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Non-invasive hemodynamic monitoring during initiation of positive airway pressure treatment in patients with obstructive sleep apnea: a feasibility study

Christoph Müller[1,4*], Jens Kerl[2] and Dominic Dellweg[3]

Abstract

Background The association of obstructive sleep apnea (OSA) with cardiovascular morbidity has been repeatedly reported in numerous studies and argues for treatment initiation even in the absence of significant day time sleepiness. While the long-term consequences of positive airway pressure (PAP) treatment on OSA related comorbidities like secondary hypertension are based on substantial clinical evidence, less is known about the immediate hemodynamic effects.

Methods This study tried to investigate the impact of PAP treatment on different hemodynamic parameters in 48 patients with OSA by extending the standard polysomnographic assessment with non-invasive hemodynamic monitoring using impedance cardiography (ICG). On two consecutive nights under diagnostic and therapeutic conditions, polysomnographic and hemodynamic data were acquired. In addition, we subdivided the participants according to their treatment related change in stroke volume (SV) and assigned the hemodynamic measurements to the corresponding sleep stage.

Results Comparing both conditions, a non-statistically significant decrease in SV and cardiac output (CO) was observed for all participants. Treatment initiation was associated with a statistically significant prolongation of the pre-ejection period (PEP) for the entire study population ($p=0.001$) and the subgroup with decreasing SV ($p=0.008$). In addition, systolic blood pressure (SBP) ($p=0.026$) and pulse pressure (PP) ($p=0.041$) were lowered significantly for patients with a therapeutically reduced SV under treatment conditions. A higher BMI ($p=0.020$) and a more pronounced reduction of the respiratory distress index (RDI) ($p=0.030$) and the arousal-index ($p=0.021$) were observed for patients with decreasing SV. Correlational analysis revealed a negative relationship between the diagnostic values for both SBP (r=-0.324, $p=0.025$) and PP (r=-0.407, $p=0.004$) with the change in SV and a positive correlation with the change of the SBP ($r=0.317$, $p=0.028$) for all participants.

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Conclusions To conclude, our results indicate that treatment with a PAP device in patients with OSA can lead to a decrease in SV which is associated with a lowering of the SBP. This may be caused by a reduced sympathetic tone due to less respiratory events and an improved sleep profile.

Keywords Obstructive sleep apnea, Positive airway pressure, Hemodynamic monitoring, Impedance cardiography

Background

Several studies have consistently reported obstructive sleep apnea (OSA) to be an independent risk factor for the development of cardiovascular comorbidities like endothelial dysfunction, arterial and pulmonary hypertension, atrial fibrillation and stroke (Feng et al. 2012; Peppard and Skatrud 2000; Arias et al. 2006; Neilan et al. 2013; Yaggi et al. 2005). The pathophysiology of OSA associated comorbidities is rather complex and includes intrathoracic pressure changes, apnea induced arousals and a disturbed sleep architecture. By restoring upper airway patency, positive airway pressure (PAP) treatment can prevent and reverse the occurrence of these pathologies. The positive effect of treating OSA is most apparently demonstrated in secondary arterial hypertension which can oftentimes be reversed after starting treatment. This can be explained by a reduced sympathetic activity due to less respiratory arousals, an improved sleep profile and a reversal of apnea induced left ventricular afterload elevation (Somers 1993; Tolle 1983).

A more direct effect results from an increase of intrathoracic pressure levels which generally manifests as a decrease of left ventricular pre- and afterload due to a reduction of venous return and the transaortic pressure gradient. Depending on the underlying cardiac status, this will either lead to an improved or a reduced cardiac performance. Presuming normal left ventricular systolic and diastolic function, the reduction in preload should predominate leading to a decrease in stroke volume (SV) (Singh and Pinsky 2018). While these effects have been the subject of several studies investigating the application of positive end-expiratory pressure in mechanically ventilated patients (Luecke and Pelosi 2005; Vargas et al. 2014), less is known about the impact of PAP treatment in patients with OSA. This is mainly due to a lack of hemodynamic monitoring in routine sleep medicine practice. The study presented demonstrates the immediate effect of PAP treatment in patients with OSA by using impedance cardiography (ICG) for continuous non-invasive hemodynamic monitoring. ICG strongly correlated with the reference method of transpulmonary thermodilution (Broomhead et al. 1997; Woltjer et al. 1996; Water et al. 2003) and demonstrated a high re-test reliability. (Sherwood et al. 1998). Unlike thermodilution, ICG provides a continuous rather than momentary measurement without the need for catheterization. By comparing the hemodynamic parameters between both conditions and relating them to the biometric and polysomnographic data, we investigated the treatment associated changes of cardiovascular parameters, correlating variables and potential predictors of the change in SV.

Methods

Participants

To investigate the effect of PAP treatment on non-invasively measured hemodynamic parameters, we included 48 patients, who referred to our sleep clinic from March 2021 until May 2022 with a suspected diagnosis of OSA. Inclusion criteria were a pathological home sleep study with predominantly obstructive events and the indication for diagnostic polysomnographic assessment. Patients were excluded if they met any of the following criteria: age younger than 18 or older than 80 years, height below 150 cm or above 210 cm, weight less than 50 kg or greater than 150 kg, clinical signs of acute heart failure and/or a significantly elevated NT-proBNP. Of the initially recruited 65 patients, a total count of 48 participants were included and underwent both diagnostic and therapeutic measurements.

Protocol

All sleep studies were performed during two consecutive nights between 10 pm and 6 am. If diagnostic polysomnography confirmed a pathologically elevated RDI, treatment was initiated with a PAP device (AirSense 10 AutoSet™, ResMed) during the following night. The device was set to auto-titration mode with a pressure range between 4 mbar and 20 mbar. Polysomnographic and hemodynamic data were gathered during the entire sleep study independent of the applied pressure level or present sleep stage. All participants gave written consent that measurements with ICG were performed in addition to the routine polysomnographic assessment during both conditions. Our study received ethical approval by the ethics committee of Marburg University and is listed in the German clinical trial register (DRKS).

Data collection

The SOMNOscreen™ polysomnography system (SOMNOmedics GmbH, Randersacker, Germany) and the CardioScreen 1000 impedance cardiograph (Medis, Illmenau, Germany) were used under diagnostic and therapeutic conditions during two consecutive nights. Airflow was measured with a thermistor and a nasal pressure transducer during the first night and with the pneumotachograph of the PAP device under treatment

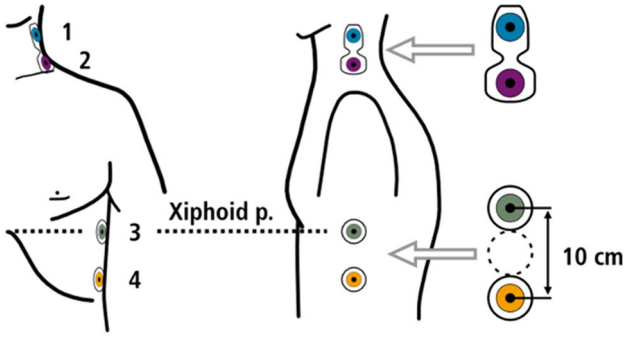

Fig. 1 Electrode placement of the impedance cardiograph device

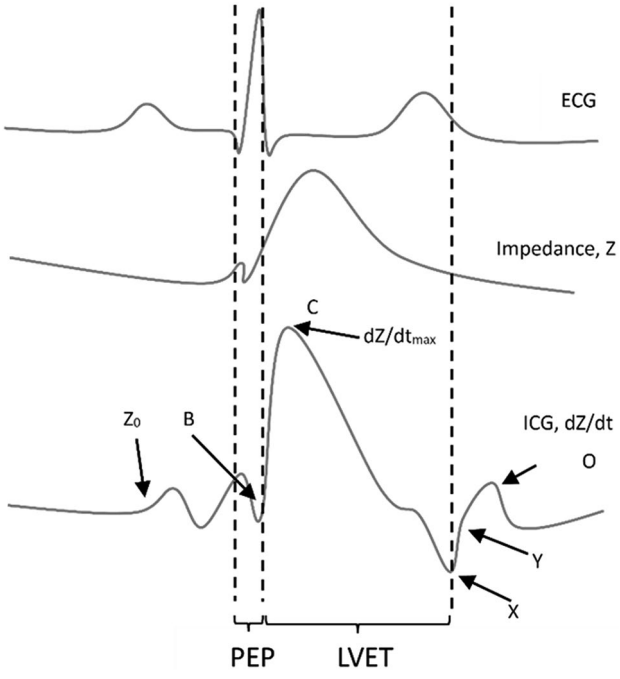

Fig. 2 Time course of the electro- and impedance cardiogram with its characteristic turning points and the derived systolic time intervals. *Abbreviations* B, opening of the aortic valve; C (dZ/dt_{max}), maximal systolic blood flow velocity; dZ/dt, maximal change in impedance; ECG, electrocardiogram; ICG, impedance cardiography; LVET, left-ventricular ejection time; 0, closure of the mitral valve; PEP, pre-ejection period; X, closure of the aortic valve; Y, closure of the pulmonic valve, Z_0, baseline

conditions. Thoracoabdominal breathing excursions were monitored with a respiratory induction plethysmograph. A finger clip oximeter was used to measure arterial oxygen saturation. Continuous blood pressure measurement was performed with the pulse transit time technique. (Gesche et al. 2012) Polysomnographic assessment was conducted according to the American Association of Sleep Medicine guidelines. (Iber et al. 2007) An obstructive apnea was scored if the thermal flow signal decreased by ≥90% for at least 10 s and a continued or increased inspiratory effort was observed. An obstructive hypopnea was defined as a decrease of the thermal flow signal by ≥30% for at least 10 s which leads to a drop of the oxygen saturation by at least 4%.

To enable hemodynamic monitoring with the impedance cardiography system two electrodes connected to two dual sensors were placed on the patients' lateral side of the neck and along the mid-axillary line of the left chest wall (Fig. 1). The outer sensors generate an alternating low amplitude current, which is sensed by the inner sensors and is used to detect the change in thoracic impedance over time. To enable a precise measurement of the cardiac cycle intervals, an additional pulsoximetry sensor was attached to one ear lobe for recording of pulse volume curves by infrared light. Based on these blood flow dependent alterations of the thoracic impedance and electrocardiographic time intervals, the software "Cardio Vascular Lab" calculates different hemodynamic parameters (Fig. 2). These include SV, stroke volume index (SVI), cardiac output (CO), cardiac index (CI), pre-ejection period (PEP), left ventricular ejection time (LVET) and systolic time ratio (STR).

Statistical analysis

Prior to statistical analysis, hemodynamic data were sorted in EXCEL according to the corresponding sleep stage. Data analysis was performed with the EXCEL software XLSTAT© (Addinsoft, New York, USA). After testing for normal distribution with the Shapiro-Wilk test, either a paired t-test or a Wilcoxon-rank test were conducted to compare diagnostic and therapeutic values. Patients were subdivided into two groups according to their change in SV under therapeutic conditions. Mean values were then compared using the unpaired t-test or the Mann-Whitney U test. The relationship between treatment associated changes in SV and biometric, polysomnographic and hemodynamic data were assessed by calculating the Pearson´s correlation coefficient or Spearman´s rank correlation coefficient. Statistical significance was assumed for a p-value ≤ 0.05.

Results

One of the main objectives of this study was to investigate the immediate effect of PAP treatment on SV in patients with OSAS. We therefore subdivided the study population depending on whether treatment initiation led to an increase or decrease of SV and compared both groups with regards to biometric, polysomnographic and hemodynamic data.

Biometric data

The patients who presented to our sleep clinic were predominantly male and middle-aged (Table 1). On average patients had an elevated body mass index (BMI) of 32.72 ± 7.31 $kg^{*}m^{-2}$ and reported mild to moderate day time sleepiness with an Epworth Sleepiness Scale (ESS)

Table 1 Biometric data of the entire study population and after subdivision into groups with decreasing and increasing stroke volume

Characteristics	Study Population ($n=48$)	SV- ($n=28$)	SV+ ($n=20$)	SV- vs. SV+ (p-value)
Age (years)	57.63 ± 10.06	56.66 ± 10.37	58.98 ± 9.72	0.435
Gender (female)	13	9	4	0.351
Height (cm)	176.77 ± 10.33	175.29 ± 10.66	178.85 ± 9.71	0.242
Weight (kg)	102.08 ± 21.64	105.25 ± 20.43	97.65 ± 23.02	0.234
BMI (kg*m^{-2})	32.72 ± 7.31	34.78 ± 7.66	29.85 ± 5.83	0.020
ESS	10.52 ± 5.50	11.72 ± 5.43	8.95 ± 5.34	0.156

Abbreviations BMI, body mass index; ESS, Epworth Sleepiness Scale; SV-, patients with decreasing stroke volume; SV+, patients with increasing stroked volume

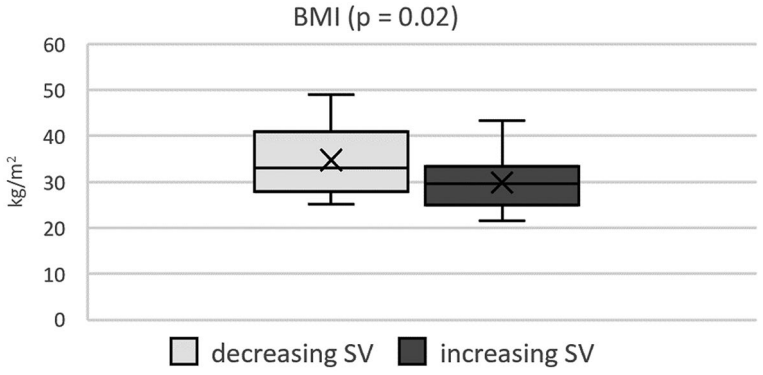

Fig. 3 Statistically significant different BMI between both subgroups. *Abbreviations* BMI, body mass index; SV, stroke volume

of 10.52±5.50. Regarding both subgroups, patients with a decreasing SV had a statistically significant higher BMI of 34.78±7.66 kg*m^{-2} compared to the group with increasing SV whose BMI was 29.85±5.83 kg*m^{-2} ($p=0.02$) (Fig. 3).

Polysomnographic parameters

The initiation of PAP treatment led to both a statistically significant reduction of the respiratory distress index (RDI) and the oxygen desaturation index (ODI) and caused an increase of counted sleep cycles (Table 2). The subgroups based on the treatment associated change in SV differed with regards to the proportion of sleep stages under diagnostic and therapeutic conditions. A statistically significant decrease in N2 ($p=0.010$) and increase in N3 sleep ($p=0.002$) under PAP conditions was noted for the entire study population. This effect also occurred in patients with decreasing SV for both N2 ($p=0.009$) and N3 ($p=0.014$) but was not observed for the subgroup with increasing SV. Patients with a therapeutically reduced SV showed a statistically significant lowering of the arousal-index ($p=0.019$). There was also a trend towards more initial respiratory events and associated oxygen desaturations with a statistically significant stronger relative reduction of the RDI ($p=0.030$) and the arousal-index ($p=0.021$) compared to patients with increasing SV.

Hemodynamic parameters

An overview of the hemodynamic differences between the diagnostic and therapeutic conditions as well as between both subgroups is given in Table 3. In addition, statistically significant changes under treatment conditions during wakefulness and each sleep stage are presented in the following sections. In both subgroups either a statistically significant increase or decrease of SV for the waking periods and all sleep stages was observed ($p\leq0.001$). As shown in Fig. 4, a non-statistically significant reduction of SV was observed during wakefulness and all sleep stages for all participants.

Comparing the hemodynamic measurements under diagnostic and therapeutic conditions of each sleep stage for the entire study population, statistically significant differences were observed for PEP, STR, SBP and PP. The PEP showed a statistically significant increase under therapeutic conditions during N1 (112.29±17.70 vs. 116.50±14.75, $p=0.001$) and during REM sleep (111.20±18.06 vs. 115.20±15.92, $p=0.009$) (Fig. 5). Correspondingly the STR also increased statistically significantly with PAP treatment during phases of wakefulness (0.37±0.07 vs. 0.38±0.07, $p=0.009$) and N1 (0.37±0.06 vs. 0.39±0.06, $p=0.008$). Under therapeutic conditions a drop of the SBP was observed which was statistically significant during N3 (131.72±18.69 vs. 129.74±17.68, $p=0.038$). This was associated with an overall reduction of the PP with statistical significance during REM sleep (45.87±16.65 vs. 39.21±15.08, $p=0.018$).

Table 2 Polysomnographic data of the entire study population and after subdivision into groups with decreasing and increasing stroke volume

Parameters	Study Population (*n* = 48)	SV- (*n* = 28)	SV+ (*n* = 20)	SV- vs. SV+ (*p*-value)
RDI, Dx (h^{-1})	26.75 ± 15.30	27.58 ± 12.76	25.60 ± 18.58	0.250
RDI, Tx (h^{-1})	12.80 ± 17.59	10.02 ± 9.92	16.70 ± 24.47	0.730
Δ RDI (%)	-38.71 ± 99.97**	-64.89 ± 30.06**	-2.05 ± 144.97*	0.028
ODI, Dx (h^{-1})	19.92 ± 15.08	21.05 ± 13.36	18.35 ± 17.45	0.177
ODI, Tx (h^{-1})	8.80 ± 12.26	8.26 ± 10.79	9.56 ± 14.33	0.933
Δ ODI (%)	-26.69 ± 155.53**	-43.86 ± 110.73**	6.72 ± 198.39*	0.604
Arousal-Index, Dx (h^{-1})	20.75 ± 12.60	19.91 ± 8.75	21.91 ± 16.79	0.867
Arousal-Index, Tx (h^{-1})	17.85 ± 15.09	14.98 ± 9.01	21.87 ± 20.47	0.213
Δ Arousal-Index (%)	9.95 ± 105.38	-19.33 ± 46.64*	50.93 ± 146.11	0.021
SC, Dx	1.58 ± 0.99	1.64 ± 1.06	1.50 ± 0.89	0.758
SC, Tx	2.29 ± 1.20	2.50 ± 1.26	2.0 ± 1.08	0.197
Δ SC (%)	61.43 ± 99.44	76.33 ± 109.97**	40.74 ± 81.09*	0.054
TST%, N1, Dx	11.67 ± 8.44	10.55 ± 7.06	13.25 ± 10.05	0.623
TST%, N1, Tx	10.66 ± 8.51	9.87 ± 8.20	11.91 ± 9.00	0.305
Δ TST%, N1 (%)	14.47 ± 103.15	0.60 ± 70.80	-37.21 ± 143.41	0.593
TST%, N2, Dx	53.56 ± 10.70	53.56 ± 13.11	53.55 ± 6.96	0.997
TST%, N2, Tx	49.39 ± 0.65	47.68 ± 11.98	51.80 ± 8.14	0.189
Δ TST%, N2 (%)	-5.85 ± 22.85**	-8.46 ± 22.77**	-1.70 ± 20.13	0.182
TST%, N3, Dx	21.62 ± 10.81	22.53 ± 11.21	20.35 ± 10.36	0.429
TST%, N3, Tx	25.73 ± 10.49	26.83 ± 11.13	24.18 ± 9.60	0.882
Δ TST%, N3 (%)	50.10 ± 118.88*	34.93 ± 8.07**	63.83 ± 171.20	0.758
TST%, REM, Dx	12.95 ± 6.82	13.00 ± 6.77	12.87 ± 7.07	0.360
TST%, REM, Tx	14.20 ± 7.13	15.80 ± 5.66	11.96 ± 8.44	0.121
Δ TST%, REM (%)	69.65 ± 218.60	69.84 ± 122.85	-85.05 ± 319.01	0.012

Abbreviations AHI, apnea-hypopnea-index; Dx; diagnostic; N, non-rapid eye movement sleep; ODI, oxygen desaturation index; REM, rapid eye movement sleep; SC, sleep cycles, SV-, patients with reduced stroke volume; SV+, patients with increasing stroke volume, TST, total sleep time; Tx, therapeutic; ** indicating $p \leq 0{,}001$; * indicating $p \leq 0{,}05$

A more pronounced prolongation of the PEP during N1 (111.06±18.51 vs. 117.97±15.00, $p=0.003$), N2 (113.41±19.73 vs. 117.07±12.68, $p=0.023$) and REM sleep (114.67±19.67 vs. 115.14±17.01, $p=0.006$) under therapeutic conditions was observed for the subgroup with a treatment related decrease in SV. This was associated with an increasing STR during wakefulness (0.37±0.07 vs. 0.38±0.05, $p=0.036$) and N1 (0.37±0.06 vs. 0.39±0.06, $p=0.004$). Figure 6 demonstrates a drop of the SBP which was statistically different during periods of wakefulness (138.19±15.46 vs. 131.16±17.66, $p=0.038$), N1 (135.84±15.41 vs. 128.26±18.70, $p=0.026$), N2 (134.64±15.42 vs. 125.47±17.20, $p=0.002$) and REM sleep (136.65±16.32 vs. 128.29±18.69, $p=0.026$). Starting PAP treatment also led to a lowering of PP for the subgroup with decreasing SV which was statistically significant during wakefulness (47.95±15.56 vs. 42.08±12.08, $p=0.040$), N2 (45.73±15.83 vs. 39.19±12.64, $p=0.035$) and REM sleep (47.92±15.61 vs. 40.48±13.03, $p=0.019$) (Fig. 7). In contrast, no treatment associated effects except for an increase of the PEP during REM sleep 106.27±14.57 vs. 115.28±14.53, $p=0.009$) and a reduction of the LVET during wakefulness (305.54±25.33 vs. 300.01±27.78, $p=0.049$) were observed for the subgroup with increasing SV.

Correlational analysis and predictors of stroke volume response to PAP treatment

Regarding the relationship of the hemodynamic parameters and the change in SV, a statistically significant negative correlation with the diagnostic SBP (r = -0.324, $p=0.025$) as illustrated in Fig. 8 and PP (r = -0.407, $p=0.004$) were observed for the entire study population. In addition, the therapeutic change of the SBP was positively correlated with the change in SV ($r=0.317$, $p=0.028$). For participants with a treatment related decrease in SV, a statistically significant negative correlation was observed with the PP under diagnostic (r = -0.447, $p=0.017$) and treatment conditions (r = -0.552, $p=0.002$). Patients with an increasing SV showed a negative relationship of the diagnostic SBP (r = -0.573, $p=0.008$), the therapeutic SBP (r = -0.483, $p=0.031$), the therapeutic DBP (r = -0.453, $p=0.045$) and a positive correlation of the change in PP ($r=0.462$, $p=0.041$) with the treatment associated increase in SV under PAP conditions.

Table 3 Hemodynamic data of the entire study population and after subdivision into groups with decreasing and increasing stroke volume

Parameters	Study Population (*n* = 48)	SV- (*n* = 28)	SV+ (*n* = 20)	SV- vs. SV+ (*p*-value)
SV (ml), Dx	102.29 ± 27.77	109.07 ± 26.35	92.80 ± 27.54	0.044
SV (ml), Tx	99.64 ± 27.64	96.35 ± 25.45	104.24 ± 31.24	0.422
Δ SV (ml)	-1.35 ± 15.74	-10.15 ± 9.39***	12.87 ± 10.38***	< 0.0001
SVI (ml*m^2), Dx	46.78 ± 9.90	49.74 ± 9.25	42.63 ± 9.47	0.012
SVI (ml*m^2), Tx	45.62 ± 10.24	43.96 ± 9.55	47.93 ± 10.96	0.266
Δ SVI (ml*m^2)	-1.35 ± 15.74	-10.15 ± 9.39***	12.87 ± 10.38***	< 0.0001
CO (ml), Dx	6.45 ± 1.87	6.89 ± 1.80	5.85 ± 1.83	0.017
CO (ml), Tx	6.36 ± 1.78	6.18 ± 1.58	6.54 ± 2.03	0.486
Δ CO (ml)	0.02 ± 15.76	-9.98 ± 6.98***	13.04 ± 15.05***	< 0.0001
CI (l*min^{-1}*m^2), Dx	2.94 ± 0.65	3.13 ± 0.64	2.68 ± 0.59	0.016
CI (l*min^{-1}*m^2), Tx	2.84 ± 0.75	2.73 ± 0.79	3.00 ± 0.67	0.358
Δ CI (l*min^{-1}*m^2)	0.02 ± 15.76	-9.98 ± 6.98***	13.04 ± 15.05***	< 0.0001
PEP (ms), Dx	111.92 ± 16.42	112.19 ± 18.48	111.54 ± 13.45	0.087
PEP (ms), Tx	115.52 ± 13.52	116.02 ± 13.47	114.84 ± 13.91	0.775
Δ PEP (ms)	4.50 ± 13.24**	5.33 ± 15.46*	3.35 ± 9.56	0.458
LVET (ms), Dx	306.20 ± 22.36	307.04 ± 21.36	305.02 ± 24.21	0.761
LVET (ms), Tx	302.86 ± 23.73	303.65 ± 21.80	301.36 ± 26.22	0.743
Δ LVET (ms)	-3.18 ± 14.97	-1.00 ± 4.79	1.16 ± 4.27	0.904
STR, Dx	0.37 ± 0.06	0.37 ± 0.07	0.38 ± 0.06	0.746
STR, Tx	0.39 ± 0.05	0.39 ± 0.05	0.38 ± 0.06	0.872
Δ STR	4.98 ± 13.93	6.80 ± 16.05	2.43 ± 10.10	0.289
SBP (mmHg), Dx	133.66 ± 16.85	135.58 ± 15.58	130.97 ± 18.56	0.356
SBP (mmHg), Tx	130.18 ± 17.57	128.06 ± 18.41	133.14 ± 16.32	0.330
Δ SBP (mmHg)	-2.13 ± 11.20	− 5.17 ± 12.03*	2.43 ± 10.10	0.024
DBP (mmHg), Dx	89.83 ± 12.14	89.31 ± 13.35	90.55 ± 10.52	0.732
DBP (mmHg), Tx	89.34 ± 12.23	87.53 ± 14.31	91.88 ± 8.19	0.227
Δ DBP (mmHg)	-0.05 ± 10,25	-1.80 ± 9.26	2.39 ± 11.28	0.166
PP (mmHg), Dx	43.83 ± 16.43	46.27 ± 15.73	40.42 ± 17.18	0.228
PP (mmHg), Tx	40.84 ± 12.27	40.54 ± 12.61	41.25 ± 12.09	0.845
Δ PP (mmHg)	3.45 ± 53,25	-6.39 ± 36.66*	17.22 ± 69.00	0.064

Abbreviations CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; Dx, diagnostic; DBP, diastolic blood pressure; LVET, left ventricular ejection time; PEP, pre-ejection period; PP, pulse pressure; SBP, systolic blood pressure; STR, systolic time ratio; SV, stroke volume; SV-, patients with decreasing stroke volume; SV+, patients with increasing stroke volume; SVI, stroke volume index; Tx, therapeutic; *** indicating $p \leq 0.0001$; ** indicating $p \leq 0.001$; * indicating $p \leq 0{,}05$

To evaluate potential predictors for the treatment associated change in SV, biometric data, polysomnographic and hemodynamic parameters were sorted categorically according to predefined cut-off values. Body weight above 90 kg (OR 2.58; 95% CI 0.81–8.21) and a BMI of more than 35 kg*m^{-2} (OR 3.67; 95% CI 0.93–14.40) were associated with a drop of SV under treatment conditions. A diagnostic AHI above 30 h^{-1} (OR 2.59; 95% CI 0.72–9.32) and a therapeutic reduction of the RDI (OR 2.44; 95% CI 0.71–8.39) and the ODI (OR 1.97; 95% CI 0.57–6.88) of more than 50% were predictors of a treatment related reduction of SV. Hemodynamic data associated with an increasing likelihood of a therapeutic reduction of SV included a diagnostic PEP < 100 ms (OR 2.27; 95% CI 0.56–9.18) and a treatment related decrease of the PEP (OR 1.97; 95% CI 0.53–7.31), the LVET (OR 2,17; 95% CI 0.66–7.09), the SBP (OR 3.00; 95% CI 0.92–9.88) and PP (OR 3.75; 95% CI 1.15–12.24).

Discussion

The study presented demonstrates that treatment initiation with a PAP device can have an immediate hemodynamic effect in patients with OSA which can be measured non-invasively with ICG. The standard polysomnographic assessment confirmed the efficacy of PAP treatment which led to an overall significant reduction of the RDI and the ODI. In addition, our study indicates that PAP treatment can induce a reduction of SV and derived parameters by decreasing sympathetic activity and contributing to an improved sleep profile.

By subdividing the study population according to the treatment related effect on SV, we could point out biometric, polysomnographic and hemodynamic differences associated with the cardiovascular response to PAP treatment. A statistically significant higher BMI was noted for the subgroup with a therapeutically decreasing SV. On polysomnography, there was a trend towards more

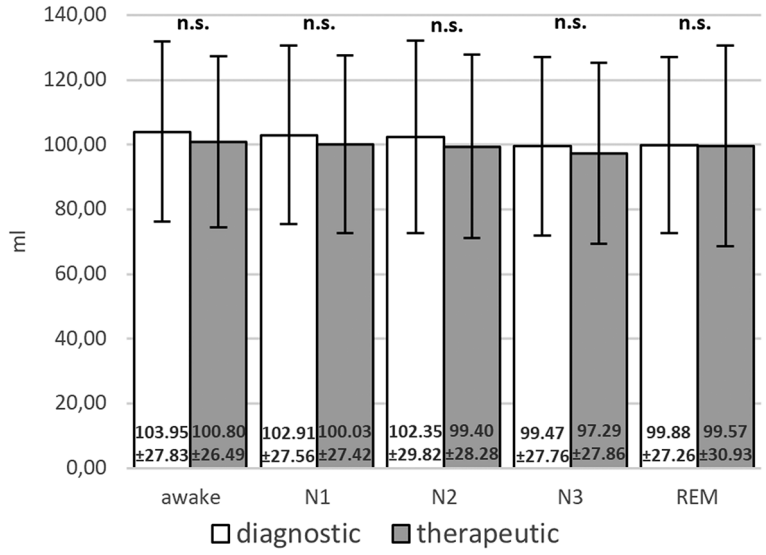

Fig. 4 SV under diagnostic and therapeutic conditions for the entire study population. *Abbreviations* N, Non-REM sleep; n.s., not significant; REM, Rapid eye movement sleep; SV, stroke volume

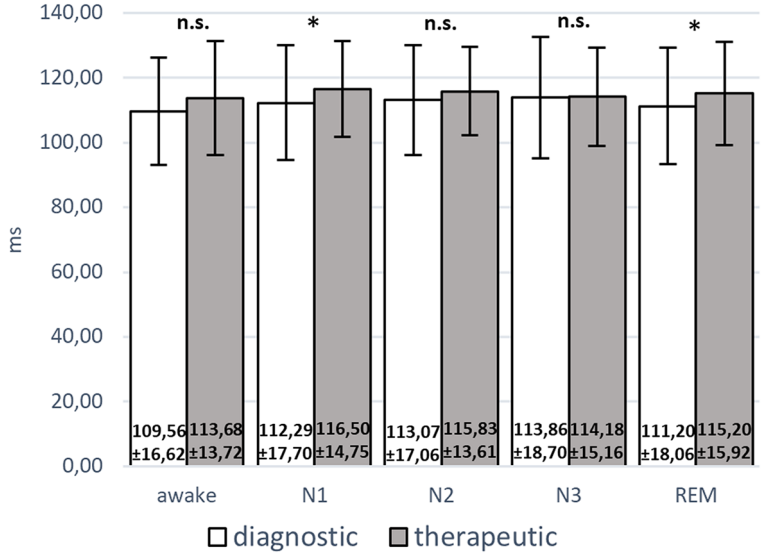

Fig. 5 PEP under diagnostic and therapeutic conditions for the entire study population. *Abbreviations* N, Non-REM sleep; n.s., not significant; REM, Rapid eye movement sleep, PEP, pre-ejection period, * indicating $p < 0.05$

initial obstructive events with stronger oxygen desaturations for patients with decreasing SV who showed a more pronounced reduction of the RDI and the arousal-index. In addition, correlational analysis indicated that higher initial blood pressure values and a stronger therapeutic reduction are associated with a decreasing SV. These findings support the hypothesis of an OSA related increase in SV and derived hemodynamic parameters which can be therapeutically reversed with PAP treatment.

From a pathophysiological perspective, a higher BMI of patients with decreasing SV may be related to more obstructive events causing a stronger activation of the sympathetic nervous system. There is extensive evidence that a higher BMI is associated with an increasing likelihood in the occurrence of OSAS. (Peppard et al. 2000; Young et al. 2005) Obstructive events related to overweight could in turn be more responsive to PAP treatment than respiratory events caused by anatomical predispositions e.g. retrognathia or macroglossia. (Caples et al. 2010; Virk and Kotecha 2016) Moreover, baseline sympathetic activity seems to be higher in obesity which could partly be explained by an increasing incidence of OSA (Grassi et al. 2019; Narkiewicz et al. 1998).

Regarding the hemodynamic impact of PAP treatment, it has to be differentiated between the direct effect of intrathoracic pressure elevation and the indirect

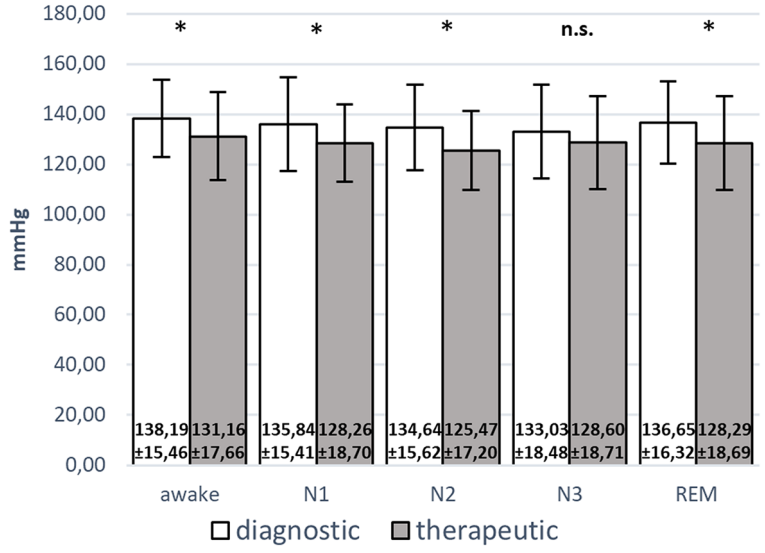

Fig. 6 SBP under diagnostic and therapeutic conditions for the subgroup with decreasing stroke volume. *Abbreviations* N, Non-REM sleep; n.s., not significant; REM, Rapid eye movement sleep; SBP, systolic blood pressure; * indicating $p < 0.05$

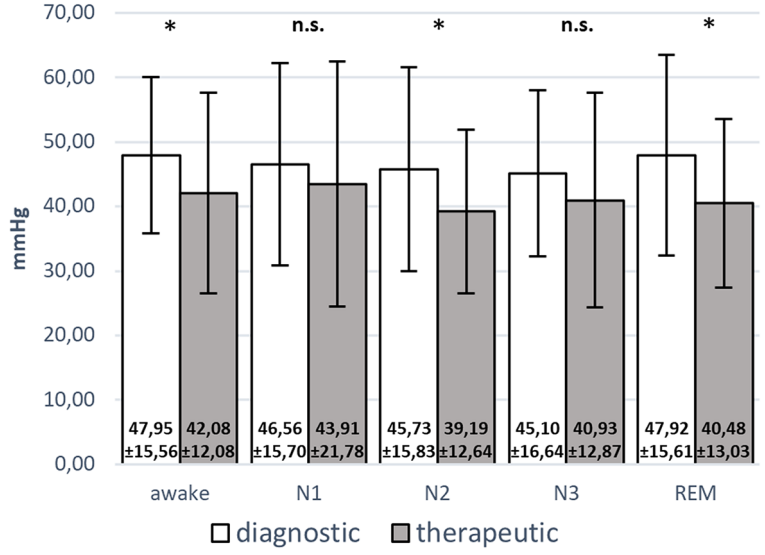

Fig. 7 PP under diagnostic and therapeutic conditions for the subgroup with decreasing stroke volume. *Abbreviations* N, Non-REM sleep; n.s., not significant; REM, Rapid eye movement sleep; SBP, systolic blood pressure; * indicating $p < 0.05$

consequences of OSA reversal. The presumed reduction of left ventricular pre- and afterload due to increased intrathoracic pressure levels would in sum cause a decrease in SV in the absence of heart failure. This is mainly explained by a decreasing transaortic (transmural) pressure gradient and a drop of the systemic venous return. (Singh and Pinsky 2018) It should be mentioned that the cardiovascular response to changes in intrathoracic pressure levels may also depend on left ventricular morphology. While a treatment related reduction of the transmural pressure gradient may reduce left ventricular wall stress improving myocardial contractility in patients with eccentric hypertrophy, (Steiner et al. 2008) the drop of venous return may be lead to hemodynamic impairment in patients with a stronger preload dependency, e.g. in concentric left-ventricular hypertrophy (Grossmann et al. 1975).

For the subgroup with a therapeutically reduced SV, a lowering of SBP and PP was observed during different sleep stages. This could partly be explained by the indirect effects of an improved sleep profile and a reduced sympathetic tone due to less respiratory arousals. (Kim and Ji 2019; Feinberg and Floyd 1979; Murali et al. 2003)

The observed statistically significant decrease in N2 sleep stage as well as the increase in slow wave sleep and counted sleep cycles indicate a trend towards a more

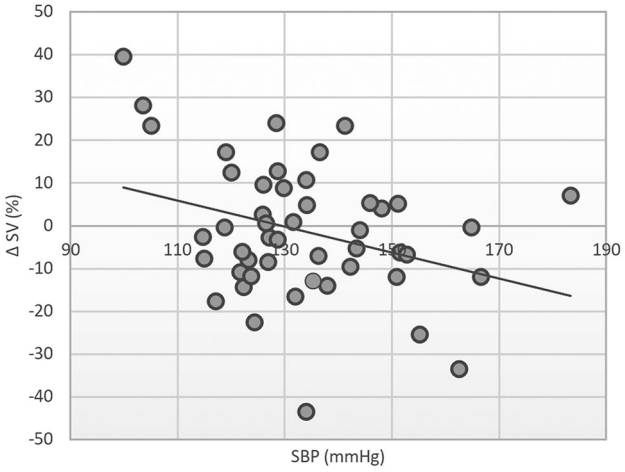

Fig. 8 Correlation between relative change in stroke volume and diagnostic systolic blood pressure for the entire study population. *Abbreviations* SBP, systolic blood pressure; SV, stroke volume

physiological sleep profile for patients with a drop of SV. (Danker-Hopfe et al. 2005) This corresponds to the opposite effect on REM sleep between both subgroups and supports the assumption of a lowered sympathetic activity with increasing sleep depth. (Burgess et al. 1997; Hilton et al. 2000; Borne et al. 1994)

A treatment related decrease of sympathetic activation would lead to reduced peripheral vasoconstriction and less beta-adrenergic myocardial stimulation thereby lowering both SBP and PP. (Imadojemu et al. 2002)

The prolongation of the PEP provides further evidence for a reduction of the sympathetic tone induced by PAP treatment. The PEP has repeatedly been reported to be strongly associated with sympathetic nervous system activation and is used as a valid surrogate parameter in this context. (Ahmed et al. 1972; Schächinger et al. 2001) In several studies, a lowering effect of PAP treatment on nocturnal stress levels was demonstrated by reduced concentrations of blood and urinary catecholamines after treatment initiation which was related to a drop of the systemic blood pressure. (Commondore and Cheema 2008; Araujo et al. 2013; Pinto et al. 2013)

However, there is only limited data available on the cardiovascular effects of PAP treatment measured with non-invasive techniques. The presumed reversal of OSA related sympathetic activation is consistent with the results by Schulze et al. (2017) who revealed a treatment related decrease of the augmentation index and left ventricular workload by combining ICG and continuous blood pressure monitoring. Our results also support earlier findings by Nelesen et al. (2001) demonstrating a decrease of myocardial contractility and a shift towards less sympathetic activation under PAP conditions measured with an impedance cardiograph.

To conclude, by extending the routine polysomnographic assessment with non-invasive hemodynamic monitoring using ICG, we could show a treatment related decrease of SV for patients with a stronger therapeutic response and a drop of the SBP. This could be explained by a reduced sympathetic activation and an improved sleep profile. In addition, our study confirmed ICG to be a useful diagnostic tool for continuous hemodynamic monitoring during PAP treatment.

Abbreviations

BMI	Body Mass Index
CI	Cardiac Index
CO	Cardiac Output
DBP	Diastolic Blood Presssure
DRKS	German Clinical Trials Register
ESS	Epsworth Sleepiness Scale
ICG	Impedance Cardiography
LVET	Left-Ventricular Ejection Time
N1	Non-rapid eye movement sleep 1
ODI	Oxygen Desaturation Index
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PEP	Pre-Ejection Period
RDI	Respiratory Distress Index
REM	Rapid Eye Movement
SBP	Systolic Blood Pressure
STR	Systolic Time Ratio
SV	Stroke Volume
SVI	Stroke Volume Index

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Author contributions
J.K. and D.D. conceptualized the study design. C.M. and J.K. conducted the hemodynamic and polysomonographic measurements and were responsible for data collection. C.M., J.K. and D.D. analyzed the data. C.M. wrote the manuscript and prepared tables and figures to illustrate the results. C.M., J.K. and D.D. discussed and interpreted the results. All authors approved the manuscript.

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Data availability
Primary data and material on which the analysed data presented in this work is based can be received by the corresponding author upon request.

Declarations

Ethical approval
Ethical approval was given by the Ethics Committee of Marburg University.

Informed consent
Informed written consent was received by all patients included in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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