Effects of ketamine infusion on breathing and encephalography in spontaneously breathing ICU patients

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Research Article

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Abstract

Background: Preclinical studies suggest that ketamine stimulates breathing. We investigated whether adding a ketamine infusion at low and high doses to propofol sedation improves inspiratory flow and enhances sedation in spontaneously breathing critically ill patients.

Methods: In this prospective interventional study, twelve intubated, spontaneously breathing patients received ketamine infusions at 5 mcg/kg/min, followed by 10 mcg/kg/min for 1 hour each. Airway flow, pressure, and esophageal pressure were recorded during a spontaneous breathing trial (SBT) at baseline, and during the SBT conducted at the end of each ketamine infusion regimen. SBT consisted of one-minute breathing with zero end-expiratory pressure and no pressure support. Changes in inspiratory flow at the pre-specified time points were assessed as the primary outcome. Ketamine-induced changes in gamma electroencephalogram power was the key secondary endpoint. We also analyzed changes in other ventilatory parameters respiratory timing, and resistive and elastic inspiratory work of breathing.

Results: Ketamine infusion of 5 and 10 mcg/kg/min increased inspiratory flow (median, IQR) from 0.36 (0.29-0.46) L/s at baseline to 0.47 (0.32-0.57) L/s and 0.44 (0.33-0.58) L/s, respectively (p=0.013). Resistive work of breathing decreased from 0.4 (0.1–0.6) J/l at baseline to 0.2 (0.1–0.3) J/l after ketamine 10 mcg/kg/min (p=0.042), while elastic work of breathing remained unchanged. Electroencephalogram gamma power (19–44 Hz) increased compared to baseline (p<0.01).

Conclusions: In intubated, spontaneously breathing patients receiving low-dose propofol, ketamine increased inspiratory flow, reduced inspiratory work of breathing, and was associated with an “activated” electroencephalographic pattern. These characteristics might facilitate weaning from mechanical ventilation.

Summary Statement

Low-dose infusion of ketamine improved inspiratory flow and decreased work of breathing, while providing analgesia and sedation. This suggests a potential use of ketamine as a pharmacological adjunct to facilitate weaning patients from mechanical ventilation.

Introduction

In endotracheally intubated patients in the intensive care unit (ICU), sedative and analgesic medications are often required to control anxiety and pain. Most sedatives and analgesics are respiratory depressants, which can prolong weaning from mechanical ventilation [1–3].

Ketamine exerts its effects by blockade of N-Methyl-D-aspartate (NMDA) and Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 1 (HCN1), as well as agonistic action towards the nicotinic acetyl-choline ion channels and the delta and mu-opioid receptors [4]. Findings from preclinical studies [5] and studies in healthy volunteers [6] suggest that ketamine activates breathing, and may have

bronchodilatory effects [7, 8]. A strong respiratory stimulating effect may be harmful in patients with respiratory failure vulnerable to self-inflicted lung injury [9, 10].

This pharmaco-physiological interventional trial investigated how sub-anesthetic doses of ketamine affect breathing and electroencephalography (EEG) in critically ill, intubated, spontaneously breathing patients. We tested the research hypothesis that adding a low-dose ketamine infusion to propofol sedation increases inspiratory flow in critically ill patients while expressing ketamine-specific electroencephalographic analgesic characteristics.

Materials And Methods

Study design

This prospective, open-label, pharmaco-physiological interventional study was conducted at Massachusetts General Hospital and Beth Israel Deaconess Medical Center in Boston, Massachusetts, United States of America (USA). Institutional review board approval was obtained from the Partners Human Research Committee at Massachusetts General Hospital (protocol number 2013P001690) and by cede review from the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (protocol number 2017C000525). Written informed consent was obtained from a patient's legally authorized representative before initiation of any study procedures. The study protocol is available in the online supplement (Section 1). The study was registered on clinicaltrials.gov (NCT01969227).

Study population

Patients aged ≥ 18 years admitted to a surgical ICU and requiring mechanical ventilation were eligible if they were suitable for spontaneous breathing trials based on standard hospital criteria (Online supplement, Section 1). We included patients who received a constant low-dose infusion rate of sedatives for ≥ 3 hours and were considered as candidates for low-dose ketamine.

Intervention

Eligible subjects received an infusion of ketamine at 5 mcg/kg/min for one hour (low-dose ketamine), followed by 10 mcg/kg/min for another hour (high-dose ketamine). After 2 hours, the ketamine infusion was discontinued. A trial of spontaneous breathing, defined as zero end-expiratory pressure and no pressure support for 1 minute, was performed at pre-specified time points: before initiation of ketamine (baseline), after 1 hour of infusion at 5 mcg/kg/min, and after 1 hour at 10 mcg/kg/min.

Outcomes

All measurements were taken during the pre-specified periods of spontaneous breathing without ventilator support. The primary outcome was inspiratory airflow. Ketamine-induced change in gamma electroencephalogram power was the key secondary endpoint.

Other secondary outcomes included changes in minute ventilation, tidal volume, respiratory rate, maximum inspiratory flow and expiratory flow, respiratory timing (inspiratory-to-expiratory ratio [I:E] and duty cycle [inspiratory time/total respiratory cycle time; T_i/T_{tot}]), esophageal pressure, inspiratory work of breathing, end-tidal carbon dioxide, and hemodynamic parameters (heart rate, blood pressure).

Respiratory measurements

Airflow was measured with a linear pneumotachometer (Hans Rudolph Inc., Shawnee, KS, USA) connected to a Pneumotach Amplifier 1, Series 1110 (Hans Rudolph Inc.). The pneumotachometer was calibrated using a 3-liter calibration syringe (Series 5530 Hans Rudolph Inc., Shawnee, KS, USA) before use. The pneumotachometer was connected to the ventilatory circuit during the spontaneous breathing trial using an HME Filter AirLife™ model 750/S (Carefusion, Vernon Hills, IL, USA). Airway and esophageal pressures were measured using a second Pneumotach Amplifier 1, Series 1110 (Hans Rudolph Inc., Shawnee, KS, USA) connected to the breathing circuit and esophageal balloon catheter, respectively. Analog signals were recorded using a PowerLab 16/30 Converter, Model ML880 (ADInstruments, Bella Vista, NSW 2153, Australia), and analyzed electronically using LabChart software ver. 8.1.15 (ADInstruments). Inspiratory and expiratory flows, tidal volume (V_T), minute ventilation, respiratory rate, and duty cycle (inspiratory time/total time of respiratory cycle) were measured using a Spirometry algorithm based on a module add-on version 2.5.4 and reviewed by an experienced physician investigator. Details are provided in the online supplement (*Supplementary Fig. S1*). Esophageal pressure (P_{es}) was measured using an adult esophageal balloon catheter set (CooperSurgical, CT, USA) inserted before ketamine initiation. The correct placement of the esophageal balloon catheter based on cardiac oscillations and an occlusion maneuver. Lung compliance was calculated as the $\Delta V_T/\Delta(P_{es})$ measured from zero flow states at the start and end of inspiration.

Assessment of work of breathing

We analyzed patient-sided inspiratory work of breathing at each of the three-time points from P_{es}-volume loops (Fig. 1). Patient-sided work of breathing was calculated for each breathing cycle by calculating the area under the inspiratory limb of the P_{es}-volume curve [11]. Work of breathing was averaged over all breathing cycles throughout the recording period. In addition, we differentiated resistive from elastic work of breathing by estimating the elastic recoil pressure curve of the lung from the two points of zero flow at beginning and end-inspiration (Fig. 1) [11]. Values were converted from cmH_2O*L to Joule (conversion factor 0.0980665) and normalized to tidal volume (J/L).

Estimation of airway resistance

Inspiratory airway resistance (R_{aw}) was estimated using the Mead and Whittenberger technique [12]. In brief, inspiratory airway resistance was determined for each breathing cycle using the previously estimated elastic recoil curve of the lung and calculated as $(Pes-Pes_{LR})/\dot{V}$. Pes corresponds to the esophageal pressure at a constant tidal volume, Pes_{LR} to the pressure on the elastic lung recoil curve, and $\dot{V}$ to the respective airway flow. These estimations were made at an absolute tidal volume of 100 milliliter

(mL) and a relative tidal volume of 2 mL per kilogram (kg) ideal body weight. Inspiratory resistance for each breathing cycle was averaged over the whole recording period. Other exploratory analyses of Raw were performed using the isovolumetric 2-point technique at 0.5, 1, 2, 3 mL per kg of ideal body weight, as described by Uhl and Lewis [13].

EEG measurements

Changes in the EEG power spectrum derived from four frontal electrodes (RD SedLine EEG Sensor [Masimo, Irvine, CA, USA]) were continuously measured using a Hospira Physiometrix EN2 SEDLine Brain Function Monitor (Hospira Inc, Lake Forest, Il, USA). The measurements were started before the initiation of ketamine and continuously recorded until the end of the study period. Baseline EEG was defined as an artifact-free, continuous measurement of 3-minute duration approximately 1 minute before the first spontaneous breathing trial. In order to confirm the impact of ketamine on the EEG in a steady state, a 3-minute artifact-free period 40 minutes after the start of the respective high- and low-dose infusion was analyzed.

For each patient, the individual power spectrum and spectrograms were calculated using multitaper spectral methods derived from the Chronux toolbox [14]. Details are provided in the online supplement (*Supplementary study protocol V*) and were previously described [15, 16].

Statistical analysis

An *a priori* sample size calculation was performed based on previous preclinical research [5]. We hypothesized that ketamine would increase inspiratory flow by 15% compared to baseline. Assuming a baseline inspiratory flow of 0.5 ± 0.1 L/s, 14 participants were required to detect a 15% increase by ketamine using a one-tailed paired t-test at a significance level of 0.05 and a power of 80%. To account for possible dropouts, a sample size of 15 participants was targeted. Continuous data is reported as median (interquartile range) or mean (standard deviation), if normally distributed. Statistical differences across the three time points were evaluated by Friedman tests. Wilcoxon tests were used for post-hoc pairwise comparisons between different ketamine doses. Statistical significance was assumed at a p-value of less than 0.05. Analyses were performed using Stata, version 17 (StataCorp, Texas, USA), and SPSS, version 23 (IBM, New York, USA).

Results

Characteristics of study population

A total of 114 participants were assessed for eligibility at two competing academic medical centers in Boston, Massachusetts, USA. Fifteen participants were enrolled in the study, of whom 3 participants were excluded: One subject was excluded after receiving bolus doses of fentanyl during the study period, which resulted in apnea; 2 participants were excluded due to ICU interventions during the study period limiting data acquisition (Fig. 2). The final study group consisted of seven female and five male participants with a mean (± standard deviation [SD]) age of 62 ± 20 years and a mean Acute Physiology

And Chronic Health Evaluation II (APACHE II) score of 16 ± 4. A summary of the baseline characteristics of the final study cohort is presented in Table 1, and individual participant characteristics are shown in Supplementary *Table S1*.

Table 1
Characteristics of the study population.

Characteristics	All participants (n = 12)
Age, years	66 (49–75)
Body mass index (BMI), kg m^{-2}	26 (23–47)
Sex	
Female	7 (58.3%)
Male	5 (41.7%)
APACHE II	15 (12–22)
Indication for ICU admission, n (%)	
Respiratory	4 (33.3%)
Trauma	3 (25.0%)
Infection	3 (25.0%)
Cardiovascular	1 (8.3%)
Postoperative	1 (8.3%)
History of pulmonary disease, n (%)	6 (50%)
Number of days intubated before study start	4 (2–7)
RASS at study start	-1 (-2 to -1)
Median dose of propofol (mcg/kg/min) during study period	29 (12–33)
SOFA	5 (4–7)
Data are expressed as median (interquartile range) or n (%).	
APACHE, Acute Physiology and Chronic Health Evaluation Score; ICU, intensive care unit; RASS, Richmond Agitation Sedation Scale; SOFA, Sequential Organ Failure Assessment.	

Primary endpoint

Ketamine increased inspiratory flow (p = 0.013) from (median, interquartile range [IQR]) 0.36 (0.29–0.46) L/s at baseline to 0.47 (0.32–0.57) L/s (p = 0.017) and 0.44 (0.33–0.58) L/s (p = 0.01), after low and

high-dose ketamine, respectively (Fig. 3A). Representative traces from recorded measurements are shown in Fig. 3B.

Key secondary endpoint: Electroencephalogram gamma power

Ketamine increased electroencephalogram gamma power (19–44 Hz) compared to baseline ($p < 0.01$). Low dose ketamine increased power between 14.2–26.4 Hz, 27.3–39.6 Hz, 40.5–42.0 Hz, 45.9–47.4 Hz, and 48.3–49.8 Hz, as well as decreased power between 2.9–9.3 Hz, compared to baseline. Similarly, high-dose ketamine was associated with increased power between 19.5–43.9 Hz and 44.9–49.8 Hz and decreased power between 0.0-11.7 Hz compared to baseline. The maximum median power increase in the gamma-range was 2.9 dB at 34.7 Hz and 4.2 dB at 39.1 Hz for low and high dose ketamine compared to baseline, respectively. These results are summarized in Fig. 4.

Ventilatory parameters

Ketamine increased minute ventilation ($p = 0.006$) from 6.95 (5.75–9.57) L/min at baseline, to 8.24 (5.78–11.5) L/min and 8.33 (6.62–11.12) L/min after low and high-dose ketamine ($p = 0.022$ and $p = 0.017$, respectively, Fig. 3A). Tidal volume increased significantly ($p = 0.006$) from 0.29 (0.23–0.4) L at baseline, to 0.39 (0.27–0.48) L and 0.39 (0.3–0.48) L after low and high-dose ketamine ($p = 0.008$ and $p = 0.012$, respectively, Fig. 3A). Representative traces from recorded measurements are shown in Fig. 3B. There were no significant differences observed in respiratory rate, respiratory timing, or end-tidal carbon dioxide during the study.

To ensure adequate recovery of breathing, we conducted a 4th spontaneous breathing trial 30 minutes after termination of the ketamine infusion ($n = 4$). Medians (IQR) of inspiratory flow, minute ventilation, tidal volume and respiratory rate were 0.28 L/s (0.23–0.43), 5.84 L/min (4.60–7.89), 0.23 L (0.17–0.35) and 25.4 bpm (20.8–32.5), with no significant difference from baseline values taken prior to ketamine infusion (p values of 1.00, 0.715, 0.465 and 0.465, respectively).

Work of breathing

Work of breathing decreased from 0.6 (0.2–1) J/L at baseline to 0.4 (0.1–0.5) J/L with high-dose ketamine ($p = 0.009$). This was associated with decreased resistive work of breathing (0.4 (0.1–0.6) J/L at baseline to 0.2 (0.1–0.3) J/L at high-dose ketamine, $p = 0.042$), while elastic work of breathing did not change (0.2 (0.1–0.4) J/l at baseline to 0.1 (0.1–0.3) J/L at high-dose ketamine, $p = 0.14$). These results are summarized in Fig. 3C.

Airway resistance and lung compliance

Inspiratory airway resistance calculated using the Mead and Whittenberger technique [12] at an absolute tidal volume of 100 ml decreased from baseline over low to high-dose ketamine (17.7 (1.7–22.4) versus 14.1 (4.6–21.6) versus 9.1 (1.1–15.3) $cmH_2O/L/s$, $p = 0.042$), however, there was no statistically significant difference when calculating airway resistance at a relative tidal volume of 2 mL/kg ideal body

weight (17.6 (6.8–20.2) versus 14.1 (8.3–19.9) versus 10.1 (4.0–14.2) cmH2O/L/s, p = 0.11). Results obtained using the isovolumetric 2-point technique at 0.5, 1, 2, and 3 mL per kg of ideal body weight, as described by Uhl and Lewis [13], are presented in Supplementary *Table S2*. Lung compliance changed from 23 (14–127) mL/cmH_2O (baseline) to 20 (12–149) ml/cmH_2O (low-dose ketamine) and 26 (22–198) mL/cmH_2O (high-dose ketamine, p = 0.042).

Hemodynamic measurements

There were no effects of ketamine on heart rate or blood pressure.

Discussion

In this study of critically ill, intubated and spontaneously breathing patients receiving propofol, we found that a continuous infusion of sub-anesthetic ketamine increased inspiratory flow, reduced the inspiratory work of breathing, and decreased EEG delta oscillation power.

We observed an increased inspiratory flow with continuous infusion of ketamine, suggesting an improvement in the “driving” (ratio of tidal volume/inspiratory time) component of ventilation, as previously described [6]. In contrast to Morel and colleagues’ study, which reported a 75% increase in minute ventilation, we observed a lower effect size. This difference may be explained by the considerably lower doses and continuous administration of ketamine in our study (5 and 10 mcg/kg/min as opposed to 1 mg/kg bolus). Our findings suggest that ketamine affects the respiratory system at substantially lower doses than previously studied [6, 7]. Our results are supported by our previous animal study conducted in spontaneously breathing rodents [5].

We found that ketamine dose-dependently reduced inspiratory work of breathing. Two components of work of breathing are relevant in a clinical setting: A resistive component, which consists of the work performed to overcome airway resistance, and an elastic component, which consists of the work performed to overcome the elastic recoil of the lung and the chest wall. When we isolated the resistive and elastic components, we found that ketamine reduced the overall work of breathing primarily by decreasing the resistive element. This observation supports a previous report which indicates a decreasing airway resistance after ketamine administration [7]. The magnitude of the bronchodilatory effects ketamine depend on the degree of bronchoconstriction present at baseline [17, 18].

Similar to previous findings [7, 8], we observed an improved static lung compliance when ketamine was administered. We also observed a numerical decrease in the elastic component of work of breathing, Together, these findings suggest that ketamine reduces the overall work of breathing primarily through mechanisms that reduce resistive work of breathing.

When an adjunctive dose of ketamine is added to a GABAergic anesthetic regimen, increased EEG beta oscillations [16, 19, 20] and decreased delta oscillations [21] are characteristic EEG findings which we also observed in our study. These relatively “activated” EEG pattern suggest that sub-anesthetic ketamine

modulated neural circuits in our cohort of critically ill patients. These findings confirm that even the low doses of ketamine studied here have biological effects in the central nervous system. However, future studies are necessary to relate this relatively activated EEG pattern to clinical outcomes.

The respiratory effects of ketamine described in this study may have important clinical implications. Failure in weaning from mechanical ventilation and subsequent failure to extubate are common in critically ill patients and often aggravated by the administration of respiratory depressant agents like sedatives and opioids. Our finding of lower work of breathing with increasing doses of ketamine is relevant in this context and has been associated with increased weaning and extubation success [1, 22, 23]. Using ketamine-based over opioid-based analgesia as it is used also in the operating room setting in opioid-sparing analgesia regimens [24] may potentially increase the likelihood of a patient to successfully engage in a spontaneous breathing trial, which ultimately may lead to better weaning from ventilation. This may be particularly relevant in trauma patients who often have severe fracture-related pain. These patients may be able to pass spontaneous breathing trials sooner with ketamine, while still receiving adequate pain management.

This pharmaco-physiological study has limitations that are related to its endpoints and sample size. Future studies should investigate the effects of low-dose ketamine on time to extubation, extubation failure and ICU discharge time.

Conclusion

In summary, ketamine, when added in sub-anesthetic doses as a continuous infusion in ICU patients sedated with propofol, increased inspiratory flow, reduced inspiratory work of breathing, and was associated with a more activated EEG pattern. These findings suggest a desirable sedation regimen without respiratory depression, which may facilitate weaning from mechanical ventilation in spontaneously breathing patients. Ketamine may be particularly beneficial in patients otherwise pain therapy during weaning from the ventilator. The clinical benefit of using ketamine in this setting warrants further investigation in a randomized controlled study.

Declarations

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Authors' contributions:

Concept and design: M.E, A.S, P.S and R.M. Acquisition, analysis, or interpretation of the data: A.S, P.S, R.M, M.H, M.S, L.W, S.R, L.B, S.C, O.J and E.K. Drafting of the manuscript: M.E, A.S, P.S and R.M. Critical

revision of the manuscript for important intellectual content: M.E, M.H, M.S, L.W, S.R, L.B, S.C and O.J. Statistical analysis: A.S, P.S, R.M, M.H, M.S, L.W and E.K. Administrative, technical, or material support: S.R, L.B, S.C, O.J and E.K. Supervision: M.E. All authors read and approved the final manuscript.

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Availability of data and materials:

Due to the sensitive nature of the data collected for this study, requests to access the de-identified dataset from qualified researchers trained in human subjects research with a defined protocol and analysis plan may be sent to Matthias Eikermann at meikermann@montefiore.org.

Ethics approval and consent to participate:

Our trial complied with the Declaration of Helsinki and Good Clinical Practices and was approved by the institutional review board at the participating centers. Institutional review board approval was obtained from the Partners Human Research Committee at Massachusetts General Hospital (protocol number 2013P001690) and by cede review from the Committee on Clinical Investigations at Beth Israel Deaconess Medical Center (protocol number 2017C000525). Written informed consent was obtained from a patient's legally authorized representative before initiation of any study procedures.

Consent for publication:

Not applicable.

Competing interests:

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Figures

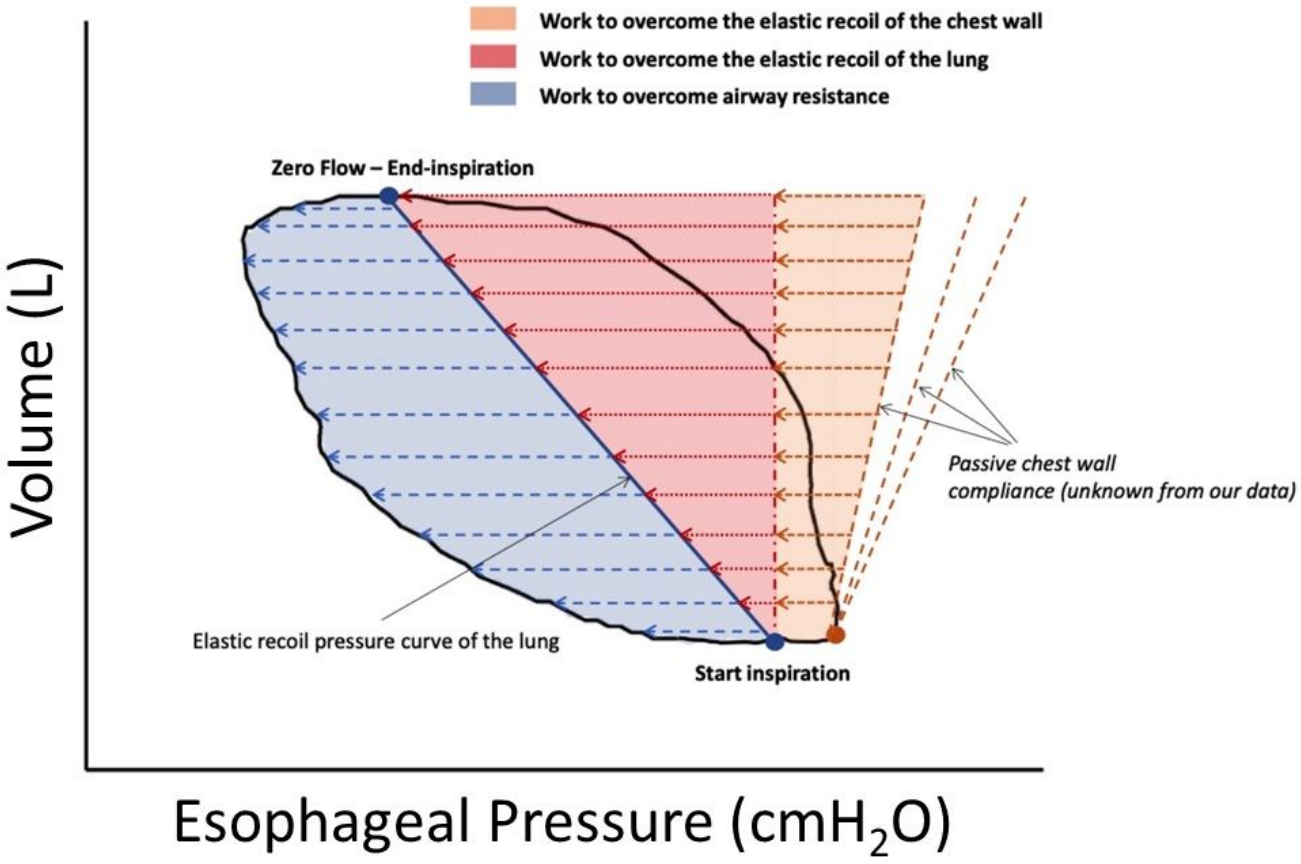

Figure 1

Exemplary Campbell diagram for the assessment of work of breathing in an active patient and changes in the work of breathing.

In spontaneously breathing patients, the work for each breathing cycle can be depicted with a Campbell diagram and is divided into three major components: at the initiation of the inspiration, work is generated to overcome the elastic recoil of the chest wall, defined as the area between the passive chest wall compliance curve and a vertical line from the esophageal pressure at the beginning of the inspiration (orange). Second, work is generated to overcome the elastic recoil of the lung itself, which is defined as the area between the esophageal pressure at the beginning of inspiration and the elastic recoil pressure curve of the lung (i.e., the respective lung volume for each esophageal pressure at zero flow, red). This curve can be estimated from two brief episodes of zero flow during spontaneous breathing, which usually occurs immediately before the initiation of inspiration (lower point) and expiration (upper point). Finally, work is generated to overcome airway resistance, which is defined as the area between the elastic recoil pressure curve of the lung and the inspiratory curve (blue).

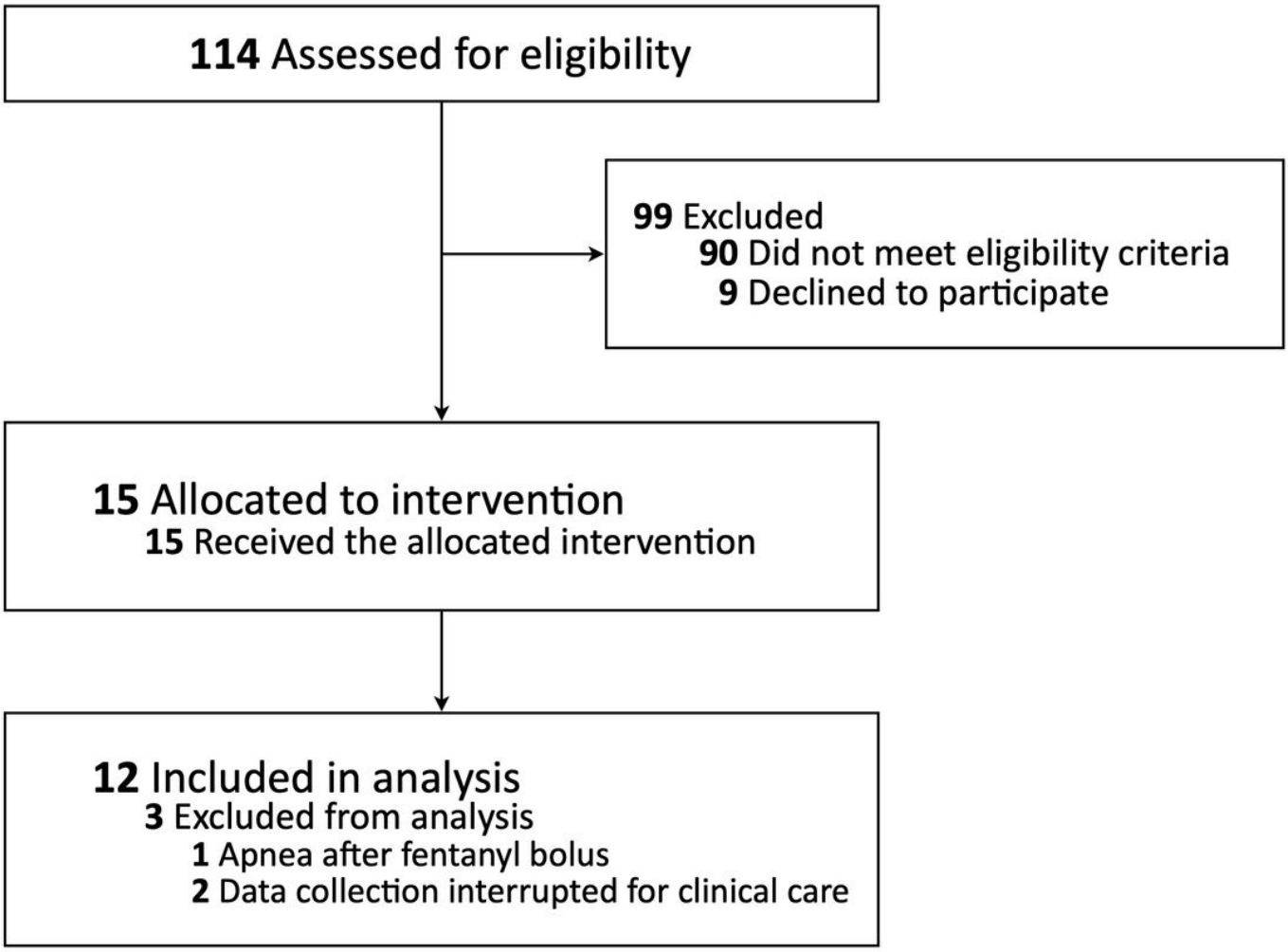

Figure 2

Study flow diagram.

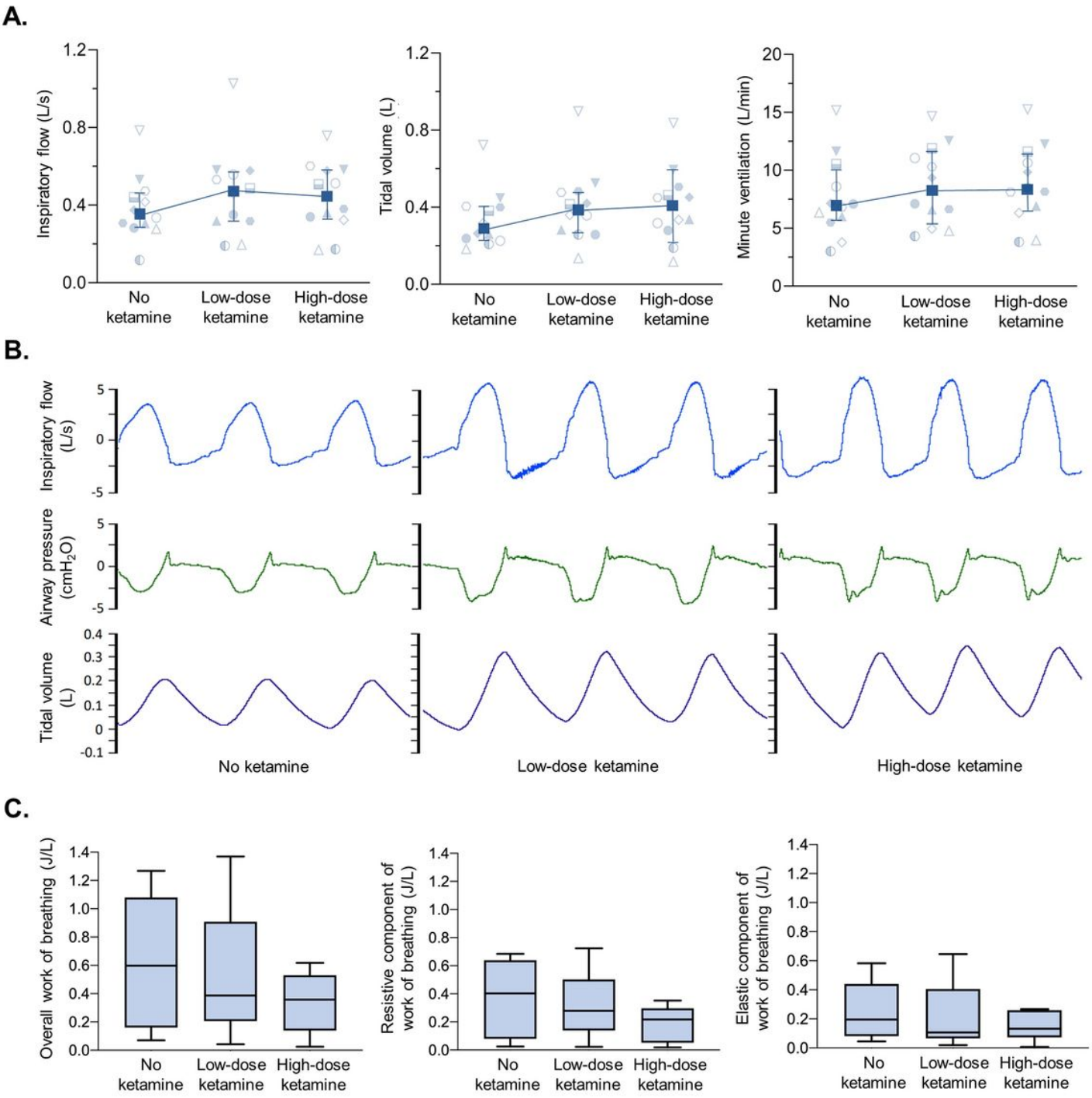

Figure 3

Changes in ventilatory parameters.

(A) Changes in the ventilatory parameters inspiratory flow, tidal volume, and minute ventilation before and after the infusion of ketamine are shown. Ketamine infusion significantly increased the inspiratory flow and minute ventilation without affecting respiratory timing. Data are presented as median and interquartile range across all patients in the dark blue line plot and the individual patients values are

depicted as the scatter plot in light blue color with each individual patients' values reflecting a different shape.

(B) Representative traces from recorded measurements of inspiratory flow, airway pressure and tidal volume are shown at baseline, after low-dose and high-dose ketamine infusions.

(C) Changes in work of breathing (overall work of breathing as well as resistive and elastic components separately) at baseline and after low- and high-dose infusion of ketamine are shown. Ketamine significantly reduced the overall work of breathing, primarily by reducing the resistive component of work of breathing. The work required to overcome the elastic recoil of the lung was not affected. Data are expressed as boxplots: lines represent the median, boxes the interquartile range, and whiskers the range from minimum to maximum. Statistical comparisons were performed using Friedman's test.

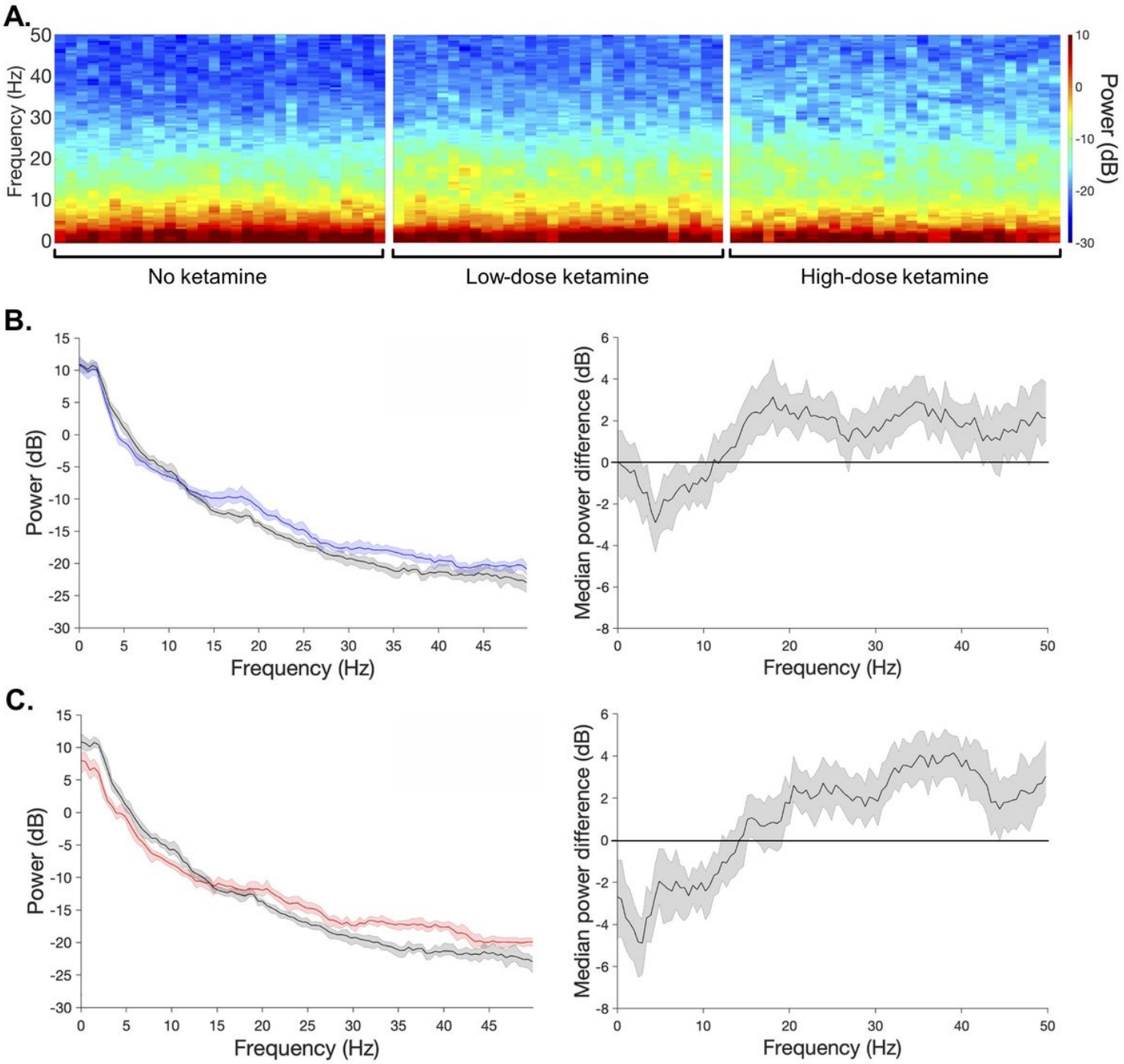

Figure 4

Ketamine-specific EEG-power in group-level spectrograms (A) and spectral analyses (B-C) for baseline, low, and high dose infusion of ketamine.

(A) One-minute median frontal spectrogram representing the three stages during the trial. Characteristic EEG-power signatures of ketamine were observed.

(B/C) Low (B, blue) and high (C, red) dose infusions compared to baseline (B/C, black): Compared to baseline, broadband beta-gamma power increased during low and high ketamine infusions. Additionally, alpha power was decreased during the high infusion state compared to baseline. The left side of B and C shows the absolute power in dB, the right side of B and C shows median power difference. Median spectra and 99% confidence intervals from bootstrapping estimations are shown. Horizontal solid black lines represent significant differences between the compared states with $p<0.01$.

Supplementary Files

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- SupplementCriticalCare042122.docx
- graphicalabstractCriticalCare.tif