The Effects of Butorphanol on Baroreflex Control of Heart Rate in Man

Zen'ichiro WAJIMA, Tetsuo INOUE and Ryo OGAWA

The effects of butorphanol injection on baroreflex control of heart rate were investigated using both pressor and depressor tests in eighteen adult patients. Baroreflex sensistivity was attenuated after butorphanol injection in the pressor test using phenylephrine, whereas it was unchanged in the depressor test using nitroglycerine. No resetting of the baroreflex occurred after butorphanol injection. After the administration of butorphanol, plasma epinephrine and norepinephrine levels increased. These results suggest that it is safe to use butorphanol clinically even when a reduction in blood pressure due to hypovolemia or unclamping of the major artery is expected and that it is disadvantageous to administer the drug when an increase in blood pressure due to cross-clamping of the major artery is predicted. (Key words: butorphanol, baroreflex, resetting, plasma epinephrine, plasma norepinephrine)

(Wajima Z, Inoue T and Ogawa R: The effects of butorphanol on baroreflex control of heart rate in man. J Anesth 7: 411–418, 1993)

Arterial baroreflex function is an important neural control system for maintaining cardiovascular stability. Elevation of pressure in the carotid and aortic baroreceptive areas leads to a reflex slowing of the heart, arteriolar dilatation in many vascular beds, decreased venomotor tone, and a lowering of myocardial contractility. The effects of decreased pressure are the reverse of those mentioned above[1]. Narcotics have been shown to alter the arterial baroreflex in humans[2–4]. As there have been no reports on the effect of narcotic agonist-antagonist analgesics, such as butorphanol, on baroreflex control of heart rate in man, we decided to investigate it.

Materials and Methods

Eighteen adult patients undergoing elective surgery with an ASA physical status of I or II, who had no history of neurological, respiratory or cardiovascular disease, were selected as subjects. Their ages ranged from 17 to 43 years. Institutional approval and informed consent from all of the patients were obtained. The patients were randomly divided into two groups. Each group consisted of 9 patients. The pressor tests were performed in one group (the pressor test group) and the depressor tests in the other (the depressor test group).

Descriptions of the procedures have been published previously[5–7].

ECG (lead II) and direct arterial blood pressure (radial artery) were recorded simultaneously on a

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J Anesth 7:411-418, 1993

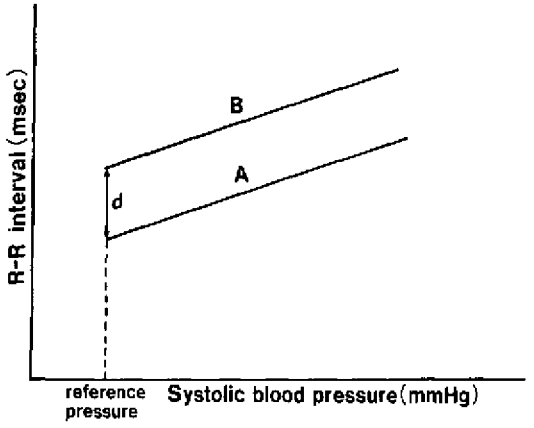

Fig. 1. The control line A and the line B obtained during a different experimental period are baroreflex slope. The resetting of the reflex is shown by the arrow, *d*.

polygraph (model CBM-3000, Nippon Colin, Japan) using a Gould P-50 transducer.

None of the patients were premedicated, and 100% oxygen was given to all of the patients by mask starting 15 min prior to the study, and spontaneous breathing of 100% oxygen was continued throughout the test period. After hemodynamic stabilization, the pressor baroreceptor response was assessed by the pressor test originally described by Smyth et al.[8]; phenylephrine, 2–3 $\mu g \cdot kg^{-1}$ was injected to raise arterial blood pressure of 20–30 mmHg. Fifteen min later, when arterial blood pressure had returned to the preinjection level, butorphanol, 0.04 $mg \cdot kg^{-1}$, was injected. Five and 15 min later, the pressor tests were repeated. Nitroglycerine, 8–10 $\mu g \cdot kg^{-1}$ was used for the depressor response. The relationship between systolic blood pressure and the succeeding R-R interval was quantitatively evaluated during the arterial pressure rise (in the pressor test) or the decline phase (in the depressor test). Systolic pressure and R-R intervals were plotted in a beat-to-beat analysis. Data were assessed using the least-square linear regression analysis of the linear part of the relationship between blood pressure and R-R interval. Only patients whose regression slopes had a correlation coefficient greater than 0.8 were included in the group mean. The slope of this linear regression expressed in msec per mmHg was used as an index of baroreflex function. These data were analyzed using package software known as "autonomic nerve system package"[9], and processed with a computer (PC-9801VX21, NEC, Japan) connected to the CBM-3000 via an RS-232C interface.

Blood gas analysis was conducted before the first pressor or depressor test as a control and five and 15 min after butorphanol injection just before the test. Plasma epinephrine and norepinephrine concentrations also were measured using high performance liquid chromatography at the same time as blood gas analysis.

Resetting of the baroreflex was determined by calculating the pulse interval at the reference pressure, as described by Bristow et al.[10], i.e., to determine reflex resetting, a vertical line was constructed at the level of the control systolic blood pressure. The resetting of the reflex is shown by the arrow, *d* (fig. 1).

The data are presented as mathematical means and central tendencies are expressed as standard deviations. ANOVA and Student's *t*-test were used to analyze the values obtained. A *P*-value less than 0.05 was used to accept or reject statistical hypotheses.

Results

There were no significant differences in age, body weight, systolic blood pressure, diastolic blood pressure, R-R interval, Pa_{O_2}, Pa_{CO_2}, or pHa between the two groups before the study (table 1).

In the pressor test group, Pa_{O_2} was

Table 1. Physical and clinical characteristics of subjects in the two groups

Group	Age (year)	Body weight (kg)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	R-R interval (msec)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa
Pressor test group	27.9 ± 9.9	62.6 ± 8.5	141.2 ± 13.6	74.0 ± 11.3	911.7 ± 134.1	620.4 ± 28.0	39.0 ± 4.0	7.435 ± 0.026
Depressor test group	26.2 ± 7.5	53.3 ± 11.2	130.4 ± 16.9	65.1 ± 7.5	923.6 ± 105.5	606.3 ± 24.8	37.9 ± 2.8	7.427 ± 0.020

Values are expressed as mean ± SD

Table 2. Blood gas analysis systolic blood pressure, diastolic blood pressure, R-R interval and R-R interval at reference blood pressure before and after butorphanol injection

Group			Control	5 min after injection	15 min after injection
Pressor test group	Pa_{O_2}	(mmHg)	620.4 ± 28.0	621.7 ± 24.4	614.4 ± 30.1
	Pa_{CO_2}	(mmHg)	39.0 ± 4.0	45.6 ± 4.5***	47.1 ± 5.6**
	pHa		7.435 ± 0.026	7.391 ± 0.027***	7.374 ± 0.030***#
	Systolic blood pressure	(mmHg)	141.2 ± 13.6	146.0 ± 14.9	146.0 ± 13.9
	Diastolic blood pressure	(mmHg)	74.0 ± 11.3	76.6 ± 12.2	75.2 ± 8.9
	R-R interval	(msec)	91.7 ± 134.1	897.2 ± 145.9	848.4 ± 130.6
	R-R interval at reference blood pressure	(msec)	892.7 ± 72.9	791.0 ± 183.1	818.0 ± 175.7
Depressor test group	Pa_{O_2}	(mmHg)	606.3 ± 24.8	599.5 ± 16.4	600.4 ± 27.0
	Pa_{CO_2}	(mmHg)	37.9 ± 2.8	46.4 ± 1.6***	47.3 ± 2.6***
	pHa		7.427 ± 0.020	7.364 ± 0.018***	7.357 ± 0.018***#
	Systolic blood pressure	(mmHg)	130.4 ± 16.9	134.2 ± 24.2	140.8 ± 25.5*#
	Diastolic blood pressure	(mmHg)	65.1 ± 7.5	68.4 ± 7.3*	69.4 ± 7.6*
	R-R interval	(msec)	923.6 ± 105.5	918.0 ± 130.4	882.2 ± 157.2
	R-R interval at reference blood pressure	(msec)	928.9 ⊥ 128.8	892.2 ± 173.9	865.2 ± 196.8

*significant difference vs. control ($P < 0.05$)
**significant difference vs. control ($P < 0.0005$)
***significant difference vs. control ($P < 0.0001$)
#significant difference vs. 5 min after butorphanol injection ($P < 0.05$)

Values are expressed as mean ± SD

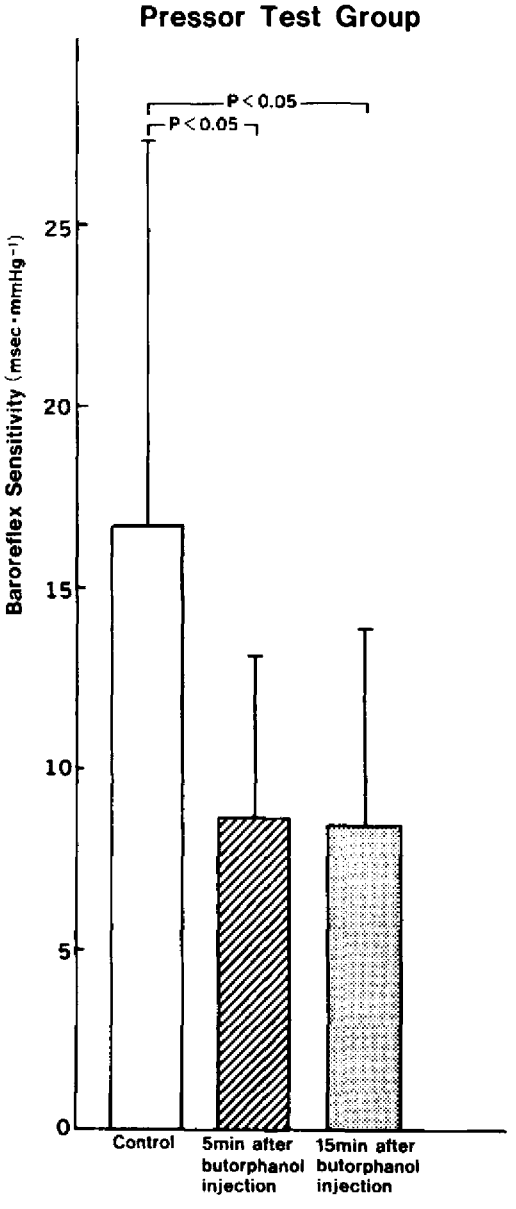

Fig. 2. Changes in baroreflex sensitivity induced by butorphanol injection, 0.04 $mg \cdot kg^{-1}$ Baroreflex sensitivity was attenuated both 5 and 15 min after butorphanol injection in the pressor test.

Values represent the mean ± SD

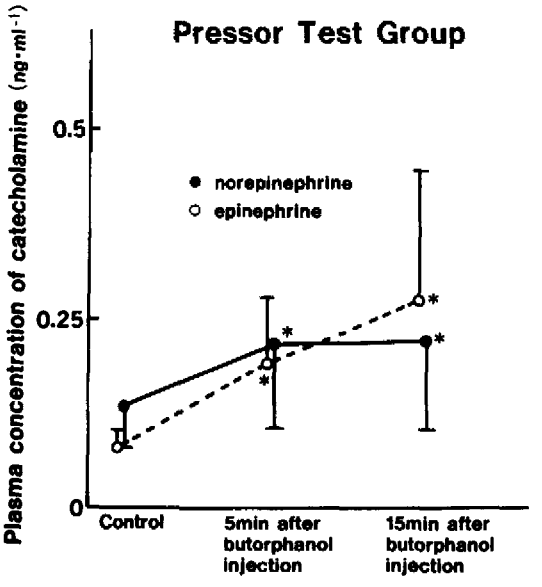

Fig. 3. Changes in plasma epinephrine and norepinephrine levels in the pressor test group.

Values represent the mean ± SD

*significant difference vs. control ($P < 0.01$)

Plasma epinephrine and norepinephrine levels were significantly increased 5 and 15 min after butorphanol injection.

not significantly changed either 5 or 15 min after butorphanol injection. Pa_{CO_2} was significantly increased 5 and 15 min after butorphanol injection, and pHa was significantly decreased 5 and 15 min after butorphanol injection. Systolic blood pressure, diastolic blood pressure and R-R interval were unchanged either 5 or 15 min after butorphanol injection. R-R interval at reference pressure was not significantly altered either 5 or 15 min after butorphanol injection (table 2), but baroreflex sensitivity was attenuated significantly 5 and 15 min after butorphanol injection (fig. 2), and plasma norepinephrine and epinephrine levels were significantly increased 5 and 15 min after butorphanol injection (fig. 3).

In the depressor test group, Pa_{O_2} was not significantly changed either 5 or 15 min after butorphanol injection. Pa_{CO_2} was significantly increased either 5 or 15 min after butorphanol injection, but pHa was significantly decreased 5 and 15 min after butor-

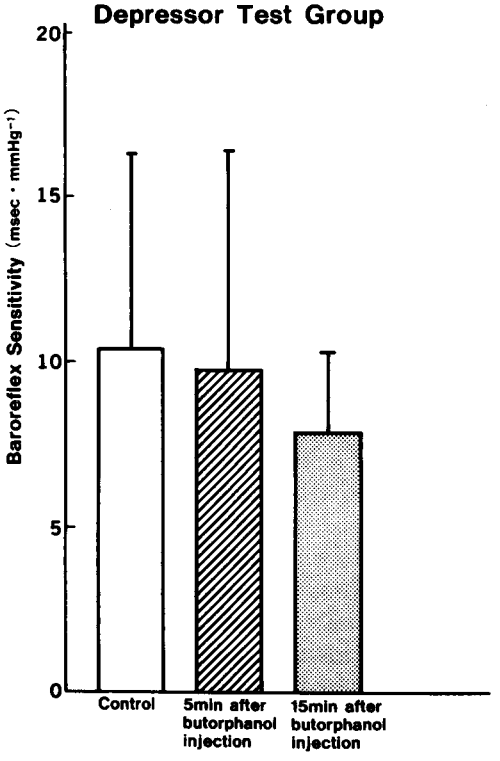

Fig. 4. Changes in baroreflex sensitivity induced by butorphanol injection, 0.04 $mg \cdot kg^{-1}$. Baroreflex sensitivity was not changed either 5 or 15 min after butorphanol injection by the depressor test.

Values represent the mean ± SD

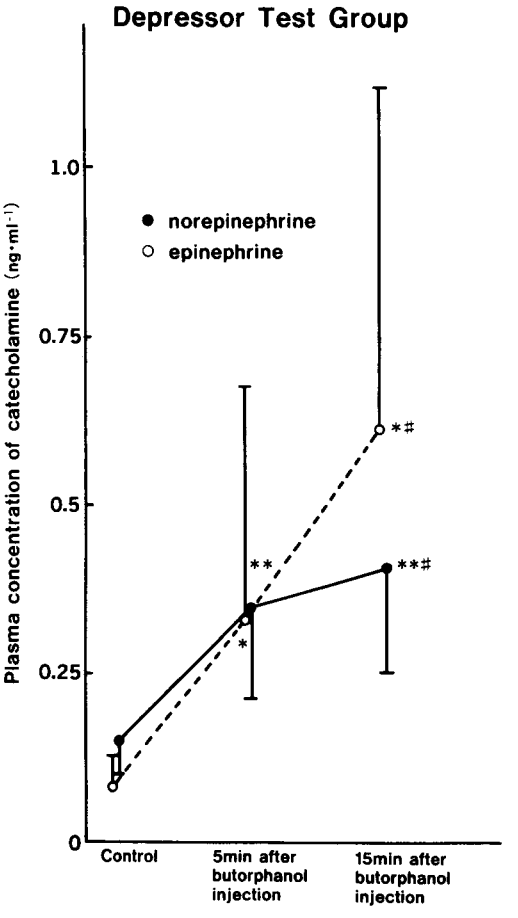

Fig. 5. Changes in plasma epinephrine and norepinephrine levels in the depressor test group.

Values represent the mean ± SD

*significant difference vs. control ($P < 0.05$)

**significant difference vs. control ($P < 0.0005$)

#significant difference vs. 5 min after butorphanol injection ($P < 0.05$)

Plasma epinephrine and norepinephrine levels were significantly increased both 5 and 15 min after the injection.

phanol injection. Systolic blood pressure was not significantly altered 5 min after butorphanol injction, but significantly increased 15 min after butorphanol injection. Diastolic blood pressure was significantly increased either 5 or 15 min after butorphanol injection. R-R interval was significantly unchanged either 5 or 15 min after butorphanol injection. R-R interval at reference pressure was not significantly altered 5 or 15 min after butorphanol injection (table 2). Baroreflex sensitivity was not significantly altered either 5 or 15 min after butorphanol injection (fig. 4), however, plasma norepinephrine and epinephrine levels were significantly increased both 5 and 15 min after the injection (fig. 5).

Discussion

Duke et al.[11] have shown that increased arterial Pa_{O_2} does not alter baroreflex responsiveness, and therefore, an F_{IO_2} of 1.0 was administered

to all subjects along with butorphanol injection.

In this study, butorphanol injection attenuated baroreflex control of heart rate under conditions of spontaneous respiration in the pressor test, but did not in the depressor test. There are two possible mechanisms for the changes in baroreflex: one is the effect of hypercapnia and the other is the effect of the opioid peptide butorphanol on the nucleus tractus solitarii (NTS) which is the termination of the primary baroreceptor afferents[12].

Cunningham et al.[13] reported that hypercapnia (10–12 mmHg above the resting level) in the presence of high oxygen levels at rest was associated with a significant fall in baroreflex sensitivity in the pressor test. In this study, Pa_{CO_2} rose 6.7 mmHg 5 min after butorphanol injection and 8.2 mmHg 15 min after the injection in the pressor test group. It is possible that the rise in Pa_{CO_2} in this study affected the baroreflex response.

Baroreceptor reflex pathways are the primary means of regulating arterial blood pressure. Opiates can modify this rgulatory pathway, as shown in the rabbit [14] and the dog[15]. High affinity binding sites for γ-aminobutyric acid (GABA) and opiate peptides were observed in the NTS area[16–17]. Wang et al.[18] investigated the possibility that putative transmitters may influence the aortic nerve stimulation-produced bradycardia and depressor responses in rabbits. The results were as follows; ipsilateral microinjection of GABA or morphine hydrochloride into the NTS area could partially block the evoked bradycardia and depressor responses produced by stimulation of the aortic nerve. Pretreatment with GABA receptor antagonist bicuculline methiodide and opiate receptor antagonist naloxone hydrochloride into the same medullary area completely abolished the effect of GABA and morphine, respectively. Application of bicuculline also mostly antagonized the effect of morphine, but the blocking effect of GABA on the evoked bradycardia and depressor responses still existed following the pretreatment of naloxone. In their study, they provided evidence that GABA may be a transmitter working in baroreceptor reflex in the NTS and opioid peptide within the NTS area exerts an inhibitory modulation in the transmission of baroreceptor reflex pathway through activation of GABA receptor in this nucleus.

Kotrly et al.[3] investigated the effect of morphine, diazepam, N_2O/O_2 anesthesia on baroreflex control of heart rate and they found that the anesthesia depressed the baroreflex. They concluded that it was likely that morphine may alter baroreflex control of heart rate through changes occurring at two different parts of the reflex arc: first, at the sinoatrial node, and secondly, in the central nervous system. They[2] further investigated the effects of fentanyl 7.5 $\mu g \cdot kg^{-1}$ (group I), 10 $\mu g \cdot kg^{-1}$ (group II) and 12.5 $\mu g \cdot kg^{-1}$ (group III) with diazepam 0.25 $mg \cdot kg^{-1}$ and 70% nitrous oxide on baroreflex control of the heart rate in humans. In group I, the pressor, depressor and neck suction baroreflex slopes decreased during anesthesia. In groups II and III, the depressor test slopes also decreased during anesthesia, but the slopes derived from the pressor and neck suction tests did not decrease. They concluded that these data suggested that baroreflex control of heart rate is attenuated during low doses of fentanyl. It might be interesting to compare the three drugs, butorphanol, morphine and fentanyl, in terms of their effect on baroreflex control of heart rate.

Although the author[5] has reported that common dose of diazepam and flunitrazepam do not affect baroreflex control of heart rate in man, it is un-

known whether modified NLA, using benzodiazepines and narcotic agonist-antagonist analgesics, influences it or not under conditions of controlled ventilation. In order to clear this, further investigation will be needed.

Plasma norepinephrine and epinephrine levels were significantly increased 5 and 15 min after butorphanol injection in both groups (figs. 3, 5). The increase in plasma norepinephrine, which indicates an increase in sympathetic activity[19] is mainly due to hypercapnia[20]. We have shown that the depressor test caused the plasma norepinephrine level to remain increased over 15 min[6]. In the depressor test group, this test also caused the plasma norepinephrine to increase.

In addition to baroreflex sensitivity, we investigated baroreflex resetting—defined as a shift in the position of the curve relating systolic arterial pressure to R-R interval. No resetting of the baroreflex occurred after butorphanol injection, since the pulse interval at reference pressure was not significantly altered.

The results obtained in the present study suggest that it is safe to use butorphanol under conditions of spontaneous respiration when a reduction in blood pressure because of hypovolemia or unclamping the major artery is expected and that it is disadvantageous clinically to administer the drug when an increase in blood pressure due to cross-clamping of the major artery is predicted.

In conclusion, butorphanol injection attenuated baroreflex control of heart rate under conditions of spontaneous respiration in the pressor test, but it did not in the depressor test. No resetting of the baroreflex occurred after butorphanol injection.

A part of this study was presented at "The 11th annual meeting of the Japan Society for Clinical Anesthesia, 1991" and "The 39th annual meeting of the Japan Society of Anesthesiology, 1992".

(Received Oct. 23, 1992, accepted for publication Jan. 18, 1993)

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