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Determinants for the Pressor Effect of Ephedrine in Awake or Anesthetized Humans: Effects of Age, General Anesthesia, or Basal Blood Pressure

Toshiaki Nishikawa*, Makoto Tanaka*, Toshihiro Naganuma* and Hiroshi Naito*

Abstract

To test the hypothesis that the pressor effect of ephedrine would be influenced by aging, general anesthesia, or basal blood pressure, we compared the pressor response to ephedrine in awake or anesthetized 103 patients, ranging in age from 13 to 82 yr.

Hemodynamic measurements were made at 1-minute intervals for 10 minutes after ephedrine 0.1 $mg \cdot kg^{-1}$ was injected as a bolus in 30 awake patients. In the remaining 73 patients general anesthesia was induced with thiamylal 5 $mg \cdot kg^{-1}$ iv, and the trachea was intubated following vecuronium 0.2 $mg \cdot kg^{-1}$ iv. Anesthesia was maintained with enflurane 0.8 − 2.0% inspired and nitrous oxide 67% in oxygen, while the lungs were mechanically ventilated to maintain normocapnia. The same hemodynamic measurements were made at 1-minute intervals for 10 minutes after ephedrine 0.1 $mg \cdot kg^{-1}$.

Although the pressor response to ephedrine was greater in anesthetized patients than awake patients, there was no relationship between age and maximal elevations in mean blood pressure following ephedrine in awake or anesthetized patients. Slight inverse correlations between the baseline values (before ephedrine injection) and the magnitude of maximal changes following ephedrine in mean blood pressure were noted in anesthetized ($r = -0.57$, $P < 0.001$) and awake ($r = -0.40$, $P < 0.03$) patients.

It is concluded that the pressor responsiveness to intravenous ephedrine depends upon the baseline values and is augmented during enflurane/nitrous oxide anesthesia, but is not altered by aging.

Key words : Age, Ephedrine, General anesthesia, Pressor effect.

Introduction

It has been demonstrated that beta adrenoceptor-mediated vascular relaxation and chronotropic effect or the intrinsic inotropic response to catecholamines are reduced in aged subjects[1~4] although the alteration in vascular responsiveness to alpha adrenergic agonist with aging remains controversial[5~7]. In clinical setting, age-related functional changes[8~11] in the autonomic nervous system, which plays a crucial role in circulatory regulation, are likely to modulate these altered vascular and myocardial responses to sympathomimetic agents. Furthermore, general anesthetics depress baroreflex function[12~14] and may further modulate alterations in cardiovascular responses with advancing age.

Ephedrine, one of the most commonly used vasopressor agents during anesthesia, possesses equal

* Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba.

potency of alpha-and beta-receptor stimulation[15]. Besides its direct action, ephedrine increases blood pressure (BP) and heart rate (HR) by facilitating the release of norepinephrine from the sympathetic nerve endings[16], which can, in turn, be affected to a considerable extent by general anesthetics[17~21] Accordingly, the overall pressor action of ephedrine may also be modified by alterations in autonomic nervous system activities associated with both aging and anesthesia. However, to our knowledge, there is no clinical report evaluating the major determinants for effect of ephedrine in awake or anesthetized humans.

Based on these considerations, we undertook this study to test the hypothesis that aging or general anesthesia would alter the pressor effects of ephedrine. In addition, to identify the major determinant for the pressor responsiveness to ephedrine, we evaluated correlations between the pressor effect of ephedrine and basal blood pressure or other variables.

Methods

One hundred and three surgical patients, ASA physical status I or II, ranging in age from 13 to 82 yr, and scheduled to have general anesthesia for their surgical procedures, were selected for this study. The study protocol was approved by our local ethical committee. Informed consent was obtained from each patient. No patient had any cardiopulmonary disorders. In addition, none of the patients was taking any medications affecting cardiovascular function. All patients received famotidine 20 mg orally 1.5 hr before arrival in the operating room. A 16-gauge intravenous catheter was placed under local infiltration with 0.5 % lidocaine for infusion of lactated Ringer's solution at an approximate rate of 15 $ml \cdot kg^{-1} \cdot h^{-1}$ during the study.

After a stable hemodynamic state was obtained in each patient, positioned supine with a pillow, for several minutes, ephedrine 0.1 $mg \cdot kg^{-1}$ was administered iv over 5 seconds in 30 awake patients. Ephedrine hydrochloride solution (Dainippon, Osaka) was diluted in a concentration of 1 $mg \cdot ml^{-1}$. BP and HR were measured at 1-minute intervals for 10 minutes after the injection of ephedrine, while lead II of the electrocardiogram (ECG; NEC San-ei Instrument, Tokyo) was continuously monitored. BP was measured oscillometrically with a BP monitoring device (BP-308 ET, Nippon Colin, Tokyo). HR was determined as an average of every 4 seconds from the ECG monitor.

In the remaining 73 patients, general anesthesia was induced with thiamylal approximately 5 $mg \cdot kg^{-1}$ iv, and tracheal intubation was facilitated with administration of vecuronium, approximately 0.2 $mg \cdot kg^{-1}$ iv. Subsequently, anesthesia was maintained with enflurane 0.8–2.0 % inspired and 67% nitrous oxide in oxygen. The patients were monitored by the ECG, a pulse oximeter (Physio-Control Lifestat 1600®, Physio-Control Co., Redmond, Washington, U.S.A.), and a capnometer (Normocap®, Datex, Helsinki, Finland). Ephedrine 0.1 $mg \cdot kg^{-1}$ was injected iv after a stable hemodynamic period of at least 10 minutes had been obtained. Immediately after the last measurements, arterial blood was sampled and analyzed for pHa, carbon dioxide tension ($Paco_2$), oxygen tension (Pao_2) and base excess with a model 178 pH/Blood Gas Analyzer (Corning, Medfield, Massachusetts, U.S.A.).

Data were expressed as mean ± SD. Mean blood pressure (MBP) was calculated as diastolic pressure plus 1/3 x pulse pressure. BP and HR responses to ephedrine were analyzed by using repeated measures ANOVA followed by a paired Student's t test with Bonferroni correction for paired data in each group. Statistical comparisons between groups were performed using two-way analysis ANOVA, followed by an unpaired Student's t test. Linear regression analysis was accomplished by least-square method to evaluate the relation between changes in mean blood pressure following ephedrine and age, baseline mean blood pressure, or other variables. $P < 0.05$ was considered the minimum level of statistical significance.

Results

There were no differences between awake and anesthetized patients with respect to age, weight, height, and ratio of men to women (table 1). The doses of thiamylal and vecuronium, inspired concentration of enflurane given for induction and maintenance of general anesthesia, and infusion rate of lactated Ringer's solution prior to ephedrine injection were 4.8 ± 0.3 $mg \cdot kg^{-1}$, 0.20 ± 0.01 $mg \cdot kg^{-1}$, 1.3 ± 0.4%, and 17.0 ± 5.6 $ml \cdot kg^{-1} \cdot h^{-1}$, respectively. The arterial blood gas analyses immediately after the last hemodynamic measurement revealed pH of 7.45 ± 0.04, $Paco_2$ of 36 ± 4 mmHg, Pao_2 of 156 ± 32 mmHg, and base excess of 1.5 ± 2.6 $mEq \cdot L^{-1}$.

Baseline BPs in anesthetized patients were lower than those in awake patients (table 2). In anesthetized patients the increase in MBP from baseline value following ephedrine injection was greater and sustained for 10 minute-observation period, when compared with awake patients, who showed a transient increase in MBP from baseline value, followed by reduction in MBP during the remainder of study period (Fig. 1). The magnitude of maximal increases in MBP from baseline values after ephedrine injection was greater ($P < 0.05$) in anesthetized patients (13 ± 6 mmHg) than in awake patients (7 ± 4 mmHg).

There was no relationship between age and maximal elevation in MBP following ephedrine in awake or anesthetized patients (Fig. 2, 3). In addition, no significant correlation was noted between age and maximal changes in HR in awake or anesthetized patients ($P > 0.05$). However, slight inverse correlations were noted between baseline values

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

	Age (yr)	Weight (kg)	Height (cm)	Sex (M/F)
Awake (n=30)	43±15	57±10	160±9	12/18
Anesthetized (n=73)	38±14	59±11	162±9	39/34

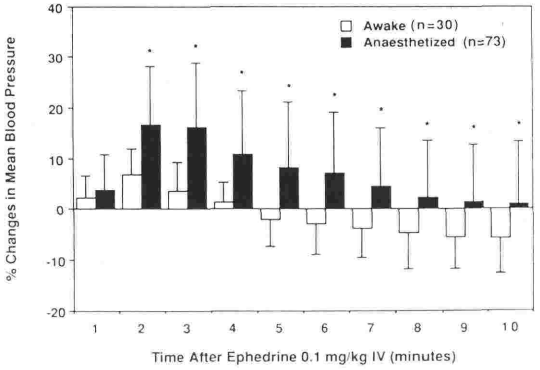

Figure 1. Percent changes in mean blood pressure (MBP) after ephedrine 0.1 $mg \cdot kg^{-1}$ i.v. in awake and anesthetized patients. Mean ± SD. *$P < 0.05$ compared with awake patients.

Table 2. Hemodynamic responses to intravenous ephedrine 0.1 $mg \cdot kg^{-1}$ in awake and anesthetized patients. Values are mean ± SD. SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MBP = mean blood pressure (mmHg); HR = heart rate (beats · min^{-1}). $P < 0.05$: *comppared with baseline; † compared with awake patients.

		Time after ephedrine (minutes)									
	Baseline	1	2	3	4	5	6	7	8	9	10
Awake (n=30)											
SBP	128±14	130±15	139±15*	134±15*	133±14*	128±14	126±15	127±16	124±15	125±14	125±14
DBP	73±10	75±11	77±9*	75±10	73±10	72±11	70±11	69±11	69±12	68±12*	67±12*
MBP	91±11	93±11	97±11*	94±11*	92±11	90±11	88±12	87±11*	87±11*	86±11*	86±11*
HR	76±14	81±16*	81±15*	81±16*	82±16*	81±15*	82±15*	81±15*	80±14*	82±14*	82±15*
Anesthetized (n=73)											
SBP	100±12†	103±14*†	115±12*†	115±12*†	111±12*†	110±10*†	107±10*†	105±9*†	104±9*†	103±9*†	102±9†
DBP	55±10†	57±11*†	64±11*†	63±9*†	60±9*†	58±9†	57±8*†	56±8†	54±8†	54±7†	54±8†
MBP	70±10†	72±11*†	81±11*†	80±9*†	77±9*†	75±8*†	74±8*†	72±8†	71±8†	70±7†	70±7†
HR	73±11	76±12*	76±12*	74±11*†	74±12†	74±11†	74±11†	74±11†	73±11†	73±11†	73±10†

(before ephedrine injection) and maximal magnitudes of increases after ephedrine in MBP in both awake ($r = -0.40$, $P < 0.03$, Fig. 4) and anesthetized ($r = -0.57$, $P < 0.001$, Fig. 5) patients.

None of patients developed arrhythmias or severe hypertension after intravenous ephedrine. There were no other adverse reactions related to ephedrine.

Discussion

The major finding of the present study is that the magnitude of pressor effect of intravenous ephedrine correlated inversely with the baseline values not but with aging in awake or anesthetized patients. In addition, the pressor response to ephedrine was greater in anesthetized patients than awake patients.

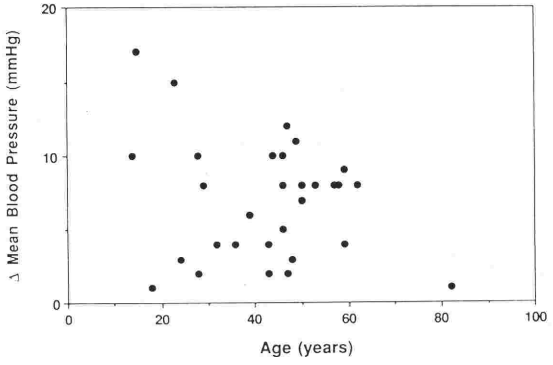

Figure 2. Correlation of age with maximal elevations in mean blood pressure (MBP) after ephedrine 0.1mg·kg^{-1} i.v. in 30 awake patients.

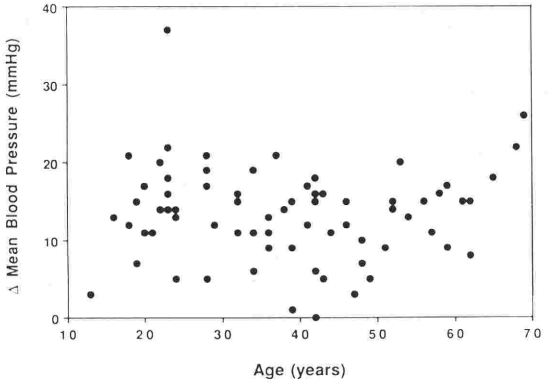

Figure 3. Correlation of age with maximal elevations in mean blood pressure (MBP) after ephedrine 0.1mg·kg^{-1} i.v. in 73 anesthetized patients.

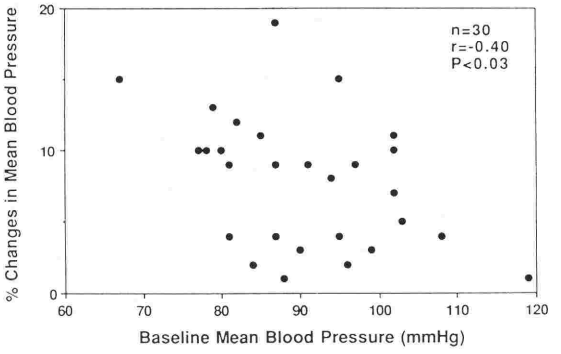

Figure 4. Correlation of baseline values (prior to ephedrine) with the magnitudes of maximal elevations in mean blood pressure (MBP) after ephedrine 0.1mg·kg^{-1} i.v. awake patients.

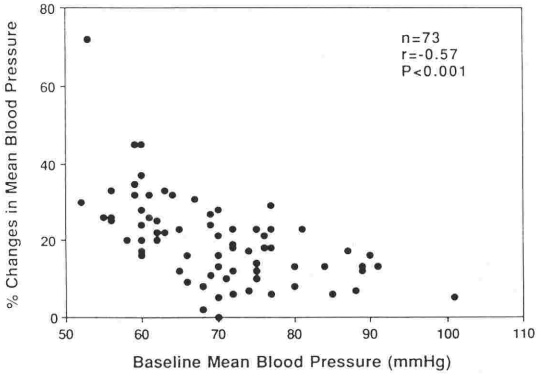

Figure 5. Correlation of baseline values (prior to ephedrine) with the magnitudes of maximal elevations in mean blood pressure (MBP) after ephedrine 0.1mg·kg^{-1} i.v. in anesthetized patients.

Although numerous factors, which can influence the pressor effect of ephedrine, have been summarized in a previous literature,[22] there is only limited information in the clinical settings. In the current results the pressor responses to ephedrine were greater in anesthetized patients than non-anesthetized patients in terms of their magnitude and duration (Fig. 1). This finding is similar to our previous report[23], and seems to be attributed to suppression of baroreceptor reflexes by enflurane and nitrous oxide anesthesia[24]. In addition, general anesthetics might have partly contributed to this enhancement of pressor effect through facilitating the catecholamine release from sympathetic nerve endings following ephedrine administration[20].

According to several previous reports[1~7], chronotropic or inotropic effect of sympathomimetic agents is reduced with advancing age, whereas vasoconstrictive effect of them is enhanced or attenuated with aging. However, in the present results the pressor effect of ephedrine was not altered with aging in awake or anesthetized patients (Fig. 2, 3). This finding agrees with Rosendorff et al's report showing no age effect on the pressor response to norepinephrine or angiotensin II[6]. No age-related change in the pressor effect of ephedrine may be ascribed to the fact that age-related functional alterations in the autonomic BP control systems[8~11] modulate the cardiovascular responses to sympathomimetic drugs, presumably resulting in diminution or disappearance of changes in pressor responses associated with age *per se*, even if these changes in pressor responses of ephedrine by aging exist in humans.

Although it remains unclear why the pressor responsiveness to ephedrine correlated inversely with basal blood pressure, based on this finding one can expect comparable BPs following ephedrine at this dose in healthy patients as in the current study. However, it should be noted that larger dose of ephedrine may be needed to restore BP to the normal level in patients with profound hypotension, because hypotensive patients with MBP less than 50 mmHg were not included in this study.

It is concluded that the pressor responsiveness to intravenous ephedrine depends upon the baseline values and is augmented during enflurane/nitrous oxide anesthesia, but is not altered by aging in patients without severe hypotension.

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