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RESEARCH ARTICLE

Novel oxygen desaturation parameters are associated with cardiac troponin I: Data from the Akershus Sleep Apnea Project

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Summary

Novel diagnostic markers for obstructive sleep apnea beyond the apnea–hypopnea index (AHI) have been introduced. There are no studies on their association with markers of subclinical myocardial injury. We assessed the association between novel desaturation parameters and elevated cardiac troponin I and T. Participants with polysomnography (498) from the Akershus Sleep Apnea study were divided into normal and elevated biomarker groups based on sex-specific concentration thresholds (cardiac troponin I: ≥4 ng/L for women, ≥6 ng/L for men; and cardiac troponin T: ≥7 ng/L for women, ≥8 ng/L for men). Severity of obstructive sleep apnea was evaluated with the AHI, oxygen desaturation index, total sleep time with oxygen saturation below 90% (T90), lowest oxygen saturation (Min SpO_2%), and novel oxygen desaturation parameters: desaturation duration and desaturation severity. How the AHI and novel desaturation parameters predicted elevated cardiac troponin I and cardiac troponin T levels was assessed by the area

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under the curve (AUC). Based on multivariable-adjusted linear regression, the AHI ($\beta = 0.004$, $p = 0.012$), desaturation duration ($\beta = 0.007$, $p = 0.004$), and desaturation severity ($\beta = 0.147$, $p = 0.002$) were associated with cardiac troponin I levels but not cardiac troponin T. T90 was associated with cardiac troponin I ($\beta = 0.006$, $p = 0.009$) and cardiac troponin T ($\beta = 0.005$, $p = 0.007$). The AUC for the AHI 0.592 (standard error 0.043) was not significantly different from the AUC of T90 (SD 0.640, $p = 0.08$), desaturation duration 0.609 (SD 0.044, $p = 0.42$) or desaturation severity 0.616 (SD 0.043, $p = 0.26$) in predicting myocardial injury as assessed by cardiac troponin I. Oxygen desaturation parameters and the AHI were associated with cardiac troponin I levels but not cardiac troponin T levels. Novel oxygen desaturation parameters did not improve the prediction of subclinical myocardial injury compared to the AHI.

KEYWORDS
Akershus Sleep Apnea Project, obstructive sleep apnea, oxygen desaturation parameters, polysomnography, troponin I

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder in the adult population. The prevalence of moderate-to-severe OSA, defined by the apnea–hypopnea index (AHI) of ≥15 events/h, has been estimated to be 8%–50% depending on the age group, country, and the American Academy of Sleep Medicine (AASM) scoring criteria used (Benjafield et al., 2019; Berry et al., 2012; Heinzer et al., 2015; Hrubos-Strøm et al., 2011). OSA is associated with an increased risk of atrial fibrillation and ventricular arrhythmias: up to 50% of patients with OSA have arrhythmias (Guilleminault et al., 1983). In addition, OSA is a recognised cause of hypertension, and patients with OSA have a significantly elevated incidence of cardiovascular disease (CVD) compared to others (Peker et al., 2006; Peppard et al., 2000; Somers et al., 2008).

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) measured with high-sensitivity assays are sensitive and specific markers of subclinical myocardial injury. Both of these markers are associated with an increased risk of fatal and non-fatal cardiovascular events (e.g. heart failure and CVD death) in the general population (Welsh et al., 2019). However, cTnI has stronger association with composite CVD and coronary artery disease (CAD). In contrast, cTnT has been associated with increased risk of non-CVD death (Welsh et al., 2019). Although the cause for this is unknown, diseases in other tissues such as skeletal muscle have been linked to an increase in circulating cTnT (Jaffe et al., 2011; Welsh et al., 2019).

We have previously reported that OSA severity, defined by increased AHI, is independently associated with increased cTnI levels (Einvik et al., 2014). An association between OSA severity and cTnT levels has also been described in several studies but exhibits sex-specific differences (Randby et al., 2012; Roca et al., 2015). However, whether higher cTnI and/or cTnT levels in patients with OSA are associated with the mechanic stress of the respiratory events, decreased oxygen supply to the heart, or both, remains unclear.

Although the AHI is the most common metric used to quantify the severity of OSA, it has several limitations. The AHI has been criticised for being too simplistic and for not including the duration of respiratory events or the duration or depth of related oxygen desaturations (Pevernagie et al., 2020). To address these shortcomings of the AHI, desaturation parameters, describing the severity of intermittent hypoxemia, such as the desaturation duration (DesDur) and desaturation severity (DesSev) have been introduced (Kulkas, Tiihonen, Eskola, et al., 2013; Kulkas et al., 2013). Parameters similar to desaturation severity have been shown to be independently associated with CVD-related mortality in patients with OSA (Azarbarzin et al., 2019; Leppänen et al., 2019). In general, these parameters quantify the severity of hypoxic load by considering the depth and duration of blood oxygen desaturation events during sleep, not only counting the frequency of events or time with low oxygen saturation (i.e., the oxygen desaturation index [ODI] and total sleep time with oxygen saturation below 90% [T90]). They can therefore provide important insight into the pathophysiology of OSA beyond parameters such as the AHI and ODI.

We hypothesised that more severe desaturations are associated with higher cTnI and/or cTnT levels as mechanical stress caused by respiratory events and oxygen desaturations have been suggested as a possible mechanism driving CVD risk in OSA. Previous studies have shown that more severe intermittent hypoxaemia, but not the AHI, was associated with increased incidence of CVD and heart failure (Azarbarzin et al., 2019, 2020). Accordingly, we investigated whether there is an association between the severity of intermittent hypoxaemia, and subclinical myocardial injury, assessed by cTnI and cTnT levels in patients with OSA. Additionally, we aimed to investigate whether novel desaturation parameters are stronger predictors for subclinical myocardial injury than the AHI and ODI.

2 | METHODS

2.1 | Study population

The Akershus Sleep Apnea Project (ASAP) is a cross-sectional, two-phased study comprising persons at high risk of OSA based on the Berlin Questionnaire that was conducted at Akershus University Hospital (Norway) in 2006–2009. The recruitment protocol has been previously described in detail (Hrubos-Strøm et al., 2011). From the original population ($n = 535$), a total of 514 participants (55% men and 45% women) agreed to participate and did not meet any of the following exclusion criteria: the use of continuous positive airway pressure therapy, pregnancy at the time of inclusion, lack of Norwegian language skills, severe physical impairment, poor sleep quality on the polysomnography (PSG), or missing blood measurements. Poor sleep quality was defined as <4 h of continuous registration with acceptable signal quality on key variables (pressure cannula, flow cannula, and oximeter) (Hrubos-Strøm et al., 2011). Data on cTnI were missing from five participants and cTnT measurements were missing from 14. Furthermore, 16 participants were excluded because the PSG recordings were of inferior quality. Thus, in total, 498 participants were included in the analysis.

2.2 | Clinical examination

All physical examinations were performed the day before the PSG recording. Blood pressure was measured in the sitting position after 15 min of rest with an automatic device (Dinamap, ProCare 400; GE Healthcare) and determined as the average of the last two out of three measurements (Williams et al., 2018). The body mass index (BMI) was calculated based on measured height and weight. Self-reported previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting was defined as CAD. Fasting blood glucose levels of ≥7 mmol/L or the use of anti-diabetic medication was defined as diabetes mellitus. Lipids were measured by standard laboratory methods. Participants were also interviewed regarding current smoking habits (Einvik et al., 2014).

2.3 | Polysomnography and scoring

The PSG recordings were performed with Embla polysomnography (Natus) including two electroencephalography signals (C4-A1 and C3-A2), electro-oculography, submental electromyography, leg electromyography, blood oxygen saturation (SpO_2), respiratory movements of thorax and abdomen (Respitrace; Ambulatory Monitoring), nasal airflow, subnasal thermistor (Protech), and body position. The PSG data were analysed with the Somnologica 3.2 software (Flaga-Medcare) by two experienced American board-certified sleep technicians and sleep stages were scored according to the Rechtshaffen and Kales scoring manual (Kales & Rechtschaffen, 1968).

In line with the AASM 2007 recommendations, the AHI was calculated as the total number of apneas and hypopneas per hour of sleep and an apnea was scored if the nasal airflow dropped to <10% from the reference amplitude for >10 s (Ruehland et al., 2009). A hypopnea was scored if the nasal airflow dropped to <70% from the reference amplitude for >10 s and was followed by an oxygen desaturation of ≥4% (Iber et al., 2007).

For the desaturation parameter analysis, the desaturation events were automatically re-scored with Noxturnal Research 6.1.0. (Nox Medical) using 3% minimum desaturation drop, 5 s minimum duration, and 30 s maximum plateau criteria. The scorings were exported and DesDur and DesSev were calculated using custom-made MatLab (MathWorks) functions. DesDur is the sum of the duration of all desaturation events and DesSev is the sum of the areas of all desaturation events, independent of respiratory events, both normalised by total sleep time as described in previous studies (Kainulainen et al., 2019; Kulkas, Tiihonen, Eskola, et al., 2013). As a sensitivity analysis, lowest oxygen saturation (Min SpO_2%) values were also calculated for each patient and the number of patients with the lowest oxygen saturation of <77% (Min SpO_2 <77%) was determined (Pengo et al., 2020).

2.4 | Cardiovascular biomarkers

Fasting venous blood samples were drawn the morning after the PSG measurements. First, both plasma and serum samples were stored for a maximum of 2 weeks at −20°C, and then, stored at −80°C. All samples remained frozen until the point of analysis and all analysis were performed at Akershus University Hospital. The cTnI was analysed with ARCHITECT STAT High Sensitivity Troponin assay (Abbott Diagnostics). The cTnT analyses were performed using the cTnT assay on a Cobas e411 platform (Roche Diagnostics). Characteristics of both the cTnI and cTnT assays and analytical variation have previously been reported (Giannitsis et al., 2010; Røsjø et al., 2012). As concentrations and their predictive values of cTnI and cTnT differ by sex, sex-specific thresholds were used when grouping the patients (Lyngbakken et al., 2016). Concentrations of ≥4 ng/L for women and ≥6 ng/L for men were used as thresholds for elevated cTnI (Sigurdardottir et al., 2018). Concentrations of ≥7 ng/L for women and ≥8 ng/L for men were used as thresholds for elevated cTnT (McRae et al., 2019). Other blood sample measurements including creatinine, fasting glucose, and blood lipids were measured with standard methods, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiological Collaboration (CKD-EPI) equation (Levey et al., 2009).

2.5 | Statistical analysis

Categorical variables were compared between participants with normal troponin levels and participants having elevated cTnI and/or cTnT with the Fisher exact test. Continuous variables were compared

between these groups with the Mann–Whitney *U* test. Multivariable linear regression analysis utilising ordinary least square was used to assess the association between different OSA parameters (AHI, ODI, T90, Min SpO_2, Min SpO_2 <77%, DesSev, DesDur), and logarithmically transformed cTnI and cTnT levels. The models were adjusted for age, sex, current smoking status, history of CVD, eGFR, BMI, and diabetes mellitus. The Wald test was used to test for equality of standardised beta coefficients of the association between AHI, ODI, T90, Min SpO_2, Min SpO_2 <77%, DesDur and DesSev, with both cTnI and cTnT levels.

Receiver operating characteristic (ROC) curves and areas under the curves (AUCs) were calculated to compare different OSA parameters' predictive powers for increased cTnI and cTnT levels. (Wieand et al., 1989) The five parameters investigated were AHI, ODI, DesDur and DesSev, and due to their correlation with each other, they were included in the models one at a time. DeLong tests were used to test differences in AUCs between the parameters. C-statistics analyses were also performed by adjusting the model for age, sex, current smoking status, history of CVD, eGFR, BMI, and diabetes mellitus. Furthermore, we conducted a sensitivity analysis including only individuals with moderate-to-severe OSA (defined as AHI ≥15 events/h) and a separate analysis including only individuals free of CVD. Threshold of statistical significance was $p < 0.05$. StataSE 16.1 (StataCorp LLC) was used for the statistical analysis.

2.6 | Ethical approval

The ASAP study was approved by the Regional Committee for Medical Research Ethics in eastern Norway, ID 13843, the National Data Inspectorate, and the Norwegian Social Science Data Services in 2005. All participants provided written informed consent.

3 | RESULTS

The cTnI levels were increased in 9.8% (27) of the men and 8.1% (18) of the women. The cTnT levels were increased in 23.9% (66) of the men and 7.7% (27) of the women. Table 1 outlines the baseline characteristics of the study population according to sex-specific thresholds for cTnI and/or cTnT. Older age, history of CAD, hypertension, higher systolic blood pressure, higher AHI, higher ODI, lower Min SpO_2, higher DesDur, higher DesSev, and decreased total sleep time were all associated with higher troponin cTnI and cTnT levels. In addition, male sex, less frequent smoking, decreased eGFR, higher BMI, Min SpO_2 <77% and increased T90 were significantly associated with higher cTnT levels (Table 1).

In adjusted multivariable linear regression models, the AHI ($\beta = 0.004$, 95% confidence interval [CI] 0.001–0.008, $p = 0.012$), T90 ($\beta = 0.006$, 95% CI 0.002–0.011, $p = 0.009$), DesDur ($\beta = 0.007$, 95% CI 0.002–0.011, $p = 0.004$) and DesSev ($\beta = 0.147$, 95% CI 0.056–0.237, $p = 0.002$) were significantly associated with cTnI levels (Table 2). However, there was no difference in the equality of the coefficients ($p = 0.85$). The ODI ($\beta = 0.001$, 95% CI −0.001 to 0.002), Min SpO_2 ($\beta = -0.008$, 95% CI −0.017 to 0.001), or Min SpO_2 <77% ($\beta = 0.073$, 95% CI −0.109 to 0.255) were not associated with cTnI. The only parameter significantly associated with cTnT levels was T90 ($\beta = 0.005$, 95% CI 0.001–0.009, $p = 0.007$). No association was found between the AHI ($\beta = 0.000$, 95% CI −0.003 to 0.003), DesDur ($\beta = 0.000$, 95% CI −0.004 to 0.004), or DesSev ($\beta = 0.031$, 95% CI −0.049 to 0.110) and cTnT levels in adjusted models. Also, no association was observed between the ODI ($\beta = 0.001$, 95% CI −0.001 to 0.001), Min SpO_2 ($\beta = -0.004$, 95% CI −0.013 to 0.00) or Min SpO_2 <77% ($\beta = 0.068$, 95% CI −0.091 to 0.227) and cTnT levels (Table 2).

In the unadjusted analysis of elevated cTnI, a AUC of 0.592 (standard error [SE] 0.043) was observed for AHI, 0.594 (SE 0.043) for ODI, 0.648 (SE 0.040) for T90, 0.400 (SE 0.043) for Min SpO_2, 0.493 (SE 0.023) for Min SpO_2 <77%, 0.609 (SE 0.044) for DesDur, and 0.616 (SE 0.043) for DesSev (Figure 1a). In the unadjusted analysis of elevated cTnT, a AUC of 0.622 (SE 0.032) was observed for AHI, 0.613 (SE 0.033) for ODI, 0.378 (SE 0.033) for Min SpO_2, 0.549 (SE 0.021) for Min SpO_2 <77%, 0.601 (SE 0.033) for DesDur, and 0.602 (SD 0.033) for DesSev (Figure 1b). There were no significant differences between AUCs by the DeLong test for cTnI ($p = 0.39$) or cTnT ($p = 0.72$) between AHI, DesSev, DesDur, ODI or T90. However, Min SpO_2 had a significantly lower AUC for cTnI compared to the other parameters ($p = 0.03$). For cTnT, the AUC for Min SpO_2 was also significantly lower ($p = 0.002$) compared to other parameters. The same applied to Min SpO_2 <77% and cTnI ($p = 0.002$) but no difference was observed in the AUC for Min SpO_2 <77% and AHI, ODI, T90, DesDur, and DesSev for cTnT ($p = 0.06$). Furthermore, there were no significant differences in the AUCs between these five OSA parameters for neither cTnI ($p = 0.26$) nor cTnT ($p = 0.79$) in adjusted models (Figure 2a,b).

In a sensitivity analysis that included only those individuals with moderate-to-severe OSA (AHI ≥15 events/h), there was still a significant association between cTnI and AHI, DesDur, DesSev, and T90 in a multivariable adjusted analysis (Table S1). However, there was still no association between cTnI or cTnT with ODI, Min SpO_2, or Min SpO_2 <77% (Table S1). Furthermore, the sensitivity analysis excluding those individuals with CVD at baseline did not change the results (Table S2). Also, in sex-specific analyses, there were no differences in the ability of AHI, ODI, DesDur, or DesSev to predict elevated cTnI or cTnT levels ($p > 0.05$).

4 | DISCUSSION

In the present study, we investigated the association between novel desaturation parameters and subclinical myocardial injury, assessed by cTnI and cTnT levels with sex-specific thresholds. After adjusting for potential confounders, the association of AHI and novel desaturation parameters with markers of subclinical myocardial injury was significant for cTnI but not cTnT. Furthermore, the performance of the AHI, ODI or novel desaturation parameters, in determining increased subclinical myocardial injury as measured by AUC did not differ in either unadjusted or adjusted models. OSA severity,

TABLE 1 Demographic data according to the groups defined by troponin levels below or over sex-specific threshold; cardiac troponin I was ≥4 ng/L for women or ≥6 ng/L for men and cardiac troponin T was ≥7 ng/L for women or ≥8 ng/L for men

	cTnI <	cTnI ≥		cTnT <	cTnT ≥	
	n = 453	*n* = 45	*p*	*n* = 405	*n* = 93	*p*
Age, years, mean (SD)	47.6 (11.1)	55.2 (10.6)	**<0.001**	46.9 (11.0)	54.5 (10.3)	**<0.001**
Male sex, *n* (%)	249 (55.0)	27 (60.0)	0.313	210 (51.9)	66 (71.0)	**0.001**
Current smoking, *n* (%)	125 (27.6)	7 (15.6)	0.053	118 (29.1)	14 (15.1)	**0.002**
CAD, *n* (%)	18 (8.4)	10 (22.2)	**0.006**	34 (8.4)	14 (15.1)	**0.043**
Hypertension, *n* (%)	245 (54.1)	33 (73.3)	**0.009**	210 (51.9)	68 (73.1)	**<0.001**
Diabetes mellitus, *n* (%)	54 (11.9)	8 (17.8)	0.181	45 (11.1)	17 (19.3)	0.047
eGFR, ml/min/1.73 m^2, median (Q1, Q3)	115 (96, 140)	107 (75, 122)	0.286	120 (84, 131)	114 (98, 141)	**0.031**
Systolic blood pressure, mmHg, mean (SD)	134 (122, 145)	149 (126, 162)	**<0.001**	134 (121, 144)	141 (128, 152)	**<0.001**
BMI, kg/m^2, mean (SD)	28.9 (5.0)	29.8 (5.4)	0.188	28.7 (5.0)	30.0 (5.0)	**0.013**
Total HDL-cholesterol ratio, mean (SD)	4.5 (1.4)	4.8 (1.8)	0.621	4.4 (1.3)	4.7 (1.7)	0.528
AHI, mean (SD)	13.6 (18.2)	17.3 (18.3)	**0.042**	12.6 (17.2)	20.0 (21.3)	**<0.001**
ODI, mean (SD)	13.0 (17.1)	17.3 (19.1)	**0.039**	12.1 (16.3)	19.3 (20.0)	**<0.001**
Mean SpO_2, %, median (Q1, Q3)	96 (94, 96)	94 (93, 95)	**0.012**	95 (94, 96)	94 (93, 95)	**<0.001**
T90, median (Q1, Q3)	0.2 (0, 2.2)	1.4 (0, 5.4)	0.059	0.1 (0, 1.8)	1.2 (0.1, 6.9)	**<0.001**
Min SpO_2, median (Q1, Q3)	87 (83, 90)	85 (80, 89)	**0.025**	87 (83, 90)	84.5 (80, 88)	**<0.001**
Min SpO_2 <77%, *n* (%)	47 (10.4)	5 (11.1)	0.801	35 (8.6)	17 (18.3)	**0.008**
DesDur, mean (SD)	16.3 (13.7)	21.2 (14.7)	**0.015**	15.8 (13.3)	20.9 (15.5)	**0.002**
DesSev, mean (SD)	0.50 (0.64)	0.71 (0.82)	**0.010**	0.48 (0.63)	0.69 (0.76)	**0.002**
Total sleep time, h, mean (SD)	7.02 (1.23)	6.30 (1.31)	**<0.001**	7.03 (1.27)	6.62 (1.13)	**0.004**

Note: Statistically significant values denoted in bold.

Abbreviations: AHI, Apnea–Hypopnea Index; BMI, body mass index; CAD, coronary artery disease; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DesDur, desaturation duration; DesSev, desaturation severity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; Min SpO_2 <77%, the number of patients with the lowest oxygen saturation <77%; Min SpO_2, lowest oxygen saturation; ODI, Oxygen Desaturation Index; Q, quartile; SD, standard deviation; T90, total sleep time with oxygen saturation <90%.

regardless of whether it is expressed as the AHI or novel desaturation parameters, is therefore associated with subclinical myocardial injury. However, for the very first time, we have shown that there is an independent association between novel desaturation parameters (DesDur and DesSev), and cTnI in participants with high risk of OSA and those parameters performed better than Min SpO_2 and Min SpO_2 <77% in predicting cTnI over cut-off and better than Min SpO_2 in predicting cTnT over cut-off.

There are several potential mechanisms explaining why cTnI levels might be increased in OSA. Firstly, oxygen desaturations (i.e., transient drops in the blood oxygen saturation) could potentially lead to less oxygenated blood reaching the heart creating a mismatch between the myocardial oxygen demand and delivery (Javaheri et al., 2017). Our cross-sectional findings of cTnI and cTnT being associated with T90 support this hypothesis. Second, the increased intrathoracic pressure changes during apneas and hypopneas may lead to subclinical myocardial injury (Javaheri et al., 2017). Cardiac TnI is strongly associated with CVD risk and has previously been independently associated with higher AHI, both in the general population and in patients with OSA presenting with acute myocardial infarction (Cheong et al., 2021; Einvik et al., 2014). Increased AHI has previously been associated with detectable high-sensitivity cTnT in the ASAP, but this association was attenuated when adjusted for hypertension (Randby et al., 2012). In the Atherosclerosis Risk in the Communities and the Sleep Heart Health Study, OSA severity, defined by the AHI, was also independently associated with cTnT (Roca et al., 2013). We found an independent association between T90 and cTnT but not between the novel desaturation parameters and cTnT in the multivariable adjusted models. Furthermore, there was no significant difference between the four OSA parameters in classifying participants with cTnI or cTnT above threshold.

Although cTnI and cTnT are both components of the contractile apparatus of cardiomyocytes, there are several important biological differences. For example, cTnI does not show diurnal variation like cTnT (Klinkenberg et al., 2016; Wildi et al., 2018). In addition, cTnI is more strongly associated with CVD, whereas cTnT has stronger association with non-CVD mortality (Welsh et al., 2019). In the present study, levels above the limit of detection were more frequently observed for cTnI than for cTnT, but cTnI was not as likely as cTnT to be over threshold values. The increased sensitivity of the cTnI assay, and enhanced signal-to-noise ratio, might provide a more accurate reflection of actual cardiac troponin release.

In a large sample of middle-aged and older participants with OSA, CVD mortality was independently associated with

TABLE 2 The association between continuous log-transformed cardiac troponin I and T and different measures of obstructive sleep apnea severity with a least-squares multivariate linear regression analysis expressed with standardised beta coefficients

	cTnI			cTnT		
	β (95% CI)	SD error	*p*	β (95% CI)	SD error	*p*
AHI	0.004 (0.001, 0.008)	0.002	0.012	0.000 (−0.003, 0.003)	0.001	0.846
ODI	0.001 (−0.001, 0.002)	0.001	0.368	0.000 (−0.001, 0.001)	0.000	0.765
T90	0.006 (0.001, 0.010)	0.002	0.009	0.005 (0.001, 0.009)	0.002	0.007
Min SpO_2	−0.008 (−0.017, 0.001)	0.005	0.099	−0.004 (−0.013, 0.004)	0.004	0.337
Min SpO_2 <77%	0.073 (−0.109, 0.255)	0.093	0.432	0.068 (−0.091, 0.227)	0.081	0.401
DesDur	0.007 (0.002, 0.011)	0.002	0.004	0.000 (−0.004, 0.004)	0.002	0.923
DesSev	0.147 (0.056, 0.237)	0.046	0.002	0.031 (−0.049, 0.110)	0.041	0.447

AHI, Apnea–Hypopnea Index; CI, confidence interval; cTnI, cardiac troponin I; cTnT, cardiac troponin T; DesDur, desaturation duration; DesSev, desaturation severity; Min SpO_2 <77%, the number of patients with the lowest oxygen saturation below 77%; Min SpO_2, lowest oxygen saturation; ODI, Oxygen Desaturation Index; SD, standard deviation; T90, total sleep time with oxygen saturation <90%.

Models were adjusted for age, sex, the status of current smoking, history of cardiovascular disease, estimated glomerular filtration rate, body mass index, and diabetes mellitus.

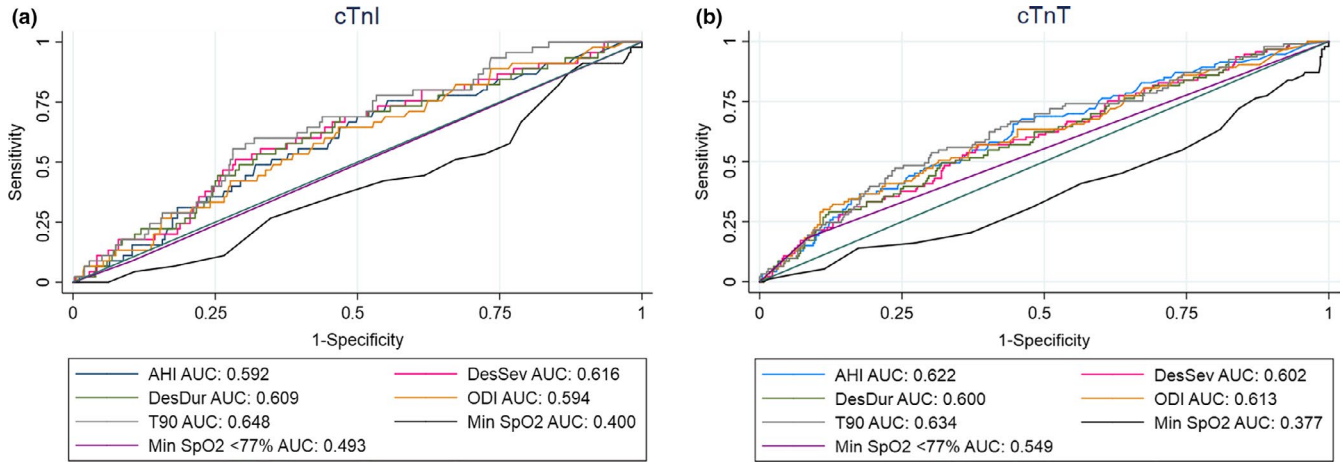

FIGURE 1 (a) Receiver operating curves (ROCs) with area under the curve (AUC) for the comparison of apnea–hypopnea index (AHI), oxygen desaturation index (ODI), desaturation duration (DesDur), desaturation severity (DesSev), total sleep time with oxygen saturation <90% (T90), lowest oxygen saturation (Min SpO_2%), and the number of patients with the lowest oxygen saturation <77% (Min SpO_2 <77%) for classifying participants with or without subclinical myocardial injury as defined by cardiac troponin I (cTnI) >4 ng/L for women and >6 ng/L for men, unadjusted. (b) ROCs with AUC for the comparison of AHI, ODI, DesDur, DesSev, T90, Min SpO_2%, and the number of patients with Min SpO_2 <77% for classifying participants with or without subclinical myocardial injury as defined by cardiac troponin T (cTnT) >7 ng/L for women and >8 ng/L for men, unadjusted

hypoxic burden, a parameter similar to the DesSev, but not the AHI (Azarbarzin et al., 2019). According to our findings, AHI, T90, DesSev and DesDur are all independently associated with subclinical myocardial injury as expressed by cTnI, which is also a strong predictor of CVD mortality. However, there was no significant difference in the ability of these markers to predict subclinical myocardial injury. There are several important differences between hypoxic burden and DesSev, the most important being that hypoxic burden measures desaturation related to respiratory events, while DesSev and DesDur measure all desaturation events (Azarbarzin et al., 2019; Kainulainen et al., 2019). Further studies are therefore needed to investigate which blood oxygenation characteristics provide additional information on the increased CVD mortality in patients with OSA over AHI.

This study has several limitations. First, the use of only a single-night PSG is a potential limitation due to the night-to-night variation in the severity of OSA (Stepnowsky et al., 2004). Moreover, the scoring criteria have changed since the study's inception in 2006. Therefore, the use of the 2007 hypopnea criterion may influence the association with cardiometabolic outcomes compared to updated and recommended AASM 2012 criterion, as the 2007 criterion underestimates the number of hypopneas. However, even though the AHIs defined based on 2007 and 2012 criteria are significantly different, they are highly correlated and both in clinical use (Ruehland et al., 2009). Another limitation of the present study is that this cross-sectional analysis does not address changes in cTnI over time. However, albeit previous population studies have addressed changes in cTnI over time they often lack sleep data, particularly PSG (Lyngbakken et al., 2019;

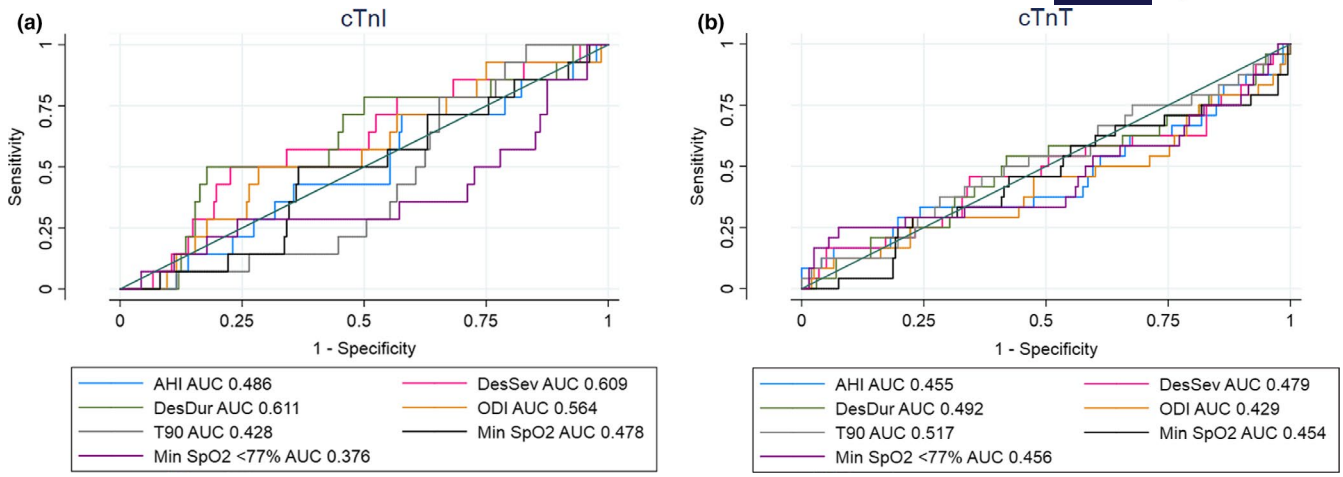

FIGURE 2 (a) Receiver operating curves (ROCs) with area under the curve (AUC) for the comparison of apnea–hypopnea index (AHI), oxygen desaturation index (ODI), desaturation duration (DesDur), desaturation severity (DesSev), total sleep time with oxygen saturation below 90% (T90), lowest oxygen saturation (Min SpO_2%), and the number of patients with the lowest oxygen saturation <77% (Min SpO_2 <77%) for classifying participants with or without subclinical myocardial injury as defined by cardiac troponin I (cTnI) >4 ng/L for women and >6 ng/L for men, adjusted for age, sex, current smoking, history of cardiovascular disease (CVD), estimated glomerular filtration rate (eGFR), body mass index (BMI), and diabetes mellitus. (b) ROCs with AUC for the comparison of AHI, ODI, DesDur, DesSev, T90, Min SpO_2%, and the number of patients with Min SpO_2 <77% for classifying participants with or without subclinical myocardial injury as defined by cardiac troponin T (cTnT) >7 ng/L for women and >8 ng/L for men, adjusted for age, sex, current smoking, history of CVD, estimated eGFR, BMI, and diabetes mellitus

Sigurdardottir et al., 2021). Furthermore, a cross-sectional study design precludes conclusions concerning causal mechanisms underlying the association between OSA and troponin release. Another important limitation is that we do not have imaging data regarding myocardial scarring or coronary artery calcium score and can therefore not account for subclinical CAD. Finally, our results do not provide evidence for any mechanism for subclinical myocardial injury in OSA.

5 | CONCLUSIONS

Oxygen desaturation parameters (i.e., DesSev and DesDur) and the AHI were independently associated with increased cTnI but not cTnT levels in patients with OSA. However, the association between oxygen desaturation parameters and elevated circulating markers was not different from that of the AHI. As oxygen desaturation parameters are easy to define, requiring only an oxygen saturation signal, they could be used as alternative tools in the risk assessment of subclinical myocardial injury in a setting where a full PSG is not available.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work. Fjola D. Sigurdardottir, Caroline Tonje Øverby, Harald Hrubos-Strøm, planned the paper and analysis. Harald Hrubos-Strøm, Torbjørn Omland, Toril Dammen, Gunnar Einvik, Inger Hilde Nordhus, Sami Nikkonen, Tuomas Karhu, Samu Kainulainen, Timo Leppänen contributed to data and analysis tools. Data analysis was performed by Fjola D. Sigurdardottir. Figures and tables were prepared by Fjola D. Sigurdardottir and Caroline Tonje Øverby. All authors interpreted data. Fjola D. Sigurdardottir and Caroline Tonje Øverby drafted the first main manuscript text and all authors contributed to revision of the first draft and writing of the final manuscript text. All authors approved the final submitted version of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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