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Effect of adaptive servo-ventilation on circulating biomarkers in patients with sleep apnoea after myocardial infarction: results of an ancillary analysis of the randomised TEAM-ASV I trial

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ABSTRACT

Background: The Treatment of sleep apnoea Early After Myocardial infarction with Adaptive Servo-Ventilation (TEAM-ASV I) trial showed that adding adaptive servo-ventilation (ASV) to treat sleep-disordered breathing (SDB) early after acute myocardial infarction (AMI) improved myocardial salvage and decreased infarct size. It is purported that ASV may mitigate the inflammatory response, cardiac congestion, or fibrosis, but evidence supporting this assertion is sparse.

Methods: This ancillary analysis of the multicentre, randomised, open-label TEAM-ASV I trial assessed patients with analysable blood samples at baseline and 12-week follow-up. Patients were randomised to early ASV treatment in addition to standard care for AMI and standard care alone (control). Changes in the levels of circulating biomarkers of inflammation (high-sensitivity C-reactive protein [hs-CRP], fibrinogen, interleukin [IL]-6, and interleukin-33 receptor [IL-33R]), fluid overload (N-terminal pro-B-type natriuretic peptide [NT-proBNP] and antigen carbohydrate [CA]-125), and fibrosis (procollagen III type aminoterminal propeptide [PIIINP] and matrix metalloproteinase [MMP]-9) were compared between the ASV and control groups.

Results: Forty SDB patients were analysed. The reduction in IL-33R was greater in the control group than in the ASV group (−1.94 [-3.88, 1.56] versus −4.30 [-6.46, −2.02] ng·ml^{-1}). However, changes in other biomarkers of inflammation (hs-CRP, fibrinogen, and IL-6), fluid overload (NT-proBNP and CA-125), and fibrosis (PIIINP and MMP-9) were similar in both groups.

Conclusions: This ancillary analysis of TEAM-ASV I does not support that treatment of SDB in the early phase after AMI with ASV has a clinically relevant short-term effect on biomarkers of inflammation, fluid overload, or fibrosis. Further studies are warranted to explain how early treatment with ASV results in increased myocardial salvage after AMI beyond the effects of SDB treatment on hemodynamics and oxygen demand–supply mismatch.

Clinical trial registration: NCT02093377.

1. Introduction

Despite advances in the treatment of acute myocardial infarction (AMI) with percutaneous coronary intervention (PCI) and optimal medical treatment (OMT), one in ten patients after first-time ST-elevation AMI still develop heart failure, with approximately half of the patients having a reduced ejection fraction and half having a mildly reduced or normal left ventricular ejection fraction [1]. Importantly, up to 13 % of patients are hospitalized or die approximately 3 years after AMI [1,2]. The newly introduced treatment option with adaptive

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servo-ventilation (ASV) has been shown in a proof-of-concept study to significantly reduce infarct size in patients with first-time AMI and sleep-disordered breathing (SDB) [3]. If such findings can be confirmed in a phase III trial, they may greatly impact the treatment of AMI, especially considering that SDB affects up to two-thirds of individuals with AMI [4,5].

Circulating biomarkers help us observe the function of the heart and other organs over time and predict outcomes [6–8]. During the acute stage of AMI, inflammatory processes accompany infarction en route to tissue rearrangement, whereby a prolonged severe inflammatory response may induce adverse left ventricular remodelling and ultimately lead to heart failure [9,10]. Increased levels of interleukin (IL)-6 and high-sensitivity C-reactive protein (hs-CRP) reflect an excessive inflammatory response and simultaneously predict a worse outcome [7,10,11]. The thrombotic occluded heart vessel promotes tissue damage at the infarct site, which in turn results in disturbances in cardiac kinetics and consequently in volume overload [12]. In addition to N-terminal pro-B-type natriuretic peptide (NT-proBNP) [13], antigen carbohydrate (CA)-125 has been proven to be a reliable biomarker of fluid overload and a predictor of mortality after AMI [14,15]. Finally, cardiomyocytes, endothelial cells, and fibroblasts orchestrate complex interactions and initiate myocardial healing and scar formation. The impaired collagen turnover accompanying the degradation of former tissue at the infarct size replaced by a newly formed scar is displayed by increased levels of an extension amino-terminal propeptide of type III procollagen (PIIINP) and matrix metalloproteinase (MMP)-9, both of which are associated with poor clinical outcomes [7,10,16–18]. Interestingly, the interleukin-33 receptor (IL33R), also known as soluble ST2, is associated with inflammation, cardiac congestion, and tissue fibrosis and provides prognostic rather than diagnostic information [7,19].

Many negative influences are to be found in SDB, be it acute intermittent hypoxemia, sleep arousals, sympathetic system activation, increased intrathoracic cardiac workload, low-grade inflammation, endothelial dysfunction, a prothrombotic milieu, or intermittent hypoxemia in the context of increased cardiac oxygen demand due to increased cardiac workload [20,21]. As a consequence, larger infarct size, reduced left ventricular function, and adverse left ventricular remodelling emerge [22,23]. Adaptive servo-ventilation (ASV) is an effective treatment option for patients with SDB with obstructive sleep apnoea (OSA) and central sleep apnoea (CSA) [24–26].

We hypothesized that if treatment with ASV prevents sleep disturbances, it would also mediate the alleviation of the inflammatory response, cardiac congestion, and fibrosis. Therefore, we sought to evaluate whether treatment of SDB early after AMI with ASV affects circulating biomarkers of inflammation, fluid overload, and fibrosis.

2. Methods

2.1. Study design

This study is an ancillary analysis of the TEAM-ASV I trial (NCT02093377), which was an investigator-initiated, randomised, open-label, parallel proof-of-concept study with blinded assessment of outcomes recruiting patients from February 2014 to August 2020. The study population and inclusion/exclusion criteria have been previously described in detail [27]. In brief, all screened patients (n = 171, Fig. S1) admitted to one of three hospitals in Germany with a first AMI with ST elevation or acute occlusion of a coronary artery, had undergone primarily successful percutaneous coronary intervention (PCI) within 24 h of symptom onset. Only patients with SDB (apnoea-hypopnoea index [AHI] $\geqslant$15 events·h^{-1}) were eligible for randomisation to the ASV (AutoSet™ CS–PaceWave, ResMed Corp., San Diego, CA, USA) or control group. Only patients with analysable blood samples at baseline and 12-week follow-up were assessed.

All patients provided written informed consent. The trial was approved by the institutional ethics committee (Ethikkommission der Universität Regensburg, approval number 11–101-0229) and conducted in accordance with the Declaration of Helsinki.

2.2. Laboratory testing

Venous blood samples were drawn during the first 2 h after morning awakening, 3–5 days after PCI, but before treatment with ASV and at the 12-week follow-up. The plasma samples were shipped under refrigeration and stored at −80 °C in one centre. The levels of human IL-6, IL33-R, and MMP-9 were then analysed in available plasma samples using a commercially available ELISA kit (R&D Systems DuoSets). The assay range of the ELISA kit for IL-6 in undiluted plasma was 9.4–600 pg ml^{-1}. The plasma was diluted 100x for IL-33R and 500x to measure the levels of MMP-9, with an assay range of 31.2–2000 pg ml^{-1}. All values were calculated as the mean of two different measurements from the same panel to account for intra-assay variabilities. Hs-CRP, fibrinogen, NT-proBNP, CA-125, and PIIINP were measured directly after blood sampling in an assigned central laboratory of each centre separately. Notably, PIIINP was quantified via radioimmunoassay (RIA-gnost® PIIIP, Cisbio Bioassays) and an ELISA kit (Cisbio Bioassays) due to the discontinuation of the radioimmunoassay method in one centre. Reference values, according to Cisbio Bioassays, ranged from 0.3 to 0.8 U ml^{-1}. According to the manufacturer's recommendation, all values measured with the ELISA kit (µg·l^{-1}) were divided by a factor of 8 for conversion in units of the enzyme's catalytic activity (U·ml^{-1}).

2.3. Polygraphy

Polygraphy (SOMNOscreenTM plus RC, SOMNOmedics, Randersacker, Germany) was performed within 3 days after PCI and at the 12-week follow-up visit in both groups [3,27]. The cardiorespiratory study consisted of a pressure cannula, thoracic and abdominal respiratory effort measures, oxygen saturation, ECG, recording of body position, light detection, and a patient marker. All the data were analysed in the central lab to ensure consistency and quality. Apnoeas and hypopnoeas were scored according to the American Academy of Sleep Medicine (AASM) 2012 criteria by one experienced sleep technician blinded to the clinical data [27]. SDB was defined as an apnoea-hypopnoea index (AHI) $\geqslant$15 events·h^{-1} based on total recording time. The patients were further categorized as predominantly OSA ($\geqslant$ 50 % of apnoeas obstructive) or predominantly CSA (<50 % of apnoeas obstructive).

2.4. Outcomes

The primary outcome of this ancillary analysis is the change in circulating levels of biomarkers (hs-CRP, fibrinogen, IL-6, IL-33R, NT-proBNP, CA-125, PIIINP, and MMP-9) between baseline and 12 weeks in patients randomised to early ASV treatment in addition to standard care for AMI patients and standard care alone (control).

2.5. Statistical analysis

Differences in the circulating levels of biomarkers at baseline and 12 weeks were analysed using the Mann−Whitney *U* test. The Wilcoxon signed-rank test was performed to compare the results of the initial and repeated measurements. A subgroup analysis of individuals with average ASV usage of $\geqslant$4 h per night versus the control group was carried out to account for ASV adherence. In addition, subgroup analyses examining the effects of expiratory positive airway pressure (EPAP) in the ASV group versus the control group were performed. The high ($\geqslant$ 6.1 cmH_2O) and low (<6.1 cmH_2O) EPAP groups were defined according to the median EPAP. The association between expiratory positive airway pressure (EPAP) and circulating biomarkers was assessed by Spearman's correlation. The Spearman correlation coefficient (r_s) indicates an association of ranks. Descriptive data are expressed as the means ± standard deviations (SD), medians with interquartile ranges (IQR), or

frequencies and percentages of each category. The sample size of this ancillary study was restricted to available measurements of the local central laboratory or collected blood samples and not to a prospective effect size calculation. Two-sided $p \leqslant 0.05$ was defined as statistically significant. Statistical analysis was performed in SPSS (SPSS Statistics for Mac OS, Version 29.0 Armonk, NY: IBM Corp.) and GraphPad Prism (Version 9.51 for Windows, GraphPad Software, La Jolla California USA).

3. Results

3.1. Study population

Seventy-nine patients with first-time AMI after successful revascularization were enrolled and further randomised to the ASV (n = 42) or control (n = 37) group. There were no serious treatment-related adverse events during the study. Analysable blood samples, both at baseline and at 12 weeks, were available for 20 patients in the ASV group and 20 patients in the control group (Fig. 1). The ASV group did not differ from the control group with respect to demographics, hemodynamic parameters, comorbidities, key AMI-specific parameters or medication at discharge (Table 1). The study population was predominantly male (80 %), with a mean age of 60 ± 9 years.

Polygraphy and CMR findings at baseline were comparable between the two groups, except for CSA, which was numerically more prevalent in the ASV group (Table 2). The mean AHI was 35.5 ± 19.7 h^{-1}, indicating predominantly severe sleep apnoea among participants. In general, the left ventricular ejection fraction was preserved (50 ± 11 %), with relative infarct size of 15 ± 7 (% left ventricular mass). Blood at baseline was drawn 3.5 ± 0.2 days after AMI and at 12 weeks. Analogous to the findings of the main TEAM-ASV I cohort [3], NT-proBNP and the glomerular filtration rate (GFR) were similar at baseline in both groups (Table 2).

3.2. Effect of ASV treatment on inflammation

Hs-CRP and fibrinogen declined in both groups, and this decline was similar in the ASV and control groups (Fig. 1, Table 3). Compared with that in the ASV group, the reduction of IL-33R in the control group was greater (Table 3, Fig. 1). The change in IL-6 was similar in the ASV and control groups (Table 3, Fig. 1).

Table 1
Baseline demographics and clinical characteristics of patients with paired blood sample data at baseline and at the 12-week follow-up.

	Total (n = 40)	ASV (n = 20)	Control (n = 20)
Age, years	60 ± 9	59 ± 10	61 ± 9
Body mass index, kg·m−2	30.8 ± 6.1	29.6 ± 3.3	32.0 ± 8.0
Male sex	32 (80 %)	16 (80 %)	16 (80 %)
Heart rate, beats·min^{-1}	74 ± 15	71 ± 13	77 ± 17
Systolic blood pressure, mmHg	119 ± 13	118 ± 12	120 ± 15
Diastolic blood pressure, mmHg	73 ± 9	72 ± 9	73 ± 10
Hypertension	26 (65 %)	12 (60 %)	14 (70 %)
Current smoker	17 (42.5 %)	8 (40 %)	9 (45 %)
Diabetes mellitus	6 (15 %)	3 (15 %)	3 (15 %)
Hypercholesterolaemia	19 (47.5 %)	9 (45 %)	12 (60 %)
Symptom-to-balloon time, h	4.1 (2.7–8.1)	3.6 (2.5–11.2)	4.8 (2.9–7.1)
Non-ST elevation	6 (15.4 %)	4 (20 %)	2 (10.5 %)
Culprit lesion			
Left main artery	1 (2.5 %)	1 (5 %)	0 (0 %)
LAD artery	24 (60 %)	12 (60 %)	12 (60 %)
Circumflex artery	9 (22.5 %)	6 (30 %)	3 (15 %)
Right coronary artery	25 (62.5 %)	12 (60 %)	13 (65 %)
TIMI flow before PCI			
Grade 0	32 (80 %)	16 (80 %)	16 (80 %)
Grade 1	6 (15 %)	2 (10 %)	4 (20 %)
Grade 2	2 (5 %)	2 (10 %)	0 (0 %)
TIMI flow after PCI			
Grade 2	4 (10 %)	0 (0 %)	4 (20 %)
Grade 3	36 (90 %)	20 (100 %)	16 (80 %)
Thrombus aspiration	8 (20 %)	3 (15 %)	5 (25 %)
Glycoprotein IIb/IIIa inhibitor	10 (25 %)	5 (25 %)	5 (25 %)
Medication at discharge			
Aspirin	38 (95 %)	20 (100 %)	18 (90 %)
ADP receptor inhibitor	39 (97.5 %)	20 (100 %)	19 (95 %)
β-blocker	32 (80 %)	17 (85 %)	15 (75 %)
ACE inhibitor/ARB	36 (90 %)	3 (15 %)	19 (95 %)
Statin	40 (100 %)	20 (100 %)	20 (100 %)
Spironolactone	15 (37.5 %)	5 (25 %)	10 (50 %)

The values are presented as the means ± standard deviations, medians [interquartile ranges], or numbers of patients (%).
ACE, angiotensin-converting enzyme; ADP, adenosine diphosphate; ARB, angiotensin receptor blocker; ASV, adaptive servo-ventilation; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

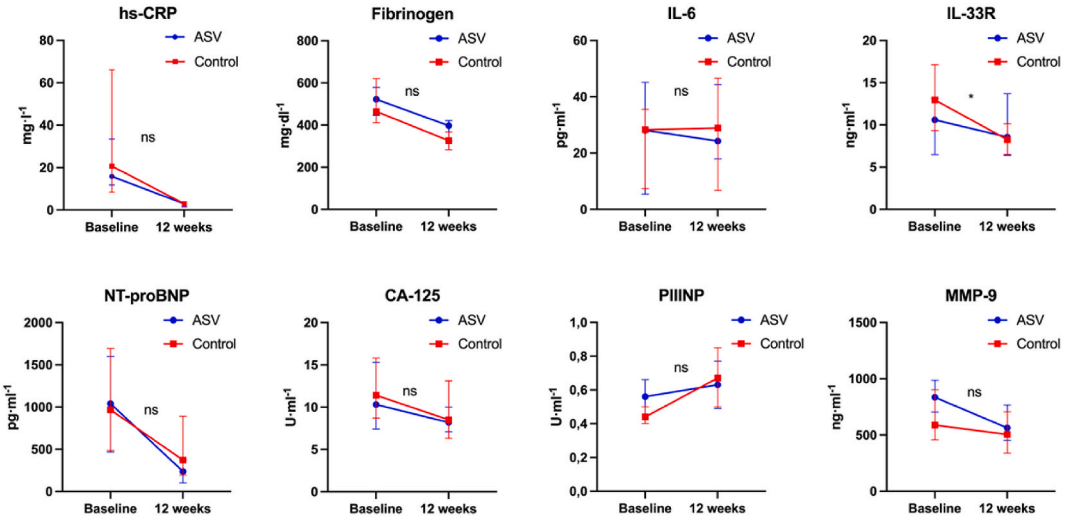

Fig. 1. Changes in circulating biomarkers between baseline and the 12-week follow-up. Only IL-33R decreased more in the control group than in the ASV group. ASV: adaptive servo-ventilation; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL33-R, interleukin-33 receptor; NT-proBNP, N-terminal pro B-type natriuretic peptide; CA-125, antigen carbohydrate-125; PIIINP, procollagen III type aminoterminal propeptide; MMP-9, matrix metalloproteinase-9.

Table 2
Polygraphy, CMR and blood work findings at baseline (evaluated patients).

	Total (n = 40)	ASV (n = 20)	Control (n = 20)
Polygraphy findings			
Apnoea-hypopnoea index, events·h^{-1}	35.5 ± 19.7	37.0 ± 21.4	34.1 ± 18.2
Apnoea index, events·h^{-1}	26.1 ± 19.9	26.7 ± 21.8	25.6 ± 18.4
Central apnoea index/apnoea index, %	41.9 ± 29.5	46.9 ± 29.5	37.0 ± 29.4
Central sleep apnoea	17 (43)	11 (55)	6 [30]
Oxygen desaturation index, events·h^{-1}	26.4 ± 20.0	28.4 ± 22.8	24.3 ± 17.0
Time with oxygen saturation <90 %, %TRT	11.5 ± 15.1	10.6 ± 13.4	12.5 ± 17.0
Minimum oxygen saturation, %	81.5 ± 6.6	82.7 ± 4.4	80.3 ± 8.1
Total recording time, h	7.9 ± 0.8	8.0 ± 0.8	7.8 ± 0.8
CMR findings			
Infarct size, %LVM	15 ± 7	16 ± 9	14 ± 6
LVEF, %	50 ± 11	51 ± 9	48 ± 12
Blood work			
NT-proBNP, ng·ml^{-1}	979 (486–1692)	1040 (467–1599)	967 (486–1694)
GFR, ml·min^{-1}·(1.73 m^2)$^{-1}$	71 (56–82)	69 (57–80)	75 (52–83)

The values are presented as the means ± standard deviations, medians [interquartile ranges], or numbers of patients (%). ASV, adaptive servo-ventilation; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume; LVESVI, left ventricular end-systolic volume; LVM: left ventricular mass; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TRT, total recording time.

3.3. Effects of ASV treatment on fluid overload

Despite the numerically lower levels of CA-125 after 12 weeks in both groups, no significant difference in the change in CA-125 was found between the ASV group and the control group (Table 3, Fig. 1). Furthermore, the change in NT-proBNP levels from baseline to 12 weeks was similar in both groups (Table 3, Fig. 1). In contrast, the level of IL-33R, a marker of fluid overload, decreased more in the control group, as indicated above.

3.4. Effects of ASV treatment on fibrosis

The levels of PIIINP increased at 12 weeks in both groups, but the change in PIIINP was similar (Table 3, Fig. 1). Furthermore, no relevant difference in the change in the levels of MMP-9 was observed across the groups (Table 3, Fig. 1).

3.5. Subgroup analysis based on ASV device usage

Eleven out of the 20 participants who were allocated to the ASV group showed average ASV usage of ⩾4 h per night at the 12-week follow-up. The levels of all measured biomarkers from baseline to the 12-week follow-up did not differ between the groups (Table S1). The levels of IL-33R decreased more in the control group. However, this difference was not significant ($p = 0.066$; Table S1).

3.6. Subgroup analysis of patients based on applied EPAP

In the high-EPAP subgroup, the level of IL-33R decreased more in the control group than in the ASV group (Table S2). In contrast, no difference in the change in IL-33R was observed in the low-EPAP subgroup (Table S2). IL-33R was strongly but not significantly correlated with higher levels of EPAP ($p = 0.10$, $r_s = 0.41$; Table S3). A similar trend was observed for CA-125 ($p = 0.08$, $r_s = 0.47$; Table S3).

4. Discussion

In this ancillary analysis of the TEAM-ASV I trial, we found that ASV treatment in the early phase after AMI in patients with SDB (be it OSA or CSA) did not show any consistent effect with respect to changes in circulating biomarkers of inflammation, fluid overload, or fibrosis over 12 weeks. In contrast to the low-EPAP subgroup, the high-EPAP subgroup showed a smaller decrease in IL-33R levels in comparison to the control group.

Our findings in AMI patients are in line with published literature regarding the role of positive airway pressure, such as CPAP or ASV treatment, on circulating biomarkers of inflammation, fluid overload, or fibrosis [28,29]. To date, the effects of ASV treatment have been studied in patients with central sleep apnoea and severe heart failure with a reduced ejection fraction but without AMI [30]. A substudy of the SERVE-HF trial assessed NT-proBNP, troponin I, troponin T, IL-33R, galactin-3, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), hs-CRP, and tumor necrosis factor (TNF)-α in patients with CSA and chronic heart failure but did not demonstrate any significant differences in changes in these biomarkers between the ASV group and the control group after 12 months [29] (Table 4).

Additionally, an ancillary biomarker analysis of the RICCADSA trial, which randomised patients with coronary artery disease (CAD) after successful revascularization [31] for continuous positive pressure therapy (CPAP), revealed no effect on the circulating levels of IL-6, IL-8, TNF-α, and hs-CRP over 12 months after revascularization [28] (Table 4).

Interestingly, another ancillary analysis of the RICCADSA trial revealed a possible detrimental effect of higher pressure applied on CPAP therapy due to lung hyperinflation, which in turn contributes to lung endothelial and epithelial inflammation [32].

Our results may strengthen this hypothesis because only the subgroup with high EPAP presented a smaller decrease in IL-33R than did the control group. Moreover, higher EPAP levels are strongly correlated with higher levels of IL-33R and CA-125, both of which are involved in the inflammatory response and cardiac congestion [14,33,34]. In addition, higher EPAP may indicate more severe and less easily controlled sleep apnoea events. However, this assumption warrants further investigation, as ASV therapy applies variable inspiratory pressure support, which differs from CPAP [27]. Interestingly, in a SERVE-HF substudy, of all 276 measured circulating protein biomarkers at baseline, IL-33R was identified as a biomarker of significant prognostic relevance if it was added to the best clinical model [35].

In view of the existing evidence from these two abovementioned randomised control trials, we assume that similar changes in circulating biomarkers in both groups over 12 weeks in the present study may be driven mostly by the natural post-AMI course and standard-care therapy followed by ASV treatment.

Some limitations should be noted. First, the TEAM-ASV I trial aimed to investigate the effect of ASV treatment on myocardial salvage index; therefore, the randomisation procedure was not designed to account for the dynamic course of baseline and follow-up values of biomarkers. Given the different dynamics of circulating biomarkers, peak values occur frequently 12–24 h after the onset of infarction, followed by a rapid reduction, as observed for IL-33R [19]. The IL-6 peak was reported

Table 3
Serum biomarkers of inflammation, volume overload, and fibrosis from baseline to 12 weeks.

	All (n = 40)		ASV (n = 20)		Control (n = 20)		
	Median (25 %, 75 %)	*n*	Median (25 %, 75 %)	*n*	Median (25 %, 75 %)	*n*	p
hs-CRP (mg·l^{-1})							
o Baseline	19.0 (11.5, 37.0)	*39*	15.8 (11.8, 33.5)	*20*	20.7 (8.4, 66.1)	*19*	
o 12 weeks	2.9 (1.6, 2.9)	*40*	2.9 (1.5, 2.9)	*20*	2.9 (2.1, 3.3)	*20*	
o **Change**	**−16.4 (-34.1, -5.8)**	***39***	**−12.3 (-32.5, -6.0)**	***20***	**−17.7 (-54.8, -5.5)**	***19***	**0.38**
P	<0.001		<0.001		<0.001		
Fibrinogen (g·l^{-1})							
o Baseline	487 (429, 589)	*37*	522 (446, 579)	*19*	464 (411, 621)	*18*	
o 12 weeks	346 (298, 420)	*39*	397 (324, 421)	*20*	326 (282, 367)	*19*	
o **Change**	**−150 (-211, -89)**	***36***	**−158 (-202, -92)**	***19***	**−128 (-243, -85)**	***17***	**0.80**
P	<0.001		<0.001		<0.001		
IL-6 (pg·ml^{-1})							
o Baseline	28.19 (6.39, 41.68)	*36*	28.08 (5.45, 45.11)	*19*	28.29 (7.34, 35.54)	*17*	
o 12 weeks	26.58 (7.38, 46.65)	*35*	24.28 (17.94, 44.25)	*17*	28.85 (6.72, 46.65)	*18*	
o **Change**	**1.22 (-10.40, 9.16)**	***33***	**−2.78 (-14.75, 9.16)**	***17***	**1.96 (-0.10, 11.36)**	***16***	**0.29**
P	0.62		0.52		0.11		
IL-33R (ng·ml^{-1})							
o Baseline	12.10 (8.58, 14.67)	*40*	10.59 (6.49, 13.12)	*20*	12.95 (9.33, 17.13)	*20*	
o 12 weeks	8.38 (6.51, 11.97)	*40*	8.56 (6.40, 13.69)	*20*	8.25 (6.51, 10.13)	*20*	
o **Change**	**−3.28 (-5.19, -0.79)**	***40***	**−1.94 (-3.88, 1.56)**	***20***	**−4.30 (-6.46, -2.02)**	***20***	**0.02**
p	0.002		0.35		<0.001		
NT-proBNP (pg·ml^{-1})							
o Baseline	979 (486, 1692)	*39*	1040 (467, 1599)	*20*	967 (489, 1694)	*19*	
o 12 weeks	314 (130, 457)	*40*	238 (103, 370)	*20*	372 (192, 890)	*20*	
o **Change**	**−714 (-1255, -302)**	***39***	**−714 (-1406, -265)**	***20***	**−714 (-1255, -302)**	***19***	**0.97**
P	<0.001		<0.001		<0.001		
CA-125 (nmol l^{-1})							
o Baseline	10.3 (7.8, 15.6)	*32*	10.3 (7.4, 15.3)	*17*	11.4 (8.7, 15.8)	*15*	
o 12 weeks	8.2 (6.3, 11.7)	*37*	8.2 (7.1, 10.0)	*17*	8.5 (6.3, 13.1)	*20*	
o **Change**	**−1.1 (-4.0, 0.5)**	***31***	**−1.0 (-4.1, 1.1)**	***16***	**−2.0 (-3.7, 0.2)**	***15***	**0.86**
p	0.051		0.18		0.20		
PIIINP (U·ml^{-1})							
o Baseline	0.50 (0.40, 0.61)	*36*	0.56 (0.40, 0.66)	*19*	0.44 (0.40, 0.50)	*17*	
o 12 weeks	0.65 (0.50, 0.83)	*39*	0.63 (0.49, 0.77)	*20*	0.67 (0.50, 0.85)	*19*	
o **Change**	**0.14 (0.00, 0.25)**	***35***	**0.14 (-0.08, 0.20)**	***19***	**0.16 (0.04, 0.26)**	***16***	**0.29**
P	<0.001		0.02		0.001		
MMP-9 (ng·ml^{-1})							
o Baseline	754 (550, 957)	*35*	836 (704, 987)	*18*	588 (457, 902)	*17*	
o 12 weeks	560 (415, 709)	*37*	564 (453, 767)	*19*	505 (339, 706)	*18*	
o **Change**	**−197 (-468, -56)**	***35***	**−194 (-462, -72)**	***18***	**−204 (-468, 69)**	***17***	**0.99**
p	0.004		0.03		0.07		

Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL33-R, interleukin-33 receptor; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CA-125, antigen carbohydrate-125; PIIINP, procollagen III type aminoterminal propeptide; MMP-9, matrix metalloproteinase-9.

to occur approximately 72 h after the onset of infarction [36]. A sequential pattern was found for PIIINP, with a peak occurring during the first 1–4 h and at days 3–5 [17,37], and a similar biphasic pattern of NT-proBNP was reported to occur in approximately half of the patients [13]. Moreover, for some biomarkers, there are no data on dynamics after AMI (CA-125, MMP-9) [15]. Second, some biomarkers were measured prospectively according to the study protocol in each centre separately and later unified to represent the same units. Some values were missing, conferring a potential selection bias in each analysis. Third, circulating biomarkers reflect synthesis throughout the organism and therefore cannot be restricted to the myocardium alone. Fourth, we used polygraphy rather than polysomnography for diagnosis and monitoring of ASV treatment, which is not the standard method and therefore may have limited accuracy. The results of the study should be

Table 4
Main characteristics and results of randomised trials with measurements of circulating biomarkers at baseline and follow-up.

Trial name	Nr. of Participants (Treatment/Control)	Phenotype of Patients	Type of SDB	Intervention	Follow-up (months)	Circulating Biomarkers	Overall Effect
TEAM-ASV I	20/20	STEMI/non-STEMI	OSA/CSA	ASV	3	hs-CRP, fibrinogen, IL-6, IL-33R, NT-proBNP, CA-125, PIIINP, MMP-9	neutral
SERVE-HF [29]	153/159	Severe chronic HFrEF	CSA	ASV	12	NT-proBNP, TnI, TnT, IL-33R, galactin-3, cystatin C, NGAL, hs-CRP, TNF-α	neutral
RICCADSA [28]	105/115	CAD (ca. 50 % AMI)	OSA	CPAP	12	IL-6, IL-8, TNF-α, hs-CRP	neutral

AMI, acute myocardial infarction; CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; IL33-R, interleukin-33 receptor; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CA-125, antigen carbohydrate-125; PIIINP, procollagen III type aminoterminal propeptide; MMP-9, matrix metalloproteinase-9; TNF-α, tumor necrosis factor; TnT, troponin.

interpreted in light of the limited diagnostic accuracy of polygraphy in distinguishing between OSA and CSA. Fifth, ASV usage was generally low, likely due to the minimal or absent symptoms associated with SDB in this patient population. Sixth, similar to previous studies the study population is predominantly male according to the epidemiology of AMI [38] and sleep apnoea [39]. Therefore, much larger studies would be necessary to study the effects in women. Last, the final sample size fell below the calculated target due to issues attributable to the COVID-19 pandemic and slow recruitment at the beginning of the study. This limits the statistical power for between-group comparisons of effects on circulating biomarkers.

5. Conclusions

In conclusion, the findings of this ancillary analysis did not provide consistent evidence that treatment of SDB in the early phase after AMI with ASV has a clinically relevant short-term effect on circulating biomarkers of inflammation, fluid overload, or fibrosis. Further larger randomised clinical trials are warranted to validate these preliminary findings.

CRediT authorship contribution statement

Jan Pec: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Henrik Fox:** Writing – review & editing, Data curation. **Stefan Stadler:** Writing – review & editing, Data curation. **Andrea Hetzenecker:** Writing – review & editing, Data curation. **Olaf Oldenburg:** Writing – review & editing, Data curation. **Michael Koller:** Writing – review & editing, Data curation. **Florian Zeman:** Writing – review & editing, Data curation. **Stefan Buchner:** Writing – review & editing, Data curation, Conceptualization. **Stefan Wagner:** Writing – review & editing, Data curation. **Michael Arzt:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Data availability statement

The study protocol, statistical analysis plan, analytic code and deidentified individual participant data will be made available from 3 months to 5 years following article publication to researchers who provide a methodologically sound proposal. Requests for the format of the proposal and the proposal should be directed to michael.arzt@ukr.de. To gain access, data requestors will need to sign a data access agreement.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michael Arzt reports financial support was provided by ResMed Foundation. Michael Arzt reports financial support and equipment, drugs, or supplies were provided by Resmed Germany Inc. Michael Arzt reports a relationship with Else Kroner-Fresenius Foundation that includes: funding grants. Michael Arzt reports a relationship with Philips Respironics Foundation that includes: funding grants. Michael Arzt reports a relationship with ResMed that includes: consulting or advisory and speaking and lecture fees. Michael Arzt reports a relationship with Philips Respironics Ltd that includes: consulting or advisory and speaking and lecture fees. Michael Arzt reports a relationship with ZOLL Respicardia Inc that includes: consulting or advisory and funding grants. Michael Arzt reports a relationship with Inspire Medical Systems Inc that includes: consulting or advisory and speaking and lecture fees. Michael Arzt: Field Editor (Sleep Medicine).

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Appendix A. Supplementary data

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References

[1] Lenselink C, Ricken KWLM, Groot HE, de Bruijne TJ, Hendriks T, van der Harst P, et al. Incidence and predictors of heart failure with reduced and preserved ejection fraction after ST-elevation myocardial infarction in the contemporary era of early percutaneous coronary intervention. Eur J Heart Fail 2024:42–9.
[2] Sulo G, Igland J, Vollset SE, Nygård O, Ebbing M, Sulo E, et al. Heart failure complicating acute myocardial infarction; burden and timing of occurrence: a nation-wide analysis including 86 771 patients from the cardiovascular disease in Norway (CVDNOR) project. J Am Heart Assoc 2016;5(1):1–8.
[3] Arzt M, Fox H, Stadler S, Hetzenecker A, Oldenburg O, Hamer OW, et al. Treatment of sleep apnoea early after myocardial infarction with adaptive servo-ventilation: a proof-of-concept randomised controlled trial. Eur Respir J 2024 Sep 1;64(3).
[4] Buchner S, Greimel T, Hetzenecker A, Luchner A, Hamer OW, Debl K, et al. Natural course of sleep-disordered breathing after acute myocardial infarction. Eur Respir J 2012;40(5):1173–9.
[5] Lee CH, Khoo SM, Tai BC, Chong EY, Lau C, Than Y, et al. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Chest (Am Coll Chest Physicians) 2009 Jun;135(6):1488–95.
[6] Braunwald E. Biomarkers in heart failure. N Engl J Med 2008 May 15;358(20):2148–59.
[7] González A, Richards AM, de Boer RA, Thum T, Arfsten H, Hülsmann M, et al. Cardiac remodelling – Part 1: from cells and tissues to circulating biomarkers. A review from the study group on biomarkers of the heart failure association of the European society of cardiology. Eur J Heart Fail 2022;24(6):927–43.
[8] Aimo A, Vergaro G, González A, Barison A, Lupón J, Delgado V, et al. Cardiac remodelling – Part 2: clinical, imaging and laboratory findings. A review from the study group on biomarkers of the heart failure association of the European society of cardiology. Eur J Heart Fail 2022;24(6):944–58.
[9] Halade GV, Lee DH. Inflammation and resolution signaling in cardiac repair and heart failure. EBioMedicine 2022;79:103992.
[10] Frantz S, Hundertmark MJ, Schulz-Menger J, Bengel FM, Bauersachs J. Left ventricular remodelling post-myocardial infarction: pathophysiology, imaging, and novel therapies. Eur Heart J 2022;43(27):2549–61.
[11] Alkouri A, Cybularz M, Mierke J, Nowack T, Biedermann J, Ulbrich S, et al. The predictive role of early CRP values for one-year mortality in the first 2 d after acute myocardial infarction. Biomarkers (Lond) 2022 Apr 3;27(3):293–8.
[12] Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF, Braunwald A. Braunwald's heart disease. eleventh ed. 2019.
[13] Carvalho LSF, Bogniotti LAC, de Almeida OLR, e Silva JCQ, Nadruz W, Coelho OR, et al. Change of BNP between admission and discharge after ST-elevation myocardial infarction (Killip I) improves risk prediction of heart failure, death, and recurrent myocardial infarction compared to single isolated measurement in addition to the GRACE score. Eur Heart J Acute Cardiovasc Care 2019;8(7):643–51.
[14] Núñez J, Bayés-Genís A, Revuelta-López E, ter Maaten JM, Miñana G, Barallat J, et al. Clinical role of CA125 in worsening heart failure: a BIOSTAT-CHF study subanalysis. JACC Heart Fail 2020;8(5):386–97.

[15] Falcão F, Oliveira F, Cantarelli F, Cantarelli R, Brito Júnior P, Lemos H, et al. Carbohydrate antigen 125 for mortality risk prediction following acute myocardial infarction. Sci Rep 2020;10(1):1–8.
[16] Lee CH, Lee WC, Chang SH, Wen MS, Hung KC. The N-terminal propeptide of type III procollagen in patients with acute coronary syndrome: a link between left ventricular end-diastolic pressure and cardiovascular events. PLoS One 2015;10(1):1–14.
[17] Poulsen SH, Høst NB, Jensen SE, Egstrup K. Relationship between serum amino-terminal propeptide of type III procollagen and changes of left ventricular function after acute myocardial infarction. Circulation (New York, N Y) 2000;101(13):1527–32.
[18] Osokina A, Karetnikova V, Polikutina O, Ivanova A, Gruzdeva O, Dyleva Y, et al. Prognostic potential of cardiac structural and functional parameters and N-terminal propeptide of type III procollagen in predicting cardiac fibrosis one year after myocardial infarction with preserved left ventricular ejection fraction. Aging 2021;13(1):194–203.
[19] Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, et al. Cardiac biomarkers in the emergency department: the role of soluble ST2 (sST2) in acute heart failure and acute coronary syndrome—there is meat on the bone. J Clin Med 2019;8(2).
[20] Cowie MR, Linz D, Redline S, Somers VK, Simonds AK. Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2021;78(6):608–24.
[21] Hetzenecker A, Buchner S, Greimel T, Satzl A, Luchner A, Debl K, et al. Cardiac workload in patients with sleep-disordered breathing early after acute myocardial infarction. Chest (Am Coll Chest Physicians) 2013;143(5):1294–301.
[22] Buchner S, Satzl A, Debl K, Hetzenecker A, Luchner A, Husser O, et al. Impact of sleep-disordered breathing on myocardial salvage and infarct size in patients with acute myocardial infarction. Eur Heart J 2014;35(3):192–9.
[23] Fisser C, Götz K, Hetzenecker A, Debl K, Zeman F, Hamer OW, et al. Obstructive sleep apnoea but not central sleep apnoea is associated with left ventricular remodelling after acute myocardial infarction. Clin Res Cardiol 2020.
[24] Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J 2017;49(1).
[25] Bradley TD, Logan AG, Filho GL, Kimoff RJ, Cantolla JD, Arzt M, et al. Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction open-label , phase 3 randomised controlled trial 2024;12(February).
[26] Randerath W, Baillieul S, Tamisier R. Central sleep apnoea: not just one phenotype. Eur Respir Rev 2024;33(171).
[27] Fox H, Hetzenecker A, Stadler S, Oldenburg O, Hamer OW, Zeman F, et al. Rationale and design of the randomised Treatment of sleep apnoea Early after Myocardial infarction with Adaptive Servo-Ventilation trial (TEAM-ASV I). Trials 2020;21(1):1–8.
[28] Thunström E, Glantz H, Yucel-Lindberg T, Lindberg K, Saygin M, Peker Y. Corrigendum: CPAP does not reduce inflammatory biomarkers in patients with coronary artery disease and nonsleepy obstructive sleep apnea: a randomized controlled trial. Sleep 2017;40(11):zsx157. https://doi.org/10.1093/sleep/zsx157. Sleep. 2019;42(2).
[29] Cowie MR, Woehrle H, Wegscheider K, Vettorazzi E, Lezius S, Koenig W, et al. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. Eur J Heart Fail 2018;20(3):536–44.
[30] Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015;373(12):1095–105.
[31] Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: the RICCADSA randomized controlled trial. Am J Respir Crit Care Med 2016;194(5):613–20.
[32] Peker Y, Celik Y, Behboudi A, Redline S, Lyu J, Wei Y, et al. CPAP may promote an endothelial inflammatory milieu in sleep apnoea after coronary revascularization. EBioMedicine 2024;101:105015.
[33] Núñez J, de la Espriella R, Miñana G, Santas E, Llácer P, Núñez E, et al. Antigen carbohydrate 125 as a biomarker in heart failure: a narrative review. Eur J Heart Fail 2021;23(9):1445–57.
[34] Aimo A, Januzzi JL, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, et al. Clinical and prognostic significance of sST2 in heart failure: JACC review topic of the week. J Am Coll Cardiol 2019;74(17):2193–203.
[35] Ferreira JP, Duarte K, Woehrle H, Cowie MR, Wegscheider K, Angermann C, et al. Biomarkers in patients with heart failure and central sleep apnoea: findings from the SERVE-HF trial. ESC Heart Fail 2020;7(2):503–11.
[36] Kucharz EJ, Wilk T. Dynamics of serum interleukin-6 level in patients with acute myocardial infarction. Eur J Intern Med 2000;11(5):253–6.
[37] Høst NB, Jensen LT, Bendixen PM, Jensen SE, Koldkjaer OG, Simonsen EE. The aminoterminal propeptide of type III procollagen provides new information on prognosis after acute myocardial infarction. Am J Cardiol 1995;76(12):869–73.
[38] Kuehnemund L, Koeppe J, Feld J, Wiederhold A, Illner J, Makowski L, et al. Gender differences in acute myocardial infarction—a nationwide German real-life analysis from 2014 to 2017. Clin Cardiol 2021 Jul 1;44(7):890–8.
[39] Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: THE HypnoLaus study. Lancet Respir Med 2015 Apr 1;3(4):310–8.