Effects of Ketamine Infusion on Breathing and Encephalography in Spontaneously Breathing ICU Patients

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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 h 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 change in beta-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 = .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 = .042), while elastic work of breathing remained unchanged. Electroencephalogram beta-gamma power (19-44 Hz) increased compared to baseline (p < .01).

Conclusions: In intubated, spontaneously breathing patients receiving a constant rate of 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.

Keywords
Ketamine infusion, ICU sedation, weaning from ventilator, spontaneous breathing trial, critical care ventilation, mechanical ventilation, inspiratory flow, brain activity

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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 studies5 and studies in healthy volunteers6 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 infusion rate of sedatives for ≥3 h 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 h, the ketamine infusion was discontinued. A trial of spontaneous breathing, defined as zero end-expiratory pressure and no pressure support for 1 min, was performed at pre-specified time points: before initiation of ketamine (baseline), after 1 h of infusion at 5 mcg/kg/min, and after 1 h 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 beta-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; Ti/Ttot]), 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 (VT), 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 (Pes) was measured using an adult esophageal balloon catheter set (CooperSurgical, CT, USA) inserted before ketamine initiation. The correct placement of the esophageal balloon catheter was based on cardiac oscillations and an occlusion maneuver. Lung compliance was calculated as the ΔVT/Δ(Pes) 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 fromPes-volume loops (Figure 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.\textsuperscript{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 (Figure 1).\textsuperscript{11} Values 
were converted from cmH$_2$O*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.\textsuperscript{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 $(P_{es}-P_{esLR})/V'$. Pes corresponds to the esoph- 
ageal pressure at a constant tidal volume, $P_{esLR}$ to the pressure 
on the elastic lung recoil curve, and $V'$ 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.\textsuperscript{13}

**EEG Measurements**

Changes in the EEG power spectrum derived from four frontal elec- 
trodes (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 keta- 
mine and continuously recorded until the end of the study period. 
Baseline EEG was defined as an artifact-free, continuous measure- 
ment of 3-min duration approximately 1 min before the first 
spontaneous breathing trial. In order to confirm the impact of ketamine 
on the EEG in a steady state, a 3-min artifact-free period 40 min 
after the start of the respective high- and low-dose infusion was 
analyzed.

For each patient, the individual power spectrum and spectro- 
grams were calculated using multitaper spectral methods 
derived from the Chronux toolbox.\textsuperscript{14} Details are provided in 
the online supplement (Supplementary study protocol $V$) and 
were previously described.\textsuperscript{15,16}

**Statistical Analysis**

An *a priori* sample size calculation was performed based on pre- 
vious preclinical research.\textsuperscript{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 (Figure 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.

Primary Endpoint

Ketamine increased inspiratory flow (p = .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 = .017) and 0.44 (0.33-0.58) L/s (p = .01), after low and high-dose ketamine, respectively (Figure 3A). Representative traces from recorded measurements are shown in Figure 3B.

Table 1. Characteristics of the Study Population.

| Characteristics                        | All participants (n = 12) |
|----------------------------------------|--------------------------|
| Age, years                             | 66 (49-75)               |
| Body mass index (BMI), kg m²            | 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 (%). Abbreviations: APACHE, acute physiology and chronic health evaluation score; ICU, intensive care unit; RASS, richmond agitation sedation scale; SOFA, sequential organ failure assessment.

Key Secondary Endpoint: Electroencephalogram beta-Gamma Power

Ketamine increased electroencephalogram beta-gamma power (19-44 Hz) compared to baseline (p < .01). Low dose ketamine increased power between 14.2 to 26.4 Hz, 27.3 to 39.6 Hz, 40.5 to 42.0 Hz, 45.9 to 47.4 Hz, and 48.3 to 49.8 Hz, as well as decreased power between 2.9 to 9.3 Hz, compared to baseline. Similarly, high-dose ketamine was associated with increased power between 19.5 to 43.9 Hz and 44.9 to 49.8 Hz and decreased power between 0.0 to 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 Figure 4.

Ventilatory Parameters

Ketamine increased minute ventilation (p = .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 = .022 and p = .017, respectively, Figure 3A). Tidal volume increased significantly (p = .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 = .008 and p = .012, respectively, Figure 3A). Representative traces from recorded measurements are shown in Figure 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 fourth spontaneous breathing trial 30 min after termination of

![Figure 2. Study flow diagram.](image-url)
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 \( (p \text{ values of } 1.00, .715, .465 \text{ and } .465, \text{ respectively}) \).

### 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 \( (p = .009) \). This was associated with decreased resistive work of breathing \( (0.4 (0.1-0.6) \text{ J/L at baseline to 0.2 (0.1-0.3) J/L at high-dose ketamine, } p = .042) \), while elastic work of breathing did not change \( (0.2 (0.1-0.4) \text{ J/L at baseline to 0.1 (0.1-0.3) J/L at high-dose ketamine, } p = .14) \). These results are summarized in Figure 3C.

### Airway Resistance and Lung Compliance

Inspiratory airway resistance calculated using the Mead and Whittenberger technique\(^\text{12}\) at an absolute tidal volume of 100 ml decreased from baseline over low to high-dose ketamine \( (17.7 (1.7-22.4) \text{ versus } 14.1 (4.6-21.6) \text{ versus } 9.1 (1.1-15.3) \text{ cmH}_2\text{O/L/s, } p = .042) \), however, there was no statistically significant difference when calculating airway resistance at a relative tidal volume of 2 mL/kg ideal body weight \( (17.6 (6.8-20.2) \text{ versus } 14.1 (8.3-19.9) \text{ versus } 10.1 (4.0-14.2) \text{ cmH}_2\text{O/L/s, } p = .11) \).
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, are presented in Supplementary Table S2. Lung compliance changed from 23 (14-127) mL/cmH2O (baseline) to 20 (12-149) mL/cmH2O (low-dose ketamine) and 26 (22-198) mL/cmH2O (high-dose ketamine, \( p = .042 \)).

**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. 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. Our results are supported by our previous animal study conducted in spontaneously breathing rodents.

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. The magnitude of the bronchodilatory effects of ketamine depends on the degree of bronchoconstriction present at baseline.

Similar to previous findings, 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 and decreased delta oscillations 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. Using ketamine-based over opioid-based analgesia as it is used also in the operating room setting in opioid-sparing analgesia regimens 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. Furthermore, propofol dose was not titrated to a specific Richmond Agitation Sedation Scale (RASS) score and there was some variation in scores ranging from −2 (briefly opening eyes to voice) to +1 (mild restlessness). Additionally, high frequency power may have been contaminated by electromyography (EMG).

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.

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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 and E.K. Supervision: M.E.

**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**

All authors read and approved the final manuscript for publication.

**Clinical Trial Registration**

“The Effects of Ketamine on Respiratory Stimulation and Transpulmonary Pressures”. NCT01969227. Registered 25 October 2013. https://clinicaltrials.gov/ct2/show/record/NCT01969227

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References
1. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. N Engl J Med. 1995;332(6):345-350.
2. Patel SB, Kress JP. Sedation and analgesia in the mechanically ventilated patient. Am J Respir Crit Care Med. 2012;185(5):486-497.
3. Hollinger A, Rüst CA, Riegger H, et al. Ketamine vs. Haloperidol for prevention of cognitive dysfunction and postoperative delirium: a phase IV multicentre randomised placebo-controlled double-blind clinical trial. J Clin Anesth. 2021;68:110099.
4. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. J Clin Anesth. 2021;68:110071.
5. Eikermann M, Grosse-Sundrup M, Zaremba S, et al. Ketamine activates breathing and abolishes the coupling between loss of consciousness and upper airway dilator muscle dysfunction. Anesthesiology. 2012;116(1):35-46.
6. Morel DR, Forster A, Gempferle M. Noninvasive evaluation of breathing pattern and thoraco-abdominal motion following the infusion of ketamine or droperidol in humans. Anesthesiology. 1986;65(4):392-398.
7. Cossen G, Gutierrez J, Reves JG, Huber FC. Ketamine in the anesthetic management of asthmatic patients. Anesth Analg. 1972;51(4):588-596.
8. Elamin E. Impact of ketamine on dynamic compliance and airway resistance of sedated and mechanically ventilated ICU patients. Crit Care. 2009;13(Suppl 1):P404.
9. Maeda Y, Fujino Y, Uchiyama A, Matsuura N, Mashimo T, Nishimura M. Effects of peak inspiratory flow on development of ventilator-induced lung injury in rabbits. Anesthesiology. 2004;101(3):722-728.
10. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med. 2017;195(4):438-442.