Effects of choline chloride in canine endotoxin shock

by

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INTRODUCTION

Endotoxins are intracellular substances liberated by bacterial disintegration (10, 50). Endotoxin shock can occur clinically in man as a consequence of bacteremias (3, 7) and experimentally in mammals by intravenously injecting endotoxin. The mechanism by which endotoxin produces shock is exceedingly complex (15, 17, 30, 31, 34, 35, 48). The initial reaction to injected endotoxin is a severe drop in blood pressure with a concurrent decrease in central venous return. This first hypotensive phase is correlated to either a pooling of blood in the liver or a decrease in cardiac output. The initial hypotension is followed by a return within thirty minutes of arterial pressure toward normal levels. In one to two hours a second decrease in systemic arterial blood pressure occurs followed by a vascular loss of plasma and a progressive hemoconcentration. The second hypotensive phase occurs when blood pools mainly in the splanchnic bed.

Choline chloride is a vasopressor drug which may be of therapeutic value in treating endotoxin shock. Mitchell (32) demonstrated some of its systemic effects following intravenous injection into normal mongrel dogs. Choline chloride increased the left ventricular systolic pressure in the heart. The ability of choline chloride to raise left

ventricular pressure may be explained by an increase in the force of cardiac contraction. The systemic arterial blood pressure is increased by choline chloride. Mitchell postulated that the increase in systemic arterial blood pressure was caused by the cardiac-stimulating ability of the drug and not by vasoconstriction. Unlike many vasopressor drugs, choline chloride produces its cardiac-stimulating response without producing extrasystoles or other cardiac arrhythmias. Furthermore, the respiratory rate is stimulated by choline chloride.

Engen (11) observed that choline chloride reversed the hypotensive effects of intravenously injected histamine. After histamine administration, the drop in arterial blood pressure returned to near normal values after choline chloride injections.

The effects produced in normal dogs after intravenous injection of choline chloride suggest that it may be an effective therapeutic agent for endotoxin shock. To demonstrate this, experimental shock was produced in dogs with E. coli endotoxin.

The objective of this study was to determine the efficiency of choline chloride in reversing the signs of endotoxin shock and increasing survival rates following administration of lethal doses of endotoxin.

LITERATURE REVIEW

Gram-negative bacteriemias were recognized early in the 19th century (42). Laennec (23) in 1831 and Boise (8) in 1897 described circulatory failure occurring with bacterial infection. In 1943, Fine and Saligman (13) observed that patients with overwhelming bacterial infections such as those from coli-form organisms in the peritoneal cavity, female reproductive organs, or the urinary tract were similar to patients with traumatic shock. In 1945, Aub, et al.(2) discovered that the muscle fluid from an ischemic canine muscle contained toxins that produced shock in test animals. The endotoxins were of anaerobic organisms. In 1951, Waisbren (42) described two clinical pictures with gram-negative bacteremias which had the gross appearance of toxicosis and shock.

Endotoxin shock caused by a bacteremia is a predominant problem in human medicine (3, 7) and is a known problem in canine medicine (22). The death rate of patients that develop endotoxin shock from bacteremia ranges between 50% to 80% (49). Bacterial endotoxin shock may occur in humans with urinary tract and pneumonic infection and in dogs with peritonitis, acute metritis, and certain acute enteric and urinary tract infections. Gram-negative bacteria seem to be the most common etiologic agents, including: Escherichia coli, Pseudomonas aeruginosa, Brucella melitensis, Salmonella

typhosa, and Serratia marcescens (3, 7, 22).

Endotoxins are intracellular substances liberated by bacterial disintegration. They constitute a relatively homogenous group of substances that exist as protein-polysaccharide-lipid complexes in the cell. Toxicity has been associated with phosphorous containing nitrogenous substances that make up a relatively small part of the complex. The endotoxin complex is highly antigenic but the toxicity is not effectively neutralized by antibody (10, 51).

The mechanism by which endotoxin produces shock is exceedingly complex and many views exist as to the importance of each of the responses resulting from endotoxin administration. There is a definite pattern of hemodynamic events and hemodynamically related events which occur after intravenous endotoxin injection. The initial reaction in the dog is usually a rapid drop in systemic blood pressure with a concurrent decrease in central venous return (46). The decreased blood pressure and venous return may be caused by a rapid pooling of blood in the liver as a result of transient hepatic venous constriction produced by histamine release (17, 30, 31). Rosenberg, et al. (34) suggested that the initial decrease in cardiac output arose from an acute cor pulmonale produced by the occlusion of pulmonary capillaries by vasospasm. This could permit damming of blood in the portal system.

The initial hypotension is usually followed by a return of arterial pressure toward normal levels, usually within thirty minutes. This may be explained by the release of pooled blood from the liver and an increase in catecholamine levels stimulated by the baroreceptor reflex (15, 31, 34, 35). Within one to two hours of the original intravenous injection of endotoxin the arterial blood pressure drops again. The final prolonged hypotension results from a peripheral pooling of blood with the vasculature of the small intestine containing the greatest volume of blood (17, 31, 46). During the later part of the second hypotensive phase, there is a loss of plasma and a progressive hemoconcentration (25, 48). Microcirculation at this time is characterized by dilated arteriolar sphincters and congested capillaries (26). The mucosa of the bowel becomes congested and a transudate which is first clear and then bloody collects in the lumen. There may be a bloody diarrhea presumably caused by the necrosis and sloughing of the intestinal mucosa as the result of intravascular clotting, ischemia, and anoxia (12).

Electrocardiographic recordings taken during experimentally produced endotoxin shock reveal three abnormalities: a reduction in voltage in the R wave with a prominent T wave elevation (11); ST segmental depressions (1, 12); and terminal arrythmias (12). The heart and respiratory rates of dogs in endotoxin shock are variable (12, 43).

Metabolic acidosis develops during the secondary hypotensive phase. The intensity of acidosis is related to the hemoconcentration and hypotension (38, 47, 48). Oliguria or anuria which occur during the second hypotensive phase are produced by a reflex renal vasoconstriction and also the hypotensive state. Decreased renal filtration enhances acidosis (12, 36, 38).

After blood is pooled, additional pathological events develop which, if untreated, lead to irreversible shock. Hardaway (14) demonstrated a hypercoagulability of the blood and the formation of microthrombi in the peripheral circulation. He suggested that this physical obstruction to the flow of blood in addition to intense vasoconstriction might account for the death of vital tissues and thereby cause irreversible shock. Evangelista, et al. (12) demonstrated that plugging of mucosal capillaries by clots occurred during the second hypotensive phase. Robb (33) observed that platelet microembolism occurs in animals during endotoxin shock and that embolic occlusion of the hepatic circulation could account for damming of blood in the portal system.

Although the exact role of endogenous vasoactive agents in the development of irreversible shock has not been established, they may be related to the peripheral pooling of blood (4). Lillehei and MacLean (29) reported that vessels in

the bowel mesentery constricted until they were scarcely visible following an intravenous injection of E. coli endotoxin. Prior injections of the alpha adrenergic blockers, chlorpromazine and dibenzyline were effective in preventing shock (27, 28). Lillehei, et al. (26) examined the microculation in the viscera of dogs and found the arterioles and venules in vasospasm. Splanchnic organs suffered profound decrease in arterial blood flow. Siegel, et al. (37) observed that precapillary arteriolar vasoconstriction occurred late after intravenous endotoxin injection and was manifested by parallel capillary resistances of low value. In contrast to normal shunting over which some degree of sympathomimetic control exists, there was a relative paralysis of regulatory control over shunts. The degree of arteriovenous shunting was then a passive consequence of the increase in flow and the presumable cause of the pooling of blood.

Lillehei, et al. (26) proposed a theoretical sequence of events to be common to hypovolemic, neurologic, and septic shock. At the onset of severe hypotension, there is an increase in secretion of corticosteroids and epinephrine from the adrenal gland. There is increased sympathetic nerve activity which liberates norepinephrine at the myoneural junctions, which causes an intense vasoconstriction at the precapillary arteriolar sphincters in the viscera, the skin

and to a lesser extent in the muscles. The purpose of this is to preserve blood flow to the brain and to the heart. The cerebral and coronary circulatory systems are not strongly effected by catecholamines. The affected tissues are pale and almost bloodless. This phase may be reversed by prompt use of fluid therapy to restore the normal circulatory dynamics. If shock is prolonged the situation progresses because of anoxia of tissues and accumulation of metabolic products, which leads to acidosis. Thus, sympathomimetic amines must be secreted in greater amounts to produce the same effects. If these conditions of shock prevail for a long period, the venule sphincters maintain tone but the arteriole sphincters do not. With the loss of arteriole sphincter constriction, blood passes into the capillary beds in increased amounts but cannot escape. The hydrostatic pressure in the capillaries increases above the colloid osmotic pressure and fluid is forced from the vasculature. As stagnation proceeds, capillaries lose integrity, allowing whole blood to suffuse into the tissues. This is the point of irreversible shock.

It has been questioned whether the alteration in cardiac performance results from a direct depressant effect of endotoxin on the heart or the hypotension. Weil, et al. (46) reported that in the hypotensive state of endotoxin shock there was a fall of 21% to 36% in the cardiac output.

However, the inferior vena cava pressure was unaffected, indicating that the fall in cardiac output could not be attributed to congestive heart failure. They suggested that pooling decreased venous return and in turn cardiac output.

Siegel and Fabian (36) reported that endotoxin depressed the myocardium in normal dogs and also in dogs with baroreceptor and chemoreceptor afferent nerves and vagal sympathetics sectioned. A decrease in contractility occurred before a substantial drop in arterial blood pressure and was progressive in all denervated animals which could not elicit reflexed contractility. Slow intravenous infusion of norepinephrine isoproterenol caused a marked reversal of the negative inotropic effect, without a substantial increase in the blood pressure. When isoproterenol was discontinued, contractility decreased to the level produced by endotoxin.

Starzecki and Spink (40) measured myocardial function and peripheral hemodynamic alterations in late stages of experimentally produced endotoxin shock in dogs. Analysis of the left ventricular functional curves indicated a decreased myocardial contractility with progressive rise in left ventricular end diastolic pressure, a rise in central venous pressure, and a declining arterial blood pressure. Their observation suggested that the mechanism of death is primarily of cardiac origin at the terminal stages of endotoxin shock.

Wangensteen, et al. (43) and Lefer (25) suggested that reduced splanchnic blood flow occurring during shock, including endotoxin shock, was the triggering cause for the production of a myocardial depressant factor. A reduced splanchnic blood flow caused the release of proteases from the splanchnic organs. Proteases are carried to the blood vasculature via the lymphatics and produce the myocardial depressant factor from blood proteins.

Histamine produces vasodilation by a direct action on small blood vessels and has been implicated in the hypotensive state of endotoxin shock. Weil and Spink (50) injected intravenously E. coli endotoxin into dogs. Histamine was detected in plasma samples within one or two minutes after the injection of endotoxin. Elevated histamine concentrations coincided with the second precipitous fall in the arterial blood pressure.

Hinshaw, et al. (18) reported that plasma histamine concentrations increased after E. coli endotoxin injection. After an initial transient decrease, whole blood histamine concentrations increased and remained elevated following endotoxin injection.

Hinshaw, et al. (16) conducted a comparative study of hemodynamic actions of histamine and endotoxin. A histamine releaser, histamine, and E. coli endotoxin were each administered intravenously into dogs. All agents produced a

rapid decrease in systemic arterial pressure and an early increase in portal venous pressure which was coincidental with a decrease in venous return.

Hinshaw, et al. (19) performed a series of experiments by perfusing an isolated dog's leg with blood from an intact dog in endotoxin shock. Vascular response of the perfused leg to pressor agents appeared abnormal in that the small vein constriction was more prolonged than the arterial constriction. The isolated leg gained weight indicating that a collection or pooling of blood occurred. In late endotoxin shock, the arterial vasodilation response to injected histamine became progressively greater. The authors suggested that the irreversible period of endotoxin shock could be a combination of abnormal pressor responses by the pre- and post-capillary segments and the increased sensitization to histamine.

Vick (41) presented data that supports histamine as the "trigger" in the mechanism of endotoxin shock. He isolated saphenous veins and measured their contractile responses while being bathed by plasma, platelets, and endotoxin. This combination produced a decreased contractile response which resembled that of histamine. Furthermore, the response was blocked by antihistamines. Vick concluded that endotoxin and some "required substance" in plasma combine to release histamine from platelets. Histamine may be

the factor involved in the mechanism of the initial hypotensive phase of endotoxin shock.

Weil and Miller (47) and Spink and Vick (38) administered E. coli endotoxin intravenously into anesthetized dogs. Metaraminol was infused intravenously fifteen minutes after the injection of E. coli endotoxin. Metaraminol maintained arterial blood pressure at near control levels and increased the survival time by two to three hours.

Starzecki, et al. (40) intravenously injected dogs with various dosages of E. coli endotoxin. One hour after injection, isoproterenol was infused at a fixed rate over four hours. Isoproterenol reduced the mortality rates significantly in all but the greatest challenge doses.

Loeb, et al. (29) demonstrated that dopamine was superior to either isoproterenol or norepinephrine when treating human patients in infectious shock. Dopamine exerts positive inotropic and chronotropic effects similar to those of norepinephrine. Dopamine, however, causes a nonadrenergic vasodilatation in the mesenteric and renal vascular beds whereas norepinephrine causes vasoconstriction in these beds. Isoproterenol could not sustain blood pressure because of the widespread vasodilatation produced in skin and skeletal muscle. Dopamine maintained mean arterial blood pressure in all but a few cases. Norepinephrine treatment resulted in higher mean arterial pressure than dopamine. Mean urine

flow was similar with both agents. Because dopamine produced higher cardiac output and lower left ventricular end diastolic pressure than norepinephrine, it was considered the more desirable of the two.

Lansing and Hinshaw (24) treated dogs with dopamine thirty minutes prior to giving E. coli endotoxin. They observed that dopamine increased cardiac output and that this increase persisted during the post-endotoxin period. Systemic arterial pressure was supported only during the early post-endotoxin period. The increase in cardiac output was a function of an increase in venous return and a reduction in peripheral resistance. Dopamine may have alpha-adrenergic action in the hepatic bed and beta-adrenergic action in the extra hepatic regions. This may prevent the pooling of blood and shunt the blood into extrahepatic regions where vasodilatation favors an increase in blood flow to the posterior vena cava. The increase in cardiac output was a function of dopamine's inotropic and chronotropic effects.

Starzecki and Spink (40) and Siegel and Fabian (36) infused isoproterenol during late endotoxin shock in dogs. Isoproterenol markedly improved myocardial function, stabilized a declining arterial blood pressure and slowed the heart. The left ventricular end diastolic pressure was also reduced with isoproterenol.

Weil, et al. (44) diverted blood in dogs from the anterior

and posterior vena cava to a reservoir. The blood collected was pumped at a constant rate to the right atrium. When endotoxin shock was produced by injecting E. coli endotoxin intravenously, a sharp decline in venous return occurred. When the decline was established, metaraminol was injected intravenously. The initial dose was given three and one-half minutes after the decline and supplementary doses were injected at one and one-half to eight-minute intervals thereafter. Metaraminol promptly halted the decline in venous return and, in fact, slightly increased the venous return. The authors suggested that metaraminol stopped the early pooling of blood associated with the decline in venous return following injection of endotoxin. In similar experiments using a variety of vasopressor agents, Weil, et al. (45) observed that angiotensin, methoxamine, phenylephrine and epinephrine elevated the arterial blood pressure and reduced the venous return. Metaraminol and norepinephrine elevated the arterial blood pressure and increased venous return.

Many investigators believe that alpha-adrenergic stimulation in the vascular beds should be blocked in an attempt to reverse the vascular abnormalities produced during endotoxin shock. The vasoconstriction produced is detrimental to adequate perfusion of vascular beds. Alpha-adrenergic blockers like phenoxybenzamine, chloropromazine, and di-

benzyline have been used with beneficial effects (9, 20, 27, 28).

Berk, et al. (5, 6) suggest that there may be excessive beta adrenergic stimulation during endotoxin shock. Dogs treated with propranolol hydrochloride, a beta-adrenergic blocker, showed increased survival rates correlating with improved parameters of tissue perfusion consistent with the closure of arteriovenous shunts. Human patients in late septic shock which were refractory to conventional treatment showed improved hemodynamic patterns and increased survival rates when treated with propranolol.

The mechanism by which endotoxin produces shock is exceedingly complex. The first hypotensive phase is correlated to either a pooling of blood in the liver or a decrease in cardiac output. The second hypotensive phase occurs when blood pools in the splanchnic bed. A direct depressant effect by endotoxin on the heart has also been suggested, as a cause of pooling. Vasoactive drugs have been used in efforts to reverse endotoxin shock. No single drug appears to be satisfactory, but dopamine and metaraminol have exhibited the most potential for reversing endotoxin shock.

MATERIAL AND METHODS

Six control beagle dogs 9 to 12 months old were injected intravenously with Escherichia coli endotoxin[1] to induce endotoxin shock. A dosage of 1.54 mg/kg produced severe shock and death in five of the dogs. The sixth dog survived despite signs of severe shock. Two dogs were each given 1.54 mg/kg of E. coli endotoxin and were infused with choline chloride in an effort to reverse the cardiovascular hypotension. The infusion rate was to be adjusted to maintain a persistent elevation near that of the control arterial blood pressure. Four other dogs that received choline chloride were given intravenous injections at either 5.0 mg/kg or 10.0 mg/kg in an effort to maintain a persistent elevation near that of the control arterial blood pressure. The intravenous injection dosages were reported by Mitchell (32) to produce significant elevations in arterial blood pressure.

Dogs were anesthetized with 2% sodium thiopental (Dipentol).[2] An endotracheal tube was inserted and methoxyflurane (Metofane)[3] was administered in a Heidbrink

[1]Difco Laboratories, Detroit, Michigan; B. G. Coli: 0/27:B8.

[2]Diamond Laboratories, Inc., Des Moines, Iowa.

[3]Pitman-Moore Division of the Dow Chemical Company, Indianapolis, Indiana.

Veterinary Anesthesia Machine[1] to maintain general anesthesia.

A skin incision was made posterior to the larynx and 1 cm lateral to the trachea. The sternohyoideus muscle was bluntly separated from the sternomastoideus muscle which exposed the carotid artery and vagosympathetic trunk. The vagosympathetic trunk was separated from the carotid artery. The carotid artery was catheterized with a 1 mm diameter poly-vinyl catheter. A purse string suture with 2-0 silk was placed in the carotid artery around the catheter to prevent hemorrhage and to allow for closure of the vessel incision after removal of the catheter.

Through the same skin incision, the jugular vein was isolated and a 14 gauge indwelling catheter[2] was inserted. A purse string suture with 2-0 silk was placed in the jugular vein around the catheter. All injections were made through this catheter. After each injection the indwelling catheter was flushed with heparinized saline to complete administration of all materials and prevent blood clotting.

Hemodynamic parameters and respiration were monitored with a Beckman Type R dynograph recorder[3]. One channel was

[1]Ohio Chemical and Surgical Company, Madison, Wisconsin.

[2]Sherwood Medical Industries, Inc., St. Louis, Missouri.

[3]Beckman Instruments, Inc., Schiller Park, Illinois.

connected to a Statham P23 Db pressure transducer[1] for recording left carotid artery blood pressure. On the second channel, the electrocardiograph (Lead II) was recorded on each dog. A third channel was connected to a thermistor[2] which was inserted in the endotracheal tube to monitor respiration.

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[1]Statham Laboratories, Inc., Hato Rey, Puerto Rico.

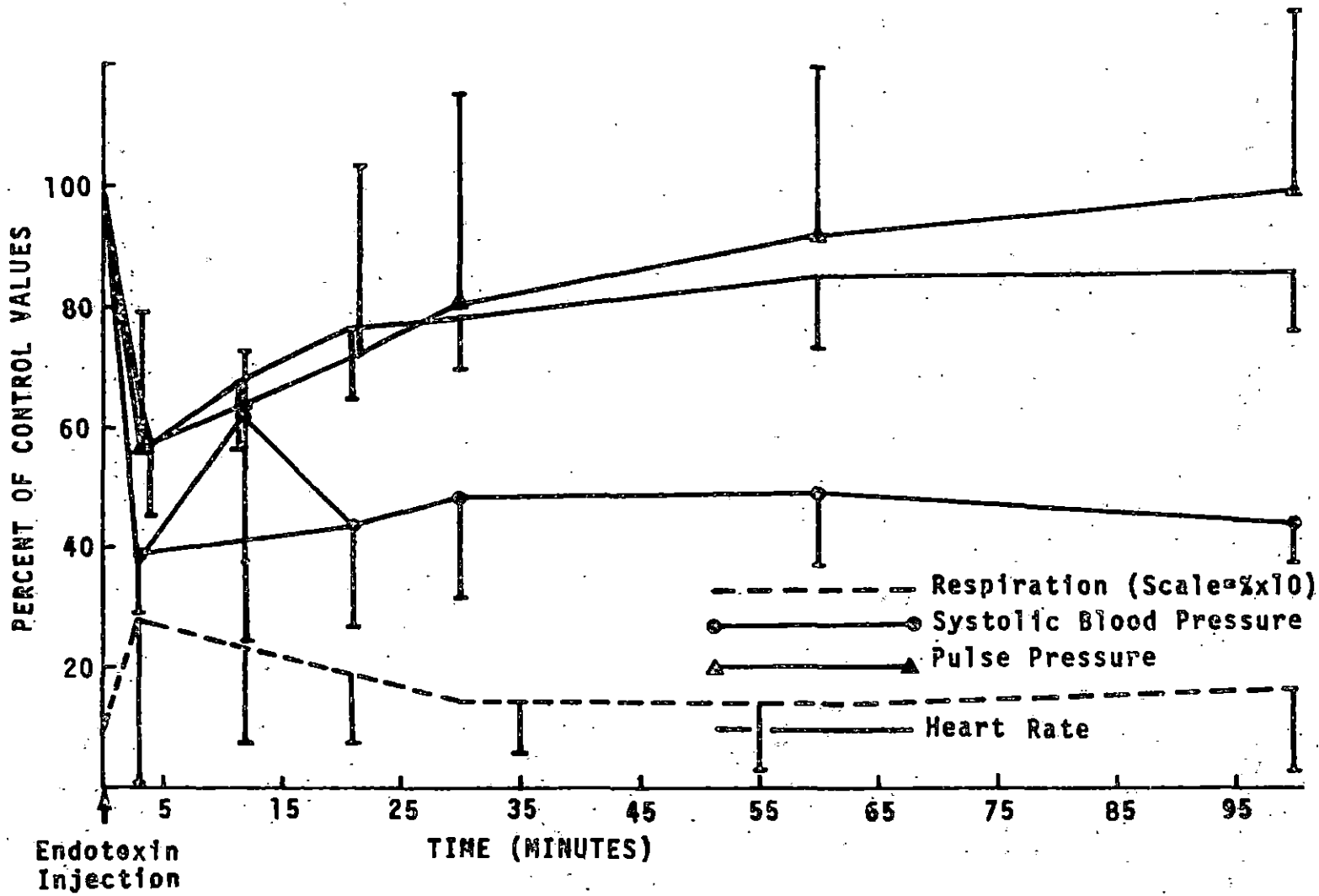
[2]Klem, R. W. and F. B. Hembrough. Nov. 15, 1966. "Inexpensive Monitoring of Cardiovascular and Respiratory Functions During Surgery". Journal of American Veterinary Medical Association 149: 1297-1302.

RESULTS

Control Dogs

The effects of intravenously injected E. coli endotoxin on the physiological variables of the 6 control dogs are summarized in Graph 1 and in Tables 1 through 10 in the Appendix. The average percentage of control values was calculated. In Graph 1, the systolic blood pressure, heart rate, pulse pressure and respiration rate are recorded for the specific time intervals of 3, 12, 21, 30, 60, and 100 minutes after endotoxin injection. E. coli endotoxin caused the systolic blood pressure to precipitously fall to an average of 40% of the preinjection values in 3 minutes and was at 48% and 44% of control values at 30 and 100 minutes, respectively. The E. coli endotoxin decreased the heart rate and pulse pressure to 56% and 46% of control level. The pulse pressure returned to control level and heart rate of 80% of control level by 100 minutes.

Respiration rate varied greatly among animals. In some of the animals, especially dog 5 and dog 6, abnormal respiratory rhythm and shallow tidal volumes occurred which increase the variability.



Graph 1. Physiological variables of six control dogs for the first 100 minutes after endotoxin injection

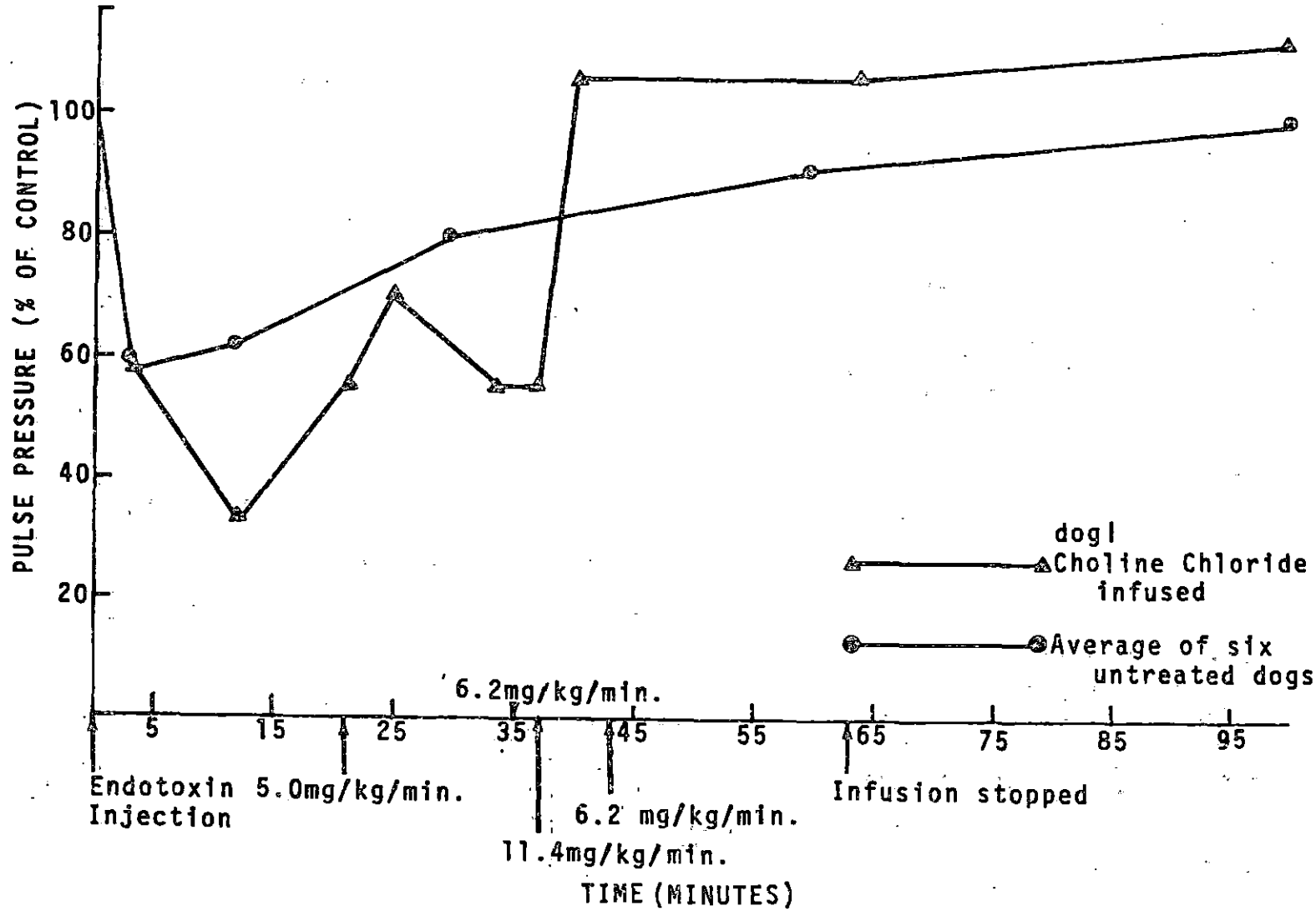
Choline Chloride Treatment Group

The results of treating dogs in endotoxin shock with choline chloride by either infusion or injection are in Graphs 2 through 13 and in Tables 11 through 16 in the Appendix. Choline chloride infusions and injections did elevate the systolic blood pressure initially. After initial infusions and injections, the dog's systolic blood pressure did not respond well to successive injections as seen in Graphs 3, 5, 7, 9, 11, and 13. The blood pressure of treated dogs 1 and 3 were elevated by choline chloride and remained for extended periods without additional choline chloride (Graphs 3 and 7).

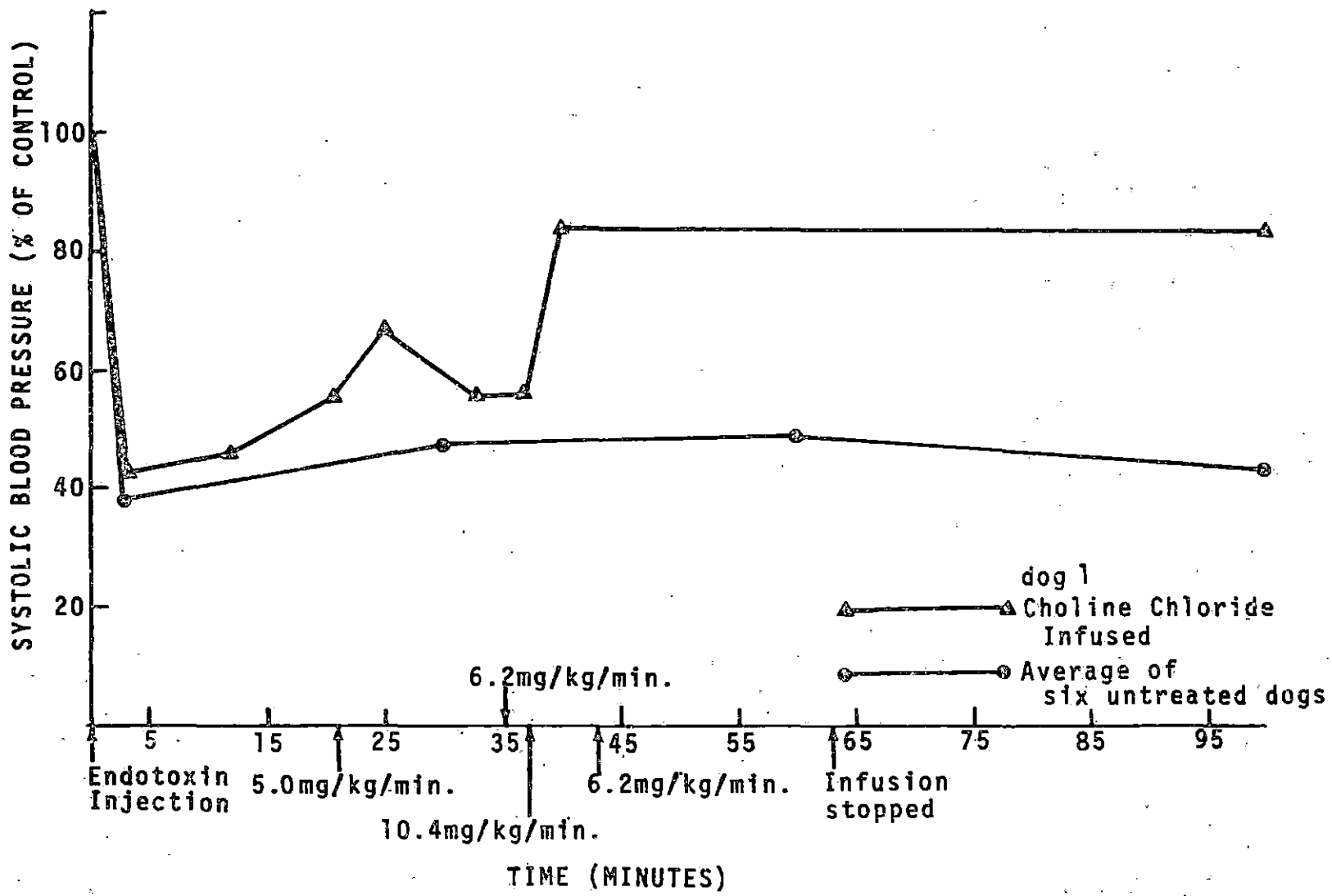
The pulse pressure was increased by choline chloride administration as seen in Graphs 2, 4, 6, 8, 10, and 12. The increase in systolic blood pressure seems related to a simultaneous increase in pulse pressure which was sustained only in dog 1 and dog 3.

Choline chloride did not produce consistent positive effects on respiratory rate or heart rate.

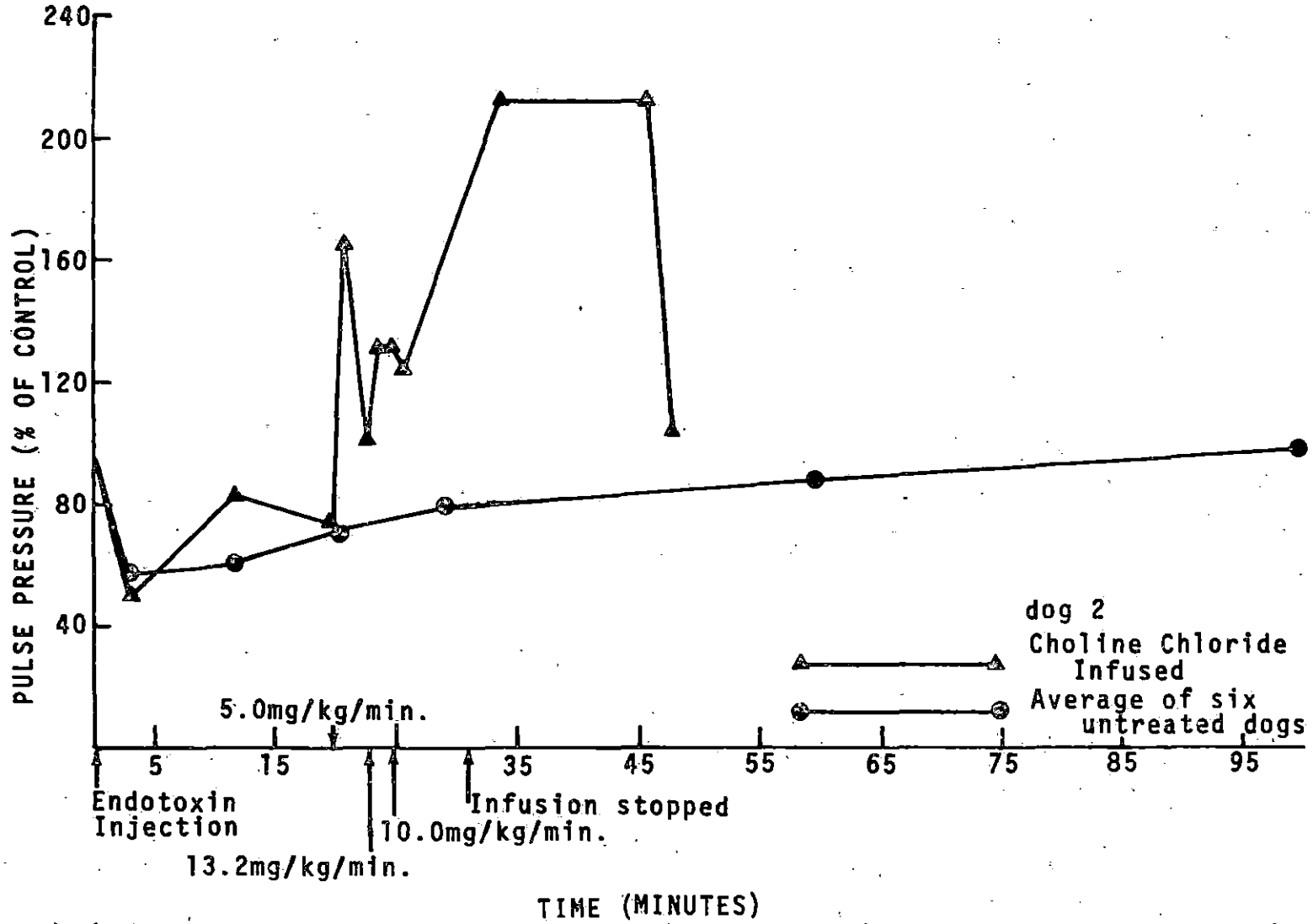
During the infusion of the first two experimental dogs, skeletal muscular twitching, hypersalivation, hypermotility of the intestinal tract, and pulmonary moist rales occurred. All subsequent animals were atropinized before being treated with choline chloride. In the third, fourth, and fifth dogs,



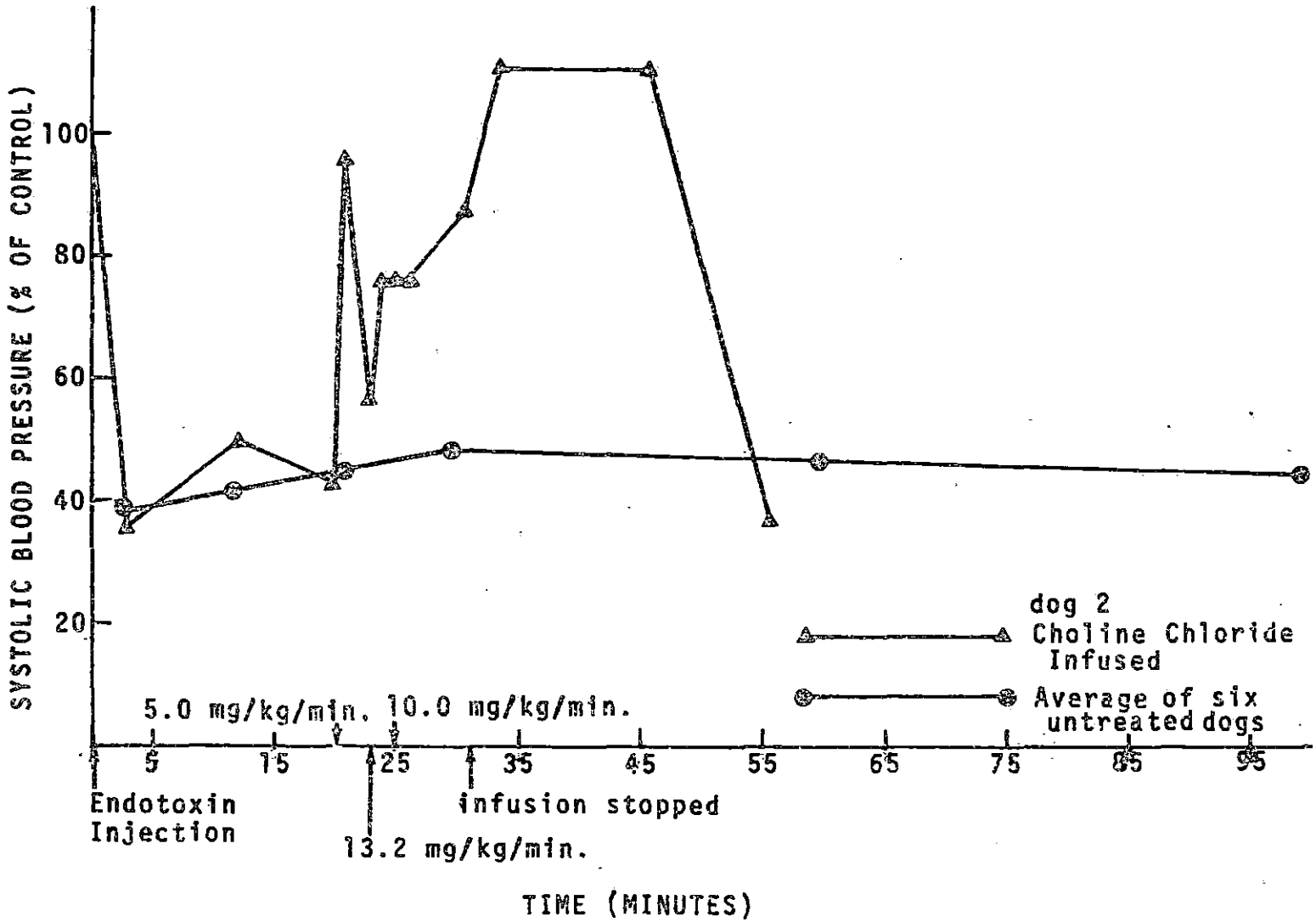
Graph 2. Pulse pressure of treated dog 1 during intravenous infusion of choline chloride



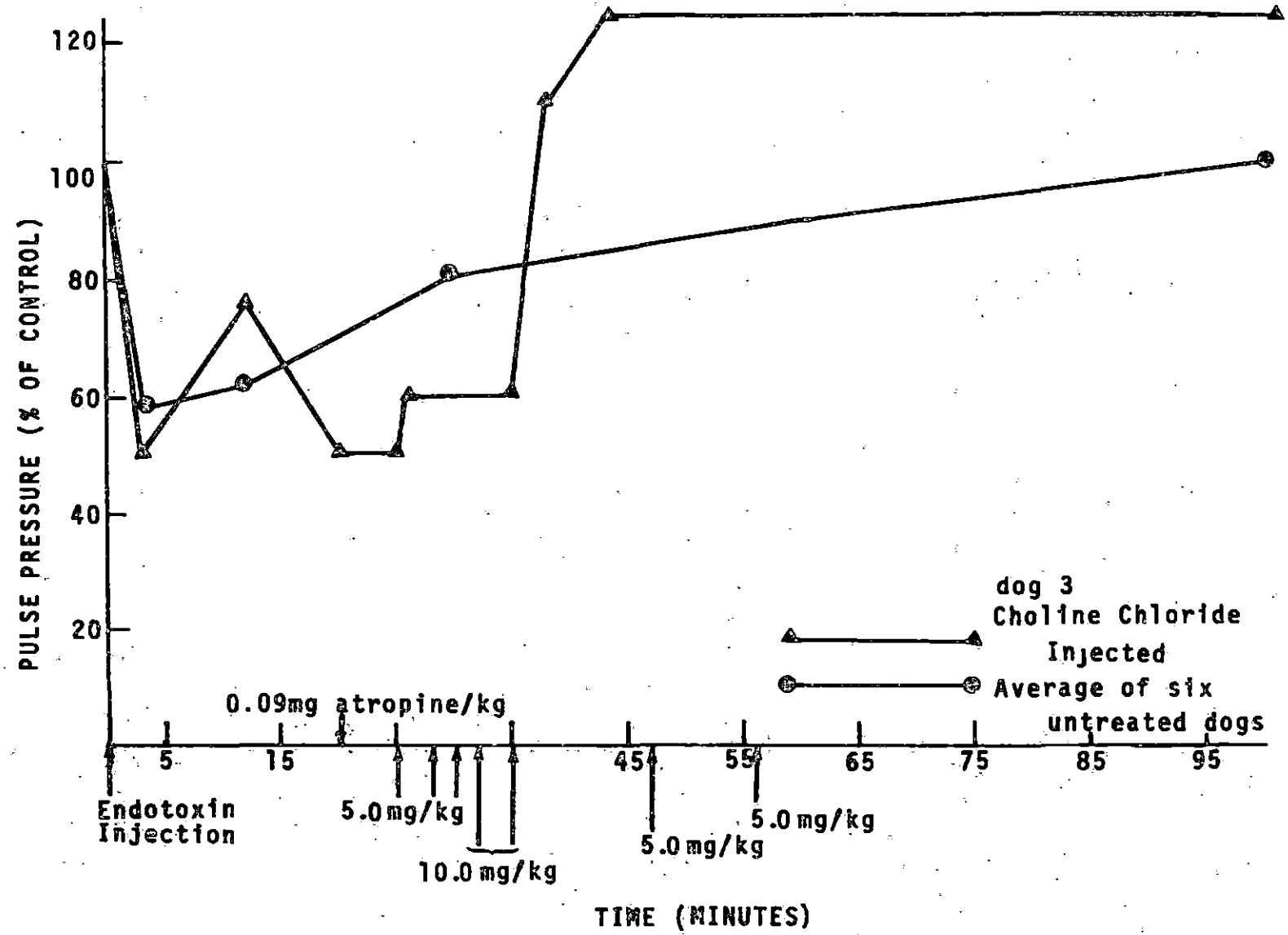
Graph 3. Systolic blood pressure of dog 1 during intravenous infusion of choline chloride



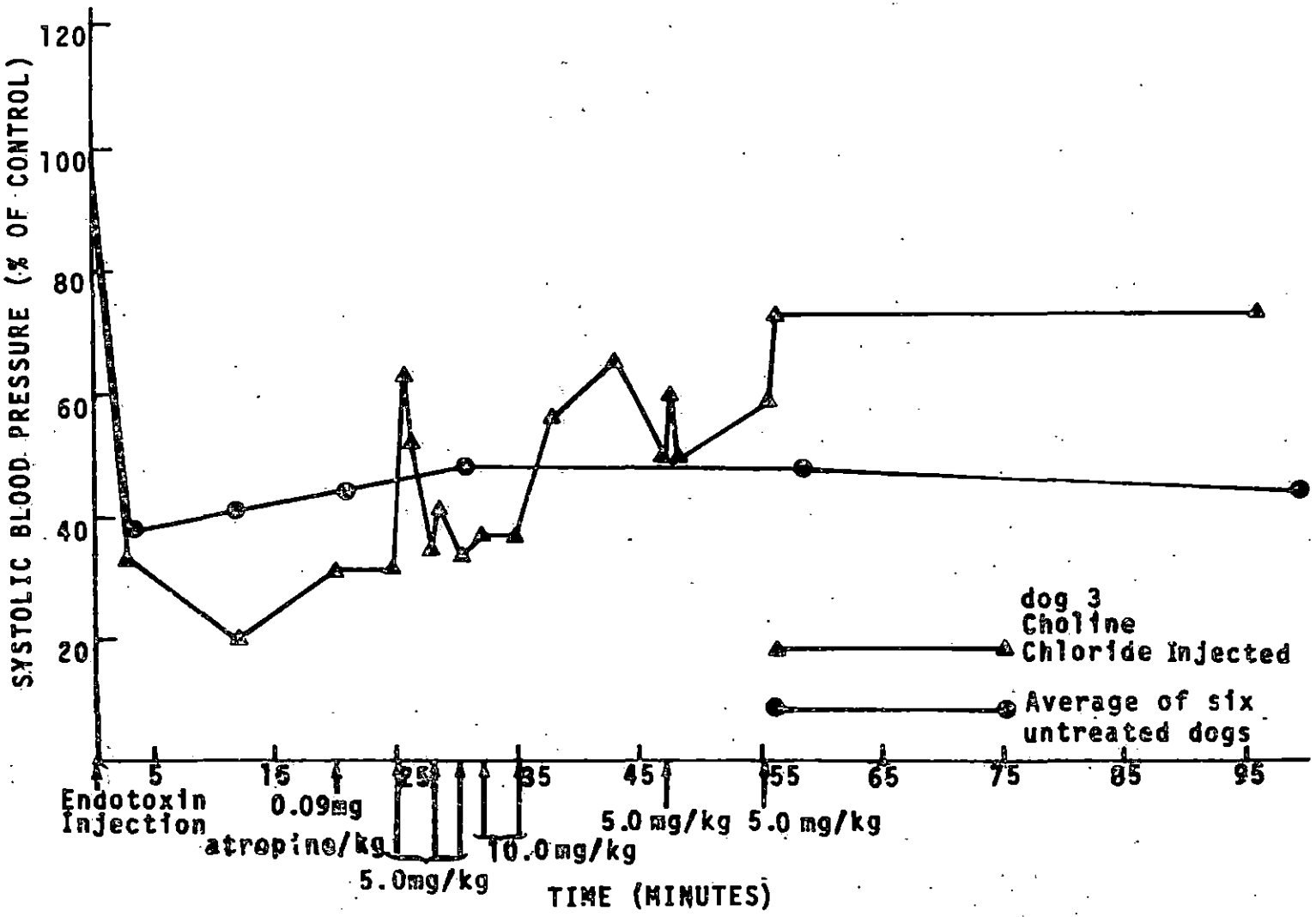
Graph 4. Pulse pressure of dog 2 during intravenous infusion of choline chloride



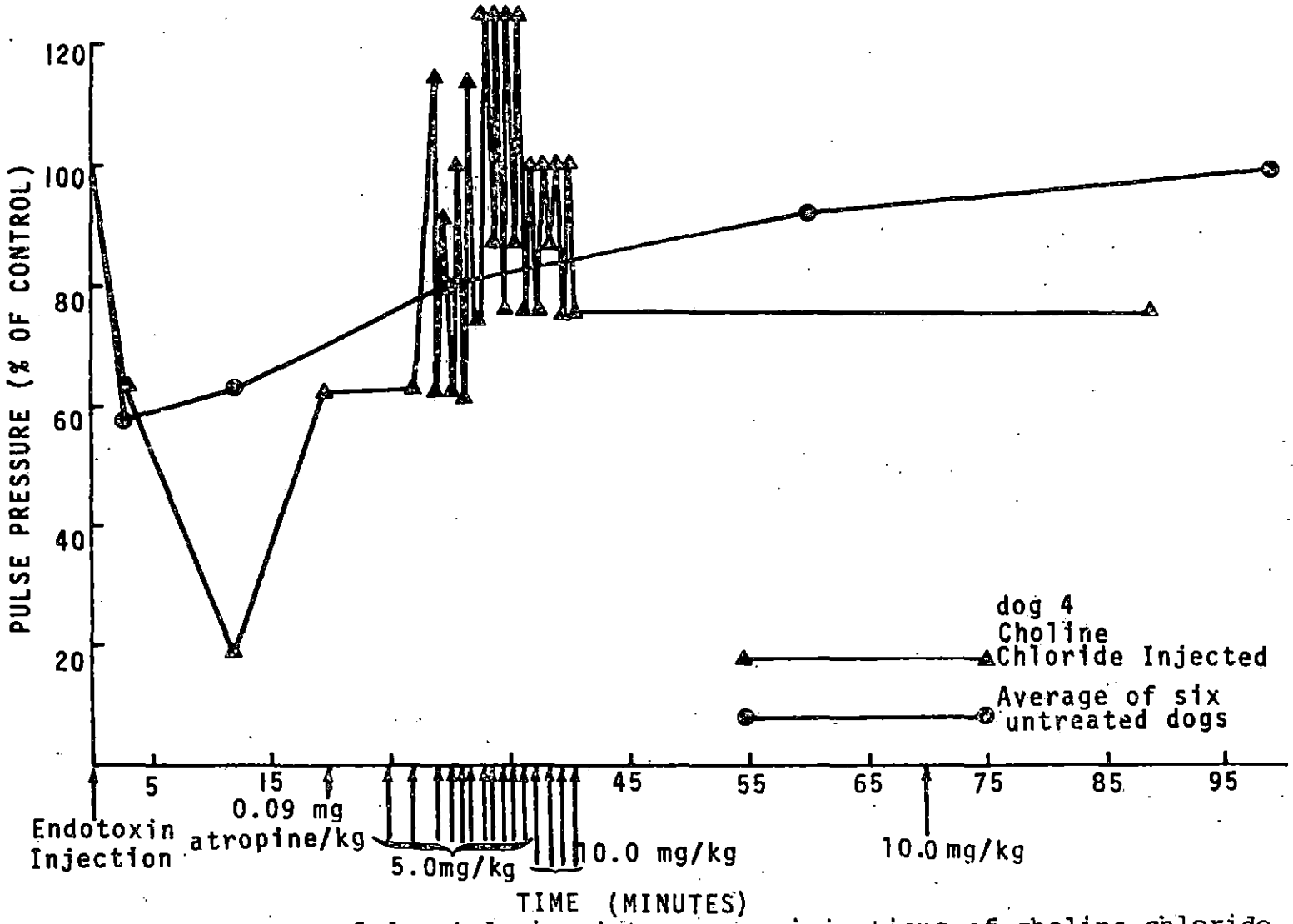
Graph 5. Systolic blood pressure of dog 2 during intravenous infusion of choline chloride



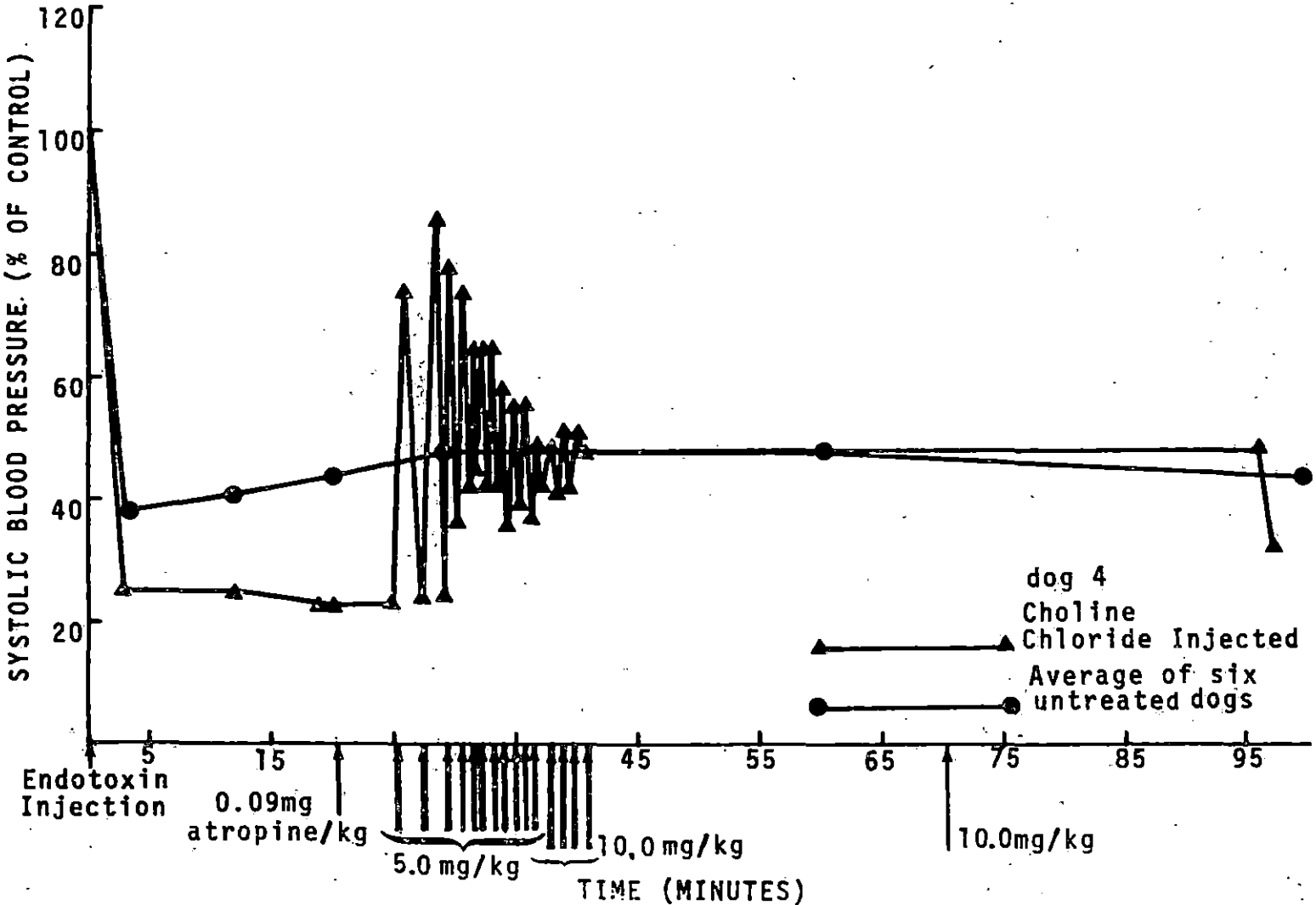
Graph 6. Pulse pressure of dog 3 during intravenous injections of choline chloride



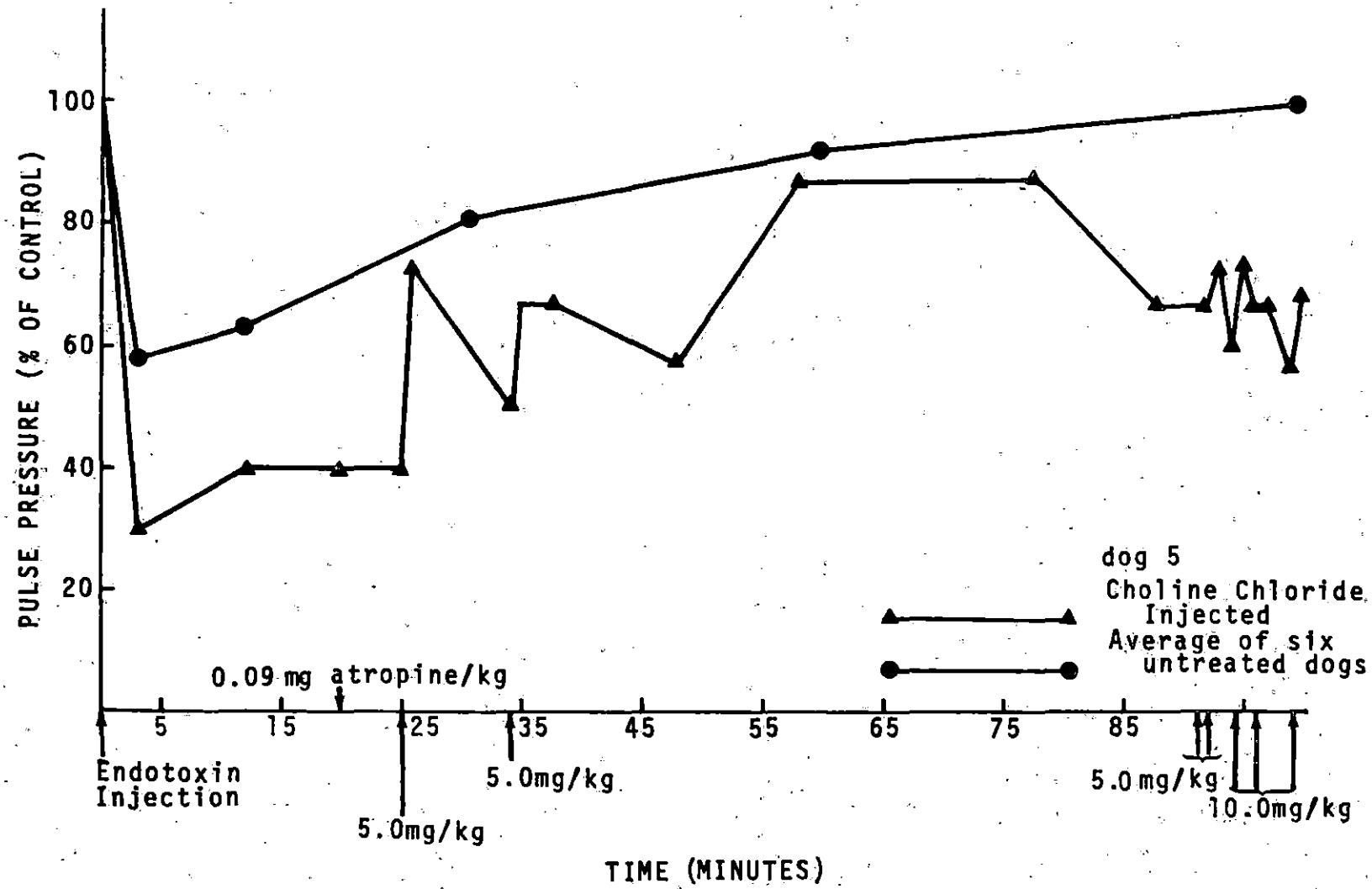
Graph 7. Systolic blood pressure of dog 3 during intravenous injections of choline chloride



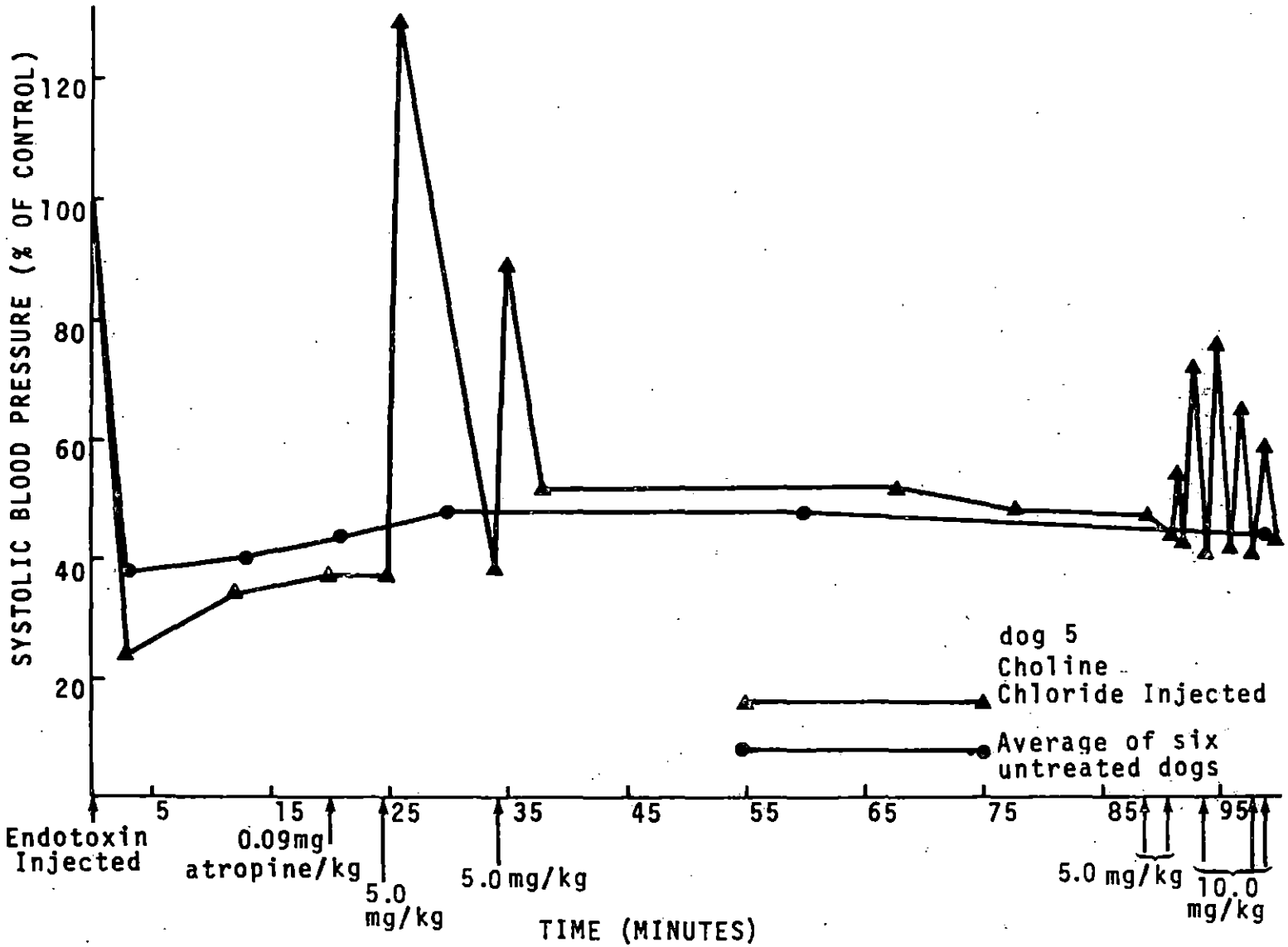
Graph 8. Pulse pressure of dog 4 during intravenous injections of choline chloride



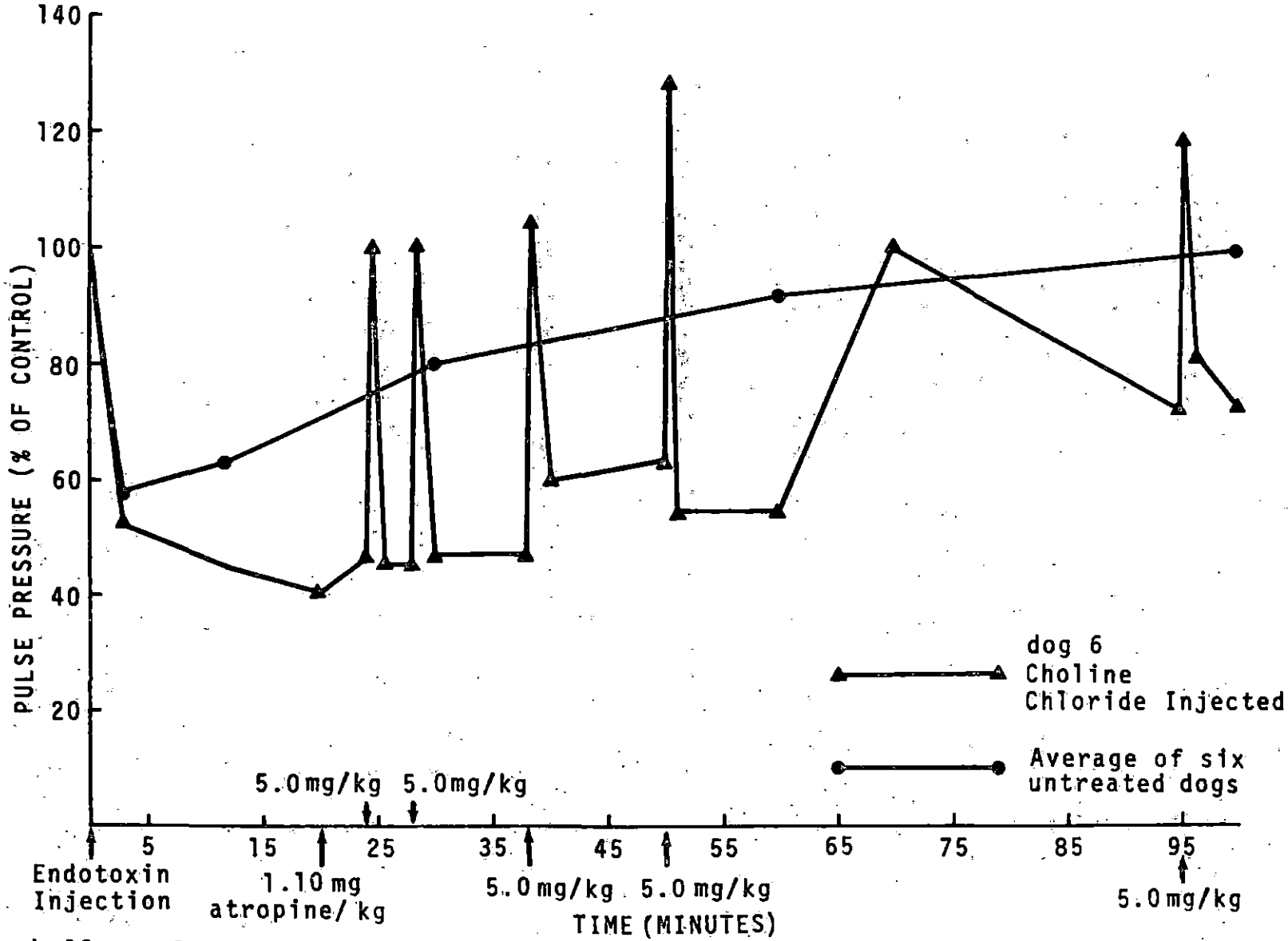
Graph 9. Systolic blood pressure of dog 4 during intravenous injections of choline chloride



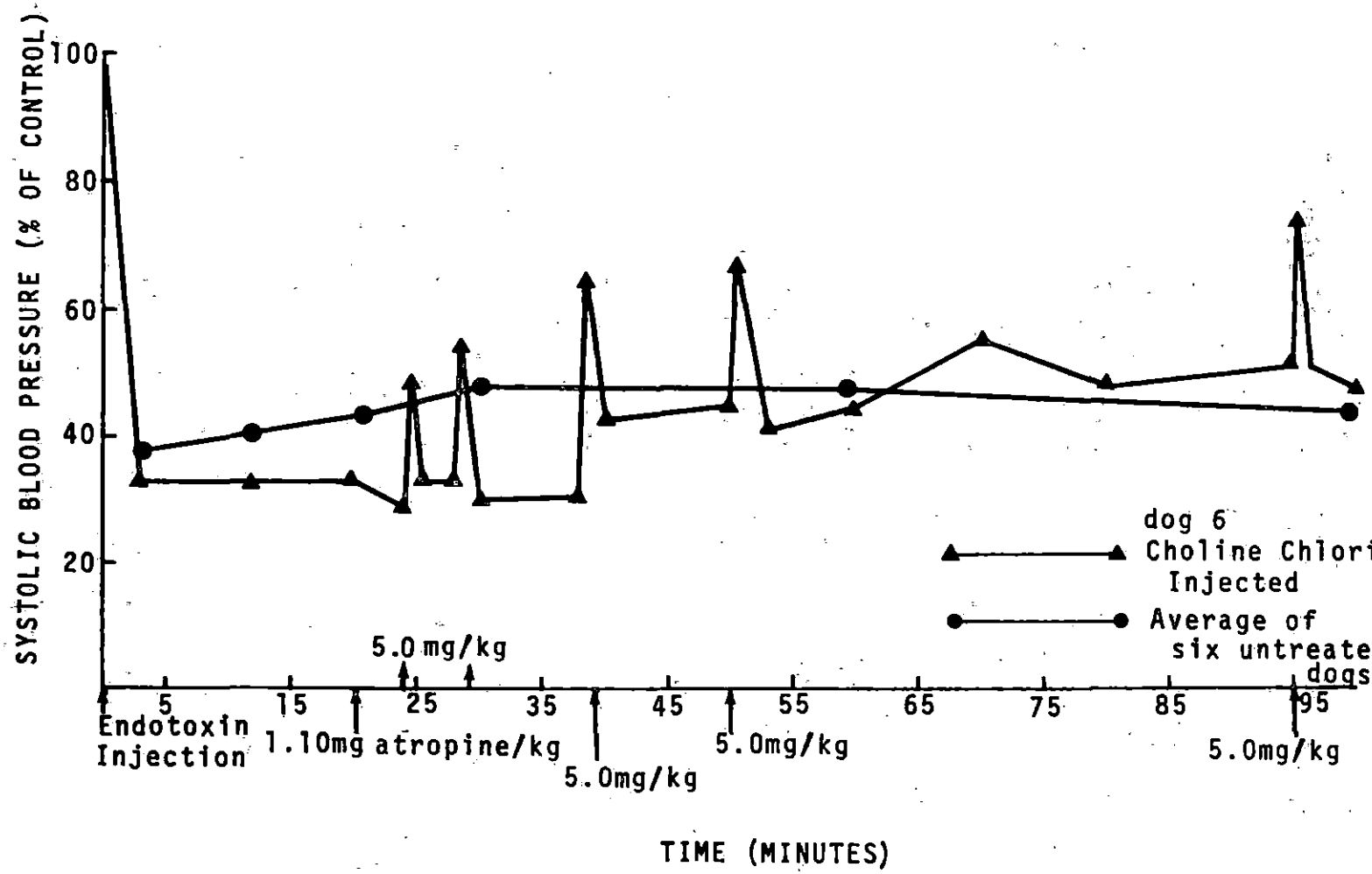
Graph 10. Pulse pressure of dog 5 during intravenous injections of choline chloride



Graph 11. Systolic blood pressure of dog 5 during intravenous injections of choline chloride



Graph 12. Pulse pressure of dog 6 during intravenous injections of choline chloride



Graph 13. Systolic blood pressure of dog 6 during intravenous injections of choline chloride

twitchings were not prevented by 0.09 mg atropine/kg., but the other signs failed to occur. The sixth dog was given 1.1 mg atropine/kg. Muscular twitchings did not occur. None of the six animals treated with choline chloride survived.

DISCUSSION

In all dogs, choline chloride infusions or injections elevated the systolic blood pressure. However, responses to similar dosages of administered choline chloride were not consistent. With the two infused dogs, the systolic blood pressure remained elevated for extended periods and then precipitously dropped. Further infusion failed to elevate the systolic blood pressure. With the injected dogs, numerous choline chloride injections were made maintaining an elevated systolic blood pressure. Extended periods occurred where the systolic blood pressure remained elevated without further injections. In all dogs but dog number 6, when the systolic blood pressure began to decrease after these extended periods, additional injections did not elevate the blood pressure. In dog number 6 the systolic blood pressure was maintained elevated past the 100 minutes when monitoring was stopped. When the systolic blood pressure did elevate within adequate perfusion pressure, the color of the dogs' mucous membranes did improve markedly in every case, indicating improved vascular perfusion.

In all experimental dogs the elevation in pulse pressure correlates with an elevation of systolic blood pressure. This could indicate that the increase in systolic blood pressure with choline chloride administration is a function

of increased myocardial contractility. Mitchell's study (32) supports this hypothesis. He observed that with increased systolic blood pressure an increase in left ventricular systolic blood pressure occurred.

This study revealed that choline chloride produced some effects which are similar to nicotinic responses. Small dosages of nicotine stimulate ganglia of the autonomic nervous system and smooth and skeletal muscles (20). The clinical responses are excessive salivation, peristalsis, vomition, skeletal muscular twitchings, and an elevated blood pressure. Infusion of choline chloride produced these responses in dogs not treated with atropine. Pretreatment with atropine blocked excessive salivation, peristalsis, and vomition. In most dogs skeletal muscular twitchings occurred and in all dogs elevated blood pressure occurred initially.

Furthermore, large dosages of nicotine cause paralysis of sympathetic autonomic ganglia (20). This can result in dilatation of vessels with a fall of blood pressure. If choline chloride produces similar responses as nicotine, this could explain the rapidly declining systolic blood pressure which occurred in those dogs after prolonged choline chloride treatment.

A LD_{90} of E. coli endotoxin was chosen for this experiment. It is possible that choline chloride treatment could have been beneficial in treating dogs given a LD_{50}. However,

it is generally thought that successful reversal of shock requires more attention than single drug treatment. Attention must be paid to cardiovascular volume, ventilation, acid-base balance, and cardiovascular muscle tone. Clinically, animals in shock are given intravenous, electrolyte-balanced fluids as determined by central venous pressure. Adequate ventilation is ensured by entubating animals when necessary. Acidosis is treated with buffers, most commonly sodium bicarbonate. Glucocorticoids are given to normalize function of blood vessel sphincters. With other supportive therapy, choline chloride could be a helpful adjunct in successfully reversing endotoxin shock. Low dosages could help maintain systolic blood pressure. A positive inotropic effect would be advantageous, producing increased cardiac output.

SUMMARY

Endotoxin shock was produced in six control dogs. A LD_{90} of E. coli endotoxin was intravenously injected into each dog. The initial severe hypotension was followed by a return toward normal then the irreversible hypotensive state.

Choline chloride, a vasopressive drug, was infused intravenously to two dogs given E. coli. The amount of choline chloride infused was determined by the systolic blood pressure. The four remaining animals in the treated group were given periodic intravenous injections of choline chloride to elevate the systolic pressure. Choline chloride did elevate the systolic blood pressure for short time intervals. Prolonged administration of choline chloride failed to maintain normal systolic blood pressures in the six animals. None of the dogs treated with choline chloride survived.

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APPENDIX

Table 1. Control dog 1

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	110	120	15	24
0.5	110	120	15	21
1.0	50	92	10	27
1.5	37	80	7	27
2.0	37	68	7	40
3.0	53	72	7	24
4.0	50	80	5	16
5.0	50	84	3	24
6.0	45	80	3	24
9.0	55	80	8	28
12.0	57	76	15	24
15.0	67	76	17	24
18.0	67	80	20	20
21.0	65	80	20	20
24.0	65	82	20	20
27.0	65	80	21	24
30.0	67	82	21	20
33.0	67	80	22	20
40.0	70	80	20	24
50.0	57	88	22	20
60.0	55	82	20	20
70.0	55	88	20	24
80.0	50	96	20	24
90.0	50	96	20	24
100.0	50	96	20	24

Table 2. Control dog 2

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	170	148	45	28
0.5	130	144	37	16
1.0	60	128	23	polypnea
1.5	47	112	20	polypnea
2.0	46	96	15	polypnea
3.0	55	88	20	12
4.0	67	96	21	16
5.0	71	100	27	16
6.0	76	104	26	12
9.0	67	104	26	polypnea
12.0	63	104	23	polypnea
15.0	62	108	21	polypnea
18.0	58	108	20	40
21.0	58	108	22	32
24.0	63	108	24	32
27.0	65	112	25	32
30.0	73	112	26	32
33.0	80	112	30	32
40.0	-	-	-	-
50.0	90	112	40	24
60.0	93	120	45	24
70.0	94	120	45	24
80.0	95	120	50	24
90.0	95	116	50	22
100.0	90	116	50	22

Table 3. Control dog 3

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	160	128	28	20
0.5	185	132	28	24
1.0	120	124	25	apnea
1.5	75	68	30	28
2.0	75	52	30	32
3.0	70	56	25	arhythmia 28
4.0	70	52	21	arhythmia 28
5.0	73	64	22	arhythmia 28
6.0	75	60	22	arhythmia 28
9.0	75	72	25	32
12.0	75	80	22	28
15.0	75	88	23	28
18.0	73	88	23	28
21.0	75	92	23	28
24.0	77	92	23	24
27.0	82	96	23	28
30.0	82	100	27	24
33.0	85	96	32	22
40.0	80	104	30	20
50.0	75	110	30	18
60.0	75	110	30	18
70.0	75	110	30	20
80.0	75	110	30	20
90.0	75	110	30	20
100.0	75	110	30	20

Table 4. Control dog 4

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	95	128	30	28
0.5	85	128	30	20
1.0	55	112	16	24
1.5	55	100	15	28
2.0	55	96	13	32
3.0	45	96	10	36
4.0	47	92	7	36
5.0	52	100	10	40
6.0	50	108	10	40
9.0	55	108	13	24
12.0	57	108	13	24
15.0	60	100	13	20
18.0	63	104	17	24
21.0	65	104	18	24
24.0	65	108	18	20
27.0	68	104	17	20
30.0	68	108	16	20
33.0	63	108	16	20
40.0	57	112	17	20
50.0	57	112	17	20
60.0	57	112	17	20
70.0	-	-	-	-
80.0	-	-	-	-
90.0	-	-	-	-
100.0	-	-	-	-

Table 5. Control dog 5 (dog survived)

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	125	124	25	12
0.5	130	120	25	8 arhythmia
1.0	85	132	15	16 arhythmia
1.5	60	128	15	24 shallow, arhythmia
2.0	40	88	12	40 shallow, arhythmia
3.0	35	60	15	72 shallow, arhythmia
4.0	32	76	12	72 shallow, arhythmia
5.0	35	88	15	60 shallow, arhythmia
6.0	35	92	15	44 shallow, arhythmia
9.0	40	96	15	47 shallow, arhythmia
12.0	40	96	15	47 shallow, arhythmia
15.0	-	-	-	-
18.0	-	-	-	-
21.0	40	120	15	40
24.0	-	-	-	-
27.0	-	-	-	-
30.0	52	114	20	36
33.0	-	-	-	-
40.0	65	128	20	40
50.0	67	128	22	52
60.0	62	128	22	44
70.0	50	120	22	48
80.0	45	120	20	64
90.0	45	134	25	52
100.0	50	130	23	48

Table 6. Control dog 6

Time (minutes)	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0	145	160	30	12
0.5	100	160	20	12 arhythmia
1.0	60	120	25	12 arhythmia
1.5	37	88	25	16 arhythmia
2.0	35	64	23	16 arhythmia
3.0	40	88	22	80 shallow
4.0	40	92	22	12 arhythmia
5.0	25	100	15	76 shallow, arhythmia
6.0	22	96	10	60 shallow, arhythmia
9.0	22	84	12	56 shallow, arhythmia
12.0	22	84	12	56 shallow, arhythmia
15.0	-	-	-	-
18.0	-	-	-	-
21.0	30	108	13	36
24.0	-	-	-	-
27.0	-	-	-	-
30.0	32	124	15	24
33.0	-	-	-	-
40.0	37	124	15	20
50.0	40	120	20	28
60.0	35	136	20	20
70.0	35	120	17	20
80.0	40	120	17	10 arhythmia
90.0	45	112	22	16 arhythmia
100.0	50	128	17	16 arhythmia

Table 7. Systolic blood pressure of control dogs

Post Endotoxin Time (min.)	Control Animals						Average Per cent of control value
	Dog 1 (mm Hg)	Dog 2 (mm Hg)	Dog 3 (mm Hg)	Dog 4 (mm Hg)	Dog 5 (mm Hg)	Dog 6 (mm Hg)	
0	110	170	160	95	125	145	%±SD
3	53(48.2)[a]	55(32.4)	70(43.7)	45(47.5)	35(28.0)	40(27.6)	37.8±9.65
12	57(51.7)	63(37.0)	75(46.8)	57(60.0)	40(32.0)	22(15.3)	40.5±15.9
21	65(59.0)	58(34.1)	75(46.8)	65(68.5)	40(32.0)	30(23.3)	43.9±17.3
30	67(60.8)	73(42.9)	82(51.3)	68(71.5)	52(41.5)	32(22.0)	48.4±17.1
60	55(50.0)	93(54.5)	75(46.8)	57(60.0)	62(49.5)	35(24.2)	47.5±12.3
100	50(45.5)	90(52.9)	75(46.8)	-	50(39.9)	50(34.5)	43.9± 7.0

[a]Per cent of control value.

Table 8. Pulse pressure of control dogs

Post Endotoxin Time (min.)	Control Animals						Average Per cent of control value
	Dog 1 (mm Hg)	Dog 2 (mm Hg)	Dog 3 (mm Hg)	Dog 4 (mm Hg)	Dog 5 (mm Hg)	Dog 6 (mm Hg)	
0	15	45	28	30	25	30	
3	7(46.6)	20(44.5)	25(89.3)	10(33.3)	15(60.0)	22(73.3)	57.8±20.7
12	15(100.0)	23(51.2)	22(78.5)	13(43.4)	15(60.0)	12(40.0)	62.2±23.1
21	20(133.3)	22(48.8)	23(82.2)	18(60.0)	15(60.0)	13(43.3)	71.3±33.2
30	21(140.0)	26(57.8)	27(96.5)	16(53.4)	20(80.0)	15(50.0)	79.6±34.6
60	20(133.3)	45(100.0)	30(100.7)	17(56.7)	22(88.0)	20(66.6)	91.9±27.9
100	20(133.3)	50(111.0)	30(100.7)	-	23(92.1)	17(56.8)	98.8±28.1

Table 9. Heart rate of control dogs

Post Endotoxin Time (min.)	Control Animals						Average Per Cent of control value
	Dog 1 (mm Hg)	Dog 2 (mm Hg)	Dog 3 (mm Hg)	Dog 4 (mm Hg)	Dog 5 (mm Hg)	Dog 6 (mm Hg)	
0	120	148	128	128	124	160	
3	72(60.0)	88(59.5)	56(43.8)	96(75.0)	60(48.3)	88(55.0)	56.9±10.8
12	76(63.3)	104(70.3)	80(62.5)	108(84.4)	96(77.4)	84(52.5)	68.4±11.4
21	80(66.7)	108(73.0)	92(71.8)	104(81.3)	120(96.8)	108(67.5)	76.2±11.4)
30	82(68.3)	112(75.7)	100(78.0)	108(84.4)	114(92.0)	124(77.5)	79.3± 8.1
60	82(68.3)	120(81.1)	110(86.0)	112(87.5)	128(103.0)	136(85.0)	85.2±11.2
100	96(80.0)	116(78.4)	110(86.0)	-	130(104.8)	128(80.5)	85.9±10.9

Table 10. Respiratory rate of control dogs

Post Endotoxin Time (min.)	Control Animals						Average Per Cent of control value
	Dog 1 (mm Hg)	Dog 2 (mm Hg)	Dog 3 (mm Hg)	Dog 4 (mm Hg)	Dog 5 (mm Hg)	Dog 6 (mm Hg)	
0	24	28	20	28	12	12	
3	24 (100.0)	12 (42.8)	28 (140.0)	36 (128.5)	72 (600.0)	80 (666.0)	279.5±276.6
12	24 (100.0)	60 (212.0)	28 (140.0)	24 (85.7)	47 (391.0)	56 (466.0)	232.5±159.8
21	20 (83.4)	32 (114.0)	28 (140.0)	24 (85.7)	40 (333.0)	36 (298.0)	175.7±110.8
30	20 (83.4)	32 (114.0)	24 (120.0)	20 (71.4)	36 (298.0)	24 (200.0)	147.8±86.2
60	20 (83.4)	24 (85.7)	18 (90.0)	20 (71.4)	44 (366.0)	20 (167.0)	143.9±114.0
100	24 (100.0)	22 (77.5)	20 (100.0)	-	48 (400.0)	16 (133.0)	162.1 (134.4)

Table 11. Choline chloride treated dog 1

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0		119	114	47	15
3		51(42.8)[a]	108	27(57.5)	30
12		55(46.2)	96	15(31.9)	30
21	5.0 mg choline chloride per kilogram body weight intravenously	67(56.3)	84	26(55.4)	8 arhythmic shallow
25		80(67.1)	84	33(70.2)	20 arhythmia
33		67(56.3)	84	26(55.4)	8
35	6.2 mg choline chloride per kilogram body weight per minute intravenously	67(56.3)	84	26(55.4)	8
37	10.4 mg choline chloride per kilogram body weight per minute intravenously	67(56.3)	84	26(55.4)	8
40		100(84)	98	50(106)	8 arhythmic apnea occurred periodically

[a]Per cent of control.

Table 11 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
43	Infusion reduced to 6.2 mg choline chloride per kilogram body weight	100(84)	98	50(106)	
63	Hypersalivation, vomition, skeletal muscular twitching, hyper peristalis occurred. Mucous membrane color improved	100(84)	98	50(106)	8
63	Infusion stopped at this time				
108	Hypersalivation, skeletal muscular twitching, hyperperistalsis continued. Mucous membrane color deteriorated. No electrocardiographic abnormalities occurred. The dog died 2 hours after infusion was stopped	100(84)	81	53(122.8)	8 arhythmic

Table 12. Choline chloride treated dog 2[a]

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)	
0		132	132	30	19	
3		47(35.6)	102	15(50)	30	
12		65(49.3)	80	25(83.3)	27	
20	5.0 mg choline chloride per kilogram body weight per minute	57(43.2)	120	22(73.4)	18	
21		125(94.7)	150	50(166.5)	18	arhythmia
23	The color of mucous membranes improved. A forceful urination occurred. 13.2 mg choline chloride per kilogram body weight per minute intravenously	75(56.7)	96	30(100)	15	arhythmia
24		100(75.7)	84	40(133)	9	arhythmia
25	Pulmonary moist rates hypersalivation occurred. 10.0 mg choline chloride per kilogram body weight per minute intravenously	100(75.7)	84	40(133)	9	arhythmia
26		100(75.7)	72	37(123.2)	9	arhythmia shallow

[a]Further infusion of choline chloride failed to elevate the blood pressure. The dog died in two hours.

Table 12 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
31	Infusion stopped	115(87.1)	66	55(183.3)	5 arhythmia shallow
34	Skeletal muscular twitching and intestinal hypermobility was prominent	145(110)	72	65(216.2)	apnea
46	Rapid drop in systolic blood pressure with rapid drop in pulse pressure at this time. Electrocardiographic abnormalities also occurred	145(110)	72	65(216.2)	shallow oligonea

Table 13. Choline chloride treated dog 3

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0		152	132	20	12
3		50(32.9)	90	10(50)	36
12		30(19.7)	136	15(75)	10 apnea bagged animal
20	Injections: 0.9 mg atropine per kilogram intravenously	47(30.8)	138	10(50)	36
25	Injection: 5.0 mg choline chloride per kilogram intravenously	47(30.8)	138	10(50)	36
25,40 sec.		95(62.5)	132	12(60)	66
25,50 sec.		80(52.6)	132	12(60)	36
28	Injection: 5.0 mg choline chloride per kilogram intravenously	50(32.9)	132	12(60)	36
28,40 sec.		63(41.4)	132	12(60)	60
30,30 sec.	Injection: 6.0 mg choline chloride per kilogram intravenously	50(32.9)	132	12(60)	36
32	Injection: 10 mg choline ghloride per kilogram intravenously	55(36.2)	132	12(60)	36

Table 13 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
35	Injection: 10.0 mg choline chloride per kilogram intravenously	55(36.2)	132	12(60)	36
38	Skeletal muscular twitching occurred	85(55.8)	126	22(110)	36 arhythmia shallow
43		100(65.7)	108	25(125)	36 arhythmia shallow
47	Injection: 5.0 mg choline chloride per kilogram intravenously	75(49.3)	108	25(125)	36 arhythmia shallow
47,20 sec.		90(59.2)	108	25(125)	36 arhythmia shallow
48		75(49.3)	108	25(125)	36 arhythmia shallow
56	Injection: 5.0 mg choline chloride per kilogram intravenously. Mucous membrane color improved. Skeletal muscular twitching occurred.	90(59.2)	108	25(125)	36 arhythmia shallow
56,20 sec.		110(72.4)	114	25(125)	36 arhythmia shallow

Table 13 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
96	A precipitous fall in blood pressure occurred. Further choline chloride injections of 5.0 mg per pound and 10.0 mg per kilogram failed to elicit any response. The dog died in four hours. Muscular twitching was not inhibited by atropinizing the dog. Hypersalivation, moist pulmonary rales, and hyperperistalsis was not observed, however.	110(72.4)	114	25(125)	36 arhythmia shallow

Table 14. Choline chloride treated dog 4

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0		155	126	40	12
3		40(25.6)	108	25(62.5	polypnea
12		40(25.6)	114	7(17.5)	36
20	Injection: 0.9 mg atropine per kilogram body weight intravenously	37(23.7)	120	25(62.5)	20
25	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	37(23.7)	120	25(62.5)	20
26		117(75.5)	120	25(62.5)	20
27	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	37(23.7)	120	25(62.5)	20
28,30 sec.		135(87.1)	120	45(112.5)	olignea shallow arhythmia
29	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	37(23.7)	120	25(62.5)	20
29,15 sec.		120(77.5)	124	37(92.5)	22 shallow
30,5 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	55(35.3)	108	25(62.5)	polypnea

Table 14 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
30,20 sec.		115(74.2)	120	40(100)	40 shallow
31,5 sec.	Injection: 5.0 mg choline chloride per kiligram body weight intravenously	65(41.9)	108	25(62.5)	polypnea
31,15 sec.		100(64.5)	108	45(112.5)	polypnea
31,45 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	70(45.2)	101	30(75)	polypnea
32		100(64.5)	108	30(75)	28 shallow
32,40 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously. The color of mucous membranes greatly improved. Skeletal muscular twitching occurred at this time	65(41.9)	108	30(75)	24 shallow
32,50 sec.		100(64.5)	108	50(125)	28 shallow
33,35 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	65(41.9)	100	35(87.5)	28 shallow
33,50 sec.		90(58.1)	100	50(125)	24 shallow
34,30 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	55(35.5)	100	30(75)	28 shallow
34,50 sec.		85(54.8)	96	50(125)	32 shallow

Table 14 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
35,25 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	60(38.7)	96	35(87.5)	28 shallow
35,45 sec.		85(54.8)	100	50(125)	28 shallow
36,20 sec.	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	60(38.7)	92	30(75)	24 shallow
36,40 sec.		75(48.4)	88	40(100)	24 shallow
37,25 sec.	Injection: 100 mg choline chloride per kilogram body weight intravenously	65(41.9)	80	30(75)	24 shallow
38		75(48.4)	84	40(100)	24 shallow
38,40 sec.	Injection: 10.0 mg choline chloride per kilogram body weight intravenously	65(41.9)	80	35(87.5)	24 shallow
39		80(51.6)	80	40(100)	24 shallow
39,35 sec.	Injection: 10.0 mg choline chloride per kilogram body weight intravenously	65(41.9)	80	30(75)	24 shallow
40		80(51.6)	80	40(100)	24 shallow
40,40 sec.	Injection: 10.0 mg choline chloride per kilogram body weight intravenously. No response. The color of mucous membrane remains good, but skeletal muscular twitching became prominent	75(48.4)	72	30(75)	24 shallow

Table 14 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
70	Injection: 10.0 mg choline chloride per kilogram body weight intravenously. No response to further injections of choline chloride occurred. The dog was euthanized when the blood pressure started dropping precipitously. Hypersalivation, moist pulmonary rales, and hyperperistalsis was not observed	75(48.4)	72	30(75)	24 shallow

Table 15. Choline chloride treated dog 5

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0		147	138	30	24
3		35(23.8)	126	9(30)	polypnea
12		50(34.0)	98	12(40)	96
20	Injection: 0.9 mg atropine per kilogram body weight intravenously	55(37.4)	98	12(40)	96
25	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	55(37.4)	98	12(40)	96
26		190(129)	180	22(73.3)	36
34	Injections: 5.0 mg choline chloride per kilogram body weight intravenously	58(39.5)	120	15(50)	96
35		130(88.5)	138	20(66.6)	96
38	The color of the mucous membrane improved. Skeletal muscular twitching did occur	77(52.4)	138	20(66.6)	96
48		77(52.4)	138	17(56.7)	84
58		77(52.4)	138	25(83.7)	90
68		77(52.4)	138	25(83.7)	90
78		71(48.3)	138	25(83.7)	81
88		70(47.6)	138	20(66.6)	81

Table 15 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
91	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	65(44.2)	138	20(66.6)	81
91,20 sec.		80(54.4)	138	22(66.6)	96
92	Injection: 10.0 mg choline chloride per kilogram body weight intravenously	65(44.2)	138	17(56.7)	96
93		105(71.5)	138	22(73.5)	90
94	Injection: 10.0 choline chloride per kilogram body weight intravenously	60(40.8)	138	18(60.0)	54
95		110(74.9)	138	22(73.5)	96
96	Injection: 10.0 mg choline chloride per kilogram body weight intravenously	60(40.8)	138	20(66.6)	48
97		95(64.6)	138	20(66.6)	96
99	Injection: 10.0 mg choline chloride per kilogram body weight intravenously	60(40.8)	138	17(56.7)	72
99,45 sec.		85(57.8)	138	22(66.6)	90
100,50 sec.	Hyper alivation, moist pulmonary rales, or hyperperistalsis did not occur. Further injection of choline chloride failed to elevate the blood pressure. The dog died within 6 hours				

Table 16. Choline chloride treated dog 6

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
0		155	180		24
3		50(33.4)	120	30(54.5)	33
12		50(33.4)	110	25(45.5)	66
20	Injection: 1.10 mg atropine per kilogram body weight intravenously	50(33.4)	120	22(40.0)	66
24	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	45(29.0)	136	25(45.5)	64
24,30 sec.		75(48.4)	125	55(100)	72
25,30 sec.		50(33.4)	132	25(45.5)	72
28	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	50(33.4)	132	25(45.5)	72
28,30 sec.		85(54.7)	138	55(100)	72
30		55(35.4)	138	26(47.3)	84
38	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	55(35.4)	138	26(47.3)	78
38,30 sec.		100(64.5)	132	60(104)	84
40		65(41.9)	132	33(60)	84
50	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	70(45.1)	132	35(63.6)	66

Table 16 (Continued)

Post Endotoxin Time (minutes)	Remarks	Systolic Blood Pressure (mm Hg)	Heart Rate (beats/ min.)	Pulse Pressure (mm Hg)	Respiratory Rate (breaths/ min.)
50,20 sec.		105(67.7)	140	70(127)	66
53		65(41.9)	144	30(54.5)	42
60		70(45.1)	144	30(54.5)	48
70		85(54.9)	150	55(100)	42
80		75(48.4)	150	50(90.0)	60
95	Injection: 5.0 mg choline chloride per kilogram body weight intravenously	80(51.6)	156	50(90.9)	54
95,20 sec.		115(74.2)	180	65(118)	36
96,20 sec.		80(51.6)	166	45(81.8)	60
100	No muscular twitching, hypersalivation, moist pulmonary rales or hyper-peristalsis was seen. The dog died 5 hours later	75(48.4)	166	40(72.7)	72