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Creating a continuum of care : smart technology in patients with cardiovascular disease

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Citation

Treskes, R. W. (2018, September 19). *Creating a continuum of care : smart technology in patients with cardiovascular disease*. Retrieved from <https://hdl.handle.net/1887/65636>

Version: Not Applicable (or Unknown)

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Note: To cite this publication please use the final published version (if applicable).

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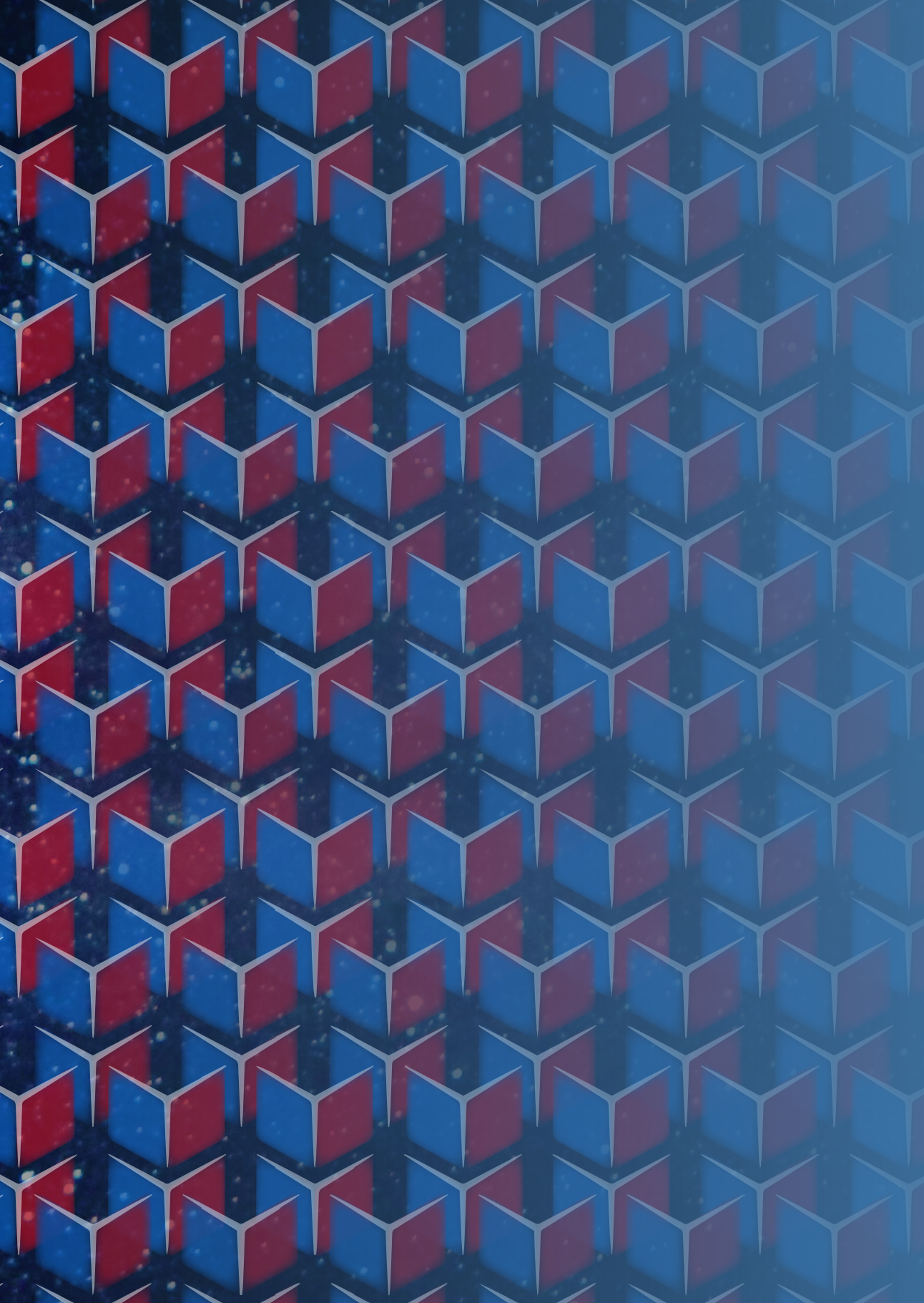


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Title: Creating a continuum of care : smart technology in patients with cardiovascular disease

Issue Date: 2018-09-19



CHAPTER 10

Mobile health application to screen for central sleep apnea in patients with stable heart failure

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Submitted

Abstract

Background

Polysomnography (PSG) is the gold standard for detection of central sleep apnea (CSA) in stable heart failure (HF) patients. PSG is however costly, time consuming and a burden to the patient and therefore unsuitable as screening method. An E-Health application to measure overnight oximetry may be an acceptable screening alternative.

Objective

The purpose of this study is therefore to assess if overnight pulse oximetry using a smartphone compatible oximeter can be used to detect CSA in a stable HF population.

Methods

A total of 26 patients with stable HF underwent one night of both a polygraph (PG) and overnight saturation by a smartphone compatible oximeter. Primary endpoint was the agreement between oxygen desaturation index (ODI) above or below 15 of the smartphone compatible oximeter and the diagnosis of the PG.

Results

Median age was 66.4 (62-71) years and 92% was male. Body mass index was 27.1 (24.4-30.8) $\text{kg}\cdot\text{m}^{-2}$. Seven patients had CSA and 6 patients had obstructive sleep apnea. Of the 7 (.32) patients with CSA that were included in the analysis, 3 (.13) had an $\text{ODI}\geq 15$. The other 4 (.18) had an $\text{ODI}<15$. Of all patients without CSA, 8 (.36) had an $\text{ODI}<15$. A McNemar's test yielded a P-Value of .549.

Conclusions

Oxygen desaturation, when measured by this E-Health application, is a weak predictor of CSA in stable HF patients.

Introduction

Central sleep apnoea (CSA) is characterized by sleep disordered breathing associated with diminished or absent respiratory effort. It is often accompanied by symptoms of tiredness, excessive daytime sleepiness and frequent nocturnal awakenings.(1, 2) CSA and Cheyne-Stokes respiratory breathing are common in congestive heart failure (CHF) patients, with a reported prevalence of 30- 50%.(3) Moreover, CSA in chronic heart failure is associated with increased mortality and reduced left ventricular function.(4) In addition, treatment of CSA with continuous positive airway pressure (CPAP) in chronic heart failure has shown to improve left ventricular function in patients who are responders to treatment.(5)

Currently, polysomnography (PSG) is the gold standard for the diagnosis of CSA. However, PSG is a burden to the patient as it disrupts sleep. Furthermore, it is time consuming for technicians to evaluate, as one PSG examination takes 2 hours to fully evaluate. In addition, the polygraph (PG) is an easier way of evaluating sleep disordered breathing as compared to full PSG, but still disrupts normal sleep for a patient with an already reduced quality of life. Other screening methods to reduce the number of P(S)Gs may therefore be preferred.

Developing new screening methods, including E-Health applications, questionnaires and wireless overnight pulse oximetry for patients with CHF might optimize the number of patients screened for CSA. Furthermore, it may be more patient friendly in a group of patients with an already diminished quality of life.

One possible screening method is the use of E-Health applications (apps). Recent developments in the E-Health industry resulted in a variety of E-Health apps which claim that they can detect sleep disordered breathing. Most of these applications are however not clinically validated. One example of an app that (according to the manufacturer) gives accurate saturation measurements is the iSpO2 app (Masimo Corporation, Irvine, California, United States of America).(6, 7) This app allows its user, by using the app and an oximeter, to record saturation, heart rate and pulse index. Digital storage of the data allows for rapid transmission and analysis, minimizing the involvement of technicians. Previous studies have suggested that overnight oximetry can be used to detect obstructive sleep apnea (OSA) in various patient populations. However, overnight oximetry has not been evaluated as screening method in patients with stable heart failure. This study is therefore performed to evaluate the possible use of overnight pulse oximetry can identify patients with CSA in a CHF population using a validated mHealth app.

Methods

Patient population

Patients with stable heart failure, who visited the outpatient clinic of the department of Cardiology of the Leiden University Medical Center, were eligible for study participation if they met all inclusion and exclusion criteria. Inclusion and exclusion criteria are listed in Table 1. Briefly, patients who had stable heart failure, according to ESC guidelines,(8) had no history of OSA or CSA, had no history of ischaemic or haemorrhagic stroke and who had a life-expectancy of more than 12 weeks (by physician’s discretion) were eligible.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Chronic heart failure, according to ESC guidelines(1)
Aged ≥18 years
Exclusion criteria
History of obstructive sleep apnea syndrome
History of central sleep apnea syndrome
History of ischaemic stroke
History of haemorrhagic stroke
History of chronic obstructive pulmonary disease
Evidence of fluid retention at the time of study inclusion
History of surgery under general anaesthesia ≤3 months before study inclusion
Intravenous injection of diuretics ≤1 month before study inclusion
Unwilling to sign the informed consent form
Life-expectancy ≤12 weeks, by physician’s discretion
History of left-ventricular assist device implantation
Use of oxygen on a daily basis
Pregnancy

Study design and conductance

The study was a single cohort non-randomized open prospective trial. Patients with stable heart failure were asked to participate by a treating cardiologist at a regularly scheduled HF outpatient clinic visit. Patients received information from a project-dedicated healthcare professional. If patients were willing to participate, they visited the department of pulmonology within 1.5 months. At day one, a project-dedicated healthcare professional with ample training applied the PG. Furthermore, the patient was given a smartphone and smartphone compatible oximeter. Patients received oral and written instructions on the use of the smartphone and smartphone compatible oximeter. Patients were instructed to attach the smartphone compatible

oximeter contralateral to the hand where the PG attached. During the first night, patients slept with both the PG and the smartphone compatible oximeter attached. After one night, patients returned the PG to the hospital. The second, third and fourth night, patients slept with only the smartphone compatible oximeter attached. After the fourth night, patients returned the smartphone compatible oximeter to the hospital. A flowchart of these events is given in Figure 1.

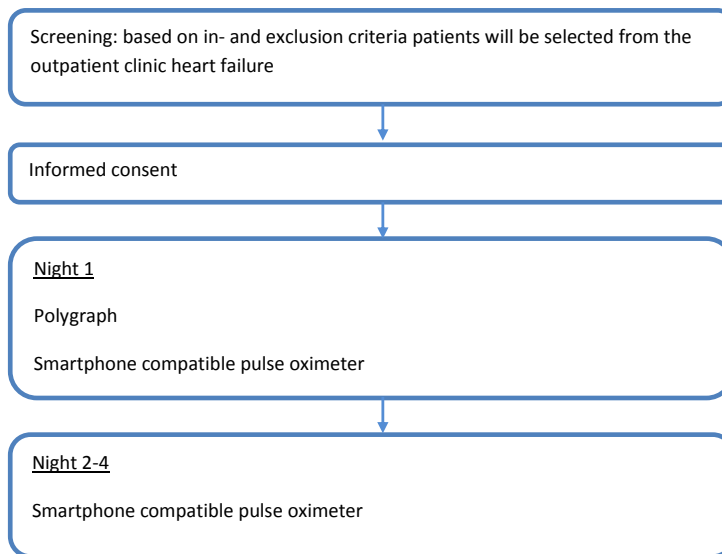


Figure 1. Flow chart of patient selection.

Devices

The PG equipment (Cidelec, Angers, France) consisted of a nasal cannula, a suprasternal sensor, thoracic and abdominal gauges, a finger pulse oximeter, a light sensor, body position and an activity sensor. The pulse oximeter has a sampling rate of 8 Hertz (Hz). Both the smartphone (iPhone 5s, Apple, Cupertino, California, United States of America) and the smartphone compatible pulse oximeter (Masimo, Irvine, California, United States of America) were provided by the hospital for the duration of study participation. The smartphone compatible pulse oximeter is worn at the fingertip and is connected with the smartphone via a wire. The pulse oximeter has a sampling rate of 1 sample/second.

Devices used in this study were battery powered and electrically safe and approved by the Hospital's Instrumentation Department.

Data analysis

CSA and OSA were diagnosed with the results of the PG, in accordance to the America Association of Sleep Medicine guidelines.⁽⁹⁾ A patient was diagnosed with sleep apnea if the PG showed an apnea-hypopnea index (AHI) of ≥ 15 per hour. Sleep apnea was subsequently classified as CSA or OSA. A patient was diagnosed with CSA if of all apnea and hypopnea events, $\geq 50\%$ were classified as “central”. A patient was diagnosed with OSA if $< 50\%$ of all apnea and hypopnea events were classified as “central”. Definitions for apnea and hypopnea events and their subdivision in central or obstructive were derived from the “AASM manual for the scoring of sleep and associated events”.⁽⁹⁾ The oxygen desaturation index (ODI) was defined as the average number of dips in saturation per hour. A cut-off value of 15 was chosen for the ODI. A dip was defined as a $\geq 3\%$ decrease in saturation which lasted ≥ 10 seconds from the baseline saturation. The baseline saturation was determined in the hospital right after the PG was attached to the patient. The PGs were reviewed by a senior pulmonary physician with ample training who was blinded to the results of the oximeter compatible application.

The oximeter compatible application (Masimo) generates a CSV file, which was imported into a dedicated Matlab script (The MathWorks, Natick, Massachusetts, United States) and average SpO₂, lowest SpO₂, total percentage of time spend with a saturation $< 90\%$ and the ODI were calculated. The ODI was again defined as the average number of dips in saturation per hour. A dip was defined as a $\geq 3\%$ decrease in saturation which lasted ≥ 10 seconds from the average saturation over the 11th minute of measurement.⁽⁹⁾ The smartphone compatible oximeter data were analysed by a project dedicated professional with ample training who was blinded to the results of the PG.

End points

The primary endpoint is the agreement between ODI of the smartphone compatible oximeter and the diagnosis of the PG, expressed as four numbers (the number of patients who have both CSA, as diagnosed by PG, and ≥ 15 dips/hour on the smartphone compatible oximeter, the number of patients who have CSA and ≤ 15 dips/hour, the number of patients who do not have CSA and ≥ 15 dips/hour, the number of patients who do not have CSA and ≤ 15 dips/hour), depicted in a 2 x 2 table.

Secondary endpoints include:

1. The percentage of detected sleep apnea (either of obstructive or central aetiology) in the study population by the PG
2. The percentage of detected CSA in the study population by the PG
3. The agreement between the ODI, measured by the PG, and sleep apnea (either obstructive or central aetiology) in the study population
4. The agreement between the ODI, measured by the PG, for CSA in the study population
5. Median difference in ODI, lowest saturation and average saturation between the PG and mobile pulse oximeter
6. The sensitivity and specificity of pulse oximetry to detect CSA by saturation dips > 15/h
7. The percentage of patients able to use the e-health device as instructed

Statistical analysis

R (R foundation for statistical computing, Vienna, Austria) was used to perform a power calculation for a McNemar's test. A alpha level of .05 was chosen and a beta level of 0.20. Based on unpublished research by our study group, we estimated the ratio of p01/p10 (p01 being the false positives and p10 being the false negatives) to be 12 and the sum of p10 and p01 to be 0.39. This yielded a sample size of 26 patients.

SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Continuous variables are expressed as median with interquartile range (IQR) from the 25th to the 75th percentile.

Significance of the primary endpoint was calculated using a McNemar's test. A $P\text{-Value} \leq .05$ was considered statistically significant. A Blant-Altman was drafted to assess the short term reproducibility of the ODI. On the x-axis, ODI of the first night is depicted. On the y-axis, the difference in ODI between the first and second night is depicted.

Results

Patient population

A total of 26 patients were included in the study. Median age was 66.4 (62-71) years and 92% was male. Body mass index was 27.1 (24.4-30.8) kg·m⁻². All patients had NYHA class I (15.4%) or NYHA class II (84.6%), 61.5% had an ischemic cardiomyopathy. Median left ventricular ejection fraction was 34% (24-45), median ProBNP was 748 (244.6-1479) ng/L and median neck circumference was 41 (38-44) cm. Population characteristics are summarized in Table 2.

Table 2. Baseline characteristics

N	26
Age, years	66.4 (62.2-70.6)
Male gender (%)	24 (92.3%)
Body Mass Index, kg·m ⁻²	27.1 (24.4-30.8)
NYHA class (%)	
I	4 (15.4%)
II	22 (84.6%)
Ischemic Cardiomyopathy (%)	16 (61.5%)
LVEF, %	34 (23.5-45)
ProBNP (%)	748 (244.6-1479)
Neck circumference, cm	41 (35-49)

Polygraph

A total of 26 PGs were issued. One PG was of insufficient diagnostic quality and one PG was too short to establish a diagnosis. Both patients were not willing to undergo a second PG. Of the 24 patients that had a PG of diagnostic quality, 14 (58%) had sleep apnea (of either aetiology). A total of 8 (33%) were diagnosed with CSA and 6 (25%) were diagnosed with OSA (secondary endpoint number 1 and number 2). In 10 (41%) cases no sleep apnea was detected. Median sleep duration was 6.5 (IQR: 5.4-7.4) hours. Median AHI was 17 (IQR: 6.5-27.8). Median ODI was 16 (IQR: 5.5-28). Median number of hypopneas per night was 62 (IQR: 30.8-79.8). Median number of dips was 92.5 (IQR: 33.3-156).

Overnight oximetry

All 26 participants transferred at least one CSV file containing the overnight saturation measured by the smartphone compatible pulse oximeter. Of the 4 patients who did not transfer a CSV file of their first night (the night they also underwent the PG), 2 patients could not be diagnosed due to a PG of insufficient quality (as described above). The other 2 patients forgot to attach the smartphone compatible pulse oximeter in their first night. Therefore, 22 patients were included in the analysis of the primary endpoint and secondary endpoint number 3, 4, 5 and 6 (Figure 2). Of the 26 patients who participated, 13 (50%) were able to transfer CSV files of four consecutive nights. A total of 9 (35%) patients transferred CSV files of 3 nights, 1 (4%) transferred CSV files of 2 nights and 3 (12%) transferred CSV files of only 1 night.

Of all files transferred, median saturation was 95.7 (IQR: 94.5-96.7). Median lowest saturation was 87 (82-90). Median ODI was 10.1 (2.9-20.3). Total dips were 75.5 (21-144.8) and total sleep was 8.1 (6.7-9.4) hours.

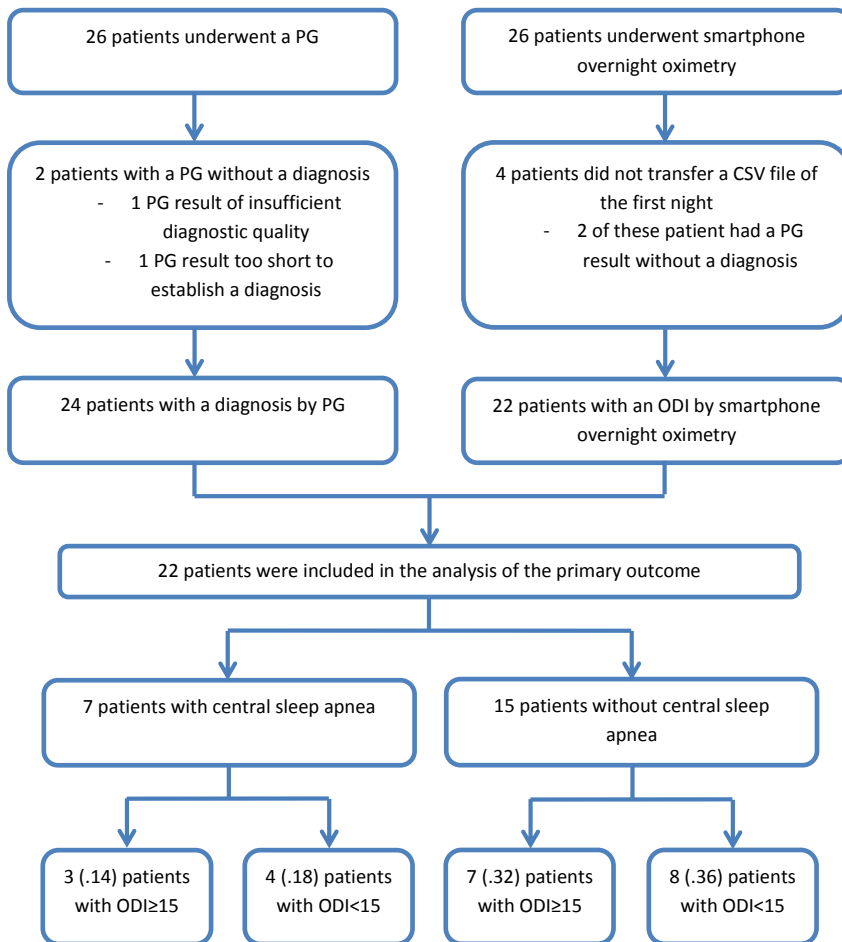


Figure 2. Flowchart of the results of the primary outcome.

Primary endpoint

Of the 7 (.32) patients with CSA that were included in the analysis, 3 (.13) had an $ODI \geq 15$. The other 4 (.18) patients had an $ODI < 15$. Of all 15 patients without CSA that were included in the analysis, 8 (.36) had an $ODI < 15$. These data are given in Table 3. A McNemar's test yielded a P-Value of .549.

Table 3. Number (proportions) of patients with central sleep apnea (yes/no) and an ODI of ≥ 15 or < 15 (as measured by the smartphone compatible oximeter)

	Central sleep apnea (+)	Central sleep apnea (-)	Total
ODI mobile pulse oximeter ≥ 15	3 (.14)	7 (.32)	10 (.45)
ODI mobile pulse oximeter < 15	4 (.18)	8 (.36)	12 (.55)
Total	7 (.32)	15 (.68)	22 (1)

Secondary endpoints

Of all 13 patients with sleep apnea, 6 had an ODI ≥ 15 , measured by Masimo. Of all 9 patients without sleep apnea, 5 had an ODI < 15 . These data are given in Table 4A.

Table 4A. Number of patients with sleep apnea (yes/no) and an ODI of ≥ 15 or < 15 (as measured by the smartphone compatible pulse oximeter)

	Sleep apnea (+)	Sleep apnea (-)	Total
ODI smartphone compatible oximeter ≥ 15	6 (.27)	4 (.18)	10 (.45)
ODI smartphone compatible oximeter < 15	7 (.32)	5 (.23)	12 (.55)
Total	13 (.59)	9 (.41)	22 (1)

Of all 7 patients with CSA, 6 had an ODI (measured by the PG) ≥ 15 . Of all patients without CSA, 9 had an ODI < 15 . These data are given in Table 4B.

Table 4B. Number of patients with central sleep apnea (yes/no) and an ODI of ≥ 15 or < 15 (as measured by the PG)

	Central sleep apnea (+)	Central sleep apnea (-)	Total
ODI PG ≥ 15	6 (.27)	6 (.27)	12 (.55)
ODI PG < 15	1 (.05)	9 (.41)	10 (.45)
Total	7 (.32)	15 (.68)	22 (1)

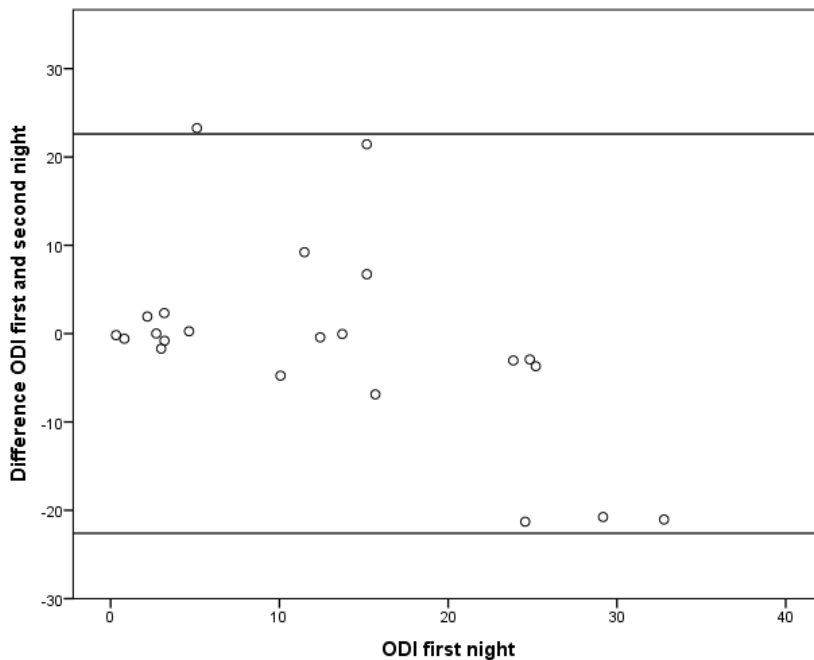
Of all 13 patients with sleep apnea (of either aetiology), 12 had a ODI ≥ 15 (measured by the PG). Of all 9 patients without sleep apnea, 9 had an ODI < 15 . These data are given in Table 4C.

Table 4C. Number of patients with sleep apnea (yes/no) and an ODI of ≥ 15 or < 15 (as measured by the PG)

	Sleep apnea (+)	Sleep apnea (-)	Total
ODI PG ≥ 15	12 (.55)	0 (0)	12 ()
ODI PG < 15	1 (.05)	9 (.41)	10 ()
Total	13 (.59)	9 (.41)	22 (1)

The sensitivity of the ODI for the detection of CSA is therefore 43%. The specificity of the ODI for CSA is 53%. The positive predictive value is 30%. The negative predictive value is 67%.

A Bland-Altman is provided in Figure 3 to show the short term reproducibility of the ODI in participating patients.

**Figure 3.** Bland-Altman of the ODI of the first night (x-axis) and the difference in ODI between the first and second night (y-axis).

Difference between the PG and mobile pulse oximeter

The median difference in ODI was 2.1 higher measured with the PG (IQR: -4.3,14.3). The smartphone compatible oximeter yielded a median saturation which was 3.1 (IQR: 2.6-4.1) percentage points higher than the saturation measured by the PG. There was no difference in the median lowest saturation measured by both devices (both 83%).

Discussion

This study investigated the use of a smartphone compatible oximeter to measure the ODI for the detection of CSA in stable HF patients. Oxygen desaturation, when measured by an e-Health device, appeared to be a weak predictor of CSA in stable HF patients. Also in this elderly group of patients correct use of this e-health device was only achieved by 50% of patients. On the other hand, ODI when measured by a validated device might be a good predictor of sleep apnea of any aetiology in stable HF patients. It was found that 58% of participating patients had sleep apnea. Of all patients, 33% had CSA and 25% had OSA. These percentages are lower than the prevalence found by Oldenburg et al.(10) In a screening study of 700 patients, they showed that 70% had sleep apnea, with 40% having CSA and 30% having OSA. This difference may be explained (at least partly) by the relatively small sample size, but possibly also by differences in severity of heart failure in these patients.

In our study, a median number of dips of 92.5 was found. This was significantly higher than in a study by Davies et al. in 12 heart failure patients, who described four dips per patient per night. We expect that this difference is largely due to the difference in definition of a “dip”. Davies et al. defined a dip as “a fall of >4% in oxygen saturation from a stable baseline that lasted >30 seconds”, while in the current study a dip was defined as a $\geq 3\%$ decrease lasting 10 seconds. This was necessary in order to define dips equally between the PG software and our smartphone compatible oximeter.

ODI as a potential screening tool for CSA

This study showed that the ODI, measured by either the PG or smartphone compatible oximeter, correlates poorly with the diagnosis of CSA. The McNemar’s test yielded a non-significant P-Value of .549. There was however a good correlation between the ODI measured by the PG and the diagnosis of sleep apnea (of either aetiology). It is acknowledged that the study was not powered on this outcome. Furthermore, it is acknowledged that hypopneas in PGs are scored based on desaturation events. Therefore, the diagnosis of sleep apnea is partially dependent on the ODI. However, the strong outcome of 0 false positives and 1 false negatives indicate that the ODI might indeed be a good screening method. This should be investigated in further research.

Implications for clinical practice

Our study found that in 58% of patients with stable HF, any form of sleep apnea (either of central or obstructive aetiology) was found. Both OSA and CSA are associated with higher mortality and lower quality of life in patients with stable HF.(4) Therefore, early diagnosis is of paramount importance. However, screening for OSA or CSA is not recommended by current guidelines, but with such a high

prevalence, routine screening of patients should be considered. But perhaps screening should not focus on the distinction between OSA and CSA, as both have clinical implications.(8). And since ODI has shown to correlate well with sleep apnea of any aetiology, research easy to perform overnight oximetry e-health devices to screen for sleep apnea in patients with stable HF still seems necessary.

e-Health utilization in a heart failure population

In this study, patients were asked to attach, record and e-mail the overnight saturations themselves. Instructions about the use of the mobile phone, the Masimo patch and the e-mailing of the CSV files were given after the PG was attached to the patient. However, of all patients, 13 were unable to transfer four CSV files. These results should be seen as hypothesis generating, but do indicate that when conducting a study in an older and vulnerable population, the e-Health system should be tailored to the patient population. Furthermore, time spend in patient education of the e-Health system should not be underestimated.

Differences in saturation measured by the PG and by the mobile pulse oximeter

Our results showed some significant differences in predictive value of the ODI for both sleep apnea of any aetiology and CSA, median ODI and median average saturation between the PG and the smartphone compatible pulse oximeter. There are several explanations for this phenomenon: first of all, the smartphone compatible oximeter used in this study has not been validated for saturation measurement during sleep. Therefore, motion during sleep and movements of the fingers might result in different results than the oximeter of the PG, which has been designed specifically for overnight saturation measurement. Secondly, patients attached the smartphone compatible oximeter themselves at home. Although instructions were given in the hospital, it is uncertain whether patients attached the device in the proper way. Improper placement usually gives no signal and therefore no saturation in the CSV file. However, slight improper placement might result in improper values in the CSV file.

Limitations

This study has experienced some limitations that have affected its results. Unfortunately, in two patients, it was not possible to get a diagnosis from the PG. These two patients were not willing to undergo a second PG. However, given the numbers of the primary endpoint and a relatively high P-Value of .549, it is unlikely that three extra patients would have changed the data significantly. Furthermore, some patients could not deal with the smartphone technology given, despite ample instructions. As a consequence, 13 patients were unable to record their overnight saturation for 4 consecutive nights. Lastly, we did not do PGs in healthy volunteers.

Therefore, the prevalence of oxygen desaturation in a healthy population (matched by age and sex) is not known.

Conclusion

Oxygen desaturation, when measured by this e-Health device, is a weak predictor of CSA in stable HF patients. The ODI, when measured by a validated device, might be a good predictor of sleep apnea of any aetiology in stable HF patients. This study also corroborated the high prevalence of sleep apnea in stable HF patients. Therefore, more research in screening for sleep apnea detection in stable HF patients is warranted, which might be possible by using validated overnight oximetry, but must be easy to perform in this kind of elderly patient group.

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