Supplement:

Ventilatory effects of isoflurane sedation via the Sedaconda ACD-S versus ACD-L: a substudy of a randomized trial

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Table S1: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Patients ≥18 years	Never at target RASS in 8 hours prior to randomization
Continuous invasive ventilation and sedation ≤48 hours at start of study sedation	History of or genetic predisposition to malignant hyperthermia
Clinically likely to need invasive ventilation and sedation ≥24 hours at randomization	Uncompensated circulatory failure (MAP <55 mmHg despite IV fluids and vasopressors)
Ongoing sedation with propofol at time of randomization	Severe hepatic impairment (Child–Pugh Score C)
Prescribed target sedation depth within the RASS range –1 to –4	Significant laboratory abnormalities
Signed informed consent, or emergency inclusion criteria fulfilled and documented	Acute neuropathology without ICP monitoring (including but not limited to stroke, neurosurgery, and head trauma)
	Scheduled for surgery within 24 hours from randomization
	Tidal volume <350 mL
	History of any clinically significant disease in the opinion of the Investigator
	Need for continuous muscle relaxation at the time of randomization
	Pregnancy
	History of allergy/hypersensitivity to isoflurane or propofol
	Known participation in any other clinical study that included drug treatment within 3 months of the first administration of study drug
	Documented limitation of medical treatment

ICP=intracranial pressure. IV=intravenous. MAP=mean arterial pressure. RASS=Richmond Agitation–Sedation Scale.

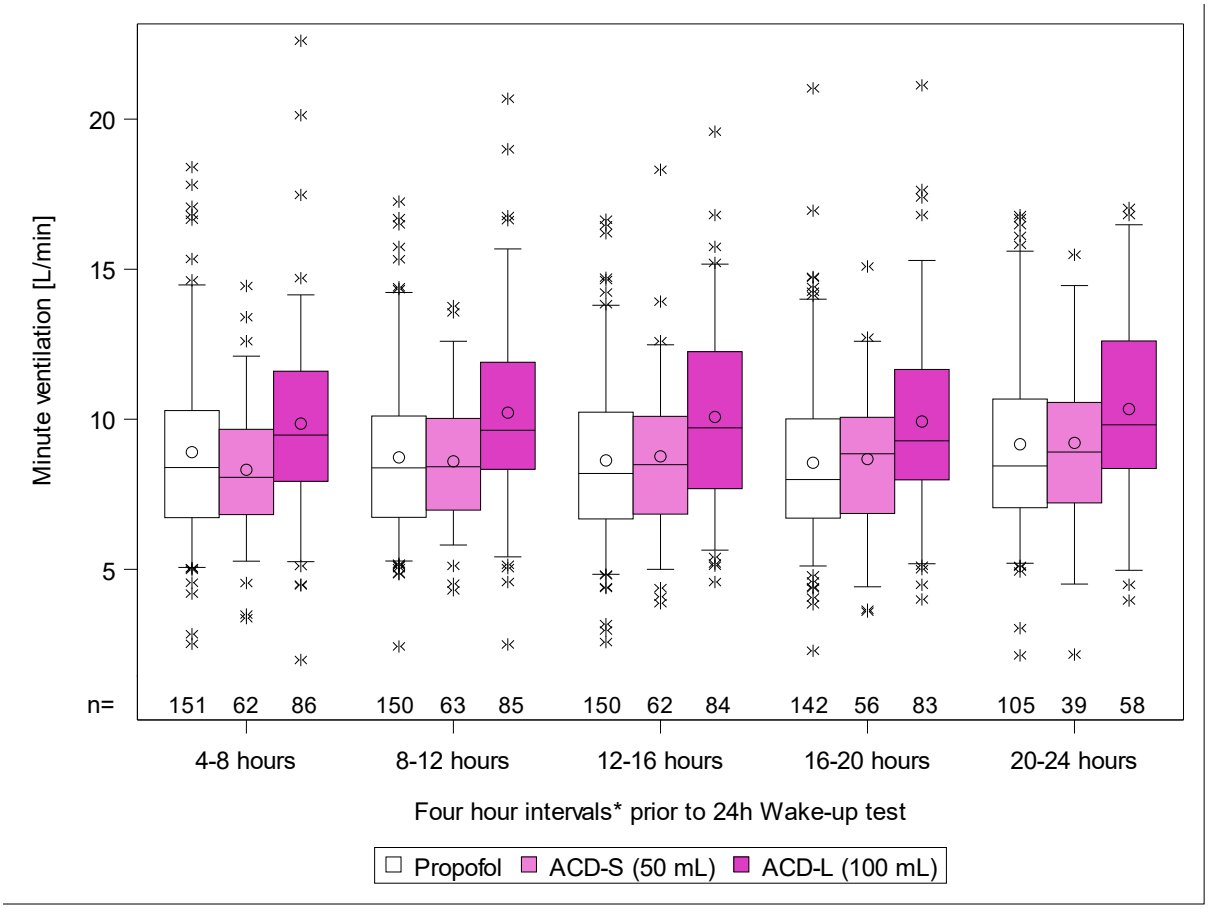


Figure S1: Minute ventilation

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 1.3 [0.7, 1.8]; p<0.001

ACD-S versus Propofol: -0.1 [-0.7, 0.6]; p=0.822

ACD-L versus ACD-S: 1.3 [0.6, 2.0]; p<0.001

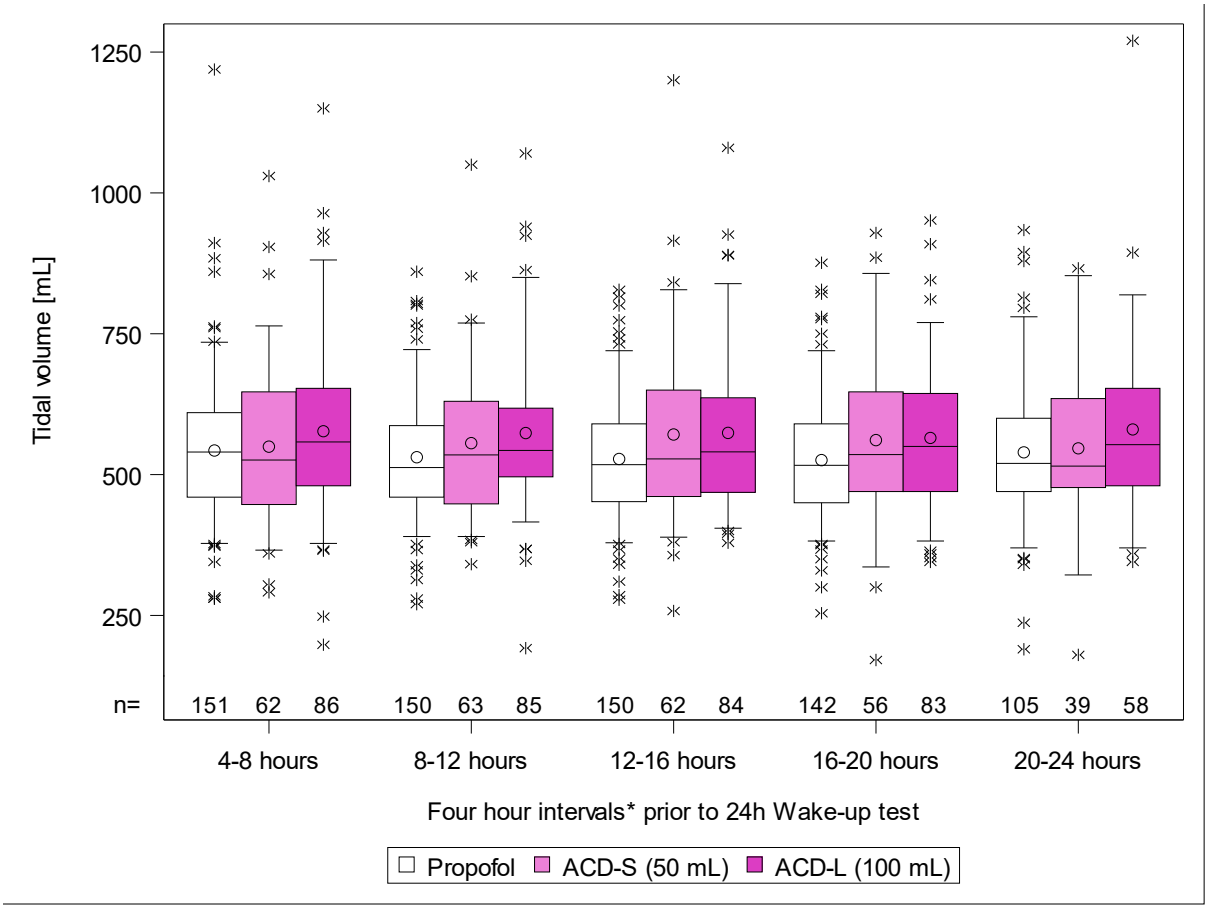


Figure S2: Tidal volume

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

Average differences [95% confidence interval]:

ACD-L versus Propofol: 44 [16, 72]; p=0.002

ACD-S versus Propofol: 24 [-7, 55]; p=0.126

ACD-L versus ACD-S: 20 [-15, 55]; p=0.255

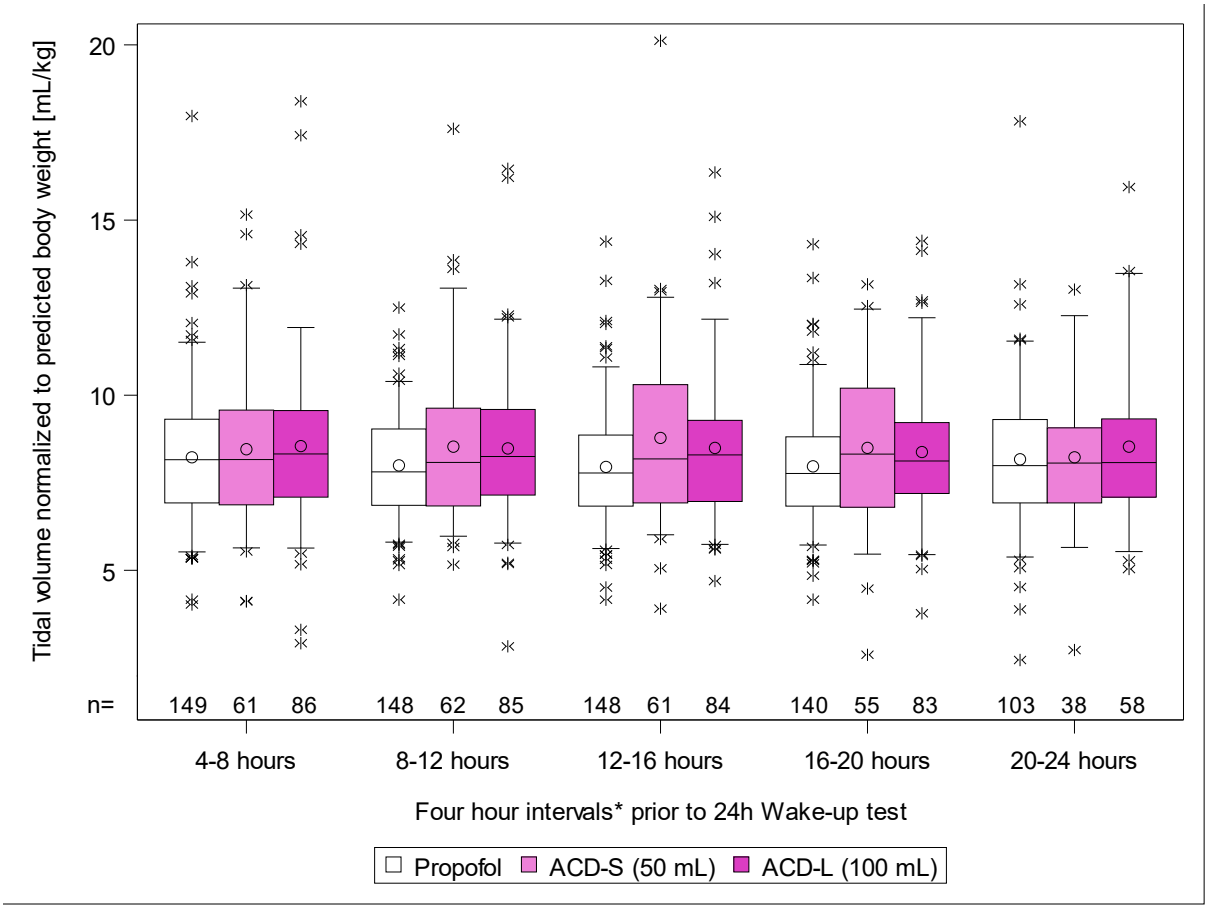


Figure S3: Tidal volume normalized to predicted body weight

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 0.45 [0.00, 0.90]; p=0.049

ACD-S versus Propofol: 0.47 [-0.03, 0.97]; p=0.067

ACD-L versus ACD-S: -0.02 [-0.58, 0.55]; p=0.951

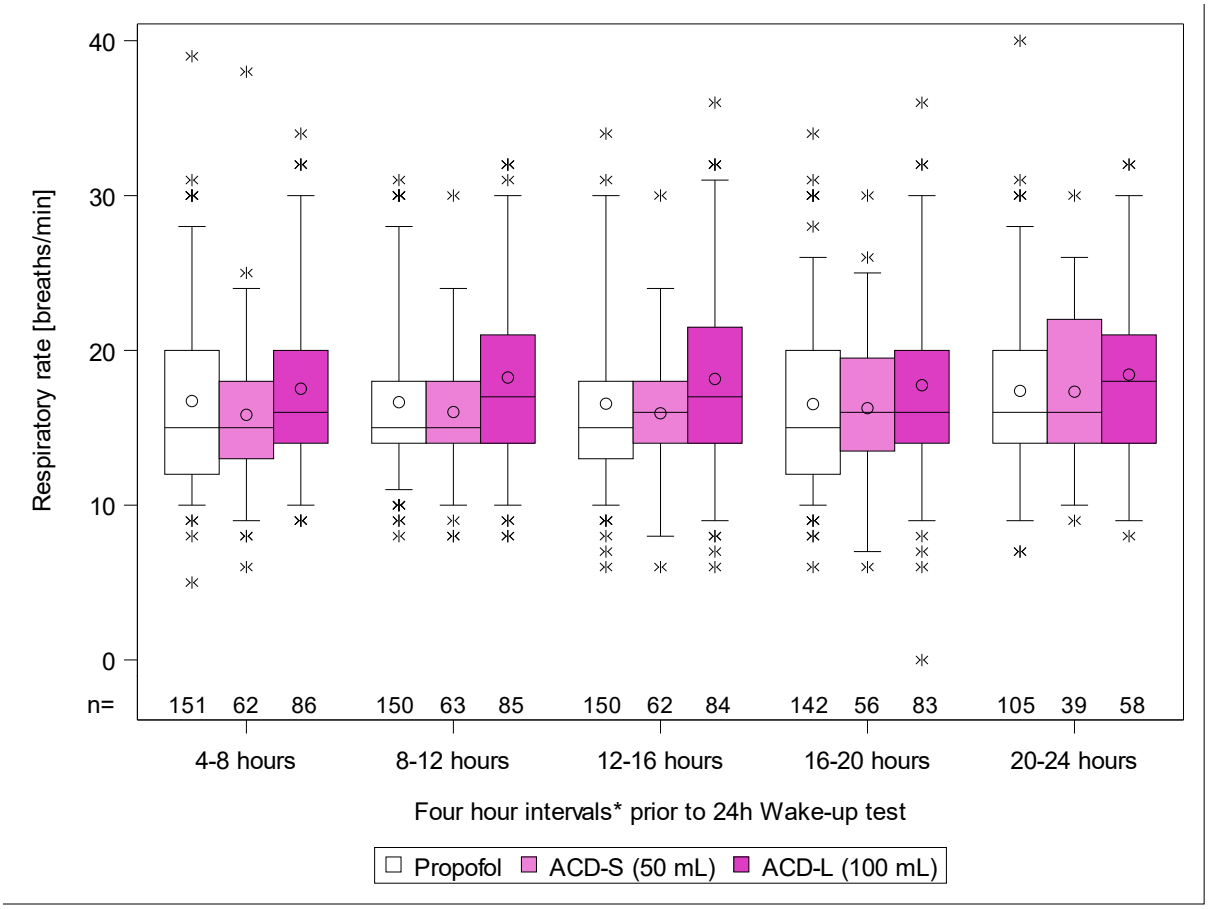


Figure S4: Respiratory rate

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>
ACD-L versus Propofol: 1.2 [0.1, 2.2]; p=0.025
ACD-S versus Propofol: -0.5 [-1.6, 0.6]; p=0.392
ACD-L versus ACD-S: 1.7 [0.4, 2.9]; p=0.011

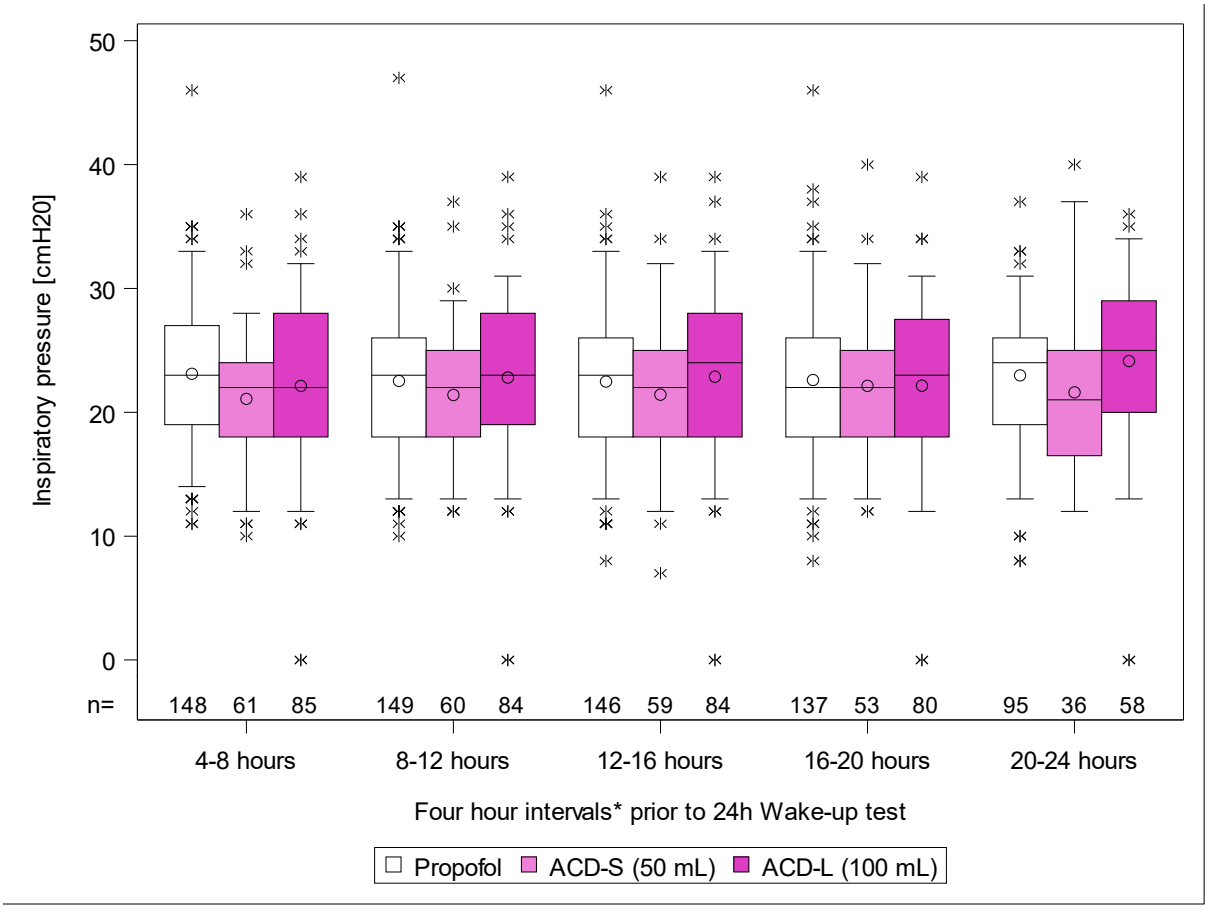


Figure S5: Inspiratory pressure

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 0.2 [-1.2, 1.6]; p=0.799

ACD-S versus Propofol: -1.3 [-3.0, 0.3] p=0.098

ACD-L versus ACD-S: 1.5 [-0.3, 3.3]; p=0.095

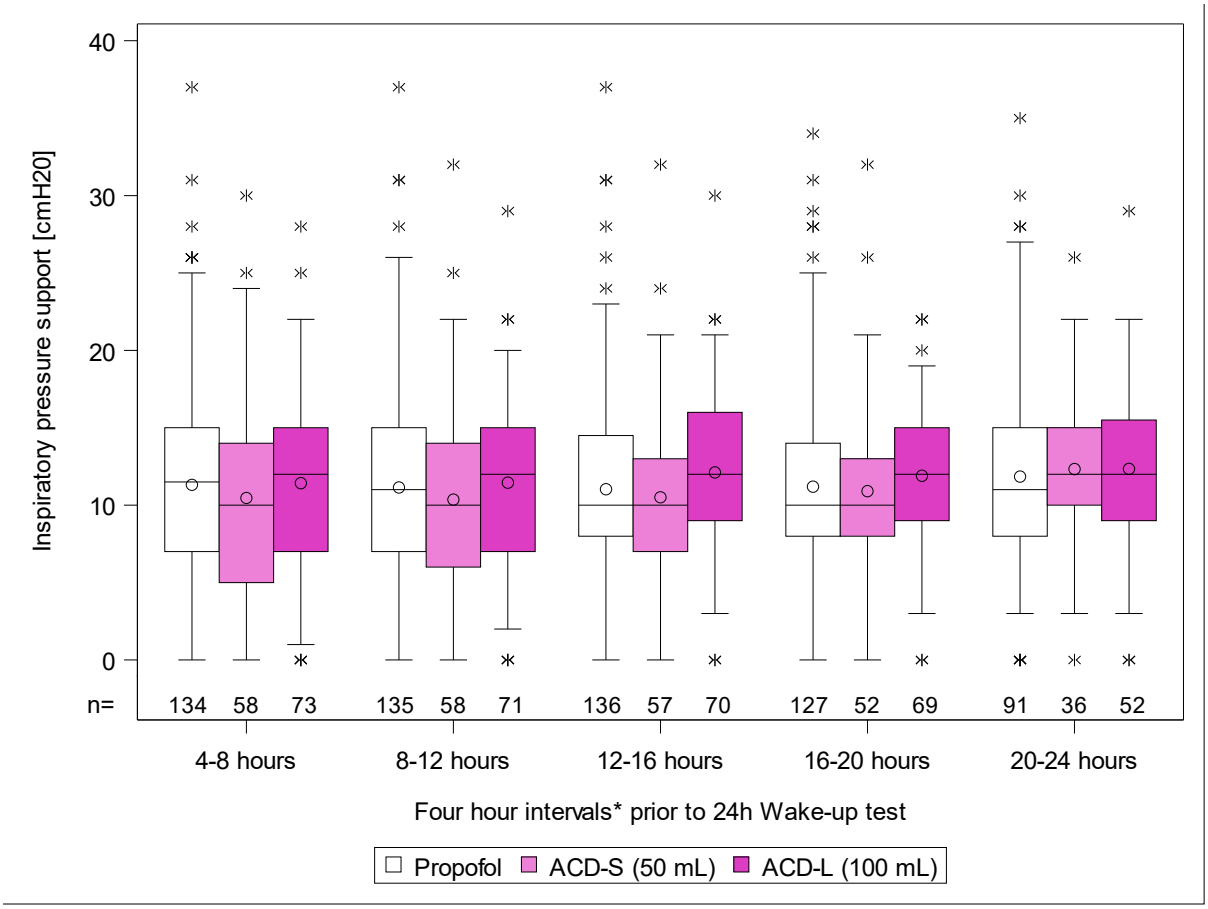


Figure S6: Inspiratory pressure support during spontaneous ventilation (pressure support above positive end-expiratory pressure)

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of §§the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 0.6 [-0.8, 2.1]; p=0.393

ACD-S versus Propofol: -0.6 [-2.2, 1.0]; p=0.492

ACD-L versus ACD-S: 1.2 [-0.6, 3.0]; p=0.197

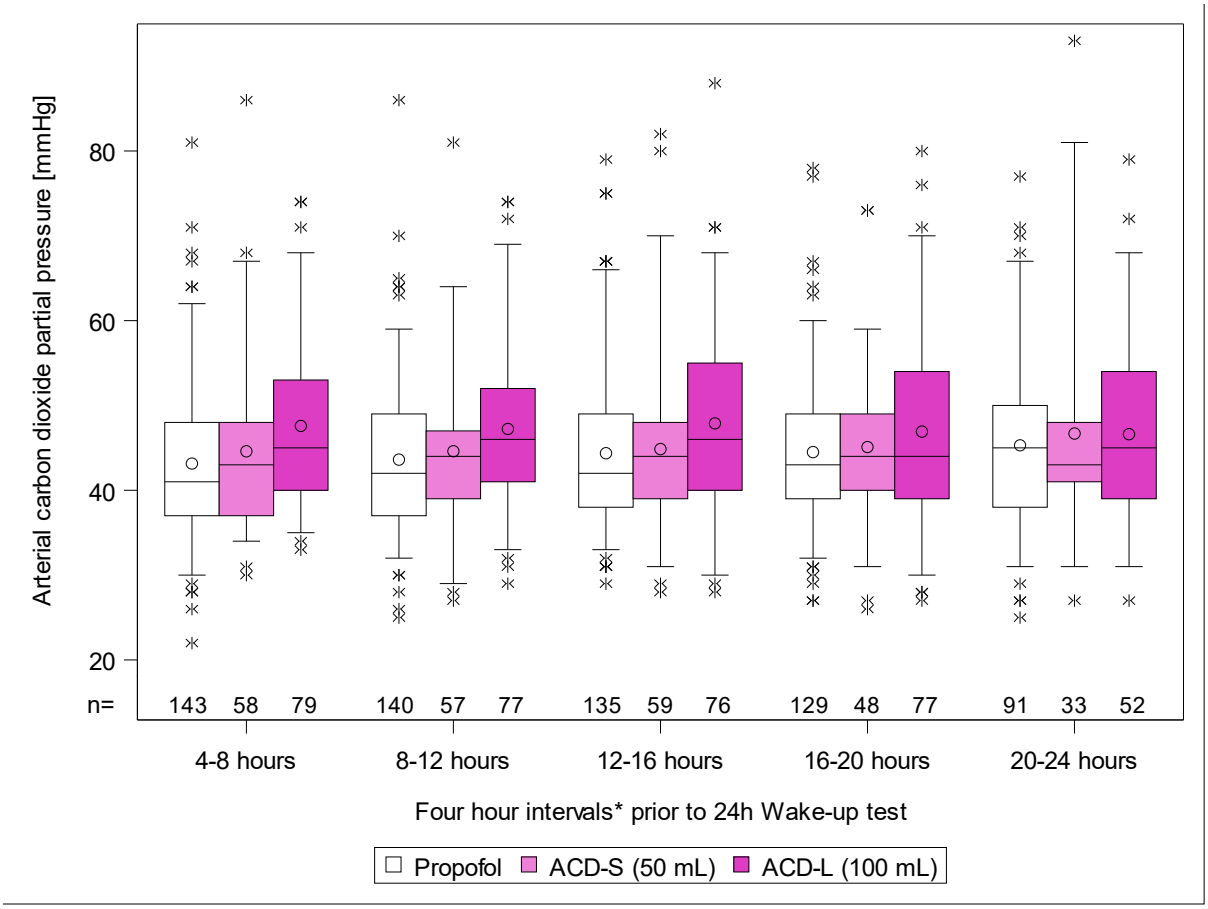


Figure S7: Arterial carbon dioxide partial pressure

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 3.4 [1.2, 5.6]; p=0.002

ACD-S versus Propofol: 1.1 [-1.4, 3.5]; p=0.380

ACD-L versus ACD-S: 2.3 [-0.4, 5.1]; p=0.098

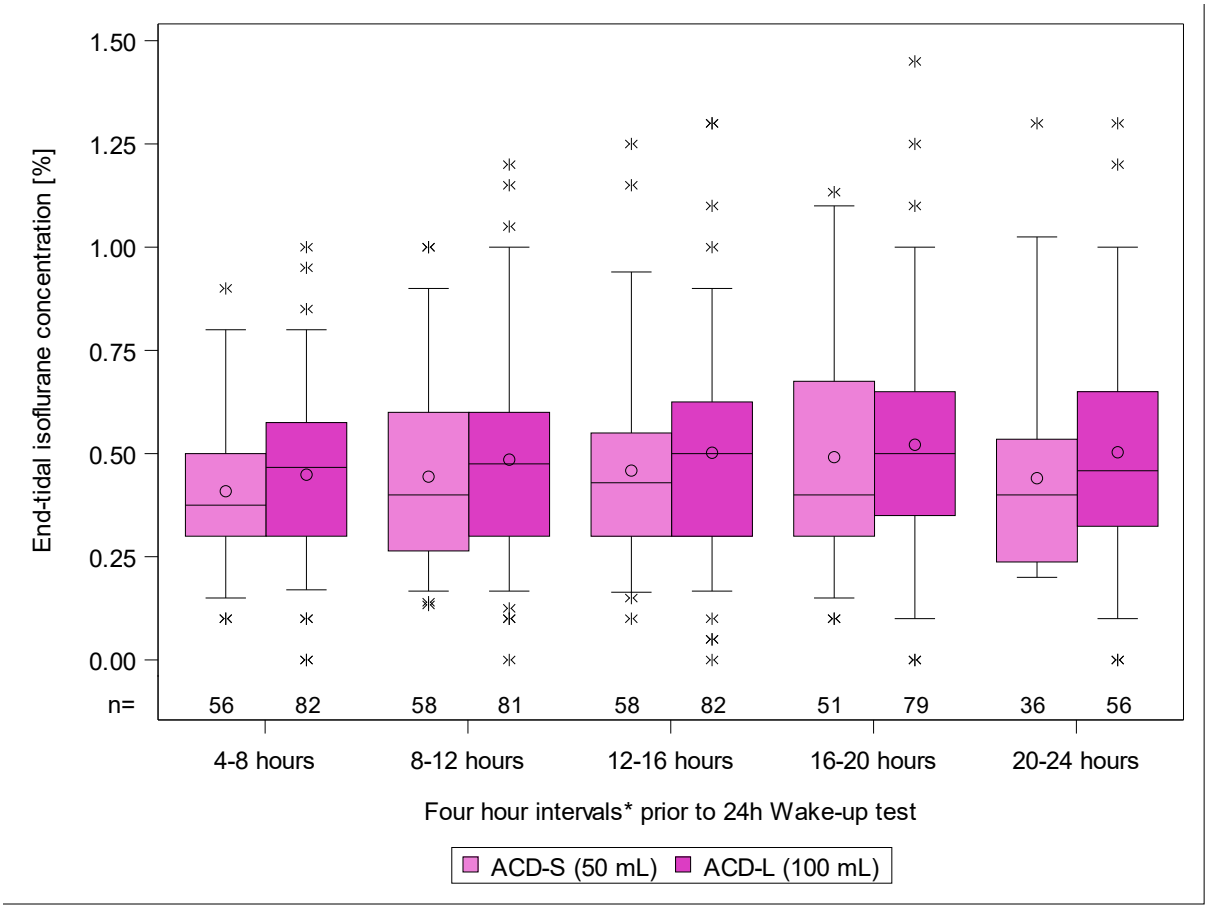


Figure S8: End-tidal isoflurane concentration

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>
ACD-L versus ACD-S: 0.04 [-0.03, 0.10]; p=0.287

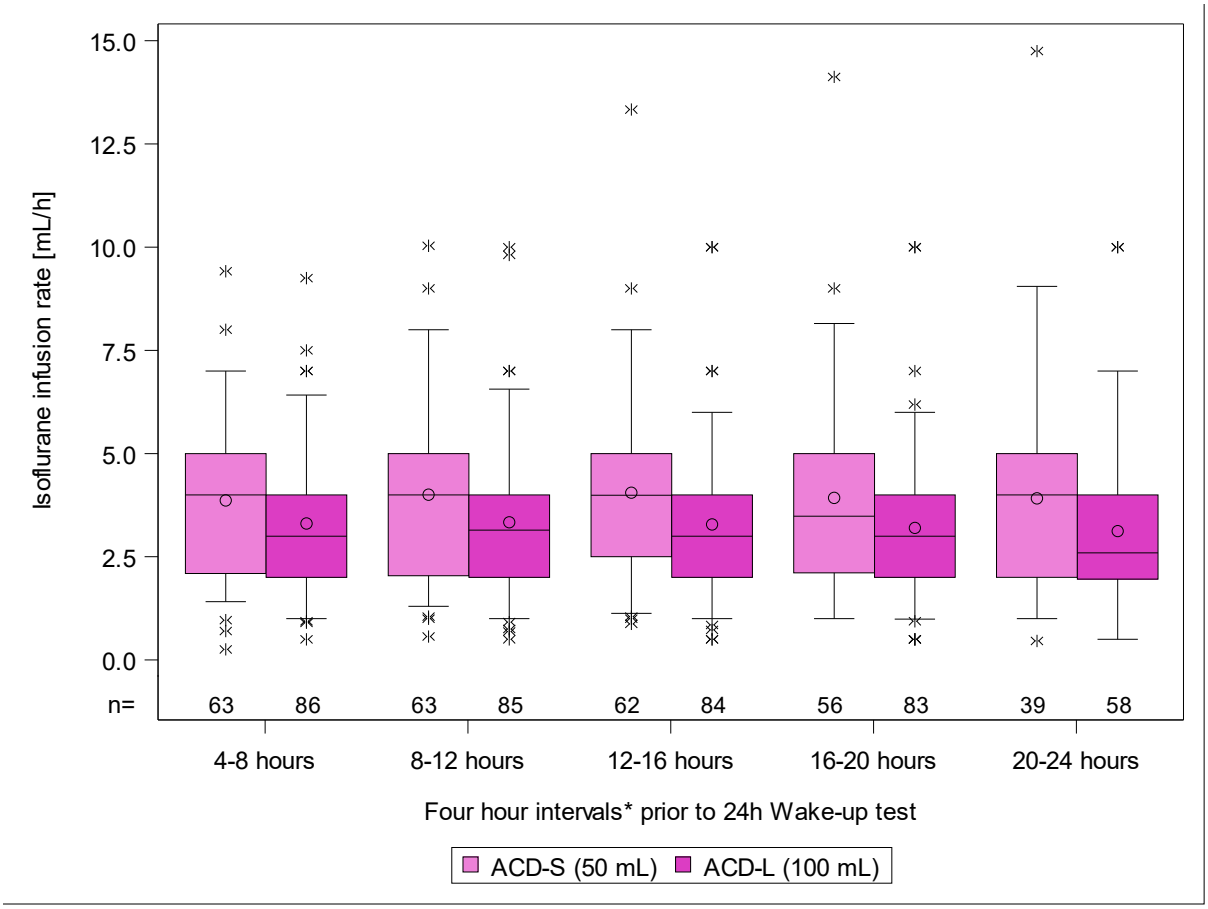


Figure S9: Isoflurane infusion rate

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

Average differences [95% confidence interval]:

ACD-L versus ACD-S: -0.7 [-1.3, 0.1] mL/h; p=0.022

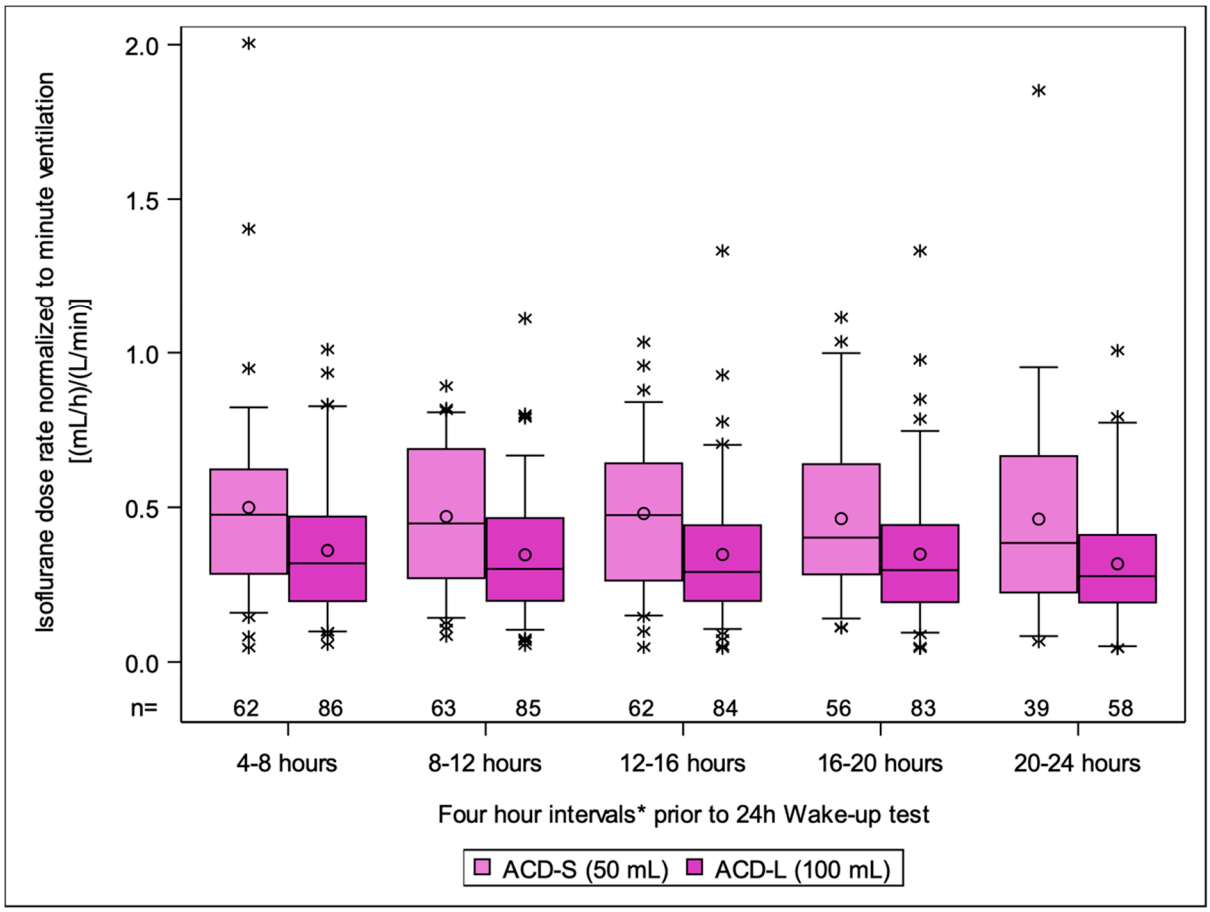


Figure S10: Isoflurane consumption normalized to minute ventilation

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus ACD-S: -0.13 [-0.20, -0.07]; p<0.001

Subgroup analysis: Chronic Obstructive Pulmonary Disease (COPD)

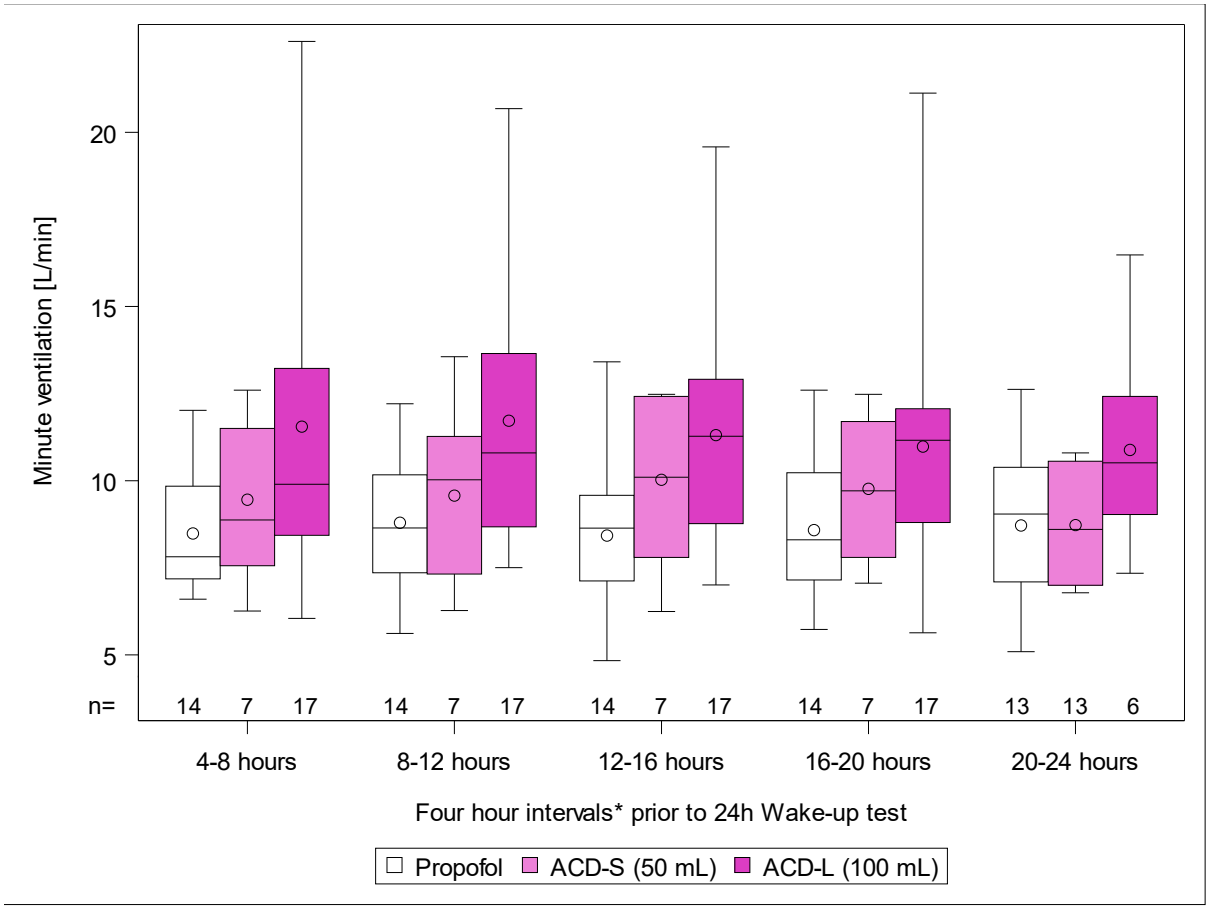


Figure S11: Minute ventilation in COPD patients

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume. COPD, chronic obstructive pulmonary disease.

Average differences [95% confidence interval]:

ACD-L versus Propofol: 2.0 [0.3, 3.7]; p=0.024

ACD-S versus Propofol: -0.8 [-3.2, 1.6]; p=0.511

ACD-L versus ACD-S: 2.8 [0.7, 4.9]; p=0.011

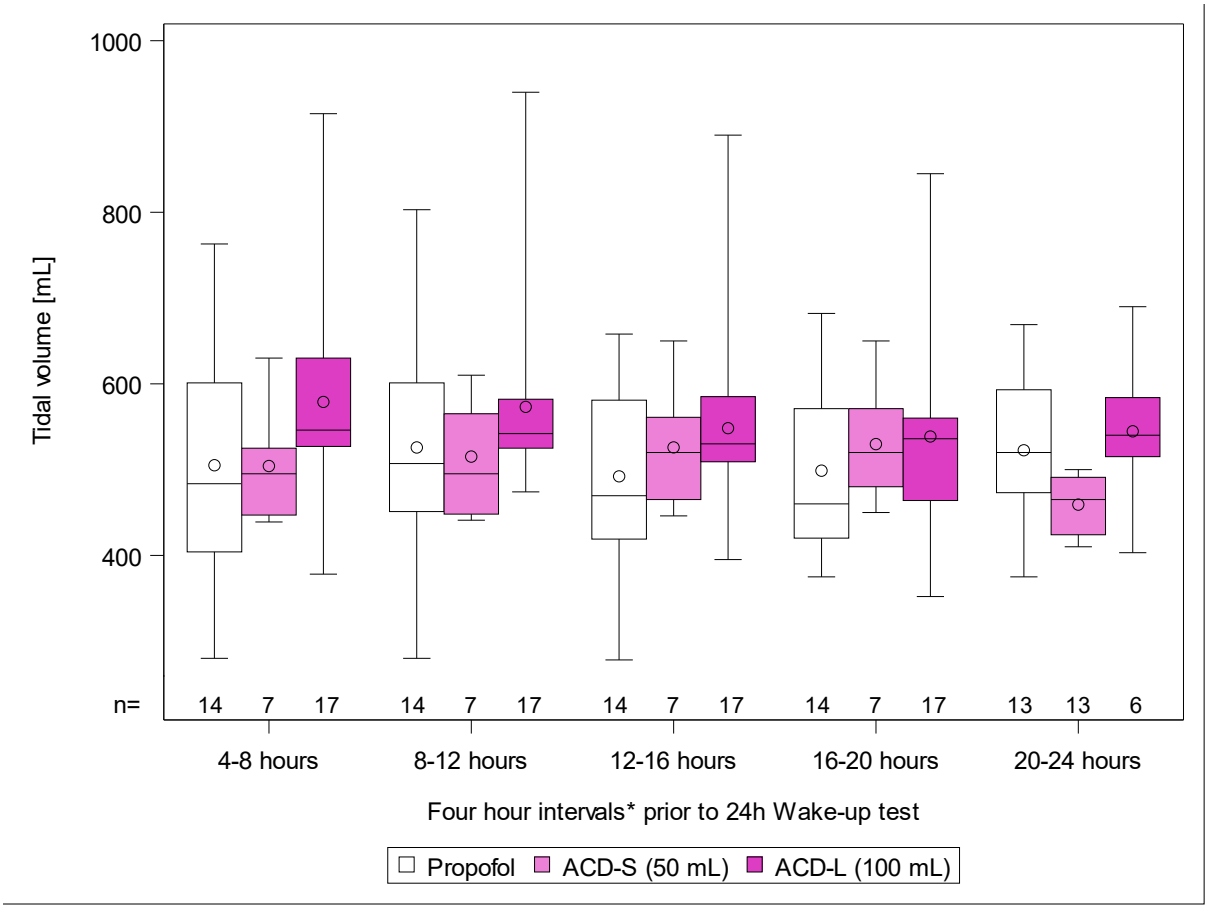


Figure S12: Tidal volume in COPD patients

* Intervals 0-4 hours and 24-28 hours have been excluded from analysis, because of the limited number of assessments available. Boxes present means, medians, and interquartile ranges. Whiskers present lowest and highest observed value within 5th percentile low and the 95th percentile high. Stars represent outliers. ACD-S, anesthetic conserving device with 50 mL internal volume. ACD-L, anesthetic conserving device with 100 mL internal volume. COPD, chronic obstructive pulmonary disease.

<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 49 [-23, 121]; p=0.171

ACD-S versus Propofol: -7.4 [-105, 90]; p=0.878

ACD-L versus ACD-S: 57 [-35, 148]; p=0.216

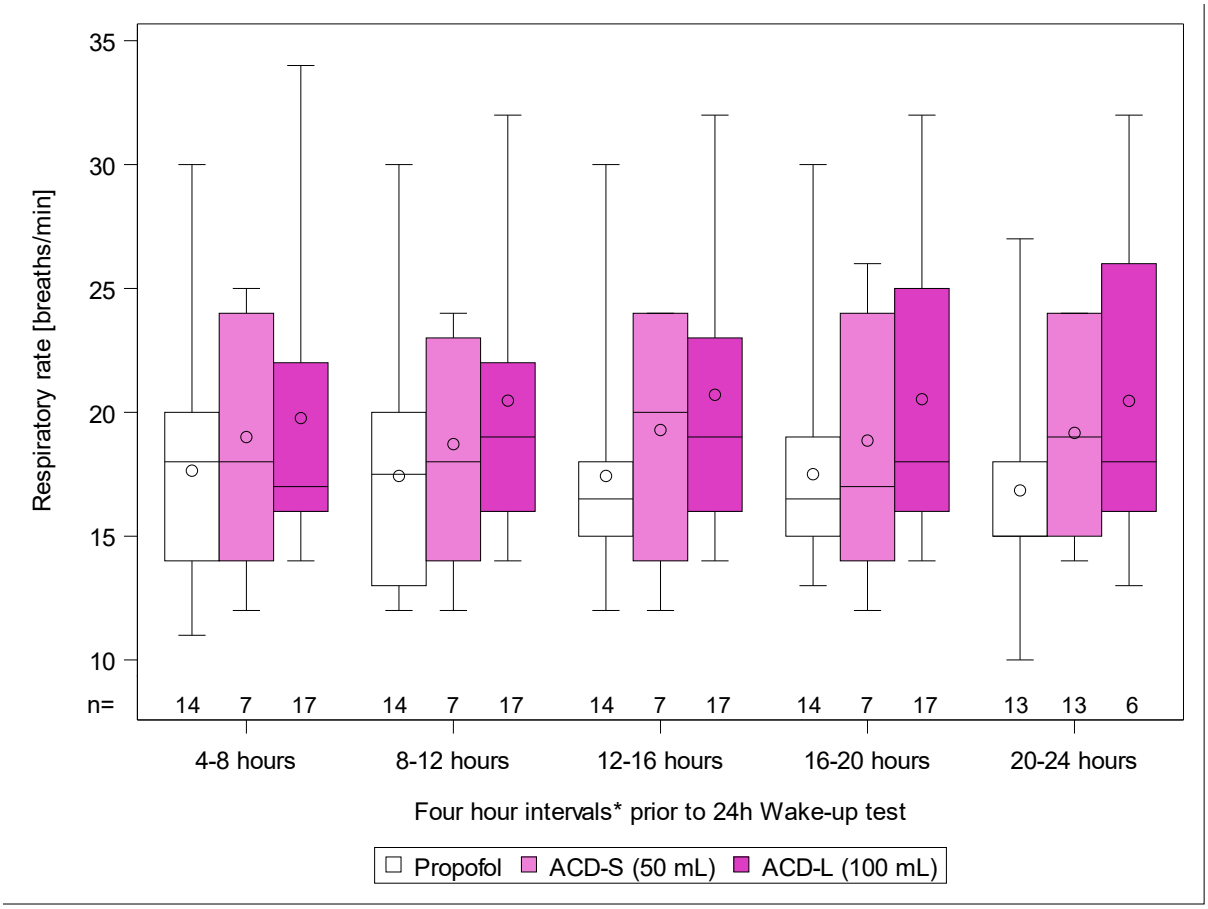


Figure S13: Respiratory rate in COPD patients

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<u>Average differences [95% confidence interval]:</u>
ACD-L versus Propofol: 2.5 [-0.8, 5.8]; p=0.129
ACD-S versus Propofol: 0.2 [-4.3, 4.8]; p=0.918
ACD-L versus ACD-S: 2.3 [-1.8, 6.3]; p=0.262

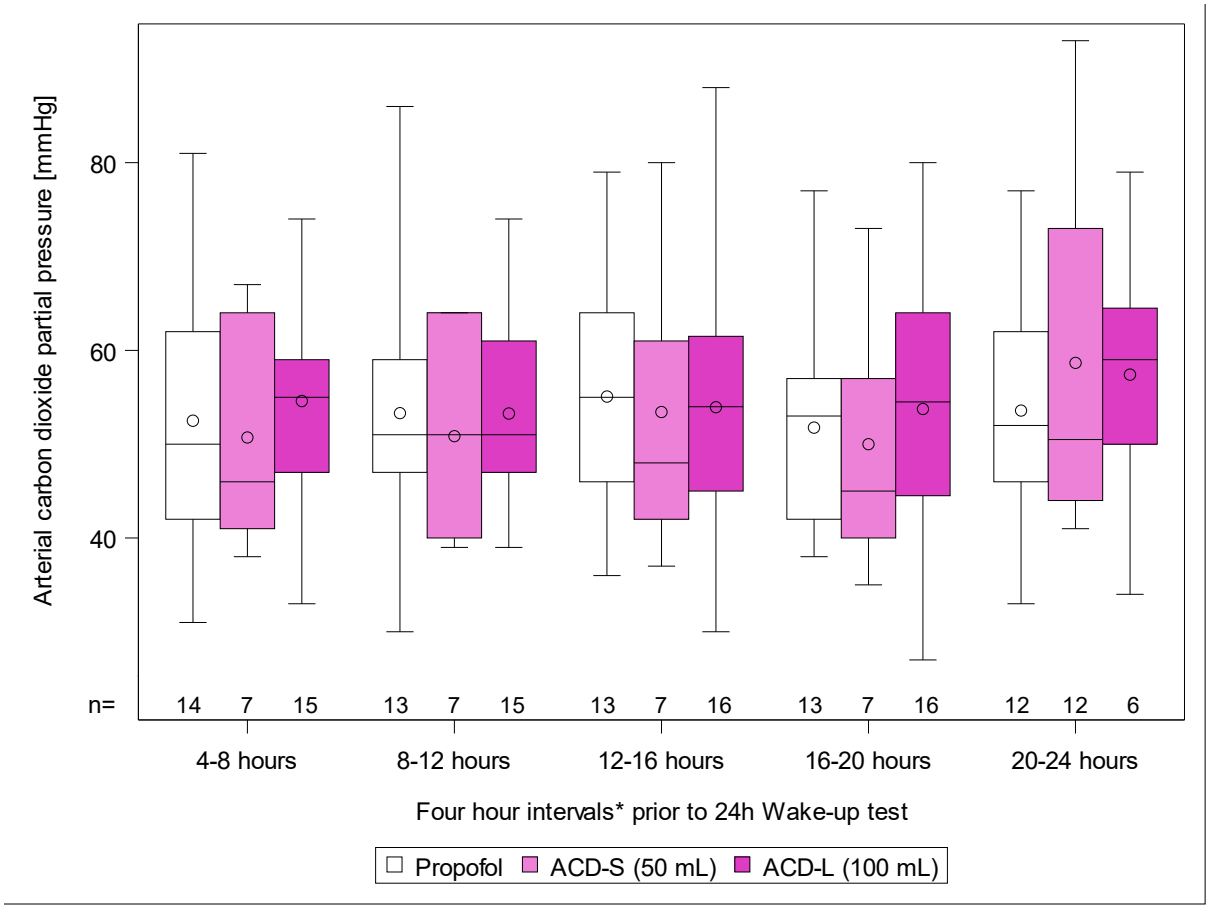


Figure S14: Arterial carbon dioxide partial pressure in COPD patients

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<u>Average differences [95% confidence interval]:</u>

ACD-L versus Propofol: 2.3 [-5.3, 9.9]; p=0.537

ACD-S versus Propofol: -2.1 [-12.5, 8.2]; p=0.680

ACD-L versus ACD-S: 4.4 [-4.7, 13.5]; p=0.327