Opiate Receptor Antagonism in Right-Sided Congestive Heart Failure

Naloxone Exerts Salutary Hemodynamic Effects Through Its Action on the Central Nervous System

Susumu Sakamoto, Charles K. Stone, Paul D. Woolf, and Chang-seng Liang

Opiate receptor inhibition causes adrenergic receptor-mediated increases in aortic pressure, cardiac output, and left ventricular contractile function in right heart failure. To study whether the effects of opiate receptor inhibition are mediated by means of an action on the central opiate system, we administered equimolar doses of naloxone hydrochloride and naloxone methobromide (MeBr) and normal saline to heart failure dogs. Chronic stable right heart failure was produced by progressive pulmonary artery constriction and tricuspid valve avulsion. Naloxone hydrochloride caused an increase in mean aortic pressure, cardiac output, left ventricular dP/dt and dP/dt/P, plasma catecholamines, and regional blood flows to the myocardium, quadriceps muscle, kidneys, and splanchnic beds. Plasma β-endorphin and adrenocorticotropin also increased. In contrast, neither normal saline nor naloxone MeBr (which does not cross the blood-brain barrier) affected the systemic or regional hemodynamics or neurohormones. Naloxone hydrochloride was also administered to anesthetized heart failure dogs. Pentobarbital anesthesia removed cortical perception of nociceptive stimulation, reduced the increase in plasma epinephrine, and abolished vasodilation in skeletal muscle that occurred in conscious dogs after naloxone hydrochloride administration but had no major effects on responses of plasma norepinephrine, systemic hemodynamics, or other regional blood flows to opiate receptor inhibition. Naloxone hydrochloride had no effect in sham-operated dogs. The results indicate that the hemodynamic effects of naloxone are mediated by an action within the central nervous system. Furthermore, since pentobarbital anesthesia did not markedly alter the hemodynamic responses to naloxone hydrochloride, the acute salutary effects of opiate receptor inhibition probably are not caused by removal of the antinociceptive effect of endogenous opioids in heart failure. (Circulation Research 1989;65:103–114)

Endogenous opiate systems play an important role in the maintenance of arterial pressure in acute circulatory shock.1 Administration of the opiate receptor antagonist naloxone [4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one] has been shown to reverse hypotension produced by endotoxin2 and hemorrhage.3,4 This finding suggests that endogenous opioids exert a circulatory depressant effect. Recently, we5 have shown that β-endorphin and adrenocorticotropin (ACTH), two hormones commonly released together from the pituitary gland into the general circulation during stress,6 are elevated in conscious dogs with chronic right-sided congestive heart failure. Additionally, we have shown that administration of the opiate antagonist nalmefene increases aortic pressure, cardiac output, and ventricular performance in conscious dogs.7,8 Thus, as in acute circulatory shock, the endogenous opiate systems are activated in chronic heart failure. Furthermore, since the hemodynamic improvements in heart failure produced by opiate receptor blockade are abolished by pretreatment with α- and β-adrenoceptor blocking agents, the opiate receptor antagonist probably exerts its hemodynamic effects through the sympathetic nervous system.9 However, the precise mechanism by which the opiate receptor antagonist causes sympathetic stimulation in heart failure remains to be determined.

Endogenous opioids, comprised of β-endorphins, enkephalins, and dynorphins, and their specific...
receptors, are present in the central nervous system, adrenal medullae, and the peripheral sympathetic nerves. To study whether the hemodynamic effects of the opiate antagonists in heart failure are mediated by an action on either the central nervous system or the peripheral sympathetic nervous system, we compared the effects of naloxone hydrochloride to those of its quaternary analogue naloxone methobromide (MeBr), which does not cross the blood-brain barrier. In addition, because endogenous opioids exert an antinociceptive action on opiate \( \mu \)-receptors, removal of such an effect by opiate receptor antagonism would be expected to heighten the animal’s sympathoadrenal responses to distress. To study whether such a mechanism plays a role in mediating the circulatory and sympathoadrenal responses to naloxone, we compared the effects of naloxone hydrochloride in conscious dogs with those in pentobarbital-anesthetized animals. Pentobarbital anesthesia nullifies the antinociceptive effect of naloxone because it depresses the higher cortical function of nociception and inhibits opiate \( \mu \)-receptors. We measured systemic hemodynamics, regional blood flows, and plasma catecholamines before and after naloxone administration. Results of our study indicate that, unlike naloxone hydrochloride, naloxone MeBr produced no circulatory stimulation in right-heart failure and that although secretion of epinephrine was reduced, the overall sympathetic and circulatory stimulation produced by naloxone hydrochloride was not altered by pentobarbital anesthesia.

Materials and Methods

Surgical Preparation

Adult mongrel dogs weighing 21–33 kg were used for production of chronic heart failure with a modification of the two-stage surgical procedure of Barger et al. Animals were anesthetized with sodium pentobarbital (25 mg/kg i.v.) and ventilated with room air by a respirator (Harvard Apparatus, South Natick, Massachusetts). Aseptic surgical techniques were used. At the first surgery, a right thoracotomy was performed through the fifth intercostal space. During transient occlusion of venous return to the right atrium, the surgeon’s index finger was inserted into the heart through a right atriotomy and the chordae tendineae of the anterior tricuspid leaflet were ruptured. A heparin-filled Tygon catheter (1.02 mm i.d.; Norton, Plastic & Synthetics Division, Akron, Ohio) was placed in the right atrium, and the atriotomy was closed. Two weeks later, a second thoracotomy was performed through the left fifth intercostal space. A silicone rubber hydraulic occluder (R.E. Jones, Silver Springs, Maryland) was placed around the pulmonary artery, and a micromanometer (Konigsberg Instruments, Pasadena, California) was inserted into the left ventricle through a stab wound at the apex. Tygon catheters were inserted into the descending aorta, the pulmonary artery, and the left atrium. All catheters and the lead from the micromanometer were exteriorized at the nape of the neck.

Beginning 2 weeks after the second surgery, the pulmonary artery occluder was progressively inflated. This procedure was repeated once or twice a week for 5–6 weeks to produce right-sided congestive heart failure, characterized by prominent ascites, elevated right atrial pressure, and reduced cardiac output. Studies were performed in dogs with stable heart failure 3–4 months after the second surgery, when all dogs had been trained to lie quietly in a decubitus position on a table. Sham-operated dogs underwent two surgical procedures without tricuspid valve avulsion or placement of the pulmonary artery occluder. Like the heart failure dogs, they were trained to lie on a table and were studied 3–4 months after left thoracotomy.

The study was approved by the University of Rochester Committee on Animal Resources and conformed to the guiding principles of the American Physiological Society in the care and use of animals and the National Institutes of Health Guide on the use of experimental animals.

Hemodynamic and Neurohormonal Measurements

The chronically implanted Tygon catheters were connected to pressure transducers (model P23Db, Statham Instruments, Oxnard, California) for continuous recording on a multichannel Bruch model 480 recorder (Gould, Instrument Systems Division, Cleveland, Ohio). The Konigsberg micromanometer was connected to the recorder to measure left ventricular pressure and its first derivative (dP/dt) with an electronic differentiator. The ratio of left ventricular dP/dt at a developed pressure of 50 mm Hg and the developed pressure (dP/dt/P) was taken as a measure of left ventricular contractility. Cardiac output was measured by indocyanine green (Cardio-Green, Hynson, Westcott & Dunning, Baltimore, Maryland) that was injected into the pulmonary artery and sampled in the aortic blood; a cardiac output system (model 140, Gilford Instrument Laboratories, Oberlin, Ohio) was used. Total peripheral vascular resistance was calculated by dividing the difference between mean aortic pressure and right atrial pressure by cardiac output.

Regional blood flows were measured by the radioactive microsphere method. NEN-TRAC microspheres (New England Nuclear, Boston, Massachusetts), 15\( \pm 2 \) \( \mu m \) in diameter and labeled with \( ^{141}\)Ce, \( ^{31}\)Cr, \( ^{113}\)Sn, \( ^{86}\)Ru, and \( ^{84}\)Se at a specific activity of 10 mCi/g, were suspended in a 10% dextran solution containing 0.01% Tween 80. For each flow measurement, 1–1.5 \( \times 10^3 \) microspheres were injected into the left atrium. Organ blood flows were calculated by a reference sample method. Organ vascular resistance was calculated by dividing the difference between mean aortic pressure and right atrial pressure by organ blood flow.
Plasma catecholamines were measured by a radioenzymatic method through use of Cat-A-Kit assay systems (Amersham, Arlington Heights, Illinois). Plasma $\beta$-endorphin was determined by radioimmunoassay after extraction on a SP-Sephadex C-25 column with reagents purchased from Immuno Nuclear, Stillwater, Minnesota. The antiserum is highly specific for $\beta$-endorphin and does not cross-react with various natural and synthetic opioid peptides or other nonrelated peptides. Plasma ACTH was measured by radioimmunoassay (Immuno Nuclear). The interassay coefficients of variations for $\beta$-endorphin and ACTH measurements in our laboratory are 16% and 9%, respectively.

**Experimental Protocol**

Heart failure animals were divided into four experimental groups. Animals in the first two groups underwent two serial studies, separated by at least 3 days. Group 1 received equimolar doses of naloxone hydrochloride and naloxone MeBr in the two studies. Group 2 received the same doses of naloxone hydrochloride on two separate occasions: one while the animals were conscious and the other after pentobarbital was administered to measure the effects of anesthesia. The order of studies was chosen randomly in the two groups. The other two groups of animals, one conscious (group 3) and the other anesthetized (group 4), received normal saline and served as controls. The experimental protocol for the latter two groups was the same as that for group 2, except that the animals received normal saline (0.38 ml/min) instead of naloxone hydrochloride.

To reduce sensory stimulation to the animals, we kept the lighting and temperature constant and minimized any noises in the room. Anesthesia was produced by sodium pentobarbital with a bolus dose (15 mg/kg) followed by a continuous infusion at a rate of 5 mg/kg/hr throughout the experiment. At least 30 minutes were allowed to elapse before baseline hemodynamic measurements were obtained. The absence of purposeful movement and no tachycardia or pressor responses to leg pinch or pinprick indicated that adequate anesthesia was maintained throughout the experiment. Spontaneous ventilation was maintained; arterial blood gases were within normal ranges and did not change during the experiment.

The experimental protocol included a 20-minute baseline period and two 20-minute stages of infusion with either naloxone hydrochloride (Sigma Chemical, St. Louis, Missouri) or naloxone MeBr (Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut). During the first stage, naloxone was administered at a dose of 0.275 $\mu$mol/kg over 1 minute, followed by a continuous infusion of 13.77 $\mu$mol/kg/min. The dose of naloxone was increased fivefold at the second stage, beginning with a bolus dose of naloxone (1.375 $\mu$mol/kg) followed by a 68.9 $\mu$mol/kg/min infusion. Naloxone was dissolved in normal saline, and for each dog its concentration was adjusted to deliver the desired dosage at a rate of 0.38 ml/min through use of a Harvard infusion pump.

Heart rate, aortic pressure, cardiac output, left ventricular $dP/dt$ and $dP/dt/P$, and left and right atrial pressures were measured at 5-minute intervals throughout the experiment. Regional blood flows and blood samples for $\beta$-endorphin, ACTH, and catecholamines were obtained during the baseline period and again between 15 and 20 minutes of each infusion.

The effects of naloxone hydrochloride also were studied in sham-operated animals. The experimental protocol was the same as that for naloxone infusions in group 1 heart failure dogs.

Furthermore, to study whether pentobarbital anesthesia affected the cardiac inotropic response to adrenergic stimulation, we measured the responses of peak left ventricular $dP/dt$ to five serially increasing doses of intravenous isoproterenol (10, 25, 50, 100, and 250 ng/kg) both before and after pentobarbital anesthesia. The doses were administered 5–10 minutes apart, after the hemodynamic changes produced by the preceding dose of isoproterenol had returned to baseline values.

At the end of the experiment, dogs were killed with lethal doses of sodium pentobarbital. Brains, hearts, livers, kidneys, spleens, stomachs, small and large intestines, quadriceps muscles, adrenal glands, and skin were removed and counted for radioactivity with a Packard Gamma Spectrometer and a model 9012 multichannel analyzer (Packard Instrument, Downers Grove, Illinois). Blood flows to stomach, small intestine, large intestine, and spleen were summed for total splanchnic flow.

**Statistical Analysis**

The experimental results are presented as the mean±SEM. Two-way analysis of variance for independent groups with repeated measures and Dunnnett’s test were used to determine the significance of the difference between the baseline and serial measurements after administration of naloxone or saline. Student’s $t$ test was used to determine the statistical significance of a difference between two means. Differences were considered statistically significant if $p<0.05$.

**Results**

**Systemic Hemodynamic Responses to Naloxone in Conscious Heart Failure Dogs**

Eight conscious heart failure dogs (group 1) received two serial doses of either naloxone hydrochloride or naloxone MeBr on two separate days. Body weight did not differ between the two experimental days (27.5±1.3 and 27.1±1.4 kg, respectively). Figure 1 shows that naloxone hydrochloride increased mean aortic pressure, cardiac output, and left ventricular $dP/dt$ and $dP/dt/P$ and decreased total peripheral vascular resistance. These changes tended to be greater during the second stage of the
experiment when the higher doses were administered. Heart rate increased transiently after each dose of naloxone hydrochloride but was not statistically different from the baseline 10 minutes after naloxone hydrochloride administration.

On the other hand, equimolar doses of naloxone MeBr produced no significant increases in heart rate, mean aortic pressure, cardiac output, and left ventricular dP/dt and dP/dt/P. The higher dose of naloxone MeBr actually produced a transient decrease in mean aortic pressure and left ventricular dP/dt. Total peripheral vascular resistance was not affected significantly.

Right atrial pressure was elevated at 13.4±0.9 and 13.5±0.9 mm Hg before administration of naloxone hydrochloride and naloxone MeBr, respectively, and was unaffected by the opiate antagonists (13.7±0.8 and 13.3±0.7 mm Hg by the end of experiments). Nor did left atrial pressure change significantly after naloxone hydrochloride (4.2±0.6 to 4.1±0.6 mm Hg) or naloxone MeBr administration (4.2±0.5 to 4.3±0.3 mm Hg).

Systemic Hemodynamic Responses to Naloxone in Anesthetized Heart Failure Dogs

Ten heart failure dogs (group 2) received two serial doses of naloxone hydrochloride in both the conscious and anesthetized states. Their body weights were similar to those of group 1 and did not differ between the two experimental sessions (26.7±1.5 vs. 27.3±1.5 kg). As in group 1, naloxone hydrochloride increased heart rate transiently in this group of dogs studied while conscious (Figure 2). Mean aortic pressure, cardiac output, and left ventricular dP/dt and dP/dt/P increased, while total peripheral vascular resistance decreased. Again, naloxone hydrochloride had no effect on either left atrial (5.2±0.6 to 5.8±0.7 mm Hg) or right atrial pressure (12.8±0.6 to 13.2±0.7 mm Hg) in these animals.

Compared with the baseline values in conscious animals, left ventricular dP/dt and dP/dt/P were significantly lower after anesthesia, but there were no differences in baseline heart rate, cardiac output, mean aortic pressure, left and right atrial pressures,
and total peripheral vascular resistance between the conscious and anesthetized states. Like the conscious dogs, the anesthetized dogs responded to naloxone hydrochloride with an increase in mean aortic pressure, cardiac output, and left ventricular dP/dt and dP/dt/P. However, the increase in cardiac output was not statistically significant until the higher dose of naloxone hydrochloride had been administered. Neither heart rate nor total peripheral vascular resistance changed significantly in the anesthetized dogs during naloxone hydrochloride infusion. Furthermore, there were no significant changes in right atrial (14.0±1.6 to 13.3±1.5 mm Hg) or left atrial pressure (4.9±0.7 to 4.9±0.6 mm Hg).

Because the changes produced by naloxone hydrochloride in the conscious state were similar in groups 1 and 2, results of the two groups were combined. Furthermore, because the hemodynamics appeared steady between 10 and 20 minutes after each dose of naloxone, we averaged the three values obtained 10–20 minutes after each dose and subtracted from that the baseline value for each of the parameters. Figure 3 shows that naloxone hydrochloride produced a dose-dependent graded increase in mean aortic pressure, cardiac output, and left ventricular dP/dt and dP/dt/P and a decrease in total peripheral vascular resistance in conscious dogs. None of these changes were produced by naloxone MeBr. Neither antagonist produced a sustained increase in heart rate.

The increase in mean aortic pressure produced by naloxone hydrochloride was similar in the conscious and anesthetized dogs (Figure 3). The increases in cardiac output and left ventricular dP/dt during the first dose of naloxone hydrochloride were smaller in the anesthetized dogs, but the magnitude of changes attained after the second dose did not differ statistically between the two experimental conditions. Nor did the changes in left ventricular dP/dt/P and total peripheral vascular resistance produced by naloxone hydrochloride differ between the two conditions.

Regional Blood Flow Responses to Naloxone in Heart Failure Dogs

Table 1 shows the effects of naloxone hydrochloride on regional blood flows and vascular resis-
tances in conscious heart failure dogs. Naloxone hydrochloride increased blood flow to the right and left ventricular myocardium, kidneys, adrenal glands, quadriceps muscles, stomach, and spleen but not to brain, skin, liver, and small and large intestines. Total splanchnic blood flow increased slightly. Vascular resistance decreased in the ventricular myocardium, adrenal glands, and quadriceps muscle. Other organ vascular resistances did not change significantly.

Naloxone MeBr had no effects on blood flow to the ventricular myocardium, quadriceps muscle, brain, kidneys, and splanchnic beds (Figure 4). Nor did it affect vascular resistance in any of the organs (Figure 5).

Compared with conscious dogs (Table 1), anesthetized dogs exhibited a significantly lower baseline blood flow to brain (50±6 ml/100 g/min), adrenal glands (88±6 ml/100 g/min), stomach (16±2 ml/100 g/min), and small intestine (33±5 ml/100 g/min). Other organ blood flows did not differ at baseline between the two groups. Like conscious dogs, anesthetized animals responded to naloxone hydrochloride with an increase in blood flow to the right and left ventricular myocardium, kidneys, and splanchnic beds and with no change in cerebral blood flow (Figure 4). However, unlike that in conscious dogs, quadriceps muscle blood flow did not increase during naloxone hydrochloride infusion in the anesthetized dogs. These two studies also differed significantly in their responses of quadriceps muscle vascular resistance to naloxone hydrochloride. Naloxone hydrochloride decreased quadriceps muscle vascular resistance in the conscious state (Table 1) but produced no significant change in the anesthetized dogs (21±3 to 23±5 mm Hg/ml/100 g/min). These changes in skeletal muscle vascular resistance are statistically different between the two experimental conditions. Other changes in organ vascular resistances did not differ significantly between the conscious and anesthetized states (Figure 5).
TABLE 1. Effects of Naloxone Hydrochloride on Regional Blood Flows and Vascular Resistances

<table>
<thead>
<tr>
<th>Organ</th>
<th>Blood flow (ml/100 g/min)</th>
<th>Vascular resistance (mm Hg/ml/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Myocardium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>150±9</td>
<td>187±16*</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>116±8</td>
<td>139±8*</td>
</tr>
<tr>
<td>Kidneys</td>
<td>353±23</td>
<td>427±38*</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>157±10</td>
<td>233±18*</td>
</tr>
<tr>
<td>Quadriceps muscle</td>
<td>4.3±0.5</td>
<td>7.3±1.2*</td>
</tr>
<tr>
<td>Stomach</td>
<td>30±5</td>
<td>59±13*</td>
</tr>
<tr>
<td>Spleen</td>
<td>89±14</td>
<td>153±23*</td>
</tr>
<tr>
<td>Brain</td>
<td>71±3</td>
<td>76±6</td>
</tr>
<tr>
<td>Skin</td>
<td>6.0±0.7</td>
<td>5.7±0.6</td>
</tr>
<tr>
<td>Liver</td>
<td>40±7</td>
<td>39±6</td>
</tr>
<tr>
<td>Small intestine</td>
<td>53±6</td>
<td>47±5</td>
</tr>
<tr>
<td>Large intestine</td>
<td>42±4</td>
<td>44±6</td>
</tr>
<tr>
<td>Splanchnic beds</td>
<td>59±5</td>
<td>69±8*</td>
</tr>
</tbody>
</table>

Values are mean±SEM; n=18.

*Significantly different from baseline at p<0.05.

Hemodynamic Effects of Normal Saline in Heart Failure Dogs

Normal saline infusion produced no hemodynamic changes in seven conscious (27.6±0.6 kg, group 3) and six anesthetized (27.2±2.6 kg, group 4) heart failure dogs. Heart rate, mean aortic pressure, cardiac output, total peripheral vascular resistance, left ventricular dP/dt and dP/dt/P, and left and right atrial pressures did not change significantly during normal saline infusion in either group of animals (Table 2). Nor did normal saline affect regional blood flows in the heart failure animals.

Hemodynamic Effects of Naloxone Hydrochloride in Sham-Operated Dogs

Table 3 shows the baseline hemodynamics of sham-operated dogs (n=6, 24.2±1.0 kg) and their responses to naloxone hydrochloride. Compared with the heart failure dogs (groups 1–3), the conscious sham-operated dogs exhibited a significantly lower heart rate, right atrial pressure, and total peripheral vascular resistance and a higher cardiac output and left ventricular dP/dt and dP/dt/P. Left atrial pressure did not differ between the heart failure and sham-operated dogs. None of the hemodynamic parameters in sham-operated dogs changed significantly after administration of naloxone hydrochloride.

Responses of Plasma β-Endorphin, Adrenocorticotropin, and Catecholamines to Naloxone

Conscious sham-operated animals showed a basal plasma level of 5±1 pM for β-endorphin, 26±3 pg/ml for ACTH, 0.17±0.03 ng/ml for norepinephrine, and 0.15±0.03 ng/ml for epinephrine. These hormones were significantly increased in dogs with heart failure (Table 4). The table also shows that naloxone hydrochloride increased plasma β-endorphin, ACTH, and catecholamines in heart failure dogs. The increases in plasma β-endorphin, ACTH, and norepinephrine were similar in the conscious and anesthetized states, but the peak plasma epinephrine in conscious dogs was significantly greater than in anesthetized dogs (t=2.67, p=0.026). On the other hand, neither naloxone MeBr nor normal saline had effects on the hormonal levels.

Left Ventricular dP/dt Response to Isoproterenol

The dose-response curves of isoproterenol on left ventricular dP/dt are shown in Figure 6. The curve was shifted to the right by anesthesia and indicates that the increase in left ventricular dP/dt produced by isoproterenol was attenuated by pentobarbital anesthesia.

Discussion

In this study, right heart failure animals exhibited ascites, high right atrial pressure, reduced cardiac output and regional blood flows, and elevated levels of plasma β-endorphin, ACTH, and catecholamines. Our present study further showed that naloxone hydrochloride increased mean aortic pressure, cardiac output, left ventricular dP/dt and dP/dt/P, and regional blood flows in the heart failure dogs both in the conscious state and after pentobarbital anesthesia. The changes are similar to those we reported previously using another opiate antagonist, nalmefene, and indicate a role of endogenous opioids in the regulation of the circulation in chronic congestive heart failure.

The Barger model for right-sided congestive heart failure has been studied extensively by us and other investigators. These animals show many of the hemodynamic, neurohumoral, and biochem-
FIGURE 4. Bar graphs of changes in regional blood flows to the right ventricular myocardium, left ventricular myocardium, quadriceps muscle, brain, kidneys, and splanchnic beds after two serial doses of naloxone hydrochloride in 18 conscious dogs (open columns), after two serial doses of naloxone methobromide in eight conscious dogs (hatched columns), and after two serial doses of nalaxone hydrochloride in 10 anesthetized dogs (dotted columns). Bars denote SEM. *Significantly different from baseline at p<0.05; †significantly different from corresponding open column at p<0.05.

FIGURE 5. Bar graphs of changes in regional vascular resistances in the right ventricular myocardium, left ventricular myocardium, quadriceps muscle, brain, kidneys, and splanchnic beds after two serial doses of naloxone hydrochloride in 18 conscious dogs (open columns), after two serial doses of naloxone methobromide in eight conscious dogs (hatched columns), and after two serial doses of naloxone hydrochloride in 10 anesthetized dogs (dotted columns). Bars denote SEM. *Significantly different from baseline at p<0.05; †significantly different from corresponding open column at p<0.05.

ical changes of clinical congestive heart failure. The inotropic and cyclic cAMP responses of the left ventricle to β-agonists are diminished in these animals,24 as in patients with congestive heart failure. In addition, the animals are notable for stable heart failure15 and thus are suitable for chronic or repetitive studies. However, unlike patients with left ventricular failure, these animals do not have an elevated left atrial pressure. Nor is the left ventricular β-receptor number reduced in these animals.24 Since the cardiac responses to opiate receptor inhibition are mediated in part through the β-adrenoceptors,3 the effects of naloxone on myocardial contractility may differ quantitatively in the left and right ventricles of the experimental animals. Responses to opiate receptor inhibition also may differ between our right heart failure dogs and patients with left heart failure. Naloxone has been shown to increase arterial pressure in patients with cardiogenic shock,31–33 but its effects on cardiac contractility and regional hemodynamics have not been systematically studied.

Unlike naloxone hydrochloride, naloxone MeBr caused no increases in mean aortic pressure, cardiac output, left ventricular systolic function, and regional blood flows in heart failure. Nor did naloxone MeBr increase plasma β-endorphin, ACTH, or catecholamines. Similarly, quaternary derivatives of naloxone do not reverse acute hypotension produced by endotoxemia34 or improve survival in anaphylactic shock.35 These findings indicate that the beneficial hemodynamic effects of naloxone hydrochloride in both acute and chronic circulatory stress are mediated by the central nervous system. That naloxone exerts its beneficial hemodynamic effects through the central nervous system is also supported by the findings that the protective effects of systemic naloxone hydrochloride can be produced by ventriculocisternal administration of naloxone hydrochloride in hypotension produced by endotoxin36,37 and in hemorrhagic shock.38,39

The secretion of endogenous opioids is regulated by a negative feedback mechanism within the central nervous system.1 In our present study, naloxone hydrochloride increased plasma β-endorphin and
TABLE 2. Systemic Hemodynamic Responses to Normal Saline Infusion in Heart Failure Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conscious dogs (n=7)</th>
<th>Anesthetized dogs (n=6)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Saline</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Saline</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>138±9</td>
<td>141±8</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>98±2</td>
<td>100±3</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.1±0.2</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>Total vascular resistance</td>
<td>2.3±0.1</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2.5±0.2</td>
<td>2.5±0.2</td>
</tr>
<tr>
<td>LV dP/dt/P (per sec)</td>
<td>6.1±1.0</td>
<td>5.9±0.8</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>16±2</td>
<td>16±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LV, left ventricular. Values for saline period were calculated from averages of three repetitive measurements taken between 30 and 40 minutes of infusion. Saline infusion produced no significant changes in any of the parameters.

ACTH. This finding suggests effective disinhibition of the negative feedback mechanism. In contrast, naloxone MeBr affected neither plasma β-endorphin nor ACTH. These findings suggest that effective opiate receptor inhibition had been produced within the central nervous system by the doses of naloxone hydrochloride used in the present study.

Anatomical and pharmacological evidence shows that endogenous opiate systems exist near the cardiovascular centers of the ventrolateral surface of the brain and in the autonomic integratory center of the hypothalamus and exert potent cardiovascular actions through sympathetic nuclei.1-7,40 Studies that use specific receptor agonists and antagonists have shown that activation of central μ-receptors causes circulatory stimulation, whereas activation of central δ-receptors leads to hypotension. These changes are caused by centrally mediated alterations in sympathoadrenal activity. In addition, endogenous opioids have been shown to inhibit catecholamine release from peripheral sympathetic nerves41 and adrenal medulla.42 Our studies with naloxone suggest that endogenous opioids act primarily on central sympathetic nuclei to reduce the sympathoadrenal activity in heart failure.

Naloxone has been shown to exert a direct positive inotropic effect on the heart, either by removal of the myocardial depressant effect of endogenous opioids7 or by a nonopiate receptor-mediated effect.43 However, the direct myocardial depressant effect of opioids is probably relatively minor in heart failure, because cardiac function is not improved by naloxone MeBr or by nalmefene after α- and β-adrenergic blockade.5

Naloxone MeBr produced a transient decrease in aortic pressure and left ventricular dP/dt in our study. A dose-dependent decrease in arterial pressure has been previously reported with naloxone.

TABLE 3. Hemodynamic Effects of Naloxone Hydrochloride in Sham-Operated Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>10-20</th>
<th>30-40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>103±5</td>
<td>104±7</td>
<td>109±8</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>107±3</td>
<td>107±4</td>
<td>109±4</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.3±0.2</td>
<td>4.3±0.2</td>
<td>4.5±0.2</td>
</tr>
<tr>
<td>Total peripheral vascular resistance (10^3 dyn · sec/cm^2)</td>
<td>2.0±0.1</td>
<td>1.9±0.1</td>
<td>1.9±0.1</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3.1±0.1</td>
<td>3.2±0.1</td>
<td>3.2±0.1</td>
</tr>
<tr>
<td>LV dP/dt/P (per sec)</td>
<td>46±2</td>
<td>46±1</td>
<td>47±2</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>6.0±0.3</td>
<td>6.3±0.3</td>
<td>6.2±0.3</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>3.6±0.8</td>
<td>3.5±0.8</td>
<td>3.8±0.8</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LV, left ventricular. Values shown for 10–20 minutes and 30–40 minutes were calculated from the averages of three repetitive measurements taken during the specified periods. Naloxone hydrochloride produced no significant changes in any of the parameters.
TABLE 4. Effects of Naloxone and Normal Saline on Plasma β-Endorphin, Adrenocorticotropin, and Catecholamines in Heart Failure Dogs

<table>
<thead>
<tr>
<th></th>
<th>Conscious dogs (n=18)</th>
<th>Anesthetized dogs (n=10)</th>
<th>Conscious dogs (n=8)</th>
<th>Conscious dogs (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Naloxone hydrochloride</td>
<td>Baseline</td>
<td>Naloxone methobromide</td>
</tr>
<tr>
<td>β-Endorphin (pM)</td>
<td>11±2</td>
<td>26±4*</td>
<td>12±3</td>
<td>14±2*</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>41±6</td>
<td>82±14*</td>
<td>48±6</td>
<td>34±11</td>
</tr>
<tr>
<td>Norepinephrine (ng/ml)</td>
<td>0.43±0.06</td>
<td>0.83±0.13*</td>
<td>0.61±0.15</td>
<td>0.37±0.07</td>
</tr>
<tr>
<td>Epinephrine (ng/ml)</td>
<td>0.28±0.04</td>
<td>0.90±0.24*</td>
<td>0.15±0.09</td>
<td>0.23±0.04</td>
</tr>
</tbody>
</table>

Values are mean±SEM. ACTH, adrenocorticotropin. Values given for the antagonists were calculated from measurements taken at 20 minutes after the second dose.

*Significantly different from baseline at p<0.05.
†Significantly different from conscious dogs receiving naloxone hydrochloride at p<0.05.

McBr.44 Although heart rate was not significantly affected in our present study, larger doses of naloxone MeBr have been shown to increase heart rate,44 which probably was caused by baroreceptor reflex-mediated sympathetic stimulation or an anticholinergic action of the antagonist.45 These effects of naloxone MeBr on arterial pressure, heart rate, and left ventricular dP/dt precluded the use of larger doses of naloxone MeBr in our study. Nevertheless, doses of naloxone MeBr like ours have been used to abolish the peripheral μ-receptor-mediated duodenal spike potentials produced by morphine11 and the δ-receptor-mediated vasoconstriction induced by leucine-enkephalin.44 Thus, it appears that the doses of naloxone MeBr we used are adequate to produce significant peripheral opiate receptor blockade.

The dose of pentobarbital used by us produced general anesthesia and abolished the animals' physical and hemodynamic responses to nociceptive stimuli. The decrease in cerebral blood flow after anesthesia probably was related to the cerebral depressant effect of pentobarbital and its resultant reduction in tissue metabolic demand. This dose of pentobarbital was, however, not large enough to significantly depress spontaneous respiration or alter arterial blood gases or pH. Compared with animals in the conscious state, the anesthetized animals had a lower left ventricular dP/dt and dP/dt/P. Heart rate, cardiac output, and mean aortic pressure were not significantly affected by this dose of pentobarbital. Furthermore, as shown in the anesthetized animals receiving normal saline, a steady hemodynamic state was present throughout the pentobarbital infusion. This occurrence suggests no significant accumulation of the anesthetic agent.

Pentobarbital-anesthetized dogs responded to naloxone hydrochloride with increases in mean aortic pressure, cardiac output, left ventricular dP/dt and dP/dt/P, and plasma catecholamines. Changes in mean aortic pressure and plasma norepinephrine were qualitatively and quantitatively similar to those in conscious animals. These findings suggest that pentobarbital anesthesia did not affect the sympathetic stimulation produced by the opiate antagonist. Conversely, as shown previously,46 naloxone hydrochloride neither nullified the anesthetic effect of pentobarbital nor increased cerebral blood flow.

The increases in cardiac output and left ventricular dP/dt produced by naloxone hydrochloride
appeared to be greater in the conscious dogs than the anesthetized dogs. In addition, the peak plasma epinephrine produced by naloxone hydrochloride was significantly greater in the conscious animals. These greater cardiac and adrenal medullary responses to naloxone in conscious animals probably were related, at least in part, to abolition of the antinociceptive effect of endogenous opioids. Furthermore, since pentobarbital reduced the responses of left ventricular dP/dt to isoproterenol, the diminished inotropic effect to naloxone hydrochloride during anesthesia could also have been caused by a nonspecific myocardial depressant effect of pentobarbital.

Naloxone hydrochloride increased regional blood flows to the right and left ventricular myocardium, kidneys, adrenal glands, splanchnic beds, and skeletal muscle in conscious heart failure dogs. Blood flow also increased to the myocardium, kidneys, and splanchnic beds in anesthetized dogs after naloxone administration. However, unlike those in the conscious dogs, neither blood flow nor vascular resistance changed significantly in skeletal muscle after naloxone hydrochloride in the anesthetized dogs. The reason for the discrepant results between the two experimental conditions cannot be stated with certainty. However, the association between skeletal muscle blood flow and plasma epinephrine concentration suggests that the naloxone-induced vasodilation in skeletal muscle in conscious dogs probably was an adrenergic $\beta_2$-receptor-mediated response.

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References


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S Sakamoto, C K Stone, P D Woolf and C S Liang

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