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Comparative Hemodynamic Responses to Intravenous Ephedrine during Halothane, Enflurane, or Isoflurane Anesthesia

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Abstract

Since the pressor effect of ephedrine is altered by various factors, this study was performed to evaluate the possible influences of volatile anesthetics.

Hemodynamic responses to intravenous ephedrine were studied in ninety surgical patients who were randomly assigned to receive either halothane, enflurane, or isoflurane anesthesia. Blood pressure (BP) was measured oscillometrically, while heart rate (HR) was recorded by an electrocardiogram monitor. General anesthesia was induced with thiamylal 4-5 $mg \cdot kg^{-1}$ i. v. and tracheal intubation was facilitated with vecuronium 0.2 $mg \cdot kg^{-1}$ i. v. Thereafter, anesthesia was maintained with end-tidal concentration of halothane 0.3-1.0 %, enflurane 0.8-2.0 %, or isoflurane 0.5-1.5 % with 67 % nitrous oxide in oxygen to keep mean BP at approximately 90 % of preinduction values. Ventilation was controlled to maintain end-tidal carbon dioxide tension between 35-40 mmHg. After a stable hemodynamics was obtained, ephedrine 0.1 $mg \cdot kg^{-1}$ was injected intravenously as a bolus. BP and HR were recorded 1-minute intervals for ten minutes after ephedrine administration.

The magnitudes of maximal increases in mean BP from baselines were similar among the three groups (15.7 ± 8.4, 13.7 ± 5.0, and 15.0 ± 7.2 mmHg in patients anesthetized with halothane, enflurane, and isoflurane, respectively). There was also no difference in maximal HR increases (5.9 ± 3.2, 6.2 ± 4.5, and 5.9 ± 4.7 beats$\cdot min^{-1}$ in patients anesthetized with halothane, enflurane, and isoflurane, respectively).

It is concluded that a bolus injection of ephedrine 0.1 $mg \cdot kg^{-1}$ increased BP and HR similarly in anesthetized patients with halothane, enflurane or isoflurane.

Key words : Ephedrine, Enflurane, Halothane, Isoflurane, Blood pressure, Heart rate.

Introduction

The effect of vasopressor drugs is influenced by several factors including circulating blood volume, acid-base balance, co-administration of other drugs[1~3]. Ephedrine, one of pressor agents widely used to treat hypotension during regional or general anesthesia, exerts its pressor action by releasing norepinephrine in addition to direct stimulation of sympathetic nervous system[1]. Its pressor effect is known to be predominantly brought by an increase in cardiac output with reduced systemic vascular resistance[1].

Among commonly used inhaled anesthetics, halothane, enflurane, isoflurane, and nitrous oxide have different effects on cardiovascular system. Halothane, enflurane and isoflurane decrease blood

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pressure (BP) from awake level in a dose-dependent manner while nitrous oxide has a moderate pressor effect[4]. However, the mechanisms of decreasing BP are not similar among these volatile anesthetics ; halothane and enflurane mainly depress cardiac contractility and decrease cardiac output while isoflurane dilates peripheral vasculature with minimal depression on cardiac contractility[4] . Based on these findings, the pressor effect of ephedrine may be least during isoflurane anesthesia.

To our knowledge, there is no available data concerning the possible different effects of volatile anesthetics upon the pressor response to intravenous ephedrine in humans. The aim of current study is to examine whether the pressor effects of ephedrine would be different among the patients under halothane, enflurane, or isoflurane anesthesia with nitrous oxide in a clinical situation.

Methods

Ninety normotensive surgical patients, ASA physical status 1 or 2, ranging in age from 16 to 70 yr, and scheduled to have general anesthesia for surgical procedures, were selected for this study. The study protocol was approved by our Clinical Investigation Committee and written informed consent was obtained from each patient. None of the patients was taking any medications affecting cardiovascular function. The patients were randomly divided into three groups ; halothane group (n=30), enflurane group (n=30) and isoflurane group (n=30). All patients were premedicated with oral famotidine 20 mg alone 90 min before arriving in the operating room.

In the operating room blood pressure (BP) was measured oscillometrically with a BP monitoring device (BP1001S, Nihon Colin, Komaki), while the lead II of the electrocardiogram (ECG ; Bioview 2F37, NEC San-ei Instrument, Tokyo) was monitored to detect arrhythmias and obtain an average value of heart rate (HR) every 4 seconds. An 18-G intravenous catheter was inserted for continuous infusion of lactated Ringer's solution at an approximate rate of 15 $ml \cdot kg^{-1} \cdot h^{-1}$. General anesthesia was induced with intravenous thiamylal (Yoshitomi, Osaka) 4-5 $mg \cdot kg^{-1}$ and tracheal intubation was facilitated with intravenous vecuronium (Sankyo, Tokyo) 0.2 $mg \cdot kg^{-1}$. Anesthesia was maintained with one of the three volatile anesthetics (end-tidal concentration of halothane 0.25-1.0 %, enflurane 0.8-2.0 %, or isoflurane 0.5-1.5 %) and nitrous oxide 67 % in oxygen. Ventilation was controlled to maintain end-tidal carbon dioxide ($ETCO_2$) between 35-40 mmHg, and end-tidal concentration of volatile anesthetic was kept constant during the study, while these variables were continuously monitored by anesthetic and ET CO_2 analyzer (Capnomac, Datex, Helsinki, Finland) . Baseline BP and HR values were recorded in each patient, when steady end-tidal volatile anesthetic concentration (stable end-tidal concentration for at least 3 min without changing inspiratory concentration) was achieved, three consecutive measurements of mean blood pressure (MBP) and HR at 1-min intervals fell within 5 %, and at least 20 min elapsed after endotracheal intubation. Ephedrine (Dainippon, Osaka) 0.1 $mg \cdot kg^{-1}$ was administered intravenously as a bolus over 5 seconds. Both BP and HR were recorded at 1-minute intervals for 10 min after the injection of ephedrine. Immediately after the last measurements, arterial blood was sampled and analyzed for pHa, carbon dioxide tension, oxygen tension, and base excess with a self-calibrating electrodes system (178pH/Blood Gas Analyzer, Corning, Medfield, MA, U.S.A.).

Data were expressed as mean ± standard deviation (SD). Maximum changes in MBP and HR from baselines after ephedrine injection were compared among the three groups. Two-way analysis of variance (ANOVA) followed by Student's t test with Bonferroni corrections was used for statistical analysis. A $P < 0.05$ was considered the minimum level of statistical significance.

Results

There were no differences among the three groups in patients' demographic data, doses of anesthetics administered, and infusion rate of crys-

talloid (tables 1 and 2). When end-tidal concentrations of volatile anesthetics were expressed as minimum alveolar concentration (MAC), there were differences among the three groups ; 2.02 ± 0.51 MAC, 1.36 ± 0.20 MAC, 1.69 ± 0.26 MAC in the halothane, enflurane, and isoflurane groups, respectively ($P<0.05$ versus each other).

Baseline MBP values prior to ephedrine injection were similar among groups (71 ± 8, 68 ± 9, and 70 ± 7 mmHg in the halothane, enflurane, and isoflurane groups, respectively). MBPs attained their peaks at 2-3 min following the injection of ephedrine, thereafter, they gradually returned to baseline values (Fig. 1). Compared with baseline values, MBPs were greater from 1 to 8, from 1 to 7, and from 1 to 7 min in the halothane, enflurane, and isoflurane groups, respectively (Fig. 1). The average duration of MBPs elevations above baseline values were 7.8 ± 2.7, 7.0 ± 2.8, and 7.9 ± 2.8 min in the halothane, enflurane, and isoflurane groups, respectively ($P>0.05$). There was also no difference in maximal changes in MBP from baseline values among groups (Fig. 2).

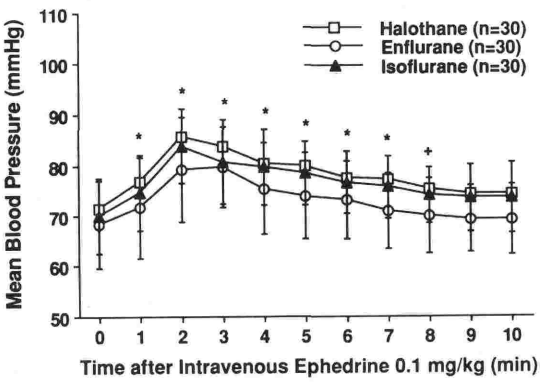

Figure 1. Changes (± SD) in mean blood pressure after intravenous bolus injection of ephedrine 0.1 $mg \cdot kg^{-1}$ in patients anesthetized with halothane, enflurane, or isoflurane, plus nitrous oxide in oxygen. Mean blood pressure attained its peak at 2-3 min following ephedrine injection. * $P < 0.05$ versus baseline in all three groups. + $P < 0.05$ versus baseline in enflurane and isoflurane groups.

Baseline HR values prior to ephedrine injection were similar among groups (68 ± 10, 71 ± 10, and 75 ± 12 beats·min^{-1} in the halothane, enflurane, and isoflurane groups, respectively). HRs attained their peaks around 1 min following the injection of ephedrine, thereafter, they gradually returned to baseline values (Fig. 3). Compared with the duration of pressor responses, positive chronotropic effects of ephedrine were sustained only for brief periods of 1 to 2 minutes following ephedrine injection in all groups. In addition, there was no difference in maximal changes in HR from baseline values among groups (Fig. 4).

Table 1. Demographic data of patients. Values are mean ± SD. There were no significant differences among the three groups.

Group	Age (yr)	Weight (kg)	Height (cm)	Sex (F/M)	ASA (I/II)
Halothane (n=30)	37 ± 16	57 ± 13	160 ± 12	15/15	27/3
Enflurane (n=30)	38 ± 15	55 ± 11	161 ± 8	15/15	29/1
Isoflurane (n=30)	37 ± 13	61 ± 12	162 ± 9	15/15	28/2

Table 2. Doses of anesthetics administered and infusion rate of crystalloid solution during study. Values are mean ± SD. There were no significant differences among the three groups.

Group	Thiamylal (mg/kg)	Vecuronium (mg/kg)	End-tidal concentration of volatile anesthetics (%)	Infusion rate of crystalloid ($ml \cdot kg^{-1} \cdot h^{-1}$)
Halothane (n=30)	4.87 ± 0.33	0.19 ± 0.02	0.94 ± 0.37	19.5 ± 7.2
Enflurane (n=30)	4.77 ± 0.28	0.20 ± 0.01	1.23 ± 0.34	21.0 ± 6.6
Isoflurane (n=30)	4.84 ± 0.42	0.20 ± 0.01	1.22 ± 0.30	17.4 ± 4.8

Arterial blood gas values were similar among groups. In some patients premature ventricular contractions (PVCs) were observed on ECG monitor during direct laryngoscopy (mainly in the halothane group), but no PVCs developed during hemodynamic measurement after ephedrine injection. There was no other adverse reaction related to the interaction between ephedrine and volatile anesthetics during and after the study.

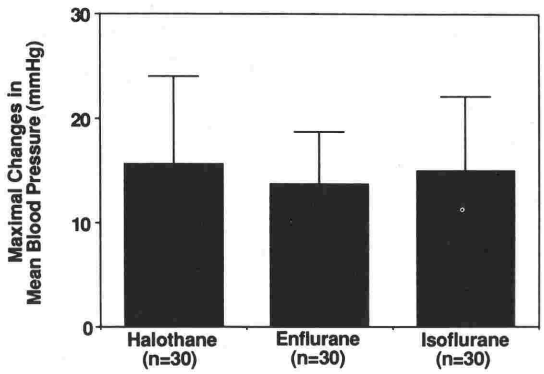

Figure 2. Maximal changes (± SD) in mean blood pressure from baseline values in patients anesthetized with halothane, enflurane, or isoflurane, plus nitrous oxide in oxygen. There were no significant differences among the three groups.

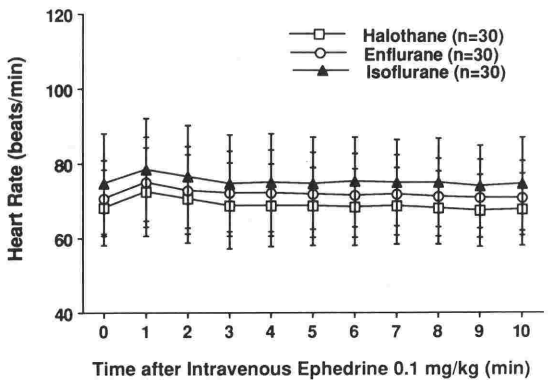

Figure 3. Changes (± SD) in heart rate after intravenous bolus injection of ephedrine 0.1 $mg \cdot kg^{-1}$ in patients anesthetized with halothane, enflurane, or isoflurane, plus nitrous oxide in oxygen. Heart rate attained its peak around 1 min following ephedrine injection. There were no significant differences among the three groups.

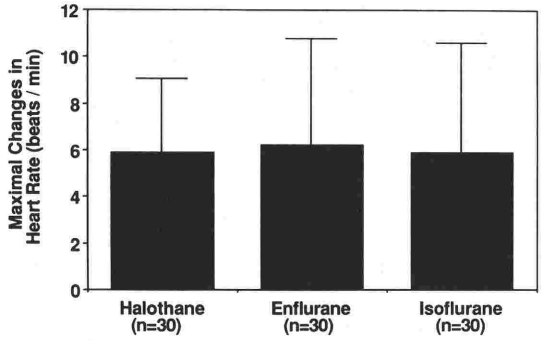

Figure 4. Maximal changes (± SD) in heart rate from baseline values in patients anesthetized with halothane, enflurane, or isoflurane, plus nitrous oxide in oxygen. There were no significant differences among the three groups.

Discussion

The current results showed that the pressor effects of a bolus intravenous injection of ephedrine 0.1 $mg \cdot kg^{-1}$, in terms of both maximal effects and duration of actions, were similar among patients anesthetized with halothane, enflurane, or isoflurane, plus nitrous oxide in oxygen. The positive chronotropic effects of ephedrine were also comparable among the three groups of patients.

The current study was the first controlled, randomized, prospective study to compare the pressor effect of ephedrine in patients anesthetized with halothane, enflurane and isoflurane. As far as the present results are concerned, the influence of volatile anesthetics on the hemodynamic effect of ephedrine was not clinically evident in terms of BP and HR changes. According to Eger's review[4], the most potent cardiodepressant agent is halothane, whereas the most potent vasodilator is isoflurane when compared at the same MAC. Enflurane is an intermediate potent agent between the two anesthetics concerning these actions. Therefore, we could anticipate greater pressor response to ephedrine during halothane anesthesia than anesthesia with other two volatile anesthetics, because ephedrine is known to exert its pressor effect predominantly by increasing cardiac output[1]. However, that was not

the case.

One should consider several limiting factors in our study protocol that may have influenced the current results. First, to make more clinically relevant situations, we used nitrous oxide in combination with volatile anesthetics. Because nitrous oxide *per se* has a moderate pressor effect[4] and a tendency of releasing noradrenaline from the sympathetic nerve endings[5], co-administration of nitrous oxide may have lessened basal hemodynamics associated with different volatile anesthetics prior to ephedrine injection. Second, the end-tidal concentration of volatile anesthetics was selected and maintained constantly throughout the study period so that it reduced MBP by approximately 10 % from preanesthetic values. Thus, when the end-tidal anesthetic concentrations were expressed as MAC, they differed from each other. Alternatively, the baroreceptor reflex is known to be suppressed more profoundly by halothane or enflurane than isoflurane[6~8]. These findings are likely to suggest that baroreflex in patients during halothane anesthesia may have been suppressed to a greater extent as compared with patients in other two groups in the present study. However, since in our previous report inhibition of baroreflex induced by volatile anesthetics was thought to have contributed partly to the potentiation of pressor effect of ephedrine during general anesthesia[3], greater hemodynamic depression by halothane may have been reversed rather easily by ephedrine *via* more profound baroreflex impairment induced by halothane.

In conclusion, a bolus intravenous injection of ephedrine 0.1 $mg \cdot kg^{-1}$ increases BP and HR to the same levels in patients under halothane enflurane, or isoflurane anesthesia plus nitrous oxide in oxygen. These results may imply that one can anticipate similar pressor effects of ephedrine regardless of underlying general anesthesia with different volatile anesthetic agents.

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