



# Comparison of Haemodynamic Response to Inhalational Bolus with Desflurane in Normotensive and Hypertensive Patients Undergoing Laparoscopic Cholecystectomy

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## Abstract

**Objective:** Desflurane causes sympathetic stimulation at high end-tidal concentrations. We conducted this study to compare the haemodynamic response to inhalational bolus with desflurane in normotensive and hypertensive patients undergoing laparoscopic cholecystectomy.

**Methods:** In this prospective, clinical trial, 40 patients aged 18-60 years and undergoing laparoscopic cholecystectomy were divided into normotensives (Group N; n=20) and hypertensives (Group H; n=20). Heart rate (HR), mean arterial pressure (MAP) and bispectral index (BIS) were measured at baseline and every 60 s for 5 min after induction, intubation, initiation and inhalational bolus of desflurane. The primary objective was to compare haemodynamic response, and the secondary objective was to assess the need for inhalational boluses and to compare the number of overcorrections and undercorrections in BIS value after each inhalational bolus. An independent t-test was used to compare the means of the study parameters between the groups, and a dependent t-test was used to compare the percentage change in the means of the study parameters within the same group. Statistical significance was defined as  $p < 0.05$ .

**Results:** No statistically significant difference in the percentage of patients responding with a decrease, increase or no change of HR or MAP were seen between the two groups after inhalational bolus of desflurane. An overcorrection of BIS (value  $< 45$ ) was seen in 60% of the patients in Group H and 15% of the patients in Group N ( $p = 0.003$ ). None of the patients in either group had an undercorrection ( $BIS > 55$ ).

**Conclusion:** BIS-guided desflurane administration and BIS-triggered inhalational boluses of desflurane is safe, feasible and does not cause sympathetic stimulation in either normotensive or hypertensive patients.

**Keywords:** Anaesthetics inhalational, bolus, cardiovascular effects, complications, desflurane

## Introduction

Desflurane is a halogenated inhalational anaesthetic agent with low blood gas solubility (0.42), and this facilitates rapid emergence (1, 2). It is not used for induction because it is known to cause hypertension, tachycardia and irritation of the respiratory tract (3). Desflurane causes sympathetic stimulation when end-tidal concentrations exceed 6 vol. % (4).

There is usually a lag time between a change in vaporiser setting and the onset or offset of the desired clinical effect. The inhalational bolus technique is based on the principle of overpressure, and it rapidly increases the end-tidal concentration of the volatile agent, which then effectively blocks any analgesic and/or hypnotic arousal effects (5).

The aim of this study was to compare the haemodynamic response to Bispectralindex™ (BIS™)-guided desflurane administration and BIS-triggered inhalational boluses of desflurane in normotensive and hypertensive patients undergoing laparoscopic cholecystectomy. The secondary objective was to assess the need of inhalational boluses between the two groups and to compare the number of overcorrections and undercorrections in BIS value after each inhalational bolus.

## Methods

After approval of the institutional ethics committee, informed consent was obtained from 40 patients scheduled for laparoscopic cholecystectomy. This was a prospective study with equal numbers of patients recruited in the two groups of normotensive (Group N; n=20) and hypertensive (Group H; n=20) patients. Group N included patients with blood pressure less than 140 mmHg systolic and 80 mmHg diastolic, whereas Group H included patients with history of primary hypertension. Cases with pre-admission blood pressure more than 180 mmHg systolic and 100 mmHg diastolic, an age of less than 18 or more than 60 years, or a history of pulmonary, cardiac or central nervous system disease, acute cholecystitis, morbid obesity, previous upper abdominal surgery, coagulopathy, jaundice, abdominal malignancy or advanced liver disease were excluded. All hypertensive patients were asked to continue their antihypertensive medications until the day of surgery.

Patients were fasted for solids for approximately 8 h prior to surgery and premedicated with 0.03 mg kg<sup>-1</sup> i.v. midazol-

am and 1.5 µg kg<sup>-1</sup> fentanyl in the operation theatre. Routine monitors were attached, including electrocardiogram, non-invasive blood pressure, pulse oxymeter and BIS monitor (BIS, Aspect Medical Systems, Newton, MA, USA), and baseline parameters such as heart rate (HR), systolic blood pressure, diastolic blood pressure, mean blood pressure and arterial oxygen saturation, were recorded. Induction was performed with propofol 1% administered at 300 mL h<sup>-1</sup> until loss of consciousness followed by vecuronium (0.1 mg kg<sup>-1</sup>) and propofol infusion to achieve a BIS value between 45 and 55. Manual ventilation at a fresh gas flow (FGF) of 6 L min<sup>-1</sup> and 50% nitrous for 5 min was followed by intubation of the trachea. On the ventilator, the tidal volume was set at 8 mL kg<sup>-1</sup> and the peak airway pressure was kept below 30 cm H<sub>2</sub>O. The respiratory rate was adjusted to achieve an end-tidal carbon dioxide pressure of 30-35 mm Hg. Desflurane was started before insertion of trocar with an FGF of 6 L min<sup>-1</sup> [N<sub>2</sub>O (2 L min<sup>-1</sup>) and O<sub>2</sub> (4 L min<sup>-1</sup>)] and a vaporiser setting of 5 vol %. The dial setting was adjusted to maintain BIS between 45 and 55, and the FGF was lowered to 2 L min<sup>-1</sup> [N<sub>2</sub>O (1 L min<sup>-1</sup>) and O<sub>2</sub> (1 L min<sup>-1</sup>)] after 20 min.

An inhalational bolus with desflurane was administered when BIS was more than 55 for 30 s. To give an inhalational bolus, the vaporiser was set to 16% and FGF to 4 L min<sup>-1</sup> [N<sub>2</sub>O (2 L min<sup>-1</sup>) and O<sub>2</sub> (2 L min<sup>-1</sup>)] for 30 s. The FGF was decreased to 2 L min<sup>-1</sup> after 30 s, and the dial setting of desflurane was increased by 25% of the baseline value. If BIS was less than 45 for 30 s, then the dial setting of desflurane was lowered by 25%. Factors influencing BIS such as body temperature and ETCO<sub>2</sub> were kept nearly constant, and temperature was maintained at 35°C-36°C and ETCO<sub>2</sub> was maintained at 30-35 mmHg throughout the intraoperative period in both groups.

The following parameters were monitored: HR, mean arterial pressure (MAP), BIS during surgery and BIS before and after the inhalational bolus technique. The numbers of overcorrections and undercorrections of BIS using this technique in both groups were also recorded. Desflurane was discontinued after the last skin stitch. Controlled ventilation with 100% oxygen at 8 L min<sup>-1</sup> was continued until the end-tidal volatile anaesthetic concentration was less than 0.1%. Neuromuscular blockade was antagonised with 0.05 mg kg<sup>-1</sup> neostigmine and 0.01 mg kg<sup>-1</sup> glycopyrrolate, the trachea was extubated, and the patient was moved to the recovery room.

## Statistical analysis

Data were analysed with the IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA version 22.0 for Windows). Continuous data, e.g. age, weight, duration of anaesthesia, HR, MAP, BIS, etc., are expressed as

**Table 1. Baseline demographic and haemodynamic characteristics of patients**

	Normotensive group (n=20)	Hypertensive group (n=20)	p
Age (years)	35.75±11.67	53.85±11.46	<0.001*
Weight (kg)	60.10±8.25	55.65±10.62	0.147
Sex (Male/Female)	11/9	7/13	0.204
Duration of anaesthesia (minutes)	82.00±28.2	69.50±14.86	0.092
BIS	95.95±3.73	93.60±11.01	0.372
HR (beats/minute)	92.35±13.168	92.20±17.680	0.976
MAP (mmHg)	85.15±(9.27)	90.70±(9.22)	0.065

Values are mean±SD except sex and number of boluses, which are in numbers.

Independent t-test was used for comparing the means of the study parameters (BIS, HR, MAP). \*p<0.05, statistically significant. BIS: bispectral index; HR: heart rate; MAP: mean arterial pressure.

means±SD. Categorical data, e.g. gender, number of boluses of desflurane administered, etc., were expressed as frequencies and percentages. The Kolmogorov–Smirnov test was used to check the normality of the continuous data. An independent t-test was used to compare the means of the study parameters, e.g. BIS, HR, MAP, etc., between the two study groups at different time intervals. A dependent t-test was used to compare the percentage change in the means of the study parameters within same study groups compared to baseline. Chi-square/Fisher’s exact test was used to test for any association between the two study groups and the categorical variables, e.g. sex, response to bolus, response to initiation of desflurane, number of boluses of desflurane administered, etc. The results are presented in tabulation/graph forms. All tests were considered two tailed with 95% confidence inter-

vals, and statistical significant was set at a p-value<0.05. The results of a pilot study showed a MAP of 85±10.2 mmHg in normotensive patients and 95±10.2 mmHg in hypertensive patients. As per the results of the pilot study, we hypothesised that the difference in the increase in MAP between the two groups is not more than 12 mmHg, and for this difference in MAP with an alpha error of 0.05 and a power of 80% a sample size of 19 patients per group was required. Thus we recruited 20 patients in each group.

### Results

Forty-five patients were assessed for eligibility, and 40 patients were included in the study. The results of all 40 patients were analysed. The CONSORT flow diagram is presented in Figure 1.

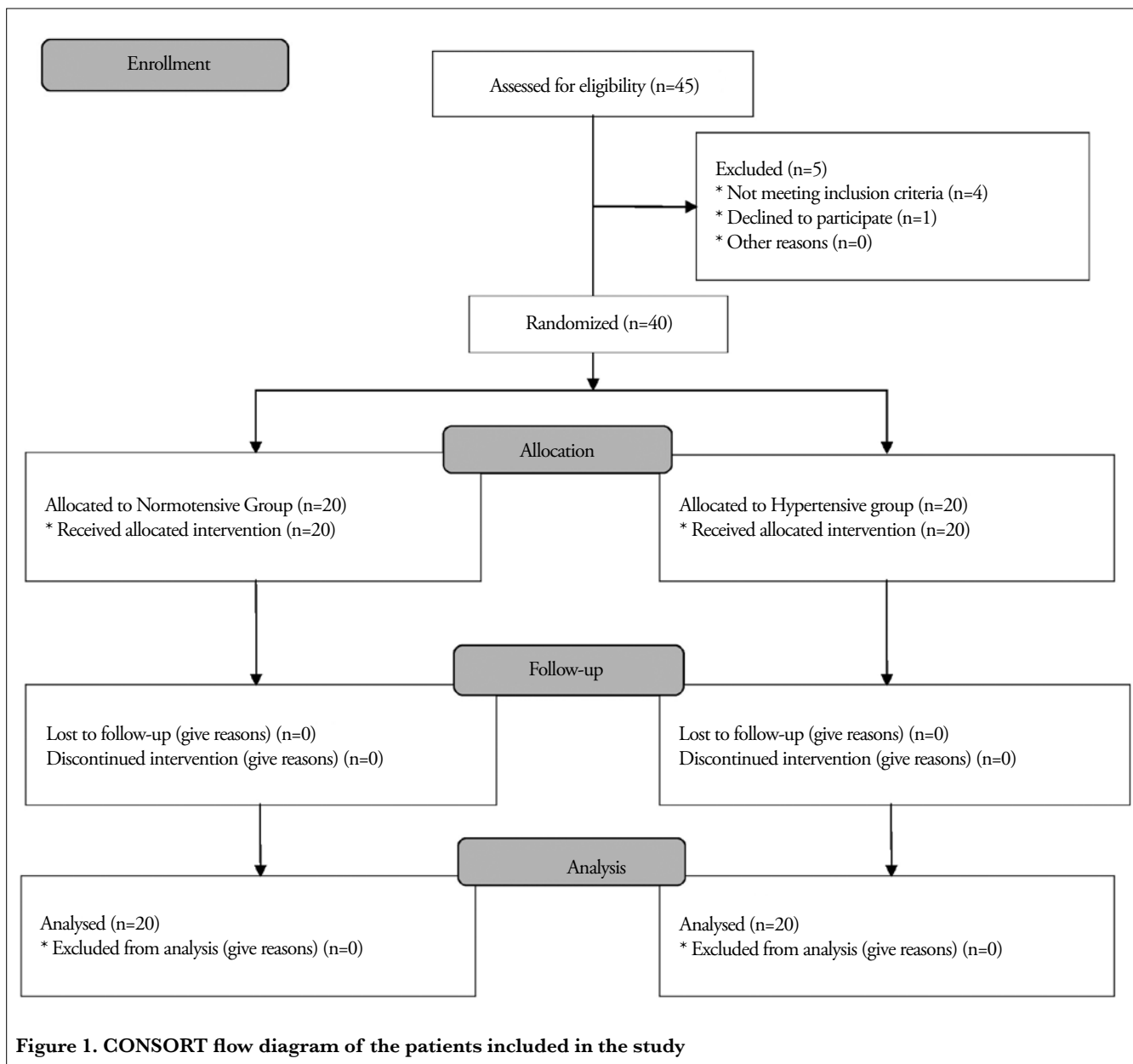


Figure 1. CONSORT flow diagram of the patients included in the study

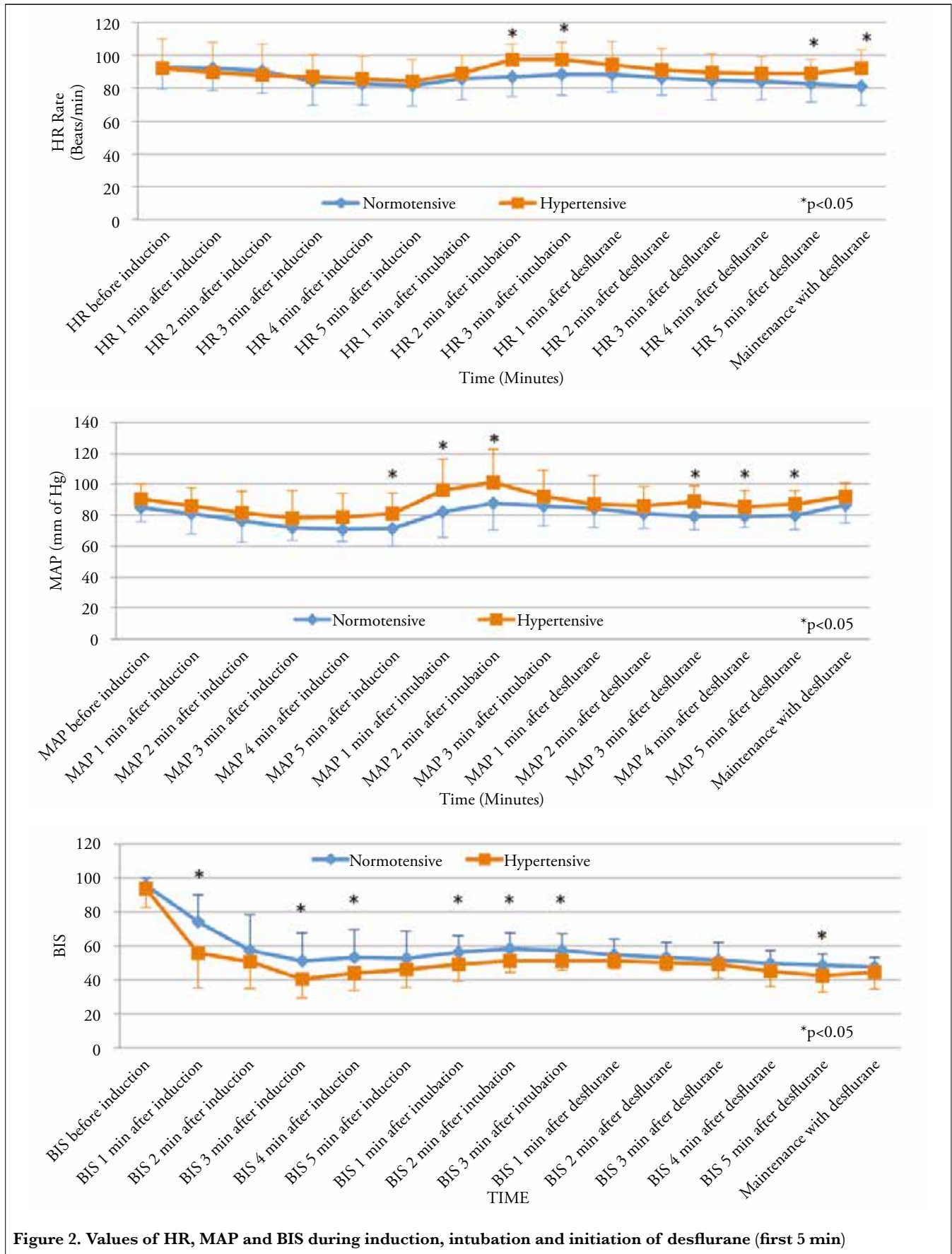


Figure 2. Values of HR, MAP and BIS during induction, intubation and initiation of desflurane (first 5 min)

Baseline demographic and haemodynamic characteristics of the patients are summarised in Table 1. A statistically significant difference was present in the mean age of the patients, and the patients in Group H were older ( $p < 0.001$ ).

Intergroup comparisons of haemodynamics (HR and MAP) and depth of anaesthesia (BIS) at induction, intubation and initiation of desflurane (first 5 min) are shown in Table 2 and Figure 2.

**Induction:** No significant difference was reported in HR between the two groups at induction. Intragroup analysis of HR after induction revealed a statistically significant decline at 3, 4 and 5 min in both the groups. No significant difference was reported in MAP between the two groups at 1, 2, 3 or 4 min after induction. Intragroup analysis of MAP showed a statistically significant decline at 2, 3, 4 and 5 min after induction in both groups. The mean value of BIS was significantly lower in Group H at 1, 3 and 4 min after induction.

**Intubation:** Statistically significant increases in HR were recorded in Group H at 2 and 3 min after intubation. However, intragroup analysis of HR in Group H did not show any significant change, while Group N showed a significant decline. MAP was significantly higher in Group H at 1 and 2 min after intubation ( $p < 0.05$ ). There was a significant increase in MAP in the intragroup analysis of Group H ( $p = 0.004$ ), but no change in the intragroup analysis of Group N. The mean

value of BIS was significantly lower in Group H at 1, 2 and 3 min after intubation.

#### Initiation and maintenance of desflurane

**Initiation:** The mean HR in Group H was significantly higher at 5 min after initiation and during the maintenance phase of desflurane compared to Group N. Intragroup comparison showed a statistically significant decline in HR at 2, 3, 4 and 5 min ( $p < 0.001$ ) after the initiation of desflurane in Group N, but no change in Group H. The MAP was significantly higher in Group H at 3, 4 and 5 min after initiation of desflurane, and a decline in MAP was seen in both groups at 3 and 4 min after initiation. The mean value of BIS was lower in Group H at 5 min after the initiation of desflurane.

**Maintenance:** There was a statistically significant ( $p < 0.001$ ) decrease in HR in intragroup analysis in Group N, but not in Group H. There were no significant intragroup changes in MAP in either group. The value of BIS was comparable between the two groups during the maintenance of desflurane.

#### Response to inhalational bolus

The total number of inhalational boluses administered were comparable (Group H=43 and Group N=30). The mean (SD) numbers of boluses per patient were 2.15 (1.78) and 1.45 (1.64) in Group H and Group N, respectively ( $p = 0.204$ ). A total of 60% of the patients in Group H and 15% of the patients in Group N had an overcorrection of BIS (value < 45) after 5 min of initiation of desflurane, and the difference was

**Table 2. Course of HR, MAP and BIS in normotensive and hypertensive groups**

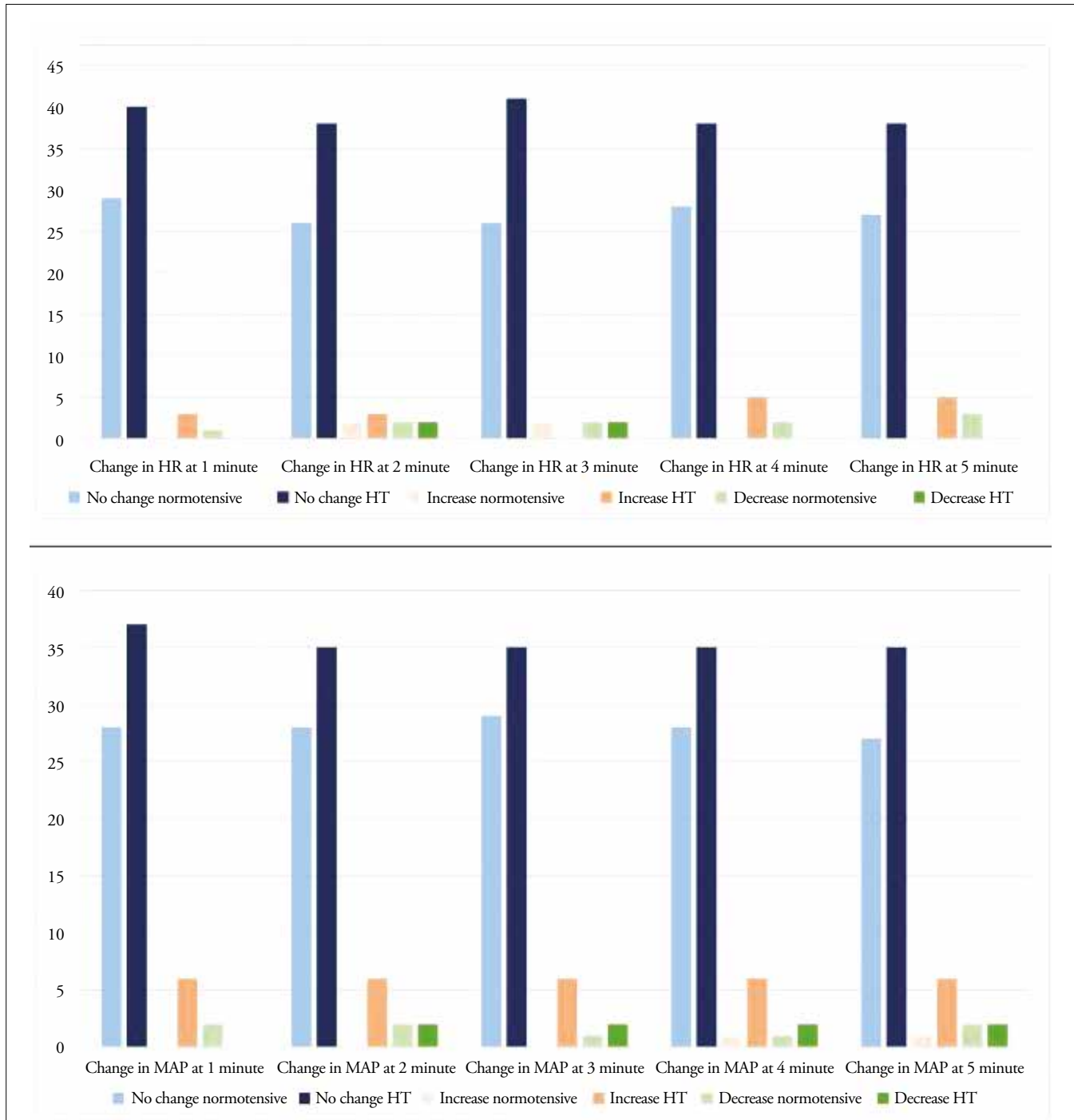
Time interval	HR		MAP		BIS	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Before Induction	92.35±13.17	92.20±17.68	85.15±9.27	90.70±9.22	95.95±3.73	93.60±11.01
1 minute after induction	92.20±13.85	89.20±18.88	81.10±13.06	86.08±11.54	74.05±16.32	55.85±20.68
2 minute after induction	90.50±13.89	87.95±18.76	76.50±14.31	81.58±14.12	57.60±20.89	50.75±15.81
3 minute after induction	84.20±14.68	86.85±13.60	72.14±8.42	78.15±18.19	51.15±16.51	40.20±10.82
4 minute after induction	82.35±12.75	85.75±13.64	71.05±8.20	78.50±15.55	53.40±16.51	44.05±10.28
5 minute after induction	81.65±12.56	84.05±13.32	71.25±11.07	81.00±13.51	52.90±15.65	46.10±10.66
1 minute after intubation	85.50±12.35	89.05±11.12	81.94±16.11	95.95±20.33	56.35±9.91	48.95±9.53
2 minute after intubation	86.60±11.71	97.20±9.89	87.55±17.34	100.98±21.6	58.40±9.44	51.40±7.04
3 minute after intubation	88.25±12.65	97.15±10.70	85.95±12.99	92.02±17.28	57.35±9.85	51.05±5.32
1 minute after desflurane	88.45±10.63	94.30±14.36	84.57±12.73	87.20±18.43	54.80±9.15	51.05±4.68
2 minute after desflurane	86.40±10.95	91.00±13.50	80.91±9.73	85.80±12.73	53.20±8.65	50.35±4.97
3 minute after desflurane	84.70±11.66	89.45±11.38	79.29±8.79	88.90±10.35	51.90±9.97	49.05±7.94
4 minute after desflurane	83.95±10.98	88.75±9.99	79.40±7.58	85.45±10.89	49.90±7.39	44.90±9.30
5 minute after desflurane	82.60±11.24	89.10±8.04	80.15±9.56	87.30±9.12	48.50±6.65	42.35±9.71
Maintenance with desflurane	80.75±11.34	92.00±11.01	86.55±11.64	92.45±8.49	47.40±5.95	44.30±9.78

Values are mean±SD

statistically significant ( $p=0.003$ ). None of the patients in either group had an undercorrection ( $BIS>55$ ). There was no statistically significant difference in the percentage of patients responding with a decrease, increase or no change of HR and MAP between the two groups after inhalational bolus of desflurane (Figure 3).

### Discussion

BIS-guided administration of desflurane and BIS-triggered inhalational bolus of desflurane is a safe anaesthetic technique for the maintenance of adequate depth of anaesthesia in normotensive and hypertensive patients undergoing laparoscopic



**Figure 3. Intergroup comparison of changes in haemodynamic parameters (HR, MAP) in hypertensive and normotensive patients administered inhalational boluses of desflurane**  
 Values on the y-axis show the percentage of patients. The x-axis shows the change in parameters classified as no change, increase and decrease compared to baseline in the normotensive and hypertensive groups. Values within  $\pm 20\%$  of baseline are labelled as no change.

cholecystectomy. In our study there were no haemodynamic disturbances with the use of this technique, and 80% of the Group H patients and 90% of the Group N patients had no significant changes in MAP. Similarly, 88% of the patients in Group H and 86% of the patients in Group N had no significant change in HR with inhalational bolus of desflurane. However, a significantly larger proportion of patients in Group H had overcorrection of BIS with this technique. The results of our study are similar to a previously published trial conducted in morbidly obese patients comparing the inhalational bolus technique using sevoflurane and desflurane where they concluded that immediate recovery was significantly faster in the desflurane group but overall hypnotic controllability as measured by BIS was less accurate with desflurane (5). Intraoperative cardiovascular stability was easily achieved with both sevoflurane and desflurane, and MAP and HR were maintained within  $\pm 20\%$  of baseline values during the maintenance period.

An inhalational bolus of sevoflurane has been reported to be more effective than an IV remifentanyl bolus for effective control of haemodynamic responses to surgical stress during major surgery (6). In the sevoflurane group, an excessive effect occurred in 12% of responses, whereas an excessive effect occurred in 26.7% in the remifentanyl group ( $p < 0.05$ ).

In healthy male volunteers, rapid increases of desflurane or isoflurane from 0.55 to 1.66 minimum alveolar concentration (MAC) have been shown to increase sympathetic and renin-angiotensin system activity and to cause transient increases in arterial blood pressure and HR (3). However, in our present study we do not report such changes because in previous studies it has been demonstrated that an initial rapid increase in desflurane to 1.1 MAC produces much more stimulation than a subsequent increase in desflurane, and it has been hypothesised that the initial cardio-stimulatory response is due to stimulation of rapidly adapting airway receptors (7). In our study, the patients were being maintained with desflurane, and the inhalational boluses were administered transiently and did not lead to cardiovascular stimulation. An FGF of  $10 \text{ L min}^{-1}$  and a delivered anaesthetic concentration of 18% desflurane for an average time of 66 s (SD 7 s) was used in a previous study (7), but we used a dial setting of 16% desflurane at an FGF of  $4 \text{ L min}^{-1}$  [ $\text{N}_2\text{O}$  ( $2 \text{ L min}^{-1}$ ) and  $\text{O}_2$  ( $2 \text{ L min}^{-1}$ )] for 30 s only.

The results of our study are in accordance with previous work reporting bradycardia and hypotension after induction with propofol (8). Lower values of BIS in hypertensive patients can be partly explained on the basis of age-related changes in the pharmacodynamics and pharmacokinetics of hypnotic agents. Patients in Group H were older in age ( $p < 0.001$ ). Intubation response was seen in Group H but not in Group N.

This is a known phenomenon, and various drugs have been advocated to reduce this effect (9, 10).

Initiation of desflurane did not cause any haemodynamic change in our study. The significant difference in vital parameters in the intergroup analysis was due to the fact that the relative decrease in HR and BP was greater for Group N at the time of induction, intubation and initiation of desflurane. This was because we had used propofol for induction, and it has been shown in a previous study that propofol reduces desflurane-mediated sympathetic activation in humans (11). Another reason was that the rise in the end-tidal concentrations of desflurane occurred in a controlled manner in our study, and a slow increase in inhaled desflurane concentration has been reported to attenuate the circulatory responses (12).

Two of the limitations of our study were that randomisation was not possible between normotensive and hypertensive patients, and the presence of an additional anaesthetist who was blinded from the monitor and the vaporiser was not feasible in our study. Similar limitations were pointed out in previous studies conducted in morbidly obese patients comparing the inhalational bolus technique with desflurane and sevoflurane (13, 14). Another limitation of our study was that the patients in Group H were significantly older ( $p < 0.001$ ). This limitation of our study can be overcome in further studies with recruitment of patients with comparable demographic profiles.

Another limitation is that we did not record the respiratory effects of the inhalation bolus technique. A previous study reported a significant increase in respiratory resistance and peak inspiratory pressure and a decrease in dynamic compliance with more than 2 MAC of desflurane for 5 min (15). We administered the inhalational bolus for a transient period of 30 s only and thus did not expect any respiratory effect. The ventilation parameters were not standardised, and changes in tidal volume/rate were made by the anaesthesiologist so as to maintain  $\text{ETCO}_2$  at 30-35 mmHg.

The validity of the BIS readings in our study were confirmed by simultaneous recordings of electromyography and by making a note of the use of electrocautery. The probability of administration of an inhalational bolus due to an artefactual reading was further reduced by initiation only after the occurrence of a BIS trigger point for more than 30 s. However, one limitation was that we did not calculate the amount of time that BIS monitoring was impossible or temporarily suspended. Body temperature and  $\text{ETCO}_2$  were maintained in the normal range in both groups, and thus we do not expect any influence of these parameters on the BIS values.

We did not use MAC equivalent doses of inhalational anaesthetic, but preferred to use BIS control as an endpoint be-

cause although the MAC is useful in comparing the relative potency of volatile anaesthetics, multiple confounding factors can affect the MAC of individual patients.

## Conclusion

Bispectralindex™ (BIS™)-guided desflurane administration and BIS-triggered inhalational boluses of desflurane in normotensive and hypertensive patients undergoing laparoscopic cholecystectomy does not cause sympathetic stimulation and is thus safe and feasible. Sensitivity of hypertensives to the inhalational bolus of desflurane is higher and leads to significantly more overcorrections of BIS. Further studies are needed for the optimisation of the amount and time of the inhalational bolus of desflurane in various subsets of patients in terms of hypnotic stability and anaesthetic depth control.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Postgraduate Institute of Medical Education and Research (1/2010/PGIMER-RM-LH/EC/Vol.I/319).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – K.K., T.S., N.B., S.S.; Design – K.K., T.S., N.B., S.S.; Supervision – K.K., T.S., V.S., N.B., S.S.; Resources – K.K., T.S., V.S., S.S., N.B.; Materials – K.K., T.S., V.S., S.S.; Data Collection and/or Processing – K.K., T.S.; Analysis and/or Interpretation – K.K., T.S., V.S., S.S.; Literature Search – K.K., T.S., V.S., S.S.; Writing Manuscript – K.K., T.S., V.S., S.S.; Critical Review – T.S., V.S., S.S.; Other – K.K., T.S., V.S.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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