Cardiovascular Effects of Fentanyl Reversal by Naloxone at Varying Arterial Carbon Dioxide Tensions in Dogs

Christopher A. Mills, MD, Joan W. Flacke, MD, Jordan D. Miller, MD, L. Jane Davis, MS, Byron C. Bloor, PhD, and Werner E. Flacke, MD

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Clinical reports, as well as animal studies, have described cardiovascular and sympathetic stimulation after the administration of naloxone (NX) to reverse opioid-induced respiratory depression. This investigation examines the effect of $Paco_2$ on hemodynamic and adrenergic responses to NX, by means of 24 experiments carried out in six dogs. Each dog underwent NX reversal of fentanyl (FEN) at three different $Paco_2$ levels: 20, 35, and 60 mm Hg. In a final series of six experiments, the dogs were exposed to increasing $Paco_2$ after autonomic block by total spinal anesthesia and vagotomy. During enflurane anesthesia, 50 μg/kg FEN decreased mean arterial blood pressure (MAP), heart rate (HR), and plasma concentrations of norepinephrine (NE) and epinephrine (EPI) significantly. NX 0.4 mg promptly returned HR and MAP to baseline or above in all experiments; catecholamine (CA) levels increased only in hypercapnic dogs. Increases in HR were the same in all series. MAP, EPI, and NE levels were significantly greater than pre-FEN baseline values only in hypercapnic dogs 1 minute after NX and were also significantly higher in hypercapnic than in hypocapnic dogs at this time. NE levels were greater in hypercapnic dogs at all time periods after NX. In blocked dogs, neither F nor NX had any effects on hemodynamic functions or plasma CA levels; the institution of hypercapnia caused significant decreases in HR, MAP, and systemic vascular resistance. This direct circulatory depressant action of an elevated Pco_2 may have attenuated the indirectly mediated excitatory hemodynamic effects of NX in intact dogs, thus explaining the relatively greater effect of hypercapnia on adrenergic than on hemodynamic responses to reversal. This study suggests that abrupt increases in blood pressure and plasma CA levels after naloxone can be blunted if normocapnia or hypocapnia is established before naloxone administration.

Key Words: ANTAGONISTS, NARCOTIC—naloxone.
ANESTHETICS, INTRAVENOUS—fentanyl.
ANALGESICS—fentanyl.

Residual effects of intraoperative narcotics on respiratory control may result in postoperative hypoventilation and hypercapnia. The pure narcotic antagonist, naloxone, is used frequently to reverse this respiratory depression. Unfortunately, the use of naloxone may be associated with excessive cardiovascular stimulation (1–6). There have been sporadic reports of untoward circulatory events, ranging from severe hypertension (1) to cardiac arrhythmias (1,5), pulmonary edema (3,7–9), and death (10). Various explanations have been given for this cardiovascular stimulation, including an acute narcotic withdrawal syndrome (11), antagonism of analgesia, and sudden awakening (12) with the resultant rapid normalization of previously narcotized autonomic regulatory processes (13,14). However, even in deeply anesthetized dogs, reversal of fentanyl with naloxone causes the sudden return of blood pressure, heart rate, and cardiac output to values sometimes greater than the baseline levels before fentanyl (15,17). These hyperdynamic events are accompanied by elevations in circulating catecholamine levels (15) although the administration of naloxone by itself does not cause them to increase (18).

On the other hand, many clinical studies make no mention of circulatory problems after reversal with naloxone (19–23), and some have reported no differences in hemodynamics in awakening patients whether or not naloxone was given (24,25). Indeed, it appears that this agent has been used uneventfully

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Address correspondence to Dr. Flacke, Department of Anesthesiology, BH-961 C.H.S., UCLA School of Medicine, Los Angeles, CA 90024.

and successfully in many thousands of patients since its introduction in 1970.

The cause of the occasional capricious effects of naloxone remains unknown. One of the variables to be considered is the arterial carbon dioxide tension existing before opioid reversal. If the patient is hypoventilating at this time, the abrupt restoration of the normal homeostatic responses to hypercapnia might be expected to precipitate not only a prompt increase in minute ventilation but also a marked adrenergic and associated hemodynamic response, as central control mechanisms are reestablished by the rapid injection of the opioid antagonist.

To determine the role of existing arterial carbon dioxide tension in events associated with narcotic reversal, we have examined the hemodynamic and adrenergic responses to acute narcotic reversal with naloxone during hypo-, normo-, and hypercapnia in a dog model (26). In addition, to ascertain to what extent autonomically mediated indirect excitatory cardiovascular effects might be "masked" or counteracted by the direct depressant effects of an elevated P_{CO_2}, an autonomically denervated animal preparation was exposed to reduced and to elevated carbon dioxide tensions.

Methods

These animal experiments were conducted within the guidelines of the American Physiological Society.

Three series of experiments were designed to investigate the effects of narcotic reversal with naloxone at three different levels of arterial carbon dioxide tension. These experiments were performed on the same six mongrel dogs (weight 15 ± 1 kg) in random order, so that each dog participated in each series and thus acted as its own control. Two weeks was allowed between experiments on any one dog. The fourth and final series of experiments, using the same six dogs, was designed to investigate the direct cardiovascular effects of carbon dioxide during complete autonomic block. In all experiments, the dogs were anesthetized with 10 mg/kg intravenous thiopental, paralyzed with 20 mg succinylcholine, and intubated. During controlled ventilation with 1.5% (inspired) enflurane in oxygen, tidal volume and rate were adjusted to achieve normal blood oxygen tensions with an arterial carbon dioxide tension of 35 mm Hg.

After induction of anesthesia, catheters were introduced percutaneously into a femoral artery for direct measurement of blood pressure and for blood sampling, and into a femoral vein for injection of drugs and administration of intravenous fluids; 5% dextrose in lactated Ringer's solution at a rate of 5 $ml \cdot kg^{-1} \cdot hr^{-1}$. ECG electrodes were attached, and heart rate and blood pressure (Statham transducer) were measured and recorded continuously (Hewlett-Packard series 7758B polygraph). Arterial blood samples were taken at the appropriate times for determination of blood gas tensions (Instrumentation Laboratories, model Micro 13) and for measurement of plasma levels of norepinephrine and epinephrine by high performance liquid chromatography (27). (Our laboratory inter- and intraassay variability for catecholamine determinations is <6%, with a sensitivity of 10 and 20 pg/ml for norepinephrine and epinephrine, respectively [28].) Enflurane and carbon dioxide concentrations were measured continuously by mass spectrometry (Perkin-Elmer, model *MGA* 1100). Esophageal temperature was maintained at 38 ± 0.5°C. All drugs used were commercial preparations: fentanyl citrate (Sublimaze, Janssen Pharmaceutica, NY); naloxone hydrochloride (Narcan, Du Pont Pharmaceuticals, Puerto Rico); succinylcholine chloride (Anectine, Burroughs-Wellcome, NC); tetracaine hydrochloride (Pontocaine, Breon Laboratories, NY); thiopental sodium (Pentothal, Abbott Laboratories, IL); and vecuronium bromide (Norcuron, Organon, NJ).

For the initial three series of experiments designed to assess the effect of hypo-, normo-, and hypercapnia on narcotic reversal, baseline measurements of heart rate, blood pressure, and plasma catecholamine levels were taken about 60 minutes after induction. Then fentanyl 50 μg/kg, was infused over 5 minutes, and measurements were again taken 5 and 40 minutes thereafter. During the next 15 minutes, respiration was adjusted (using end-tidal carbon dioxide tension as a guideline) as required to produce the arterial carbon dioxide tension determined by the randomization protocol: 20 mm Hg (hypocapnic dogs) or 60 mm Hg (hypercapnic dogs). Ventilation in normocapnic dogs was not changed, so that their carbon dioxide tensions remained at 35 mm Hg. The nonparalyzed dogs were observed for signs of light anesthesia including respiratory movement; additional fentanyl was to have been given had this occurred, but none was required.

At the specified carbon dioxide tension, another set of measurements was taken. Preliminary experiments had indicated that hypercapnic dogs would fight the respirator after administration of naloxone, thus interfering with measurements. Therefore, all dogs were treated with vecuronium 0.1 mg/kg 2 minutes before naloxone 0.4 mg was given as a bolus. Measurements were taken 1, 5, and 10 minutes

thereafter; then normocapnia was restored. Enflurane was discontinued, and the percutaneous intravenous and arterial lines were removed. After adequate spontaneous respirations had returned, the dogs were extubated, observed until completely recovered, given naloxone 0.4 mg IM, and returned to the vivarium.

To assess the direct effects of varying carbon dioxide tensions on hemodynamic functions, a final series of experiments was performed after autonomic denervation in the same six dogs. Induction, intubation, and maintenance were the same as previously described, and ventilation was adjusted to obtain normocapnia ($Paco_2$ 35 mm Hg). The femoral artery and vein were surgically isolated and cannulated, and the vagus nerves were isolated in the neck. A flow-directed pulmonary artery catheter was placed through the right external jugular vein. To prepare for subsequent spinal anesthesia, a 19-gauge catheter was surgically introduced into the subarachnoid space at the atlantooccipital junction and advanced to the lower lumbar level. Measurements consisted of those obtained in the previous three series of experiments plus continuous central venous and pulmonary arterial pressure and thermodilution cardiac outputs (Edwards computer, model 9520A) measured in duplicate.

After cardiovascular stability was obtained, dextrose in lactated Ringer's solution was given as needed to keep central venous and pulmonary capillary wedge pressures constant throughout the experiment. Baseline measurements were made, the vagi were severed in the neck, and then tetracaine was injected into the subarachnoid space in 5-mg increments at four equidistant points as the catheter was withdrawn along the thoracolumbar cord (total dose 20 mg). Measurements were taken when hemodynamic conditions were again stable. Fentanyl (50 μg/kg) was infused over 5 minutes, and measurements were repeated 5 minutes later, still at normocapnia. Next, respiration was increased to reduce arterial carbon dioxide tension to 20 mm Hg, and repeat measurements were made. Finally, ventilation was decreased to produce an arterial carbon dioxide tension of 60 mm Hg, and measurements were repeated. Then 0.4 mg naloxone was given, and final measurements were done.

To summarize, the four series of experiments in each of the six dogs were as follows:

1. Fentanyl followed by reversal with naloxone during hypocapnia.
2. Fentanyl followed by reversal with naloxone during normocapnia.
3. Fentanyl followed by reversal with naloxone during hypercapnia.
4. Autonomic denervation, followed by fentanyl, normocapnia, hypocapnia, and hypercapnia in sequence, then reversal with naloxone.

Statistics

Before statistical analysis, plasma catecholamine levels were normalized through log conversion. Intraseries changes in these and in hemodynamic values were examined by means of analysis of variance for repeated measure, followed by Bonferroni's modified *t*-test. $P < 0.05$ was considered statistically significant. One-way analysis of variance was used to test for interseries differences. When significance was demonstrated ($P < 0.05$), individual differences (e.g., hypercapnic vs. normocapnic or hypocapnic dogs, etc.) were isolated using a weighted *t*-test in which the critical probability for significance (P) was calculated as P/g, where g was equal to the number of series of experiments in intact dogs. Thus, to achieve significance at the 5% level, *P* had to be $<0.05/3$ or <0.017.

Results

All results are reported as mean values ± SEM. Because the protocol for all experiments in the intact dogs was identical until the time of changing the arterial carbon dioxide tension, the data for the first three measurement points from the three series were pooled (Figs. 1–4). The rest of the measurement points are shown separately for each series and are compared only with their own paired values in the determination of intraseries changes.

Effect of CO_2 on Narcotic Reversal

The administration of fentanyl produced a significant and persistent decrease in heart rate (Fig. 1), mean arterial blood pressure (Fig. 2), and plasma norepinephrine (Fig. 4). Hemodynamic values remained unchanged during the next 45 minutes, but plasma levels of both catecholamines declined further (Figs. 3 and 4). Thus, epinephrine levels were also significantly below baseline values 45 minutes after fentanyl. Adjustment of the ventilation (as described in Methods) caused no significant intraseries changes in blood pressure or heart rate. However, even in the narcotized state, plasma levels of norepinephrine

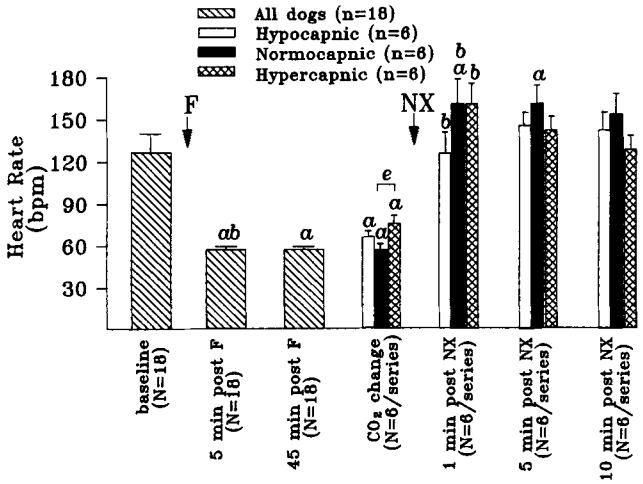

Figure 1. Mean (±SEM) heart rates in autonomically intact hypocapnic, normocapnic, and hypercapnic dogs at the time points indicated. Data from all experiments have been pooled for the three observations preceding change in CO_2. Statistically significant differences ($P < 0.05$) are indicated as *a*, different from baseline values ; *b*, different from preceding values; *c*, different from (paired) values before change in $Paco_2$; *d*, values in hypercapnic animals different from those in hypocapnic animals; *e*, values in hypercapnic animals different from those in normocapnic animals.

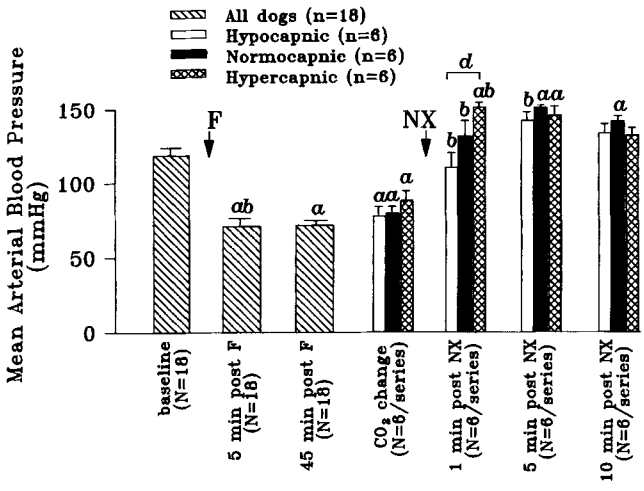

Figure 2. Mean values (±SEM) of mean arterial pressure in the three sets of experiments. See legend to Figure 1 for explanation.

(Fig. 4) increased when the dogs were made hypercapnic ($P < 0.01$), and at this time norepinephrine levels were significantly greater in hypercapnic than in either hypocapnic or normocapnic dogs ($P < 0.02$ for both). Although hypercapnia did not cause a significant increase in epinephrine levels, the absolute values reached were also significantly greater at this time than epinephrine levels in either hypocapnic ($P < 0.01$) or normocapnic ($P < 0.05$) dogs.

Naloxone caused a significant ($P < 0.001$) increase in heart rate over prenaloxone values in all three

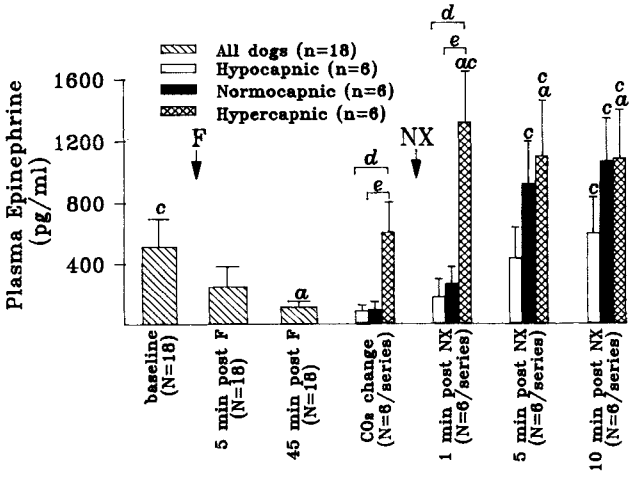

Figure 3. Plasma epinephrine levels (mean values ± SEM). See legend to Figure 1 for explanation.

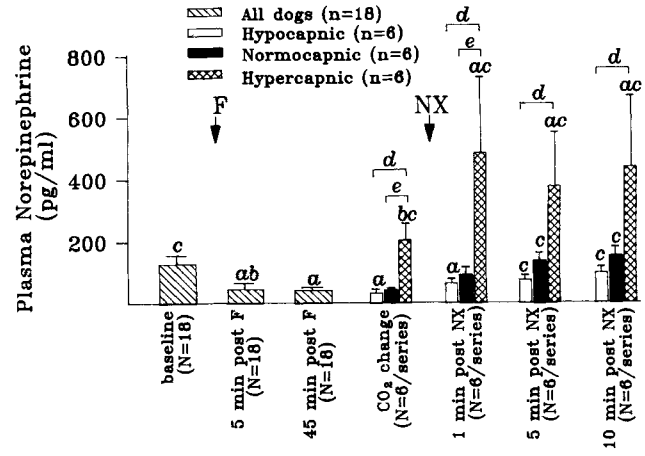

Figure 4. Plasma norepinephrine levels (mean values ± SEM). See legend to Figure 1 for explanation.

groups 1, 5, and 10 minutes after its administration (Fig. 1). The heart rates were significantly greater than the prefentanyl baseline values only in normocapnic dogs, which had somewhat lower baseline heart rates on the days of those experiments; however, there were no interseries differences in the absolute heart rates at any time after naloxone. Mean blood pressure (Fig. 2) also increased significantly ($P < 0.003$) in all three groups 1 minute after naloxone, but the absolute values reached were significantly higher in hypercapnic dogs than in those with a low CO_2 ($P < 0.01$). Moreover, at this 1-minute time point, blood pressures were significantly greater than baseline levels only in hypercapnic dogs. By 5 and 10 minutes after naloxone, blood pressure had increased to greater than baseline values in normocapnic dogs also, but not in hypocapnic ones.

One minute after naloxone, plasma epinephrine levels were significantly higher in hypercapnic dogs

Table 1. Mean Values (±SEM) for Mean Arterial Blood Pressure (MABP), Heart Rate (HR), Cardiac Index (CI), and Systemic Vascular Resistance Index (SVRI) in Six Dogs Exposed to Normo-, Hypo-, and Hypercapnia, in Turn, after Parasympathetic and Sympathetic Block

	Baseline	After spinal	After fentanyl (35 mm Hg)	Hypocapnia (20 mm Hg)	Hypercapnia (65 mm Hg)	After naloxone
MABP (mm Hg)	107 ± 8	82 ± 9*,†	88 ± 5	85 ± 6	49 ± 2*,†,‡	65 ± 7*
HR (beats/min)	111 ± 6	106 ± 4	108 ± 5	115 ± 6	95 ± 5*,†,‡	98 ± 5*
CI (L $min^{-1} \cdot m^{-2}$)	4.4 ± 0.4	4.0 ± 0.4	4.0 ± 0.3	4.7 ± 0.4	4.3 ± 0.3	4.5 ± 0.4
SVRI (dynes·sec·$cm^{-5} \cdot m^2$)	1993 ± 178	1752 ± 296	1848 ± 210	1490 ± 165	955 ± 107*,‡	1178 ± 127*

Statistically significant differences ($P < 0.05$) are indicated as * different from baseline; † different from preceding values; ‡ different from postfentanyl normocapnic values.

than in the other two series of experiments (Fig. 3). Moreover, only under hypercapnic conditions did the 1-minute epinephrine levels increase significantly over baseline values ($P < 0.01$), as well as over the levels present before the change in CO_2 ($P < 0.01$). Although there were later (5 and 10 minutes) increases in plasma epinephrine levels in the hypocapnic and normocapnic experiments also, these were never significantly increased over either prenaloxone or baseline values.

The administration of naloxone caused no significant increase in plasma norepinephrine levels in hypocapnic or normocapnic dogs (Fig. 4). Further elevation of norepinephrine (i.e., above the already elevated prenaloxone values) occurred in five of the six hypercapnic dogs, and at 1 minute after naloxone the mean norepinephrine level in the hypercapnic series was significantly greater than baseline. Individual increases in norepinephrine levels after naloxone ranged from 26 to 270%. The mean absolute norepinephrine level reached at 1 minute was also significantly greater than the mean value in either hypocapnic or normocapnic dogs ($P < 0.05$); these intergroup differences persisted throughout the 5- and 10-minute sampling periods.

Effect of CO_2 in the Absence of Autonomic Tone

After vagotomy and with the onset of spinal sympathetic blockade, there was a barely significant reduction in blood pressure ($P = 0.05$) and no change in heart rate, cardiac index, or systemic vascular resistance index (Table 1). Plasma epinephrine and norepinephrine decreased to scarcely detectable levels and remained so throughout the rest of the experiment, even when hypercapnia was instituted. In autonomically blocked dogs, the administration of neither 50 μg/kg fentanyl nor 0.4 mg naloxone had any significant effect on any parameter measured.

Decreasing arterial carbon dioxide tension to 20 mm Hg had no hemodynamic effects (Table 1). However, hypercapnia caused persistent and significant decreases in heart rate, blood pressure, and systemic vascular resistance. Cardiac index was not affected by changes in arterial carbon dioxide tensions during autonomic blockade, nor were the very low levels of catecholamines.

Discussion

The influence of hypo- and hypercapnia on adrenergic and hemodynamic functions has been known for a long time. Hence it was obvious to explore the role of carbon dioxide tension on the magnitude of cardiovascular changes brought about by narcotic reversal. To elucidate the relative contributions of indirect, i.e., neurogenic and hormonal, and direct actions of $Paco_2$ on cardiovascular endorgans, the design included experiments in intact as well as in autonomically denervated animals.

Although the literature cites many examples of patients emerging from anesthesia in whom the administration of naloxone resulted in calamity (1–10), the arterial Pco_2 at the time of narcotic reversal is rarely stated. However, it would seem that patients emerging from anesthesia and being coaxed to breath spontaneously by a "light hand on the bag" are quite likely to have an elevated carbon dioxide tension, as will those patients who are hypoventilating in the recovery room. In our experiments in intact dogs, an attempt was made to mimic a nonhypoxic but hypercapnic patient awakening from inhalation anesthesia after a moderate dose of a narcotic, to whom a narcotic antagonist is given in a quantity sufficient to abruptly and completely reverse the residual narcosis.

In the 18 experiments carried out in our six autonomically intact dogs, the decreases in blood pressure and heart rate after administration of fentanyl were accompanied by reduced central sympathetic outflow, as reflected by significant decreases in plasma levels of catecholamines. The fact that the

alteration in autonomic tone was the only reason for the decreased hemodynamic function—that is, that the fentanyl had no direct actions on the endorgans—is confirmed by the lack of hemodynamic effect of fentanyl in the same dogs after pharmacologic autonomic denervation, as has been previously reported (29). Thus, one might say that in dogs under basal enflurane anesthesia and in the absence of stimulation, the fentanyl-induced relaxation of central sympathetic outflow approached, to some degree, that seen after sympathetic block.

Even after 50 μg/kg of fentanyl, however, the rapid institution of fairly severe hypercapnia in the intact dogs significantly elevated sympathetic tone, as reflected in elevated plasma catecholamine levels, without significant changes in heart rate or blood pressure. This lack of accompanying excitatory changes in hemodynamic function may have been due to the concomitant and counteracting *direct* depressant effects of hypercapnia on the circulation (see later). In spite of the activation of central sympathetic outflow by hypercapnia alone, before naloxone, the intact dogs appeared still to be adequately anesthetized: none moved, and there were no respiratory efforts, without doubt because of the narcotic-induced shift of the CO_2 response curve.

The administration of naloxone to the intact dogs produced dramatic increases in cardiovascular and adrenergic functions even though the dogs remained under enflurane anesthesia. However, these changes occurred more rapidly and abruptly in hypercapnic dogs, so that absolute values of blood pressure, as well as plasma levels of both catecholamines, were highest in this series by 1 minute after naloxone and exceeded baseline values. In contrast, the responses of all measured variables occurred more slowly in both normocapnic and hypocapnic dogs and never exceeded baseline levels in the latter. Perhaps the rapid onset of the changes in circulatory and adrenergic functions brought about by naloxone reversal under hypercapnic conditions is as important in the etiology of the clinical problems described as are the absolute levels of blood pressure or plasma catecholamine concentrations reached.

Hypertension and tachycardia after naloxone were seen in dogs despite the fact that no attempt was made to replete the vascular volume as fentanyl decreased sympathetic tone. Some of the more profound hemodynamic events reported in the clinical literature, particularly those involving morphine, may have been exacerbated by an intraoperative relative volume overload (3). It is apparent from case reports of misadventure after naloxone administration that there is extreme variability in the sensitivity of the cardiovascular center to narcotic antagonism in humans. Hypercapnia may account for some but not all of this variability. In all likelihood, the influence of existing arterial carbon dioxide tension (and pH) in clinical conditions is greater than that observed in the present experiments. To avoid pain and awareness, enflurane anesthesia was maintained in these dogs, and this inhalation anesthetic would have depressed the normal sensitivity to carbon dioxide. In human patients, however, inhalation anesthesia has usually been discontinued before administration of naloxone, and the resultant hemodynamic *and adrenergic* events can be expected to be even more marked in hypercapnic patients than those observed by us in these hypercapnic and anesthetized dogs.

Since each dog participated in all experiments, we had an opportunity to measure baseline plasma concentration levels under identical conditions four times. Although the induction of anesthesia was the same for all dogs, it was apparent that for any given dog baseline catecholamine values were extremely variable. Regardless of the baseline, fentanyl profoundly depressed plasma epinephrine and norepinephrine levels in all dogs. However, in one dog, catecholamine levels failed consistently to increase during narcotic reversal even though blood pressure and heart rate responses to naloxone administration were at or above the mean of the series at all carbon dioxide tensions. Clearly the hemodynamic response to narcotic reversal does not correlate in every case with plasma catecholamine levels as measured under our protocol.

As in dogs, baseline catecholamine levels will differ from patient to patient. The "more excitable" individual, with higher sympathetic tone, will experience a greater depression of cardiovascular and adrenergic function after narcotic administration (30,31). Therefore, it is not unreasonable to assume that such a patient will be stimulated to a greater than average extent by narcotic reversal, perhaps with a tendency to "overshoot," resulting in the untoward hemodynamic events reported in the literature (1–10). Variability in abruptness and completeness of reversal may be additional factors.

The results after autonomic denervation indicate that when reflex sympathetic responses, with their resultant excitatory effect on the cardiovascular system, were eliminated, the direct circulatory effects of hypercapnia (negative chronotropic effect and systemic vasodilatation) were unmasked. These direct depressant effects of an elevated carbon dioxide tension, which have been reported also in dogs in whom reflex sympathetic activation was prevented by hexamethonium infusion (32), would tend to diminish the

magnitude of the indirect tachycardiac and pressor response. Perhaps this explains in part the fact that naloxone reversal brought about relatively greater differences in plasma catecholamines than in blood pressure between hypercapnic dogs and those in the other two series.

In conclusion, fentanyl is again shown to be without direct cardiovascular effects, although it is a potent depressor of central sympathetic outflow. However, even after fentanyl, inducing hypercapnia caused an adrenergic response in neurogenically intact dogs. Antagonism of the narcotic with naloxone further elevated plasma catecholamine levels and reversed the hemodynamic quiescence that fentanyl had induced. Reversal effects were more rapid in onset and greater in magnitude during hypercapnic conditions, in spite of the concomitant direct cardiovascular depressant effects of hypercapnia, as demonstrated after autonomic block.

These observations support the recommendation that normocapnia or slight hypocapnia should be established before naloxone is administered to the postanesthetic patient.

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