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Effects of Naloxone on Regional Blood Flow Distribution in Canine Hemorrhagic Shock (42003)

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Abstract. The opiate antagonist naloxone increases arterial pressure, maximal left ventricular *dp/dt* and cardiac output when administered to dogs subjected to hemorrhagic shock. The purpose of this study was to investigate regional blood flow changes associated with naloxone treatment in anesthetized hypovolemic and normovolemic dogs. Hypovolemic dogs ($n = 10$) were bled over 30 min ($t = -30$ to $t = 0$) to a pressure of 45 mm Hg which was maintained for 1 hr. At $t = 60$, five dogs received naloxone (2 mg/kg + 2 mg/kg·hr), and five received an equal volume of saline. Regional blood flows were determined at $t = -30$, 45, and 90 min using 15-μm microspheres. Normovolemic dogs ($n = 10$) were subjected to the same protocol except they were not bled. During hypovolemia, naloxone produced significant increases in myocardial, intestinal, hepatic, and adrenal blood flows whereas saline treatment did not. No significant changes in skin, muscle, fat, pancreatic, renal, or brain flows were detected. The increases in blood flow were not associated with significant changes in vascular resistance. Naloxone had no significant effects on any hemodynamic parameter during normovolemia. The beneficial effects of naloxone in hemorrhagic shock include increased blood flow to vital organs due to increased perfusion pressure which is secondary to improved cardiac performance.

Adrenocorticotropin and β-endorphin are synthesized from a common precursor (1) and are released in equimolar amounts in response to stress (2). Systemic administration of exogenous (3) or endogenous opioids (4) produces hypotension. This information leads to the hypothesis that endogenous opioids are released in and contribute to the cardiovascular suppression seen in hemorrhagic shock. Faden and Holaday showed that the opiate antagonist naloxone increases mean arterial pressure, pulse pressure, and survival when administered to rats subjected to hemorrhagic shock (5). Naloxone also increases myocardial contractility and cardiac output when administered to dogs in hemorrhagic shock (6).

An increase in mean arterial pressure without an increase in cardiac output or redistribution of blood flow to vital organs would not be likely to result in increased cardiac performance or survival. If naloxone acted solely as a pressor agent in shock, it might actually decrease survival since cardiac work and oxygen demand would increase, but oxygen delivery would not, resulting in an exacerbation of myocardial hypoxia. On the other hand, increased coronary perfusion after naloxone treatment might contribute to the improved cardiovascular function seen.

It is known that the coronary vasculature does not maximally dilate in response to hemorrhage (7) and that β-endorphin is released during canine hemorrhagic shock (8). Since intracerebroventricularly administered opiates cause coronary vasoconstriction (9), it is possible that during shock, β-endorphin suppresses myocardial function by increasing coronary vascular resistance, thereby reducing coronary perfusion. Furthermore pharmacologic augmentation of coronary flow in hemorrhagic shock improves cardiac function (10); therefore, naloxone may be exerting its beneficial effect by reversing endogenous opioid mediated coronary vasoconstriction. If this hypothesis is true, then naloxone would be expected to decrease coronary vascular resistance in hypovolemic dogs.

In addition to possible changes in cardiac blood flow, naloxone may have effects on other regional blood flows. Investigation of these changes may help elucidate the mechanism for the increased cardiovascular function and survival seen after naloxone treat-

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ment. The effects of naloxone on regional blood flow distribution have been investigated but in a model in which cardiac output did not change (11). The purpose of this study is to investigate changes in regional blood flow in a model in which naloxone is known to increase myocardial contractility, cardiac output, and survival (6).

Materials and Methods. Experiments were conducted on 20 mongrel dogs of either sex weighing 17.3 ± 0.2 (mean ± SEM) kg and tested negative for Microfilariae and Dirofilariae. The dogs were anesthetized with pentobarbital (30 mg/kg) intravenously, intubated, and permitted to breathe room air spontaneously. They were placed on a heating pad to maintain core temperature over 37.5°C. The left brachial artery was cannulated for measuring systemic mean arterial pressure (MAP) and for rapid blood withdrawal. Left ventricular and left ventricular end diastolic pressures were measured with a pigtail catheter which was inserted into the left femoral artery and advanced into the left ventricle. The pressure signal from this catheter was differentiated with respect to time to generate an output, the maximum value of which (LV *dp/dt*) can be used as a measure of myocardial contractility. A thermistor-tipped Swan-Ganz catheter was inserted into the left femoral vein and advanced into a wedge position in the pulmonary vasculature. Central venous pressure (CVP) and pulmonary arterial wedge pressure were measured through proximal and distal ports of this catheter. Cardiac output (CO) was determined using the thermodilution technique with an Edwards Laboratories Model 9520A cardiac output computer. Total peripheral resistance was calculated as (MAP–CVP)/CO. Heart rate was calculated from the time interval between LV *dp/dt* peaks. Cardiac work was calculated as MAP·CO. Pressure catheters were connected to Statham P23 ID transducers which were connected to a Beckman R411 dynograph recorder. Catheters were inserted into the right femoral vein (for drug administration) and the right femoral and brachial artery for blood withdrawal during microsphere injections.

Sodium heparin was administered as an intravenous bolus of 250 units/kg with supplemental doses of 125 units/kg given at 30-min intervals. Dogs were then separated into hypovolemic and normovolemic categories. Normovolemic dogs were subjected to the same protocol as hypovolemic dogs except that they were not hemorrhaged. After control measurements were taken ($t = -30$ min), hypovolemic animals were slowly bled into a reservoir until the MAP was 45 mm Hg ($t = 0$). This pressure was maintained for 1 hr (to $t = 60$) by adjusting the height of the reservoir as needed. At that point, the reservoir was clamped, and half the dogs in each group ($n = 5$) received an intravenous bolus of 2 mg/kg naloxone HCl plus an infusion of 2 mg/kg·hr and the other half an equal volume of saline. After final measurements were taken ($t = 90$), the dogs were exsanguinated.

Arterial blood gas determinations were made at $t = -30$, 0, 30, 60, and 90 min, using an Instrumentation Laboratories Micro 13 analyzer. After each blood gas determination, any metabolic acidosis was half corrected with 7.5% sodium bicarbonate. Plasma cortisol and ACTH levels were determined at $t = -30$, 45, and 90 min using radioimmunoassays described elsewhere (12). Regional blood flow determinations were made at $t = -30$, 45, and 90 min by utilizing the microsphere technique (13). Blood was withdrawn from brachial and femoral reference arteries at 2.06 ml/min. Thirty seconds later, radioactively labeled microspheres (which had been vortex mixed for 4 min) were injected into the left ventricle over 30 sec using 5 ml of saline flush. Each injection used approximately 1.6×10^6 microspheres labeled with one of the following isotopes: ^{85}Sr, ^{46}Sc, ^{141}Ce, ^{95}Nb, ^{113}Sn, or ^{153}Gd (35 μCi), with a diameter of 15 ± 3 μm suspended in 0.3 to 0.9 ml of 10% Dextran (New England Nuclear, Boston, Mass.). Blood withdrawal was continued for an additional 3 min after microsphere injections. After exsanguination, samples were taken from the organs listed in Table I, weighed, and counted in a Packard gamma counter. Blood flows were calculated as milliliters per minute per 100 g, using standard formulas (14). Vascular resistances were calculated as (MAP–CVP)/blood flow. Naloxone and saline responses were defined as the differences between the values of a given parameter at $t = 90$ and $t = 45$ min.

TABLE I. REGIONAL BLOOD FLOW DISTRIBUTION IN CANINE HEMORRHAGIC SHOCK[a]

Tissue	$t = -30$		$t = 45$		Change after treatment ($t = 90$–$t = 45$)		
	Nal	Sal	Nal	Sal	Nal	Sal	Two-tailed P
Brain	77 ± 11	85 ± 13	50 ± 6	79 ± 13	3 ± 5	−7 ± 7	0.257
Heart	162 ± 26	175 ± 12	103 ± 12	154 ± 33	118 ± 13	24 ± 25	0.015
Adrenal	387 ± 48	325 ± 70	178 ± 29	214 ± 49	283 ± 47	−24 ± 55	0.003
Kidney	939 ± 106	791 ± 74	139 ± 27	130 ± 27	102 ± 53	−2 ± 53	0.204
Liver (arterial)	43 ± 24	24 ± 12	14 ± 3	19 ± 6	18 ± 5	−5 ± 6	0.022
Spleen	171 ± 37	196 ± 30	10 ± 4	12 ± 5	14 ± 7	−4 ± 6	0.092
Pancreas	75 ± 13	87 ± 33	8 ± 1	16 ± 2	7 ± 1	2 ± 3	0.188
Stomach	83 ± 37	25 ± 4	8 ± 2	15 ± 3	11 ± 6	−3 ± 3	0.084
Duodenum	118 ± 36	116 ± 24	23 ± 5	36 ± 8	15 ± 5	−13 ± 7	0.012
Jejunum	100 ± 23	75 ± 14	19 ± 7	23 ± 7	9 ± 2	−3 ± 5	0.046
Ileum	113 ± 39	99 ± 30	19 ± 2	35 ± 8	8 ± 2	−17 ± 8	0.020
Colon	136 ± 15	174 ± 56	32 ± 9	41 ± 17	12 ± 0	−17 ± 9	0.022
Muscle	40 ± 13	48 ± 23	3 ± 1	7 ± 1	5 ± 1	4 ± 2	0.586
Skin	16 ± 7	9 ± 2	0 ± 0	1 ± 0	1 ± 0	0 ± 0	0.226

Note. Nal = naloxone 2 mg/kg + 2 mg/kg·hr, $t = 60$; Sal = saline 10.5 ml + 10.5 ml/hr, $t = 60$.
[a] (ml/min/100 g).

The unpaired Student t test was used for statistical comparisons between treatment responses in any two groups. An analysis of variance (ANOVA) was used to analyze data if more than two populations of animals were compared. P values of less than 0.05 were considered significant.

Results. *Cardiovascular measurements.* No significant differences were detected between the groups for any of the cardiovascular parameters measured during baseline ($t = -30$). Prior to treatment with saline or naloxone at $t = 60$, there were no significant differences between treatment groups in either hypovolemic or normovolemic dogs.

Mean arterial pressure: Removal of 42 ± 2 ml/kg of blood from hypovolemic dogs caused a drop in MAP from control levels (148 ± 4 mm Hg) to 45 mm Hg (Fig. 1). From $t = 0$ to $t = 60$ an additional 20 ± 2 ml/kg of blood was shed. Naloxone treatment increased MAP by 40 ± 6 mm Hg, which was significantly greater than the response seen with saline treatment (−3 ± 5 mm Hg). In normovolemic dogs, no significant difference between naloxone and saline responses was detected.

Maximum left ventricular *dp/dt:* In hypovolemic dogs, LV *dp/dt* fell from 4.2 ± 0.4 to 1.2 ± 0.1 mm Hg·10^3·sec^{-1} during hemorrhage (Fig. 2). Naloxone increased LV *dp/dt* by 2.8 ± 0.2 mm Hg·10^3·sec^{-1} which was significantly greater than the increase of 0.4 ± 0.3 mm Hg·10^3·sec^{-1} seen in saline treated dogs. No significant difference between naloxone and saline responses was detected in normovolemic dogs.

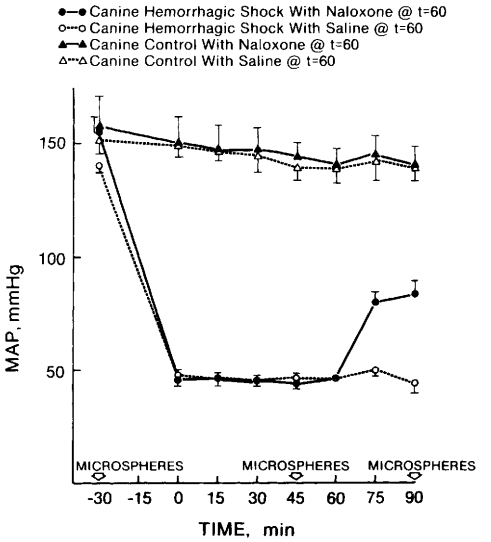

FIG. 1. Mean arterial pressure rises after treatment with naloxone in hypovolemic but not normovolemic dogs.

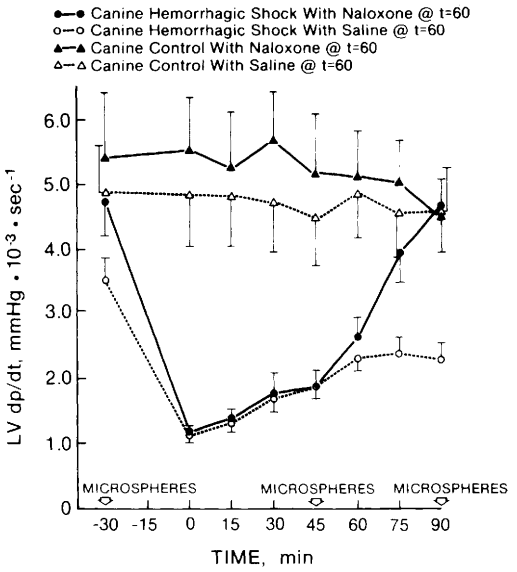

FIG. 2. Maximal left ventricular *dp/dt* rises after treatment with naloxone in hypovolemic but not normovolemic dogs.

Cardiac output: Initially, CO fell during hemorrhage in hypovolemic dogs (Fig. 3) and then modestly increased over the next 45 min. The increase in cardiac output (0.7 ± 0.1 liter/min) seen after naloxone treatment was significantly greater than the increase seen in saline treated dogs (0.2 ± 0.1 liter/min). At t = 45 min, the mean CO of dogs treated with naloxone was less than that of dogs treated with saline. Therefore, though the changes in CO between these two groups were significantly different, the absolute cardiac outputs at t = 90 min were not. Cardiac output fell during the course of the experiment in normovolemic dogs. These modest declines may have been due to anesthesia administrations, microsphere injections, or both. Normovolemic dogs showed no significant difference between the responses to naloxone or saline.

Total peripheral resistance: Resistance rose with initiation of hemorrhage but declined in the later phases of hypovolemia. This fall in resistance was less in naloxone treated hypovolemic dogs than that seen with saline treatment, but the difference was not statistically significant. Normovolemic dogs showed no significant difference between the responses to naloxone or saline (data not shown).

Heart rate: Initially HR increased during hemorrhage, but by t = 0, it had fallen to below control levels. Less than 30 sec after treatment with naloxone heart rate dropped by 25 ± 5 bpm which was significantly different than the response to saline. This response was transient, and by t = 90, no significant difference between the heart rates of naloxone or saline treated dogs was detected. In normovolemic dogs, neither naloxone or saline had a significant effect on heart rate.

Central venous pressure, pulmonary arterial wedge pressure, and left ventricular and diastolic pressure fell with hemorrhage. Neither naloxone nor saline treatment had any significant effect on these parameters (data not shown).

Regional blood flows. The results of analysis of tissue counts in hypovolemic dogs are summarized in Table I. The P values listed are for two-tailed comparisons of the changes in flow between naloxone and saline treatments from t = 45 to t = 90 min. Hypovolemic dogs treated with naloxone exhibited increases in myocardial, intestinal, hepatic, and adrenal blood flow which were significantly greater than the changes seen in saline treated controls. Blood flow to the intraventricular septum is reported for the myocardial

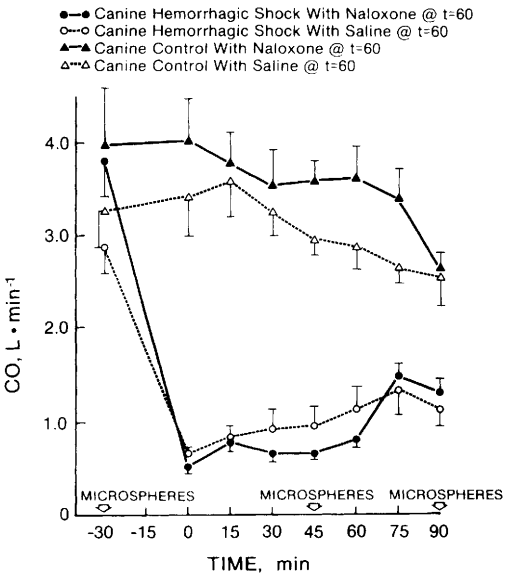

FIG. 3. Cardiac output rises after treatment with naloxone in hypovolemic but not normovolemic dogs.

blood flow, but similar responses were seen in left ventricular free wall tissues. No significant changes in skin, muscle, fat, pancreatic, renal, or brain flows were detected. Blood flow to the cerebral cortex is reported for the brain blood flow, but similar responses were seen in hypothalamic, midbrain, pons, and medullary tissues. The increases in blood flow were not associated with significant changes in vascular resistance. In normovolemic dogs, naloxone had no significant effect on regional blood flow distribution or vascular resistance.

Metabolic effects. Blood gases and pH: Naloxone or saline treatment had no effect on pO_2 or pCO_2 in either group of dogs. The metabolic acidosis that developed during hypovolemia was partially reversed at $t = 90$ by naloxone (pH = 7.24 ± 0) in contrast to the saline treated dogs (pH = 7.15 ± 0.03), and the naloxone treated dogs required significantly less sodium bicarbonate to correct the acidosis (5.2 ± 0.9 vs 11.2 ± 1.0 meq in controls). Normovolemic dogs showed no significant changes in response to naloxone or saline treatments.

Plasma cortisol and ACTH: Changes in plasma ACTH and cortisol are summarized in Table II. Naloxone increased plasma ACTH in normovolemic dogs; however, this increase was not significantly different from the response to saline. Naloxone had no effect on plasma ACTH in hypovolemic dogs. It is possible that naloxone did not increase ACTH secretion in hypovolemic dogs because its release was already under maximal stimulation. Cortisol levels rose during hemorrhage and after naloxone treatment; plasma cortisol increased significantly more than with saline administration and was maintained at a significantly higher level (21 ± 2 μg/dl vs 11 ± 1 μg/dl) than in saline treated dogs. Naloxone had no significant effect on plasma cortisol in normovolemic dogs.

Discussion. Since increased coronary flow can improve coronary function during hypotension (10), it might be argued that cardiac function was limited by poor myocardial perfusion and that naloxone may have induced a coronary vasodilation, which resulted in the improved performance and increases in MAP, LV *dp/dt,* and CO. This is unlikely for two reasons. First, if coronary vasodilation was the mechanism responsible for increased coronary flow, one would expect a drop in resistance, which was not detected. Second, if cardiac performance was limited by coronary flow, cardiac work should increase in proportion to coronary flow. However, in these dogs, cardiac work increased by 274% while left ventricular and septal flows increased by only 132 and 115%, respectively. It therefore seems more likely that naloxone administration was associated with a myocardial stimulation which resulted in increased cardiac performance, including MAP, and that coronary flow increased due to increased perfusion pressure.

One possible mechanism for the increased cardiac work could be an increase in circulating levels of catecholamines. This might have occurred in response to the increased blood flow to the adrenal gland found in our model which may have permitted more catecholamine production and release. Though this possibility cannot be excluded, naloxone

TABLE II. PLASMA ACTH AND CORTISOL LEVELS IN CANINE HEMORRHAGIC SHOCK

	Normovolemic			Hypovolemic		
	$t = -30$	45	90	−30	45	90
			ACTH (pg/ml)			
Saline ($t = 60$)	207 ± 81	286 ± 115	290 ± 116	162 ± 47	805 ± 76	777 ± 325
Naloxone	240 ± 95	283 ± 120	665 ± 117	183 ± 71	1016 ± 321	706 ± 186
			$P = 0.068$[a]			$P = 0.386$
			Cortisol (μg/dl)			
Saline ($t = 60$)	6 ± 3	13 ± 4	19 ± 6	7 ± 3	15 ± 3	11 ± 1
Naloxone ($t = 60$)	7 ± 2	12 ± 4	22 ± 2	5 ± 2	19 ± 2	20 ± 2
			$P = 0.441$			$P = 0.042$

[a] P values are two-tailed comparisons of responses to saline vs naloxone after 30 min of treatment.

treatment of canine hemorrhagic shock has not been associated with significant increases in plasma catecholamines (15). It is also unlikely that increased adrenal catecholamine release was responsible for this cardiac stimulation because naloxone exhibited its usual beneficial effects in cortisol pretreated adrenalectomized dogs which were incapable of adrenal catecholamine release (16).

Since the adrenals also secrete corticosteroids, plasma cortisol might also be expected to increase as adrenal blood flow increased. The effect of naloxone on corticosterone levels in stressed animals is variable (17, 18) but appears to increase cortisol levels in this study. It could be argued that the hemodynamic response to naloxone is due to increased plasma cortisol since glucocorticoids have been shown to increase the inotropic effects of catecholamines when given 2 hr after hypovolemia (19), and this may be due to the corticosteroids' ability to attenuate the desensitization of β-adrenergically mediated adenyl cyclase activity (20). Furthermore, glucocorticoids have been shown to increase catecholamine effects since they are required for biosynthesis (21), potentiate the peripheral vascular effects (22), and inhibit catabolism of catecholamines (23). However, since naloxone improved cardiovascular performance in dogs incapable of synthesizing cortisol (16), the hemodynamic response to naloxone probably is not due to an increase in plasma cortisol.

Increased glucocorticosteroid levels could also improve survival rates by maintaining reticuloendothelial system function (24) or by preventing myocardial depressant factor (MDF) release (25). Naloxone treatment has been shown to reduce MDF levels in cats (26), and the increased steroid levels seen in naloxone treated animals may be partially responsible for this action. Since ACTH levels did not change in hypovolemic dogs, naloxone appears to potentiate the steroidogenic effect of existing ACTH stimulation on the adrenal cortex. Using pharmacokinetic parameters (27), the plasma concentration of naloxone in our dogs was calculated to be about 0.6 μM, a concentration which potentiates ACTH-stimulated corticosterone secretion (28). It is also possible that increased cortisol production was due to increased substrate delivery or increased plasma levels were due to increased "washout" of cortisol secondary to increased adrenal blood flow. A final possible explanation of the increased cortisol level is that naloxone inhibited cortisol metabolism; however, there is no evidence in support of this.

Naloxone may also increase survival by increasing hepatic arterial and intestinal blood flow. Increased blood flow to these organs during hemorrhagic shock has been shown to increase survival (29, 30). Although survival was not determined in this experiment, we have previously shown that naloxone converts this 100% lethal canine hemorrhagic shock model to 100% survival (6).

As naloxone had no significant effect on cardiovascular performance or regional blood flows in normovolemic dogs, it appears that animals must be in shock for naloxone to exert its hemodynamic effects. The response to naloxone in hypovolemic dogs includes increases in cardiac, adrenal, hepatic, and intestinal blood flows, as well as significant increases in plasma cortisol levels. These changes in blood flow and cortisol levels may contribute to the increased survival seen in naloxone treated dogs, but they probably are not responsible for the increases in MAP, LV dp/dt, and CO seen 30 min after treatment.

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