The role of endogenous opioids in congestive heart failure: effects of nalmefene on systemic and regional hemodynamics in dogs

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ABSTRACT We studied the role of endogenous opiates and their interrelationships with the sympathetic nervous system in an experimental preparation of right-sided congestive heart failure (CHF) produced by surgical tricuspid avulsion and progressive pulmonary arterial constriction. Three groups of dogs with CHF and one group of sham-operated dogs were studied. One group of dogs with CHF was given normal saline as pretreatment, while the other two groups were pretreated with either propranolol alone (β-blockade) or propranolol plus prazosin (α- plus β-blockade). CHF was characterized by weight gain, ascites, elevated right atrial pressure, tachycardia, and reduced cardiac output. Compared with sham-operated animals, animals with CHF exhibited significantly higher baseline levels of plasma β-endorphin and cortisol. Furthermore, only the animals with CHF responded to the opiate receptor--antagonist naloxene with significant increases in plasma β-endorphin, cortisol, and adrenocorticotropic hormone. Administration of naloxene increased aortic blood pressure, cardiac output, left ventricular dp/dt and dp/dt/P, and blood flow to the myocardium, skeletal muscle, and kidneys in dogs with CHF, but had no appreciable effects in sham-operated dogs. β-Receptor blockade abolished the increase in cardiac output, left ventricular performance, and blood flow produced by naloxene, but had no effect on the pressor response to naloxene. The increase in mean aortic pressure in the β-blockade group was accompanied by an increase in skeletal muscle vascular resistance. Addition of prazosin in the α- plus β-blockade group abolished the increases in mean aortic pressure and skeletal muscle vascular resistance, suggesting that the changes after propranolol probably resulted from unmasking of α-receptor–mediated vasoconstriction. Our present study indicates that the heightened opiate system accompanying CHF limits sympathetic activation, and that the beneficial effects of opiate-receptor inhibition are mediated, at least in part, via stimulation of the sympathetic nervous system.


Several endogenous opioid polypeptides have been recently identified and shown to have complex and diverse actions. β-Endorphin is one of the major endogenous opiates. It is formed from posttranslational cleavage of the adrenocorticotropic hormone (ACTH) precursor proopiomelanocortin. β-Endorphin and ACTH are released together into the general circulation from the anterior pituitary gland in response to stresses such as shock4 or physical exertion. Increasing evidence suggests that β-endorphin plays an important role in the pathogenesis of a variety of circulatory stresses. Holaday and Faden5 were the first to demonstrate that the opiate receptor antagonist naloxone reversed the hypotension produced by endotoxia. Subsequently, the opiate antagonist has been shown to reverse hemorrhagic hypovolemic shock,6–8 spinal shock,9 and septic shock.10 Blood pressure also improves after administration of naloxone in patients with cardiogenic shock refractory to conventional therapy.11,12 The response to naloxone appears to be mediated by the sympathetic nervous system, since inhibition of the sympathetic nervous system abolishes the improvement with naloxone.13,14 However, it is not known whether the chronic hypo-
perfused state of congestive heart failure (CHF) represents a sufficient stress to stimulate endogenous opiate secretion or whether β-endorphin contributes to clinical cardiac dysfunction and hypotension accompanying CHF. Therefore, we used an animal preparation of congestive right heart failure to determine whether β-endorphin and ACTH are elevated in CHF and whether antagonism of the opiate receptors would improve cardiac function and systemic perfusion. The new opiate-receptor antagonist nalmefene (17-(cyclopropylmethyl)-4, 5α-epoxy-6-methylenemorphinan-3,14-diol) was used because it has a longer half-life than naloxone. In addition, we administered nalmefene to separate groups of animals after they had been pretreated with propranolol, a β-receptor-blocking agent, or propranolol plus prazosin, an α₁-receptor-blocking agent, to determine whether the effects of opiate-receptor inhibition are modulated via the adrenergic receptors in CHF.

Methods

Surgical preparation. Right ventricular failure was produced in adult mongrel dogs weighing between 19.3 and 34.5 kg by a modified technique of Barger et al. Two stages of surgery were performed aseptically. Before the surgery each animal was anesthetized with sodium pentobarbital (25 mg/kg iv) and ventilated with room air with use of a Harvard respirator (Harvard Apparatus Co., Inc., S. Natick, MA). A right thoracotomy was performed through the fifth intercostal space during the first surgical procedure. The pericardial sac was opened, and a purse-string suture was placed at the base of the right atrium. With venous return transiently occluded, an incision was made within the purse-string, and an index finger was inserted into the right ventricle to rupture the chordae tendineae of the anterior tricuspid leaflet. A heparin-filled Tygon catheter (inner diameter, 1.02 mm, Norton Co., Plastic & Synthesis Division, Akron, OH) was then inserted into the right atrium and the atrium was closed by tightening the purse-string suture. Approximately 2 weeks later, a left thoracotomy was performed via the fifth intercostal space for placement of a silicone rubber Jones’ hydraulic occluder (Silver Springs, MD) around the pulmonary artery; a Konigsberg micromanometer (Konigsberg Instruments, Inc., Pasadena, CA) was placed into the left ventricle via a stab wound at the apex. Tygon catheters were then inserted in the left atrium, pulmonary artery, and descending thoracic aorta. All catheters and tubing of the occluder were exteriorized to the back of the neck and the chest was closed.

After recovering for at least 2 weeks, the animals were returned to the laboratory for gradual inflation of the pulmonary arterial balloon to increase the right atrial pressure. This was repeated one to two times weekly until right atrial pressure stabilized at 10 to 17 mm Hg and ascites were evident.

A group of sham-operated dogs was included for comparison. These animals underwent surgical procedures identical to those described above, except that the pulmonary arterial occluder was not placed and the tricuspid valve was not avulsed.

Experimental procedure and measurements. By the time of the final experimental studies, all animals had acclimated to the laboratory environment. They were trained to lie quietly in a decubitus position on a table with minimal restrictions, and none of the animals received premedication.

Atraumatic electrocardiographic electrodes were applied to the limbs of the dogs. The previously placed indwelling catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Inc., Oxnard, CA) and a multichannel Brush model 480 recorder (Gould Inc., Instrument Systems Division, Cleveland). Left ventricular pressure was obtained from the Konigsberg micromanometer also attached to the Brush recorder. The dp/dt was measured with an electronic differentiator. The ratio of the left ventricular dp/dt at a developed pressure of 50 mm Hg during isovolumic systole and the developed pressure (dp/dt/P) was obtained and used as a measure of left ventricular contractility independent of aortic pressure. Cardiac output was determined by injecting indocyanine green (Cardio-Green, Hynson, Westcott & Dunning, Inc., Baltimore) into the pulmonary artery and sampling arterial blood for the dye concentration with a Gilford Model 140 cardiac output system (Gilford Instrument Laboratories, Inc., Oberlin, OH).

Regional blood flows were determined by the radioactive microsphere method with the use of 1 to 1.5 x 10⁶ microspheres, 15 μm in diameter, labeled with ¹¹¹Ce, ¹³¹I, or ⁶⁸Ga (New England Nuclear, Boston). Organ blood flows were calculated by reference to a sample method with the use of the gamma counts from an aortic blood sample obtained during the infusion of microspheres and samples from the organs measured by a Packard Gamma Spectrometer with a model 9012 multichannel analyzer (Packard Instrument Co., Inc., Downers Grove, IL). Organ vascular resistances were calculated by dividing the difference between mean aortic pressure and mean right atrial pressure by organ blood flow.

Concentrations of norepinephrine were measured by a modified high-pressure liquid chromatographic method with use of an electrochemical detector (Bioanalytical System, Inc., Lafayette, IN). β-Endorphin levels were determined by radioimmunoassays after extraction on a SP-Sephadex C-25 column, with use of reagents purchased from Immuno Nuclear Corp. (Stillwater, MN). The antisem is highly specific for β-endorphin and has no cross-reaction with various natural and synthetic opioid peptides or other nonrelated peptides, including β-lipotropin. Radioimmunoassays were also used to determine plasma ACTH (Immuno Nuclear Corp., Stillwater, MN) and cortisol levels (Clinical Assays, Cambridge, MA). In our laboratories, the interassay coefficients of variations for β-endorphin, ACTH, and cortisol measurements are 16%, 6%, and 9%, respectively.

Experimental protocol. Dogs with CHF were randomly assigned to one of the following three pretreatment groups: (1) the control group (n = 11), which received 10 ml of normal saline intravenously, (2) the β-blockade group (n = 10), which received propranolol (Ayerst Laboratories Inc., New York, NY), 1.25 mg/kg iv, and (3) the α₂- plus β-blockade group (n = 6), which received propranolol, 1.25 mg/kg iv, plus prazosin hydrochloride (Pfizer Co., New York, NY), 0.2 mg/kg bolus, followed by a 2 μg/kg/min infusion throughout the experiment. The pretreatments were begun 30 min before the start of the experiment. The effectiveness of β-adrenergic–receptor blockade with propranolol was assessed by measurement of the heart rate response to increasing doses of intravenous isoproterenol before the drug pretreatment and at the end of the experiment. The dose of isoproterenol that produced an increase in heart rate of 25 beats/min was used to indicate β-adrenergic–receptor sensitivity. The α₂-adrenergic–blocking effect of prazosin was determined by measurement of the increases in aortic pressure produced by intravenous methoxamine (0.1 mg/kg) before and after pretreatment with prazosin. Sham-operated dogs were given normal saline pretreatment and nalmefene without β- or α₂-adrenergic blockade (group 4, n = 8).
The experimental protocol for the studies entailed a 20 min baseline period followed by two doses of nalmefene (Key Pharmaceuticals, Inc., Miami), 0.2 and 1.0 mg/kg, given intravenously 25 min apart. Nalmefene was administered slowly over a 5 min period. Heart rate, aortic blood pressure, cardiac output, left ventricular dp/dt and dp/dt/P, and left and right atrial pressures were measured at 5 min intervals during the baseline period and after each dose of nalmefene. Regional blood flows were measured at the end of the control period and 20 min after each dose of nalmefene. Blood samples were also obtained for measurements of levels of β-endorphin, ACTH, cortisol, and norepinephrine before and after nalmefene in the two groups of animals not pretreated with either propranolol or prazosin.

After the experiment, animals were killed with lethal doses of pentobarbital. Hearts, brains, livers, stomachs, small intestines, large intestines, spleens, kidneys, quadriceps muscles, and femurs were removed, cleansed, and prepared for radioactivity counting. Organ flows to spleen, stomach, small intestine, and large intestine were summed for measurement of total splanchnic flow.

Statistical analyses. The experimental results are presented as the mean ± SE. Two-way analysis of variance for independent groups with repeated measures27 and Dunnett's test28 were used to determine the significance of the difference between the baseline and serial measurements after administration of nalmefene. Student's t test was used to determine the statistical significance of a difference between two means. Changes were considered statistically significant if p < .05.

Results

Plasma β-endorphin, ACTH, and cortisol. Table 1 shows that baseline levels of β-endorphin and cortisol were significantly higher in dogs with CHF (group 1) than in sham-operated controls (group 4). However, plasma ACTH did not differ significantly in the two groups at baseline. Nalmefene increased plasma β-endorphin, ACTH, and cortisol in the dogs with CHF, but had no significant effects in the sham-operated dogs.

Systemic hemodynamics. At the time of hemodynamic measurements, animals with CHF (group 1) had heavier body weights (27.5 ± 1.3 kg) than sham-operated dogs (group 4, 22.8 ± 1.4 kg; t = 2.46, p < .01). The animals with CHF also exhibited a significantly higher heart rate (146 ± 8 vs 115 ± 8 beats/min), lower cardiac output (3.0 ± 0.2 vs 4.1 ± 0.5 liters/min), and lower left ventricular dp/dt (2164 ± 270 vs 3477 ± 387 mm Hg/sec), but the difference in mean aortic pressure in the two groups (100 ± 4 vs 112 ± 6 mm Hg) was not statistically significant.

Figure 1 shows that cardiac output and left ventricular dp/dt increased significantly after the first dose of nalmefene in the dogs with CHF (group 1). In addition, left ventricular dp/dt/P (33 ± 3 to 37 ± 3 sec⁻¹; t = 3.53, p < .01) increased. However, the increases in mean aortic pressure and heart rate produced by the first dose of nalmefene did not consistently reach statistical significance. Nevertheless, mean aortic pressure increased significantly after the second dose of nalmefene (1 mg/kg). Cardiac output and left ventricular dp/dt and dp/dt/P also appeared to increase further after the second dose of nalmefene. On the other hand, neither left atrial pressure (6.1 ± 1.0 to 7.1 ± 1.2 mm Hg) nor right atrial pressure (17.1 ± 0.8 to 17.1 ± 0.6 mm Hg) changed significantly.

Since the changes produced by nalmefene reached a steady state between 10 and 25 min after each dose, the four measurements obtained during that interval were averaged. The averaged values were analyzed statistically and their changes from the baseline were compared with those produced by nalmefene in sham-operated dogs (figure 2). Unlike those in dogs with CHF, serial administration of nalmefene produced no statistically significant effects on heart rate, mean aortic pressure, cardiac output, or left ventricular dp/dt in the sham-operated group. There were also no significant changes in left ventricular dp/dt/P (50 ± 8 to 51 ± 8 sec⁻¹), left atrial pressure (6.8 ± 1.0 to 7.0 ± 0.8 mm Hg), or right atrial pressure (6.6 ± 0.9 to 6.1 ± 0.5 mm Hg). The response to nalmefene of mean aortic pressure was significantly higher in dogs with CHF than in sham-operated controls.

<p>| Table 1 |
| Effects of CHF and nalmefene on plasma levels of β-endorphin, ACTH, and cortisol |</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>β-Endorphin (pM)</th>
<th>ACTH (pg/ml)</th>
<th>Cortisol (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-operated dogs (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.2 ± 1.1</td>
<td>47 ± 7</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>7.9 ± 1.5</td>
<td>50 ± 9</td>
<td>4.0 ± 1.1</td>
</tr>
<tr>
<td>Dogs with CHF (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.7 ± 1.8B</td>
<td>53 ± 6</td>
<td>8.5 ± 1.8B</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>20.3 ± 4.0A,B</td>
<td>97 ± 16A,B</td>
<td>14.6 ± 2.1A,B</td>
</tr>
</tbody>
</table>

Values are mean ± SE; n = number of experiments.

*P < .05 compared with baseline.

**P < .05 compared with corresponding values in the sham-operated group.
pressure, cardiac output, and left ventricular dP/dt and dP/dt/P in the dogs with CHF and sham-operated animals differed significantly (figure 2).

Before nalmefene, plasma levels of norepinephrine were higher in dogs with CHF (0.58 ± 0.06 ng/ml) than in sham-operated dogs (0.32 ± 0.07 ng/ml; t = 3.06, p < .01). Administration of nalmefene caused a further increase in plasma norepinephrine in the dogs with CHF (0.90 ± 0.18 ng/ml; p < .05), but not in the sham-operated dogs (0.51 ± 0.14 ng/ml).

Adrenergic-receptor inhibition. Production of β- and α-receptor blockade was accomplished with propranolol and prazosin, respectively. β-Adrenergic-receptor blockade was evidenced by the increased doses of isoproterenol required to raise heart rate by 25 beats/min (0.09 ± 0.02 μg/kg before administration of propranolol vs 0.90 ± 0.35 μg/kg at the end of the experiment; p < .001). α-Receptor blockade was demonstrated by the attenuation of pressor response to methoxamine (22.4 ± 3.4 mm Hg before prazosin vs 3.4 ± 1.2 mm Hg at the end of the experiment; p < .001). The β-blockade and α- plus β-blockade groups had body weights of 26.5 ± 1.1 and 29.7 ± 1.3 kg, respectively, neither of which differed significantly from that in group 1.

Compared with animals in group 1, the β-blockade group had a lower heart rate (116 ± 5 vs 146 ± 8 beats/min; t = 3.18, p < .01), but there was no difference in mean aortic pressure (108 ± 6 vs 100 ± 4 mm Hg), cardiac output (2.59 ± 0.15 vs 3.02 ± 0.21 liters/min), left ventricular dP/dt (1920 ± 124 vs 2164 ± 270 mm Hg/sec), or dP/dt/P (34 ± 2 vs 33 ± 3 sec⁻¹) in the two groups. Baseline heart rate was also lower in group 3 (119 ± 5 beats/min; t = 2.80, p < .05) than group 1. In addition, baseline mean aortic pressure was lower in group 3 (85 ± 3 mm Hg; t = 3.05, p < .01) than group 1, but cardiac output (2.77 ± 0.16 liters/min), left ventricular dP/dt (1617 ± 72 mm Hg/sec), and left ventricular dP/dt/P (29 ± 1 sec⁻¹) did not differ significantly in the two groups.

β-Adrenergic-receptor blockade with propranolol (group 2) abolished the increases in cardiac output and left ventricular dP/dt, but had no effect on the pressor response to nalmefene that occurred in group 1 animals (figure 3). This increase in mean aortic pressure, however, was abolished by the addition of prazosin in group 3.

Organ weights and regional blood flows. Compared with sham-operated dogs, animals with CHF had significantly larger right ventricles and livers, but neither the left ventricle nor the gastrointestinal tract differed significantly in weight in the two groups (table 2). To further assess the degree of right ventricular hypertrophy, we normalized the right ventricular weight for

FIGURE 1. Changes in mean aortic pressure, heart rate, cardiac output, and left ventricular (LV) dP/dt after two doses of nalmefene in 11 dogs with CHF. Bars indicate SE. Asterisks denote values that differ significantly from the baseline at p < .05 by Dunnett’s test.

FIGURE 2. Changes in mean aortic pressure, heart rate, cardiac output, and left ventricular (LV) dP/dt produced by two doses of nalmefene in 11 dogs with CHF and eight sham-operated dogs. Bars indicate SE. Asterisks denote values that differ significantly from the baseline at p < .05. Daggers indicate values that differ from those in the sham-operated group at p < .05.
body and left ventricular weight. Both of these ratios were greater in group 1 than in sham-operated dogs.

At baseline, right ventricular myocardial blood flow was significantly higher in dogs with CHF than in sham-operated dogs, but left ventricular myocardial blood flow did not differ in the two groups (table 3). The blood flow to the kidneys and quadriceps muscle was significantly reduced in animals with CHF. The splanchnic and liver (hepatic artery) flow also tended to be reduced in these dogs, but the differences between the sham-operated animals and those with CHF were not statistically significant. Blood flow to the brain and femur did not differ in the two groups at baseline.

Nalmefene caused a redistribution of cardiac output in dogs with CHF. It increased blood flow to the right and left ventricular muscle, quadriceps muscle, and kidneys in group 1. Concomitantly, vascular resistance decreased in these organs (figures 4 to 6). Blood flow to other organs and their vascular resistances were unchanged after nalmefene. In contrast, no significant changes occurred in any of the blood flow responses of the sham-operated dogs after administration of nalmefene (table 3).

Figures 4 to 6 show the baseline values and effects of adrenergic-receptor blockade on the regional circulations in response to nalmefene. β-Adrenergic-receptor blockade decreased baseline right ventricular myo-

![Graphs showing effects of nalmefene on heart rate, aortic pressure, cardiac output, and left ventricular dp/dt](image)

**FIGURE 3.** Effects of β-blockade (n = 10) and α- plus β-blockade (n = 6) on the changes in heart rate, mean aortic pressure, cardiac output, and left ventricular (LV) dp/dt produced by two doses of nalmefene. Open columns indicate the changes in the control group after normal saline pretreatment (n = 11). Bars indicate SE, and asterisks that the changes produced by nalmefene are statistically significant at p < .05. Daggers indicate values that differ from those in the control group at p < .05.

cardial blood flow (figure 4). β-Receptor blockade also attenuated the increase in myocardial blood flow and abolished the reduction in myocardial vascular resistance produced by nalmefene in group 2. The remaining increase in myocardial blood flow was abolished in group 3 with the addition of prazosin.

Blood flow to quadriceps muscle (figure 5) and kidneys (figure 6) was not different in the three CHF groups at baseline. Baseline vascular resistance, however, was reduced in skeletal muscle in group 3. Propranolol pretreatment abolished the increase in skeletal muscle blood flow that occurred after administration of nalmefene in group 1. Skeletal muscle vascular resistance actually increased slightly after nalmefene in the β-blockade group; this increase was not observed in group 3. Propranolol pretreatment also abolished the increase in renal blood flow and the decrease in renal vascular resistance that occurred after administration of nalmefene in group 1.

**Discussion**

Our present study indicates that the chronic systemic hypoperfusion accompanying CHF provides a stress inducing β-endorphin and cortisol secretions. Plasma ACTH, however, does not increase significantly. Such differential changes between the β-endorphin and ACTH responses have been previously reported in “stressed” rodents. Our findings that plasma β-endorphin, ACTH, and cortisol increased markedly in dogs with CHF after nalmefene further suggest that the opiate system is activated in CHF; enhanced secretions of β-endorphin and ACTH result when the negative feedback control of their own release is inhibited by the opiate antagonist. In contrast, there is relatively little activation of the opiate system in the normal state; the interruption of negative feedback inhibition caused

**TABLE 2**

Effects of CHF on organ weight

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated dogs</th>
<th>Dogs with CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>37 ± 4</td>
<td>51 ± 4*</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>100 ± 4</td>
<td>97 ± 5</td>
</tr>
<tr>
<td>Liver</td>
<td>757 ± 42</td>
<td>1102 ± 109*</td>
</tr>
<tr>
<td>Spleen</td>
<td>256 ± 24</td>
<td>272 ± 24</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>866 ± 32</td>
<td>822 ± 38</td>
</tr>
<tr>
<td>Weight ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV/BW (g/kg)</td>
<td>1.6 ± 0.1</td>
<td>2.0 ± 0.1*</td>
</tr>
<tr>
<td>RV/LV (g/g)</td>
<td>0.37 ± 0.03</td>
<td>0.58 ± 0.02*</td>
</tr>
</tbody>
</table>

Values are mean ± SE; n = 11.
RV = right ventricle; LV = left ventricle; BW = body weight.
*p < .05 compared with the sham-operated group.
TABLE 3  
Effects of nalmefene on organ blood flow in sham-operated dogs and those with CHF

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sham Baseline</th>
<th>Nalmefene</th>
<th>CHF Baseline</th>
<th>Nalmefene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle</td>
<td>106±10</td>
<td>111±14</td>
<td>178±24&lt;sup&gt;A&lt;/sup&gt;</td>
<td>227±35&lt;sup&gt;A,B&lt;/sup&gt;</td>
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<tr>
<td>Left ventricle</td>
<td>154±10</td>
<td>163±11</td>
<td>138±11</td>
<td>181±22&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kidneys</td>
<td>481±28</td>
<td>497±49</td>
<td>309±35&lt;sup&gt;B&lt;/sup&gt;</td>
<td>383±30&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quadriceps muscle</td>
<td>7.5±1.0</td>
<td>7.8±1.6</td>
<td>3.2±0.3&lt;sup&gt;B&lt;/sup&gt;</td>
<td>7.0±1.1&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>Liver (hepatic artery)</td>
<td>44±10</td>
<td>40±7</td>
<td>25±6</td>
<td>28±6</td>
</tr>
<tr>
<td>Splanchnics</td>
<td>56±7</td>
<td>55±6</td>
<td>41±6</td>
<td>42±7</td>
</tr>
<tr>
<td>Brain</td>
<td>73±7</td>
<td>70±5</td>
<td>77±8</td>
<td>84±11</td>
</tr>
<tr>
<td>Femur</td>
<td>7.5±1.6</td>
<td>8.1±1.9</td>
<td>5.3±1.3</td>
<td>6.6±1.5</td>
</tr>
</tbody>
</table>

Values are mean ± SE, ml/100 g/min.  
<sup>A</sup>p < .05 compared with baseline.  
<sup>B</sup>p < .05 compared with corresponding values in the sham-operated group.

no significant increases in plasma β-endorphin or ACTH in the sham-operated dogs in our study.

CHF was evidenced in our animals by ascites, increased body weight, hepatomegaly, high right atrial pressure, increased heart rate, and reductions in cardiac output, left ventricular dP/dt and dP/dt/P, and regional blood flows. Right ventricular hypertrophy was also evident, as judged by the increase in absolute and normalized right ventricular weight in the animals with CHF.

In addition to having a longer duration of action, nalmefene is more potent than naloxone and is orally active. The doses of nalmefene we used are much larger than those that have been shown to produce significant opiate antagonism. In our present study, nalmefene increased mean aortic pressure, cardiac output, and left ventricular dP/dt and dP/dt/P in dogs with CHF. These changes in blood pressure and cardiac output are similar to those produced by naloxone in shock. Pharmacologic blockade or surgical dis-
opioids appear to modulate the baroreceptor reflex at the nucleus of tractus solitarius. In the peripheral tissues, opioid peptides are located in the peripheral sympathetic system and endocrine glands. They have been shown to inhibit the release of norepinephrine during nerve stimulation from adrenergically innervated peripheral tissues and to modulate peripheral adrenergic transmission. Conversely, the effects of opiate peptides have been shown to be modified by the degree of sympathetic nervous system activation.

Endogenous opioids have also been shown recently to have a local depressant effect on the heart. However, compared with the effects mediated by inhibition of the sympathetic nervous system, the direct myocardial depressant effects of opioids were probably relatively minor in our animals with CHF, since nalmeafene produced no appreciable increase in cardiac function in the animals that had been pretreated with both propranolol and prazosin.

Along with cardiac output, regional blood flow to the myocardium, kidneys, and quadriceps muscle increased in dogs with CHF after nalmeafene. No significant changes in organ blood flow occurred after nalmeafene in sham-operated dogs. The increase in myocardial blood flow after nalmeafene in the animals with CHF is consistent with a metabolic stimulus to blood flow with the increased workload of the heart. Myocardial blood flow did not increase after nalmeafene in the animals that had been pretreated with propranolol plus prazosin, a combination that blocked both the inotropic and pressor responses. These findings suggest that endogenous opioids do not cause direct active coronary vasodilation. Skeletal muscle and renal vascular resistance decreased after nalmeafene in dogs with CHF, but skeletal muscle vascular resistance increased after β-adrenergic blockade in group 2. These changes paralleled the increase in mean aortic pressure, and probably were caused by unmasking of α-adrenergic receptor-mediated vasoconstriction. This hypothesis was supported by the abolition of the pressor response and increase in skeletal muscle vascular resistance after nalmeafene in group 3, which received combined α- and β-receptor blockade.

Like opiate antagonists, ACTH has been shown to improve cardiovascular function and survival in animals subjected to hemorrhagic shock. These effects of ACTH were not abolished by adrenalectomy. Exogenous corticosteroids also have been shown to block the effect of naloxone in hemorrhagic shock. The results indicate that the “antishock” action of ACTH is a result of neither intact adrenal glands nor adrenal release of corticosteroids. Instead, the beneficial ef-
fects of ACTH in hemorrhagic shock have been shown to be antagonized by morphine, suggesting that ACTH probably exerts its action by inhibiting endogeneous opioids. Whether ACTH exerts similar effects in the presence of CHF is not known.

In conclusion, β-endorphin is elevated in chronic CHF, and the endogenous opioids probably contribute significantly to the circulatory dysfunction observed in CHF. Opiate-receptor antagonism leads to an increase in cardiac output, mean aortic pressure, left ventricular dP/dt and dP/dt/P, and blood flow to the myocardium, skeletal muscle, and kidneys. This improvement in systemic and regional hemodynamics in CHF after opiate-receptor inhibition is probably mediated by the disinhibition of sympathetic nervous system activity, since responses to naloxone are abolished by adrenergic receptor--blocking agents.

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