Central Sleep Apnea Is Associated with an Abnormal P-Wave Terminal Force in Lead V1 in Patients with Acute Myocardial Infarction Independent from Ventricular Function

Jan Pec 1, Michael Wester 1, Christoph Fisser 1*, Kurt Debl 1, Okka W. Hamer 2, Florian Poschenrieder 2, Stefan Buchner 3, Lars S. Maier 1*, Michael Arzt 1 and Stefan Wagner 1,⁎

1 University Heart Center Regensburg, University Hospital Regensburg, 93053 Regensburg, Germany; jan.pec@klinik.uni-regensburg.de (J.P.); michael.wester@ukr.de (M.W.); christoph.fisser@ukr.de (C.F.); kurt.debl@ukr.de (K.D.); Lars.Maier@klinik.uni-regensburg.de (L.S.M.); Michael.Arzt@klinik.uni-regensburg.de (M.A.)
2 Department of Radiology, University Hospital Regensburg, 93053 Regensburg, Germany; Okka.Hamer@klinik.uni-regensburg.de (O.W.H.); Florian.Poschenrieder@klinik.uni-regensburg.de (F.P.)
3 Department of Internal Medicine, Cham Hospital, 93413 Cham, Germany; stefan.buchner@sana.de
* Correspondence: stefan.wagner@ukr.de

Abstract: Sleep-disordered breathing (SDB) is highly prevalent in patients with cardiovascular disease. We have recently shown that an elevation of the electrocardiographic (ECG) parameter P wave terminal force in lead V1 (PTFV1) is linked to atrial proarrhythmic activity by stimulation of reactive oxygen species (ROS)-dependent pathways. Since SDB leads to increased ROS generation, we aimed to investigate the relationship between SDB-related hypoxia and PTFV1 in patients with first-time acute myocardial infarction (AMI). We examined 56 patients with first-time AMI. PTFV1 was analyzed in 12-lead ECGs and defined as abnormal when ≥4000 µV*ms. Polysonomography (PSG) to assess SDB was performed within 3–5 days after AMI. SDB was defined by an apnea-hypopnea-index (AHI) >15/h. The multivariable regression analysis showed a significant association between SDB-related hypoxia and the magnitude of PTFV1 independent from other relevant clinical co-factors. Interestingly, this association was mainly driven by central but not obstructive apnea events. Additionally, abnormal PTFV1 was associated with SDB severity (as measured by AHI, B 21.495; CI [10.872 to 32.118]; p < 0.001), suggesting that ECG may help identify patients suitable for SDB screening. Hypoxia as a consequence of central sleep apnea may result in atrial electrical remodeling measured by abnormal PTFV1 in patients with first-time AMI independent of ventricular function. The PTFV1 may be used as a clinical marker for increased SDB risk in cardiovascular patients.

Keywords: acute myocardial infarction; p wave terminal force; central sleep apnea; sleep-disordered breathing

1. Introduction

Sleep-disordered breathing (SDB) is a common co-morbidity in patients with cardiovascular disease [1–3]. Nearly 50% of patients undergoing coronary artery bypass surgery (CABG) were found to have SDB [4]. Obstructive sleep apnea (OSA) is characterized by the presence of repetitive episodes of upper airway collapse. In contrast, central sleep apnea (CSA) is caused by an intermittent lack of centrally controlled respiratory drive, which often manifests as Cheyne–Stokes respiration and leads to significant oxygen desaturation. Epidemiologic studies indicate a strong association between both OSA and CSA and atrial fibrillation (AF) [5,6]. The most commonly used treatment is continuous positive airway pressure (CPAP), which can alleviate the clinical symptoms of SDB. However, the adherence to this therapy is generally poor and no significant benefit has been shown regarding cardiovascular outcome in patients with OSA [7,8]. The recent randomized controlled trial led by Traaen et al. demonstrated that CPAP treatment does not affect the burden of AF
after 5 months of therapy [9]. Moreover, adaptive servo-ventilation has even been reported to increase the risk of cardiovascular death in patients with reduced left ventricular ejection fraction (LV EF) and CSA [10]. Therefore, identification of novel risk markers and new treatment options are of utmost importance.

The P wave terminal force in electrocardiographic (ECG)-lead V1 (PTFV1) was firstly introduced by Morris et al. in 1964 [11]. It is defined as the algebraic product of the amplitude and duration ($\mu$V*ms) of the negative area of the P-wave in lead V1 (Figure 1). Accumulating evidence has since linked an abnormally large PTFV1 to atrial dysfunction [4] and AF [12] with increased risk for cardioembolic or cryptogenic stroke [13,14]. Moreover, an abnormally PTFV1 has also been shown to predict cardiovascular risk and cardiac death or hospitalization for heart failure in patients with prior myocardial infarction [15].

Interestingly, we have recently shown that an abnormally large PTFV1 was associated with atrial functional and electrical remodeling by activation of Ca/calmodulin-dependent protein kinase II (CaMKII). CaMKII-dependent dysregulation of cardiomyocytes ion homeostasis has already been associated with atrial pathologies [16], and increased CaMKII-dependent atrial pro-arrhythmic activity was found in cardiovascular patients with SDB [4]. Since CaMKII can be activated by oxidation, intermittent hypoxia could be an important upstream factor.

To date, however, it is unclear which pathophysiologic factor—be it negative intrathoracic pressure fluctuations, intermittent hypoxia, increased production of reactive oxygen-species (ROS), or autonomic imbalance [17]—might be most significant for atrial electrical remodeling. In addition, little is known about the relationship between PTFV1 and SDB in patients with acute myocardial infarction. Therefore, this present study investigated the relationship between SDB and SDB-related hypoxia with PTFV1 in patients presenting with acute myocardial infarction.

2. Materials and Methods
2.1. Study Approval and Design

We performed a sub-analysis of a prospective observational study in patients with acute MI that were enrolled at the University Medical Center Regensburg (Regensburg, Germany) between March 2009 and March 2012. Details of the study design have been published previously [3].

Patients (age 18–80 years) with a first-time AMI and successful percutaneous coronary intervention (PCI) treated at the University Hospital Regensburg within 24 h after symptom onset were eligible for inclusion. Exclusion criteria were previous MI or previous PCI, indication for surgical myocardial revascularization, cardiogenic shock, contraindications for cardiac magnetic resonance imaging (CMR), and severe comorbidities (e.g., lung disease, stroke, treated SDB). The study protocol was reviewed and approved by
the local institutional ethics committee (Regensburg, 08-151) and is in accordance with
the Declaration of Helsinki and Good Clinical Practice. A written informed consent was
obtained from all patients prior to enrolment.

Of 252 consecutive patients who underwent percutaneous coronary intervention, 74
patients were eligible for the prospective observational study, which involved an evaluation
of cardiac function (CMR) and SDB severity at the time of MI. In total, 34 patients were
excluded from this sub-analysis due to missing CMR (n = 10), missing polysomnography
(n = 6), and atrial fibrillation (n = 2). The final sub-analysis included 56 patients, who were
divided into two cohorts depending on the PTFV\textsubscript{1} (PTFV\textsubscript{1} < 4000 \(\mu\text{V} \cdot \text{ms}\) [n = 40] and
PTFV\textsubscript{1} \(\geq\) 4000 \(\mu\text{V} \cdot \text{ms}\) [n = 16]) (Figure 2).

2.2. Electrocardiography

Standard 12-lead electrocardiograms were recorded at a paper speed of 50 mm/s and a
standardization of 10 mm/1 mV. All ECGs were digitally processed and scaled using ImageJ
(Version 2.00; Java-based image processing program; LOCI, University of Wisconsin, USA)
and individually analyzed by two skilled physicians (mean of 3 consecutive P waves). Both
investigators were blinded to the clinical and MRI data. PTFV\textsubscript{1} was defined as the algebraic
product of amplitude (\(\mu\text{V}\)) and duration (ms) of the terminal negative component of the P
wave in lead V\textsubscript{1} (Figure 1) also known as Morris-Index [11]. A PTFV\textsubscript{1} of \(\geq\) 4000 \(\mu\text{V} \cdot \text{ms}\)
was considered to be abnormal.

Figure 2. Flow diagram.
2.3. Polysomnography

Polysomnography (PSG) was performed in all subjects using standard polysomnographic techniques (Alice System; Respironics, Pittsburgh, PA, USA) as previously described [3]. Briefly, respiratory efforts were measured with the use of respiratory inductance plethysmography and airflow by nasal pressure. Sleep stages and arousals, as well as apneas, hypopneas, and respiratory effort-related arousals, were determined according to the American Academy of Sleep Medicine guidelines [18] by an experienced sleep technician blinded to the clinical data. Hypopneas were classified as obstructive if there was out-of-phase motion of the ribcage and abdomen, or if airflow limitation was present. In order to achieve optimal distinction between obstructive and central hypopneas without using an esophageal balloon, we used additional criteria, such as flattening, snoring, paradoxical effort movements, arousal position relative to hypopneas, and associated sleep stage (rapid eye movement (REM)/non-REM). SDB was defined by an apnea-hypopnea-index (AHI) > 15/h determined as the number of central or obstructive apnea and hypopnea episodes per hour of sleep. CSA was defined as >50% central apneas and hypopneas of all apneas and hypopneas. Pulse oximetry implemented in PSG was used to measure oxygen saturation and ODI (number of events per hour in which oxygen saturation decreased by ≥3% from baseline).

2.4. Cardiovascular Magnetic Resonance

Details of CMR data acquisition have been previously described [3]. Shortly, CMR studies were performed on a clinical 1.5 Tesla scanner (Avanto, Siemens Healthcare Sector, Erlangen, Germany) using a phased array receiver coil during breath-hold and that was ECG triggered. Examination of ventricular function was performed by acquisition of steady-state free precession (SSFP) cine images in standard short axis planes (trueFISP; slice thickness 8 mm, inter-slice gap 2 mm, repetition time 60.06 ms, echo time 1.16 ms, flip angle 60°, matrix size 134 × 192, and readout pixel bandwidth 930 Hz*pixel−1). The number of Fourier lines per heartbeat was adjusted to allow the acquisition of 25 cardiac phases covering systole and diastole within a cardiac cycle. The field of view was 300 mm on average and was adapted to the size of the patient. Calculation of left ventricular volumes and EF was performed in the serial short axis slices using commercially available software (syngo Argus, version B15; Siemens Healthcare Sector).

2.5. Statistical Analysis

Continuous variables were compared by Student’s T-test or Welch’s Test depending on their variance. The Chi-square or Fisher’s exact test were used for categorial variables depending on the number of observations. Continuous variables are expressed as mean ±95% confidence interval (CI), and categorial variables as frequencies and percentages, respectively. After linear regression of PTFV1 or AHI with important clinical factors, multivariate linear regression was performed for all variables with a p value < 0.2. An intra class correlation (ICC, by two-way mixed model, type absolute agreement) was used to assess the reproducibility of PTFV1 analysis. All reported P values are two-sided and the threshold for significance was set at p < 0.05. Statistical analysis was performed in SPSS (SPSS Statistics for Mac OS, Version 26.0 Armonk, NY, USA: IBM Corp.).

3. Results

3.1. Study Population

A total of 56 patients consisting of 80% men with an age of 55 ± 9.9 years were separated into groups with normal and abnormal PTFV1 (baseline characteristics in Table 1). There was no significant difference in demographic parameters or comorbidities, such as age, gender, arterial hypertension, diabetes mellitus, hypercholesterolemia, or smoking.
Table 1. Baseline characteristics: normal PTFV$_1$ and abnormal PTFV$_1$.

|                          | Normal PTFV$_1$                  | Abnormal PTFV$_1$                  | p Value |
|--------------------------|----------------------------------|------------------------------------|---------|
| Age [years]              | Mean ± SD                        | Mean ± SD                          |         |
| BMI [kg·m$^{-2}$]        | 28.52 ± 3.06                     | 28.82 ± 3.99                       | 0.771   |
| Male [n, %]              | 34 (85%)                         | 11 (68%).                           | 0.263   |
| Arterial hypertension [n, %] | 19 (47.5%)                       | 9 (60%)                             | 0.409   |
| Diabetes mellitus [n, %] | 6 (15%)                          | 3 (20%)                             | 0.692   |
| Hypercholesterolemia [n, %] | 12 (30%)                         | 5 (33.3%)                           | 1.000   |
| LDL-cholesterol [mg·dl$^{-1}$] | 136.5 ± 35.33                    | 111.5 ± 23.4                       | 0.018   |
| Smoking [n, %]           | 30 (75%)                         | 11 (73.3%)                          | 1.000   |
| Systolic blood pressure [mmHg] | 127.43 ± 7.45                     | 127.67 ± 7.55                      |         |
| Diastolic blood pressure [mmHg] | 83.93 ± 6.01                      | 83.63 ± 6.01                       |         |
| NT-proBNP at discharge [pg·ml$^{-1}$] | 774.47 ± 835.61                  | 2201.19 ± 1390.37                  | 0.002   |
| NT-proBNP at discharge [pg·ml$^{-1}$] | 95.16 ± 16.53                     | 83.63 ± 28.03                      | 0.152   |
| Resting heart rate [min$^{-1}$] | 75.46 ± 12.13                    | 75.33 ± 22.14                      | 0.983   |
| Systolic LA area [cm$^2$] | 25.9 ± 4.19                      | 24.67 ± 3.53                       | 0.369   |
| Diastolic LA area [cm$^2$] | 18.11 ± 3.03                     | 18.44 ± 3.82                       | 0.764   |
| ACEi/ARB at discharge [n, %] | 16 (42.1%)                       | 10 (66.7%)                          | 0.107   |

ACEi: ACE-inhibitor; ARB: angiotensin receptor blocker; AH: apnea-hypopnea-index; BMI: body mass index; CK: creatine kinase; EF: ejection fraction; eGFR: estimated glomerular filtration rate; FAC: fractional area change; LA: left atrium; LV: left ventricle; NT-proBNP: N-terminal pro-B-type natriuretic peptide; MRA: Mineralocorticoid receptor antagonist; PTFV$_1$: P wave terminal force in lead (abnormal ≥4000 μV·ms); RV: right ventricle; SD: standard deviation; SDB: sleep-disordered breathing; STEMI: ST-elevation myocardial infarction; TAPSE: tricuspid annular plane systolic excursion. Bold values mean statistical significance calculated by the two-sided Student’s t-test($^T$), Welch’s t-test($^W$), chi-square test($^F$) or Fisher’s exact test($^F$).

Patients with abnormal PTFV$_1$ presented significantly less with ST segment elevation myocardial infarction (STEMI) ($p = 0.035$) and had higher levels of NT-proBNP at discharge ($p = 0.002$) (Table 1). The LV EF was mildly reduced in both groups but worse in patients with abnormal PTFV$_1$ (43.15 ± 11.51% vs. 48.93 ± 7.45%, $p = 0.035$). Interestingly, volumetric parameters for LA size and function, such as LA fractional area change (FAC) or systolic LA area, were not significantly increased in patients with abnormal PTFV$_1$ (Table 1), indicating that the magnitude of PTFV$_1$ more likely reflects electrical but not structural remodeling as published previously [19].

3.2. Central Sleep Apnea Is Independently Associated with Abnormal PTFV$_1$

Respiratory and sleep characteristics are shown in Table 2. The Epworth Sleepiness Scale score reflecting the daytime sleepiness was within the normal range in both groups (Table 2). Interestingly, in patients with abnormal PTFV$_1$, SDB was highly prevalent (86.7%), with significantly more patients exhibiting central but not obstructive sleep apnea (Table 2). In contrast, only a minority of patients with normal PTFV$_1$ had SDB (42.5%) and...
if so, a majority was obstructive (Table 2). Moreover, central (cAHI) but not obstructive (oAHI) apnea events were significantly associated with the magnitude of PTFV1 (Table 3). Importantly, the extent of oxygen desaturation (ODI) was an even stronger predictor of the extent of PTFV1 than that of the frequency of central apneas ($R^2 = 0.268$, Table 3). In contrast to this association, the mean arterial oxygen saturation was similar in both groups. There was a trend towards lower minimum arterial oxygen saturation in the group with patients with abnormal PTFV1 (85.74 ± 5.87 vs. 82.20 ± 6.09, $p = 0.055$) (Table 2).

Table 2. Respiratory and sleep characteristics.

|                     | Normal PTFV1 ($n = 40$) | Abnormal PTFV1 ($n = 16$) |       |       |       |
|---------------------|-------------------------|---------------------------|-------|-------|-------|
|                     | Mean                    | SD                        | Mean  | SD    | $p$   |
| SDB [%]             | 17 (42.5%)              | n.a.                      | 13 (86.7%) | n.a. | 0.003 Chi |
| -OSA [%]            | 10 (25.6%)              | n.a.                      | 6 (40%) | n.a. | 0.333 F |
| -CSA [%]            | 7 (17.9%)               | n.a.                      | 7 (46.7%) | n.a. | 0.043 F |
| AHI [h-1]           | 14.64 ± 13.91           | 36.14 ± 24.87             |       |       | <0.001 T |
| oAHI [h-1]          | 8.10 ± 8.16             | 12.82 ± 10.43             |       |       | 0.084 T |
| cAHI [h-1]          | 6.75 ± 9.55             | 23.32 ± 27.03             |       |       | 0.034 W |
| ODI [h-1]           | 11.39 ± 9.88            | 28.77 ± 23.69             |       |       | 0.018 W |
| SaO2 mean %         | 93.18 ± 2.26            | 93.00 ± 1.73              |       |       | 0.783 T |
| SaO2 min %          | 85.74 ± 5.87            | 82.20 ± 6.09              |       |       | 0.055 T |
| Sleep efficiency %  | 72.15 ± 16.25           | 69.95 ± 12.77             |       |       | 0.653 T |
| REM %               | 16.07 ± 6.17            | 14.13 ± 7.23              |       |       | 0.327 T |
| ESS                 | 7.32 ± 4.57             | 5.75 ± 2.60               |       |       | 0.147 W |

AHI: apnea-hypopnea-index; CSA: central sleep apnea; ESS: Epworth Sleepiness Scale score; ODI: oxygen desaturation index; OSA: obstructive sleep apnea; PTFV1: P wave terminal force in lead (abnormal ≥ 4000 µV*ms); REM: % of total sleep time spent in rapid eye movement sleep stage; SD: standard deviation; SaO2: arterial oxygen saturation; SDB: sleep-disordered breathing; Bold values mean statistical significance calculated by the two-sided Student’s t-test(T), Welch’s t-test(W), chi-square test(Chi) or Fischer’s exact test(F).

Table 3. Univariate linear regression of PTFV1.

| PTFV1 [µV·ms] | B               | 95% CI            | $R^2$ (adj.) | $p$ Value |
|---------------|-----------------|-------------------|--------------|-----------|
| ODI [h-1]     | 68.116          | 35.992 to 100.240 | 0.268        | <0.001    |
| AHI [h-1]     | 48.845          | 22.644 to 75.045  | 0.197        | <0.001    |
| cAHI [h-1]    | 46.810          | 15.375 to 78.246  | 0.128        | 0.004     |
| oAHI [h-1]    | 56.127          | -7.940 to 120.194 | 0.039        | 0.085     |
| NT-proBNP at discharge [pg/mL] | 0.628 | 0.109 to 1.148 | 0.097 | 0.019 |
| LV EF [%]     | -60.863         | -132.377 to 10.651| 0.036        | 0.094     |
| Age [y]       | 47.404          | -9.450 to 104.258 | 0.032        | 0.100     |
| eGFR [mL·min$^{-1}$·1.73 m$^{-2}$] | -23.099     | -51.033 to 4.845  | 0.032        | 0.103     |
| RR sys [mmHg] | 19.564          | -8.311 to 47.438  | 0.018        | 0.165     |
| BMI [kg/m$^2$] | 87.580          | -88.265 to 263.446| <0.001       | 0.322     |
| Trop I max [ng/mL] | 3.950   | -4.516 to 12.416 | -0.002       | 0.353     |
| Systolic LA area | -71.394     | -239.042 to 96.255| -0.006       | 0.395     |
| CK max [U/l]  | 0.132           | -0.276 to 0.540    | -0.011       | 0.518     |
| Smoking       | 402.290         | -943.843 to 1748.422| -0.012       | 0.551     |
| Male sex      | -303.380        | -1741.292 to 1134.532| -0.015       | 0.674     |
| Diabetes mellitus | 251.791 | -1286.227 to 1799.809| -0.017       | 0.745     |
| LA FAC [%]    | -10.620         | -85.278 to 64.038  | -0.022       | 0.775     |

AHI: apnea-hypopnea-index; BMI: body mass index; BNP: brain natriuretic peptide; CI: confidence interval; CK: creatine kinase; EF: ejection fraction; eGFR: estimated glomerular filtration rate; FAC: fractional area change; LA: left atrium; LV: left ventricle; ODI: oxygen desaturation index; PTFV1: P wave terminal force in lead V1; RA: right atrium; RRsys: systolic blood pressure; Trop: Troponin I; Bold values mean statistical significance.
To test for possible confounding, multivariate linear regression was performed. The association of both ODI and cAHI with the magnitude of PTFV$_1$ remained significant after inclusion of important co-factors, such as age, LVEF, eGFR, and NT-proBNP at discharge. Importantly, the associations of both ODI and cAHI were also independent from obstructive apnea events. For cAHI, $R^2$ was 0.256 (adj. $R^2 = 0.186$; $p = 0.014$, Table 4), and for ODI, $R^2$ was 0.408 (adj. $R^2 = 0.317$; $p = 0.002$, Table 4).

Table 4. Multivariate linear regression of PTFV$_1$.

| Model 1 (with ODI) | Model 2 (with AHI) | Model 3 (with cAHI) |
|-------------------|-------------------|-------------------|
| **PTFV$_1$ [$\mu$V*ms]** | **$B^*$ [95% CI]** | **$B^*$ [95% CI]** | **$B^*$ [95% CI]** |
| ODI [h$^{-1}$] | 65.619 | 0.001 | | | |
| | [29.717 to 101.522] | | | | |
| AHI [h$^{-1}$] | 45.170 | 0.009 | | | |
| | [11.903 to 78.437] | | | | |
| cAHI [h$^{-1}$] | 45.172 | 0.009 | | | |
| | [11.905 to 78.440] | | | | |
| oAHI [h$^{-1}$] | −7.992 | 0.822 | | | |
| | [−27.626 to 101.983] | | | | |
| NT-proBNP at discharge [pg/mL] | 0.402 | 0.146 | | | |
| | [−0.146 to 0.950] | | | | |
| LV EF [%] | −50.472 | 0.166 | | | |
| | [−122.825 to 21.881] | | | | |
| Age [y] | −40.917 | 0.323 | | | |
| | [−123.642 to 41.808] | | | | |
| eGFR [mL*min$^{-1} 1.73 m^{-2}$] | −30.710 | 0.102 | | | |
| | [−67.831 to 6.411] | | | | |

AHI: apnea-hypopnea-index; CI: confidence interval; EF: ejection fraction; eGFR: estimated glomerular filtration rate; LV: left ventricle; NT-proBNP: N-terminal pro-B-type natriuretic peptide; ODI: oxygen desaturation index; PTFV$_1$: P wave terminal force in lead V$_1$; Bold values mean statistical significance, $^*$ beta coefficient, $^# p$ value.

3.3. PTFV$_1$ as a Diagnostic Marker for Predicting Sleep-Disordered Breathing

Univariate linear regression for AHI indicated that beside PTFV$_1$, BMI, NT-proBNP at discharge, systolic LA area, LVEF, and smoking status may correlate with apnea and hypopnea events. Strikingly, after incorporation of these factors into a multivariate linear regression model, only PTFV$_1$ significantly correlated with the magnitude of AHI (model 1, $R^2 = 0.326$ (adj. $R^2 = 0.213$); $p = 0.021$, Table 5). Similarly, after dichotomizing PTFV$_1$ into normal and abnormal, the presence of an abnormal PTFV$_1$ significantly predicted a more severe AHI in multivariate linear regression (model 2, B 21.495; CI [9.097, 20.193]; $p < 0.001$, Table 5).
Interestingly, no meaningful interactions were found with myocardial ischemia markers, such as troponin I or creatine kinase and abnormal PTFV₁ (Table 5), despite the higher prevalence of STEMI in the group with normal PTFV₁ (92.5% vs. 68.8%).

4. Discussion

In the present study, we investigated the relationship between SDB and SDB-related hypoxia with PTFV₁ in patients presenting with acute myocardial infarction.

We show here that nocturnal oxygen desaturation in SDB was associated with atrial electrical remodeling measured by abnormal PTFV₁ in patients with first-time AMI independent of ventricular function. Moreover, we propose PTFV₁ as a broadly available clinical marker for increased SDB risk in cardiovascular patients.
4.1. Possible Mechanisms for an Abnormal PTFV₁ in SDB

We report here a prevalence of SDB in patients with AMI of 54.5% with 25.9% central sleep apnea, which closely resembles previous data reporting an SDB prevalence ranging from 33.1% to 50% with about 20% central sleep apnea [4,20,21].

CSA in patients with heart failure is commonly explained by pulmonary congestion due to ventricular overload with consequent autonomic triggered tachypnea and subsequently reduced PaCO₂, which results in the occurrence of an apnea episode. This leads to accumulation of PaCO₂ and restoration of respiratory effort. However, CSA could also have pathophysiologica effects on the heart that are independent of ventricular dysfunction. A small study by Lanfranchi showed that severe CSA was associated with increased arrhythmic risk without association to the severity of hemodynamic impairment due to LV dysfunction. This association may be caused by CSA-mediated nocturnal desaturations, which have been proposed as a consequence of impaired autonomic control and disturbed chemoreflex–baroreflex interactions frequently found in CSA [22].

Interestingly, for patients with AMI, a high probability of CSA-dependent nocturnal oxygen desaturations has already been shown [21]. We observe here a high ODI among patients with AMI, which strongly correlates with abnormal PTFV₁ independent from many clinical covariates including left ventricular ejection fraction, which might provide an interesting insight into the pathogenesis of atrial remodeling and the development of atrial cardiomyopathy.

There is growing evidence that atrial structural and electrical remodeling even in the absence of atrial fibrillation can also increase the risk of clot formation and cardioembolic stroke. The latter alterations, also known as atrial cardiomyopathy, expand the traditional view of clot formation [13,23–25]. In fact, the ongoing ARCADIA trial is investigating the optimal anticoagulant therapy (anticoagulant therapy vs. standard ASA therapy) in patients with cryptogenic stroke and atrial cardiomyopathy and specifically uses an abnormal PTFV₁ as an additional clinical marker for atrial cardiomyopathy [26]. We have recently shown that an abnormal PTFV₁ is linked to increased CaMKII-dependent atrial pro-arrhythmic activity and atrial contractile dysfunction [4,19]. Atrial CaMKII is a key regulator of cardiac excitation-contraction coupling and plays an important role in triggering arrhythmias and atrial electrical remodeling [4]. Beside arrhythmias, it is tempting to speculate that CaMKII-dependent atrial contractile dysfunction may also be involved in atrial clot formation even in the absence of atrial fibrillation. Thus, CaMKII may be a promising novel treatment target for patients with atrial cardiomyopathy. In this context, the mechanisms of CaMKII activation should be elucidated in more detail. Beside the canonical Ca-dependent activation, CaMKII has been shown to be activated by increased amounts of reactive oxygen species (ROS) [27,28]. SDB-related intermittent hypoxia with consequently increased generation of ROS [29] may result in activation of atrial CaMKII and CaMKII-dependent electrical remodeling manifesting as abnormal PTFV₁, but this remains to be shown. Additionally, only little is known about SDB-related hypoxia and electrical atrial remodeling before atrial fibrillation emerges.

Interestingly, in patients with abnormal PTFV₁, atrial fibrosis was less likely to be observed [19], indicating that the generation of abnormal PTFV₁ may require functional cardiomyocytes.

Beside SDB and SDB-related hypoxia, acute myocardial infarction may also lead to acute ventricular contractile dysfunction, which could also contribute to atrial functional and/or structural alterations.

A longitudinal study recently demonstrated that increasing NT-proBNP levels were associated with LA remodeling and LA contractile dysfunction [30]. In the current study, we observed significantly higher NT-proBNP levels at discharge and lower LV EF in the group with abnormal PTFV₁, which may contribute to impaired atrial function and abnormal PTFV₁. In accordance, we recently demonstrated a significant negative correlation between functional LA parameters, such as LA conduit and reservoir function, as measured by feature-tracking (FT) strain analysis of cardiac magnetic resonance (CMR) images, and
the extent of PTFV₁ [19]. In contrast to atrial strain, volumetric MRI parameters for LA function such as systolic LA area or LA FAC did not show a significant association with PTFV₁ in the present study, which agrees with previous studies [31,32].

On the other hand, multivariate linear regression analysis revealed that neither higher NT-proBNP levels nor lower LVEF were significantly associated with the magnitude of PTFV₁ if SDB and SDB-related hypoxia were also incorporated in the multivariate model. This suggests that ventricular contractile dysfunction is unlikely to contribute decisively to the extent of PTFV₁, at least when there is concomitant SDB.

Consistent with this, in the current study, there was also no association of PTFV₁ with acute ischemia markers (creatinine kinase, troponin I), which may correlate with infarct size and affect LV function. In addition to the possible subordinate role of LV dysfunction for PTFV₁, an explanatory approach could also be that a proportion of patients were protected from more extensive infarct-associated ventricular myocardial injury by ischemic preconditioning due to the repetitive SDB-associated hypoxia, which has been shown previously [33]. However, the latter phenomenon should be interpreted with caution and cannot be generalized to all patients after AMI, because the healing process, as measured by myocardial salvage and reduction in infarct size, was worse in patients with SDB within three months after AMI [34]. In addition, patients with AMI and SDB showed worse hospital outcomes [21,35,36]. Regardless of a possible protective or detrimental role of SDB for ventricular injury after AMI, the role of ventricular injury for atrial remodeling and the extent of PTFV₁ may be less important, as discussed above.

4.2. PTFV₁ as a Diagnostic Marker for SDB and SDB-Related Arrhythmias

It has been found that patients with SDB especially CSA have higher severity of ACS and worse prognosis with longer hospital stay and more complications during hospitalization [21]. However, a clinical marker identifying patients at highest risk is lacking. In our cohort, oxygen desaturation index as a measure of nocturnal desaturation was significantly associated with abnormal PTFV₁. Therefore, measurement of PTFV₁ may be a simple and cost-effective tool for stratifying patients admitted to the hospital with a first-time AMI. Measurement of PTFV₁ was highly reliable in different observers (Table A1). Therefore, we suggest that all patients with abnormal PTFV₁ should receive PSG and be stratified according to their SDB risk for follow-up care.

Unfortunately, CPAP therapy may be without benefit for patients with sleep apnea [7–10], so new treatment options are urgently needed. We have recently shown that increased CaMKII activity is significantly associated with abnormal PTFV₁ [19]. Currently, several CaMKII inhibitors are under preclinical investigation [37]. One could speculate that abnormal PTFV₁ might help in selecting patients who could benefit from specific pharmacological treatment, such as CaMKII inhibition.

4.3. Limitations

This was a cross-sectional study at a single center with a relatively small sample size that was not designed to examine long-term follow-up of clinical endpoints. In addition, we do not know whether the abnormal PTFV₁ we detected at the time of myocardial infarction is a transient phenomenon or persists over time. Larger studies are needed to validate our findings and to investigate the impact on cardiac arrhythmias and serious adverse cardiac events including heart failure exacerbations. Moreover, the definition of the negative part of the P-wave based on the isoelectric line in a slightly rising PR segment is sometimes difficult. However, the interobserver variability ICC for PTFV₁ measurements in this study showed very good accuracy (ICC 0.888; lower CI 0.647; upper CI 0.951, Table A1).

5. Conclusions

This study shows that abnormal PTFV₁ is tightly linked to SDB and especially to central instead of obstructive sleep apnea. Therefore, we hypothesize that atrial dysfunction expressed as abnormal PTFV₁ is caused by stimulation of ROS-dependent pathways due
to intermittent hypoxia represented here predominantly in CSA independent of ventricular function.

We show that the severity of SDB can be easily recognized by PTFV$_1$. This ubiquitously available ECG parameter may thus be a simple and cost-effective tool to stratify patients admitted to hospital with first-time AMI for further PSG. Therefore, all patients with abnormal PTFV$_1$ should obtain PSG and be stratified for follow-up care.

**Author Contributions:** Conceptualization, J.P. and S.W.; methodology, J.P.; software, J.P. and M.W.; validation, J.P., M.W. and S.W.; formal analysis, J.P. and S.W.; investigation, J.P., M.W., C.F., K.D., O.W.H., F.P.; resources, S.B., L.S.M., M.A.; data curation, S.W.; writing—original draft preparation, J.P.; writing—review and editing, M.W. and S.W.; visualization, J.P.; supervision, S.W.; project administration, S.W.; funding acquisition, M.A. and S.W. All authors have read and agreed to the published version of the manuscript.

**Funding:** M.W. and C.F. are supported by the local ReForM-program. M.A. received grants and personal fees from Philips Respironics (Murrysville, PA 15668), grants and personal fees from ResMed Germany (Martinsried, Germany), grants from the ResMed Foundation (La Jolla, CA 92037), personal fees from Boehringer-Ingelheim, personal fees from Novartis, personal fees from Bresotec, personal fees from NRI, outside the submitted work. S.W. is funded by DFG grants WA 2539/7-1, and 8-1. LSM is funded by DFG grants MA 1982/7-1. SW and LSM are also supported by the DFG SFB 1350 grant (Project Number 387509280, TPA6). M.A. received grant support from the Else-Kröener Fresenius Foundation (2018_A159). CF received a grant from the German Heart Foundation/German Foundation of Heart Research (F/15/20).

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital Regensburg (Regensburg, 08-151).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study will be shared on reasonable request to the corresponding author. The data are not publicly available due to privacy restrictions.

**Conflicts of Interest:** The authors declare no conflict of interest.

### Appendix A

#### Table A1. Reproducibility of PTFV$_1$.

| Inter-Observer Reproducibility | ICC  | CI$_{lower}$ | CI$_{upper}$ |
|-------------------------------|------|-------------|-------------|
| PTFV$_1$                      | 0.888 | 0.647       | 0.951       |

ICC: intra class correlation; CI: confidence interval; PTFV$_1$: P wave terminal force in lead V$_1$.

### References

1. Uchôa, C.H.G.; Danzi-Soares, N.D.J.; Nunes, F.S.; de Souza, A.A.L.; Nerbass, F.B.; Pedrosa, R.P.; César, L.A.M.; Lorenzi-Filho, G.; Drager, L.F. Impact of OSA on cardiovascular events after coronary artery bypass surgery. *Chest* 2015, 147, 1352–1360. [CrossRef] [PubMed]

2. Oldenburg, O.; Lamp, B.; Faber, L.; Teschler, H.; Horstkotte, D.; Töpfer, V. Sleep-disordered breathing in patients with symptomatic heart failure. A contemporary study of prevalence in and characteristics of 700 patients. *Eur. J. Heart Fail.* 2007, 9, 251–257. [CrossRef]

3. Buchner, S.; Greimel, T.; Hetzenecker, A.; Luchner, A.; Hamer, O.W.; Debl, K.; Poschenrieder, F.; Fellner, C.; Riegger, G.A.; Pfeifer, M.; et al. Natural course of sleep-disordered breathing after acute myocardial infarction. *Eur. Respir. J.* 2012, 40, 1173–1179. [CrossRef]

4. Lebek, S.; Pichler, K.; Reuthner, K.; Trum, M.; Tafelmeier, M.; Mustroph, J.; Camboni, D.; Rupprecht, L.; Schmid, C.; Maier, L.S.; et al. Enhanced CaMKII-Dependent Late INa Induces Atrial Proarrhythmic Activity in Patients with Sleep-Disordered Breathing. *Circ. Res.* 2020, 126, 603–615. [CrossRef]
27. Wagner, S.; Ruff, H.M.; Weber, S.L.; Bellmann, S.; Sowa, T.; Schulte, T.; Anderson, M.E.; Grandi, E.; Bers, D.; Backs, J.; et al. Reactive oxygen species-activated Ca/calmodulin kinase IIδ is required for late INa augmentation leading to cellular Na and Ca overload. *Circ. Res.* 2011, 108, 555–565. [CrossRef] [PubMed]

28. Erickson, J.R.; Joiner, M.-L.A.; Guan, X.; Kutschke, W.; Yang, J.; Oddis, C.V.; Bartlett, R.K.; Lowe, J.S.; O’Donnell, S.E.; Aykin-Burns, N.; et al. A Dynamic Pathway for Calcium-Independent Activation of CaMKII by Methionine Oxidation. *Cell* 2008, 133, 462–474. [CrossRef]

29. Dewan, N.A.; Nieto, F.J.; Somers, V.K. Intermittent Hypoxemia and OSA Implications for Comorbidities. *Chest* 2015, 147, 266–274. [CrossRef]

30. Varadarajan, V.; Ambale-Venkatesh, B.; Hong, S.Y.; Habibi, M.; Ashikaga, H.; Wu, C.O.; Chen, L.Y.; Heckbert, S.R.; Bluemke, D.A.; Lima, J.A.C. Association of Longitudinal Changes in NT-proBNP With Changes in Left Atrial Volume and Function: MESA. *Am. J. Hypertens.* 2021, 34, 626–635. [CrossRef]

31. Petersson, R.; Berge, H.M.; Gjerdalen, G.F.; Carlson, J.; Holmqvist, F.; Steine, K.; Platonov, P.G. P-wave morphology is unaffected by atrial size: A study in healthy athletes. *Ann. Noninvasive Electrocardiol.* 2014, 19, 366–373. [CrossRef]

32. Tsao, C.W.; Josephson, M.E.; Hauser, T.H.; O’Halloran, T.D.; Agarwal, A.; Manning, W.J.; Yoon, S.B. Accuracy of electrocardiographic criteria for atrial enlargement: Validation with cardiovascular magnetic resonance. *J. Cardiovasc. Magn. Reson.* 2008, 10, 7. [CrossRef] [PubMed]

33. Shah, N.; Redline, S.; Yaggi, H.K.; Wu, R.; Zhao, C.G.; Ostfeld, R.; Menegus, M.; Tracy, D.; Brush, E.; Appel, W.D.; et al. Obstructive sleep apnea and acute myocardial infarction severity: Ischemic preconditioning? *Sleep Breath.* 2013, 17, 819–826. [CrossRef] [PubMed]

34. Buchner, S.; Satzl, A.; Debl, K.; Hetzenecker, A.; Luchner, A.; Husser, O.; Hamer, O.W.; Poschenrieder, F.; Fellner, C.; Zeman, F.; et al. Impact of sleep-disordered breathing on myocardial salvage and infarct size in patients with acute myocardial infarction. *Eur. Hear. J.* 2014, 35, 192–199. [CrossRef] [PubMed]

35. Lee, C.-H.; Khoo, S.-M.; Chan, Y.Y.M.; Wong, H.-B.; Low, A.F.; Phua, Q.-H.; Richards, A.M.; Tan, H.-C.; Yeo, T.-C. Severe obstructive sleep apnea and outcomes following myocardial infarction. *J. Clin. Sleep Med.* 2011, 7, 616–621. [CrossRef] [PubMed]

36. Correia, L.C.L.; Souza, A.C.; Garcia, G.; Sabino, M.; Brito, M.; Maraux, M.; Rabelo, M.M.N.; Esteves, J.P. Obstructive sleep apnea affects hospital outcomes of patients with non-ST-elevation acute coronary syndromes. *SLEEP* 2012, 35, 1241–1245. [CrossRef]

37. Lebek, S.; Ploßl, A.; Baier, M.; Mustroph, J.; Tarnowski, D.; Lücht, C.; Schopka, S.; Flörchinger, B.; Schmid, C.; Zausig, Y.; et al. The novel CaMKII inhibitor GS-680 reduces diastolic SR Ca leak and prevents CaMKII-dependent pro-arrhythmic activity. *J. Mol. Cell. Cardiol.* 2018, 118, 159–168. [CrossRef]