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LETTER

Rapid temperature increases under isoflurane sedation

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Dear Editor,

Impairment of thermoregulation by inhaled and intravenous anesthetics has been extensively studied and essentially all anesthetics blunt thermoregulatory responses [1]. Interestingly, isoflurane—unlike propofol—shows a non-linear dose response suggesting largely preserved thermoregulatory responses within low dose ranges [2, 3]. Fever may thus develop more rapidly under isoflurane sedation. Similarly, more prominent temperature increases were observed during dexmedetomidine compared to predominant propofol sedation [4]. We therefore compared characteristics of temperature increases between isoflurane and propofol sedation in a one-year cohort of critically ill patients treated at our surgical intensive care unit.

This study was approved by the responsible ethics committee (2020-11-23, 295/20, Saarland Medical Association, Saarbrücken, Germany). Patients were ventilated for at least 96 hours in 2019 and received isoflurane or propofol for at least 48 hours. Patient characteristics are presented in the electronic supplementary material (ESM, Tables S1 and S2). Core temperatures were measured via urinary catheter temperature probes, digitally collected, and validated by the responsible intensive care nurse. Frequency of fever and temperature increases were assessed with adjustments for age, sex, body mass index, opioid intake, length of sedation, Simplified Acute Physiology Score (SAPS) II on admission, and daily Sequential Organ Failure Assessment (SOFA) score using logistic or linear generalized estimating equations regression.

Overall, 97 patients were included; 13 received isoflurane, 21 received propofol, and 63 received both sedatives sequentially on different sedation days. Across a total of 725 sedation days, isoflurane was administered on 257 (35%) and propofol on 468 (65%) days. Fever defined by core temperatures ≥ 38.5°C was twice as common in isoflurane-sedated patients: 41/257 days (16%) vs. 41/468 days (9%); odds ratio [95% confidence interval (CI)]: 2.4 [1.1, 5.1], p = 0.021.

Temperature increases on fever days were more rapid under isoflurane, and both the fever threshold (≥ 38.5°C) and peak temperatures were reached more quickly: average difference [95% CI]: − 320 minutes [− 454, − 187], p < 0.001; − 302 minutes [− 465, − 138], p < 0.001 (Fig. 1). Maximum increases observed within 1 or 2 hours were significantly greater under isoflurane than propofol sedation: 0.13°C/h [0.02, 0.23], p = 0.019; 0.17°C/2h [0.05, 0.29], p = 0.006 (Fig. 1). Baseline temperatures were slightly higher in isoflurane-sedated patients: 0.33°C [0.07, 0.59], p = 0.012; but peak temperatures were similar: 0.07°C [− 0.09, 0.23], p = 0.407. Procalcitonin and leucocyte count on fever days indicated infections but were similar with each sedation. Symptoms of malignant hyperthermia (e.g., unexplained increases in end-tidal carbon dioxide, muscle rigidity, increased laboratory markers of muscle damage) did not occur.

Our findings are consistent with drug-induced impairment of thermoregulatory responses, such as vasoconstriction and shivering. Whereas typical sedative propofol plasma concentrations of 2–4 µg/ml correspond to a decrease in the vasoconstriction threshold of 1.2–2.4°C, typical sedative end-tidal isoflurane concentrations of 0.3–0.5% correspond to a decrease less than 1°C [2, 3]. In addition, most of the isoflurane-induced thermoregulatory impairment becomes only apparent when end-tidal concentrations exceed 0.5% [3]. Consistently, lower

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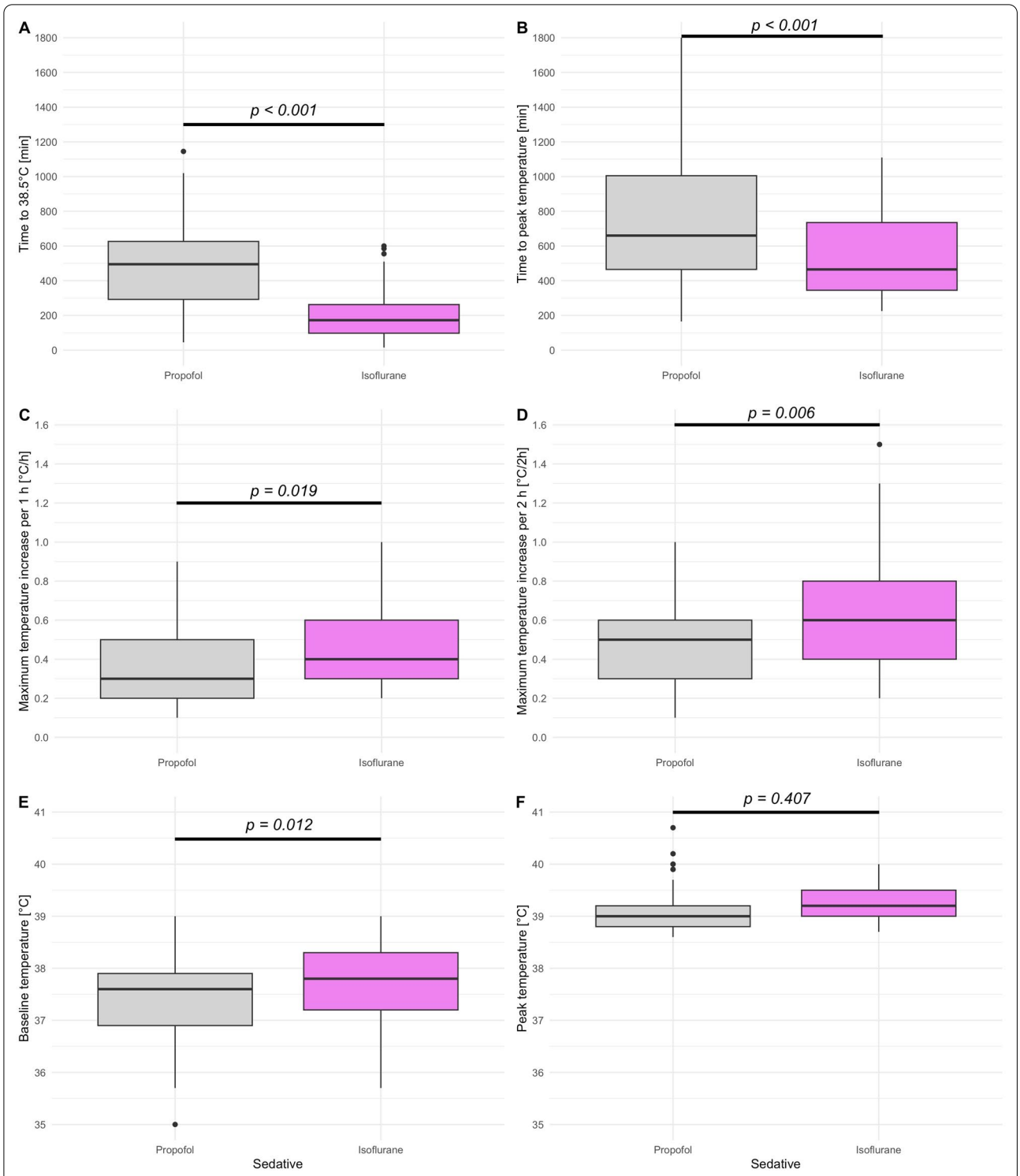

Fig. 1 Body temperature increases—isoflurane versus propofol sedation. Differences in the characteristics of core temperature increases between patients receiving isoflurane or propofol were assessed by linear generalized estimating equations regression adjusted for age, sex, body mass index, opioid intake, length of sedation, SAPSII, and SOFA score.

average temperatures were reported with propofol versus isoflurane sedation [5].

More rapid temperature increases with isoflurane than with propofol sedation most likely reflect less-attenuated thermoregulation within sedative dose ranges and should not be attributed to malignant hyperthermia unless other typical symptoms occur. The clinical significance remains to be determined.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-023-07090-z.

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Data availability statement
Data analyzed for the current study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest
LMMW received speaker fees and reimbursement of expenses for a scientific lecture on inhaled sedation of intensive care patients from Sedana Medical (Danderyd, Sweden). TV and AM received consulting fees from Sedana Medical.

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