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KETAMINE-BASED VERSUS FENTANYL-BASED REGIMEN FOR RAPID-SEQUENCE ENDOTRACHEAL INTUBATION IN PATIENTS WITH SEPTIC SHOCK: A RANDOMISED CONTROLLED TRIAL

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Abstract

***Objective:** The aim of this work is to compared ketamine-based versus fentanyl-based regimens for endotracheal intubation in patients with septic shock undergoing emergency surgery.*
***Design:** This was a randomised double-blinded controlled trial.*
***Participants:** Patients with septic shock on norepinephrine infusion scheduled for emergency surgery.*
***Setting and Interventions:** At induction of anaesthesia, patients were allocated into ketamine group (n=23) in which the participants received ketamine 1 mg/kg, and fentanyl group (n=19) in which the participants received fentanyl 2.5 mcg/kg. Both groups received midazolam (0.05 mg/kg) and succinyl choline (1 mg/kg).*
***Measurement:** The primary outcome was mean arterial blood pressure. The secondary outcomes included: heart rate, cardiac output, and incidence of postintubation hypotension defined as mean arterial pressure ≤80% of baseline value.*
***Results:** Forty-two patients were available for final analysis. The mean blood pressure was higher in the ketamine group than in the fentanyl group at 1, 2 and 5 minutes after the induction of anaesthesia. Furthermore, the incidence of postinduction hypotension was lower in the ketamine group than in the fentanyl group (11 [47.8%] versus 16 [84.2%], P-value= 0.014). Other hypodynamic parameters, namely the heart rate and cardiac output, were comparable between both groups; and were generally maintained in relation to the baseline reading in each group.*
***Conclusion:** The ketamine-based regimen provided better hemodynamic profile compared to fentanyl-based regimen for rapid-sequence intubation in patients with septic shock undergoing emergency surgery.*

Keywords

Ketamine • fentanyl • septic shock • endotracheal intubation • anaesthesia • hypotension

Introduction

Hypotension is a common and life-threatening complication after endotracheal intubation, especially when intubation is performed in emergency settings [1,2]. Mounting evidence suggests that the risk of serious sequelae of hypotension is present even with very short periods of low blood pressure [3,4]. In the operating room, the early intraoperative period between induction of anaesthesia and surgical skin incision is the critical period at which nearly 30% of hazardous hypotension occurs [5,6].

Patients with septic shock commonly require endotracheal intubation in emergency departments and intensive care units. Furthermore, patients with septic shock frequently undergo surgical procedures, for which general anaesthesia is the usual choice. Patients with septic shock are characterised by refractory hypotension [7]; therefore, they are at higher risk of deleterious hypotension after induction of anaesthesia. The ideal regimen for induction of anaesthesia and/or endotracheal intubation in hypotensive patients should provide adequate hypnosis without further decrease in blood pressure [8]. However, most of the intravenous hypnotic agents have negative cardiovascular effects [8,9]. Therefore, induction of anaesthesia and/or endotracheal intubation in patients with circulatory failure presents a challenging problem for intensivists, anaesthesiologists, and emergency physicians.

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Ketamine is an induction anaesthetic with unique sympathomimetic properties [8]; thus, its use is usually associated with increased arterial blood pressure and cardiac output in patients whose sympathetic nervous activity is intact [9]. However, the use of ketamine in patients with acute circulatory failure showed conflicting evidence. Fentanyl is an ultrashort-acting opioid receptor agonist which is commonly used for sedation and analgesia in the operating theatre as well as the intensive care unit [10]. Fentanyl is widely used in the operating theatre, especially in cardiac surgery. However, its use in rapid sequence intubation in patients with septic shock was not adequately investigated. We hypothesized that fentanyl in rapid sequence induction may give a better hemodynamic profile than ketamine.

In this study, we compared ketamine-based versus fentanyl-based regimens for rapid-sequence induction of anaesthesia in patients with septic shock.

Methods

Between September 2018 and September 2019, this randomised controlled trial was performed in the surgical theatre at the emergency department of Cairo University Hospital. The study was approved by the Research Ethics Board of Faculty of Medicine, Cairo University (N-12-2018) and registered at the clinicaltrials.gov registry system before enrolment of the first participant (identifier: NCT03251170; principal investigator: Ahmed Hasanin; date of registration: 12 August 2017). The study was conducted in a double-blinded design and the participants were randomised using a computer-generated sequence of codes which was performed by a statistician. The codes were inserted in opaque envelopes which contained the instructions for preparation of study drugs. The investigators acquired informed consents from the participants or their surrogates before inclusion in the study.

Inclusion and exclusion criteria: The study included patients who fulfilled the following criteria: age between 18 and 65 years; experiencing septic shock; scheduled for emergency surgery to control the source of sepsis. *Septic shock* was defined as hypotension which required infusion of norepinephrine to maintain mean arterial pressure (MAP) > 65 mmHg with elevated serum lactate level (above 2 mmol/L) despite adequate fluid resuscitation in addition to the presence of infection [7]. Exclusion criteria were burns, traumatic brain injury or history of any cerebrovascular disorders.

Before induction of anaesthesia, initial resuscitation and hemodynamic management were performed according to the surviving sepsis campaign guidelines [11]. Initially, a 30 mL/Kg bolus of Ringer's lactate solution was administered. Subsequent infusion of fluids was guided by dynamic methods for fluid responsiveness [12] until the patient was non-respondent. Norepinephrine infusion was titrated to keep MAP > 65 mmHg.

The following monitors were applied to the patients during resuscitation and surgery: electrocardiograph (ECG), pulse oximetry, and non-invasive blood pressure monitor. Invasive blood pressure monitor was connected to a radial arterial catheter. Non-invasive cardiac output measurement was obtained through electrical cardiometry ICON^{R} monitor (Osyka Medical, Inc., La Jolla, California and Berlin, Germany) which was applied to the patients' neck and upper trunk through ECG electrodes. Four sites were used for placement of the electrodes; all at the left side: (1) At the upper neck below the ear; (2) At the clavicle, one centimetre cephalad to the midpoint; (3) At the mid-axillary line at the level of the xiphoid process; (4) Two inches caudad from the third site. The validity of the measurements of the electrical cardiometry was confirmed through the quality of the indicator bar signals and the ECG waveform.

Before induction of anaesthesia, patients were allocated into one of the two study groups according to the randomisation code:

– Ketamine group (n=23): this group received intravenous (IV) ketamine (1 mg/Kg) plus IV midazolam (0.05 mg/Kg).
– Fentanyl group (n=19): this group received IV fentanyl 2.5 ug/Kg plus midazolam (0.05 mg/Kg).

After reaching the endpoint for hypnosis, an endotracheal tube was inserted after administration of IV succinyl choline (1 mg/kg). The endpoint for adequate hypnosis was defined as loss of the ability to respond to simple verbal orders [13,14]. Maintenance of hypnosis was achieved by isoflurane at concentration of 1%. After fading of succinyl choline activity, paralysis was secured using atracurium (initial bolus of 0.5 mg/kg followed by 10 mg increments). The ventilator settings were adjusted at a tidal volume of 6 mL/Kg and a respiratory rate was set at 12–15 per minute to achieve a target end-tidal CO_2 at 30–35 mmHg.

If the patient developed postintubation hypotension, norepinephrine infusion rate was increased till reaching MAP > 65mmHg. Postintubation hypotension was considered if the MAP decreased to ≤ 80% from the pre-induction value. In cases of severe or persistent hypotension, the isoflurane concentration was decreased by 50% until the norepinephrine infusion achieved MAP > 65mmHg

The primary outcome was the mean arterial pressure at 1 min after induction of anaesthesia. Other outcomes included the incidence of postinduction hypotension (MAP ≤ 80% the baseline value during the period from induction of anaesthesia until 10 min). The mean arterial pressure, heart rate, and cardiac output were analysed at baseline value, 1, 2, 3, 4, 5, and 10 mins after the induction of anaesthesia. Serum lactate at baseline and 1 min after the induction of anaesthesia was also analysed.

Sample size calculation and statistical analysis

Our primary outcome was MAP one minute after induction of anaesthesia. In a previous study [14], the MAP one minute after induction of anaesthesia in the ketamine group was 65±7 mmHg. The sample size of this study was calculated to detect a mean difference of 10% (i.e. 6.5 mmHg) between the two study groups. The study power was set at 80% and the alpha error was set at 0.05. The MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium) was used for estimation of the sample size and the minimum number of participants was calculated to be 38 patients (19 patients per group). The number of envelopes was increased by 20% to 46 envelopes to compensate for possible dropouts.

Statistical package for social science (SPSS) software, version 26 for Microsoft Windows (Armonk, NY: IBM Corp) was used for data analysis. Categorical data were presented as frequency (%) and were analysed using the chi-square test. Continuous data was presented as either mean (standard deviation), or median (quartiles), as appropriate. Continuous unpaired data was analysed using the unpaired *t*-test and the Mann–Whitney *U* test on ranks (for normally distributed data and skewed data, respectively). The repeated measures analysis of variance test was used to evaluate drug (between-groups factor) and time (repeated measures). Bonferroni test was used to adjust for multiple comparisons. *P*-value ≤ 0.05 was considered statistically significant.

Results

Fifty patients were evaluated for eligibility for the study. Four patients were excluded for not meeting the inclusion criteria. Forty-six patients were randomized to receive one of the two interventions. Twenty-three patients in the ketamine group and 19 patients in the fentanyl group were available for final analysis (Figure 1). Demographic data and baseline

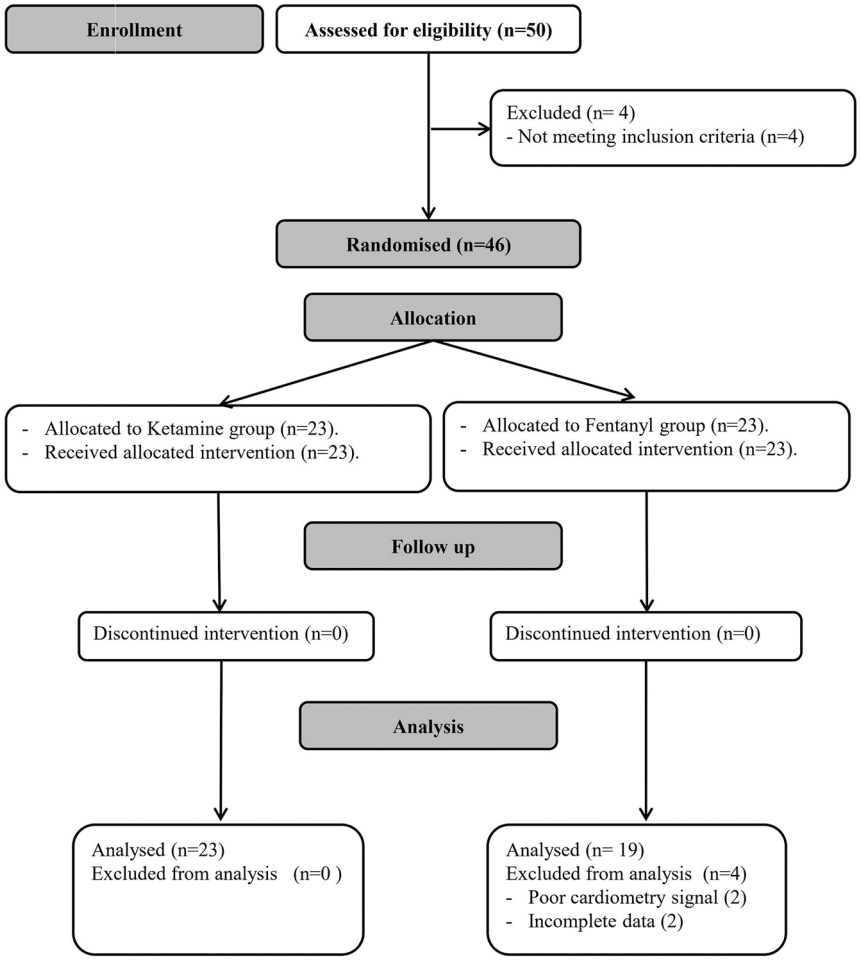

Figure 1. CONSORT's flow chart.

characteristics were comparable between both study groups (Table 1).

The mean blood pressure was higher in the ketamine group than in the fentanyl group at 1, 2 and 5 minutes after the induction of anaesthesia. The mean blood pressure was maintained in relation to the baseline reading during the first 10 minutes after induction in the ketamine group. In the fentanyl group, the MAP decreased in relation to baseline reading at 1 minute after the induction of anaesthesia (Figure 2).

The number of patients with postinduction hypotension was lower in the ketamine group than in the fentanyl group (11 [47.8%] versus 16 [84.2%], *P*-value= 0.014) (Table 2). Other hypodynamic parameters, namely the heart rate (Figure 3) and cardiac output (Figure 4), were comparable between both groups; these were generally maintained in relation to the baseline reading in each group.

Table 1: Demographic data and baseline characteristics. Data are presented as mean (standard deviation), median (quartiles), and frequency (%).

	Ketamine group (n=23)	Fentanyl group (n=19)	*P*-value
Age (years)	44 (40-60)	56 (46-63)	0.356
Male gender (%)	11 (47.8%)	8 (42.1%)	0.763
Source of sepsis • Abdominal • Other	 17 (73.9%) 6 (26.1%)	 18 (94.7%) 1 (5.3%)	 0.071
Mean arterial pressure (mmHg)	74 (13)	67 (9)	0.113
Heart rate (bpm)	111 (21)	109 (24)	0.837
Shock index	1.1 (0.3)	1.2 (0.3)	0.563
Stroke volume (ml)	63 (30)	78 (28)	0.114
Cardiac output (L/min)	7.1 (3.4)	8.5 (3.5)	0.209
Systemic vascular resistance (dynes/seconds/cm^5)	821 (325)	715 (389)	0.350
Haemoglobin (g/dL)	10.7 (9.5, 11.7)	10.8 (8.8, 11.5)	0.411
Prothrombin concentration (%)	59 (18)	58 (12)	0.773
Urea (mg/dL)	51 (27, 113)	49 (29, 98)	0.889
Creatinine (mg/dL)	1.4 (1.0, 2.1)	1.4 (1.2, 3.1)	0.447

Table 2: Intraoperative outcomes. Data are presented as mean (standard deviation), median (quartiles), and frequency (%).

	Ketamine group (n=15)	Fentanyl group (n=16)	*P*-value
Mean blood pressure at 1 min (mmHg)	77 (13)	63 (6)	0.001
Patients with post-induction hypotension	11 (47.8%)*	16 (84.2%)	0.014
Serum lactate (baseline) (mmol/dL)	3.2 (2.3, 4.1)	2.8 (2.2, 4.3)	0.544
Serum lactate (after 15 minutes) (mmol/dL)	2.2 (1.8, 3.4)†	2.6 (2.2, 3.6)†	0.471

* denotes statistical significance between both groups. † denotes significance in relation to baseline lactate reading in each group <0.001 in ketamine group, 0.008 in fentanyl group.

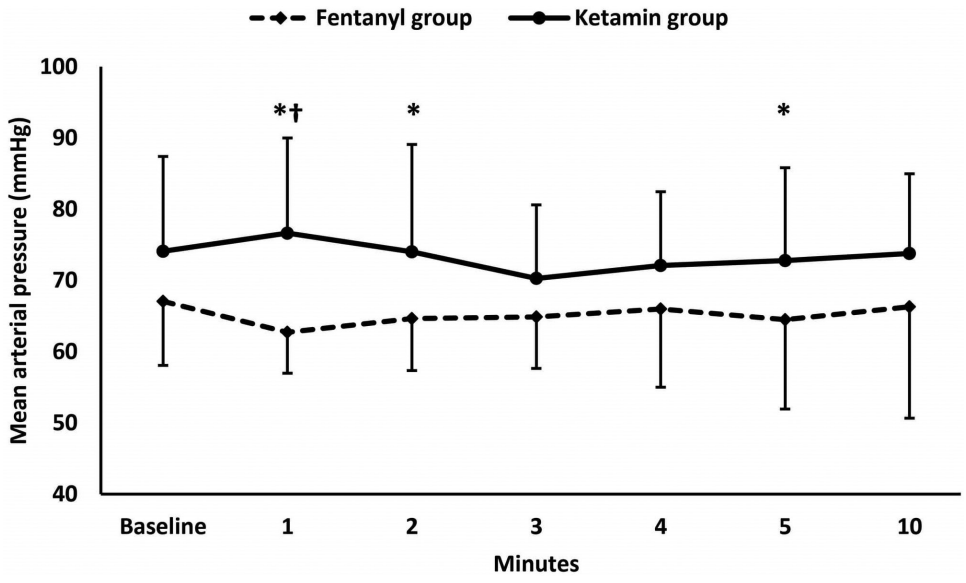

Figure 2. Mean arterial pressure. Markers are means and error bars are standard deviations. * denotes statistical significance between both groups, † denotes statistical significance compared to the baseline reading within fentanyl group.

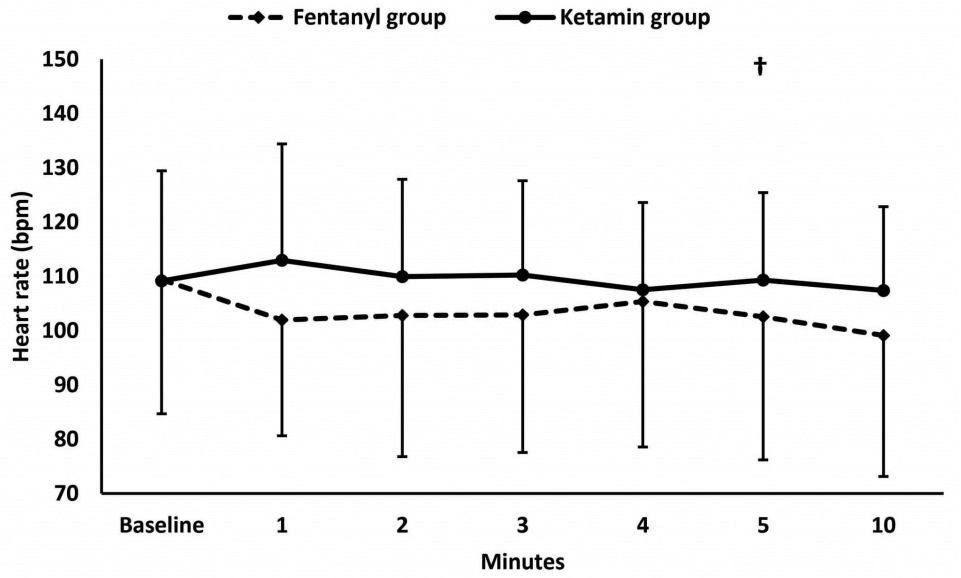

Figure 3. Heart rate. Markers are means and error bars are standard deviations. † denotes statistical significance compared to the baseline reading within fentanyl group.

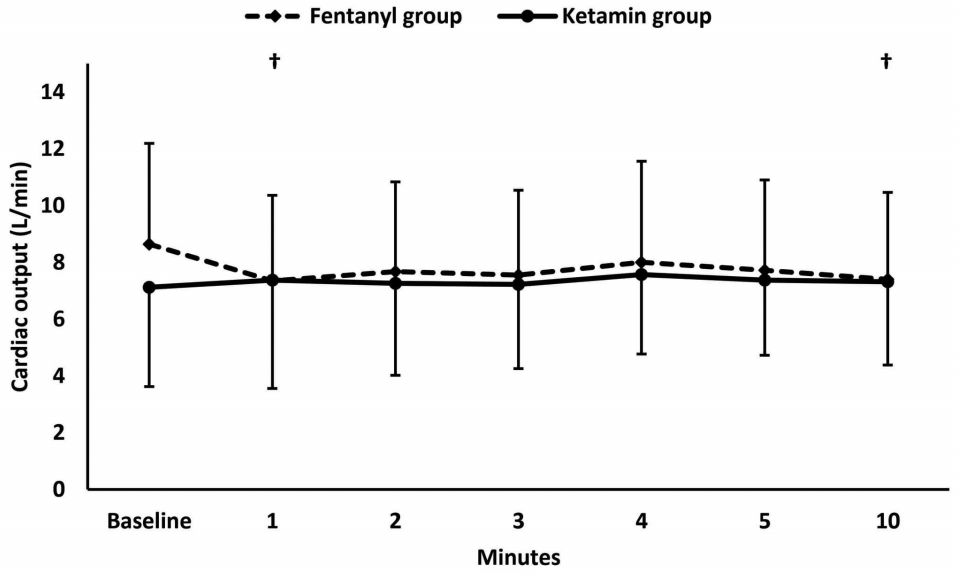

Figure 4. Cardiac output. Markers are means and error bars are standard deviations. † denotes statistical significance compared to the baseline reading within fentanyl group.

Discussion

We compared two regimens for rapid-sequence intubation in patients with septic shock and found that the ketamine-based regimen was associated more stable cardiovascular profile compared to the fentanyl-based regimen.

In patients with normal arterial blood pressure, induction of hypnosis with ketamine was associated with the most stable hemodynamic profile among different hypnotic agents [9]. Ketamine is a sympathomimetic agent which increases the cardiac output by 40–50% [15,16,17]. However, the use of ketamine in patients with shock was

not adequately explored. In vitro studies have shown that ketamine reduces contractility in failing myocardial muscle fibres [18,19]. However, clinical studies favoured the use of ketamine in patients with shock. In an observational study, Ishimaru et al. had reported that ketamine is associated with a lower risk of post-intubation hypotension compared to midazolam and propofol when used in undifferentiated hemodynamically unstable patients, defined by high shock index, in the emergency department [20]. Another retrospective study favoured ketamine over midazolam in stable patients with ST elevation myocardial infarction [21]. Our study has the advantage of randomised controlled design. Furthermore, our comparison focused on one subgroup of patients, septic shock patients, and compared ketamine versus fentanyl in induction of anaesthesia. Finally, we included more critical patients who were on norepinephrine infusion at enrolment.

Fentanyl is widely used in patients with cardiac morbidities, especially those undergoing cardiac surgery [10]; however, its use in patients with shock was not adequately evaluated. Two recent observational studies had reported that pre-treatment with fentanyl before sedative agents increases the incidence of post-intubation hypotension in the emergency department [22,23].

To the best of our knowledge, this is the first randomised controlled trial comparing ketamine-based versus opioid-based endotracheal intubation in patients with septic shock during emergency procedures. Our results support ketamine over fentanyl in this high-risk group of patients. Rapid-sequence endotracheal intubation in emergency patients is commonly associated with hypotension due to many factors such as cardiovascular depression by sedative agents, decreased venous return due to positive pressure ventilation [24] and increased pulmonary vascular resistance [25]. Post-intubation hypotension had been recently reported as a risk factor for peri-intubation cardiac arrest. In the special subgroup of patients with septic shock, refractory hypotension [7] is sometimes associated with myocardial dysfunction [26]. Hence, proper choice of the induction protocol would avoid further aggravation of hypotension during induction of anaesthesia.

Our study has the advantage of randomised controlled double-blinded design. Furthermore, the study focused on a special group with high shock index plus norepinephrine infusion. The study has some limitations: it is based on a single centre, the results cannot be extrapolated to patients with other types of shock, and our results might differ if other combinations of drugs were used. Also, special studies in the elderly and children should be performed.

In conclusion, the ketamine-based regimen provided a better hemodynamic profile compared to the fentanyl-based regimen for rapid-sequence intubation in patients with septic shock undergoing emergency surgery.

Abbreviation

ECG electrocardiograph
MAP mean arterial pressure

Declarations: None.

Conflict of interest: The authors declare that they have no conflicts of interest.

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References

[1] Green RS, Edwards J, Sabri E, Fergusson D. Evaluation of the incidence, risk factors, and impact on patient outcomes of post-tintubation hemodynamic instability. CJEM 2012; 14: 74–82.

[2] Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping STJ, Bentt DR, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiol 2015; 123: 307–319.

[3] Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, et al. Perioperative quality initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122: 563–574.

[4] Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiol 2013; 119: 507–515.

[5] Maheshwari K, Turan A, Mao G, Yang D, Niazi AK, Agarwal D, et al. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: a retrospective cohort analysis. Anaesth 2018; 73: 1223–1228.

[6] Südfeld S, Brechnitz S, Wagner JYY, Reese PCC, Pinnschmidt HOO, Reuter DAA, et al. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. Br J Anaesth 2017; 119: 57–64.

[7] Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and

assessing new clinical criteria for septic shock. JAMA 2016; 315: 775.

[8] Morris C, Perris A, Klein J, Mahoney P. Anaesthesia in haemodynamically compromised emergency patients: Does ketamine represent the best choice of induction agent? Anaesth 2009; 64: 532–539.

[9] White PF. Comparative evaluation of intravenous agents for rapid sequence induction--thiopental, ketamine, and midazolam. Anesthesiol 1982; 57: 279–284.

[10] Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. Anesthesiol 1984; 61: 731–755.

[11] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017; 43: 304–377.

[12] Hasanin A. Fluid responsiveness in acute circulatory failure. J Intensive Care 2015; 3: 50.

[13] Tverskoy M, Ben-Shlomo I, Vainshtein M, Zohar S, Fleyshman G. Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine. Br J Anaesth 1997; 79: 798–800.

[14] Fathy S, Hasanin A, Mostafa M, Ramzy E, Sarhan K, Almenesey T, et al. The benefit of adding lidocaine to ketamine during rapid sequence endotracheal intubation in patients with septic shock: A randomised controlled trial. Anaesthesia, Crit Care Pain Med. 2020; Published Ahead of Print.

[15] Olofsen E, Sigtermans M, Noppers I, Niesters M, Mooren R, Bauer M, et al. The dose-dependent effect of S(+)-ketamine on cardiac output in healthy volunteers and complex regional pain syndrome type 1 chronic pain patients. Anesth Analg 2012; 115: 536–546.

[16] Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, et al. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Anesthesiol 2009; 111: 892–903.

[17] Ivankovich AD, Miletich DJ, Reimann C, Albrecht RF, Zahed B. Cardiovascular effects of centrally administered ketamine in goats. Anesth Analg; 53: 924–933.

[18] Sprung J, Schuetz SM, Stewart RW, Moravec CS. Effects of ketamine on the contractility of failing and nonfailing human heart muscles in vitro. Anesthesiol 1998; 88: 1202–1210.

[19] Hanouz JL, Persehaye E, Zhu L, Lammens S, Lepage O, Massetti M, et al. The inotropic and lusitropic effects of ketamine in isolated human atrial myocardium: The effect of adrenoceptor blockade. Anesth Analg 2004; 99: 1689–1695.

[20] Ishimaru T, Goto T, Takahashi J, Okamoto H, Hagiwara Y, Watase H, et al. Association of ketamine use with lower risks of post-intubation hypotension in hemodynamically-unstable patients in the emergency department. Sci Rep 2019; 9: 1–8.

[21] Zuin M, Rigatelli G, Dell'Avvocata F, Faggian G, Conte L, Giatti S, et al. Ketamine and midazolam differently impact post-intubation hemodynamic profile when used as induction agents during emergency airway management in hemodynamically stable patients with ST elevation myocardial infarction. Heart Vessels, Springer Japan 2018; 33: 213–225.

[22] Takahashi J, Goto T, Okamoto H, Hagiwara Y, Watase H, Shiga T, et al. Association of fentanyl use in rapid sequence intubation with post-intubation hypotension. Am J Emerg Med, Elsevier Inc 2018; 36: 2044–2049.

[23] Ferguson I, Bliss J, Aneman A. Does the addition of fentanyl to ketamine improve haemodynamics, intubating conditions or mortality in emergency department intubation: A systematic review. Acta Anaesthesiol Scand 2019; 63: 587–593.

[24] Manthous CA. Avoiding circulatory complications during endotracheal intubation and initiation of positive pressure ventilation. J Emerg Med 2010; 38: 622–631.

[25] Pinsky MR. The hemodynamic consequences of mechanical ventilation: an evolving story. Intensive Care Med 1997; 23: 493–503.

[26] Schmittinger CA, Dünser MW, Torgersen C, Luckner G, Lorenz I, Schmid S, et al. Histologic pathologies of the myocardium in septic shock. Shock 2013; 39: 329–335.