and oxidative stress in the formation of atrial fibrosis (Guiterrez & Van Wagoner, 2015). The examination of atrial tissue in patients with atrial fibrillation showed an upregulation of inflammatory markers. Likewise, it was shown that anti-inflammatory medication has beneficial effects in such patients (Harada et al., 2015). Inflammation is associated with oxidative stress, apoptosis and fibrosis, which can then cause atrial fibrillation (Sovari, 2016). COPD is characterized by systemic inflammation, especially when patients are exacerbated and this inflammation may play an important role in the formation of atrial fibrosis and thus trigger atrial fibrillation (Barnes, 2016). Acar et al., evaluated the atrial electromechanical delay and its relationship to inflammation and oxidative stress in 43 patients with COPD and 50 healthy controls. It was found that atrial electromechanical delay intervals were significantly prolonged in patients with COPD than healthy subjects. Similarly, the high sensitive C-reactive protein, an indicator for inflammation, was higher in patients with COPD than healthy subjects. Similar results were also shown by our patients. In our study, patients with AECOPD had a higher C-reactive protein than patients with stable COPD. However, no correlation between the C-reactive protein and the PA-TDI interval was found.

In summary, patients with AECOPD have a prolonged PA-TDI interval which is a surrogate marker for increased risk of atrial fibrillation. Simultaneously, AECOPD patients were characterized by an increased inflammation. When considering all study subjects (stable and exacerbated COPD) the PA-TDI interval was related to age, BMI and left atrial dimension as shown by significant correlations.

5.2 Prolonged QTc

It was also shown that patients with AECOPD had a longer QTc than patients with stable COPD. Another study showed that COPD patients with autonomic neuropathy had a greater probability of a prolonged QTc (Stewart et al., 1995). In this study, it was also shown that COPD patients with autonomic neuropathy were more hypoxemic than COPD patients without autonomic neuropathy (Stewart et al., 1995). The exact mechanism of the prolonged QTc has not been understood. Acquired forms of QTc prolongation have mainly been related to specific drugs. The main group of drugs causing acquired forms of QTc prolongation are antiarrhythmic medication, antipsychotic medication and antimicrobial medication (Kallergis et al., 2012). Multiple clinical risk factors contribute also to the prolongation of the QTc. These risk factors include hypokalaemia, structural heart disease, congestive heart failure and electrophysiological disorders (Kallergis et al., 2012). Maybe an imbalance of the autonomous nervous system plays also an important role in the prolongation of the QTc as shown in the aforementioned study (Stewart et al., 1995). After myocardial infarction in dogs, it was shown that parasympathetic vagal stimulation reduced the occurrence of arrythmias and sudden death (Vanoli et al., 1991). A rise in the heart rate stimulates the vagal tone which then slows down the rise of the heart rate and therefore protects the QTc from prolonging. Such findings have an important clinical implication in patients with COPD. High risk groups in patients with COPD can be selected and early intervention could improve life expectancy.

QTc prolongation has also been identified as a risk marker for sudden cardiac death (SCD) (Algra et al., 1991). Another large population-based cohort study among 14926 subjects found an increased risk for SCD in patients with COPD as opposed to patients without COPD (Lahousse et al., 2015). This study found a particularly increased risk in COPD patients with frequent exacerbations. Differences in the QTc were not found in this study. However, another study found evidence of a prolonged QTc in COPD patients (Nilsson et al., 2019). In stable COPD patients Nilsson et al. found QTc prolongation in patients with COPD as opposed to healthy subjects with normal lung function. Moreover, the study found a correlation between a prolonged QTc and the severity of COPD as assessed by the GOLD criteria. Likewise, COPD patients with a prolonged QTc had an increased risk of mortality in comparison to patients with normal lung function and prolonged QTc (20.5 versus 9.4%) (Nilsson et al., 2019). A relationship between lung function characteristics and QTc prolongation was also found by a multicenter, prospective cohort study (Multi-Ethnic Study of Atherosclerosis (MESA)) (Armstrong et al., 2017). Hypokalemia, cardiac troponin concentration and conduction abnormalities on ECG were identified to be independently associated with QTc prolongation (Van Oekelen et al., 2018). Oekelen et al., also showed in their retrospective study that a prolonged QTc was a rather common finding in approximately 30% of patients with AECOPD. Furthermore, an increased troponin concentration and a prolonged QTc were regarded as

potential marker for an underlying cardiovascular disease or increased right ventricular strain during an AECOPD (Van Oekelen Int et al., 2018). Interestingly, when a comparison was drawn between the QTc prolongation in AECOPD patients and patients with other acute respiratory diseases then no significant differences were found between these two patient groups. A relationship between QTc prolongation and mortality was not found in patients with AECOPD (Van Oekelen et al., 2018). Mandyam et al., used the QTc to predict the incident of atrial fibrillation (Mandyam et al., 2013). For this purpose, the QTc in 14538 Atherosclerosis Risk in Communities (ARIC) study participants was examined. The study showed that the ARIC participants with a prolonged QTc had an approximately 2-fold increased risk of atrial fibrillation.

In conclusion, there is increasing evidence of QTc prolongation in COPD patients that has been related to the severity of COPD, hypoxemia, hypokalaemia or increased troponin concentrations. A prolonged QTc could be regarded as risk marker for mortality. However, this fact needs further investigation in large scale clinical studies.

5.3 Autonomic Dysfunction

One of the objectives of this study was to compare the level of autonomic function between patients with stable COPD and AECOPD. Our results showed that the heart rate variability between patients with stable COPD and AECOPD was not different. Among fifteen studies that analysed heart rate variability in patients with COPD and healthy controls, most had lower heart rate variability in patients with COPD as compared with patients without COPD (Mohammed et al., 2015).

Similarity, baroreceptor sensitivity did not differ between patients with stable and AECOPD but there was a tendency for a reduced baroreflex sensitivity in patients with AECOPD. Thus, there is an assumption of lower parasympathetic activity in patients with AECOPD. Comparably results were demonstrated in five other studies that were assessing baroreceptor sensitivity in patients with COPD (Costes et al., 2004; Bernardi et al., 2008; Bartels et al., 2012; Haider et al., 2009; Raupach et al., 2008). In these five studies, baroreceptor sensitivity was significantly reduced in patients with COPD as opposed to healthy controls. The baroreflex is important in the short-term regulation of blood pressure. Possible explanations for this depression of the baroreceptor sensitivity in patients with AECOPD are the higher degree of hypoxia, oxidative stress and intrathoracic pressure changes (van Gestel et al., 2011). This impairment of the baroreflex sensitivity could also be an explanation why the patients with AECOPD in our study had a higher systolic blood pressure as opposed to patients with stable COPD. The initial increase in the blood pressure observed in patients with AECOPD would trigger a stretch in the baroreceptors, but these baroreceptors would fail to enhance the parasympathetic nervous system. This would result in a failed decrease of the heart rate and the total peripheral

resistance (Pang, 2001). As a result, impaired baroreflex sensitivity causes an increase in sympathetic activity (Cournand et al., 1948; Raupach et al., 2008).

In our study, there was a tendency for the chemoreflex sensitivity to be lower in patients with AECOPD than stable COPD, but this difference was not statically significant. COPD is characterized with hypoxemia and can affect the autonomic nervous system. It was shown that acute hypoxemia raises the sympathetic nervous activity by stimulating the arterial chemoreceptors in health humans (Hardy et al., 1994). However, other mechanisms apart from hypoxia may also play a role. It was observed that both hypoxemic and normoxemic patients with COPD (Scalvini et al., 1999) had signs of autonomic dysfunction. Therefore, the relationship between chemoreceptor sensitivity and autonomic dysfunction is difficult to estimate because the sensitivity of the chemoreceptors may be modified over time.

In this study, the cold face test showed that the systolic blood pressure had a greater tendency of rising in the patient group with stable COPD as opposed to AECOPD. This could imply that the sympathetic activation is impaired in patients with AECOPD. A similar study assessing sympathetic skin response reported that sympathetic skin response was reduced in patients with COPD as opposed to health controls (Bir et al., 2005). However, more evidence is needed to show the impairment of sympathetic skin response.

The actual function of the autonomic nervous system could not be directly measured which was a great limitation in our study. The method to derive values for the autonomic function for each of our patients was non-invasive. More information would be acquired via a direct measurement of the autonomic nervous system and this would be more invasive, but an invasive approach would be less feasibly to implement in humans. In our study, the patients with AECOPD could not undergo the autonomic function test upon arrival in the accident and emergency department. Only after receiving adequate medical therapy for a few days, they would undergo the autonomic function test. By that time, some of the autonomic function imbalances may have been alleviated so that we could not detect them in our autonomic function test. Additionally, our population of patients was 32 in this study. Perhaps more patients in our study would have provided more statistical accuracy and precision in the assessment of autonomic function.

5.4 Conclusion

One of the aims of this study was to look at the probability of new onset atrial fibrillation in patients with stable COPD and AECOPD. For this purpose, we used an echocardiographic predictor for atrial fibrillation, namely the PA-TDI interval. Previous studies had shown that a prolonged PA-TDI interval was associated with a higher risk of atrial fibrillation. Assessing the PA-TDI interval in patients with stable and AECOPD, it was demonstrated that the PA-TDI interval was longer in patients with AECOPD than stable COPD. This finding had not been shown before. Furthermore, it was shown that a greater age and BMI correlated with the length of the PA-TDI interval. This would mean that older people with COPD had a longer PA-TDI interval and thus a higher risk of atrial fibrillation, possibly due to the higher degree of atrial fibrosis found in older people. Coincidentally, it was also illustrated that patients with AECOPD had a prolonged QTc and therefore a higher risk of atrial fibrillation. A possible pathophysiological pathway for this increased likelihood of atrial fibrillations in patients with COPD could be autonomic dysfunction. Previous studies had shown a higher degree of autonomic function in patients with COPD (Andreas et al., 2005; Camillo et al., 2011; van Gestel et al., 2011; Suh et al., 2013). The degree of autonomic dysfunction was assessed with a special monitoring system (Task Force ® Monitor). In this study, we did not see a statistically significant difference in the autonomic nervous system between patients with stable COPD and AECOPD. There was a tendency for a reduced baroreflex sensitivity and a reduced chemoreflex sensitivity in patients with AECOPD. Further studies are needed to understand the pathophysiological link between the increased risk of atrial fibrillation in patients with AECOPD as compared to patients with stable COPD.

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