Haemodynamic response to induction of anaesthesia with ketamine/midazolam

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The haemodynamic responses following induction of anaesthesia with ketamine and midazolam have not been determined previously. Twenty adult patients for elective myocardial revascularization were randomized to two regimens for induction of anaesthesia. Patients in Group I received ketamine, 2 mg · kg^{-1}, and midazolam, 0.2 mg · kg^{-1} and those in Group II received ketamine, 2 mg · kg^{-1}, and midazolam, 0.4 mg · kg^{-1}. Measurements were recorded at baseline, 1 min post-induction, and at one, three, five and ten minutes after tracheal intubation. Tachycardia and hypertension (>20% increases from awake baseline values) were treated with esmolol, 250 μg · kg^{-1}. There were 11 patients in Group I and nine patients in Group II. There were no significant intergroup differences in demographic or haemodynamic variables. Both groups had decreases ($P < 0.05$), in stroke volume, pulmonary capillary wedge pressure, and right ventricular end-diastolic volume at multiple study intervals following anaesthetic induction. None of these changes required clinical intervention. Five patients (all in Group II) had hypertensive responses to tracheal intubation. Preoperative hypertension (mean arterial pressure ≥ 100 mmHg) was a predictor ($P < 0.05$) of a hypertensive response to intubation, independent of the midazolam dose. Intravenous ketamine and midazolam was associated with a high incidence (25%) of haemodynamic responses to tracheal intubation. The higher dose of midazolam did not provide any haemodynamic advantage.

La réponse hémodynamique après induction de l'anesthésie avec kétamine et midazolam n'a pas été déterminée à date. Vingt patients adultes, pour une chirurgie de revascularisation myocardique, furent randomisés en deux groupes. Le groupe I a reçu de la kétamine 2 mg · kg^{-1}, et du midazolam 0,2 mg · kg^{-1} alors que le groupe II a reçu de la kétamine 2 mg · kg^{-1} et du midazolam 0,4 mg · kg^{-1}. Les mesures furent enregistrées avant l'induction, une minute post-induction, et à trois, cinq et dix minutes après l'intubation trachéale. La tachycardie et l'hypertension (>20% des valeurs de base après induction) furent traitées avec de l'esmolol, 250 μg · kg^{-1}. Il y avait 11 patients dans le groupe I et neuf patients dans le groupe II. Il n'y avait aucune différence significative entre les groupes dans les données démographiques et les variables hémodynamiques. Les deux groupes avaient une diminution significative ($P < 0,05$) dans le volume d'éjection, la pression capillaire pulmonaire bloquée, le volume en fin de diastole du ventricule droit aux différents intervalles de l'étude après induction de l'anesthésie. Aucun de ces changements n'a requis une intervention clinique. Cinq patients (tous du groupe II) ont présenté une hypertension lors de l'intubation. L'hypertension préopératoire (pression artérielle moyenne ≥ 100 mmHg) pouvant prédire ($P < 0,05$) la réponse hypertensive lors de l'intubation et indépendamment de la dose de midazolam. L'administration intraveineuse de kétamine et de midazolam fut associée à une indicence élevée (25%) de réponse hémodynamique lors de l'intubation. La dose élevée de midazolam n'a pas fourni d'avantage hémodynamique.

Key words

ANAESTHETIC TECHNIQUES: induction;
ANAESTHETICS, INTRAVENOUS: ketamine, midazolam;
SURGERY: cardiac.

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Ketamine is a dissociative intravenous anaesthetic agent that has many favourable characteristics, including amnesia, analgesia, and bronchodilation.[1] However, the use of ketamine as a sole anaesthetic agent is complicated by unpleasant emergence phenomena and sympathomimetic effects.[2] The sympathomimetic effects are thought to be due to a centrally mediated release of catecholamines.[3] In addition, circulating catecholamine levels are increased by an inhibition of reuptake. Central inhibition of catecholamine reuptake may also contribute to ketamine cardiovascular stimulation.[4] Benzodiazepines have been reported to blunt the sympathomimetic effects, and help to prevent emergence phenomena associated with ketamine.[5] This is probably related to the central inhibitory

and amnesic effects of the benzodiazepines.[6] Midazolam is theoretically preferable to diazepam for this purpose because its pharmacokinetic profile is similar to that of ketamine.[7]

A preliminary investigation in cardiac surgical patients suggested that the combination of ketamine and midazolam was associated with haemodynamic stability.[8] However, no previous study has determined if conventional doses of midazolam would blunt the undesirable haemodynamic effects associated with ketamine during induction of anaesthesia and tracheal intubation. The current study examined the effects of two different doses of midazolam in combination with ketamine during anaesthetic induction and tracheal intubation, in patients undergoing myocardial revascularization surgery.

Methods

Twenty adult patients presenting for elective myocardial revascularization surgery were studied. Written informed consent was obtained from each patient, and the study protocol was approved by the institutional research administrative committee. All patients had a preoperative left ventricular ejection fraction >40% and were haemodynamically stable. Preanaesthetic medication consisted of morphine 0.1 $mg \cdot kg^{-1}$ and scopolamine 0.006 $mg \cdot kg^{-1}$ *im*. Cardiac medications, including beta-adrenergic blockers, calcium channel blockers, and nitrates, were continued until the time of surgery.

Peripheral venous and radial arterial catheters were placed using local anaesthesia. Electrocardiographic leads II and modified V_5 were also monitored. In addition to standard monitoring, a rapid-response thermistor pulmonary artery catheter (capable of calculating the right ventricular ejection fraction) was inserted before the induction of anaesthesia.

The patients were randomly divided into two groups. Those in Group I received midazolam 0.2 $mg \cdot kg^{-1}$ and ketamine 2 $mg \cdot kg^{-1}$ and those in Group II received midazolam 0.4 $mg \cdot kg^{-1}$ and ketamine 2 $mg \cdot kg^{-1}$ for anaesthetic induction. The investigators were blinded to the induction dose, and the midazolam dose was diluted to equal volumes with bacteriostatic H_2O. Awake baseline (T_0) values were obtained with the patient breathing 100% oxygen by face mask. The midazolam dose was then injected over 30 sec, followed immediately by the ketamine dose over 30 sec. Following loss of the eyelash reflex, vecuronium 0.1 $mg \cdot kg^{-1}$ was given *iv*. Haemodynamic and thermodilution measurements were obtained starting one minute following anaesthetic induction during mask ventilation with 100% oxygen (T_1). The thermodilution measurements took 90–120 sec to complete. Tracheal intubation was performed three minutes following the injection of the anaesthetic induction doses. Measurements were repeated at one (T_2), three (T_3), five (T_4), and ten minutes (T_5) after tracheal intubation. Following the induction of anaesthesia, ventilation with 100% oxygen was controlled to maintain an end–tidal CO_2 of 30–35 mmHg using mass spectroscopy.

A clinically significant haemodynamic response to tracheal intubation was defined as an increase in either HR or MAP >20% from the baseline (T_0) recorded value. These were treated with an *iv* bolus of esmolol, 250 $\mu g \cdot kg^{-1}$. A second *iv* bolus of esmolol, 250 $\mu g \cdot kg^{-1}$, was administered if the initial dose did not control the haemodynamic response.

Electrocardiographic and pressure tracings were recorded on a multi-channel pressure recorder for subsequent analysis. Before each set of measurements was made, the zero reference point of the transducers was positioned at the level of the right atrium, 5 cm posterior to the sternal angle of Louis. Intravenous fluid infusions were not started until arrival in the operating room, and were restricted to less than 1000 ml of a crystalloid solution during the entire study period. The fluid administration protocol was standard in the experimental groups.

Measured haemodynamic variables included heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and thermodilution cardiac output (CO). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using standard formulae.[9]

Thermodilution data were collected using an American Edwards rapid-response thermistor pulmonary arterial catheter and an American Edwards REF-1® Cardiac Output Computer (American Edwards, Santa Ana, CA).[10] Ten ml of iced 5% dextrose solution were injected until three cardiac output values within 10% of each other were obtained. (A maximum of five injections was possible during the two-minute intervals between T_2–T_3 and T_3–T_4.) Cardiac output (CO) and right ventricular ejection fraction (RVEF) were both measured from each thermodilution curve. Three cardiac output and RVEF values were averaged for each study interval, and stroke volume (SV), right ventricular end-systolic volume (RVESV), and right ventricular end-diastolic volume (RVEDV) were calculated by the cardiac output computer.

Continuous data were analyzed using repeated-measures ANOVA and Scheffe's multiple contrasts. Contingency data were analyzed using Fisher's Exact Test. A P value of < 0.05 was considered statistically significant.

Results

All 20 patients completed the experimental protocol. There were 11 patients in Group I, and nine in Group II.

TABLE I Demographic data

	Group I	*Group II*
Age (y)	61 ± 11	64 ± 9
Sex	9 male, 2 female	9 male
Nitrates	91%	78%
Beta-blockers	55%	67%
Calcium entry blockers	82%	56%
Anti-hypertensives	18%	0%
Triple-vessel coronary artery disease	91%	88%

The groups were comparable in preoperative drug therapy and demographic background (Table I).

All 20 patients tolerated loss of consciousness without hypertension, hypotension, bradycardia, or tachycardia. Five patients required treatment for immediate post-intubation hypertension. (Two of these patients also exhibited tachycardia.) The five patients were all in Group II (higher midazolam dose), all had a starting MAP ≥ 100 mmHg, and all had a satisfactory response to *iv* esmolol, 250 $\mu g \cdot kg^{-1}$. Of the 11 patients in Group I, none required treatment for post-intubation hypertension or tachycardia.

The incidence of hypertension was also analyzed independently of group assignment (i.e., midazolam dose). Of the 11 patients (in either group) with a baseline (T_0) MAP ≥ 100 mmHg, five developed clinically significant tachycardia or hypertension following tracheal intubation. Of the nine patients (in either group) with a baseline MAP < 100 mmHg, none developed a haemodynamic response to intubation ($P < 0.05$) (Table II). There were no episodes of laryngospasm, bronchospasm, chest wall rigidity, excessive secretions, or prolonged (>30 sec) intubation attempts in any patient.

TABLE II Incidence of hypertension following tracheal intubation

	>20% rise in MAP	*<20% rise in MAP*
Baseline MAP < 100 mmHg	0	9
Baseline MAP ≥ 100 mmHg	5	6

$P < 0.05$.

Contingency table demonstrating the relationship between baseline hypertension (MAP = mean arterial pressure) and haemodynamic responses to tracheal intubation following anaesthetic induction with ketamine, 2 $mg \cdot kg^{-1}$, and midazolam, 0.2 or 0.4 $mg \cdot kg^{-1}$.

The haemodynamic changes are summarized in Tables III and IV. There were no significant differences in HR, CO, RVEF, or RVESV between groups throughout the study period. Decreases in SV, as compared with the baseline (T_0) value, were noted in both groups at T_1 through T_5. A decrease was also seen in MAP at T_4 and T_5 in Group I, while decreases in RVEDV at T_2 and in PCWP at T_3 were noted in Group II. None of the above represented clinically significant changes, and none required intervention during or after the study period.

Discussion

The current study investigated the haemodynamic and right ventricular responses to anaesthetic induction and tracheal intubation using ketamine 2 $mg \cdot kg^{-1}$ in combination with 0.2 or 0.4 $mg \cdot kg^{-1}$ of midazolam. Loss of consciousness was accompanied by haemodynamic stability in the entire study sample of 20 patients.

Five patients became hypertensive (and two of these five also became tachycardic) following tracheal intubation. These haemodynamic responses to tracheal intuba-

TABLE III Left ventricular haemodynamic changes in Groups I and II

	T_0	T_1	T_2	T_3	T_4	T_5
Group I						
HR (bpm)	65 ± 12	68 ± 11	79 ± 17	76 ± 18*	73 ± 18	69 ± 16
MAP (mmHg)	95 ± 13	79 ± 8†	99 ± 12	88 ± 12	84 ± 13	78 ± 13†
PCWP (mmHg)	17 ± 8	12 ± 4*	13 ± 5	12 ± 4*	12 ± 4*	11 ± 4*
SV (ml)	69 ± 22	60 ± 17*	54 ± 18†	56 ± 15†	55 ± 16†	56 ± 17†
SVR (d-sec · cm^{-5})	1715 ± 749	1562 ± 606	1917 ± 732	1682 ± 582	1673 ± 663	1606 ± 752
Group II						
HR (bpm)	65 ± 17	65 ± 14	75 ± 13	74 ± 10	68 ± 9	65 ± 8
MAP (mmHg)	104 ± 15	95 ± 16	120 ± 22	106 ± 22	97 ± 22	91 ± 21
PCWP (mmHg)	17 ± 5	14 ± 4	16 ± 6	13 ± 5†	12 ± 3†	12 ± 3†
SV (ml)	82 ± 19	69 ± 14†	65 ± 12†	69 ± 15†	65 ± 12†	64 ± 10†
SVR (d-sec · cm^{-5})	1556 ± 304	1594 ± 329	1800 ± 446	1603 ± 337	1626 ± 329	1623 ± 397

Mean ± SD.

*$P < 0.05$ compared with T_0.

†$P < 0.01$ compared with T_0.

(HR = heart rate, MAP = mean arterial pressure, PCWP = pulmonary capillary wedge pressure, SV = stroke volume, SVR = systemic vascular resistance).

TABLE IV Right ventricular haemodynamic changes in Groups I and II

	T_0	T_1	T_2	T_3	T_4	T_5
Group I						
MPAP (mmHg)	24 ± 8	20 ± 4	21 ± 4	19 ± 5	19 ± 4*	19 ± 4*
RAP (mmHg)	11 ± 7	10 ± 4	9 ± 3	9 ± 4	9 ± 4	9 ± 3
SV (ml)	69 ± 22	60 ± 17*	54 ± 18†	56 ± 15†	55 ± 16†	56 ± 17†
RVEF	0.50 ± .09	0.50 ± .09	0.51 ± .10	0.51 ± .09	0.49 ± .09	0.46 ± .09
RVEDV (ml)	137 ± 29	121 ± 31	105 ± 32†	110 ± 28†	112 ± 29†	119 ± 27*
RVESV (ml)	68 ± 17	61 ± 22	52 ± 20*	56 ± 22	59 ± 21	64 ± 17
PVR (d-sec·cm^{-5})	149 ± 127	192 ± 138	173 ± 115	154 ± 54	163 ± 81	167 ± 92
Group II						
MPAP (mmHg)	24 ± 6	20 ± 4	23 ± 7	21 ± 6	19 ± 5	18 ± 4†
RAP (mmHg)	10 ± 3	11 ± 2	10 ± 3	10 ± 3	10 ± 3	9 ± 2
SV (ml)	82 ± 19	69 ± 14†	65 ± 12†	69 ± 15†	65 ± 12†	64 ± 10†
RVEF	0.52 ± .07	0.54 ± .07	0.58 ± .05	0.57 ± .05	0.52 ± .04	0.54 ± .07
RVEDV (ml)	157 ± 35	128 ± 24*	112 ± 17†	124 ± 34†	131 ± 28	119 ± 21†
RVESV (ml)	75 ± 22	60 ± 15	47 ± 9†	55 ± 22	66 ± 29	56 ± 16
PVR (d-sec·cm^{-5})	100 ± 47	109 ± 42	122 ± 80	127 ± 29	121 ± 22	112 ± 44

*$P < 0.05$ compared with T_0.
†$P < 0.01$ compared with T_0.
(HR = heart rate, MPAP = mean pulmonary arterial pressure, RAP = right atrial pressure, SV = stroke volume, RVEF = right ventricular ejection fraction, RVEDV = right ventricular end-diastolic volume, RVESV = right ventricular end-systolic volume, PVR = pulmonary vascular resistance).

tion were seen only in those patients who were hypertensive before induction of anaesthesia, and all of these episodes responded to *iv* esmolol. None of the patients who were normotensive before anaesthetic induction exhibited clinically significant haemodynamic responses to intubation. The patients who had clinically significant haemodynamic responses to intubation had all received the higher dose of midazolam (0.4 mg·kg^{-1}). This higher dose of midazolam (in combination with ketamine) did not blunt the haemodynamic response to tracheal intubation.

Tuman *et al.* have determined that a combination of ketamine and diazepam provided stable perioperative haemodynamics in cardiac surgical patients.[11] That study also found that ketamine/diazepam anaesthesia was associated with decreased fluid and vasopressor requirements, and decreased length of stay in the intensive care unit. However, the ability of midazolam to block the sympathomimetic effects of ketamine during anaesthetic induction, and the haemodynamic response to tracheal intubation has not been conclusively demonstrated.

The preliminary data of Tuman *et al.*[8] showed overall haemodynamic stability using ketamine 2 mg·kg^{-1} and midazolam 0.5 mg·kg^{-1} for induction in five cardiac surgical patients, all of whom were receiving beta-adrenergic blockers.* The current study involved a larger group of patients ($n = 20$), of whom more than 50% ($n = 11$) were mildly hypertensive prior to induction. It is known that hypertensive patients may have an exaggerated response to noxious stimuli in the perioperative period.[12,13] The current data suggest that preoperative hypertension (MAP > 100 mmHg) was an important predictor of post-intubation hypertension in patients receiving ketamine/midazolam anaesthesia.

Concurrent preoperative medical therapy, such as calcium-entry blocking agents and beta-adrenergic blocking agents, did not appear to play an important role in preventing the haemodynamic responses to intubation in the current study. Three of the five patients who became hypertensive following intubation were receiving beta-adrenergic blockers preoperatively, two of the five patients received calcium-entry blockers, and one patient received both. Nine of the 15 patients who did not have a hypertensive response had also received beta-adrenergic blocking drugs. However, the effectiveness of the doses of these drugs could not be measured with the methodology employed in this study.

Statistically significant decreases in PCWP, RVEDV, and SV occurred in both treatment groups following anaesthetic induction. These changes are consistent with mild venodilation three to ten minutes after intubation in unstimulated mechanically ventilated patients. No clinically significant episodes of hypotension requiring treatment were seen.

In the statistical analysis, there were no increases in HR or MAP in Group II at one minute after intubation (T_2) despite the five patients who required treatment for hypertension and/or tachycardia. There are two reasons

*Tuman K. Personal communication.

for this: (1) the patients received esmolol within 30 sec of intubation and were already responding to therapy; and (2) a strict multiple-comparison analysis (Scheffe's) was used to prevent Type I statistical errors.

In conclusion, the use of ketamine, 2 $mg \cdot kg^{-1}$, and midazolam, 0.2–0.4 $mg \cdot kg^{-1}$, for anaesthetic induction in cardiac surgical patients was associated with a hypertensive and/or tachycardic response to tracheal intubation in 25% of the patients studied. This response was seen only in those patients who were hypertensive preoperatively, and was not prevented by the higher dose of midazolam, but was readily treated with a single bolus of intravenous esmolol, 250 $\mu g \cdot kg^{-1}$. The combination of intravenous ketamine and midazolam for anaesthetic induction and tracheal intubation can only be recommended in normotensive patients. The larger dose of midazolam does not appear to offer any haemodynamic advantage.

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