

Predictors of delirium after cardiac surgery in patients with sleep-disordered breathing

- Online data supplement -

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Assessment of sleep-disordered breathing

The night before CABG, nasal flow, pulse oximetry, and thoracic breathing effort were measured with the Alice NightOne device (Philips Respironics, Murrysville, USA). The sleep data acquired by the Alice NightOne devices was scored by trained medical staff using the corresponding Sleepware G3 sleep diagnostic software (Philips Respironics, Murrysville, USA). Apnea was defined as a ≥ 90 decrease in airflow for ≥ 10 seconds, hypopnea as a decrease in airflow by ≥ 30 -90% versus baseline for ≥ 10 seconds, and desaturation as a $\geq 4\%$ decrease in oxygen saturation [1, 2]. The apnea-hypopnea index (AHI) is expressed as the frequency of apnea or hypopnea events per hour recording time, and an AHI of ≥ 15 /hour was considered the cut-off for the diagnosis of SDB. Patients with SDB and $\geq 50\%$ of central apnea events were classified into the CSA group and patients with $< 50\%$ of central apnea events into the OSA group.

We performed an internal validation study in a sub-sample of 50 consecutive patients by a blinded trained investigator, who classified the hypopneas into their central and obstructive nature. Among the 50 patients, 23 (46%) had no SDB and 27 (54%) had SDB, of those 21 (42%) had OSA and 6 (12%) had CSA according to the definition used in the main analysis of the present study. Using an alternative definition including central and obstructive hypopnoeas "Patients with SDB and $\geq 50\%$ of central apnoea and hypopnoea events were classified into the CSA group and patients with $< 50\%$ of central apnoea and hypopnoeas events into the OSA group" only one patient changed from the CSA to the OSA group. Thus, both definitions for diagnosing CSA and OSA provide similar results ($p=0.945$). Moreover, the ratios central apnoea index/obstructive apnoea index and central apnea-hypopnea index/obstructive apnoea-hypopnea index were similar (0.17 [0.01; 0.80] versus 0.23 [0.09; 0.58], $p=0.806$).

Standardized clinical treatment

In general, all patients undergoing elective CABG surgery at the Department of Cardiothoracic Surgery of the University Medical Center Regensburg (Germany) get admitted to the hospital one day prior to CABG surgery. Predisposing risk factors for postoperative delirium, such as demographics, common comorbidities, medication, and laboratory data were assessed by means of the patients' clinical records. No premedication was routinely administered the night prior to surgery.

Anesthesia was induced with a standardized regimen of sufentanil, etomidate, and rocuronium and maintained with sufentanil and sevoflurane. Details of the maintenance of anesthesia were at the discretion of the anesthesiologist. After surgery, all patients were transferred to the intensive care unit (ICU) while being intubated and sedated. Standardized postoperative sedation consisted of propofol and opioids.

All patients received postoperative treatment according to the 'fast-track recovery' care protocol that aims at early extubation, prompt implementation of mobility, and occupational therapy within ICU and intermediate care (IMC) settings [3, 4]. Patients were weaned from mechanical ventilation at the discretion of the ICU physicians. All patients received supplemental oxygen according to the standards of the surgical ICU and IMC, but not with the intention to treat sleep-disordered breathing. Within the standard postoperative care of patients, special emphasis was placed on the rational titration of sedatives and opioids, reduced exposure to benzodiazepines, and appropriate use of antipsychotic drugs [5, 6]. Further strategies for the prevention of postoperative delirium included optimization of hydration and electrolytes [7], promotion of sleep [8], continuous administration of oxygen, non-supine positioning, and adequate monitoring of oxygen saturation levels [9]. Moreover, visual and hearing adaptations were provided for patients with sensory impairments.

Figure legends**Figure E1: CAM-ICU worksheet**

The CAM-ICU worksheet is a concise description on how to conduct CAM-ICU in a standardized manner.

Figure E2: Postoperative oxygen flow rates

Oxygen flow rates in liter per minute (l/min) during the postoperative period, starting upon termination of invasive ventilation until the fourth postoperative night. Data are shown in median (25./75. percentile) for patients without SDB, with OSA and with CSA (A) and for patients without and with postoperative delirium (B).

Figure E3 Parameters of nocturnal hypoxia as predictors of postoperative delirium

Forest plot of parameters of nocturnal hypoxia as preoperative risk factors for postoperative delirium. Values are presented as OR: Odds ratio and 95% CI: confidence interval. ¶ mean SpO₂ < median 92%; § time of SpO₂ <90%/total recording time > median 9.4.

Table E1 Patient characteristics

	overall	sub-analysis population	drop-out population	p-value
n (%)	241	141 (100)	100 (100)	
Age, years	68 ± 9	68 ± 9	68 ± 9	0.632 ^T
Male sex, n (%)	194 (85)	123 (87)	71 (81)	0.180 ^{Chi}
Body mass index, kg/m ²	28.5 ± 4.2	28.7 ± 4.0	28.2 ± 4.4	0.377 ^T
NT-proBNP, pg/ml	435 (119; 1102)	408 (112; 1166) [*]	452 (135; 931) [†]	0.921 ^W

Baseline variables of the sub-analysis population and of patients who were excluded from the sub-analysis population (drop-out population). Data are presented as mean ± standard deviation or median (25.; 75. percentile) unless otherwise stated. NT-pro BNP: N-terminal pro-brain natriuretic peptide; TIA: transient ischemic attack; ^{*}n=131, [†]n=64.

Table E2 Patient characteristics

	overall	no postoperative delirium	postoperative delirium	p-value
n (%)	141 (100)	108 (77)	33 (23)	
Age, years	68 ± 9	66 ± 8	73 ± 7	<0.001 ^T
Male sex, n (%)	123 (87)	95 (85)	28 (88)	0.639 ^{Chi}
Body mass index, kg/m ²	28.7 ± 4.0	29.1 ± 4.0	27.2 ± 3.7	0.017 ^T
Cardiovascular risk factors				
Hypertension, n (%)	119 (84)	88 (81)	31 (94)	0.084 ^{Chi}
Hyperlipoproteinemia, n (%)	91 (64)	68 (63)	23 (70)	0.479 ^{Chi}
Diabetes mellitus, n (%)	45 (32)	30 (28)	15 (45)	0.057 ^{Chi}
Smoking, n (%)	88 (62)	67 (62)	21 (64)	0.868 ^{Chi}
Family history of CAD, n (%)	50 (36)	43 (40)	7 (21)	0.108 ^{Chi}
Comorbidities				
Heart failure (NT-proBNP cut-off)* [†] , n (%)	41 (31)	23 (23)	18 (56)	<0.001 ^{Chi}
NYHA class III/IV, n (%)	44 (31)	32 (30)	12 (36)	0.465 ^{Chi}
LV ejection fraction, %	58 ± 10	59 ± 10	57 ± 9	0.467 ^T
LV ejection fraction <55%, n (%)	29 (21)	18 (17)	11 (33)	0.053 ^{Chi}
Atrial fibrillation, n (%)	31 (22)	21 (19)	10 (30)	0.187 ^{Chi}
History of TIA or stroke, n (%)	20 (14)	9 (8)	11 (33)	<0.001 ^{Chi}
Respiratory disease, n (%)	9 (6)	7 (6)	2 (6)	0.931 ^{Chi}
Depression, n (%)	6 (4)	4 (4)	2 (6)	0.557 ^{Chi}
History of alcohol abuse, n (%)	17 (13)	15 (15)	2 (7)	0.276 ^{Chi}
Laboratory data				
NT-proBNP, pg/ml*	408 (112; 1166)	182 (87; 766)	1536 (593; 3432)	<0.001 ^W
Hemoglobin, g/dl	14.2 (12.7; 15.2)	14.3 (13.2; 15.3)	13.0 (12.0; 14.9)	0.005 ^W
Creatinine, mg/dl	1.0 (0.9; 1.2)	0.9 (0.8; 1.1)	1.2 (1.0; 1.3)	0.001 ^W
GFR, ml/min/1.73qm	75 (57; 89)	81 (63; 91)	60 (46; 69)	<0.001 ^W
Sodium, mmol/l	140 (139; 142)	140 (139; 142)	140 (138; 143)	0.662 ^W
Albumin, g/l [#]	37.8 (36.4; 40.0)	38.6 (36.9; 40.6)	37.0 (35.4; 38.3)	0.054 ^W

Baseline variables of the study population of patients (n=141) without and with postoperative delirium. Data are presented as mean ± standard deviation or median (25.; 75. percentile) unless otherwise stated. *n=131; ^Tstudent's t-test; ^{Chi}Chi-square test; ^WWilcoxon-Mann-Whitney test. CAD: coronary artery disease; NYHA: New York Heart Association; LV: left ventricular; NT-pro BNP: N-terminal pro-brain natriuretic peptide; TIA: transient ischemic attack; GFR: glomerular filtration rate; [†]NT-proBNP ≥450 pg/mL (patients < 50 years of age), ≥900 pg/mL (patients ≥50 and <75 years of age) or ≥1800 pg/mL (patients ≥75 years of age); [#] n=48.

Table E3 Nocturnal respiration

	overall	no postoperative delirium	postoperative delirium	p-value
Nocturnal respiration				
Total recording time, min	483 (465; 500)	483 (464; 500)	484 (466; 501)	0.737 ^w
Apnea hypopnea index, per hour	15.8 (9.6; 29.2)	14.4 (8.4; 26.0)	23.7 (12.0; 38.0)	0.028^w
Obstructive apnea index, per hour	4.2 (1.9; 8.9)	3.8 (1.7; 8.9)	5.4 (3.4; 8.5)	0.106 ^w
Central apnea index, per hour	2.0 (0.5; 8.5)	1.6 (0.4; 6.2)	7.3 (0.9; 22.4)	0.025^w
Oxygen desaturation index, per hour	13.6 (6.6; 27.0)	12.1 (5.8; 23.7)	21.1 (8.2; 33.1)	0.098 ^w
Mean SpO ₂ , %	92 (91; 93)	92 (91; 93)	92 (90; 93)	0.714 ^w
Min SpO ₂ , %	82 (77; 85)	82 (77; 85)	82 (76; 86)	0.542 ^w
Time of SpO ₂ <90%/Total recording time	9.4 (1.9; 22.4)	9.7 (1.3; 22.1)	8.2 (2.3; 27.2)	0.961 ^w
Sleep-disordered breathing, n (%)	72 (51)	50 (46)	22 (67)	0.040^{Chi}
Obstructive sleep apnea, n (%)	37 (26)	32 (30)	5 (15)	0.098 ^{Chi}
Central sleep apnea, n (%)	35 (25)	18 (17)	17 (51)	<0.001^{Chi}

Nocturnal respiration data of the study population of patients without and with postoperative delirium. Data are presented as median (25.; 75. percentile) unless otherwise stated. ^{Chi} Chi-square test; ^w Wilcoxon-Mann-Whitney test.

Table E4 Postoperative opioid administration

	overall	no postoperative delirium	postoperative delirium	p-value
Opioids				
Pethidine, n (%)	55 (39)	42 (39)	13 (39)	0.958 ^{Chi}
Piritramide, n (%)	135 (96)	103 (95)	32 (97)	0.690 ^{Chi}
Hydromorphone (oral), n (%)	80 (57)	64 (60)	16 (49)	0.250 ^{Chi}
Morphine (oral), n (%)	10 (7)	7 (7)	3 (10)	0.563 ^{Chi}
Morphine (i.v.) dose equivalent, mg	18.2 (11.5; 30.0)	18.2 (11.1; 30.1)	18.6 (14.4; 29.5)	0.814 ^W

Postoperative administration of opioids and total total Morphine (i.v.) dose equivalent during the first three postoperative days in patients with and without postoperative delirium. Data are presented as numbers and percentages or as median (25.; 75. percentile). ^{Chi} Chi-square test, ^W Wilcoxon-Mann-Whitney test.

Table E5 Perioperative data

	overall	no postoperative delirium	postoperative delirium	p-value
Type of surgery				
CABG and valve surgery, n (%)	34 (24)	22 (20)	12 (36)	0.110 ^{Chi}
CABG and aortic valve surgery, n (%)	28 (20)	19 (18)	9 (27)	
CABG and mitral valve surgery, n (%)	6 (4)	3 (3)	3 (9)	
Surgery details				
Number of performed grafts, n	2 (2; 3)	2 (2; 3)	2 (2; 3)	0.434 ^W
Duration of ischemia, min	54.0 (43.8; 73.3)	52.5 (41.0; 70.5)	63.0 (46.3; 78.8)	0.085 ^W
Duration of bypass, min	89.5 (68.3; 114.5)	87.5 (66.0; 108.5)	104.0 (82.3; 129.3)	0.020 ^W
Anaesthetics				
Ketamine, n (%)	12 (9)	11 (11)	1 (3)	0.231 ^{Chi}
Etomidate, n (%)	104 (79)	81 (79)	23 (79)	0.938 ^{Chi}
Propofol, n (%)	65 (49)	50 (49)	15 (52)	0.762 ^{Chi}
Midazolam, n (%)	43 (33)	35 (34)	8 (28)	0.516 ^{Chi}
Sufentanil, n (%)	132 (100)	103 (100)	29 (100)	
Pancuronium, n (%)	120 (91)	92 (89)	28 (97)	0.231 ^{Chi}
Rocuronium, n (%)	12 (9)	11 (8)	1 (1)	0.231 ^{Chi}
Sevoflurane, n (%)	131 (99)	102 (99)	29 (100)	0.594 ^{Chi}

Perioperative data of patients without and with postoperative delirium. Data are presented as median (25.; 75. percentile) or numbers and percentages. ^{Chi} Chi-square test; ^W Wilcoxon-Mann-Whitney test. CABG: coronary artery bypass grafting.

Table E6 **Extended multivariable logistic regression model for postoperative delirium as a dependent variable**

Variable	OR	95% CI	p-value
CSA (reference: no SDB or OSA)	4.33	(1.17; 16.11)	0.029
Age ≥70 years	6.51	(1.93; 21.95)	0.003
Male sex	0.96	(0.20; 4.71)	0.960
Body mass index <25 kg/m ²	3.14	(0.74; 13.33)	0.121
Diabetes mellitus	1.00	(0.30; 3.30)	0.994
Heart failure [‡]	2.58	(0.73; 9.19)	0.142
History of transient ischemic attack or stroke	5.35	(1.28; 22.37)	0.022
Anemia [*]	2.74	(0.76; 9.88)	0.123
Renal failure [†]	0.83	(0.22; 3.07)	0.779
CABG and valve surgery	1.08	(0.31; 3.79)	0.905
Preoperative need for loop diuretics	4.44	(1.19; 16.54)	0.026

Multivariable regression analysis. Association of preoperative parameters with postoperative delirium. Values are presented as OR: Odds ratio and 95% CI: confidence interval. OSA: obstructive sleep apnoea; CSA: central sleep apnoea; SDB: sleep-disordered breathing; ^{*}Hemoglobin <12 g/dl (women) or <13 g/dl (men); [†] GFR <60 ml/min/1.73 m²; [‡] NT-proBNP ≥450 pg/mL (patients < 50 years of age), ≥900 pg/mL (patients ≥50 and <75 years of age) or ≥1800 pg/mL (patients ≥75 years of age).

Table E7 Studies evaluating the association between sleep-disordered breathing and postoperative delirium

Study, year	study type	source of patients	n	SDB assessment	delirium assessment	mean age \pm SD (years)	prevalence of postoperative delirium	endpoints	p-value	independent risk factors for delirium
CONSIDER AF sub-analysis	prospective observational, single center	CABG \pm valve surgery	141	PG, AHI \geq 15/h	CAM-ICU	67.7 \pm 8.6	23.4%	prevalence of postoperative delirium	<0.001	age \geq 70 years history of TIA or stroke CSA heart failure anemia
								no SDB 15.9%		
								OSA 13.5%		
								CSA 48.6%		
Flink et al., 2013 [10]	prospective observational, single center	knee arthroplasty	106	PSG, medical records	CAM-ICU DRS-R98	\geq 65	25%	severity of SDB	0.0123	OSA
								no postoperative delirium AHI: 14.4/hour		
								postoperative delirium AHI: 23.7/hour		
Roggenbach et al. 2014 [11]	prospective observational, single center	cardiac surgery	92	PG	CAM-ICU	67.5 \pm 9	48%	prevalence of postoperative delirium	0.001	preoperative AHI age smoking status blood transfusion
								no OSA 20.9%		
								severity of SDB		
								no postoperative delirium AHI: 13.2/hour		
								postoperative delirium AHI: 27.7/hour		

Figure E1 RASS and CAM-ICU worksheet

RASS and CAM-ICU Worksheet

Step One: Sedation Assessment

The Richmond Agitation and Sedation Scale: The RASS*

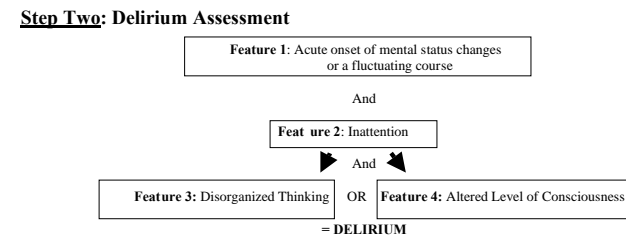
Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	Physical Stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	
-5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

- Observe patient**
 - Patient is alert, restless, or agitated. (score 0 to +4)
- If not alert, state patient's name and say to open eyes and look at speaker.** (score -1)
 - Patient awakens with sustained eye opening and eye contact. (score -1)
 - Patient awakens with eye opening and eye contact, but not sustained. (score -2)
 - Patient has any movement in response to voice but no eye contact. (score -3)
- When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.**
 - Patient has any movement to physical stimulation. (score -4)
 - Patient has no response to any stimulation. (score -5)

If RASS is -4 or -5, then **Stop** and **Reassess** patient at later time
 If RASS is above -4 (-3 through +4) then **Proceed to Step 2**

*Sessler, et al. AJRCCM 2002; 166:1338-1344. Ely, et al. JAMA 2003; 289:2983-2991.



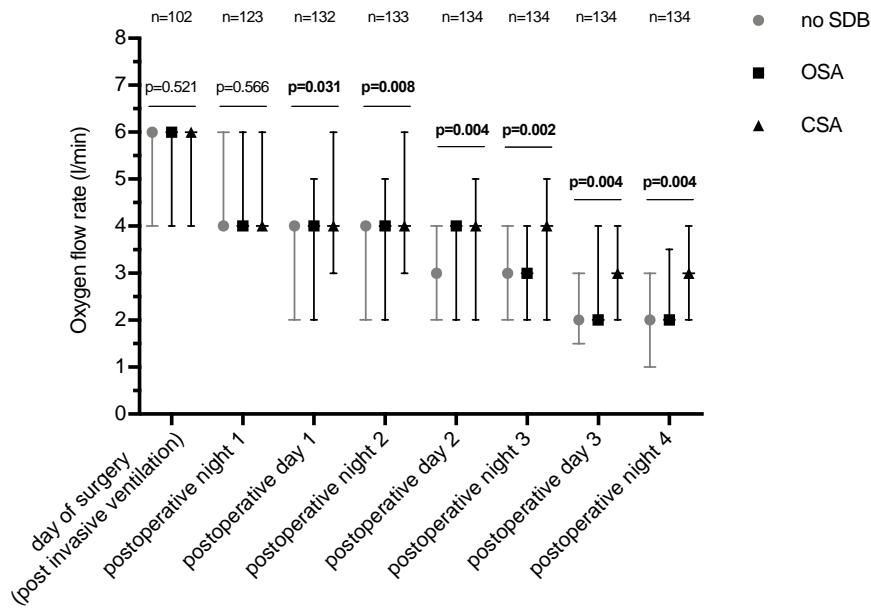
CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course Positive if you answer 'yes' to either 1A or 1B.	Positive	Negative
1A: Is the pt different than his/her baseline mental status? Or 1B: Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS, or previous delirium assessment?	Yes	No
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. Attempt the ASE letters first. If pt is able to perform this test and the score is clear, record this score and move to Feature 3. If pt is unable to perform this test or the score is unclear, then perform the ASE Pictures. If you perform both tests, use the ASE Pictures' results to score the Feature.	Positive	Negative
2A: ASE Letters: record score (enter NT for not tested) <i>Directions:</i> Say to the patient. "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone. S A V E A H A A R T Scoring: Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Score (out of 10): _____	
2B: ASE Pictures: record score (enter NT for not tested) Directions are included on the picture packets.	Score (out of 10): _____	
Feature 3: Disorganized Thinking Positive if the combined score is less than 4	Positive	Negative
3A: Yes/No Questions (Use either Set A or Set B, alternate on consecutive days if necessary): <div style="display: flex; justify-content: space-between;"> <div> Set A 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? </div> <div> Set B 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do two pounds weigh more than one pound? 4. Can you use a hammer to cut wood? </div> </div>	Combined Score (3A+3B): ____ (out of 5)	
3B: Command Say to patient: "Hold up this many fingers" (Examiner holds two fingers in front of patient) "Now do the same thing with the other hand" (Not repeating the number of fingers). *If pt is unable to move both arms, for the second part of the command ask patient "Add one more finger" Score ____ (Patient earns 1 point if able to successfully complete the entire command)		
Feature 4: Altered Level of Consciousness Positive if the Actual RASS score is anything other than "0" (zero)	Positive	Negative
Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Positive	Negative

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Figure E2 Postoperative oxygen flow rates

A



B

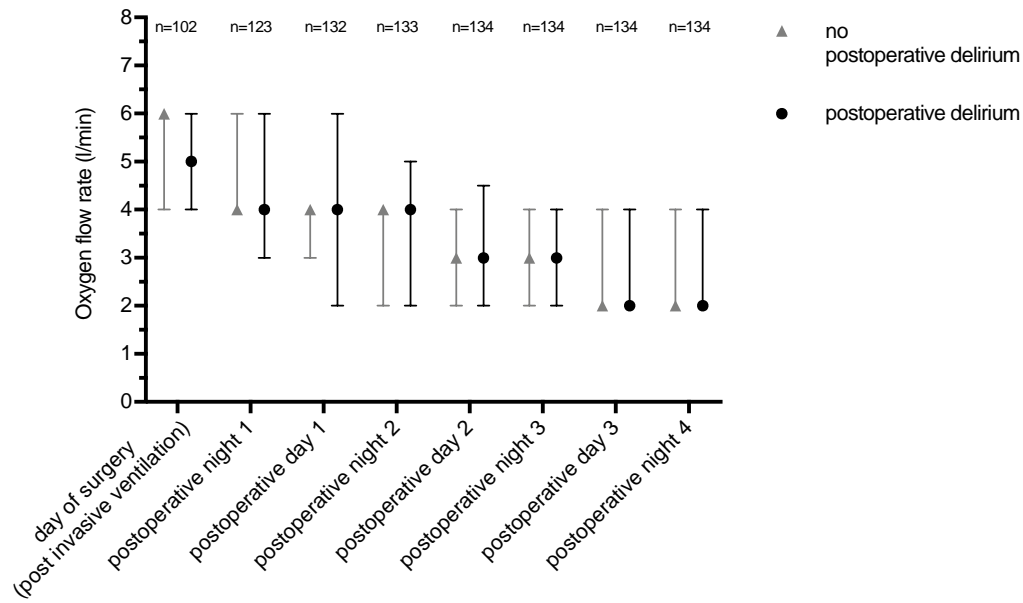
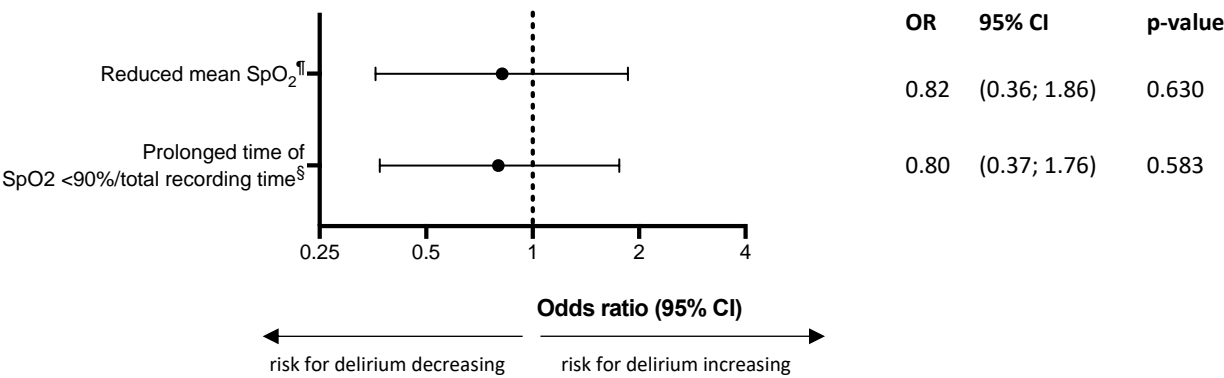


Figure E3 **Parameters of nocturnal hypoxia as predictors of postoperative delirium**



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