Development of novel diagnostic approaches based on pulmonary physiology

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Applications in acute pulmonary embolism and
obstructive sleep apnea

T.M. Fabius

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Development of novel diagnostic approaches based on pulmonary physiology

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DISSERTATION

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General Introduction

T.M. Fabius

The aim of the research presented in this thesis was to develop and validate diagnostic approaches for acute pulmonary embolism and obstructive sleep apnea. Though these pathologies have many disparate characteristics, they share one important feature. Both pulmonary embolism and obstructive sleep apnea impair the main function of the lungs: gas exchange (i.e. the uptake of oxygen and the removal of carbon dioxide). This shared feature was used for the development of novel diagnostic tools. In this chapter, an introduction to acute pulmonary embolism and obstructive sleep apnea is presented.

ACUTE PULMONARY EMBOLISM

Acute pulmonary embolism (PE) is an acute obstruction of blood flow through the pulmonary arteries. Often, this obstruction is caused by a blood clot that originated from the deep peripheral veins in the legs. PE is common and requires treatment when diagnosed. In 2016 in the Netherlands, PE accounted for more than 16.000 hospital admissions and was listed as primary cause of death in 340 cases [1,2]. Though subjects suffering from PE may have severe complaints (e.g. dyspnea, thoracic pain, tachycardia, hemoptysis) it may also present without apparent symptoms [3].

The cornerstone of the treatment of PE is anticoagulation [4]. Management of the acute phase of PE depends on its severity. In hemodynamically unstable patients reperfusion using thrombolysis is warranted [5]. Of the stable patients, some become unstable within 24 to 48 hours after diagnosis. To identify these patients, risk stratification should be applied. The Pulmonary Embolism Severity Index (PESI) uses eleven several clinical characteristics to classify patients into five categories (from very low to very high risk of adverse events) [6]. Due to the complexity of the original version of the PESI, a simplified version was developed (sPESI) [7]. The sPESI is considered aberrant if the patient is either aged > 80 years, has a history of cancer, has a history of heart failure or chronic lung disease, has a pulse rate ≥ 110 /min, has a systolic blood pressure < 100 mmHg or has an arterial oxyhemoglobin saturation <90% [7]. If none of these criteria are present (i.e. the sPESI score is normal) there is a low risk of adverse events within 30 days after diagnosis and home treatment may be considered [8]. If the risk of adverse events is determined to be intermediate (i.e. the patient is hemodynamically stable but the sPESI or some other stratification rule is aberrant) the patient should be admitted and estimates of right ventricle overload and cardiac markers should be obtained. This can be done using imaging findings (such as the ratio of the width of the right ventricle to the width of the left ventricle [9]) and determination of laboratory markers of right ventricular dysfunction (such as N-terminal-pro brain natriuretic peptide (NT-proBNP) [10]) or myocardial injury (such as troponin [11]). If aberrant markers are found, close monitoring of vital functions should be applied during the first 48 – 72 hours to enable early recognition of deterioration [8].

Depending on the extent of the obstruction, PE may result in significant increased load on the right ventricle and hypoperfusion of the parts of the lung distal to the obstruction. As ventilation of these parts is unaltered, a ventilation / perfusion mismatch will occur (i.e. dead space ventilation). This may result in hypoxemia. An increase in arterial carbon dioxide levels may also be present but is likely to be corrected due to a compensatory increase in ventilation.

The physiologic effects of PE (increased vascular resistance and dead space ventilation) are potentially lethal. The mortality of untreated PE is often reported as 20 – 30% based on a small randomized controlled trial in the early 1960s [12]. If treated properly, mortality decreases substantially [13]. However, even with treatment, mortality within three months after diagnosis may still be substantial, but probably influenced by comorbidities associated with PE [14]. Given the high mortality rate and potential beneficial effects of treatment, a definite exclusion of PE is warranted when it is suspected. However, diagnosis of PE can be challenging as symptoms (mostly dyspnea and thoracic pain) are nonspecific. Several strategies have been developed to determine the risk of PE. These strategies often use a clinical decision rule (such as the Wells or revised Geneva score [15,16]) in combination with the D-dimer level in the blood. A low or moderate clinical probability combined with a D-dimer below 500 µg/L safely excludes PE [17]. If the clinical probability is high or the D-dimer is above 500 µg/L, imaging is warranted. The gold standard imaging technique for the confirmation or exclusion of PE is a ventilation / perfusion scan or computed tomography pulmonary angiography (CTPA) [8]. Despite the use of the previously mentioned selection strategies, PE is still confirmed in only 20-30% of the CTPA scans [18]. Due to the inherent limitations of these imaging techniques (i.e. costs, limited availability and requirement of irradiation) several improvements to increase the specificity of the previously mentioned screening strategies have been proposed. It was recognized that D-dimer levels increase with age. This led to the development of an age-dependent cutoff for the D-dimer level (i.e. 10 times the age with a minimum of 500 µg/L) [19]. A large randomized trial showed no differences in thromboembolic events after three months between the group with a static cutoff and the age-adjusted cutoff [20]. Another study identified the three most important items of the Wells-score (i.e. clinical signs of deep venous thrombosis, hemoptysis and PE being the most likely diagnosis) and implemented them in the YEARS algorithm [21]. If either one of the mentioned items is present, the conventional D-dimer cutoff of 500 µg/L should be applied. If none of the items is present, a D-dimer cutoff of 1000 µg/L can be used. In a large validation study, applying the YEARS algorithm did not lead to more thromboembolic events and need for CTPA scans was decreased with 14% compared to the conventional strategy of a static cutoff combined with the Wells-score [22].

In the first chapters of this thesis we investigated if measurements which may indicate impaired gas exchange, can safely be applied to exclude PE. If so, they might be used to decrease the need for imaging and thus potentially decrease costs and diagnostic delay. In **chapter 2**, we first tested the diagnostic accuracy of the diffusion capacity of the lungs for carbon monoxide and nitric oxide. As PE obstruct a part of the pulmonary vasculature, it seems logical that the

diffusion capacity is decreased. Indeed, several studies have shown that the diffusion capacity (or transfer factor) for carbon monoxide is decreased in PE [23,24]. For nitric oxide however, this decrease in diffusion capacity may be absent as the binding capacity for nitric oxide with hemoglobin is much higher compared to carbon monoxide making it virtually non-dependent to the vascular component of diffusion capacity [25]. The ratio of the diffusing capacity of the lungs for carbon monoxide and nitric oxide might thus indicate pulmonary vascular abnormalities [26]. One study in sheep showed that acute obstruction of a pulmonary artery indeed increases this ratio [27]. However, whether the nitric oxide / carbon monoxide transfer factor ratio is also affected in humans with PE has not been investigated earlier. In **chapter 2** we measured the diffusion capacity in patients presenting to the emergency department due to suspected PE. The results of the diffusion measurements were compared with the results of the CTPA scan to determine the diagnostic accuracy of the nitric oxide / carbon monoxide transfer factor ratio for the exclusion of PE.

In **chapter 3** we investigated the use of another physiologic measurement, volumetric capnography, for the exclusion of PE. Volumetric capnography can be used to reflect dead space ventilation [28]. Most studies using capnography in the diagnostic process of PE either used only end-tidal carbon dioxide levels or the combination of end-tidal carbon dioxide with arterial carbon dioxide levels [29]. In **chapter 3** we obtained volumetric capnograms in subjects presenting to the emergency department with suspected PE. We specifically compared a novel parameter, which combines conventional capnography parameters (without the need for arterial blood gas analysis) with the results of the CTPA scans, and sought to determine a cutoff that could safely exclude PE (i.e. a negative predictive value of 100%).

In **chapter 4** we used the data of a previous large study on volumetric capnography in the diagnostic process of PE to perform an external validation of the novel capnography parameter and the cutoff identified in **chapter 3**.

Obstructive Sleep Apnea

The hallmark feature of obstructive sleep apnea (OSA) is repetitive breathing stops during sleep caused by an obstruction of the upper airway. The frequent breathing stops cause sleep fragmentation. Consequently, patients suffering from OSA often experience snoring, excessive daytime sleepiness, morning headaches, and mood swings [30]. Paradoxically, patients also often complain about insomnia [31]. Apart from the clinical symptoms, patients have an increased risk of traffic accidents [32] and an increased risk of many comorbidities such as myocardial infarction and stroke [33,34]. Though obesity is often indicated as the main cause of OSA, its exact pathogenesis is more complex and still not fully understood. Research over the past two decades has shown that mechanical collapsibility is an important aspect but other factors such as sensitivity and responsiveness to decreasing intrathoracic pressures (caused by an apnea) may also be vital for the development of OSA [35,36].

The severity of OSA is often expressed as the amount of apneas and hypopneas per hour sleep, represented in the apnea-hypopnea index (AHI). The prevalence of OSA highly depends

on the definition that is used. A study in the early 1990s estimated that approximately two to four percent of middle-aged men has an AHI ≥ 5 and associated symptoms [37]. Despite this high prevalence, it was estimated that approximately 93% of all women and 82% of all men with moderate or severe OSA (i.e. AHI ≥ 15) were not clinically diagnosed [38]. Regardless of the definition used, the prevalence of OSA increased substantially over the past decades. In 2013, a relative increase of 14% and 55% (depending on the subgroup) was reported [39]. In 2015, a large population based study from Switzerland reported an even higher prevalence for moderate-to-severe sleep apnea (defined as an AHI ≥ 15); 23.4% in middle-aged women and 49.7% in middle-aged men [40]. It should be noted that this study did not require the presence of associated symptoms for an OSA diagnosis.

The gold standard for the diagnosis of OSA is full in-laboratory polysomnography (PSG) [41]. Full PSG may include the nightly measurement of: oximetry, airflow, snoring, respiratory effort, end-tidal carbon dioxide, esophageal pressure, electrocardiography (ECG), electroencephalography (EEG), actigraphy, electromyography (EMG), electrooculography (EOG) and video recordings. Using all these signals, sleep wake activity, respiration and muscle activity can be scored reliably during sleep. According to the most recent American Academy of Sleep Medicine (AASM) guidelines, an apnea is defined as a decrease in airflow of at least 90% regardless of other physiologic signals [42]. A hypopnea is defined as a decrease in airflow of 30-90% accompanied by a significant desaturation (≥ 3 or 4%) or an arousal [42]. Performing a full PSG is expensive both in terms of time and costs. Given the high prevalence of OSA, portable monitoring (PM) was developed to reduce the need for in-laboratory PSG. PM is performed in the patient's home and typically consists of less signals than full PSG. When there is no objective measurement of sleep (i.e. no EEG, EMG and EOG) a PM is often referred to as polygraphy (PG). The obvious downside of PG vs PSG is that sleep is not measured accurately and thus the denominator of the AHI may not be correct. Moreover, arousals cannot be determined and thus will hypopneas with arousal but without significant desaturations be missed. Consequently, a PG is likely to result in a lower AHI compared to a PSG. However, if clinical suspicion of OSA is high and there are no relevant comorbidities, PG is considered sufficient for confirmation of the diagnosis [41,43]. For exclusion of OSA however, PSG is still considered the only right tool. According to the results of a large questionnaire of the Dutch Apnea Society, most patients evaluated for OSA in the Netherlands underwent PG [44]. Despite the lower costs of PG compared to PSG, they are still substantial. This prohibits the use of PG for screening of large populations. To be able to select those who are at increased risk (and should therefore get further testing) many questionnaires have been developed. An example of an often used questionnaire is the STOP-BANG questionnaire, which consists of eight items (Snoring, Tiredness, Observed apneas, hyPertension, BMI, Age, Neck-circumference and Gender), and results in a score between 0 to 8 [45]. This questionnaire was originally developed for the pre-operative setting to select patients who are at increased risk of OSA and therefore for peri- and post-operative complications [45]. A score on the STOP-BANG ≥ 5 has a sensitivity of 36% and specificity of 80% for an AHI >5 [46].

A recent study in the Netherlands developed a two-step screening strategy using a questionnaire (the Philips Questionnaire) and nasal flow recording. If the questionnaire indicates a low risk of OSA, no further investigation is needed. If the questionnaire shows a high risk of OSA, referral to a sleep center should be made. If the questionnaire shows an intermediate risk of OSA, nasal flow recording should be performed to decide whether sleep center evaluation is indicated. In a company workers population this strategy resulted in a sensitivity of 63% with a specificity of 90% [47].

Long-term management of OSA should always include lifestyle modification when indicated (e.g. weight loss and abstention of alcohol). The remaining treatment options for OSA depends on its severity. According to the AASM, an AHI 5-15 is considered as mild, an AHI 15-30 as moderate and an AHI ≥ 30 as severe OSA [48]. In moderate-to-severe cases (i.e. AHI ≥ 15), treatment with continuous positive airway pressure (CPAP) is usually indicated. The positive pressure that is applied through a (oro-)nasal mask prohibits collapse of the upper airway. As it only prevents the airway from collapsing and does not treat the cause of OSA, CPAP should be used continuously during sleep. Generally, CPAP normalizes the AHI but compliance to the treatment is often poor with non-adherence rates reported up to 40% [49,50]. In cases with mild or moderate OSA (i.e. AHI 5-30), a mandibular advancement device (MAD) might be beneficial. The protrusion of the lower mandible enlarges the upper airway surface and thereby reduces the chance on collapse. The effect of MAD therapy on the AHI is lower compared to CPAP (mean difference in decrease of AHI approximately 8 events/hour), but overall compliance is substantially higher (approximately one hour/night) and the effect on symptoms is similar [51,52]. Surgery (such as uvulopalatopharyngoplasty or bimaxillary osteotomy) may be useful in subjects with evident anatomical impairments such as enlarged tonsils or a severe retrognathia. Again, the effect on the AHI is generally lower than CPAP with only approximately 30% of the cases reaching an AHI <10 , but all subjects are completely compliant (for obvious reasons) [53]. In patients with positional OSA (i.e. only an increased AHI in supine position), positional therapy (i.e. avoiding a supine sleeping position) may be an effective tool. If the nonsupine AHI is normal (< 5), positional therapy is as effective as CPAP and MAD therapy in normalization of the AHI [54,55]. To prevent the supine position, putting a tennis ball or other bulky mass between the shoulder blades is as effective as more advanced devices such as the Sleep Position Trainer, which measures position and starts vibrating in supine position. However, in a randomized controlled trial, compliance and sleep quality were significantly in favor of the Sleep Position Trainer [56]. One of the most recent treatment options for OSA is hypoglossal nerve stimulation. By stimulating the hypoglossal nerve during sleep, the genioglossus muscle is activated and thereby collapse of the upper airway may be prevented. In a large trial in strictly selected OSA patients (AHI ≥ 15 , BMI < 32 and no relevant neuromuscular, cardiovascular or psychiatric comorbidities) with CPAP failure, hypoglossal nerve stimulation successfully reduced the AHI and improved symptoms and self-reported compliance was high (86%) [57].

As outlined above the prevalence of OSA is high and increasing but its diagnosis requires laborious testing. This has caused many sleep centers to reach the maximum of their capacities. Therefore, there is a high need for simple, cheap and easily applicable measurement methods for the screening of OSA, which might decrease the need of “unnecessary” referrals (i.e. subjects who do not have OSA). Oximetry seems to satisfy the requirement of being cheap, simple and easily applicable. To determine its validity for the screening of OSA we first investigated the resemblance of the oxygen desaturation index (ODI, which can be determined using oximetry only) and the AHI in a large sleep center PG database in **chapter 5**. We specifically aimed to determine a cutoff for the ODI that excludes an aberrant AHI (i.e. ≥ 5). In **chapter 6** we prospectively investigated the diagnostic accuracy of this cutoff and its combination with the Philips questionnaire to exclude a sleep center OSA diagnosis in patients with suspected OSA in primary care. In **chapter 7** we investigated the use of another potential screening tool; exhaled breath measurements. We hypothesized that the many systemic processes caused by OSA may be reflected in exhaled breath. In **chapter 7** we primarily aimed to identify the diagnostic accuracy of exhaled breath measurements to discriminate patients who have a clinical suspicion of OSA but an $AHI < 15$ from patients with an $AHI \geq 15$. Secondly, we aimed to identify which OSA related parameter seems to have the most influence (specifically AHI or hypoxemia related parameters) on exhaled breath profiles.

OUTLINE OF THIS THESIS

In **chapter 2** we investigated the transfer factor of the lungs for carbon monoxide and nitric oxide for the exclusion of PE. In **chapter 3**, we developed a novel parameter based on conventional volumetric capnography parameters for the exclusion of PE. This novel parameter was externally validated in **chapter 4**. In **chapter 5** we compared oximetry (expressed as the oxygen desaturation index (ODI)) to the AHI. The findings of this study were used to develop a two-step strategy using the ODI and the Philips questionnaire to screen for OSA in primary care. This strategy was prospectively validated in **chapter 6**. In **chapter 7** we investigated if exhaled breath profiles can be used to distinguish OSA from non-OSA subjects. Finally, **chapter 8** discusses the findings of the presented research in a broader context.

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The TL,NO / TL,CO ratio cannot be used to exclude pulmonary embolism

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ABSTRACT

Background

The existing screening modalities for pulmonary embolism (PE), such as D-dimer and clinical prediction rules, have low positive predictive values. With its capability to indicate pulmonary vascular abnormalities, the ratio of the transfer factor of the lungs for nitric oxide and the transfer factor of the lungs for carbon monoxide (TL,NO/TL,CO) might be an additional discriminating parameter.

Methods

CO/NO diffusion measurements were performed on unselected patients seen on the emergency department for which due to suspected PE a computed tomography pulmonary angiogram (CTPA) was ordered.

Results

A total of 28 patients were included, PE was found in 12 on CTPA. Median TL,NO/TL,CO ratio was 4.09 (IQR 3.83 – 4.40) in the no PE group versus 4.00 (IQR 3.78 – 4.32) in the PE group ($p=0.959$). Median alveolar volume was 77.1% of predicted in the no PE group versus 71.0% of predicted in the PE group ($p=0.353$). Median TL,CO was 75.8% of predicted in the no PE group versus 68.8% of predicted in the PE group ($p=0.120$). Median TL,NO was 69.3% of predicted in the no PE group versus 60,5% of predicted in the PE group ($p=0.078$).

Conclusion

The presented data indicate that the TL,NO/TL,CO ratio cannot be used to exclude PE.

1. INTRODUCTION

Due to its potentially lethal consequences, pulmonary embolism (PE) needs to be ruled out when suspected. The nowadays widely used tools to select patients with suspicion of PE are D-dimer [1] and Wells-score [2]. Positive D-dimer or high Wells-score warrant further investigation. Current golden standard to confirm or exclude PE is a computed tomography pulmonary angiogram (CTPA) [3]. In over 75% of all CTPAs requested due to suspected PE, the disease can be safely ruled out [4]. To prevent unnecessary irradiation and admissions due to the need for prehydration, an additional fast and cheap tool to exclude PE is desirable. With its capability to indicate pulmonary vascular abnormalities, the $T_{L,NO}/T_{L,CO}$ ratio might be such a tool.

The transfer factor of the lungs (T_L) for a gas can be described by the Roughton-Forster equation:

$$\frac{1}{T_L} = \frac{1}{Dm} + \frac{1}{\theta V_c}$$

in which Dm indicates the membrane diffusion capacity, θ the binding capacity of the gas with the erythrocytes and V_c the pulmonary capillary blood volume [5]. In the case of carbon monoxide (CO) the transfer factor is more weighted by θV_c than on Dm . In the case of nitric oxide (NO), θV_c is much greater than Dm [6]. Therefore, the transfer factor of NO ($T_{L,NO}$) is more dependent on Dm than on θV_c . Hughes and van der Lee have shown that, given that Dm_{NO} equals αDm_{CO} (in which α is a theoretic constant), the ratio of $T_{L,NO}$ and the transfer factor for CO ($T_{L,CO}$) is dependent on the Dm/V_c ratio and α . As α is (assumed to be) a constant, the $T_{L,NO}/T_{L,CO}$ ratio is a reflection of the Dm/V_c ratio without the need of further assumptions. A rise of this ratio might thus suggest pulmonary vascular abnormalities. [7] The $T_{L,NO}/T_{L,CO}$ ratio has been reported to be increased in heavy smokers [8], chronic thromboembolic pulmonary hypertension and diffuse parenchymal lung disease [9]. In the case of PE, one would expect V_c to be decreased and therefore $T_{L,NO}/T_{L,CO}$ to be increased. This has been investigated in prone anesthetized sheep by Harris et al. who reported a significant higher $T_{L,NO}/T_{L,CO}$ ratio after pulmonary artery obstruction compared to baseline [10]. To the best of our knowledge, the $T_{L,NO}/T_{L,CO}$ ratio in PE has not yet been reported in humans. Therefore, the aim of this study was to investigate the value of the $T_{L,NO}/T_{L,CO}$ ratio in the exclusion of PE.

2. METHODS

2.1 Design

This study was conducted at Medisch Spectrum Twente in Enschede, the Netherlands, in combination with another research project on the value of volumetric capnography in pulmonary embolism. Inclusion criteria were: patients at the emergency department with suspected PE for which a CTPA-scan was requested due to either elevated Wells-score or D-dimer and age ≥ 18

years. Exclusion criteria were: hemodynamic instability, pregnancy and oxygen administration. After inclusion, capnography and CO/NO-diffusion measurements were performed within 4 hours after the request for a CTPA was filed and before the results of the CTPA were reported to the pulmonologist. Both the local ethics committee as well as the board of directors of Medisch Spectrum Twente approved the study protocol.

2.2 Measurements

CO/NO-diffusion was measured on the MasterScreen™ PFT Pro system (CareFusion, Amsterdam, the Netherlands) using the single-breath method with a breath-hold time of 10 seconds and an inspired NO fraction of 50 ppm. According to the ATS/ERS guidelines, a measurement was considered repeatable when the results of at least two tests were within 10% of the highest resulting values for $T_{L,CO}$ and $T_{L,NO}$ and the vital capacity (VC) was at least 85% of the highest VC measured before the diffusion test [11]. Predicted values for $T_{L,CO}$, K_{CO} and alveolar volume were provided by the MasterScreen™ PFT Pro software. Predicted values for $T_{L,NO}$ and K_{NO} were calculated using the prediction equations of van der Lee et al. [12].

2.3 Statistical Analysis

Continuous variables are expressed as median with interquartile range (IQR); categorical variables as counts with corresponding percentages. Baseline differences between the groups with and without PE were for continuous variables compared using the Mann-Whitney U-test. For categorical variables, the Chi-square test or Fisher's Exact test were used as appropriate. Diagnostic performances of $T_{L,CO}$, $T_{L,NO}$ and the $T_{L,NO}/T_{L,CO}$ ratio were quantified with the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. All AUCs were tested against the null-hypothesis that the true area is equal to 0.5. Differences were considered significant if the statistic p is smaller than 0.05. Data were analyzed using SPSS version 22 (SPSS Inc. Chicago IL, USA).

3. RESULTS

Subjects were included from the end of July 2014 till the begin of May 2015. During this period, 36 patients were approached for participation in the study. Five of the approached patients refused participation, leading to 31 included subjects. PE was found in 13 patients on CTPA. Diffusion measurements failed in three patients (two no PE, one PE). Characteristics and presenting symptoms of the included patients are provided in table 1.

Three patients in both groups had a history of previous PE or deep venous thrombosis ($p=1.000$). In the group without PE, three patients had known airflow obstruction versus no patients with known airflow obstruction in the PE group ($p=0.238$). Wells-score, D-dimer levels and the number of abnormal chest X-rays were significantly higher in the PE group compared to the no PE group. No other significant differences in characteristics were found.

Table 1 – Patient characteristics. Data are presented as median (interquartile range) unless stated otherwise. BMI denotes body mass index, PE denotes pulmonary embolism, DVT denotes deep venous thrombosis. * indicates a statistically significant difference ($p < 0.05$).

	No PE (N=16)		PE (N=12)		P-value
	Median	IQR	Median	IQR	
Age (y)	56	(42 - 69)	49	(41 - 67)	0.415
Females (N (%))	9	(56.3)	6	(50.0)	0.743
Height (cm)	177	(168 - 183)	177	(166 - 184)	0.816
Weight (kg)	83	(72 - 95)	78	(63 - 98)	0.378
BMI (kg/m ²)	29.0	(24.2 - 33,7)	25.3	(23.2 - 28.5)	0.137
Active smoker (N (%))	6	(37.5)	2	(16,7)	0.401
Wells-score	2.8	(0.0 – 3.0)	3.0	(3.0 – 4.5)	0.011*
D-dimer (µg/L)	804	(640 - 1758)	2820	(1097 - 6049)	0.001*
Abnormal CXR (N (%))	1	(6.3)	9	(75.0)	0.000*
Thoracic pain (N (%))	13	(81.3)	8	(66.7)	0.418
Dyspnea (N (%))	11	(68.8)	10	(83.3)	0.662

Results of the measurements are provided in table 2. A boxplot of the distribution of the $T_{L,CO}/T_{L,NO}$ ratio in the no PE and PE groups is given in figure 1. No statistically significant differences between the PE and no PE groups were found. $T_{L,CO}/T_{L,NO}$ ratio and alveolar volume were all lowered ($< 80\%$ of predicted) in both the PE and no PE groups. AUC of the $T_{L,NO}/T_{L,CO}$ ratio was 0.453 (95% confidence interval (CI) 0.230-0.676, $p=0.676$). The AUCs of all diffusion parameters were also not statistically significant higher than 0.5.

Table 2 – Results of the CO/NO diffusion measurements. Data are presented as median (interquartile range) unless stated otherwise. IVC denotes the inspiratory vital capacity, VA denotes the alveolar volume, $T_{L,CO}$ the transfer factor of the lungs for carbon monoxide, K_{CO} the transfer coefficient of the lungs for carbon monoxide, $T_{L,NO}$ the transfer factor of the lungs for nitric oxide and K_{NO} the transfer coefficient of the lungs for nitric oxide.

	No PE (N=16)		PE (N=12)		P-value
	Median	IQR	Median	IQR	
IVC (L)	3.03	(2.33 – 3.73)	2.86	(2.26 – 3.71)	0.834
IVC % predicted	81.6	(70.0 – 93.0)	66.4	(61.1 – 90.5)	0.330
VA (L)	4.79	(3.96 – 5.19)	4.40	(3.53 – 5.57)	0.516
VA % predicted	77.1	(65.5 – 87.8)	71.0	(65.0 – 81.4)	0.353
$T_{L,CO}$ (mmol/kPa/min)	7.16	(5.27 – 8.90)	6.62	(5.21 – 7.45)	0.330
$T_{L,CO}$ % predicted	75.8	(62.9 – 89.6)	68.8	(58.5 – 75.7)	0.120
K_{CO} (mmol/kPa/min/L)	1.47	(1.35 – 1.62)	1.46	(1.20 – 1.80)	0.926
K_{CO} % predicted	99.9	(85.8 – 111.7)	100.5	(87.7 – 107.3)	0.610
$T_{L,NO}$ (mmol/kPa/min)	29.9	(23.0 – 37.9)	25.8	(20.0 – 30.3)	0.286
$T_{L,NO}$ % predicted	69.3	(57.0 – 76.1)	60.5	(46.6 – 68.9)	0.078
K_{NO} (mmol/kPa/min/L)	6.10	(5.24 – 7.10)	5.98	(5.33 – 6.81)	0.642
K_{NO} % predicted	89.5	(76.4 – 95.5)	83.9	(77.0 – 91.1)	0.330
$T_{L,NO} / T_{L,CO}$	4.09	(3.83 - 4,40)	4,00	(3,78 - 4,32)	0,959

Figure 1 – Boxplots of the distribution of the $T_{L,NO}/T_{L,CO}$ ratio in the no PE and PE groups. The value of the $T_{L,NO}/T_{L,CO}$ ratio found in healthy subjects by van der Lee et al. was 4.36 ± 0.6 [9].

4. DISCUSSION

Due to the results of Harris et al., and the physiological theory behind the $T_{L,NO}/T_{L,CO}$ ratio, it was expected that the ratio is increased in PE compared to no PE patients. Our data show lowered $T_{L,CO}$ and $T_{L,NO}$ and normal $T_{L,NO}/T_{L,CO}$ ratios in both groups. The value of $T_{L,CO}$ in PE has been investigated several times. Wimalaratna et al. for instance reported a $T_{L,CO}$ of less than 75% of predicted in PE patients which failed to normalize within three months in most cases [13]. Oppenheimer et al. report decreased $T_{L,CO}$ values in chronic thromboembolic disease [14] but it is hard to compare these values to acute PE. In 2011, Piirilä et al. reported lowered $T_{L,CO}$ in acute PE similar to the values found by Wimalaratna et al. (74% of predicted) which were still lowered after seven months [15]. The $T_{L,CO}$ values we found (69% of predicted) are comparable with the results of both Wimalaratna et al. and Piirilä et al.

Besides the difference in $T_{L,CO}$, Piirilä et al. also investigated other parameters (including Dm and V_C). Although they did not find a significant difference in Dm/ V_C ratio (on which the $T_{L,NO}/T_{L,CO}$ ratio is dependent) and V_C between the PE group and the healthy controls, they did observe significant lower values of Dm between the PE group and the healthy controls in both the acute phase and after seven months. Moreover, they reported a (weak) correlation between Dm and the extent of the pulmonary embolism measured by central embolism mass ($r=0.31$, $p=0.047$). Piirilä et al. argue that Dm is influenced more by the reduction in alveolar volume compared to V_C . As $T_{L,NO}$ is directly related to Dm, this argument agrees with the finding of van der Lee et al.

that $T_{L,NO}$ is influenced more by a reduction in alveolar volume than $T_{L,CO}$ [12]. Moreover, from table 2 a trend towards lower $T_{L,CO}$ and $T_{L,NO}$ compared to predicted in the PE group compared to the no PE group can be seen (though not statistically significant due to a small number of subjects). Concluding, the present findings do not correspond with the data of Harris et al. found in sheep but are consistent with earlier measurements of $T_{L,CO}$ in PE in humans.

First of all, a probable cause of the lack in increased $T_{L,NO}/T_{L,CO}$ ratios might be the relatively small extent of the pulmonary emboli included in the current study, as hemodynamic unstable and oxygen dependent patients were excluded. Moreover, recent research showed that total occluding emboli result in perfusion defects [16], in non-occluding emboli a slight decrease in both D_m and V_c can be expected. Finally, hypocapnic bronchoconstriction might shift ventilation towards well perfused regions [17] which could also diminish the negative effects of PE on the diffusion capacity of the lungs.

Detailed inspection of the current data reveals another possible explanation for the lack in increased $T_{L,NO}/T_{L,CO}$ ratios. The measured alveolar volume is decreased in both groups (77.1% of predicted in the no PE group versus 71.0% of predicted in the PE group). This decreased alveolar expansion is likely to be caused by the thoracic pain of which almost all patients suffered (see table 1). This hypothesis is supported by the reduced inspiratory vital capacity in both groups, indicating an extrathoracic restriction. A reduced alveolar volume greatly influences the measured transfer factors. A reduction in alveolar volume will decrease the surface area and increase the thickness of the alveolar-capillary membrane (and therefore decreases D_m and thus $T_{L,NO}$). $T_{L,CO}$ is approximately equal dependent on D_m and V_c and is therefore less dependent on a decrease in alveolar volume. Therefore, the $T_{L,NO}/T_{L,CO}$ ratio decreases with a decrease in alveolar volume. [12,18] This might explain the slightly lowered $T_{L,NO}/T_{L,CO}$ ratios found in our data. In the data of van der Lee et al. an alveolar volume of 70-80% of its value at total lung capacity (TLC) results in a measured $T_{L,NO}/T_{L,CO}$ ratio of approximately 4.00 [12] which corresponds with the now presented data. The previous reports of Wimalaratna et al. and Piirilä et al. on $T_{L,CO}$ in PE do not report alveolar volumes compared to its predicted value. They do report K_{CO} compared to its predicted value. Piirilä et al. report normal K_{CO} values indicating decreased alveolar volumes which corresponds with our data. Surprisingly, Wimalaratna et al. report lowered K_{CO} values when compared to their predicted value (calculated from mean data). This difference can be caused by changes between 1989 and now in measurement protocol and the reference equations used to calculate predicted values.

5. CONCLUSION

Our data indicate that the $T_{L,NO}/T_{L,CO}$ ratio cannot be used in the exclusion of pulmonary embolism. Lowered $T_{L,CO}$ and $T_{L,NO}$ combined with normal K_{CO} and K_{NO} were noted in both the no PE and the PE group. The decrease in transfer factors is likely to be caused by the decreased

alveolar volume (possibly due to thoracic pain) which was also noted in both groups. The present findings do not correspond with the $T_{L,NO}/T_{L,CO}$ ratio found in sheep but are consistent with earlier measurements of $T_{L,CO}$ in pulmonary embolism in humans.

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Conflicts of Interests

The authors declare to have no conflicts of interests.

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Volumetric capnography in the exclusion of pulmonary embolism at the emergency department: a pilot study

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ABSTRACT

Rationale

The analysis of the P_{CO_2} in expired air as a function of the exhaled volume (volumetric capnography) might result in a more specific exclusion tool for pulmonary embolism (PE) in addition to the Wells-score and D-dimer. A novel combination of volumetric capnography parameters ($VCO_2 \times \text{slopeIII}/RR$) should be decreased in PE and could possibly be used to decrease the number of requested computed tomography pulmonary angiograms (CTPA).

Methods

Volumetric capnography measurements were performed on consecutive patients seen on the emergency department for which, due to suspected PE (due to increased D-dimer level or Wells-score), a CTPA was ordered.

Results

A total of 30 subjects were included, of which in 13 PE was seen on CTPA. Median PET_{CO_2} was 4.36 kPa (IQR 3.92 – 4.88) in the no PE group versus 4.07 kPa (IQR 3.37 – 4.39) in the PE group ($p=0.086$). Median of the novel parameter $VCO_2 \times \text{slopeIII}/RR$ was 1.85 Pa.min (IQR 1.21 – 3.00) in the no PE group versus 1.19 Pa.min (IQR 0.61 – 1.39) in the PE group ($p=0.006$). Using a threshold for the new parameter of 1.90 Pa.min or higher to exclude PE resulted in a negative predictive value of 100% (95% CI: 77%-100%) and would have potentially excluded PE in 47% (95% CI: 26% - 69%) of the no PE group without the need of CTPA.

Conclusion

This pilot study introduces a novel parameter $VCO_2 \times \text{slopeIII}/RR$ which is significantly decreased in PE subjects. Future studies addressing aspects such as reproducibility and normalization after treatment are needed to confirm its usability in excluding PE at the emergency department.

1. INTRODUCTION

Pulmonary embolism (PE) is a potentially lethal pathology which is hard to diagnose without expensive imaging techniques. Several tools to exclude PE, such as D-dimer [1] and the Wells-score [2] exist. The combination of these tests can safely rule out PE but cannot be used to confirm it. The gold standard for confirming PE is a computed tomography pulmonary angiogram (CTPA).[3] Due to the low specificity of the D-dimer and Wells-score for PE, many CTPAs are needed. In most of the CTPAs (up to 75%) the result is negative, and PE is ruled out. [4] Therefore, the search for an additional, fast, cheap and easily applied screening method to exclude PE continues.

In 1959, the end-tidal partial carbon dioxide pressure (PET_{CO_2}) has been suggested as possible screening tool for PE.[5] Several studies on PET_{CO_2} in suspected PE patients have been performed since (e.g. [6,7]). Most of the studies reported a significant lower PET_{CO_2} in subjects with PE compared to subjects without PE. However, there are many other causes which may result in a lowered PET_{CO_2} . [8] To gain more information from capnography measurements, volumetric capnography was introduced, which allows analysis of the entire curve of exhaled CO_2 . Using this, parameters such as (functional) dead space (which physiologically should be increased in PE) can be quantified. In a meta-analysis of 14 studies Manara et al. concluded that (volumetric) capnography might be used to exclude PE in patients with a pretest probability less than 10%. [9] However, almost all studies reviewed by Manara et al. only investigated the end-tidal alveolar dead space fraction, i.e. a quantification of the difference in PET_{CO_2} and arterial P_{CO_2} (P_{aCO_2}). Verschuren et al. reported the value of several volumetric capnogram characteristics during PE in spontaneously breathing patients. [10,11] Using more characteristics of the total volumetric capnogram (such as the slope of the alveolar phase) might add substantial value to the screening capabilities of volumetric capnography. Preliminary collected data showed differences in body weight between the groups with and without PE. As body weight is known to influence several respiratory physiologic processes [12], a new, weight independent, parameter combining several volumetric capnography characteristics was introduced as further outlined in the discussion section. This parameter consists of the amount of CO_2 exhaled per breath (VCO_2) multiplied with the slope of phase III (slope III) divided by the respiratory rate ($VCO_2 \times \text{slope III} / RR$). It was hypothesized that this new parameter is decreased in subjects suffering from PE compared to subjects with PE.

2. THE VOLUMETRIC CAPNOGRAM

In a volumetric capnogram, the recorded exhaled P_{CO_2} is plotted as a function of the exhaled volume and can be divided into three phases (I, II and III). Phase I consists of air originating from the conducting airways, phase II of an admixture of air from the conducting airways and

the alveoli and phase III solely of air from the alveoli. The slope of phase III is an indication for the (ventilation) homogeneity and perfusion of the lungs.[13,14] Using Fowler’s method the amount of physiological airway dead space (VDaw) can be calculated from the volumetric capnogram.[15]

Figure 1 - Example of a volumetric capnogram where the measured P_{CO_2} (indicated by the solid line) is plotted as a function of the exhaled volume. Phase I consists of air originating from the conducting airways. Phase II consists of the transition to alveolar air; Phase III consists of alveolar air). A linear approximation of phase III is indicated by the diagonal dashed line.

3. METHODS

3.1 Design

This study was conducted at teaching hospital Medisch Spectrum Twente in Enschede, the Netherlands. Consecutive subjects seen on the emergency department for which a CTPA due to suspected PE was requested were included in the study during times when the researchers were available. Following the 2014 ESC/ERS guidelines on PE, CTPA was only ordered if Wells-score > 4 or D-dimer ≥ 500 $\mu\text{g/L}$ [3]. Subjects who were hemodynamic unstable, pregnant, or needed oxygen administration were excluded. Both the local ethics committee (METC Twente, approval number: K14-25) and the board of directors of Medisch Spectrum Twente approved the study protocol.

3.2 Measurements

A volumetric capnogram was obtained using a Novamatrix Co2smoPlus mainstream capnograph (Co2smo Plus! 8100, Novamatrix Medical Systems Inc, now Philips Respironics Inc., Murrysville, Pennsylvania, USA) contains a CO_2 sensor combined with a fixed orifice differential pressure

pneumotachometer. Measurements were performed within 4 hours of the request for the CTPA scan and before the results of the scan were reported to the pulmonary physician. The researcher was therefore blinded to the results of the CTPA scan at the moment of measurement. No clinical interventions were performed between the volumetric capnography and the CTPA scan. The CTPA scan was assessed by the attending radiologist according to current guidelines. The radiologist was unaware of the results of the capnography measurements. If the results of the CTPA scan were indeterminate, the subject was excluded from further analysis. The subject was asked to breath normally via a mouthpiece connected to the mainstream capnograph, with nostrils clipped. Every 90 seconds the data was saved and automatically analyzed using a custom script in Mathworks Matlab (Matlab R2014a, The MathWorks Inc., Natick, Massachusetts, USA). Measurements were ended when at least two datasets of 90 seconds meeting the validity criteria were obtained as described in section 3.3. If less than two usable datasets could be obtained within 15 minutes, the patient was excluded from further analysis.

3.3 Analysis

The obtained data was subdivided into individual exhalations based on the flow data. The 10 most similar exhalations were selected by minimizing the total z-score (i.e. the number of standard deviations a sample deviates from the mean) for tidal volume (V_T), exhalation duration and PET_{CO_2} by iteratively removing the exhalation with the highest z-score until 10 exhalations remained. Assessment of the validity of the measurement was done using the criteria of Verschuren et al. in which the coefficient of variation (i.e. standard deviation divided by the mean) for V_T and duration of exhalation may not exceed 20%, and the coefficient of variation of PET_{CO_2} may not exceed 5%.[10] Starting points of phase II and III were determined using the method described by Tusman et al. in which the start and end of phase II are determined as the first and second inflection points of the volumetric capnogram [16]. Airway dead space was calculated using the equal area method of Fowler et al.[15] The amount of exhaled CO_2 was calculated by integration of the volumetric capnogram. The mean of respiratory rate, V_T , V_{CO_2} , the slope of phase III and $VDaw$ were stored for statistical analysis.

3.4 Statistical Analysis

Continuous variables are expressed as median with interquartile range (IQR); categorical variables as counts with corresponding percentages. Differences in continuous variables between the groups with and without PE were compared using the Mann-Whitney U-test. Categorical variables were compared using either the Chi-square test or Fisher exact test. Diagnostic performances of PET_{CO_2} and the new parameter were quantified with the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Both AUCs were tested against the null hypothesis that the true area is equal to 0.5. Differences were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS version 22 (SPSS Inc. Chicago IL, USA).

4. RESULTS

Subjects were included from the end of July 2014 till the begin of May 2015 during which 32 subjects were included. The Wells score and D-dimer were increased in 7 and 29 subjects respectively. PE was found on CTPA in 13 subjects. The results of the CTPA-scan were indeterminate in one subject, which was excluded. Within the subjects with PE, the median Pulmonary Embolism Severity Index (PESI) score was 79 (IQR 58 – 89) which indicates (on average) allow risk of adverse outcome [17]. The volumetric capnogram of one subject (without PE) could not be analyzed due to a small tidal volume resulting in a lack of alveolar air in the expired air, therefore this subject was excluded resulting in 30 included subjects. In all included subjects the first two recorded datasets of 90 seconds met the validity criteria. Total measurement time did not exceed five minutes per subject. No adverse events occurred during the measurements. A flowchart of the included subjects is provided in figure 2. Characteristics of the included patients are provided in table 1. As expected, Wells-score and D-dimer levels were significantly higher in the PE group. No other significant differences in characteristics were found.

Results of the volumetric capnography measurements are provided in table 2. Only the new parameter $VCO_2 \times slopeIII/RR$ was significantly lower in the PE group.

Figure 2 – Flow chart of the included subjects.

Table 1 - Patient characteristics. Data are presented as median (interquartile range) unless stated otherwise. PE denotes pulmonary embolism, DVT denotes deep venous thrombosis. Statistically significant differences ($p < 0.05$) are indicated with *.

	No PE (N=17)		PE (N=13)		P-value
	Median	IQR	Median	IQR	
Age (y)	57	(45 - 72)	50	(41 - 69)	0.356
Gender(F/M)	9 / 8		6 / 7		0.713
Height (cm)	176	(165 - 183)	177	(167 - 183)	0.630
Weight (kg)	83	(72 - 95)	76	(64 - 96)	0.250
Active smoker (N (%))	5	(29.4)	2	(15.4)	0.427
Wells-score	3.0	(0.8 - 3.0)	3.0	(3.0 - 5.0)	0.017*
D-dimer ($\mu\text{g/L}$)	890	(658 - 1802)	3649	(1408 - 5918)	0.001*
History of PE/DVT (N (%))	3	17.6	3	23.1	1.000
Malignancy (N (%))	1	5.9	3	23.1	0.290
Thoracic pain (N (%))	14	82.4	8	61.5	0.242
Dyspnea (N (%))	12	70.6	11	84.6	0.427
Cough (N (%))	4	23.5	1	7.7	0.355

Table 2 - Results of the volumetric capnogram measurements. Data are presented as median (interquartile range) unless stated otherwise. RR denotes the respiratory rate, V_T the tidal volume per kilogram body weight, VD_{aw} the calculated airway dead space, PET_{CO_2} the end-tidal partial CO_2 pressure, Slope III the slope of the linear approximation of the slope of phase III of the volumetric capnogram and V_{CO_2} the amount of CO_2 expired per breath. Statistically significant differences ($p < 0.05$) are indicated with *.

	No PE (N=17)		PE (N=13)		P-value
	Median	IQR	Median	IQR	
RR (breaths/min)	14.3	(11.9 - 16.9)	17.1	(14.4 - 17.9)	0.060
VT (mL/kg)	8.47	(6.37 - 9.39)	7.89	(6.12 - 9.30)	0.900
PET_{CO_2} (kPa)	4.36	(3.92 - 4.88)	4.07	(3.37 - 4.39)	0.086
V_{CO_2} (mL/breath)	18.2	(12.8 - 20.5)	12.2	(10.7 - 16.9)	0.079
VD_{aw} (mL/kg)	2.68	(2.32 - 3.07)	2.98	(2.60 - 3.33)	0.149
VD_{aw}/VT	0.33	(0.31 - 0.40)	0.39	(0.32 - 0.47)	0.148
Slope III (kPa/L)	1.30	(0.99 - 2.51)	1.70	(0.91 - 2.30)	0.950
$V_{CO_2} \times \text{slope III} / RR$ (Pa.min)	1.85	(1.21 - 3.00)	1.18	(0.61 - 1.38)	0.006*

AUC of the ROC curve of PET_{CO_2} was not significantly higher than 0.5. The ROC curve of the new parameter $V_{CO_2} \times \text{slope III} / RR$ is provided in figure 3. AUC of the ROC curve of the new parameter was 0.79 (95% CI 0.64-0.95, $p=0.006$).

Figure 3 - The receiver operating characteristic curve of the new parameter $VCO_2 \times \text{slopeIII}/RR$. Area under the curve is 0.79 (95% CI 0.64-0.95, $p=0.006$).

The lowest threshold for this new parameter providing a negative predictive value of 100% was 1.90 Pa.min which resulted in a sensitivity of 100% (95% CI: 77%-100%), specificity of 47% (95% CI: 26%-69%), negative predictive value of 100% (95% CI: 68% - 100%) and positive predictive value of 59% (95% CI: 39%-77%). A cross tabulation of the new parameter using the cut-off value of 1.90 Pa.min by the results of the CTPA-scans is provided in table 3.

Table 3 – Cross tabulation of the cut-off value of the new parameter of 1.9 Pa.min by the results of the CTPA-scan.

	PE	No PE	Total
New Parameter < 1.90 Pa.min	13	9	22
New Parameter $\geq$ 1.90 Pa.min	0	8	8
Total	13	17	30

5. DISCUSSION

5.1 Conventional parameters

No statistical significant differences in any of the conventional individual volumetric capnography parameters between the subjects with PE and the subjects without PE was found. Applying two earlier suggested thresholds of PET_{CO_2} higher than 4.30 kPa [18] or 3.70 kPa (combined with low clinical probability) [19] to exclude PE, resulted in five false negative readings (38% of the PE group). Our data seem more consistent with a third proposed threshold of PET_{CO_2}

higher than 4.8 kPa to safely rule out PE[7]. This threshold also provides a negative predictive value of 100% in our data, but it has to be noted that only four subjects without PE (24%) had a PET_{CO_2} above 4.8 kPa. Using this threshold seems therefore to have little added value to current clinical practice or the use of the novel parameter $VCO_2 \times slopeIII/RR$. A possible cause for the lack of differences in PET_{CO_2} between the groups may be the severity of the PE included in this study. Due to the exclusion criteria, only patients with low and moderate risk PE were included which is reflected in the low PESI scores. Furthermore, it has been shown that in non-occluding emboli pulmonary blood flow is preserved[20]. Even if total occluding emboli are present, ventilation may shift to better perfused regions due to hypocapnic bronchoconstriction[21]. Both mechanisms will reduce the effect of the emboli on respiratory physiology and may therefore result in only little abnormalities of the volumetric capnogram.

The differences in results in PET_{CO_2} between the earlier reported data and our data might be caused by the time of measurement. In our study, volumetric capnography was always performed in the acute phase (within four hours of the filing of the CTPA request and before the results of the scan were reported to the pulmonary physician) whereas several other studies performed the measurements within 24 hours. The symptoms of the patients without PE might have normalized during these 24 hours. Hence, diagnostics should be performed as soon as possible after presentation at the emergency department. From our data it can be concluded that almost all patients with clinical suspicion of PE (supported by either elevated D-dimer or Wells-score) had a lowered PET_{CO_2} . Given that most of these patients are tachypnoeic (often one of the reasons for their presence at the emergency department), this finding seems plausible. Therefore, the clinical usability of PET_{CO_2} to discriminate between patients with and without PE in the acute phase cannot be confirmed with the presented data.

5.2 New parameter

The novel, body weight independent, parameter $VCO_2 \times slopeIII/RR$ showed promising results. This parameter was designed as preliminary results showed differences in body weight between the groups with and without PE. As body weight is known to influence several respiratory physiologic processes[12], the differences in body weight could potentially diminish the effects of PE on our original outcomes. The slope of phase III is known to decrease in both a decrease of pulmonary blood flow[22] and an increase of body weight[23]. An increased body weight also increases metabolic production of CO_2 and is therefore likely to increase V_{CO_2} whereas pulmonary embolism is likely to decrease V_{CO_2} . However, as the production of CO_2 does not decrease in pulmonary embolism, the respiratory rate needs to increase to compensate for the decrease in the amount of CO_2 exhaled per breath. Combining all these characteristics, the new parameter $VCO_2 \times slopeIII/RR$ was designed.

The strengths of this possible new parameter for the exclusion of PE are the short duration of measurement (typically less than five minutes) and the fully automated analysis and thus

objective outcome. Moreover, volumetric capnography can easily be applied at the bedside without interfering with usual clinical care.

As hypothesized, the new parameter was indeed significantly decreased in subjects with PE compared to the subjects without PE. As PE is a potentially lethal disease, a threshold providing a negative predictive value close to 100% is warranted. The associated threshold of the novel parameter providing this negative predicted value resulted in a specificity of 47% which seems to indicate that the use of this novel parameter would have substantially decreased the need for CTPA to exclude PE in the current study population (which consisted of patients with increased D-dimer level or Wells-score). Nevertheless, the lower bound of the 95% confidence interval is low (26%) due to the small sample size. Validation of the new parameter in larger datasets should confirm the true sensitivity and specificity. Furthermore, studies should investigate reproducibility of the new parameter in diseased and healthy subject as well as reversibility of the value to baseline after treatment.

5.3 Limitations

The major limitation of this study is the small number of included subjects. This is also reflected in the wide 95% confidence intervals of the sensitivity and specificity of the established cut-off of the new parameter. However, the aim of this pilot study was to investigate the usability of (a combination of) volumetric capnography derived parameters to safely exclude PE without the need of CTPA. The established threshold of the new parameter $VCO_2 \times slopeIII/RR$ should be externally validated in larger patient numbers to confirm its true usability.

6. CONCLUSION

This pilot study introduces a novel volumetric capnography derived parameter $VCO_2 \times slopeIII/RR$ for the exclusion of pulmonary embolism (PE) at the emergency department. It is shown that the novel parameter is significantly decreased in subjects with PE compared to subjects without PE on CTPA. Future studies addressing aspects such as reproducibility and normalization after treatment are needed to confirm its usability in excluding PE at the emergency department.

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Conflicts of Interests

All authors declare to have no conflicting interests regarding the content of this study.

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Retrospective validation of a new volumetric capnography parameter for the exclusion of pulmonary embolism at the emergency department

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ABSTRACT

Background

Volumetric capnography might be used to exclude pulmonary embolism (PE) without the need of computed tomography pulmonary angiography. In a pilot study, a new parameter combining the amount of CO₂ exhaled per breath (VCO₂), the slope of phase 3 of the volumetric capnogram (slope3) and respiratory rate ($\frac{VCO_2 \times Slope3}{RR}$, CapNoPE) showed promising diagnostic accuracy.

Aim

To retrospectively validate CapNoPE for the exclusion of PE in a large multicenter dataset of volumetric capnograms in subjects with suspected PE at the emergency department.

Methods

The volumetric capnograms of 205 subjects (68 with PE) were analyzed. Area under the curve (AUC) of the receiver operating characteristics (ROC) curve and diagnostic accuracy of the in the pilot study established threshold (1.90 Pa.min) were calculated.

Results

CapNoPE was 1.56 ± 0.97 Pa.min in the subjects with PE versus 2.51 ± 1.67 Pa.min in those without PE ($p < 0.001$). AUC of the ROC curve was 0.714. (95%CI 0.64 – 0.79). For the cutoff of ≥ 1.90 Pa.min sensitivity was 64.7%, specificity 59.9%, negative predictive value 77.4% and positive predictive value 44.4%.

Conclusions

The novel volumetric capnography derived parameter CapNoPE is decreased in patients with PE but its diagnostic accuracy seems too low to use in clinical practice.

INTRODUCTION

Pulmonary embolism (PE) has a high incidence and the mortality is high when untreated [1]. The current gold standard (computed tomography pulmonary angiography, CTPA) to confirm or exclude the presence of emboli in the pulmonary arteries requires irradiation, is relatively expensive and cannot be directly applied in all patients seen on the emergency department (ED). To reduce the amount of CTPA scans needed, several strategies have been developed. The most used strategy to select the right patients for CTPA scanning, the Christopher algorithm, includes the use of a clinical prediction tool (such as the Wells-score) and D-dimer testing [2]. Though its negative predictive value is satisfying (enabling the safe exclusion PE), the positive predictive value of this strategy is poor (i.e. less than 30%) [2,3]. Therefore the search for additional fast and cheap diagnostics to safely exclude PE at the emergency department without the need of CTPA continues.

The use of capnography in the exclusion of PE has been studied several times. Most of these studies focus on the usability of end-tidal CO_2 (ETCO_2), often combined with arterial PCO_2 to calculate the alveolar dead space fraction (AVDSf) which represents the fraction of ventilation that is wasted on dead space. Though the results of several individual studies seemed promising (e.g. [4,5]), a meta-analysis showed a pooled sensitivity of 80% for both ETCO_2 and AVDSf, and 73% the AVDSf alone [6]. Given the high mortality of untreated PE, these sensitivities are too low to justify the use of ETCO_2 or AVDSf in clinical practice.

In volumetric capnography the PCO_2 in the exhaled air is plotted as a function of the exhaled volume (see figure 1 for an example). The resulting curve is often divided into three phases; anatomic dead space (containing no CO_2), a transition phase (in which CO_2 rapidly increases) and finally a plateau resembling alveolar air (in which a slight linear increase of CO_2 is seen due to continuous diffusion of CO_2 from the capillaries into the alveoli). An extensive review of volumetric capnography and its potential clinical applications is provided in [7] and [8].

The volumetric capnogram and its phases contain more information than only ETCO_2 . It can be hypothesized that some (or a combination) of the volumetric capnography parameters are influenced by the presence of pulmonary emboli (and thus may be useful in the exclusion of PE). The number of studies investigating the usability of volumetric capnography in the exclusion of PE is limited. Patel et al. performed a neural network analysis on the volumetric capnogram of six subjects with PE and six subjects without PE. This analysis resulted in seventeen volumetric capnography parameters which were associated with the presence of PE. In 1989, Eriksson et al. proposed a novel parameter: the late dead-space fraction (F_{dlate}) which equals 1 minus the ratio of PCO_2 at an exhaled volume of 15% of the predicted total lung capacity (TLC) and the volumetric capnogram is extrapolated to obtain the PCO_2 at 15% of TLC. They showed that F_{dlate} is increased in subjects with PE compared to healthy subjects and subjects with obstructive pulmonary diseases [9]. In 2004, Verschuren et al. compared the diagnostic accuracy of F_{dlate} , the arterial-end-tidal CO_2 gradient and the slope of phase 3

(slope3, i.e. the alveolar phase of the volumetric capnogram) [10]. In this analysis, the Fdlate ratio seemed to have the highest diagnostic properties. The use of the slope of phase 3 seems physiologically justified as a decrease in pulmonary perfusion decreases slope3. Some years later, Verschuren et al. performed a larger study comparing Fdlate, AVDSf and a new parameter named PE-index which equals the arterial to end-tidal CO_2 gradient divided by the slope of phase 3 ($\frac{\text{PaCO}_2 - \text{ETCO}_2}{\text{Slope3}}$) [11]. Unfortunately, the volumetric capnography based parameters (the PE-index and Fdlate) did not show better diagnostic properties when compared with the sole ratio of end-tidal and arterial PCO_2 . In a recent pilot study we proposed a novel volumetric capnography derived parameter, CapNoPE, which consists of the amount of CO_2 exhaled per breath (VCO_2) multiplied with slope3 and divided by the respiratory rate (RR): $\frac{\text{VCO}_2 \times \text{Slope3}}{\text{RR}}$ [12]. As PE is likely to decrease Slope3 and VCO_2 and might increase RR, we hypothesized that CapNoPE is decreased in subjects with PE and independent of body weight (which is known to influence several capnography parameters). The pilot study results showed that the parameter was indeed significantly decreased in PE and a threshold of 1.90 Pa.min resulted in a sensitivity of 100% with a specificity of 47%. However, given the limited number of included subjects the 95% confidence intervals of the diagnostic accuracies were wide. As diagnostic properties are often overestimated in derivation sets, external validation is warranted [13]. The aim of the current study is to do so by retrospectively assessing the diagnostic properties of CapNoPE for the exclusion of PE in data of the study performed by Verschuren et al. [11].

Figure 1 – Example of a volumetric capnogram. A linear approximation of phase 3 of the capnogram (Slope3) is indicated by the dotted line. The VCO_2 can be calculated by dividing the area under the volumetric capnogram (indicated by the grey area) by the atmospheric pressure. Arterial PCO_2 (PaCO_2) is indicated by the dashed line. CapNoPE: $\text{VCO}_2 \times \text{Slope3} / \text{Respiratory rate}$. PE-index: $\text{PaCO}_2 - \text{ETCO}_2 / \text{Slope3}$. Fdlate: $1 - (\text{extrapolated } \text{PCO}_2 \text{ at 15\% of total lung capacity (TLC)} / \text{PaCO}_2)$. Alveolar dead space fraction: $\text{PaCO}_2 - \text{ETCO}_2 / \text{PaCO}_2$.

METHODS

The original study population consisted of subjects (aged > 18 years) with suspected PE with elevated D-dimer levels at the ED of three academic hospitals in Brussels, Paris and Geneva and was part of a larger trial on the diagnosis of PE [14]. In this study, patients with suspected PE were randomized to venous compression ultrasonography and, if negative, CTPA or CTPA alone. PE was considered confirmed when shown on the ultrasonography, CTPA or PE or deep venous thrombosis was diagnosed within a follow-up of three months.

The volumetric capnography measurements were performed between February 2005 and September 2006. Valid capnograms were obtained in 205 subjects. PE was diagnosed in 68 (33%) subjects. Of these, three were diagnosed by a positive venous compression ultrasonography finding alone. Among those in whom PE was excluded during the initial presentation, none were diagnosed with any thromboembolic event during the three month follow-up. At the time of measurement, the observer was unaware of the diagnosis. The original study was approved by the relevant ethical committees. All participating subjects provided written informed consent.

The volumetric capnography data of the included 205 subjects were used to calculate CapNoPE. The diagnostic properties of CapNoPE were assessed using the area under curve (AUC) of the receiver operating characteristic (ROC) curve and compared with the ROC curves of Fdlate, PE-index, AVDSf and ETCO₂ alone. Furthermore, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for the threshold of CapNoPE of ≥ 1.90 Pa.min to exclude PE.

Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. Categorical variables were expressed as counts with corresponding percentages. Differences in continuous variables were tested using independent samples T-tests when normally distributed or Mann-Whitney U tests when non-normally distributed. Differences in categorical variables were tested using the Chi-square test or Fisher exact test. Test outcomes were considered significant if $p < 0.05$. All analyses were performed using IBM SPSS Statistics version 22 (IBM Corp. Armonk, NY, USA).

RESULTS

Baseline characteristics of the included 205 subjects are provided in table 1. In total, 68 patients (33%) had confirmed PE. Compared to those without, the subjects with PE had a significantly higher clinical probability (as depicted by the revised Geneva scores), higher D-dimer values, and were longer on the ED before volumetric capnography measurements were performed. Detailed characteristics (e.g. comorbidities and presenting symptoms) are provided in the original publication by Verschuren et al. [11]. The outcomes of the several volumetric cap-

nography variables are provided in table 2. All investigated capnography variables (CapNoPE, Fdlate, PE-index, AVDSf and ETCO₂) were significantly different in the subjects with confirmed PE compared to those without PE. The ROC curves of these parameters are provided in figure 2. Area under curve of the ROC curve of the novel volumetric capnography derived parameter was 0.71 (95%CI, 0.64 – 0.79) and did not significantly differ with those of other parameters: 0.74 (0.67 – 0.82) for the PE-index, 0.73 (0.65 – 0.80) for AVDSf, 0.69 (0.60 – 0.77) for Fdlate and 0.72 (0.65 – 0.80) for ETCO₂ (Figure 2). Cross tabulation of the proposed threshold of 1.90 Pa.min of CapNoPE against the diagnosis of PE is provided in table 3. A total of 106 subjects had a value of CapNoPE $\geq$ 1.90 Pa.min of which 24 were false-negatives. Of the 99 subjects with a value of CapNoPE < 1.90 Pa.min, 55 were false-positive. This resulted in a sensitivity of 64.7% (95%CI 52.2 – 75.9%) with a specificity of 59.9% (95%CI 51.1 – 68.1%), a NPV of 77.4% (95%CI 68.2 – 84.9%) and a PPV of 44.4% (95%CI 34.5 – 54.8%).

Table 1 - Characteristics of the study population.

Variable	Total (N=205)	PE (N=68)	No PE (N=137)	P-value [#]
Females, N (%)	108 (52.7)	35 (51.5)	73 (53.3)	0.65
Age, years (SD)	65.1 (16.8)	66.4 (16.5)	64.4 (16.9)	0.42
Height, cm (SD)	169 (9)	170 (10)	168 (8)	0.21
Weight, kg (SD)	75.4 (16.8)	76.0 (14.4)	75.2 (17.9)	0.76
Active smoker, N (%)	45 (22.0)	11 (16.2)	34 (24.8)	0.13
COPD, N (%)	24 (11.7)	5 (7.4)	19 (13.9)	0.17
Previous PE, N (%)	38 (18.5)	18 (26.5)	20 (14.6)	0.04*
Heart failure, N(%)	17 (8.3)	4 (5.9)	13 (9.5)	0.41
Cancer, N (%)	16 (7.8)	5 (7.4)	11 (8.0)	0.87
Heart frequency, beats/min (SD)	89 (21)	94 (22)	86 (21)	0.01*
Pulse oximetry, % (IQR)	95 (92 – 97)	94 (90 – 96)	96 (93 – 98)	0.003*
Thoracic pain, N (%)	124 (60.5)	39 (57.4)	85 (62.0)	0.48
Dyspnea, N (%)	154 (75.1)	56 (82.4)	98 (71.5)	0.11
Signs of DVT, N (%)	24 (11.7)	10 (14.7)	14 (10.2)	0.36
D-dimer, µg/L (IQR)	1412 (921 – 2926)	3070 (1600 – 5117)	1080 (764 – 1929)	<0.001*
Hours in ED (IQR)	5.0 (3.0 – 11.0)	5.5 (3.3 – 14.0)	5.0 (2.0 – 8.0)	0.03*
Hours symptoms (IQR)	72 (24 – 168)	72 (24 – 168)	72 (24 – 180)	0.91
Revised Geneva score (IQR)	5 (3 – 7)	6 (5 – 8)	4 (3 – 6)	<0.001*

*Data are presented as mean with corresponding standard deviation (SD), median with corresponding interquartile range (IQR) or number with corresponding percentage. #: P-value for differences between subjects with and without PE. Statistical significant differences (p<0.05) are indicated with *. COPD: Chronic obstructive pulmonary disease; PE: Pulmonary embolism; DVT: Deep venous thrombosis; ED: Emergency department.*

Table 2 – Values of the arterial blood gas and volumetric capnography variables in the groups with and without PE.

Variable	PE (N=68)	No PE (N=137)	P-value
PaO2, kPa (SD)	9.6 (2.4)	10.4 (2.5)	0.03*
PaCO2, kPa (SD)	4.4 (0.7)	4.6 (0.7)	0.01*
Tidal volume, mL (SD)	694 (303)	636 (305)	0.20
Resp. rate, min ⁻¹ (SD)	18.9 (5.9)	17.9 (5.9)	0.23
ETCO ₂ , kPa (SD)	3.41 (0.89)	4.09 (0.71)	<0.001*
VDaw/VT, % (SD)	38.9 (8.7)	39.0 (8.9)	0.96
VCO ₂ , mL/breath (SD)	13.4 (7.0)	14.9 (9.1)	0.24
Slope3, kPa/L (IQR)	1.94 (1.06 – 3.39)	2.70 (1.54 – 5.24)	0.001*
PE index, mL (IQR)	422 (144 – 1048)	146 (67 – 286)	<0.001*
Fdlate, % (SD)	0.73 (45.7)	-15.2 (34.1)	<0.001*
Alveolar dead space fraction, % (SD)	22.1 (14.1)	11.3 (9.9)	0.01*
CapNoPE, Pa.min (SD)	1.56 (0.97)	2.51 (1.67)	<0.001*

Data are presented as mean with corresponding standard deviation (Std) or median with corresponding interquartile range (IQR). Statistical significant differences (P<0.05) are indicated with *.

Table 3 - Cross tabulation of the proposed threshold of 1.90 Pa.min of the new capnography parameter against the diagnosis of PE.

	PE	No PE	Total
CapNoPE < 1.90	44	55	99
CapNoPE ≥ 1.90 Pa.min	24	82	106
Total	68	137	205

Figure 2 - Receiver operating characteristic curves for five capnography parameters: CapNoPE; end-tidal CO₂; pulmonary embolism index; Fdlate and the Alveolar dead space fraction. AUC: area under the curve.

DISCUSSION

The results confirm those of our pilot study which showed that the novel volumetric capnography derived parameter CapNoPE is significantly decreased in patients with PE compared to those without. Furthermore, its diagnostic accuracy as expressed in the AUC of the ROC curve is similar to the earlier proposed parameters AVDSf, PE-index, Fdlate and ETCO₂.

The large advantage of CapNoPE over AVDSf, PE-index and Fdlate is that it does not need arterial sampling and therefore is less burdensome for the patient. On the other hand, some form of dead space fraction is simpler to interpret by clinicians whereas CapNoPE represents an abstract entity. Furthermore, in the presence of respiratory comorbidities (such as COPD) arterial parameters might be essential for the differentiation between effects of PE and the comorbidity. Diseases such as COPD are known to alter the volumetric capnogram (mainly slope3) [15] and might thus affect CapNoPE. Unfortunately, the number of included subjects with COPD is too low to investigate this potential influence.

Moreover, ETCO₂ alone also does not need arterial sampling and its diagnostic accuracy is, in the current study population (with a relatively low number of subjects with respiratory comorbidities), also comparable to the more advanced parameters.

The rationale behind this study is to find an easily accessible tool (in addition to the current diagnostic strategy) to exclude PE at the emergency department. Volumetric capnography is easy to apply in the emergency department and the cutoff for CapNoPE of ≥ 1.90 Pa.min to exclude PE showed a promising sensitivity and specificity in a pilot study. However, the confidence intervals of the diagnostic properties were wide, warranting further validation. Unfortunately, in the current larger dataset the proposed threshold results in a sensitivity 64.7% and a NPV of 77.4%. There are no obvious differences in patient characteristics between the population of the current presented data and the pilot study that seem to explain the lower diagnostic properties. Of note, there were no differences in the distribution of CapNoPE between these data and those of the pilot study ($p=0.22$ for subjects with PE and $p=0.43$ for subjects without PE). The development of CapNoPE was based on the hypothesis that VCO₂ and slope3 are decreased in the presence of PE whereas the respiratory rate is likely to increase. It was reasoned that the effects of PE on each parameter alone might be too small to detect and therefore they were combined to increase the differences. Indeed, the pilot study did not show significant differences in slope3, VCO₂ and the respiratory rate (although there was a non-significant trend towards a higher respiratory rate and lower VCO₂ in the subjects with PE) whereas the combination of these three parameters into CapNoPE was significantly decreased in PE subjects. The now presented results show no differences in both respiratory rate and VCO₂ between the subjects with and without PE but slope3 is significantly decreased. The lower diagnostic properties found in the now presented data might be explained by the larger number of included subjects. As indicated earlier, the confidence intervals of the diagnostic properties found in the pilot study were wide (due to a limited number of included subjects).

Though the diagnostic properties of the proposed threshold are lower, it should be noted that the AUC of the ROC curve is well within the confidence interval of the AUC found in the pilot study. However, given the potentially lethal consequences of PE, the NPV (77.4%) is unacceptable for excluding PE safely. The ROC curve also shows that the cutoffs with an acceptable negative predictive value (>97%) have poor specificity (and PPV <30%). As the PPV of the current diagnostic strategy is already 20-30%, these cutoffs would have no added value in the diagnostic workup of patients with suspected PE. This also yields for the other capnography derived parameters ETCO₂, AVDSf, PE-index and Fdlate. This seems to imply that volumetric capnography alone will not be sufficient to exclude PE. One reason for this might be the extent of some emboli. As the specifications of the imaging standards improve, smaller emboli are detected. Furthermore, the imaging standards detect the presence of clots in the pulmonary circulation, not their consequences on gas exchange. Another reason for the limited diagnostic capacity of capnography might be the high variability of breathing (and thus CO₂ exchange). However, prolonged periods of data were recorded and averaged. The data was only used for analysis if variability was low, as pre-specified by several strict criteria (based on tidal volume, breathing frequency and PETCO₂) and visible inspection of the capnograms did not reveal obvious measurement errors [11]. This strategy is likely to have maximized the chance on representable measurements.

The current study has some limitations. As already mentioned CapNoPE is more abstract and therefore harder to interpret compared to dead space fractions. However, all these parameters also require some level of physiologic expertise. The use of other tools, such as the age-adjusted D-dimer [16] or the YEARS algorithm [17], to increase the PPV of the diagnostic workup of PE suspected patients may therefore be more likely to succeed. The major limitation of this study is the relatively low number of included subjects. To be able to draw a definite conclusion on the usability of CapNoPE for the exclusion of PE, a much larger prospective trial (also including several respiratory and cardiovascular comorbidities) would be required. The definition of PE used in the original trial (positive CTPA or ultrasound at initial presentation, or a thromboembolic event during three month follow-up) might also appear as a limitation. A positive venous ultrasonography finding alone or the occurrence of a thromboembolic event during follow-up does not necessarily implicate that PE was present during the initial presentation when the volumetric capnography was performed. However, no thromboembolic events were recorded during the follow-up of the subjects in whom PE was excluded at the initial presentation. Furthermore, PE was diagnosed based solely on a positive venous ultrasonography finding in only three subjects. Therefore it seems unlikely that this influenced the results of the current analysis.

Conclusion

The new volumetric capnography derived parameter CapNoPE ($\frac{VCO_2 \times Slope3}{RR}$) is significantly decreased in subjects with pulmonary embolism (PE) compared to subjects without. Furthermore,

its overall diagnostic properties are essentially equal to the diagnostic properties of ETCO₂, PE-index, Fdlate and the alveolar dead space fraction. However, the negative predictive value of the earlier established threshold of ≥ 1.9 Pa.min to exclude PE seems too low to use in clinical practice.

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Conflicts of Interest

Prof. Sanchez reports grants and personal fees from Bayer, grants and other from Daiichi, grants from Actelion, grants and personal fees from MSD, personal fees from BMS and personal fees from SANOFI AVENTIS, all outside the submitted work. Prof. Verschuren reports grants from Portola Pharmaceutical, Boehringer and Daiichi, all outside the submitted work. All other authors declare they have no conflicts of interest.

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Validation of the oxygen desaturation index in the diagnostic workup of obstructive sleep apnea

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ABSTRACT:

Introduction

Obstructive sleep apnea (OSA) is common and diagnosis requires expensive and laborious testing to assess the apnea hypopnea index (AHI). We performed an analysis to explore the relationship between the oxygen desaturation index (ODI) as measured with pulse oximetry and the AHI in our large portable monitoring (PM) database to find an optimal cutoff value for the ODI in order to be able to exclude $AHI \geq 5$ on PM.

Methods

3413 PM recordings were randomly divided into a training set ($N=2281$) and a test set ($N=1132$). The optimal cutoff for the ODI to exclude an $AHI \geq 5$ on PM was determined in the training set and subsequently validated in the test set.

Results

Area under the curve of the ODI to exclude an $AHI \geq 5$ on PM was 0.997 in the training set and 0.996 in the test set. In the training set, the optimal cutoff to predict an $AHI < 5$ was an $ODI < 5$. Using this cutoff in the test set provided a sensitivity of 97.7%, a specificity of 97.0%, a positive predictive value of 99.2% and a negative predictive value of 91.4%.

Conclusion

An $ODI < 5$ predicts an $AHI < 5$ with high sensitivity and specificity when measured simultaneously using the same oximeter during PM recording.

INTRODUCTION

The prevalence of obstructive sleep apnea (OSA), defined as an Apnea Hypopnea Index (AHI) $\geq$ 5 events per hour sleep) is high. In the early nineties, at least two to four percent of the middle-aged population was affected [1] and over two decades this has increased to over ten percent [2]. Although it is increasingly recognized, there is still only a small group that has actually been diagnosed with OSA[3,4].

OSA often requires lifelong treatment with multidisciplinary management. Before initiating treatment, it is important to have an appropriate diagnosis and to know the severity. Therefore, a valid method is necessary to prove or exclude sleep apnea. The diagnosis usually relies on a thorough sleep history and interpreting the clinical symptoms, physical examination and sleep recording with type III portable monitoring (PM) or polysomnography (PSG) recording according to the algorithm proposed by the 2012 update of the American Academy of Sleep Medicine (AASM) guidelines [5]. Following these guidelines, the oxygen desaturation index (ODI) is defined as the number of desaturations per hour of at least 3% from baseline.

Nowadays, there is an increasing interest in screening for OSA in specific groups like patients in general practice, patients with hypertension, obesity or diabetes, subjects in groups with demanding tasks like commercial drivers, and in the preoperative setting [6]. The prevalence of OSA in these specific groups and the general population is likely to be lower than the prevalence of OSA in patients referred to a sleep center. Therefore, extensive sleep monitoring is too cumbersome and too expensive in these populations [7]. As a desaturation is often present in hypopneas and apneas, it can be hypothesized that the ODI may be used as substitute of the AHI. As oximetry is cheaper and less burdensome than type III PM and PSG, its use (possibly combined with a questionnaire) seems an attractive option to screen for OSA in the general practice and for treatment follow-up (e.g. mandibular advancement device, positional therapy, weight reduction). Modern pulse oximeters have the potential to achieve this [8,9]. Multiple studies have shown good agreement between PSG or PM derived AHI with oximetry alone [9–11]. In setting up a screening study in general practice we performed an analysis to explore the relationship between the ODI as measured with pulse oximetry and the AHI in our large PM database.

METHODS

Study population

The study was conducted at the Medisch Spectrum Twente, Enschede, the Netherlands. The study included all PM recordings performed between January 2013 and December 2015. Exclusion criteria were: age < 18 years; effective recording time < 4 hours; missing patient

characteristics (age, height, weight); missing AHI, apnea index, hypopnea index or ODI; missing conclusion or conclusion “failed measurement”.

Sleep recording

Sleep recordings were all done with the NOX T3 Sleep Monitor (Nox Medical, Reykjavík, Iceland), a $S_3C_4O_1P_2E_1R_2$ type III PM device [12] which measures the following signals: nasal flow, effort by inductive belts (thorax and abdomen), oximetry using the Nonin WristOx₂[™] model 3150 wrist-worn pulse oximeter (Nonin Medical, Inc., Plymouth, Minnesota, USA), acoustic snoring sound detection, body movement activity and body position. Raw data were stored in a database and adaption of the recording time was performed by visual judgement of the pulse rate and body activity or general artefacts in all signals. According to the most recent AASM rules, an apnea was defined as a flow decrease of $\geq 90\%$ and a hypopnea was defined as a flow decrease between 30-90% with a desaturation of $\geq 3\%$ [13]. All respiratory events did have a duration of at least 10 seconds. A PM recording was first automatically analysed by Noxturnal version 4 (Nox Medical, Reykjavík, Iceland) and all signals (including the respiration and oxygen saturation signals) were subsequently manually assessed by a trained respiratory technician (i.e. hypopneas, apneas and desaturations were added or deleted when appropriate according to the AASM guidelines). The analysed results were stored in a database.

Data collection

The data of all available PM recordings from January 2013 to December 2015 were extracted from the database. Hereafter, the data were anonymized and the exclusion criteria were applied.

Ethical Considerations

This retrospective study was approved by the Medical Ethical Committee Twente at Enschede, as well by the board of directors of the Medisch Spectrum Twente, Enschede, the Netherlands.

Statistical analysis

The data was randomly divided into two groups: a training set (2/3 of the data) and a test set (1/3 of the data). The training set was divided in a sub-training set (3/4 of training set) and sub-validation set (1/4 of training set). The sub-training set was used to search for the optimal cutoff value for the ODI to predict an AHI < 5 using a Receiver Operating Characteristic (ROC) curve. The diagnostic accuracy (expressed as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and area under the curve (AUC) of the ROC curve with corresponding 95% confidence intervals (95%CI)) of this cutoff value was subsequently assessed in the sub-validation group. The best cutoff value was then assessed in the test set. Continuous variables are expressed as mean with standard deviation or median with interquartile range

(IQR), as appropriate. Categorical variables are expressed as counts with corresponding percentages. Data were analysed using SPSS version 22 (SPSS Inc. Chicago IL, USA). To be able to assess the characteristics of the recordings with a large difference in AHI and ODI the data was divided into three sets: those with a large negative difference (i.e. AHI was smaller than ODI, defined as the data below the 10th percentile of the AHI-ODI difference), those with a normal difference (defined as the data between the 10th and 90th percentile of the AHI-ODI difference) and those with a large positive difference (i.e. AHI was larger than ODI, defined as the data above the 90th percentile of the AHI-ODI difference). Differences in characteristics (age, weight, BMI and signal quality) between the large negative vs the normal group and the large positive vs the normal group were performed with independent samples t-tests or Mann-Whitney U tests as appropriate. A p-value < 0.025 was considered to indicate a statistically significant difference.

RESULTS

A total of 4154 PM recordings were included. After applying the exclusion criteria, 3413 recordings remained for analysis. Characteristics of the included recordings are provided in table 1. The recordings were divided into two groups: a training set of 2281 recordings and a test set of 1132 recordings. The training set was divided in a sub-training set of 1705 recordings and a sub-validation set of 576 recordings. Patient characteristics did not differ between the sets (data not shown).

Table 1 – Patient characteristics of the complete dataset. Continuous variables are presented as mean with corresponding standard deviation (std) or median with corresponding interquartile range (IQR). Categorical variables are presented as number with corresponding percentage of the total population.

<i>N = 3413</i>	<i>Mean or median</i>	<i>Std, % or IQR</i>
<i>Age (years)</i>	53.6	13.4
<i>Males (N(%))</i>	2399	70.3
<i>Weight (kg)</i>	92.5	18.6
<i>BMI (kg/m²)</i>	29.6	5.7
<i>AHI ≥ 5 (N(%))</i>	2726	79.9
<i>AHI (N/hour)</i>	12.1	(5.9 – 23.9)
<i>ODI (N/hour)</i>	11.9	(5.7 – 23.9)

In the sub-training set, the AUC of the ODI to predict AHI < 5 was 0.997 (95%CI 0.995 – 0.999). From the ROC curve it was concluded that the optimal cutoff of ODI to predict AHI < 5 was a value of 5 desaturations per hour. Using this cutoff provided a sensitivity of 97.8%, a specificity of 97.4%, a PPV of 99.3% and a NPV of 91.8%. The diagnostic performance of this cutoff in all sets is provided in table 2.

Table 2 – Diagnostic performance of ODI < 5 to predict AHI < 5 in the sub-training, sub-validation and test sets. Data are provided as percentage (95% confidence interval). PPV: positive predictive value. NPV: negative predictive value. LR+: Positive likelihood ratio. LR-: Negative likelihood ratio.

	Sub-training set (N = 1705)	Sub-validation set (N = 576)	Test set (N = 1132)
Sensitivity	97.8 (96.8 – 98.5)	98.1 (96.3 – 99.1)	97.7 (96.5 – 98.6)
Specificity	97.4 (95.1 – 98.8)	99.1 (95.1 – 100.0)	97.0 (93.8 – 98.8)
PPV	99.3 (98.7 – 99.7)	99.8 (98.8 – 100.0)	99.2 (98.4 – 99.7)
NPV	91.8 (88.5 – 94.4)	92.5 (86.2 – 96.5)	91.4 (87.1 – 94.6)

In the sub-validation set the diagnostic performance was similar to the performance in the sub-training set. AUC of the ODI to predict AHI < 5 in the test set was 0.996. As these values were satisfying, the cutoff of ODI < 5 was finally tested in the test set, which provided a sensitivity of 97.7%, a specificity of 97.0%, a PPV of 99.2%, a NPV of 91.4%, a positive likelihood ratio of 32.1, and a negative likelihood ratio of 0.02. The resulting cross tabulation is provided in table 3.

Table 3 – Cross tabulation of ODI < 5 to predict AHI < 5 in the test set.

	AHI ≥ 5	AHI < 5	Total
ODI ≥ 5	881	7	888
ODI < 5	21	223	244
Total	902	230	1132

A scatter plot of the measured ODI versus the measured AHI is provided in figure 1 ($R^2 = 0.99$). Of the 21 false negative patients, 1.9% of all recordings in the test set, with ODI < 5 but AHI ≥ 5, median AHI was 5.2 with a minimum of 5.0 and a maximum of 8.6.

Figure 1 - Scatter plot of the ODI versus the AHI in the test set ($R^2 = 0.99$). The vertical dashed line indicates ODI = 5, the horizontal dashed line indicates AHI = 5. In order to be able to assess the false negatives and false positives the axes are limited to 30 events per hour for both the AHI and ODI.

A Bland-Altman plot of the AHI versus the ODI in the test is provided in figure 2. Mean difference between AHI and ODI (AHI minus ODI) was +0.21 (95%CI -2.98; 3.41) events per hour. The test set contained a total of 45911 apneas (median per recording: 10 (IQR 3 – 35)) of which 2897 (6.3%) were not associated with a desaturation (median per recording: 0 (IQR 0 – 2)). The total number of desaturations was 142133 (median per recording: 84 (IQR 40 – 162)) of which 6645 (4.7%) were not associated with a respiratory event (median per recording: 2 (IQR 1 – 6)).

Figure 2 - Bland-Altman plot of the AHI versus the ODI in the test set.

Compared with those with a difference in AHI and ODI between the 10th and 90th percentiles, the subjects with recordings with a difference in AHI and ODI below the 10th percentile (i.e. AHI was smaller than ODI) had a significantly higher weight (100.3 ± 18.2 vs 91.7 ± 17.9 kg, $p < 0.001$), higher BMI (33.0 ± 6.0 vs 29.3 ± 5.5 kg/m², $p < 0.001$) and were older (58.2 ± 12.8 vs 53.0 ± 13.1 years, $p < 0.001$). The signal quality was also significantly lower but the absolute differences were small (99.4 (IQR $97.2 - 99.8$)% vs 99.6 (IQR $98.8 - 99.9$)%, $p = 0.016$).

Compared with those with a difference in AHI and ODI between the 10th and 90th percentiles, the subjects with recordings with a difference in AHI and ODI above the 90th percentile (i.e. AHI was larger than ODI) were significantly older (57.7 ± 13.7 vs 53.0 ± 13.1 years, $p < 0.001$). There were no significant differences in weight, BMI and signal quality between these groups.

DISCUSSION

The results clearly indicate that, with the current assessment criteria, the measured ODI is highly correlated with the measured AHI during PM recordings. Using a cutoff value of an ODI < 5 to exclude an AHI < 5 on PM resulted in only 21 (1.9%) misclassified patients. All of these subjects had an AHI marginally higher than 5. This is visualized in figure 1 where almost no

circles are present in the upper left quadrant. Given the low false negative rate (and small negative likelihood ratio), these results suggest that the ODI can safely be used to rule out an $AHI < 5$ on a PM recording, at least in a population referred to a sleep center. As pulse oximetry is less expensive and less time-consuming than PM recordings, it is more suitable as a screening tool.

In the Netherlands it is standard care that the general practitioner, if the presence of sleep apnea is suspected, refers a subject to a sleep center. The sleep center performs a PM recording or PSG, often in the home setting. Hereafter, the results are discussed with the patient and the appropriate therapy (continuous positive pressure, oral appliances, positional therapy, or no therapy) is started. We propose that modern pulse oximetry can be used by the general practitioner as an easily accessible screening method. It is important to note that this is only true in the population in which a PM recording is deemed valid. Two recent large randomized controlled trials showed that, in the right population (i.e. subjects with a high pre-test probability of moderate to severe OSA), PM recording is sufficient for the diagnosis and treatment of OSA [14,15]. The recent clinical practice guideline of the American Academy of Sleep Medicine also recommends that "polysomnography, or home sleep apnea testing with a technically adequate device, be used for the diagnosis for OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA" [16]. The population of the current presented data consists of patients in whom the sleep physician deemed PM valid as diagnostic recording. Consequentially, if oximetry would be used as a screening tool for OSA by the general practitioner, this would only be a valid strategy if the right patients are selected for screening. The use of a questionnaire (such as the Philips questionnaire [3]) might enable this selection [17].

The subjects with a high positive difference in AHI and ODI were older, suggesting that the ODI may be less useful to represent the AHI in older patients perhaps due to the presence of relevant comorbidities. Furthermore, the subjects with a high negative difference in AHI and ODI had a higher BMI and were also older. Both high age and high BMI might cause hypoxemia, which can explain the high ODI compared to AHI. The opposite may also be true: young subjects without cardiopulmonary comorbidities are less prone to desaturations and therefore oximetry (but also PM recording) is unsuitable to detect OSA in these subjects. Unfortunately the current database does not cover information on hypoxemia and comorbidities. The influence of several characteristics on the usability of pulse oximetry to resemble AHI should be investigated in further research. However, the number of false negatives (and false positives) seem already acceptable.

When the appropriate patient is selected and the pulse oximetry measurement shows an $ODI < 5$ the patient should not undergo a subsequent PM recording as the currently presented data show that the probability of an $AHI < 5$ on a PM is low in these subjects. Instead, a PSG may be performed. The high correlation between ODI and AHI makes it tempting to use the ODI as a complete substitute of the AHI, and therefore replace the PM recording with a sole pulse oximetry measurement. However, this cannot be recommended yet. The earlier mentioned

recent randomized controlled trial on PSG versus PM as diagnostic tool for OSA showed equal outcomes for PSG and type III PM but not for PSG and only oximetry on all outcomes (although there might be some bias in these results caused by reduced confidence of the physician in the oximetry measurement outcomes) [14]. Another randomized controlled trial showed that general practitioners can implement treatment of (sleepy) OSA patients with the same outcome (reduction in ESS) as sleep specialists using a two-step (questionnaire and oximetry) screening strategy [17]. These results are promising but were performed using trained nurses (of which one had previous sleep medicine experience). Therefore, more (“real-life”) prospective studies on the use of the ODI as diagnostic modality to start treatment (and to investigate in which populations this is valid) are necessary. If these studies show that the ODI can be used to start treatment this may be even initiated by the general practitioner in some cases, which will decrease the load of the sleep centers.

There are some limitations to the current study. The high correlation between ODI and AHI was to be expected as no arousals were measured during the PM recordings and a desaturation is part of the hypopnea definition. Additionally, PSG indexes will always be more accurate and higher than indexes derived from limited sleep studies, where only recording time (with additional wake periods) is available and no arousal detection is possible. So PM and oximetry have the potential to underestimate OSA [9]. Therefore, in patients with a negative PM and marked symptoms (especially unexplained daytime sleepiness) a PSG should be performed[5]. This difference is reflected in the lower AUC found in other studies comparing ODI with PSG derived AHI. Dawson et al. for instance found an AUC of 0.857 whereas Chung et al. found a AUC of 0.908 for the ODI in predicting $AHI \geq 5$ during a PSG recording [10,18]. Also, in our study, the same time basis (visual corrected recording time) was used for calculation of the ODI and AHI. These factors might explain the somewhat lower correlations between ODI and AHI found in other studies on PSG data in which arousals can be measured and different time bases were applied [9,10,19].

It should be mentioned that pulse oximetry may be less reliable in dark skin type subjects [20], whereas the vast majority of our population consisted of light skin type subjects. Another explanation for the higher correlation in our data compared to previous and especially the older publications might be the improvement in desaturation detection of the modern pulse oximeters. A short moving averaging time and a high data storage rate are now recommended [21,22]. Furthermore, the type and location of the oximeter might influence the results. During this study, the same oximeter was used for calculation of the ODI and AHI. Using a different type of oximeter, e.g. an oximeter with a different sampling frequency or other filtering settings or applying the oximeter to another part of the body (such as the earlobe) might lower the resemblance between the AHI and ODI found in this study. Nevertheless, a recent study reported good agreement between the ODI as measured by finger transmission pulse oximetry (as done in the current presented data) an AHI measured by several signals including forehead reflectance oximetry [23]. Finally, wider use of the last AASM hypopnea definition with one

defined decrease of flow (30%) and one defined depth of desaturation (3%) with or without an arousal will (by definition) increase the agreement with oximetry using a 3% desaturation definition [13]. As reported by Guilleminault and Reuhland applying the two definitions of the AASM 2007 hypopnea definition and the so-called Chicago 1999 definition in the same patient group resulted in a more than 60% change in OSA detection. These studies formed the basis for the new sensitive hypopnea definition [13,24,25].

The ODI was measured simultaneously during the PM recordings. Although the saturation signal is assessed independently from the other signals, some bias may be present. A prospective validation study in which the correlation between ODI, derived from a sole pulse oximetry measurement, with AHI during PM recordings should therefore be performed. Another limitation is the population used in this study. The ultimate goal is to find an easy to use screening tool for OSA in a low prevalence population. The studied population however, is a sleep center referral population with a high prevalence of OSA. Although the difference in prevalence might influence the negative predictive value, it will not influence the specificity. Furthermore, we expect no physiologic differences between our sleep center referral population and a more general screening population, which might influence the accuracy of pulse oximetry.

Concluding, an ODI < 5 predicts an AHI < 5 with high sensitivity and specificity when measured simultaneously using the same oximeter during PM recording. Similar to a negative PM recording, a negative oximetry should be followed by a PSG to rule out OSA completely.

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Conflict of Interest: JB reports shares in DiagnOSAS B.V., a company that aims to facilitate screening for sleep apnea in a primary care setting. All other authors (TF, LB, JvdP, FdJ and ME) certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Both the local ethics committee and the board of directors of the Medisch Spectrum Twente approved the study protocol.

Informed consent: This study is based on anonymous data. Therefore, obtaining informed consent was deemed unnecessary (as approved by the local ethics committee).

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The use of oximetry and a questionnaire in primary care enables exclusion of a subsequent obstructive sleep apnea diagnosis

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ABSTRACT

Purpose

To prospectively validate the prognostic value of oximetry alone or combined in a two-step strategy with a questionnaire for the exclusion of obstructive sleep apnea (OSA) in primary care.

Methods

A total of 140 subjects with suspected OSA were included from 54 participating primary care practices. All subjects completed the Philips questionnaire and underwent one night of oximetry prior to referral to a sleep center. The prognostic value of two strategies was evaluated against the diagnosis of the sleep center as the gold standard: 1) assume OSA and subsequently refer to a sleep center if the oxygen desaturation index (ODI) is ≥ 5 ; and 2) assume OSA and refer to a sleep center if the Philips questionnaire score is $\geq 55\%$ (regardless of the ODI), or if the Philips questionnaire score is $< 55\%$ and the ODI is ≥ 5 .

Results

OSA was diagnosed in the sleep centers in 100 (71%) of the included subjects. Using $\text{ODI} \geq 5$ alone resulted in a sensitivity of 99.0%, a specificity of 50.0%, a negative predictive value of 95.2%, and a positive predictive value 83.2%. Using the two-step strategy, oximetry would be performed on 39% of the subjects. This strategy resulted in a sensitivity of 100%, a specificity of 35.0%, a negative predictive value of 100%, and a positive predictive value of 79.4%.

Conclusions

In a Dutch primary care population with a clinical suspicion of OSA and low frequency of cardiovascular comorbidities, the use of oximetry alone or combined in a two-step strategy with a questionnaire enables exclusion of a sleep center diagnosis of OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder that causes patients to stop breathing during sleep. Over the past decades, the hazardous effects of OSA on personal health[1] and society[2,3] have become more and more clear. Still, it is estimated that more than half of all patients suffering from OSA are undiagnosed and therefore untreated[4].

Diagnosing OSA and setting up an appropriate treatment requires specialized care that is generally only available in sleep clinics. In the Netherlands, the number of referrals to sleep clinics for OSA approached 100.000 in 2017 and has increased rapidly over the past few years[5]. Of all patients referred by their general practitioner, up to one third (30%) eventually does not have OSA upon final poly(somno)graphy[5]. This may be explained by the heterogeneous and often non-specific symptoms of OSA, making it difficult to distinguish OSA from other diagnoses.

Simply increasing the number of referrals to sleep clinics would result in more treated OSA patients, but also in an unacceptable rise in costs due to an associated increase in expensive poly(somno)graphies performed in patients without OSA. In addition, the capacity of sleep clinics is limited, resulting in (extended) waiting lists when the number of referred patients grows. To maximize the number of treated OSA patients without increasing costs or waiting lists, we propose to focus on optimization of the selection process regarding which patients should (not) be referred.

In an attempt to triage referral based on the pre-test probability of OSA, several screening strategies have been developed. Examples include questionnaires (e.g. STOP-BANG[6,7], Berlin[8], Epworth Sleepiness Scale[9]) or a two-step screening strategy (e.g. the Philips questionnaire combined with nasal flow recording[10]). However, although some are suitable for screening in low prevalence populations, none of these have shown acceptable sensitivity to safely rule out OSA when used in a high-prevalence referral population. In 2016, Kunisaki et al. reported on a prospective observational study in which overnight oximetry was applied to detect OSA in 234 veterans referred for sleep testing[11]. Based on a positive predictive value of 92 to 100%, the authors concluded that overnight oximetry could significantly reduce the number of patients requiring referral for polysomnography.

In this study, we hypothesized that overnight oximetry alone, or combined with a previously published questionnaire in a two-step strategy, could be used to safely rule out OSA in patients visiting their general practitioner with potentially OSA-related complaints, thereby reducing the number of patients requiring referral for sleep testing. We prospectively validated this hypothesis in a high prevalence population of patients with suspected OSA in the general practice setting.

METHODS

Participants

This was a prospective observational validation study in 54 general practitioner practices located in the catchment area of the sleep centers of two large teaching hospitals. All adult (≥ 18 years) subjects referred to one of the sleep centers by a participating general practitioner due to suspected OSA were eligible for inclusion. Patients were approached and included by their general practitioner. Subjects who were unable to undergo oximetry or had missing data (i.e. missing questionnaire, oximetry, or sleep center diagnosis) were excluded from the analysis.

All participating subjects provided written informed consent. The study protocol was approved by the Medical Ethical Committee Twente (Enschede, the Netherlands) and registered at the Netherlands Trial Register (www.trialregister.nl, ID: NTR5786).

Measurements

Included subjects completed an online version of the Philips questionnaire[10] and underwent overnight oximetry using the Nonin WristOx₂[™] model 3150 wrist-worn pulse oximeter (Nonin Medical, Inc., Plymouth, MN, USA). The questionnaires were completed without the presense or further explanation of a healthcare professional. Of the patient characteristics body weight and height were patient reported. Neck circumference was measured at the general practitioner's practice. For the oximetry, subjects were instructed to start the measurement when they went to bed. The oxygen desaturation index (ODI, number of saturation drops ($\geq 3\%$) divided by recording time) was automatically obtained from the oximetry data using a custom build script in Matlab (The Mathworks, Inc., Natick, MA, USA).

All measurements were performed before OSA was diagnosed or excluded in the sleep center. The diagnosis or exclusion of OSA in the sleep center was based on regular care (i.e. symptoms, medical history, physical examination, and poly(somno)graphy). Similar to those of the American Academy of Sleep Medicine, the Dutch guideline for diagnosis and treatment of OSA in adults recommends a diagnosis of OSA if poly(somno)graphy results in an apnea-hypopnea index (AHI) ≥ 15 or an AHI between 5 and 15 combined with specific symptoms or comorbidities[12,13]. The poly(somno)graphy data were analyzed according to the American Academy of Sleep Medicine guidelines[14]. Desaturation were defined as a $\geq 3\%$ decrease from pre-event baseline. In polygraphy, hypopneas had to be associated with a desaturation. In polysomnography, hypopneas had to be associated with either a desaturation or an arousal. In case of OSA associated symptoms but a negative polygraphy (i.e. AHI < 5), a polysomnography was performed (as per AASM and Dutch guidelines). The healthcare professionals of the sleep centers were unaware of the results of the questionnaire and overnight oximetry.

Statistical Analysis

The primary aim of this study was to validate a predefined strategy to rule out OSA using oximetry alone or combined with the Philips questionnaire in a two-step strategy. For oximetry, an $\text{ODI} < 5$ has high resemblance with an $\text{AHI} < 5$ when measured simultaneously[15]. Therefore, an $\text{ODI} < 5$ was chosen as cutoff for the oximetry. The Philips questionnaire was originally developed in a population of healthy blue- and white-collar workers and results in a score ranging from 0 to 100%. A score below 35% indicated a low risk of OSA, a score between 35 and 55% an intermediate risk, and a score of 55% and above a high risk[10]. The development and validation (along with a full text English version of the questionnaire) are published elsewhere[10]. In the current study, the questionnaire was combined in a two-step strategy by ruling out OSA in those patients with an $\text{ODI} < 5$ and a score on the Philips questionnaire below 55% (i.e. those with an $\text{ODI} \geq 5$ or a high risk of OSA according to the Philips questionnaire should be referred to a sleep center).

The results of the oximetry alone and the two-step strategy were compared with the diagnosis from the sleep centers using cross-tabulation. Subsequently, sensitivity, specificity, negative predictive value, positive predictive value, and area under the receiver operating characteristics curve (AUC) were calculated. Data were analyzed using SPSS, version 24 (SPSS Inc., Chicago, IL, USA).

A secondary exploratory analysis was performed to identify optimal cutoffs for the questionnaire and oximetry for the exclusion of OSA.

Sample Size

Given the burden of untreated OSA, a high sensitivity is desirable. For this study, a sensitivity of 97% with a precision of 10% and a lower boundary of the 95% confidence interval (95%CI) of 90% was deemed acceptable. To achieve this, 68 subjects with subsequent sleep center diagnosis of OSA should be included. The prevalence of OSA in patients referred to the participating sleep centers is approximately 70%. It was expected that the general practitioners might be keener on referring patients with suspected OSA due to study participation, resulting in a lower prevalence of OSA in those referred. The prevalence in the study population was therefore estimated at 50%, resulting in 136 subjects needed with complete data. With an estimated dropout of 10%, it was expected that a total of 150 subjects needed to be included.

RESULTS

Of 164 included subjects, 140 had complete data (see flowchart, figure 1). Of these, 119 (85%) had an $\text{ODI} \geq 5$ and 85 (61%) a Philips questionnaire score $\geq 55\%$. OSA was diagnosed in the sleep centers in 100 subjects (71%). Characteristics of the analyzed subjects are provided in table 1.

Figure 1 – Flowchart of the included subjects.

Using an ODI < 5 alone ruled out OSA in 21 (15%) subjects of which one did have OSA diagnosed in the sleep center. Cross-tabulation of the use of ODI alone against the sleep center diagnosis is provided in table 2. This strategy resulted in a sensitivity of 99.0% (95%CI 94.5 – 100.0%), a specificity of 50.0% (95%CI 33.8 – 66.2%), a negative predictive value of 95.2% (95%CI 76.2 – 99.9%), a positive predictive value of 83.2% (95%CI 75.2 – 89.4%), a positive likelihood ratio of 1.98 (95%CI 1.45 – 2.70), a negative likelihood ratio of 0.02 (95%CI 0.00 – 0.14), and a corresponding AUC of 0.75 (95%CI 0.64 – 0.85). The subject who was diagnosed with OSA in the sleep center while the screening oximetry resulted in an ODI<5 had a score of 98% on the Philips questionnaire, an ODI of 3/hr and a respiratory event index in the sleep center of 6.4/hr as measured by polygraphy.

Table 4 – Characteristics of the included subjects.

	Total (N=140)	OSA diagnosed in sleep center (N=100)	OSA excluded in sleep center (N=40)	P-value
<i>General characteristics</i>				
Age, years (SD)	49.3 (13.7)	52.4 (12.6)	41.4 (13.1)	<0.001
Males, N (%)	101 (72.1)	78 (78.0)	23 (57.5)	0.02
Weight, kg (SD)	96.3 (18.0)	99.4 (18.2)	88.6 (15.0)	0.001
Body Mass Index, kg/m ² (IQR)	29.4 (25.7 – 33.3)	30.7 (26.4 – 34.4)	26.7 (24.7 – 29.4)	<0.001
Heart failure, N (%)	1 (0.7)	1 (1.0)	0 (0.0)	1.00
Cardiac ischemia, N (%)	7 (5.0)	6 (6.0)	1 (2.5)	0.67
Atrial Fibrillation, N (%)	9 (6.4)	9 (9.0)	0 (0.0)	0.06
Hypertension, N (%)	35 (25.0)	33 (33.0)	2 (5.0)	0.001
Hypercholesterolemia, N (%)	12 (8.6)	10 (10.0)	2 (5.0)	0.509
Diabetes Mellitus, N (%)	12 (8.6)	11 (11.0)	1 (2.5)	0.18
Malignancy, N (%)	6 (4.3)	6 (6.0)	0 (0.0)	0.18
Hypothyroidism, N (%)	9 (6.4)	4 (4.0)	5 (12.5)	0.12
Stroke, N (%)	5 (3.6)	4 (4.0)	1 (2.5)	1.00
COPD, N (%)	3 (2.1)	2 (2.0)	1 (2.5)	1.00
<i>Measured by the General practitioner</i>				
Neck circumference, cm (SD)	40.6 (3.9)	41.5 (3.6)	38.4 (3.6)	<0.001
Oxygen Desaturation Index (IQR)	11.9 (6.1 – 22.1)	16.2 (10.6 – 25.4)	5.1 (3.1 – 7.0)	<0.001
Oxygen Desaturation Index ≥ 5, N (%)	119 (85.0)	99 (99.0)	20 (50.0)	<0.001
Philips Questionnaire, % (IQR)	70.1 (46.6 – 93.1)	89.2 (51.8 – 94.8)	46.6 (28.0 – 65.8)	<0.001
Philips Questionnaire ≥ 55%, N (%)	85 (60.7)	73 (73.0)	12 (30.0)	<0.001
<i>Measured at the Sleep center</i>				
Epworth Sleepiness Scale (SD, N=125)	7.3 (4.5)	7.6 (4.7)	6.6 (4.1)	0.30
Apnea Hypopnea Index (IQR)	13.6 (6.3 – 23.8)	18.2 (12.9 – 31.8)	3.3 (2.5 – 4.8)	<0.001
Apnea Index (IQR)	1.0 (0.4 – 5.5)	2.8 (0.5 – 9.2)	0.3 (0.0 – 0.7)	<0.001
Hypopnea Index (IQR)	10.1 (4.7 – 16.6)	13.7 (8.6 – 18.7)	2.8 (1.5 – 4.3)	<0.001
Apnea Hypopnea Index 5-15, N (%)	47 (33.6)	38 (38.0)	9 (22.5)	0.079
Apnea Hypopnea Index 15-30, N (%)	35 (25.0)	35 (35.0)	0 (0.0)	<0.001
Apnea Hypopnea Index ≥ 30, N (%)	27 (19.3)	27 (27.0)	0 (0.0)	<0.001

Data are presented as mean with standard deviation (SD), median with interquartile range (IQR) or number with corresponding percentage.

Table 2 – Cross tabulation of the use of oximetry alone versus the diagnosis of the sleep centers.

	OSA diagnosed	OSA excluded	Total
ODI ≥ 5	99	20	119
ODI < 5	1	20	21
Total	100	40	140

ODI: Oxygen Desaturation Index.

Table 3 – Cross tabulation of the two-step strategy alone versus the diagnosis of the sleep centers.

	OSA diagnosed	OSA excluded	Total
<i>PQ</i> ≥ 55% or <i>ODI</i> ≥ 5	100	26	126
<i>PQ</i> < 55% and <i>ODI</i> < 5	0	14	14
Total	100	40	140

PQ: Philips Questionnaire; ODI: Oxygen Desaturation Index.

The two-step strategy to refer to the sleep center if the Phillips questionnaire is ≥ 55% or the ODI is ≥ 5 (i.e. OSA is only excluded if the Philips questionnaire is < 55% and ODI < 5) ruled out OSA in 14 (10%) subjects of which none had OSA diagnosed in the sleep centers. Cross tabulation of the two-step strategy against the sleep center diagnosis is provided in table 3. This strategy resulted in a sensitivity of 100% (95%CI 96.3 – 100.0), a specificity of 35.0% (95%CI 20.6 – 51.7%), a negative predictive value of 100% (95%CI 76.8 – 100.0%), a positive predictive value of 79.4% (95%CI 71.2 – 86.1%), a positive likelihood ratio of 1.54 (95%CI 1.23 – 1.93), a negative likelihood ratio of 0.00 (95%CI not applicable), and a corresponding AUC of 0.68 (95%CI 0.57 – 0.79).

The explorative analysis showed that an optimal combination of sensitivity and specificity could be achieved by assuming OSA (and subsequently refer to the sleep center) if one of the following three conditions applied: 1) the Philips questionnaire was ≥ 92%, or 2) the ODI rounded to the nearest integer was ≥ 10, or 3) the rounded ODI was between 5 and 10 and the Philips questionnaire was ≥ 46.5%. Cross-tabulation of these optimized cutoffs versus the final diagnosis of the sleep centers is provided in table 4. These cutoffs would result in a sensitivity of 99.0% (95%CI 94.6 – 100.0%), a specificity of 65.0% (95%CI 48.3 – 79.4%), a negative predictive value of 96.3% (95%CI 81.0 – 99.9%), a positive predictive value of 87.6% (95%CI 80.1 – 93.1%), a positive likelihood ratio of 2.83 (95%CI 1.85 – 4.32), a negative likelihood ratio of 0.02 (95%CI 0.00 – 0.11), and a corresponding AUC of 0.82 (95%CI 0.73 – 0.91).

Table 4 – Cross tabulation of the optimal (according to the post-hoc analysis) two-step strategy versus the diagnosis of the sleep centers. This strategy was deemed positive (i.e. OSA is assumed likely and a subject should be referred to a sleep center) if 1) the Philips questionnaire was ≥ 92%, or 2) the ODI rounded to the nearest integer was ≥ 10, or 3) the rounded ODI was between 5 and 10 and the Philips questionnaire was ≥ 46.5%.

	OSA diagnosed	OSA excluded	Total
Optimal strategy positive	99	14	113
Optimal strategy negative	1	26	27
Total	100	40	140

OSA: Obstructive Sleep Apnea; ODI: Oxygen Desaturation Index.

DISCUSSION

The primary aim of this study was to validate the use of oximetry alone or combined with a questionnaire to exclude OSA in primary care. The results show that both predefined strategies have a high sensitivity (slightly higher for the two-step strategy) and moderate specificity (slightly higher for oximetry alone). The strength of oximetry alone is the higher specificity, which would significantly decrease the number of subjects referred for further workup. However, this strategy seems to erroneously exclude OSA in approximately 1% of the subjects with subsequently diagnosed OSA when referred to a sleep center whereas no OSA case was missed using the two-step strategy. Furthermore, if the two-step strategy is applied, oximetry would only be needed in 39% of the patients. On the other hand, the two-step strategy excludes OSA in fewer subjects (10 vs 15%). Moreover, the respiratory event index resulting from the sleep center analysis in the one false-negative subject in the oximetry-only strategy was only slightly higher than the cutoff of 5 events per hour. This may have been caused by the known night-to-night variation in OSA severity[16]. Both strategies seem to have their strengths and the exact costs will strongly depend on the local costs of an oximetry reading and the local health care system. An extensive cost-effectiveness analysis elaborating on the abovementioned screening strategies was recently published elsewhere[17].

The exploratory analysis resulted in cutoffs that can substantially increase the specificity of the two-step strategy with only a limited decrease in sensitivity. This would add substantially to the clinical applicability of the strategy. However, it would require oximetry recordings in all subjects whereas the predefined cutoffs would only require oximetry in those with a low to moderate score on the Philips questionnaire. Again, whether the added costs of the oximetry reading will outweigh the saved costs of the prevented sleep center referrals strongly depends on the local health care system. More importantly, the optimized cutoffs should be validated prospectively before they can be used in clinical practice.

The findings of this study confirm that a referral to a sleep center for the diagnosis of OSA can be omitted in primary care using oximetry alone or a two-step strategy combining oximetry and a questionnaire. A recent study in Spain showed that the workup and management of OSA in primary care was non-inferior to the workup and management of OSA in a specialized sleep center[18]. Similar results were reported earlier from a study in Australia[19]. We aimed to validate the exclusion of OSA in primary care rather than its confirmation and management. Although the mentioned trials suggest that management is also feasible, it is important to note that both studies only included uncomplicated patients and management was performed by trained nurses. In our study, only subjects who were unable to undergo oximetry or refused informed consent were excluded. Furthermore, no strict inclusion criteria were applied. The findings of our study seem therefore applicable to a broader population. It should be noted, however, that our study was not powered to validate the proposed strategies in subpopulations (e.g. subjects with several significant comorbidities).

With the right in- and exclusion criteria one might argue that an aberrant oximetry recording alone might be sufficient to start a CPAP trial. However, the use of oximetry alone (rather than a P(S)G recording) has inherent limitations. Foremost, an oximetry reading provides much less information than a P(S)G recording. For instance, oximetry will not allow to differentiate between central and obstructive events or if there is a significant positional dependence. Both might enable (or even require) other treatment strategies than plain CPAP. Nevertheless, oximetry alone may be sufficient for a selected (sub-) group of patients. The key will lie in the way this group of patients is selected. A large Australian study already investigated the use of full PSG vs PG vs oximetry as the basis for the management of OSA [20]. The results showed that oximetry alone (compared to PSG) resulted in shorter CPAP usage and less improvement in reported sleep apnea symptoms. Though subjects with significant comorbidities were excluded, all ranges of the ODI were used for management decisions. One might argue that the combination of a high ODI (e.g. > 30 or 40/hr), the absence of significant comorbidities (such as heart failure and neuromuscular conditions) and a high clinical probability of OSA (according to a sleep expert) might enable selection of those patients in whom CPAP can be started without additional testing. If (as was done in our study) the ODI is calculated automatically, we recommend manual affirmation of the automated analysis. In addition, future prospective studies are needed to investigate this interesting hypothesis. Our study has some limitations. First, the clinical diagnosis rather than a test result was used as reference standard. This choice was based on the recent reports indicating a very high prevalence of an increased AHI in the general population of which many do not have any symptoms[21]. Although the debate on whether all asymptomatic individuals with an increased AHI can be left untreated is still ongoing, we feel that the diagnosis of OSA should be based on the combination of AHI with symptoms. This is partly reflected in our results, as OSA was not diagnosed in 10 subjects with an elevated AHI. A second point worthy of note is the number of included subjects. Based on the sample size analysis, 68 subjects in whom OSA was subsequently diagnosed should have been included. However, 100 were included. This was mainly caused by a delay between inclusion (and study measurements) and the time of diagnosis in the sleep centers. Another noteworthy element is that a negative screening result does not exclude the presence of other sleep pathology. If implemented in clinical practice, it should be emphasized that the screening strategies are only capable of excluding OSA and subsequent referral to a sleep center for some other sleep pathology might still be useful. The addition of other (non-OSA) sleep-related questions might help the general practitioner to recognize such cases. As an example, the Athens Insomnia Scale[22] is already incorporated in the Philips questionnaire[10].

Finally, although it was not an exclusion criterion, the prevalence of co-morbidities that might significantly influence the results of an oximetry reading such as COPD, heart failure or neuromuscular disorders was low in the study population. Furthermore, the study population was predominantly male. This may reflect clinical practice but there are significant differences in OSA pathophysiology and presentation between males and females [23]. This may influence

the accuracy of diagnostic strategies. We did not observe large differences in accuracy of the three presented strategies between males and females (see supplementary data). However, our study was not powered to prove differences in diagnostic accuracy between males and females. This precludes a firm conclusion on the use of oximetry for OSA screening in females and subjects with specific comorbidities. Future studies should address the accuracy of oximetry (combined with a questionnaire) in specific comorbidities and females.

Summarizing, in a Dutch primary care population with a clinical suspicion of OSA and low frequency of cardiovascular comorbidities, the use of oximetry alone or combined in a two-step strategy with a questionnaire enables exclusion of a sleep center diagnosis of OSA. The two-step strategy with oximetry only in those with a low probability for OSA (based on the Philips questionnaire) results in a higher sensitivity but lower specificity when compared with oximetry alone. The two-step strategy may be more cost-effective as fewer oximetry recordings would be needed.

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Supplementary Data

Table S1 – Diagnostic accuracy of the three tested strategies for the sleep center diagnosis of OSA in males and females. The explorative analysis was deemed positive if 1) the Philips questionnaire was ≥ 92%, or 2) the ODI rounded to the nearest integer was ≥ 10, or 3) the rounded ODI was between 5 and 10 and the Philips questionnaire was ≥ 46.5%.

	ODI ≥ 5		ODI ≥ 5 or PQ ≥ 55%		Explorative analysis	
	Sens (95%CI)	Spec (95%CI)	Sens (95%CI)	Spec (95%CI)	Sens (95%CI)	Spec (95%CI)
Total (N=140)	99,0 (94,6 - 100,0)	50,0 (33,8 - 66,2)	100,0 (96,4 - 100,0)	35,0 (20,6 - 51,7)	99,0 (94,6 - 100,0)	65,0 (48,3 - 79,4)
Males (N=101)	98,7 (93,1 - 100,0)	52,2 (30,6 - 73,2)	100,0 (95,4 - 100,0)	30,4 (13,2 - 52,9)	98,7 (93,1 - 100,0)	69,6 (47,1 - 86,8)
Females (N=39)	100,0 (84,6 - 100,0)	47,1 (23,0 - 72,2)	100,0 (84,6 - 100,0)	41,2 (18,4 - 67,1)	100,0 (84,6 - 100,0)	58,8 (32,9 - 81,6)

OSA: Obstructive Sleep Apnea; ODI: Oxygen Desaturation Index; PQ: Philips Questionnaire;

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General Discussion

T.M. Fabius

The aim of this thesis was to develop and validate new diagnostic tools based on pulmonary physiology for acute pulmonary embolism (PE) and obstructive sleep apnea (OSA). The common ground for the two pathologies is their influence on gas exchange. Together they show the two ends of the spectrum of ventilation / perfusion mismatches in the lungs. In PE, perfusion is diminished but ventilation is normal. During an apnea, ventilation is diminished but perfusion is normal. Both types of ventilation / perfusion mismatches will result in hypoxemia as long as the obstruction of the vasculature or airway persists. An obvious but important difference between the two pathologies is the duration of the mismatch. In PE the duration is typically hours to days while in OSA the duration is typically in the order of half a minute. Consequently, aberrant measurements may be expected in PE as long as the obstruction persists, whereas in OSA only during the apneas and hypopneas deviations in gas exchange can be observed. Moreover, in OSA the frequency of aberrant values (as expressed in the apnea-hypopnea index (AHI)) is conventionally deemed more important than their severity.

In the case of PE measurement of (the consequences of) the ventilation / perfusion mismatch during the symptomatic episode might enable easier diagnosis or exclusion of PE. In **chapter 2**, we investigated the use of the transfer factor of the lungs for carbon monoxide (TL,CO) and nitric oxide (TL,NO) in patients presenting to the emergency department with suspected PE. As PE obstructs a part of the pulmonary vasculature, the total surface area in the lungs at which gas exchange can take place is decreased. Previous reports showed that TL,CO indeed can be decreased in PE [1,2]. Only one previous study on the effects of PE on TL,NO was available, a small study in sheep, which showed an increased TL,NO / TL,CO ratio when half of the pulmonary vasculature was blocked [3]. This is in line with the theory that TL,CO is dependent on both a membrane component and the pulmonary capillary blood volume whereas TL,NO is primarily dependent on the membrane component due to the much higher affinity to bind with hemoglobin. Nevertheless, in **chapter 2** we showed that in humans no significant difference was found in the TL,NO / TL,CO ratio between subjects in whom PE was confirmed on computed tomography pulmonary angiography (CTPA) compared to those in whom PE was excluded on CTPA. Furthermore, the data showed that the inspired volume was often less than predicted, probably explained by the thoracic pain of which patients with PE often complain. This makes the measurement of the transfer factor less attractive as diagnostic tool since the accuracy of both TL,CO and TL,NO highly depends on the ability of a subject to inhale to total lung capacity. An important cause for the lack of differences in transfer factor is probably the extensiveness of the obstruction of the pulmonary vasculature. In the earlier mentioned study in sheep, one of the main pulmonary artery was completely blocked by inflating a balloon. Clinically, this would result in hemodynamic instability (which was an exclusion criterion in our study). In reality, obstruction of the vasculature is often less and a clot might not completely obstruct a vessel but merely decrease the flow through it. The use of CTPA as gold standard further amplifies this effect. Even small, subsegmental perfusion defects are visible. Since the introduction of multidetector CTPA, the proportion of confirmed PE that consists of isolated

subsegmental PE nearly doubled from approximately 5% to 9% [4]. There is ongoing debate if all visible defects should be treated [5–7]. Interestingly, the recent CHEST guidelines for antithrombotic therapy recommend clinical surveillance rather than anticoagulation in those patients with isolated subsegmental PE, without accompanying deep venous thrombosis and a low risk of recurrent thromboembolic events [8]. Moreover, a recent post-hoc analysis of the YEARS and Christopher studies showed that if the YEARS algorithm is used a substantially smaller proportion of subsegmental PE is found compared to the Wells-score with a static D-dimer cutoff (absolute difference 6%) whereas this did not result in more thromboembolic events during three months of follow-up [9]. This suggests that the clinical relevance of isolated subsegmental PE is low. Despite this controversy, the definition of PE in our study included all extents, including subsegmental PE. This might have influenced the results.

As noted, measurement of TL,CO and TL,NO is possibly impaired by the frequently present thoracic pain due to the requirement of maximal ex- and inhalation. Moreover, specialized equipment is needed, which is often only present at a pulmonary function department, limiting the applicability in PE to those who are stable enough to transfer. In capnography, the exhaled carbon dioxide (CO₂) levels is monitored continuously and only normal tidal breathing is required. Furthermore, as the needed equipment is portable, measurements can be performed at the bedside. The use of capnography in (the diagnosis of) PE originated many years ago [10]. In the end of the 1990s it became more popular and several studies focused on the use of end-tidal carbon dioxide levels (PETCO₂) combined with arterial CO₂ levels (PaCO₂) [11–13]. The combination of PETCO₂ and PaCO₂ can be used to quantify the amount of dead space ventilation [14,15]. The use of volumetric capnography enables the use of many more parameters [16,17]. Already in 1999, a neural network analysis showed that volumetric capnography can be used to distinguish PE from non PE [18]. The results of this study seem in line with our study presented in **chapter 3**. The final neural network used six parameters that all reflect either impaired gas exchange (i.e. PETCO₂ and the slope of phase III of the volumetric capnogram) and the compensatory increase in ventilation (i.e. minute ventilation, expiratory peak flow and inspiratory time) [18]. Unfortunately the weighing factors for the resulting model were not reported, prohibiting external validation. Verschuren et al. also used volumetric capnography for the exclusion of PE. They recognized the variability of several parameters between individuals. To correct for this, they extrapolated the PETCO₂ using the slope of phase III to a value at a fictive tidal volume of 15% of the predicted total lung capacity. This value was then incorporated in the novel parameter Fdlate, which equals one minus the ratio of the extrapolated PETCO₂ and PaCO₂. They observed that Fdlate was indeed significantly increased in PE, with a resulting area under (AUC) the receiver operator characteristics (ROC) curve of 88% [19]. In a validation study however Fdlate showed substantial smaller diagnostic accuracy with an AUC of 69% [20]. Interestingly, Fdlate performed approximately identical in terms of AUC to the earlier mentioned (and often used) quantification of dead space based on PETCO₂ and PaCO₂ [20]. The downside of all these parameters is that arterial blood gas analysis is needed

to determine their value. Apart from the extra burden for the patient one could also debate how the measurements should be synchronized as small changes in breath pattern may have important influence on PETCO₂. The novel parameter CapNoPE we developed in **chapter 3** only used volumetric capnography parameters. All parameters were extracted automatically using a custom script diminishing the relevance of inter- and intra-observer variability. In the pilot study a cutoff value for CapNoPE of 1.90 Pa.min provided a sensitivity 100% with wide confidence intervals due to the small sample size. In the validation study presented in **chapter 4** the sensitivity associated with this cutoff value was substantially lower (65%). We could not identify obvious reasons for this difference other than the small sample size of the pilot study. The AUC of the ROC curve found in the validation study was well within the confidence intervals of the AUC found in the pilot study. Unfortunately, no other clinically relevant cutoff for CapNoPE could be identified (i.e. all cutoffs with acceptable sensitivity had poor specificity). This underlines the need for external validation of cutoff values. Despite the lower sensitivity of the earlier found cutoff, the overall diagnostic accuracy (expressed as the AUC of the ROC curve) of CapNoPE was (again) more or less equal to the accuracy of earlier reported parameters. Moreover the trajectories of the ROC curves were also almost identical. This suggests that the diagnostic accuracy of capnography (with or without arterial blood gas analysis) has a ceiling. Apparently, not all PE will lead to those changes measurable with capnography with or without arterial blood gas analysis. Again, this might be partially explained by inclusion of subjects in whom only a small proportion of the pulmonary vasculature is blocked as in subsegmental PE. Whether anticoagulation is indicated in patients with subsegmental PE (despite the minimal effects of gas exchange) is probably dependent on the risk of future thromboembolic events. It seems unlikely that capnography will be useful to determine this risk. Nevertheless, there might be other physiologic measures with better diagnostic accuracy. In other settings (e.g. cardiopulmonary exercise testing), the alveolar-to-arterial gradient for oxygen (A-a gradient) is often used. In the case of a ventilation / perfusion mismatch an increased A-a gradient will be present. The utility of the A-a gradient in PE has been studied extensively, mostly in the mid of the 1990s. Main conclusion of these studies was that the A-a gradient is indeed aberrant in most PE cases but a significant proportion of patients with PE had normal values [21–23]. The combination of oxygen related parameters and PETCO₂ has also been studied. The ratio of PETCO₂ and end-tidal oxygen levels (PETO₂) showed promising results, but again could only safely exclude segmental and central PE [24,25].

The measurement of exhaled breath profiles, in which patterns rather than exact substances are determined, might further increase the diagnostic accuracy. The rationale behind the use of exhaled breath profiles is that many (pathologic) processes produce volatile compounds that are released into the blood and will therefore pass the lungs [26]. Though the use of exhaled breath profiles has been studied extensively in many pathologies such as asthma [27,28] and cancer [29], data on breath profiles in PE are scarce. A pilot study showed that in patients without comorbidities breath profiles were able to distinguish PE from non-PE patients (AUC

90%) [30]. We also performed a pilot study in patients suspected of PE using a more recent portable electronic nose, which relies on sophisticated big data analysis [31]. Briefly, first data is needed to develop a neural network. In each new iteration of the network, a small sample of the data is not used for the model derivation allowing validation. In the pilot study we measured exhaled breath profiles in 61 subjects with suspected PE [32]. The AUC (73%) of the resulting neural network was lower than the AUC reported in the previous pilot study but this was for all subjects (with or without comorbidities) [32]. Furthermore, we were able to identify a cutoff in the neural network output with a sensitivity of 90% and specificity of 54% [32]. Inclusion of more data to train the neural network is likely to result in higher diagnostic accuracy (or at least in a higher certainty of the found results). Therefore, a larger study using the newest version of this electronic nose is now ongoing (Netherlands Trial Register ID NTR6352, <https://www.trialregister.nl/trial/6352>).

The use of exhaled breath profiles may also be usable in OSA. The aim of previous research with exhaled breath profiles in OSA has been roughly twofold: 1) gain more insight in the pathophysiology of OSA and 2) distinguish OSA from non-OSA subjects. For the first goal the identification of specific substances rather than breath patterns seems usable. Olopade et al. showed that pentane nitric oxide levels (both markers of inflammation) are substantially increased in OSA [33]. Aoki et al. found that levels of acetone (amongst others linked to diabetes and infections [34]) and isoprene (a byproduct of cholesterol synthesis [35]) are increased in OSA and decrease after CPAP treatment [36]. Fluctuations in acetone and isoprene in exhaled breath can also occur due to other reasons than OSA. A study on continuous monitoring of acetone and isoprene during sleep in healthy subjects showed that acetone levels increase overnight and isoprene levels show distinct peaks, which were correlated to leg movements [37]. Another study studied exhaled breath components in known OSA subjects one week after CPAP withdrawal. They found increased levels of 16 metabolites, of which one (benzothiazole) has been linked previously to pulmonary vascular resistance [38,39].

The main advantage of the identification of specific substances rather than breath profiles is that it allows for more specific analysis of the (patho-)physiologic processes. The downside however is that often highly specialized equipment (such as gas chromatography-mass spectrometry) is needed which is often not readily available in clinical practice. The measurement of breath profiles however can be made using (portable) equipment enabling clinical use.

For the discrimination between OSA and non-OSA subjects studies have shown somewhat conflicting results. One early study reported that the breath profiles could separate OSA and healthy subjects with high accuracy (AUC of 85%) [40]. Another study found similar results (with 77% correctly classified subjects) but only if measurements were performed in the morning directly after the sleep test [41]. It is important to note that most studies included known OSA patients and (asymptomatic) healthy controls.

In **chapter 7** we investigated the use of exhaled breath profiles for the screening for OSA. Notably, we included only subjects who were clinically suspected for OSA and would therefore

undergo sleep testing. The results showed that the exhaled breath profiles could not be used to reliably distinguish subjects with an AHI ≥ 15 from those with an AHI < 15 . The poor discriminatory value was mainly caused by an overlap in subjects with an AHI 5-15 and subjects with an AHI 15-30. Nevertheless, the breath profile was significantly correlated with the AHI as a continuous parameter. This seems to underline the arbitrariness of exact cutoffs of the AHI for the definition of OSA. There is ongoing debate on the value of the AHI as sole parameter for the classification of OSA [42,43]. Several studies have suggested alternative parameters, of which most are hypoxia related [44–46]. Interestingly, the recent Dutch guidelines on OSA now discourage the use of the AHI as sole parameter for the severity classification of OSA [47]. An important factor in the discussion on the usability of the AHI is its definition. That is, the definition of the hypopnea varies considerably. The first obvious difference is the use of polygraphy (PG) vs polysomnography (PSG) of which in the latter hypopneas with associated arousal but without desaturation can be scored whereas in PG only hypopneas with desaturations can be scored. To prevent confusion, the American academy for sleep medicine (AASM) encourages the use of the term respiratory event index (REI) rather than AHI if sleep was not measured objectively [48]. Data from the European Sleep Apnea Cohort (ESADA) showed that on average, patients who underwent PG were likely to have a 30% lower AHI compared to patients who underwent PSG [49]. Apart from the diagnostic method used, several definitions for an hypopnea have been applied. In 1999, the AASM produced a consensus statement on the scoring of respiratory events (also known as the ‘Chicago criteria’). It states that a hypopnea should be scored when there is an obvious (but $< 50\%$) decrease in airflow which is accompanied by an arousal or a desaturation of at least 3% [50]. In 2001 (and this definition was later used in the first AASM manual for scoring of sleep and associated events in 2007), a new AASM position paper recommended a reduction in airflow of at least 30% accompanied by a desaturation of at least 4% [51]. The 2007 manual also provided an alternative hypopnea definition of a reduction in airflow of at least 50% accompanied by a desaturation of at least 3%. In 2012, an update of the AASM guidelines advised the use of one uniform hypopnea definition with at least 30% airflow reduction accompanied by either an arousal or a desaturation of at least 3% [52]. Several studies have investigated the influence of the different definitions. Unsurprisingly, the 2007 definitions result in a significant lower AHI compared to the 1999 and 2012 definitions [53,54]. Consequently, the definition used also influences the prevalence and severity (and thus treatment options) of OSA [55]. The association with comorbidities and mortality is also different. One study reported that in elderly, an AHI ≥ 30 was associated with increased risk of mortality from cardiovascular events if hypopneas were defined as a $\geq 30\%$ reduction in airflow accompanied by a $\geq 4\%$ (2007 definition) or $\geq 3\%$ desaturation (2012 definition for sleep tests without EEG) but not if hypopneas were scored with either a $\geq 3\%$ desaturation or an arousal (2012 definition) [56]. Another study reported that those who have OSA according to the 2012 criteria but not according to the 2007 criteria do not have an increased risk of arrhythmia whereas all subjects identified with the 2007 criteria did [57]. Despite the lack of increased

risk in those with mild OSA, severe OSA subjects according to the 2012 criteria ($AHI \geq 30$) also had an increased risk of arrhythmia [57]. Summarizing, adding arousals to desaturations in the definition of OSA seems to dilute the relationship with cardiovascular risk. This seems to suggest that the hypoxia related parameters (reflected by the desaturations) rather than the frequency of events (expressed as the AHI or arousals) are more important in the association with mortality and cardiovascular morbidity. Indeed, a recent pooled analysis of the Sleep Heart Health study and Osteoporotic Fractures in Men study reported that hypoxic burden was a better predictor of cardiovascular related mortality compared to the AHI [58]. Somewhat contrarily, another recent analysis of the Sleep Heart Health study reported that short event duration also predicts mortality [59]. We hypothesized that if hypoxemia related parameters are better predictors than the AHI for cardiovascular comorbidities and mortality, hypoxemia might also be more reflected in exhaled breath profiles. Nevertheless, the results presented in **chapter 7** show this hypothesis had to be rejected. Moreover, when trying to predict the exhaled breath profile in a multivariate model with both AHI and hypoxia, only the AHI remained as independent significant predictor. This suggests that the frequency rather than the severity of events influences systemic processes that in turn influence the exhaled breath profile. It should be remarked though that the AHI was determined using PG. Consequently, hypopneas could only be scored if a desaturation was present. Therefore, most events were associated with some degree of hypoxemia as at least a 3% desaturation had to be present for hypopneas. The AHI used in our study may thus also be a reflection of hypoxemia related processes. This could have caused a decrease in the added value of hypoxic burden over the AHI in the prediction of exhaled breath profiles. Future research might investigate if there is a difference in association with exhaled breath profiles between events accompanied by a desaturation and events accompanied by an arousal.

The results of **chapter 7** show that exhaled breath profiles were unable to distinguish OSA from non-OSA based on a cut-off of $AHI \geq 15$. This cutoff is often used in biomarker studies in OSA as it is assumed that mild OSA has only limited effects on systemic processes. Furthermore, in the Netherlands a diagnosis of mild OSA requires the presence of associated symptoms whereas moderate or severe OSA only requires an $AHI \geq 15$. Nevertheless, mild OSA is clinically relevant. Hence we used an $AHI \geq 5$ as cutoff for OSA in **chapter 5**. In this chapter we showed that an oxygen desaturation index (i.e. the number of $\geq 3\%$ desaturations per hour) < 5 excludes the presence of OSA (if defined as an $AHI \geq 5$) with high certainty when measured simultaneously during PG. Furthermore, the association between the AHI and ODI was high ($R^2=0.99$). One could argue that oximetry alone would therefore be a suitable screening tool. This would be a further simplification of the PSG. PG was the first step (eliminating EEG, EMG and EOG measurements) and though there are significant differences in their results (i.e. PG will result in a lower AHI), PG has been extensively shown to be effective in the diagnosis OSA in most patients if the correct population is selected (i.e. those with a high clinical suspicion of OSA) [60,61]. We believe that adding a questionnaire substantially adds to the value of the screening

tool for several reasons. First, if used in a two-step strategy (i.e. oximetry is only performed in those with a normal questionnaire result) not all subjects will have to undergo oximetry reducing the costs. Second, it enables analysis of the combination of subjective symptoms with objective test results.

In **chapter 6**, we included a primary care population with a clinical suspicion of OSA. We aimed to miss no clinically relevant OSA and therefore validated the strategy to refer to a sleep center when either the oximetry or the Philips questionnaire showed aberrant results. This strategy resulted in optimal sensitivity with a potential reduction in referrals of 10%. This will prevent unnecessary healthcare costs and reduce the workload of the sleep centers (which is likely to increase given the high and increasing prevalence of OSA[62]). If only oximetry would have been used, sensitivity was slightly smaller (99%) but the potential reduction in referrals increased to 15%. It should be noted that these two strategies were pre-specified and are therefore now validated and may be used in clinical practice. In an additional explorative analysis new optimal thresholds for both the questionnaire and oximetry were identified. This strategy really combined symptoms and objective test results. Basically, this strategy would only refer if either the oximetry or the questionnaire results are clearly aberrant or if the oximetry is mildly increased but the questionnaire indicates a clear risk of OSA. Applying this strategy would have not altered sensitivity (still 99%) but further increased the potential reduction in referrals to 19%. As this strategy resulted from an explorative analysis it should be validated in future studies. The high resemblance with oximetry and PG makes it tempting to use the oximetry for diagnosis rather than screening. This has been tested in a large trial on the use of PSG versus PG versus oximetry on clinical outcomes [60]. The results showed no differences in clinical outcomes between PSG and PG but oximetry resulted in lower CPAP compliance, and less improvement in symptoms compared to PSG [60]. Moreover, physicians had less diagnostic confidence in oximetry compared to PSG and PG (which might have influenced the compliance of the patients to CPAP therapy) [60]. This suggests that, if the right population can be selected (i.e. severe OSA with clear symptoms) oximetry might be usable for the diagnosis of OSA. Given the results of earlier studies that an $AHI \geq 30$ is only associated with cardiovascular related mortality if arousals are not used for the hypopnea definition combined with the high resemblance of ODI and AHI in PG, an $ODI \geq 30$ is probably also indicative for an increased risk of cardiovascular events. Therefore, only in case of an $ODI \geq 30$ combined with a high risk of OSA according to a questionnaire (based on symptoms and clinical characteristics) the results could be usable for the diagnosis of OSA. In any other case further workup should be performed. It would be interesting to test this hypothetical strategy in future research. Despite the lack of validation (to the best of our knowledge) such a strategy has been implemented in New Zealand since 2007, which significantly reduced waiting time for treatment and the need for extensive sleep tests [63].

Conclusions

The main conclusions of this thesis are:

- The TL,NO / TL,CO ratio cannot be used for the exclusion of PE.
- The volumetric capnography derived parameter CapNoPE is significantly decreased in PE.
- The diagnostic accuracy of CapNoPE is comparable to other gas-exchange related parameters but too low to use in clinical practice for the diagnosis or exclusion of PE.
- An ODI < 5 excludes OSA (AHI $\geq$ 5) with high certainty when measured simultaneously during PG
- The use of oximetry and the Philips questionnaire enables exclusion of OSA in primary care
- Exhaled breath profiles cannot reliably diagnose OSA (defined as AHI $\geq$ 15) in subjects who are clinically suspected of OSA.
- Exhaled breath profiles are associated with the AHI as continuous parameter.
- The AHI is a better predictor of exhaled breath profiles than hypoxemia related parameters.

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Summary

SUMMARY

The most important function of the lungs is gas exchange. They are able to do so due to a sophisticated balance between ventilation (allowing inhalation of fresh oxygen rich air and exhalation of carbon dioxide rich air) and perfusion (allowing transportation of oxygen to the organs and vice versa transportation of carbon dioxide). A mismatch between the ventilation and perfusion of the lungs may cause desaturation and hypercapnia. In acute pulmonary embolism (PE) the perfusion of the lungs is affected due to an obstruction of (a part of) the pulmonary vasculature. In obstructive sleep apnea (OSA), ventilation is impaired due to a (partial) obstruction of the upper airway. Both PE and OSA share one other characteristic: in both cases novel diagnostic approaches are desirable.

As PE is a potentially lethal disease, it needs to be ruled out with a high certainty when suspected to be able to discharge the patient safely (or continue workup for some other diagnosis). To do so, a computed tomography pulmonary angiography (CTPA) needs to be performed. However, symptoms of PE (mainly dyspnea and thoracic pain) are non-specific. Consequently, the proportion of CTPA scans that confirm PE is low (approximately 25-30%). This leads to a need for novel tools to exclude PE.

OSA is often accompanied by excessive daytime sleepiness and is associated with an increased risk of cardiovascular related adverse events. The prevalence of OSA is increasing rapidly (mainly due to increasing obesity rates). However, the diagnosis of OSA requires expensive and laborious testing, which leads to a rapid increase in OSA-related health care costs and an increased load on sleep centers. Nevertheless, a substantial proportion of patients referred due to suspected OSA do not suffer from it (up to 30%). Hence, there is a need for cheap, fast, but valid tools that enable exclusion of OSA. The research presented in this thesis focused on the development of novel diagnostic tools using the consequences of ventilation / perfusion mismatches in PE (**chapters 2-4**) and OSA (**chapters 5-7**).

In **chapter 2** we measured the transfer factors of the lungs for nitric oxide (TLNO) and carbon monoxide (TLCO) in subjects with suspected PE and compared the ratio of these transfer factors to the CTPA results. The transfer factor of the lungs for a certain gas depends on an alveolar-capillary membrane component (e.g. a thickened membrane will result in less diffusion) and a hemodynamic component (e.g. a decrease in pulmonary blood volume will result in less diffusion). Due to a high affinity to bind with hemoglobin, TLNO is virtually independent from the hemodynamic component whereas TLCO is approximately equally dependent from the membrane and hemodynamic component. The ratio of TLNO and TLCO should therefore provide some indication of pulmonary hemodynamics. The results of our study presented in **chapter 2** showed no differences in TLNO / TLCO ratio between subjects in whom PE was confirmed and those in whom PE was excluded on CTPA. Moreover, on average, TLNO and TLCO were decreased in subjects with and without PE. This decrease was likely (at least partially) caused by a decreased alveolar volume. This decreased alveolar volume might be the result of

suboptimal maximal inhalation caused by thoracic pain, which most subjects with suspected PE experience. These data indicated that the TLNO / TLCO ratio cannot be used to exclude PE.

In **chapter 3** we investigated the use of volumetric capnography to exclude PE in the emergency department. Under normal physiological circumstances, the amount of carbon dioxide in exhaled air at the end of exhalation (PETCO₂) is approximately equal to the amount of carbon dioxide in the arterial blood (PaCO₂). PE will result in increased dead space ventilation (i.e. a part of the lungs is ventilated but not perfused). In the parts without perfusion, no carbon dioxide can diffuse into the alveolar air resulting in lowered carbon dioxide levels in exhaled air. Previous studies on capnography in PE mainly focused on the use of (a combination of) PETCO₂ and PaCO₂. Volumetric capnography (i.e. measurement of exhaled carbon dioxide levels as a function of the exhaled volume) enables the measurement of many more parameters than solely PETCO₂. In **chapter 3** we designed a novel parameter that combines several volumetric capnography characteristics that may be affected by PE. This novel parameter was defined as the amount of carbon dioxide exhaled per breath (VCO₂) multiplied with the slope of the alveolar phase of the volumetric capnogram (slopeIII), divided by the respiratory rate (RR) (i.e. $VCO_2 \times slopeIII/RR$). Both VCO₂ and slopeIII are likely to decrease in PE whereas RR is likely to increase (to compensate for the decrease in VCO₂). Thus, we hypothesized that our novel parameter is decreased in subjects with PE compared to those without. In the study presented in **chapter 3** we measured volumetric capnograms in 30 subjects with suspected PE, automatically determined the novel parameter, and compared it with the CTPA scans. As hypothesized, the novel parameter was decreased in subjects with confirmed PE compared to subjects without. The area under the receiver operating characteristic (ROC) curve (AUC) of the novel parameter to exclude PE was 0.79 (95% confidence interval (CI) 0.64-0.95). A value of the novel parameter ≥ 1.90 Pa.min seemed to exclude PE with a high certainty (sensitivity 100% (95%CI 77%-100%, negative predictive value 100% (95%CI 68%-100%) and specificity 47% (95%CI 26%-69%)).

Given the small number of included subjects (and thus wide confidence intervals), validation of the novel parameter (CapNoPE) was needed. In **chapter 4** we performed an external validation of CapNoPE in a dataset of an earlier study on volumetric capnography in PE. This study measured volumetric capnograms in 205 subjects with suspected PE at the emergency department. Diagnosis of PE was obtained using CTPA or proven deep venous thrombosis combined with thoracic symptoms. The results presented in **chapter 4** showed that CapNoPE was again significantly decreased in subjects with PE compared to those without. The AUC of the ROC curve for CapNoPE to exclude PE was 0.71 (95%CI 0.64-0.79) and was essentially equal to the AUC of more conventional capnography parameters (with or without the need of PaCO₂). Nevertheless, the diagnostic accuracy of the cutoff of ≥ 1.90 Pa.min to exclude PE was too low to use in clinical practice (sensitivity 64.7% (95%CI 52.2%-75.9%), negative predictive value 77.4% (95%CI 68.2%-84.9%) and specificity 59.9% (95%CI 51.1%-68.1%)).

In **chapters 5-7** we investigated diagnostic tools for OSA. The diagnosis of OSA relies on the determination of the frequency of apneas and hypopneas during sleep, expressed as the apnea

hypopnea index (AHI). According to current guidelines, a hypopnea needs to be accompanied by either an arousal or a substantial desaturation ($\geq 3\%$ or $\geq 4\%$ depending on the definition used). A full polysomnography (PSG), in which amongst others sleep, flow, respiratory effort, desaturations and arousals can be measured, is considered the gold standard diagnostic method for OSA. However, performing full PSGs is expensive and time consuming. In an uncomplicated case a polygraphy (PG) (in which flow, respiratory effort and desaturations can be measured) is sufficient. Although a PG is substantially simplified compared to PSG it is still associated with substantial costs and warrants manual scoring. We hypothesized that the use of oximetry (possibly combined with a questionnaire) might be a further simplification that can be used to exclude OSA. To support this hypothesis we first investigated the correlation between the AHI and oxygen desaturation index (ODI, number of $\geq 3\%$ desaturations per hour) in PGs (**chapter 5**). Specifically, we sought to identify and validate a cutoff for the ODI that could exclude OSA (defined as an AHI ≥ 5). To do so we divided 3413 PGs into a training set and validation set. In the training set an ODI < 5 seemed to best predict an AHI < 5 . In the validation set this resulted in a sensitivity of 97.7% (95%CI 96.5% - 98.6%), a negative predictive value of 91.4% (95%CI 87.1% - 94.6%) and a specificity of 97.0% (95%CI 93.8% - 98.8%).

Given the high diagnostic accuracy of oximetry shown in **chapter 5**, we performed a prospective study on the use of automatically analyzed oximetry combined with the Philips questionnaire in 140 patients in whom their general practitioner suspected OSA (**chapter 6**). The Philips questionnaire consists of a combination of several OSA screening questionnaires and was developed using a middle-aged company-worker population. In the study presented in **chapter 6** we investigated the diagnostic accuracy of two predefined strategies for the referral to a sleep center for OSA workup: 1) refer to a sleep center for OSA workup if the ODI is ≥ 5 and 2) refer to a sleep center for OSA workup if the ODI is ≥ 5 and/or the Philips questionnaire score is $\geq 55\%$ (indicative of a high risk of OSA). These strategies were compared to the results of sleep center diagnostic workup. The sleep center diagnostic workup did not result in a diagnosis of OSA in 40 of the 140 included subjects (29%). The strategy to refer to a sleep center using only ODI ≥ 5 excluded OSA in 15% of the included subjects and resulted in a sensitivity of 99.0% (95%CI 94.5% - 100.0%), a negative predictive value of 95.2% (95%CI 76.2% - 99.9%), a specificity of 50.0% (95%CI 33.8% - 66.2%) and a positive predictive value of 83.2% (95%CI 75.2% - 89.4%). The two-step strategy to refer to a sleep center when the ODI is ≥ 5 and/or the Philips questionnaire score is $\geq 55\%$, excluded OSA in 10% of the included subjects and resulted in a sensitivity of 100.0% (95%CI 96.3% - 100.0%), a negative predictive value of 100.0% (95%CI 76.8% - 100.0%), a specificity of 35.0% (95%CI 20.6% - 51.7%) and a positive predictive value of 79.4% (95%CI 71.2% - 86.1%). Exploratively, an optimal strategy was sought to further reduce the number of referrals for OSA workup. An optimal diagnostic accuracy could be achieved if at least one of three conditions applied: 1) the Philips questionnaire score was $\geq 92\%$, or 2) the rounded ODI was ≥ 10 or 3) the rounded ODI was 5-10 and the Philips questionnaire score was $\geq 46.5\%$. This strategy would have excluded OSA in 19% of the included subjects and would result

in a sensitivity of 99.0% (95%CI 94.6% - 100.0%), a negative predictive value of 96.3% (95%CI 81.0% - 99.9%), a specificity of 65.0% (95%CI 48.3% - 79.4%) and a positive predictive value of 87.6% (95%CI 80.1% - 93.1%). Concluding, the use of oximetry with or without a questionnaire enabled reliable exclusion of OSA. The advantage of the predefined two-step strategy is that oximetry would only be needed in those with a low or intermediate risk of OSA (i.e. a Philips questionnaire score < 55%). On the other hand, the advantage of the predefined strategy using oximetry alone is that a higher proportion of “unnecessary” referrals can be avoided. The explorative analysis resulted in the identification of an even higher proportion of subjects without OSA but needs to be validated before it can be used in clinical practice.

In **chapter 7** we investigated whether exhaled breath analysis using an electronic nose could reliably distinguish OSA (defined as an AHI ≥ 15) from non-OSA subjects using 83 sleep center patients suspected of OSA and scheduled for a PG. We hypothesized that the many systemic (pathologic) processes caused by OSA might be reflected in exhaled breath. The results presented in **chapter 7** showed that one principal component (PC4) from the exhaled breath data was significantly different in subjects in whom OSA was confirmed compared to those without OSA. However, diagnostic accuracy to distinguish OSA from non-OSA subjects using PC4 was fair at most (cross-validation value 68.7%). Nevertheless, PC4 could predict the AHI as continuous parameter ($R^2=0.38$). The addition of known OSA-related factors in a multivariate model improved the accuracy of the prediction of the AHI ($R^2=0.53$). We were also interested which OSA-related parameter could best predict the exhaled breath profiles. Though hypoxic burden did predict PC4 in univariate analysis ($R^2=0.11$), in a multivariate model only the AHI added significantly to the prediction of PC4 ($R^2=0.43$). This suggests that the frequency of breathing events rather than their duration and severity (expressed as hypoxic burden) influence processes that are reflected in exhaled breath profiles. We concluded that the exhaled breath profiles could not be used to reliably exclude OSA (when OSA is defined as an AHI ≥ 15).

In **chapter 8** we discuss the results presented in **chapters 2-7** and put them in context. An important topic is the definitions used for PE and OSA and the implications they may have on the data presented in this thesis.

Samenvatting

SAMENVATTING

De belangrijkste functie van de longen is gasuitwisseling. De longen kunnen dit bereiken door een geraffineerde balans tussen ventilatie (welke het mogelijk maakt om verse, zuurstofrijke lucht te inhaleren en koolstofdioxide-rijke lucht weer uit te ademen) en perfusie (welke transport van zuurstof naar de organen en vice versa transport van koolstofdioxide mogelijk maakt). Een onbalans tussen ventilatie en perfusie van de longen kan desaturatie en hypercapnie veroorzaken. In het geval van acute longembolie (LE) is de perfusie aangedaan door een obstructie van (een deel van) de pulmonale vaten. In het geval van obstructief slaapapneu (OSA) is de ventilatie aangedaan door een (gedeeltelijke) obstructie van de bovenste luchtweg. Zowel LE als OSA delen nog een belangrijke eigenschap: in beide gevallen is een nieuwe diagnostische strategie gewenst.

Omdat LE een potentieel dodelijke ziekte is, moet het met hoge zekerheid uitgesloten zijn (indien aan LE gedacht wordt) voordat iemand ontslagen wordt uit het ziekenhuis (of diagnostiek naar overige pathologie ingezet wordt). Om dit te kunnen doen moet een computed tomography pulmonary angiography (CTPA)-scan verricht worden. De symptomen die zouden kunnen passen bij LE (voornamelijk kortademigheid en thoracale pijn) zijn echter aspecifiek. Daarom is het deel van de CTPA-scans waarop ook daadwerkelijk LE wordt aangetoond laag (ongeveer 25-30%). Dit leidt er toe dat er nieuwe strategieën nodig zijn om LE uit te kunnen sluiten om kosten en onnodige belasting van patiënten te voorkomen.

OSA gaat vaak gepaard met overmatige slaperigheid overdag en is geassocieerd met een verhoogd risico op cardiovasculaire problemen. De prevalentie van OSA stijgt snel (voornamelijk door de stijging in de prevalentie van obesitas). De diagnose van OSA vereist echter uitgebreide en dure testen, wat er toe leidt dat er een snelle stijging is in OSA-gerelateerde gezondheidszorgkosten en belasting van de slaapcentra. Desalniettemin lijdt een belangrijk deel van de mensen die verwezen worden vanwege verdenking op OSA niet aan deze aandoening (tot 30%). Daarom is er een behoefte aan goedkope, snelle, en valide mogelijkheden om OSA uit te sluiten. Het onderzoek dat in dit proefschrift gepresenteerd wordt, richt zich dan ook op de ontwikkeling van nieuwe diagnostische strategieën gebruikmakend van de ventilatie / perfusie onbalans bij LE (**hoofdstuk 2-4**) en OSA (**hoofdstuk 5-7**).

In **hoofdstuk 2** hebben we de diffusiecapaciteit van de longen voor stikstofmonoxide (TLNO) en koolstofmonoxide (TLCO) gemeten bij personen die verdacht werden van een LE en hebben we de ratio van deze diffusiecapaciteiten vergeleken met de resultaten van de CTPA-scans. De diffusiecapaciteit van de longen voor een bepaald gas is afhankelijk van een alveolair-capillaire membraan component (bijvoorbeeld een verdikt membraan zal leiden tot verminderde diffusie) en een hemodynamische component (bijvoorbeeld een afname in pulmonaal bloedvolume zal leiden tot verminderde diffusie). Door de hoge bindingsaffiniteit met hemoglobine is TLNO theoretisch vrijwel onafhankelijk van de hemodynamische component, terwijl TLCO ongeveer evenveel afhankelijk is van de membraan en hemodynamische component. De ratio van TLNO

en TLCO zou daarom een indicatie moeten geven van de pulmonale hemodynamiek. De resultaten van onze studie die we presenteren in **hoofdstuk 2** lieten geen verschillen zien in de TLNO / TLCO ratio tussen personen waarbij LE was aangetoond en personen waarbij LE was uitgesloten middels een CTPA-scan. Daarbij waren zowel TLNO als TLCO, gemiddeld genomen, verlaagd in zowel personen met als zonder LE. Deze afname werd waarschijnlijk (tenminste deels) veroorzaakt door een afname in alveolair volume. Dit afgenomen alveolair volume kan op zijn beurt weer veroorzaakt zijn door de thoracale pijn (waar de meeste LE patiënten last van hebben,) welke kan leiden tot suboptimale inademing. Onze data leken er op te wijzen dat de TLNO/TLCO ratio niet gebruikt kan worden om LE uit te sluiten.

In **hoofdstuk 3** hebben we het gebruik van volumetrische capnografie om LE uit te sluiten op de spoedeisende hulp onderzocht. Onder normale fysiologische omstandigheden is de hoeveelheid koolstofdioxide in de uitgeademde lucht aan het eind van de uitademing ($PETCO_2$) ongeveer gelijk aan de hoeveelheid koolstofdioxide in het arteriële bloed ($PaCO_2$). LE geeft een verhoogde dode ruimte ventilatie (een deel van de longen wordt wel geventileerd maar niet doorbloed). In de delen zonder perfusie kan geen koolstofdioxide diffunderen naar de alveolaire lucht wat leidt tot een verlaagde hoeveelheid koolstofdioxide in de uitgeademde lucht. Vorige onderzoeken naar capnografie bij LE waren vooral gericht op het gebruik van (een combinatie van) $PETCO_2$ en $PaCO_2$. Volumetrische capnografie (het meten van de hoeveelheid koolstofdioxide in de uitademing als een functie van het uitgeademde volume) maakt het mogelijk om veel meer parameters te bepalen dan alleen $PETCO_2$. In **hoofdstuk 3** hebben wij een nieuwe parameter ontwikkeld die verschillende volumetrische capnografie eigenschappen combineert. Deze nieuwe parameter was gedefinieerd als de per ademteug uitgeademde hoeveelheid koolstofdioxide (VCO_2) vermenigvuldigd met de helling van de alveolaire fase van het volumetrische capnogram ($slope_{III}$), gedeeld door de ademprequentie (RR) (dus $VCO_2 \times slope_{III}/RR$). Zowel VCO_2 als $slope_{III}$ zullen waarschijnlijk verlaagd zijn bij LE terwijl de ademprequentie waarschijnlijk toeneemt (om te compenseren voor de afname in VCO_2). Onze hypothese was dan ook dat onze nieuwe parameter verlaagd is bij personen met LE vergeleken met personen zonder LE. In het onderzoek dat we presenteren in **hoofdstuk 3** hebben we volumetrische capnogrammen gemeten bij 30 personen die verdacht werden van LE, hebben we automatisch onze nieuwe parameter bepaald, en hebben we deze vergeleken met de CTPA-scans. In lijn met onze hypothese was de nieuwe parameter verlaagd bij personen waarbij LE bevestigd was vergeleken met personen waarbij LE uitgesloten was. De oppervlakte onder de receiver operating characteristic (ROC) curve van onze nieuwe parameter om LE uit te sluiten was 0.79 (95% betrouwbaarheidsinterval (BI) 0.64-0.95). Een waarde van de nieuwe parameter ≥ 1.90 Pa.min leek LE met hoge zekerheid uit te sluiten (sensitiviteit 100% (95%BI 77%-100%), negatief voorspellende waarde 100% (95%BI 68%-100%) en specificiteit 47% (95%BI 26%-69%).

Door het kleine aantal geïncludeerde personen (en daarmee brede betrouwbaarheidsintervallen) was het nodig de nieuwe parameter (CapNoPE) te valideren. In **hoofdstuk 4** voerden we een externe validatie van CapNoPE uit in een dataset van een eerdere studie naar volume-

trische capnografie bij LE. In deze studie werd van 205 personen volumetrische capnogrammen verkregen. De diagnose LE werd gesteld met een CTPA-scan of met een bewezen diepe veneuze trombose gecombineerd met thoracale klachten. De resultaten in **hoofdstuk 4** lieten zien dat CapNoPE opnieuw significant verlaagd was bij personen met LE vergeleken met personen zonder LE. De oppervlakte onder de ROC curve van CapNoPE om LE uit te sluiten was 0.71 (95%BI 0.64-0.79) en was in essentie gelijk aan de oppervlakte onder de ROC curves van meer conventionele capnografie parameters (zowel degenen waarin PaCO₂ gebruikt wordt als degenen zonder de noodzaak van PaCO₂). Desalniettemin was de diagnostische precisie van de afkapwaarde van ≥ 1.90 Pa.min om LE uit te sluiten te laag om te gebruiken in de klinische praktijk (sensitiviteit 64.7% (95%BI 52.2%-75.9%), negatief voorspellende waarde 77.4% (95%BI 68.2%-84.9%) en specificiteit 59.9% (95%BI 51.1%-68.1%)).

In **hoofdstukken 5-7** hebben we diagnostische strategieën voor OSA onderzocht. De diagnose OSA is gebaseerd op de frequentie van apneus en hypopneus tijdens slaap, welke uitgedrukt wordt in de apneu-hypopneu-index (AHI). Volgens de huidige richtlijnen moet een hypopneu gepaard gaan met ofwel een wekreactie (arousal) ofwel een substantiële desaturatie ($\geq 3\%$ of $\geq 4\%$ afhankelijk van de gebruikte definitie). Een volledige polysomnografie (PSG), waarbij onder andere slaap, ademhaling, respiratoire inzet (effort), desaturaties en arousals gemeten kunnen worden, wordt beschouwd als de gouden standaard diagnostische methode voor OSA. Het verrichten van een volledige PSG is echter duur en tijdsintensief. In ongecompliceerde gevallen is een polygrafie (PG), waarbij ademhaling, respiratoire inzet en desaturaties gemeten kunnen worden, voldoende. Hoewel een PG al een substantiële versimpeling van PSG is, zijn ook hieraan nog substantiële kosten verbonden en bovendien is het nog steeds noodzakelijk iedere registratie handmatig te beoordelen. Wij vermoedden dat het gebruik van oximetrie (mogelijk gecombineerd met een vragenlijst) een verdere versimpeling zou kunnen zijn die gebruikt kan worden om OSA uit te sluiten. Om dit vermoeden te staven, hebben we eerst de correlatie onderzocht tussen de AHI en de oxygen desaturation index (ODI, het aantal $\geq 3\%$ desaturaties per uur) in PGs (**hoofdstuk 5**). Het specifieke doel was een afkapwaarde voor de ODI te identificeren en valideren waarmee OSA (gedefinieerd als een AHI ≥ 5) uitgesloten kon worden. Om dit te bereiken verdeelden we 3413 PGs in een training-set en een validatie-set. In de training-set bleek een ODI < 5 de beste voorspeller van een AHI < 5 . In de validatie-set resulteerde dit in een sensitiviteit van 97.7% (95%BI 96.5% - 98.6%), een negatief voorspellende waarde van 91.4% (95%BI 87.1% - 94.6%) en een specificiteit van 97.0% (95%BI 93.8% - 98.8%).

Vanwege de hoge diagnostische precisie van oximetrie in **hoofdstuk 5**, verrichtten we vervolgens een prospectieve studie naar het gebruik van automatisch beoordeelde oximetrie gecombineerd met de Philips vragenlijst bij 140 personen bij wie hun huisarts een OSA vermoedde (**hoofdstuk 6**). De Philips vragenlijst bestaat uit een combinatie van verschillende OSA-screenings vragenlijsten en is ontwikkeld in een populatie van werknemers van middelbare leeftijd. In het onderzoek dat we presenteren in **hoofdstuk 6** onderzochten we de diagnostische precisie van twee vooraf gedefinieerde strategieën voor het verwijzen naar een slaapcentrum voor verdere

diagnostiek naar OSA: 1) verwijs naar een slaapcentrum voor OSA diagnostiek als de ODI ≥ 5 is en 2) verwijs naar een slaapcentrum voor OSA diagnostiek als de ODI ≥ 5 is en/of de score op de Philips vragenlijst $\geq 55\%$ is (welke wijst op een hoog risico op OSA). Deze strategieën werden vergeleken met de resultaten van de diagnostiek in de slaapcentra. Deze diagnostiek leidde niet tot een diagnose van OSA bij 40 van de 140 geïnccludeerde personen (29%). De strategie om te verwijzen naar een slaapcentrum als de ODI ≥ 5 is, sloot OSA uit in 15% van de geïnccludeerde personen en resulteerde in een sensitiviteit van 99.0% (95%BI 94.5% - 100.0%), een negatief voorspellende waarde van 95.2% (95%BI 76.2% - 99.9%), een specificiteit van 50.0% (95%BI 33.8% - 66.2%) en een positief voorspellende waarde van 83.2% (95%CI 75.2% - 89.4%). De tweetraps-strategie om te verwijzen naar een slaapcentrum als de ODI ≥ 5 is en/of de score op de Philips vragenlijst $\geq 55\%$ is sloot OSA uit in 10% van de geïnccludeerde personen en resulteerde in een sensitiviteit van 100.0% (95%BI 96.3% - 100.0%), een negatief voorspellende waarde van 100.0% (95%BI 76.8% - 100.0%), een specificiteit van 35.0% (95%BI 20.6% - 51.7%) en een positief voorspellende waarde van 79.4% (95%BI 71.2% - 86.1%). Naast validatie van deze twee strategieën zochten we in de data ook naar een optimale strategie die het aantal verwijzingen nog verder zou kunnen doen dalen. Volgens deze exploratieve analyse kon een optimale diagnostische precisie worden bereikt als verwezen zou worden naar een slaapcentrum indien één van de volgende drie criteria aanwezig was: 1) de score op de Philips vragenlijst was $\geq 92\%$, of 2) de afgeronde ODI was ≥ 10 , of 3) de afgeronde ODI was 5-10 én de score op de Philips vragenlijst was $\geq 46.5\%$. Deze strategie zou OSA uitgesloten hebben in 19% van de geïnccludeerde personen en zou geresulteerd hebben in een sensitiviteit van 99.0% (95%BI 94.6% - 100.0%), een negatief voorspellende waarde van 96.3% (95%BI 81.0% - 99.9%), een specificiteit van 65.0% (95%BI 48.3% - 79.4%) en een positief voorspellende waarde van 87.6% (95%BI 80.1% - 93.1%). Concluderend, het gebruik van oximetrie met of zonder een vragenlijst maakte het betrouwbaar uitsluiten van OSA in de huisartsenpraktijk mogelijk. Het voordeel van de tweetraps-strategie is dat oximetrie alleen nodig zou zijn bij degenen met een laag of matig risico op OSA (dat wil zeggen, een score op de Philips vragenlijst $< 55\%$). Aan de andere kant kon het aantal “onnodige” verwijzingen verder verlaagd worden met de strategie waarbij alleen oximetrie nodig is. De exploratieve analyse liet zelfs een strategie zien welke een nog hoger aantal personen zonder OSA zou kunnen identificeren maar deze strategie moet gevalideerd worden voordat zij in de klinische praktijk toegepast kan worden.

In **hoofdstuk 7** onderzochten we of analyse van uitgeademde lucht met een elektronische neus gebruikt kan worden om personen met OSA (gedefinieerd als een AHI ≥ 15) te herkennen in 83 personen die gepland stonden voor een PG vanwege verdenking op een OSA. Wij vermoedden dat de vele systemische (pathologische) processen die veroorzaakt worden door OSA weerspiegeld zouden kunnen worden in de uitgeademde lucht. De in **hoofdstuk 7** gepresenteerde resultaten lieten zien dat één principale component (PC4) van de uitgeademde lucht data significant anders was in personen waarin OSA werd bevestigd vergeleken met personen waarin OSA werd uitgesloten. De precisie om personen met OSA te onderscheiden van perso-

nen zonder OSA was echter op zijn hoogst redelijk (cross-validation value 68.7%). PC4 kon wel gebruikt worden om de AHI als continue parameter te voorspellen ($R^2=0.38$). Door bekende OSA-gerelateerde factoren toe te voegen in een multivariaat model verbeterde de nauwkeurigheid van de voorspelling van de AHI substantieel ($R^2=0.53$). We waren ook geïnteresseerd in welke OSA-gerelateerde parameter het beste de uitademingsprofielen kon voorspelen. Hoewel hypoxie last ("hypoxic burden") wel PC4 kon voorspellen bij univariate analyse ($R^2=0.11$), liet een multivariaat model zien dat alleen de AHI significant toegevoegde waarde had bij de voorspelling van PC4 ($R^2=0.43$). Dit suggereert dat de frequentie en niet de ernst van apneus en hypopneus tijdens slaap een grotere invloed heeft op processen die weerspiegeld worden in uitademingsprofielen. We concludeerden dat uitademingsprofielen niet gebruikt kunnen worden om OSA betrouwbaar uit te sluiten (als OSA gedefinieerd wordt als een $AHI \geq 15$).

In **hoofdstuk 8** bespreken we de resultaten die we in **hoofdstuk 2-7** presenteren en zetten we deze in perspectief. Een belangrijk onderwerp is de definities die gebruikt worden voor LE en OSA en de implicaties die ze zouden kunnen hebben op de resultaten.

Dankwoord

DANKWOORD

Dit proefschrift is het resultaat van 4 (of eigenlijk 5) jaar onderzoek. Door de inzet en hulp van velen (zowel direct als indirect) is dit onderzoek tot een goed einde gebracht. In dit dankwoord wil ik een poging doen iedereen persoonlijk te bedanken.

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Curriculum vitae

CURRICULUM VITAE

Timon Fabius, son of Marius Fabius and Heleen Mülder, and brother of Jasper Fabius and Lidwien Fabius, was born in Leiden, the Netherlands, on the 16th of August 1991. He graduated from grammar school in 2009 at the CSG Liudger in Drachten. After graduation, he moved to Enschede to study Technical Medicine at the University of Twente. Timon obtained his Master's degree in Technical Medicine (specialization track "Medical Sensing and Stimulation") in 2015. He performed his master thesis on the use of volumetric capnography and CO/NO diffusion for the exclusion of pulmonary embolism at the department of pulmonology of the Medisch Spectrum Twente hospital at Enschede, the Netherlands, under the supervision of Michiel Eijsvogel, MD, and Frans de Jongh, PhD.

After graduating from Technical Medicine, Timon part-time started at the department of pulmonology of the Medisch Spectrum Twente as a PhD-student under the supervision of his promotor professor Job van der Palen, co-promotors Frans de Jongh, PhD and Marjolein Brusse-Keizer, PhD and pulmonologist Michiel Eijsvogel, MD. During his PhD-trajectory he continued to work on the research project on volumetric capnography and CO/NO diffusion in pulmonary embolism and multiple projects on the exclusion of obstructive sleep apnea using cheap, simple and valid tools. Simultaneously, he started part-time to perform clinical activities as a technical physician in the sleep center of the Medisch Spectrum Twente under the supervision of Michiel Eijsvogel, MD, and Michiel Wagenaar, MD, PhD.

Next to his own research and clinical activities Timon was involved in the supervision of several (Technical Medicine) students and assistance with setting up various research projects at the department of pulmonology. Additionally, he acts as an examiner in the Pulmonary Function Technologist BSc program (Leidse Onderwijs Instellingen, Leiderdorp, the Netherlands) and was a member of the scientific committee of the Dutch Society of Technical Medicine from 2015-2019.

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