EVALUATION OF THE pH-STAT MODIFIED APPROACH FOR THE TREATMENT OF NON-RESPIRATORY (LACTIC) ACIDOSIS AND VASCULAR HYPOREACTIVITY CAUSED BY HEMORRHAGIC SHOCK IN DOGS

DISSERTATION

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By

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ABSTRACT

The objective of this dissertation was to determine if the pH-stat modified therapy is more effective than the pH-stat therapy in treating hemorrhagic shock and vascular hyporeactivity in dogs. The specific aims were to compare the effectiveness of these two treatments on systemic hemodynamics and acid-base balance and to evaluate their efficacy in preventing vascular hyporeactivity in dogs with hemorrhagic shock. Twenty-three anesthetized dogs were randomly assigned to four groups: I: One (1) dog included as control to provide baseline and control data; II: Seven (7) hemorrhaged, hypothermic [HT] (32 ºC) dogs received lactated Ringer's solution (LRS); III: Seven (7) hemorrhaged, HT dogs received LRS and were subjected to the pH-stat therapy; IV: Eight (8) hemorrhaged, HT dogs received LRS and underwent the pH-stat modified therapy. Dogs were intubated and mechanically ventilated on room air and end tidal CO_2 of 35-40 mm Hg. Approximately 40% of each dog's blood volume was removed until mean arterial pressure (MAP) reached 50 mm Hg. MAP was held constant for 60 minutes. After bleeding, all dogs were treated with LRS. Dogs in group II received LRS. Dogs in group III and IV received LRS and either pH-stat or pH-stat modified therapies. pH-stat keeps arterial pH at 7.40 and PCO_2 at 40 mm Hg regardless of body temperature. PaO_2, PCO_2 and pH were corrected for body temperature. pH-stat modified maintains a fixed

PCO_2 of 60 mm Hg and a pH of 7.30. Hemodynamics and acid-base data were measured at baseline, through hemorrhage, end of treatment, and at 60, 120 and 180 minutes post-resuscitation. Vascular reactivity to norepinephrine infusion and blood flow to the hind limb and small intestine were determined. Through bleeding, heart rate increased insignificantly in all groups and returned to values not different from baseline. None of the treatments was superior in sustaining left ventricular systolic pressure and preload. The 3 methods produced transient improvements in physiological variables that did not persist with time. All systemic arterial pressures behaved nearly identically during hemorrhage and subsequent fluid resuscitation. They fell at the end of hemorrhage due to reduced preload, returned to normal at the end of resuscitation and drifted to subnormal values consistent with venous pooling. Blood flow was better with pH-stat modified than with the other 2 interventions. Blood flow was also superior with pH-stat-modified when animals received norepinephrine and when occlusion was applied. High lactate levels leading to both low arterial pH (pHa) and bicarbonate were seen in all groups 3 hours after resuscitation, confirming the presence of non-respiratory acidosis. The lowest lactate concentration was seen with pH-stat modified therapy. Nonetheless, differences among groups were not significant. Animals which received pH-stat modified exhibited lower pHa levels than animals with other interventions. Apparently, there were no significant differences produced by one volume replacement over another, with the exception of flow improvement to tissues in animals which received pH-stat modified therapy.

DEDICATION

To my parents *in memoriam* because they symbolize my existence

To my wife, for her profound love and confidence in me

To my children, for all the true love they give

To my brothers and sisters, for their profound solidarity in all circumstances

QUOTE

"PERSISTENCE IS WHAT MAKES THE IMPOSSIBLE POSSIBLE, THE POSSIBLE LIKELY, THE LIKELY DEFINITIVE."

ROBERT HALF

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LIST OF ABBREVIATIONS

HR: Heart Rate (beats/min)

SAP: Systolic Arterial Pressure (mm Hg)

DAP: Diastolic Arterial Pressure (mm Hg)

MAP: Mean ArteryPressure (mm Hg)

mPAP: Mean Pulmonary Arterial Pressure (mm Hg)

mRAP: Mean Right Atrial Pressure (mm Hg)

LVSP: Left Ventricular Systolic Pressure (mm Hg)

LVEDP: Left Ventricular End Diastolic Pressure (mm Hg)

LV + dP/dt: Rate of Left Ventricular pressure Rise (mm Hg x sec^{-1})

LV - dP/dt: Rate of Left Ventricular Pressure Fall (mm Hg x sec^{-1})

TAU: Time Constant of Relaxation (msec)

FABF: Femoral Artery Blood Flow (mL/min)

CMABF: Cranial Mesenteric Artery Blood Flow (mL/min)

CO: Cardiac Output (mL/kg/min)

RPP: Rate Pressure Product (beats x mm Hg/min)

SVR: Systemic Vascular Resistance (dynes x sec/cm^5)

RR: Respiratory Rate (breaths/min)

$ETCO_2$: End Tidal Carbon Dioxide (mm Hg)

BT: Blood Temperature (°C)

ET: Esophageal Temperature (°C)

AT: Abdominal Temperature (°C)

DO_2: Oxygen delivery (mL/min/100 g)

VO_2: Oxygen Consumption (mL/min/100 g)

O_2ER: Oxygen Extraction Ratio (%)

LACTATE: Blood Lactate (mmol/L)

pHa: Arterial pH (pH units)

$aPCO_2$: Arterial Partial Pressure of Carbon Dioxide (mm Hg)

aPO_2: Arterial Partial Pressure of Oxygen (mm Hg)

$aHCO_3^-$: Arterial Bicarbonate Concentration (mmol/L)

aBE: Arterial Base Excess Concentration (mmol/L)

pHv: Venous pH (pH units)

$vPCO_2$: Venous Partial Pressure of Carbon Dioxide (mm Hg)

vPO_2: Venous Partial Pressure of Oxygen (mm Hg)

$vHCO_3^-$: Venous Bicarbonate Concentration (mmol/L)

vBE: Venous Base Excess (nmol/L)

PCV: Packed Cell Volume (%)

TP: Total Proteins (g/dL)

COP: Colloid Osmotic Pressure (mm Hg)

INTRODUCTION

Profuse hemorrhage of either internal or external origin that leads to hemorrhagic shock has been classified third and fifth, respectively, among the top ten most life-threatening complications associated with trauma in dogs and cats [15].

Hemorrhagic shock causes an imbalance between oxygen and nutrient transport to tissues and the removal of the end products of cellular metabolism. The response to hypoperfusion results in reduced oxygen consumption that eventually leads to tissue damage and death, if not treated promptly [33, 21, 10, 23].

The compensatory responses to severe hemorrhage are typified by hyperpnea, tachycardia and vasoconstriction, and reduced urine production in proportion to the severity of hemorrhage. Moderate to severe hemorrhage often results in the development of vicious cycles, which cause reductions in arterial pressure and tissue perfusion that lead to the production of a non-respiratory (lactic) acidosis [26, 17].

The vasculature becomes refractory to the administration of catecholamines (norepinephrine, dopamine, dobutamine) resulting in a phenomenon termed vascular hyporeactivity [25, 20, 35].

This phenomenon is a frequent occurrence in animals that have suffered from severe hemorrhage and demonstrate an initial yet fleeting recovery only to die in 24 to 48 hours from multiple system organ failure, which is a complication of the systemic

inflammatory response syndrome and has been defined as *« a distorted organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention. «* [19, 8].

Adequate tissue perfusion and acid-base therapy must be provided immediately if shocked animals are to survive and many die regardless of fluid therapy due to tissue hypoxia, lactic acidosis (lactate concentration > 5 mM/L, pH value < 7.35), electrolyte disturbances, and abnormalities in the coagulation process (disseminated intravascular coagulation)**.**

Even though significant progress has been made in the understanding of the mechanisms involved in the production of hemorrhagic shock, the application of novel therapies and in the development of new treatments, there has been little improvement in the outcome of patients suffering from this clinical condition [2, 3, 4, 5, 6, 7, 9, 16, 31, 33, 37, 38, 39, 40, 41].

Recent experiments have provided some explanation for the inefficacy of these treatments: low tissue oxygen tension, a decrease in functional capillary density and capillary perfusion, and vascular hyporeactivity [44, 27].

Two therapies to resolving the acid-base derangements that occur during tissue hypoperfusion have been developed in conjunction with cardio-pulmonary bypass procedures in human patients: the alpha-stat approach and the pH-stat approach [29, 28, 30, 24, 36, 11, 12, 22, 18, 13, 43].

In the alpha-stat approach, blood pH is allowed to change with cooling so as to preserve a constant hydroxyl to hydrogen ratio $[OH^-]$: $[H^+]$ necessary for the enzymatic machinery of the body to function appropriately. Consequently, the arterial pH value is

7.40 and has a partial pressure of CO_2 (PCO_2) of 40 mm Hg when measured at a blood temperature of 37 °C. At the same time, *in vivo* hypothermic blood is hypocapnic and alkalotic [34].

The principle of the pH-stat approach establishes that both arterial pH and PCO_2 should remain at constant values. This strategy is based on the effect of body temperature on hydrogen ion (H^+) concentration in body compartments. Temperature influences dissociation constants (pK_a) and solubility of CO_2 therefore bringing on changes in pH. An increase in body temperature produces a decrease in pH (an increased concentration of H^+) and vice versa in such a way that blood pH changes by 0.015-0.02 units of pH/°C. These temperature-dependent changes in both intracellular and extracellular pHs are believed to be critical in maintaining a constant $[OH^-]$: $[H^+]$ ratio of 16:1 throughout the body.

With this approach, PCO_2 is temperature-corrected and kept at 40 mm Hg to maintain a pH of 7.40 near the actual temperature. To achieve this during hypothermia, it is necessary to perform a hypoventilatory manipulation by increasing the CO_2 content of the breathing medium because blood pH is more alkaline during cooling. With this method, blood is hypercapnic and acidotic when measured at 37 °C [13, 24, 42, 14, 34].

The alpha-stat and the pH-stat therapeutic approaches have demonstrated benefits in terms of both myocardial and brain protection in humans undergoing cardiopulmonary bypass procedures and hypothermic surgical procedures to remove brain tumors [4, 44, 43]. Surprisingly, neither therapeutic technique has been applied to the more frequent clinical condition of hemorrhagic shock.

In the clinical context of hemorrhagic shock the pH-stat therapy is ineffective because it does not exert any influence on blood flow, which is a critical event in hemorrhagic shock.

The acid-base therapeutic strategy used was a modification of the pH-stat approach (the pH-stat modified therapy). The pH and the PCO_2 were controlled independently. This modification introduces two aspects: the administration of CO_2 to increase PCO_2 to 60 mm Hg to produce a mild hypercapnia and the administration of sodium bicarbonate ($NaHCO_3$) to keep an arterial pH of 7.30.

The rationale for using this modified approach is manifold [1]: An elevated PCO_2 increases cardiac output. The increase in CO_2 may lead to a sympathetically mediated release of catecholamines that enhances cardiac output. Conversely, the elevation of CO_2 increases flow by local vasodilatation that might also increase cardiac output. The improvement of cardiac output by hypercapnia increases peripheral tissue oxygenation.

Since a non-respiratory lactic acidosis is a common finding in hemorrhagic shock, the administration of $NaHCO_3$ would keep the pH at 7.30 (the lower range of the slightly extracellular alkalotic normal pH), and would correct the acidosis.

This therapeutic procedure is intended to improve tissue perfusion, to remove the metabolic disturbance. The administration of fluids is aimed at restoring the effective circulating blood volume.

The general objective of this dissertation focused on determining if the pH-stat modified strategy is more effective than the pH-stat strategy in treating hemorrhagic shock and vascular hyporeactivity in an experimental and clinically applicable model of hemorrhagic hypovolemic shock in dogs.

The specific aims were to compare the effectiveness of the pH-stat versus the pH-stat modified therapeutic approaches on systemic hemodynamics and acid-base balance in hemorrhagic hypovolemic shock in dogs. Another goal was to evaluate the effectiveness of the pH-stat modified versus the pH-stat therapeutic approaches in preventing vascular hyporeactivity in dogs undergoing hemorrhagic hypovolemic shock.

The results of the present study will help to clarify the importance of vascular hyporeactivity in hemorrhaged, hypothermic dogs and the efficacy of the pH-stat modified versus the pH-stat therapies in preventing this problem. At the same time, we think that the results obtained in this investigation will provide useful information that may help to reduce death in patients suffering form hemorrhagic shock.

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CHAPTER 1

1. Literature Review

Almost two centuries have elapsed since the word shock was used to indicate an abrupt breakdown in the clinical condition of a patient suffering from severe trauma [4]. It was Napoleon's surgeon, Larrey, who first coined the word shock in 1817 to connote circulatory failure (cited by Bloch et al, 1966) [15]. Since then, shock has been widely studied by many investigators, and a vast literature on the subject has been published [112].

In 1879, Mapother [99] supported the vasoconstriction theory of shock. He believed that the most remarkable physical change produced by shock was the contraction of arterioles. He noticed that shock paralyzed the dilator nerves.

Crile in 1899 [32] performed numerous studies in surgical shock in dogs and proposed that vasodilatation was produced during shock as a result of a disproportionate nervous stimulation in which the vasomotor center was exhausted. He supported the vasomotor exhaustion theory of shock formulated by Malcom [98] in 1905 and popular during the nineteenth century, in opposition to the prevailing vasomotor paralysis theory of Mapother.

Erlanger et al in 1919 [37] described a number of changes that occur in the circulation of anesthetized dogs with traumatic shock when the intestines are exposed and manipulated. They also suggested that the failure of the vasomotor center to respond with a forceful constriction to the stimulus of a low arterial pressure was a secondary event in this type of shock. The same year, Erlanger and Gasser [36] performed animal studies using a combination of hypertonic solutions of gum acacia and glucose and showed their beneficial effects upon the circulation in experimental shock.

Prior to 1930 (cited by Hess et al) [60], it was believed that trauma and shock were associated to a substance similar to histamine, which produced vasodilatation. In 1930, Blalock [12] undertook experiments in dogs to ascertain if the hypotension of trauma to the extremities was due to the formation of a substance that exerts a general effect in the organism or whether the hypotension was due to a local effect of hemorrhage. He could only demonstrate that a sufficient loss of blood volume accounts for the reduction in blood pressure.

Freeman in 1932 [45] in experiments with cats studied the reduction in the circulating blood volume caused by the hyperactivity of the sympathetic nervous system after the injection of adrenalin in physiologic amounts or from the spontaneous emotional activity of the pseudoaffective state after decortication. He showed that the reduction in blood volume does not occur if the vasoconstrictor action of the sympathetic nervous system is inhibited by ergotoxine.

Phemister and Livingstone in 1934 [125] established the difference between primary and secondary shock. They applied the name primary shock to those situations in which shock develops rapidly and is caused by activity of the nervous system being nearly synonymous with the original medical term. In contrast, the term secondary shock was applied to those cases in which the disturbances are initiated by factors that lower blood pressure such as reduction in body fluids, mainly blood loss, anesthesia, bacterial toxins, mechanical obstruction embracing wide areas of circulation, extensive local edema, and certain endocrine disorders. The authors stated that those two entities should be distinguished based on their etiology instead of on the difference in their time of occurrence.

Subsequently, Brooks and Blalock in 1934 [21] classified shock from the etiological standpoint. They also conducted studies with specific reference to hemorrhage and trauma to muscle and suggested that an oxygen deficit might be responsible for tissue alterations that occur when both blood volume and pressure are reduced.

Heuer and Andrus [61] in 1934 performed experiments in dogs and used aqueous extracts of closed intestinal loops to evaluate their effects on blood pressure, blood volume and survival rate. They found that the intravenous injection of such extracts causes a significant initial fall in blood pressure followed by a secondary rise, which in turn produces a gradual fall in blood pressure leading to shock and death.

Werle et al [180] in 1942 working with dogs showed that the state of hypotension following severe hemorrhage is not necessarily equivalent to shock. They argued that in many animals, arterial pressures and pulses return to normal for several hours after

withdrawn blood has been reinfused even when such animals are coming closer to cardiac or respiratory failure and the viscera reveal no abnormal changes at autopsy.

However, Wiggers and Werle [181] in 1942 reported that the designation of hemorrhagic shock is justified only if progressive circulatory failure takes place after hypotension and the reinfusion of all withdrawn blood.

Frank et al [44] in 1945 assessed the existence of a state of "irreversibility" in hemorrhagic shock and also evaluated other intravenous infusion therapies for hemorrhagic shock refractory to the replacement of all shed blood.

In 1945, Lamson and De Turk [85] studied hemorrhagic shock in a canine model based on the use of a pressure bottle system. They designed a method of studying hemorrhage by fixing an effect, that is, a specified reduction of blood pressure by hemorrhage. They introduced a cannula into the femoral artery and connected it to a pressure bottle by using a rubber tube, located at a height above the dog's heart at which the column of blood to the bottle would sustain the desired pressure. When the artery is open, blood will run into the bottle and the pressure will fall immediately to the target shock level. Bleeding will continue until equilibrium is reached and then blood will be found to flow in (take-up) or out of the animal, but the pressure will remain constant provided that the animal is able to maintain it. Their work established the basis for most of the research in hemorrhagic shock for more than four decades.

Wiggers et al [182] in 1945 studied the effects of local versus general anesthesia on the hemodynamic changes that occur during the irreversible phase of hemorrhagic hypotension in dogs. They found a greater susceptibility to such changes in locally anesthetized when compared to barbitalized dogs.

These revolutionary investigations became the basis for the use of blood and blood substitutes to resuscitate the wounded during World War II. Nonetheless, morbidity and mortality due to hemorrhagic shock were still exceedingly high.

Between 1941 and 1945, sufficient data were accumulated that allowed Wiggers [183] in 1950 to conduct a series of investigations that set the basis and criteria for experimental hemorrhagic shock and the factors involved in its production. Wiggers delineated three stages of hemorrhagic shock: a phase of hemorrhagic hypotension in which the animal is able to recover, depending on the amount of blood loss; an imminent shock state with more than 40% of blood loss in which the animal is also able to recover if the sustained hypotension is overcome through the administration of adequate therapy; and a late phase of irreversible shock that is produced during the hypotensive period (40 mm Hg), from which survival is not possible despite restoration of the original blood volume.

In 1956, Yard and Nickerson [190] using light pentobarbital anesthesia in dogs, demonstrated that prolonged infusions of noradrenaline in amounts equivalent to those received by patients could cause death associated with typical signs of irreversible shock.

Walton et al [174] in 1959 explored the effects of the sympathetic nervous system during hemorrhagic shock. They observed progressive increases in the concentration of epinephrine attaining extreme levels at terminal stages; norepinephrine increased moderately, but the force and pressor responses declined in association with progressive acidosis.

In 1961, Rosenberg et al [137] contributed to the knowledge of hemorrhagic shock by studying the relationship between circulating vasoactive amines (epinephrine, norepinephrine, and serotonin) and vasomotor changes. They found that following the beginning of hemorrhagic hypotension, peripheral concentrations of endogenous epinephrine rise significantly compared to control values. Subsequently, they decrease but never approach normal levels. After reinfusion of shed blood, catecholamines decrease in a similar remarkable trend to which they increase. They also found that pronounced changes in serum serotonin concentrations do not occur during hemorrhagic shock. They stated that hemorrhagic shock results from ischemic changes of the bowel, liver or kidney, secondary to vasopressor amine activity superimposed on oligemia. They also suggested that preferential vasoconstriction serves to preserve blood flow to the heart and brain, which do not share in the increased resistance in their vascular beds.

1.1 PATHOPHYSIOLOGY OF HEMORRHAGIC SHOCK

In hemorrhagic shock, the reduction of the effective circulating blood volume in concert with the diminished cardiac output contributes to the curtailment of tissue oxygen delivery, making tissue hypoperfusion the common denominator in all forms of shock [139].

A series of physiological responses intended to produce compensatory adjustments to the hemorrhagic insult occur. These responses entail hemodynamic, neuroendocrine, metabolic, and inflammatory changes (Fig. 1.1).

Hemodynamic and Neuroendocrine Changes

The hemodynamic adjustments in hemorrhagic shock will depend on the degree of Hemorrhage. For example, in man, if blood loss is minimal (<15 %); the vascular response produces an early transfer of extracellular fluid into the intravascular compartment (ultrafiltration of fluid back into the circulation) in an attempt to replace the diminished plasma volume [30]. With moderate hemorrhage (~ 30 %), the arterioles respond with vasoconstriction, blood flow to skin and muscle is reduced, heart rate is increased, and cardiac output is reduced. Mild non-respiratory (lactic) acidosis occurs and a decrease in both urine volume and urinary sodium ensues. The clinical expression is thirst, orthostatic hypotension, weakness, and pallor [30]. When blood loss is severe (> 40%), cardiac output significantly declines, hypotension appears and splanchnic blood flow is impaired. Marked non-respiratory lactic acidosis, oliguria and hypoxia result. Clinically, there is air hunger and altered mentation [30].

A biphasic hemodynamic response characterizes hemorrhagic shock. The initial phase is typified by intense vasoconstriction due to an increase in sympathetic nervous activity resulting in a marked elevation of circulating catecholamines. Specific high pressure baroreceptors (stretch receptors reflexes) and chemoreceptors located at the level of the aortic arch and the carotid sinus, and low-pressure and stretch receptors located in the atria are activated. Low-pressure as well as stretch receptors sense the decrease in the effective circulating blood volume and blood pressure, respectively. These receptors carry vagal afferent fibers that send inhibitory messages to the nucleus *tractus solitarius* (central processor) in the medulla oblongata, which modulates the activation of the autonomic sympathetic nervous system setting off an array of events

leading to the stimulation of catecholamine synthesis and the release of these mediators by both peripheral adrenergic nerves (increased vasomotor tone) and the adrenal medulla [120, 121].

There is a spillover of norepinephrine from synaptic clefts of peripheral nerves and degranulation of the A cells of the adrenal medulla releasing epinephrine and norepinephrine with epinephrine being secreted in greater amounts. The degranulation of the adrenal medulla is rapid, taking approximately 5 minutes after the initiation of hemorrhage. At the systemic level, catecholamines interact with β_1-adrenoreceptors in the heart increasing myocardial contractility and heart rate. Venous return is also augmented by constriction of capacitance vessels. The body also tries to increase systemic perfusion pressure primarily through mediation of α_1-adrenoceptors that cause vasoconstriction. Furthermore, additional nonadrenergic mechanisms (the rennin angiotensin system and other pressor agents) play a role of varied degrees in these hemodynamic changes [117].

High levels of hydrogen ions increases in CO_2 levels, or a low O_2 concentration stimulate different receptors, located in the aortic and carotid bodies. Low arterial O_2 content stimulates peripheral chemoreceptors. In contrast, CO_2 and H^+ are capable of stimulating central chemoreceptors [121].

The initial adjustments of the neuroendocrine system are favorable causing early tachycardia, vasodilatation of the coronary arteries, and constriction of the arteries in skeletal muscle and in the splanchnic circulation. These compensatory responses assure a preferential circulation to critical organs such as the heart, brain and liver at the expense of the skin, skeletal muscle, and the viscera [133, 137, 72, 43, 80, 121].

The sympathetic drive also occurs in the microcirculation, but it must be emphasized that the vasomotor changes are not homogeneous and that a marked redistribution of blood flow occurs [104, 121].

Initially, the activation of the sympathetic nervous system leads to a constriction on both sides of the capillary bed. But the arteriolar constriction causes the precapillary resistance to increase to a greater degree than the resistance in the venous side (at the post-capillary level), resulting in a decrease of mean hydrostatic capillary pressure; therefore, the Starling equilibrium, which tries to preserve the balance between fluid exchange into and out of the blood and tissue compartment is modified in such a way that fluid moves back to the intravascular compartment. Yet, despite this compensatory response, the vasoconstriction mediated by the sympathetic nervous system causes a reduction in blood flow through the capillaries, with blood being redirected through arteriovenous and capillary shunts. In consequence, even though this widespread sympathetic response maintains perfusion pressure, venous return, circulating blood volume, and myocardial contractility, it does so by compromising the "effective" circulating blood volume and microcirculatory flow. Apparently, this reduced tissue perfusion is capable of sustaining minimal oxidative cellular metabolism for a limited period of time [121].

The second late phase of hemorrhagic shock is a stage of decompensation set off when the initial compensatory responses are no longer favorable. The vasculature does not respond to either endogenous or exogenous catecholamines resulting in a phenomenon known as vascular hyporeactivity.

Vascular hyporeactivity is characterized by progressive vasodilatation and hypotension that leads to “irreversible” shock if the animal remains untreated.

The irreversible phase of hemorrhagic shock has been delineated as that stage in which there is a non-homogenous distribution of blood flow in the face of fluid resuscitation [121]. Flow reappears in the skeletal muscle beds, but with a marked maldistribution.

According to Peitzman [121], in normal conditions, 90% of capillaries are open. In contrast, during the period of hemorrhagic shock, only 30% to 50% of capillaries are open. Fluid resuscitation restores normal blood pressure, but arteriolar flow achieves only 40% of normal within 2 hours after resuscitation.

As mentioned in the Introduction, it is believed that the second phase is caused by poor tissue perfusion, a reduction in functional capillaries, the development of nonrespiratory (lactic) acidosis and a loss of vasomotor tone [121, 94].

The reduced systemic pressure and the subsequent increase in peripheral resistance caused by hemorrhagic shock impinge upon the microcirculation resulting in a severe imbalance in both hydrostatic capillary and colloid osmotic pressures. With time, a gradual overall sluggish flow in most of the capillaries develops. During this period, the hydrostatic capillary pressure begins to increase somewhat.

According to Zweifach and Fronek [194], at this stage hemodilution is maximal so that even if the hydrostatic capillary pressure were below normal, it would still be higher than the existing coll oid osmotic pressure. Furthermore, there is increased capillary permeability. The final result is a transfer of fluid from plasma into the interstitial space. The accumulation n of products of anaerobic metabolism (lactic acid) and certain

vasoactive agents such as prostaglandins (PGE2 and PG12) worsen the microvascular refractoriness perpetuating the attendant vasodilatation that occurs in this syndrome [139]. The outcome of this refractoriness is hemoconcentration, increased blood viscosity, and decreased velocity of flow in the microcirculation. This condition is further complicated by the presence in vessels of platelets, erythrocytes, and granulocytes that form thrombi that adhere to the vessel walls therefore creating an obstruction to blood flow [121].

Other hormonal responses to acute blood loss are involved. The renin-angiotensin system is a complex endocrine unit that includes the kidney, liver, and vascular endothelium. Angiotensinogen is a powerful vasoconstrictive α_2-globulin secreted by the liver that is converted to angiotensin I through an enzymatic reaction catalyzed by renin (a protease secreted by the kidney). Angiotensin I is then transformed into angiotensin II by the angiotensin-converting enzyme located in the vascular endothelium [169,131].

The renin secretion from the juxtaglomerullar apparatus is controlled by three mechanisms [169, 69,131]**:** The macula densa pathway, the intrarenal baroreceptor pathway, and the β-adrenergic receptor pathway. The macula densa is a region of the kidney that lies adjacent to the juxtaglomerular apparatus and is composed of specialized cells located in the wall of the thick ascending limb between the afferent and efferent arterioles. Variations in Na^+ balance are sensed by the macula densa causing the transmission of chemical signals that stimulate the release of renin.

The intrarenal baroreceptor pathway responds to increases and decreases in blood pressure. When hemorrhagic hypotension ensues, the afferent renal arteriole baroreceptors react by increasing renin release leading to the formation of angiotensin II resulting in vasoconstriction.

The β-adrenergic mechanism is mediated by the release of norepinephrine from postganglionic sympathetic nerve terminals. The activation of β_1-adrenoceptors on the juxtaglomerular apparatus enhances renin secretion.

Trachte [169] states that an acute blood loss increases renin secretion more than a slow hemorrhage and that the increase in plasma renin activity does not disappear with time but is sustained during the decompensatory stage of hemorrhagic shock.

In hemorrhagic shock, angiotensin II enhances sympathetic nerve activity. Angiotensin II, with its potent pressor action causes direct constriction of arteriolar smooth muscle. It also increases blood pressure by direct action on the brain and autonomic nervous system. This hormone stimulates autonomic ganglia, increases the release of epinephrine from the adrenal medulla, and facilitates sympathetic transmission by an action on adrenergic nerve terminals. Angiotensin II also stimulates the biosynthesis of aldosterone by the adrenal cortex [131].

Angiotensin II causes renal vasoconstriction, increases proximal tubular sodium reabsorption and inhibits the secretion of renin by a servomechanism (the so-called short-loop negative feedback). Angiotensin II acts in concert with ADH to constrict splachnic blood vessels.

Aldosterone is a mineralocorticoid hormone synthesized in the adrenal cortex. Its concentration is elevated due to an increased release of renin. Aldosterone tries to compensate for the decreased blood volume by increasing Na^+ reabsorption and K^+ and H^+ excretion at the distal and collecting renal tubules [143, 131].

The antidiuretic hormone (ADH) is involved in the compensatory responses to hemorrhagic shock as well. ADH is synthesized by the neurohypophysis and its secretion is normally mediated by osmoreceptors located in the hypothalamus in response to increased body fluid osmolality, decreases in blood volume, blood pressure, or β-adrenergic stimulation. ADH has been shown to play a role in the maintenance of blood pressure during hemorrhagic shock by causing a powerful splanchnic vasoconstriction, and by increasing distal renal tubular and collecting duct reabsorption of water [139, 115].

Glucocorticoids also take part in the compensatory adjustments during hemorrhagic shock. Their effects are the result of their metabolic actions. Some of the effects are the consequence of direct actions in the cell. Glucocorticoids have permissive effects by facilitating the action of other hormones such as insulin and glucagon.

In hemorrhagic shock, there is increased biosynthesis and secretion of glucocorticoids. It is believed that high physiologic concentrations of cortisol may be necessary for a normal homeostatic response in hemorrhagic shock.

The actions of glucocorticoids in hemorrhagic shock include increases in plasma glucose concentrations. Glucocorticoids potentiate the hyperglycemic response of epinephrine in hemorrhagic shock [169, 52].

Metabolic Changes

Changes in the metabolic pattern of tissues take place as a result of low flow or perfusion states. Increased glycolysis and lipolysis, increased glucose, fatty acids and lactate levels in blood occur [149].

It has been considered that the most important metabolic effects of a low flow state like shock are manifested at a cellular level, in the energy-producing pathways**.** The diminished blood flow to tissues in circulatory shock causes low oxygen concentrations. Tissues require oxygen for the generation of high-energy phosphate bonds through oxidative phosphorylation; therefore cells will suffer from depletion in the generation of high-energy substrates such as ATP resulting in an energy deficit [149].

Derangements in mitochondrial function are seen in low flow states. Such derangements are manifested as increased mitochondrial free fatty acids and Ca^{2+} levels, decreased adenine nucleotide translocase activity as well as a serious damage in cell membrane transport processes [26].

Alterations in hepatic Na^{+}-K^{+} transport and Ca^{++} regulation in liver cells have been reported. These findings suggest that these alterations may partly be responsible for the impairment in hepatic glucose production but the mechanisms are unknown [142].

Nahas [111] reported in dogs increased VO_2 after moderate hemorrhage at normal pH and suggested that the increase could be related to the stimulation of the sympathoadrenal system and cathecholamine release despite a reduction in DO_2 due to hemorrhage. The author also suggested that acidosis limits the increase in VO_2 and might embody an additional interference to O_2 utilization by tissues during severe shock.

However, Radisavljevic [127] obtained different results when he performed *in vitro* experiments on isolated femoral arteries of rabbits undergoing hemorrhagic shock. This investigator evaluated the effects of a β-adrenergic agonist (isoproterenol) and showed a significant increase in VO_2 compared to control when isoproterenol was administered. The author suggested that the decreased VO_2 observed in the femoral artery during hemorrhagic shock probably occurs because of positional changes at the level of connection of β-adrenergic receptors.

Blood Flow to Organs

As mentioned earlier, in order to maintain adequate perfusion to key metabolic organs such as the heart and brain, neuroendocrine adjustments cause marked redistribution of CO among different vascular territories (preferential circulation).

Mathematical models [144] designed from *in vivo* experiments in dogs subjected to progressive hemorrhage suggest that redistribution of whole body DO_2 among organs (liver, intestine, kidney, and remaining carcass) enhances the ability of the whole animal to maintain VO_2 supply independent. Their data support the hypothesis that redistribution of flow is most probably mediated by regulation of regional vasomotor tone, thus enhancing the ability of the whole body to utilize O_2 efficiently to a state in which fractional distribution of flow among organs remains constant.

In 2000, Ba et al [6] found that flow redistribution alters local DO_2 and VO_2. According to them, due to regional maldistribution of blood flow, alterations in oxygen extraction occur. Consequently, the evaluation of systemic O_2 utilization after

hemorrhagic shock may not correctly reflect the severity of changes occurring at individual organs because DO_2, VO_2, and O_2ER would be altered both systemically and regionally.

It has been well established [140] that the main cause of death in patients suffering from acute respiratory distress syndrome, sepsis syndrome, and septic shock is multiple system organ failure. A pathologic dependence of VO_2 on DO_2 has been invoked as the pathophysiologic mechanism responsible for death in those patients. As a result, some authors [151, 74] have suggested that increasing DO_2 and VO_2 to supranormal levels are the physiologic goals of therapy in the critically ill patient because they correlate with better survival. According to them, hemorrhagic shock is a hypermetabolic state and reaching supranormal levels of DO_2 supplies the needs of an increased metabolism associated with hemorrhagic shock.

However, others [140, 136] do not advocate the use of these strategies. In fact, studies in humans concerning the pathologic dependence of VO_2 (the dependent variable) on DO_2 (the independent variable) indicate that those variables share the measurements of CO and arterial oxygen content. These authors argue that the problem of the effect of mathematical coupling of shared variables is that the correlation between VO_2 and CO is entirely artificial (artifactual), leading to an incorrect understanding of the relationship between whole body DO_2 and VO_2. Fig. 1.2 depicts the central role of O_2 in metabolism and the consequences of its absence.

Role of the Mesenteric Circulation in Hemorrhagic Shock

The contribution of the mesenteric circulation to the understanding of the hemorrhagic shock syndrome is crucial. Lillehei [91] in 1957 studied bowel lesions in dogs to determine their role in the production of irreversibility in hemorrhagic shock. The remarkable findings were mucosal congestion and necrosis of the bowel. He suggested that the lesions were seemingly the consequence of the critical ischemia that occurs during the shock period, possibly enhanced by the rich bacterial flora present.

Esrig et al [38] in 1977 undertook experiments in rats to determine if animals resuscitated from hemorrhagic shock are more susceptible to infection than animals not suffering from hemorrhagic shock. A sublethal dose of bacteria (*Escherichia coli*) resulted in 100 per cent mortality. Although the authors suggested that resuscitation from hemorrhagic shock impairs the host defense mechanisms predisposing to infection, they did not provide an explanation as to the precise mechanism involved in the deaths of these animals.

Stephan et al in 1987 [159] performed *in vitro* experiments using a nonlethal and clinical relevant hemorrhagic shock model without significant tissue trauma in endotoxin-resistant mice and showed a significant depression of cellular immunity (depressed proliferation of T lymphocytes) following hemorrhage despite fluid resuscitation, thus enhancing susceptibility to sepsis. The authors suggested that interleukin 2 production by splenocytes is severely depressed after hemorrhage and antigen presentation capability is impaired during hemorrhage.

Flynn et al in 1991 [42] performed *in vivo* video microscopic studies of the intestinal microcirculation in rats and showed that hemorrhage causes vasoconstriction of first and second order arterioles with decrease blood flow. Third order and fourth order arterioles are dilated and blood flow is heterogeneous. Flow in postcapillary venules is sluggish with the presence of an increased number of white blood cells adhering to the venule walls. They also showed that fluid replacement and the addition of a pharmacological agent such as pentoxifylline to the rat in hemorrhagic shock restores intestinal microvascular blood flow.

Theuer et al in 1995 [166] conducted intravital microscopy studies to determine if arteriolar vasoconstriction is mediated by α-adrenergic receptors during hemorrhagic shock and resuscitation in rats anesthetized by means of a precolicular stereotactic brainstem transection. Their findings revealed that hemorrhaged and resuscitated animals develop A_1 constriction and hypoperfusion with A_3 arteriolar dilatation. They found that α-adrenergic stimulation is a major mechanism of arteriolar vasoconstriction during hemorrhage. According to the authors, the intestinal microcirculatory responses are heterogeneous and might be attributed to multiple control mechanisms. They postulated that an inhibition of vasodilators (decreased secretion or increased consumption) would likely contribute to progressive constriction. On the other hand, the arteriolar dilatation was explained in terms of the presence of β-adrenergic receptors in the intestinal circulation, which would mediate dilatation.

Garrison and his associates [50] in 1998 worked with rats undergoing hemorrhagic shock and resuscitation with sequential bacteremia and reported increased dilatation in premucosal vessels and enhanced constrictor forces in inflow vessels. Their findings

showed that hemorrhagic shock along with resuscitation followed by bacteremia alters intestinal microvascular endothelial cell control. The authors suggested that these changes contribute to the hyperdynamic cardiovascular state seen during the initial developmental phases of multiple systemic organ failure.

Baker et al in 1998 [7] reported that rats subjected to longer periods (90 minutes) of hypotension previous to reinfusion of shed blood had both a higher mortality and an elevated occurrence of bacterial translocation than rats exposed to lesser periods (30 or 60 minutes) of shock. They suggested a possible relationship between the duration of the shock period and the incidence and extent of bacterial translocation. They raised the hypothesis that hemorrhagic shock injures the intestinal mucosal barrier allowing bacterial translocation.

More recently (2001), Reilly et al [132] called the attention with regard to the role of the mesenteric hemodynamic response to circulatory shock. They stated that the mesenteric response to both cardiogenic and hemorrhagic shock is the reflection of the systemic neurohumoral response added as a dominant feature and essentially superseding the local hemodynamic control mechanisms such as pressure-flow autoregulation, particularly regarding the precapillary resistance vessels.

In summary, the events that take place in the hypoperfused gut are key to the understanding of the multiple factors involved in the pathogenesis of hemorrhagic as well as other types of shock. Gut hypoperfusion ensuing after shock plays a crucial role in the generation of the systemic inflammatory response syndrome and multiple systemic organ failure commonly seen in hemorrhagic shock. [58].

1.2 VASCULAR HYPOREACTIVITY IN HEMORRHAGIC SHOCK

During the development of hemorrhagic shock, the circulation responds with compensatory mechanisms [4], which tend to counterbalance the diminished effective circulating blood volume. As mentioned earlier, two phases have been described in hemorrhagic shock: An early phase, characterized by a neurohumoral reaction with the activation of the sympathetic nervous system and the release of circulating catecholamines from the adrenal medulla (norepinephrine, epinephrine) and the activation of the renin-angiotensin system. These reactions cause vessel constriction and an increase in heart rate [179, 9]. This compensatory autonomic response mechanism initially elevates peripheral vascular resistance. The second phase develops late in shock when the peripheral vasculature (mainly the skeletal muscle vascular bed, the skin and the viscera) falls in a state of enduring vasodilatation and becomes refractory to the action of cathecolamines of intrinsic or extrinsic origin. This phenomenon has been termed vascular hyporeactivity or vascular hyporesponsiveness. Vascular hyporeactivity is considered to be one of the mechanisms linked to the transition from the compensated to the decompensated phase (irreversibility) that occurs in hemorrhagic shock after blood reinfusion [20].

Vascular hyporeactivity is not a new finding. In 1943, Page [116] studied the result of trauma to the central nervous system and of marked hemorrhage and the vascular response to angiotensin in dogs and cats. He thought that the diminished response was the consequence of both “abuse” to the nervous system and marked hemorrhage. He noticed that the syndrome was also produced in the absence of the kidneys and the adrenal glands.

The same year, Kohlstaedt and Page [79], conducted studies in dogs and observed that hemorrhage decreases the response to angiotensin and that restoration of normal blood pressure does not necessarily imply the return to vascular responsiveness. They also reported that animals did not survive unless there was an immediate normalization of pressor response after treatment.

Remington et al in 1950 [133] evaluated the circulatory responses of dogs undergoing serial hemorrhage. They reported a general loss of vascular responsiveness that was not exclusively attributed to epinephrine. They suggested that the lack of responsiveness could also be associated to the acute hypoxic state.

In 1953, Kovách and Takács [81] working with dogs in hemorrhagic and ischemic shock reported diminished splanchnic and adrenaline responses. They suggested that vascular hyporeactivity was largely due to a reduced amount of blood in the circulation.

Walton et al in 1959 [174] working with dogs reported a virtually total refractoriness of the circulatory system to catecholamines at the terminal stages of hemorrhagic shock despite an increase in the concentration of these amines.

Rothe et al in 1963 [138] worked with dogs and provided data supporting the hypothesis that the neurogenic control of the cardiovascular system progressively deteriorates leading to a decreased total peripheral resistance during the period of reinfusion. The authors argued that even though there is incomplete failure of peripheral resistance vessel tone during severe hypotension, the failure is a small component of the progressive cardiovascular failure and is not the origin of irreversibility.

The same year, Mellander and Lewis [104] in studies with cats, found that the reduction of regional blood flow to skeletal muscle impairs and abolishes the reactivity of the skeletal muscle vascular bed to stimulation of lumbar sympathetic vasoconstrictor nerve fibers and to close intra-arterial infusions of norepinephrine.

Hildebrand and Says in 1967 [63] studied the pressor responses to acetylcholine during hemorrhagic shock in rabbits and found an altered reactivity of vascular smooth muscle to neurohumoral agents. They suggested that the hyporeactivity was probably due to membrane depolarization and that such hyporeactivity could be the common denominator in the pathogenic mechanism of hemorrhagic as well as endotoxic shock.

In 1968, Calvert and Lum [24] performed experiments on a standardized hemorrhagic shock model in dogs and found reduced pressor responses to the injection of norepinephrine, epinephrine and tyramine, following reinfusion of blood.

The decade of the seventies brought more progress to the knowledge of vascular hyporeactivity. Heistad and Wheeler in 1970 [59] demonstrated in humans that acute hypoxia interferes with vasoconstrictor responses of adrenergic stimulation (neurogenic reflexes). They drew attention to the importance that neurogenic vasoconstriction has regarding compensation for acute blood loss.

In 1974, González and Bond [54] conducted studies on skeletal muscle vasculature in dogs and reported an increase in conductance. They deduced that the early rise in skeletal muscle vascular conductance is not originated by a neurogenic malfunction, but is due to dilatory factors affecting the arterioles.

Bond et al in 1977 [18] studied blood-borne and neural-mediated mechanisms during skeletal muscle vascular decompensation and did not find any correlation between vascular decompensation and perfusion pressure, arterial blood gases, arterial pH, blood flow and elements present in the arterial blood of shocked dogs. They suggested that the decompensation was the result of a local depression of hyperactive adrenergic receptors or an enhanced activation of vasoinhibitory fibers as the major factor responsible for the inconsistent skeletal muscle vascular decompensation that occurs during prolonged hypovolemic hypotension.

In 1982, Perbeck and Hedqvist [123] using a fixed model of hemorrhagic shock in anesthetized rats studied the blood pressure responses that occur during hypovolemia and found an association between a decrease in the norepinephrine response and the length of the hypovolemic period and to the arterial perfusion pressure as long as the pressure is lower than 60 mm Hg. They also postulated that high concentrations of catecholamines, substrate fatigue and acidosis are secondary factors responsible for vascular hyporeactivity, emphasizing the importance of adequate tissue perfusion as a protective mechanism against this disorder.

Zhao et al in 1985 [191], conducted *in vivo* studies with intravital preparations of skeletal muscle of rats subjected to hemorrhagic hypotension and replacement of blood volume. They observed different pressor responses between survivors and non-survivors. There was depressed sensitivity to epinephrine in arterioles in non-survivors postinfusion, as opposed to a maintained arteriolar responsiveness in survivors after reinfusion.

Korner et al [80] in 1990, working with rabbits, studied the local vascular effects of hemorrhage and the influence of neural and hormonal constrictor effects. They found that the maintenance of MAP was completely mediated by the central nervous system at the beginning of hemorrhage. They also demonstrated that the constrictor actions of arginine-vasopressin and angiotensin II play a significant role during the hypotensive phase following bleeding (interval). When total autonomic blockade is produced, the hormonal constrictor influences are markedly improved during and post-hemorrhage, but the neural mechanisms are more effective in maintaining blood pressure.

The Microcirculation during Hemorrhagic Shock

Numerous factors can contribute to the development of the shock syndrome, but the majority of researchers have chosen to use hemorrhage as the mechanism for precipitating the circulatory insufficiency in a distinct progression of events [194]. The peripheral circulation and the microcirculation interact when homeostasis is disrupted during hemorrhagic shock. Severe hemorrhage activates a series of compensatory reactions intended to save the animal's life. The peripheral circulation plays a crucial role in this compensation by means of hemodynamic, neuroendocrine, biochemical, and inflammatory adjustments.

As mentioned earlier, the fall in MAP is sensed by specific stretch receptors activating the baroreceptor reflexes. These in turn will activate the sympathetic autonomic nervous system leading to the stimulation of peripheral adrenergic nerves and the adrenal medulla. Catecholamines such as adrenaline (the major hormone of the adrenal medulla) and noradrenaline (from postganglionic sympathetic fibers of peripheral nerves) are released and cause simultaneous increases in HR and the contractile force of

the heart and widespread peripheral vasoconstriction. Furthermore, other nonadrenergic mechanisms (the renin-angiotensin system, the arginine-vasopressin system and aldosterone) play a role in these hemodynamic changes as well [117].

The neuroendocrine system initially exerts favorable adjustments in hemorrhagic shock, sustaining a preferential circulation to critical organs such as the heart, brain, and liver at the expense of the skin, skeletal muscle, and splanchnic organs [133, 72, 43, 80].

However, as hemorrhagic shock persists, the heart is not capable of sustaining an effective CO so that blood pressure remains subnormal despite extensive peripheral vasoconstriction. Therefore, therapeutic measures (fluid therapy, plasma substitutes) have to be taken, to avoid the animal's demise. If hypotension extends (2 hours or longer), the circulation worsens despite replacement of volume deficit [194].

One of the significant aspects that cause the disruption in the stability of the circulation is that in the face of hypoperfusion, the central and peripheral requirements of blood through the tissues are different. Despite the existence of interplay between central and peripheral factors, the mechanisms of adjustment have opposite effects. As mentioned above, at a systemic level, the autonomic sympathetic nervous system exerts control of the failing circulation by increasing the inotropic property of the heart and by causing an initial increased peripheral resistance. At the same time, at the microcirculation, the precapillary vessels relax to try to overcome the inadequacy of blood flow that creates hypoperfusion [194, 55].

The microcirculation has been structurally defined as a unit comprising all microvessels with a diameter smaller than 250 μm. In contrast, the larger arteries and veins are termed the macrocirculation [86].

Different techniques such as video image shearing and splitting [68] and microscopic transillumination [16] have been used to describe and characterize microcirculation vessel diameters, vascular geometry, and red cell velocities. Basically, the microcirculation has been divided into three groups: the arterioles, with a size between 8 μm and 250 μm, the capillaries, with less than 8 μm, and the venules, with a size equal or greater than 8 μm and less than 250 μm [86]. The microcirculation nomenclature is assigned in accordance with a branching order [55].

Further subdivisions have been described for the arterioles as well as for the accompanying vessels; for example, the arterioles (A vessels) have been subdivided in first order (A_1), second order (A_2), third order (A_3), fourth order arterioles (A_4), central arteriole, transverse arterioles, and precapillary sphincters. (See Table 1.1 for details).

From the physiological standpoint, the microcirculation serves the purpose of conveying nutrients to tissues and removing cellular waste [55]. The microcirculation locally regulates blood flow when the arterioles and capillary sphincters constrict to change the level of perfusion and affect the flow heterogeneity of the network [86].

Each organ has a specifically designed microcirculation according to the organ's needs. Blood enters the capillary bed through the arterioles and leaves through the venules. Blood that comes from the arterioles passes through a series of metarterioles (the terminal arterioles). From the metarteriole, blood penetrates the capillaries. After passing through the capillaries, blood forces its way into the venules and returns to the general circulation [55].

It has been suggested [86] that the microcirculation might contain 40%-50% of the total blood volume. The arterioles and capillaries have been represented as a resistance unit whereas the arterial and venous microcirculations have been modeled as the capacitance components [86].

The involvement of the microcirculation in hemorrhagic shock has been studied for many years and has been the subject of debate by many researchers in the field. In fact, certain characteristics of the capillary circulation are accentuated in hemorrhagic shock: increases in vasomotion and exaggerations of reactivity of the capillary bed smooth muscle components to different stimuli [193, 194].

Zweifach and his associates in 1944 [193] conducted studies in rats anesthetized with sodium pentobarbital. They evaluated the vasomotion as well as the reactivity of the vascular smooth muscle components of the capillary bed to mechanical (cuff compression of the thigh) and chemical (topical application of epinephrine) stimuli and concluded that the worsening of perfusion was not a failure inherent to the intrinsic properties of the capillary bed, but rather of a feeble force from the lowered blood pressure.

Lewis and Mellander in 1962 [89] compared the effects of sympathetic control and tissue metabolites on resistance and capacitance vessels and capillary filtration in skeletal muscle of cats and showed that the precapillary side (resistance vessels, precapillary sphincters) responses are more under the influence of local dilating metabolic factors than the postcapillary (postcapillary resistance vessels, capacitance venules) responses. According to the authors, these postcapillary responses are more susceptible to the influence of extrinsic nervous factors.

In 1963, Schumer and Durrani [145] in experiments with dogs described a depression in reactivity of arteriolar and capillary sphincters which led to a stagnation of blood in the capillary area. They also noticed that blood was no longer confined to the main vessels.

Hutchins et al [66] in 1973 evaluated the microvasculature of skeletal muscle of rats anesthetized with a combination of urethane and chloralose and reported that venular dilatation is the vascular defect associated with the onset of irreversibility in hemorrhagic shock. However, differential responses in the skeletal muscle microcirculation have been found in hemorrhagic hypotension. In 1980, Amundson et al [5] reported the existence of blood flow maldistribution in skeletal muscle capillary bed of cats subjected to hemorrhagic shock. They also found that leukocytes were lodged and adhered to capillaries and venules. In addition, they reported metabolic changes manifested by increases in lactate, glucose and glucose-6-phsophate.

Flint et al in 1984 [41] studied the responses of the microcirculation to norepinephrine in unanesthetized decerebrate rats undergoing hemorrhagic shock. They reported that larger arterioles (143 to 152 μm) show persistent constrictor responses with lowered sensitivity to norepinephrine. In contrast, smaller arterioles (11 to 22 μm) and venules dilate but preserve constrictor responses to norepinephrine. They suggested that dilator responses contribute to decompensation in small arterioles and venules, but the decompensation is not linked to norepinephrine constrictor response.

In 1985, Colantuoni et al [29] studied the behavior of vessels in the microcirculation in the skin of unanesthetized hamsters under hemorrhagic shock and found that vasomotion disappears, but can be restored after reinfusion of shed blood.

They also demonstrated that arterial vasculature reacts in a different way during hemorrhage depending on the vessel type and the branching order. They showed that A_1, A_2, and A_3 arterioles contract; in contrast, A_4 arterioles markedly dilate. The authors suggested that the heterogeneity of arteriolar response is a consequence of the competition among sympathetic activity, production of local metabolites, activation of β-adrenergic receptors, and myogenic effects.

Garrison and Cryer [49] in 1989, conducted investigations in decerebrate rats with hemorrhagic shock using a cremaster muscle preparation and reported vasoconstriction in larger arterioles (A_1 and A_2) and venules (V_1 and V_2) and vasodilation in smaller arterioles (A_3 and A_4). They suggested that this phenomenon could be the result of autoregulation: vasodilatation with low perfusion pressure as a result of the release of dilator substances including nitric oxide in tissue, changes in tissue PO_2, PCO_2, or pH or changes in the capacity of certain vessels to respond to constrictor substances such as norepinephrine.

More recently, biomedical research [86] has provided evidence indicating that the microcirculation has a more critical role as a reservoir than the venous system to compensate for blood volume loss. These investigations call attention to the importance of the microcirculation as both a focus for therapy and effective diagnosis.

Hemorrhagic Shock and the Endothelium

An important breakthrough in cardiovascular physiology was the discovery in 1980 by Furchgott and Zadwaszki [47, 48] of nitric oxide (NO). They, along with other investigators [67, 128, 192, 167] demonstrated that NO is one of the mediators responsible for the hyporeactivity in both hemorrhagic and endotoxic shock due to excess

synthesis. NO is a messenger, synthesized at the level of the endothelium and other regions of the body. NO is one of the mediators of the relaxation of vascular smooth muscle elicited by acethylcholine. These authors showed that vascular smooth muscle relaxation was possible if the integrity of the endothelium was preserved [118, 170, 192, 77, 150].

Aisaka et al [2] in 1989**,** working with guinea pigs showed a continuous basal release of nitric oxide from vascular endothelial cells. These cells modulate vascular smooth muscle tone through the synthesis and release of endothelium-derived relaxing and contracting factors.

The ubiquitous gas NO was later shown to be a major mediator in the regulation of vascular tone and myocardial contractility *in vivo* in humans as well as in other species [93].

The role of NO as a modulator of peripheral resistance and blood pressure has been confirmed in rats during hemorrhagic shock. Lieberthal et al [90] in 1991, showed that the inhibition of nitric oxide by analogues of L-arginine (a precursor in the synthesis of nitric oxide) increases blood pressure and modulates peripheral resistance in both normovolemic and hypovolemic rats. They concluded that the excessive production of NO is a contributing factor in the hypotension and renal hypoperfusion seen in severe hemorrhagic shock in this species.

Thiemermann et al in 1993 [167] conducted in *vivo* and *in* vitro experiments in rats and demonstrated that the vascular hyporeactivity that develops following prolonged periods of hemorrhagic shock is mediated by the enhanced formation of NO.

In 1995, Koch et al [78] worked with conscious rabbits and provided additional evidence on the role of NO in hemorrhagic shock. They used a NOS inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME), and showed that NO is partially responsible for the vasodilation seen during the acute hemorrhagic phase in this species.

In an experimental model of hemorrhagic shock, Goldstein et al [53] in 1999, treated rabbits with L-NAME and reported both increased efferent sympathetic cardiac activity and elevated mean arterial pressure, suggesting a role of NO in this syndrome.

The use of more potent NOS inhibitors to resuscitate animals in the early phase of hemorrhagic shock has shed light into the action of NO. Vromen et al [173] in 1996, evaluated S-isopropyl isothiourea and showed an improvement in blood pressure and renal and splachnic blood flow, suggesting that it was due to an increased perfusion pressure.

In vivo studies [80] in arteries of cats suffering from hemorrhagic shock have also revealed regional differences in both contractile and endothelium-dependent relaxant properties with preponderance for middle cerebral arteries.

Work *in vitro* with feline middle cerebral arteries [161] has demonstrated that even hypotension of short duration in conjunction with retransfusion significantly inhibits NO-mediated, agonist-induced endothelium-dependent cerebrovascular responses. Their work suggested that an exhaustion of the endogenous vascular L-arginine pools could occur.

In 1989, Mazzoni et al [101] provided evidence of capillary lumenal narrowing in skeletal muscle capillaries of rabbits. According to them, swelling of endothelial cells produces endothelial narrowing. This finding reflects the complex hemodynamic

alterations in experimental shock. Similar studies [162] have shown a selective impairment of the endothelium-dependent reactivity from the vascular bed of the kidney during and after hemorrhagic shock.

Many investigators have addressed the importance of NO as one of the mediators in the pathogenesis of hemorrhagic shock. Yao et al (1996) [189] in studies with rats subjected to prolonged (180 minutes) hemorrhagic shock, evaluated the role of NO in pathophysiological alterations and multiple organ failure and found an increase in endogenous endotoxin in the circulation at the end of resuscitation, and a high incidence of bacterial translocation in the wall of small and large intestines, together with formation of tumor necrosis factor (TNF, a type of cytokine secreted by macrophages, lymphocytes, and nonimmune cells). The authors suggested that increased concentrations of endotoxin and TNF resulting from the hypotensive insult could be responsible for the enhanced induction of NO.

In 1998, Hierholzer et al [62] in experiments with rats provided evidence indicating that an inducible NO (iNO), induced by a specific NOS, is necessary for upregulation of the inflammatory response in resuscitated hemorrhagic shock and that this messenger is involved in the end organ damage under these conditions. They suggested that organ damage is probably due to the combination of NO to form peroxynitrite, which could exert direct toxicity in lung and liver.

In 1999, Menezes et al [105] showed in rats that NO plays a role in shock-induced tissue injury. The authors also demonstrated that suppression of NO availability with NO scavengers may reduce the pathophysiological sequelae of severe hemorrhage.

In 2000, Tamion et al [165] found in a rat model of hemorrhagic shock followed by resuscitation that reactive oxygen species (ROS) contribute to the production of proinflammatory cytokines and macrophages in the systemic and mesenteric circulation during posthemorrhagic resuscitation. They suggested that ROS are major contributors of tissue injury and systemic inflammatory response and contribute to the production of cytokines by different cell types.

Inflammatory Responses

Hemorrhagic shock induces the reactivation of an inflammatory response (Fig. 1.3) typified by the upregulation of cytokine (an inflammatory mediator) expression and a buildup of neutrophils in a variety of tissues. Hypoperfusion, ischemia-reperfusion injury, bacterial products, or immune reactions trigger this response [139, 56, 121].

Depression of cellular immunity along with enhanced susceptibility to sepsis has been found following hemorrhage despite fluid resuscitation. This immunosupression has been linked to depressed proliferation of T cell lymphocytes [159].

Hemorrhagic shock activates the inflammatory cascade and the ischemic or injured vascular endothelium upregulates receptors for monocytes and neutrophils adherence. The activation of leukocytes takes place, leading to the synthesis of cytokines, prostanoids, and other soluble factors, causing additional injury [103].

In summary, research in hemorrhagic shock has brought important contributions to the knowledge of this very complex entity. This syndrome embraces a multiplicity of events along with the involvement of different organ systems, which makes the study of this disorder more difficult. However, significant progress has been made in the knowledge of its pathogenesis. Investigations have tried to elucidate the role of vascular

hyporeactivity as one of the factors implied in the decompensation of hemorrhagic shock. Researchers have also concentrated their attention to study hemorrhagic shock at different levels (clinical, pharmacological, cellular, and molecular) to shed more light into its pathophysiology. Investigations have also provided vital information that demonstrates that during the development of hemorrhagic shock, the gastrointestinal tract participates in the production of the systemic inflammatory response syndrome as a complication of the multiple system organ failure.

More work is needed to clarify the contribution that each section of the cardiocirculatory system (periphery, microcirculation, heart) has in bringing about the disruption of the homeostatic mechanisms that lead to the patient's demise.

Lack of improvement in patients suffering from hemorrhagic shock has encouraged investigators to look for additional therapies (colloids, blood substitutes, inflammation inhibitors). Important progress has been made in the treatment of hemorrhagic shock with the use of fluids and blood substitutes [175, 176, 177, 25, 51, 135]. The availability of modern technology foresees a promising future for research in this field (See Table 1.2 for chronology of events in the study of hemorrhagic shock).

1.3 NON-RESPIRATORY (LACTIC) ACIDOSIS IN HEMORRHAGIC SHOCK

The diminished effective circulating blood volume (Fig. 1.2) leads to a reduction in venous return reflected in a fall in cardiac output. As a consequence, flow to different vascular beds is proportionately reduced. Tissues require oxygen to perform their metabolic functions, but oxygen transport to tissues is insufficient; furthermore, since hemorrhagic shock is a state of hypermetabolism, tissue oxygen demands are enhanced.

Consequently, there is a shift from aerobic to anaerobic metabolism and alternative pathways metabolize glucose. The end product of these pathways is lactic acid.

Lactic acid is metabolized in the liver to glycogen, but blood flow to this organ is compromised. The end result is the development of a non-respiratory lactic acidosis. Excessive lactic acid production renders lysosomal membranes susceptible to breakdown and once ruptured, they release their contents into the circulation causing autolysis and contributing to mortality [97].

As already discussed, the fall in pressure also stimulates high pressure baroreceptors, which send messages to the central processor in the medulla oblongata activating the thoracolumbar sympathetic outflow tract discharging norepinephrine from postganglionic sympathetic nerve fibers and adrenaline from the adrenal medulla. This in turn, causes general vasoconstriction to maintain the falling blood pressure. As a result, peripheral blood flow is further reduced and the effects of tissue hypoperfusion and oxygen deprivation form the so-called stagnant anoxia.

The importance of lactic acidosis in hemorrhagic shock has always been recognized. Tobian et al [168] conducted *in vitro* experiments with strips of rat aorta and showed that under simulated conditions of respiratory or metabolic acidosis, the contraction of arterial smooth muscle in response to norepinephrine is diminished. The hyporesponsiveness to norepinephrine was more marked with respiratory acidosis than with metabolic acidosis. They suggested that the greater inhibition of response with respiratory acidosis might be due to a higher CO_2 lipophilicity.

Hardaway et al [57] in experiments with dogs undergoing hemorrhagic and endotoxin shock showed that the rapid metabolic acidosis (within 14 min) that results is the consequence of a stagnant circulation and accumulation of metabolites due to low blood pressure. According to them, acidosis was not lethal but its correction would probably not prevent irreversible shock.

Darby and Watts [34] assessed epinephrine levels in dogs anesthetized with pentobarbital and subjected to hemorrhagic shock and demonstrated that the main reason for the increase in the concentration of epinephrine during acidosis was an increased release from the adrenal gland.

Studies in patients [124] evidenced a high correlation between lactate levels and survival. A high level of lactate was associated with high mortality. In contrast, systemic arterial pressure was of less prognostic value. There was also a very high correlation between arterial pH and lactate concentrations in arterial blood samples in the initial phase of hemorrhagic shock and previous to the administration of alkalinizing agents.

Silberschmid et al [153] studied the circulatory effects of acute lactic acidosis in dogs undergoing hemorrhagic shock and presented evidence indicating that lactic acidosis impairs cardiac function, as indicated by a fall in arterial pressure, an elevation of central venous pressure, and a marked reduction in cardiac output. They concluded that hemorrhage with acidosis does not affect peripheral vasculature, suggesting that the effect of acidosis is mostly on the heart and not on peripheral vessels.

Schumer [147] sustained that the body has to divert blood from peripheral tissues in order to preserve a normal blood flow to vital organs. In doing so, perfusion to the cell decreases hence producing anoxia. His experiments in dogs revealed that the increased in

H^+ from anaerobic metabolism is responsible for hyporesponsiveness to reinfusion. He also noticed changes in the omental microcirculation reflected in cellular aggregation, pooling and absence of blood flow in the capillaries when HCl was added.

The same investigator [148] evaluated lactate concentrations in graded hemorrhage in dogs and showed a direct relationship between hemorrhage and intracellular lactate, between intracellular and extracellular lactate concentrations until reinfusion, when serum lactate was elevated and intracellular lactate was reduced. They also observed that the increased lactate levels were reduced by the use of vasodilators, suggesting a role of vasodilatation in improving tissue perfusion and decreasing anoxia.

Cloutier and his associates [28] evaluated the acid-base profile of patients in hemorrhagic shock and determined a wide spectrum of acid-base disturbances. Their study suggested that the observation of pH alone is not enough to determine the character of the disturbance.

Emerson et al [35] performed *in vivo* studies on skeletal muscle of dogs and found that step-wise decreases in pH produced by infusion of lactic acid or acetic acid were associated with step-wise decreases in skeletal muscle vascular resistance. They suggested that the reduction in vascular resistance seems to result from active dilatation since the hyporesponsiveness occurred at constant blood flow and during decreases in transmural pressure.

Bond and his associates [19] conducted studies in dogs subjected to hemorrhagic hypotension and found that the high sympathetic tone present during hemorrhagic hypotension along with tissue ischemia and acidosis afford the optimal conditions for free fatty acids extraction from the blood. Free fatty acids may initiate an increased synthesis

and release of prostaglandin E_1 (PGE_1) that would inhibit the release of adrenergic neurotransmitters causing the vasoconstricted vessels to relax. The authors suggested that vasodilatation might be interpreted as skeletal muscle vascular decompensation that could contribute to the fall in total peripheral vascular resistance. This vascular decompensation may then move forward to a condition known as irreversible shock.

Cryer et al [33] studied the effects of tissue acidosis on skeletal muscle microcirculation in unanesthetized rats and noticed that tissue acidosis attenuates constrictor responses of larger arterioles (100-170 μm) and venules to hemorrhagic hypotension. In contrast, tissue acidosis does not exert any effect on the dilator responses of small arterioles (10-30 μm). The authors concluded that tissue acidosis is an important contributor factor to loss of arteriolar resistance and to decreased venous return that occurs during the decompensatory phase of hemorrhagic shock.

Alfaro et al [3] assessed the mechanisms of acid-base regulation during acute graded blood loss in anesthetized rats and found that the imbalance of strong inorganic ions plays a primary role in the production of acid-base disturbances. Later in time, when mean arterial pressure falls significantly, lactic acid contributes to the metabolic acid component. Strong inorganic ions as well as lactic acid were accountable for a considerable reduction in strong-ion difference of arterial plasma that reflected the development of a metabolic acid-base disorder. The authors called attention in extrapolation of results of anesthetized animals compared to conscious ones.

In summary, as time elapses, the hypoperfusion caused by both the reduced effective circulating blood volume and cardiac output leads to tissue hypoxia. The normal metabolic processes that occur under aerobic circumstances are compromised under this low flow state.

An imbalance of the acid-base status occurs, allowing a change in the pyruvate: lactate ratio in favor of lactate. The anaerobic condition prevails and lactate is synthesized in large amounts leading to a nonmetabolic (lactic) acidosis. This lactic acidosis modifies vascular tone making the vasculature response refractory to the action of catecholamines.

A vicious cycle is produced: diminished circulating blood volume, low venous return, low cardiac output, hypoperfusion, non-homogeneous blood flow to different vascular beds, increased oxygen demand, increased anaerobic metabolism, lactic acidosis, vascular hyporeactivity, perpetuated vasodilatation, capillary escape [66, 123, 191, 41].

If proper therapy is not given in a timely manner, irreversible shock irremediably ensues. It has not been clarified yet why, despite fluid therapy, many animals still die. The lactic acidosis, along with the vascular hyporeactivity creates favorable conditions for the hemorrhagic shock insult to prime the systemic inflammatory response syndrome that leads to multiple system organ failure and death.

1.4 HYPOTHERMIA AND HEMORRHAGIC SHOCK

The Physiology of Cold

Bligh and Johnson [14] defined hypothermia in mammals from the physiological point of view as *"a core temperature for that mammal greater than one standard deviation (SD) below the mean normal temperature, under resting conditions in a thermoneutral environment."* In humans, hypothermia has been simply defined as a body temperature < 35 °C [134, 186, 122].

Temperature variations in different parts of the body, diurnal changes in an individual's normal temperature, and species differences make the allotment of particular numerical values to hypothermic patients useless.

It is well known that small animals, especially dogs and cats, are very susceptible to hypothermia, due to their high body area to body mass ratio [158, 109, 1, 23]. From the etiological perspective, hypothermia can be classified as primary and secondary [114]. Hypothermia of primary origin results from exposure to low environmental temperatures. Secondary hypothermia is produced by different causes that include underlying disease, trauma, toxins, immobility, prolonged surgical procedures, hemorrhagic shock, anesthesia, infusion of cold fluids, administration of substances that contain alcohol and promote heat loss by evaporation, and the use of vasodilating drugs (See Table 1.3).

Heat loss from the body is governed by physical mechanisms. These are: convection, the transfer of heat by air currents or particles of water that have been heated by contact with the body; conduction, the transfer of heat from the body surface to colder objects in direct contact with the skin; evaporation of water in contact with the skin or respiratory tract, which dissipates into the air dragging heat with it; and radiation, the

transfer of energy by nonparticulate means, such as heat loss from the body and objects in the environment that are not in contact with the skin [134, 1, 114]. Homeotherms preserve their body temperature close to 37 °C irrespective of the ambient circumstances. This maintenance of temperature in homeothermic mammals is carried out by a combination of behavioral and physiological responses.

The behavioral mechanism is the most effective from the quantitative standpoint. When hypothermia ensues, the hypothalamus senses the drop in temperature and sends signals to the cerebral cortex. This gives the individual the sensation of feeling cold. The modified behavior translates into increased motor activity (shivering), moving to warmer surroundings or wearing additional clothing. In mammals, to preserve heat, they huddle together, seek shelter, and assume a curled-up position [157].

The physiological control system (See Fig. 1.4) is composed of peripheral and central receptors; an integrating control center and an efferent response system in charge of providing compensatory actions. The thermal receptors for cold and warm are placed mainly in the skin, spinal cord, a number of viscera, and adjacent to the great veins [22, 114]. Specific cold receptors innervated by type A-δ fibers located in the skin and mucous membranes sense the thermal input. These receptors respond to both long-term and sudden temporary changes in environmental temperature. This afferent input is sent to a central processor situated in the hypothalamus. There are also central cold receptors of seemingly less importance whose effects are superseded by the predominant peripheral influence [22].

The central control mechanism for body temperature is governed by the hypothalamus. This structure sets up mean body temperature by incorporating thermal signals from the periphery and innermost structures, and comparing regular body temperature with a pre-determined reference temperature or set point. The set point temperature is defined as the narrow temperature range (36.7-37.1 °C, for humans) in which no effector response is elicited. The set point has also been named a "thermoneutral zone" or "interthreshold range" [22].

According to Cabel et al [23], normal body temperature in dogs ranges from 37.8 - 39.5°C. Therefore, in that species, hypothermia can be defined as a core body temperatrure of less than 37.8 °C.

Once the thermal information has reached the temperature-regulating centers located in the anterior hypothalamus, this structure processes the afferent information, whilst the posterior region of the hypothalamus controls the descending information that goes to effectors.

Furthermore, specialized temperature-sensitive and temperature-insensitive neurons for heat as well as for cold are found in the pre-optic area of the hypothalamus. The cooling of the pre-optic area provokes an intensification of the rate of firing of the cold-sensitive neurons. The posterior hypothalamus is an integrator that combines the cold afferent signals arriving from the periphery with heat-sensitive stimulation coming from the pre-optic area of the hypothalamus thus initiating effector responses [22].

The efferent pathway operates at the level of the skin by acting upon the vasomotion of cutaneous vascular smooth muscle. During hypothermia, an initial strong sympathetic response arises resulting in profound vasoconstriction causing shivering,

nonshivering thermogenesis, and behavioral changes, as mechanisms of heat conservation. VO_2, respiratory rate, stroke volume, cardiac output, and blood pressure increase. The effector reaction is described [22] by behavioral changes, vasomotor responses (vasoconstriction and piloerection in response to cold), shivering and increased metabolic rate.

It is important to point out that in addition to the shivering thermogenesis governed by the neural control, acting via the autonomic nervous system in response to cold, there is also a non-shivering thermogenesis mediated by both the thyroid and adrenal glands. The shivering thermogenesis provides rapid control of heat dissipation, whereas the non-shivering thermogenesis involves a more delayed increase in heat production [134, 65].

1.5 HYPOTHERMIA AND THE MICROCIRCULATION

Löfström [92] studied the vascular changes in blood volume and capillaries in rabbits and found that during induced hypothermia, total plasma volume decreased. The author suggested that plasma volume was probably reduced due to the anesthetic used (ether). This anesthetic diminishes the plasma volume and increases the extracellular volume. The author also reported a reduction in the total amount of effectively circulating hemoglobin at 20 °C concurrent with severe anemia. He suggested that intravascular aggregation might be the cause of the reduction in white blood cells and platelets during hypothermia.

Wilson and his associates [185] subjected dogs to cooling (22 °C) and reported a prolongation of clotting time, a decrease in the number of circulating platelets, an abrupt drop in the total number of lymphocytes with intravascular agglutination of erythrocytes, and a reduction of flow rate with sticking of white cells to venule walls.

Levy [88] demonstrated that progressive hypothermia (36-10°C) has an effect on all organ systems. In addition to the reduction in renal blood flow, due to increased blood viscosity and in some measure to vasoconstriction, renal oxidative metabolism is also drastically diminished. The author performed perfusion studies on dog kidneys and established that these reductions are an expression of the declined velocity of chemical reactions during cooling.

In work with anesthetized dogs, Bond et al [17] used high-speed cinephotography and recorded the behavior of the red cell in the mesentery microcirculation before and after profound hypothermia (5 °C-15 °C). They observed aggregation of red cells within the vessels and low capillary flow and concluded that a large part of the blood bypasses the capillaries of the mesenteries via arteriovenous shunts.

Significance of the Effects of Hypothermia in Hemorrhagic Shock

The therapeutic benefits of hypothermia have long been recognized. Hypothermia is a helpful ally in cardiovascular surgery and neurosurgery [100, 141]. Nonetheless, the therapeutic significance of hypothermia is not obvious because hypothermia is difficult to assess in terms of its effects on different physiologic variables. In addition, conflicting data have arisen regarding the experimental models used, the degrees of hypothermia produced, and the species involved [134, 106, 163, 164].

Beneficial Effects of Hypothermia

Friedman et al [14] underscored the beneficial effects of hypothermia when they investigated the importance of tolerance to hemorrhagic shock in dogs during cooling. The ability to endure severe hemorrhagic shock was substantially increased when dogs were precooled to 28 °C. The results of their experiments demonstrated that cooling

protects the antibacterial defense mechanism resulting in increased survival, if accompanied by antibiotic therapy. In contrast, this protective mechanism is lost in normothermic dogs.

Physicochemical studies [145] performed on dogs subjected to hemorrhagic shock, demonstrated that moderate cooling (33-36 °C) reduces the metabolic rate to nonvital tissues so that there is a relative reduction in the anoxic effect of low flow states. It also prevents an increase in both lactate-pyruvate ratio and cellular aggregation.

Meyer and Horton [106] demonstrated protective and therapeutic effects of moderate hypothermia (33 °C) in a model of severe hemorrhagic shock in dogs. They showed decreased metabolic demands and preservation of both myocardial performance and perfusion compared with normothermic hemorrhaged dogs. They also noticed an increased left ventricular work accompanied by no change in fiber length, indicative of a positive inotropic response to hypothermia. The authors found metabolic acidosis without respiratory compensation, reflected in a lower respiratory rate and a high lactate concentration.

Kim et al [75] working with rats used an uncontrolled hemorrhagic shock model and evaluated the use of moderate hypothermia (30 °C) and minimal fluid resuscitation. Their findings showed that moderate hypothermia or limited fluid resuscitation (or their combination) increases survival during and after uncontrolled hemorrhagic shock. According to them, the underlying principle for using moderate hypothermia during hemorrhagic shock is its capacity to “protect” vital organs if hypothermia is induced previous to and maintained during ischemia. They did not offer an explanation as to the precise protective mechanisms of moderate hypothermia during hemorrhagic shock.

Wladis et al [186] examined the metabolic and endocrine effects of moderate hypothermia (30 °C) in a porcine model of hemorrhagic shock and found an elevation of arterial oxygen tension, an absence of metabolic acidosis, a stabilization of K^+ serum levels, and a reduction in the concentration of catecholamines. According to the authors, the absence of metabolic acidosis was due to the controlled and fixed ventilation, which is an indication of the unaltered DO_2 when metabolic demands are diminished. They suggested that the significant reduction in catecholamine levels during hypothermia might be advantageous because hypothermia reduces the metabolic rate and prevents cardiac toxicity mediated by catecholamines.

Kim et al [76] assessed the effects of moderate hypothermia (30 °C) in rats. They used a combination of volume-controlled hemorrhage followed by uncontrolled hemorrhagic shock. They found that hypothermia induces a minor increase in blood pressure, decreases in heart rate, respiratory rate, and survival time prolongation, when compared with normothermia. No increase in bleeding was produced. In contrast, breathing 100% oxygen had no effect on mean arterial pressure, blood loss, or survival time. The authors demonstrated that moderate hypothermia, but not the increase in the fraction of inspired oxygen ($F_I O_2$), prolongs survival time during untreated, uncontrolled hemorrhagic shock.

Similar studies in ratsl [164] using a clinically-realistic model of uncontrolled hemorrhagic shock and subjecting the animals to both mild (32° to 36 °C) and moderate (28° to 32 °C) hypothermia have reported an increase blood pressure and survival time.

Kawaguchi et al [73] showed in cats that mild hypothermia (33 °C) is involved in the increased survival rate and prolongation of the period of tolerance to severe hemorrhage. Hypothermia modifies blood vessel contractility as well as relaxation in the brain and in certain vascular territories.

Bergstein et al [10] conducted an investigation in rats subjected to hemorrhagic shock and resuscitation to determine if post-traumatic hypothermia is associated with hemorrhage or resuscitation. They showed that hypotension resulting from hemorrhage alone could cause hypothermia without the effect of ambient temperature or fluid resuscitation. The authors also demonstrated that anesthesia (pentobarbital) did not cause hypothermia; rather hypothermia was almost practically present during hemorrhage, with very little temperature drop during fluid resuscitation. Their study demonstrated that the rate of fall in temperature is intimately related to the period of hypotension and hypoperfusion. They concluded that hypothermia is not related to the administration of cold intravenous fluids and blood, but rather to physiologic processes related to shock, such as impairment in aerobic metabolism.

More recently, it has been shown in rats [87] that moderate hypothermia (32°C) plus 100% oxygen inhalation during volume-controlled hemorrhagic shock in awake rats lessens hypotension and increases the likelihood of survival even after 3 hours of moderate hemorrhagic shock. According to the authors, the underlying principle for using 100% breathing lies in its capacity to increase PO_2 therefore increasing to some extent plasma O_2. In addition, high PO_2 might enhance O_2 diffusion from the arterial side of capillaries to mitochondria. According to them, the fundamental principle for using hypothermia is its ability to reduce cerebral and oxygen requirements in general.

Wladis et al [188] investigated in pigs if induced hypothermia limits the metabolic, endocrine, immunological, and hemodynamic effects of combined trauma (high-energy gunshot wound) and hemorrhagic shock. They found that moderate hypothermia (30 °C) followed by a high-energy soft-tissue injury along with hemorrhagic shock reduces VO_2, while DO_2 is well preserved. Hypothermia resulted in a limitation of the hemodynamic response to hemorrhage and offset the high plasma catecholamine, interleukin 6, and potassium concentrations and the leukocytosis observed in the controls. There was no indication of damaging effects of hypothermia. From the results, the authors suggest that moderate hypothermia may be advantageous. Table 1.4 summarizes the major beneficial effects of hypothermia.

Detrimental Effects of Hypothermia

Luna et al [96] documented a high incidence of hypothermia among critically illed patients. He reported a relationship between initial severe hypothermia and injury severity, suggesting that critically illed patients are not capable of maintaining body temperature immediately after injury.

Jurkovich et al [71] conducted a clinical study of hypothermia in trauma patients and suggested that a temperature of 32-33 °C is the critical level below which trauma patients cannot live. The authors questioned whether it is the hypothermia or the seriousness of the injury that is responsible for the resulting mortality in hemorrhagic shock.

In a retrospective study in patients, Ferrara et al [40] evaluated the adequacy of resuscitation and their findings revealed that hypothermia was present in 80% of nonsurvivors and in 36% of survivors. Their data showed that nonsurvivors died of irreversible shock and were significantly more acidotic and hypothermic. The

hypothermia was related to severe coagulopathy and acidosis despite adequate blood, plasma, and platelet substitution. However, the contribution of each variable to the high mortality rate in those patients was not clarified. In a similar study, Bernabei et al [11] obtained comparable results.

In a 2-year prospective study, Cosgriff and his associates [31] analyzed patients who received massive transfusion. They used a multiple logistic regression model that included four significant risk factors: pH < 7.10; temperature < 34 °C; injury severity score > 25 and systolic blood pressure < 70 mm Hg. They showed that persistent hypothermia and progressive acidosis were predictive factors that determine the serious post-injury coagulopathy that occurs in the critically injured patient in need of massive transfusion.

Silbergleit et al [152] using the swine as a clinically relevant large-animal model of hemorrhagic shock demonstrated that ambient-tempearature crystalloid resuscitation causes small reductions in core body temperature. According to them, resuscitation and not the shock state *per se* is responsible for decreased body temperature.

Krause et al [83] performed experiments on swine to elucidate the influence of hemorrhagic shock and hypothermia (32 °C) on hemodynamic and coagulation parameters. They used an acute model of hemorrhage that mimicks the clinical situation that occurs in the trauma patient. They found that cardiac output was reduced despite volume resuscitation. Blood parameters such as prothrombin time and partial thromboplastin time were significantly prolonged in hypothermic animals. The authors also reported that the reinfusion of shed blood did not modify or resulted in any modification in these parameters.

Wladis et al [187] studied the acute hemodynamic effects of induced hypothermia (30 °C) in an experimental model of hemorrhagic shock in anesthetized swine and found that hemorrhagic shock leads to an increase in heart rate and a decrease in both cardiac output and mean arterial pressure, which corresponded with the depression of temperature. The hemorrhagic shock condition was worsened by hypothermia, but mortality did not increase. (Table 1.5 summarizes the major detrimental effects of hypothermia).

In summary, small animals can suffer from primary hypothermia due to their high body area to body mass ratio. In addition, secondary hypothermia is a frequent accompaniment of prolonged surgical procedures, anesthesia, shock, infusion of cold fluids, et cetera.

Hypothermia has an effect on all organ systems. The beneficial effects of hypothermia are recognized. In hemorrhagic shock, deep hypothermia improves tolerance to hemorrhage, reduces cardiac output, decreases metabolic demands, and prevents capillary permeability. At the same time, moderate and mild hypothermia reduce metabolic rate, prevent increases in lactate, improve cardiac performance and reduce VO_2, DO_2.

In contrast, deleterious effects have also been described. Different degrees of hypothermia have been related to injury severity, irreversible shock and acidosis, coagulopathies such as prolonged prothrombin and thromboplastin times, impaired cerebral regulation, and rapid acceleration of death.

The importance of hypothermia in hemorrhagic shock has been underscored, but different investigations have given divergent results. Therefore, in order to elucidate the role of hypothermia in hemorrhagic shock, future research should be focused on clarifying the discrepancies encountered among different investigators. Furthermore, investigation should aim at using models of hemorrhagic shock that are relevant in the context of the clinical situation.

Experimental evidence has demonstrated that different species react in a different way to hypothermia. In consequence, careful consideration has to be given to species differences when attempting to extrapolate experimental results.

1.6 HYPOTHERMIA AND ACID-BASE BALANCE

It is well known that hypothermia shifts the dissociation curve of the hemoglobin molecule to the left. A decrease in temperature causes an increase in the alkalinity of blood resulting in an additional leftward displacement of the dissociation curve of hemoglobin. This displacement has physiological consequences. For a certain partial pressure more oxygen is combined with hemoglobin, indicating a high affinity of oxygen for hemoglobin and a reduced availability of oxygen to tissues.

During hypothermia, a reduced amount of oxygen is released during the short period that red blood cells pass through the tissue capillaries. In addition, hypothermia brings about a decreased rate of molecular diffusion of oxygen from capillaries to tissues when compared to warm tissues [13].

Other investigators [171, 39] have expressed that it is difficult to determine the normal acid-base balance during hypothermia because of the diverse effects of cold and the lack of criteria for adequate pulmonary ventilation. In clinical hypothermia, there is

increased production of fixed acids. An elevated lactate concentration is a frequent finding made more noticeable by shivering, anaerobic glycolysis resulting from vasoconstriction, hypovolemia or venous inflow occlusion [39].

The effects of hypothermia on the cardiovascular system have been recognized. Studies in dogs [102] subjected to moderate hypothermia (28 °C) showed that the mammalian heart works more efficiently when pH is not kept at 7.40 but adjusted in relation to the neutrality point of water, as in the case of poikilotherms which modify their body pH with changes in temperature. These investigations suggest that keeping the blood pH at 7.40 during hypothermia might impose an unphysiologic constraint on the mammalian cardiovascular system.

Becker et al [8] subjected dogs to 60 minutes of circulatory arrest with surface hypothermia (22 °C), followed by extracorporeal circulation (17 °C) and showed that keeping pH at 7.4 causes inadequate cardiac output (hypotension, acidosis). Cerebral blood flow significantly fell (75%). The post-ischemic myocardial performance declined, despite cardioplegic protection. In contrast, adjusting pH (7.75) by manipulating PCO_2, allowed a significant improvement in cardiac output with normalization of lactate metabolism. Post-ischemic myocardial performance was not altered.

Meyer and Horton [107] conducted studies in dogs using a modified Wiggers hemorrhagic shock model in dogs and evaluated different degrees of hypothermia. They found that severely hypothermic (28 °C) dogs had higher bicarbonate levels and a lower lactate concentration compared to normothermic shocked dogs, indicating that the metabolic component of acidosis was less. Dogs with severe hypothermia had reduced respiratory rates and a markedly elevated arterial PCO_2 compatible with respiratory

acidosis. Hypothermic hemorrhaged dogs had better myocardial contractility than normothermic dogs, regardless of profound respiratory acidosis and hypothermia. They suggested that adequate ventilatory support in dogs with hemorrhagic hypothermic shock might further improve cardiac performance.

Clancy and González [27] examined the influence of different degrees of temperature (25, 30, and 38 °C) on the inotropic effect of metabolic acidosis in isolated papillary muscles of anesthetized cats and demonstrated that the temperature of the medium has an effect on the contractile properties of the myocardium as well as on the negative inotropic effect exerted by metabolic acidosis. At 25 °C, metabolic acidosis did not affect myocardial contractility. In contrast, at 30 ° and 38 °C, contractility was decreased. The authors suggested that acid-base changes occur within the cell during metabolic acidosis and that those changes would be related to a net HCO_3^- outflux, which would make the interior of the cell more acidotic.

Sinet al, [154, 155] provided evidence against the above assumption. They performed in *vitro* experiments using a blood-perfused preparation of working heart in rats. They examined whether preserving or not pH at 7.4 during moderate hypothermia (26 °C) would disturb the functional properties of a heart subjected to an increased workload. They found that slight variations in extracellular pH during moderate hypothermia (26 °C) do not impair myocardial performance and the DO_2 to VO_2 ratio. They suggested that moderate changes (within a range of pathophysiological values) in extracellular acid-base equilibrium during hypothermia do not disturb mechanical heart performance. They pointed out that the absence of changes in heart performance could be due to an increased intracellular buffering capacity against changes in PCO_2.

1.7 TREATMENT OF NON-RESPIRATORY (LACTIC) ACIDOSIS IN HEMORRHAGIC SHOCK

Despite the existence of novel therapies for the treatment of hemorrhagic shock, there has been little improvement in the condition of these patients. As alluded in the Introduction, the inefficacy of treatments may be linked to a low tissue oxygen tension, a decrease in functional capillary density and capillary perfusion, and vascular hyporeactivity [126].

Two therapeutic approaches (Table 1.6) to resolving acid-base derangements that occur during tissue hypoperfusion have been developed in conjunction with cardio-pulmonary bypass procedures in human patients: the alpha-stat approach and the pH-stat approach [129].

In the alpha-stat therapy, blood pH is allowed to change during hypothermia so as to preserve a constant hydroxyl to hyodrogen ratio $[OH^-]$: $[H^+]$ necessary for the enzymatic machinery of the body to function adequately. Accordingly, the arterial pH value is 7.40 and has a PCO_2 of 40 mm Hg when measured at 37 °C. At the same time, *in vivo* hypothermic blood is hypocapnic and alkalotic [156].

The theoretical background of the alpha-stat approach states that the fractional dissociation of the imidazole group (α_{IM}) of the histidine residue of the hemoglobin molecule remains constant with temperature changes and varies with pH during isothermal (constant temperature) in order to preserve acid-base balance. This residue is considered the most important of the dissociable groups in charge of keeping a constant $[OH^-]$: $[H^+]$ ratio [112, 110].

According to Reeves, [130], in an open system, the α_{IM} of the histidine molecule (an abundant protein in the organism) is regulated by the animal so as to maintain a constant protein charge state, that is to say, irrespective of how the animal regulates its acid-base balance when body temperature changes, the fractional dissociation of imidazole and hence the mean protein net charge, is maintained constant. If radical changes in pH take place, the protein histidine dissociation and the relative alkalinity are preserved with essentially no change in blood or intracellular protein net charge state [130].

Reeves [129] also stated that air breathers ectotherms regulate the fractional dissociation of imidazole mainly by rapid adjustments of ventilation to secure the required PCO_2 at each temperature. When changes in temperature are produced, tissue buffers modify PCO_2 (at constant gas content), due to the presence of histidine. This way, α_{IM} is kept basically invariable. The PCO_2 passively produced by temperature changes closely matches the PCO_2 which must be provided by ventilatory control when the tissue functions as an open CO_2-producing system. According to this author, this distinctive property of passively reacting to a temperature change to maintain protein charge state constant precludes the need for either filling or emptying tissue CO_2 stores. These buffering properties permit steady-state acid-base conditions to prevail as rapidly as tissue temperature can be altered.

Another important aspect of the imidazole buffer is that its pK_a value of 6.4-6.7 falls within the range of intra and extracellular pH values and varies with temperature with basically the same coefficient as the pH of ectotherm blood, the pH of neutral water, and the intracellular pH (pH_i) [110].

The pH-stat therapeutic approach states that both arterial pH and PCO_2 should remain at constant values. With this therapy, PCO_2 is corrected at patient temperature and kept at 40 mm Hg to maintain a pH of 7.40 near the actual temperature. In order to attain this during hypothermia, it is necessary to increase the CO_2 content of the breathing medium (hypoventilatory management) because blood pH is more alkaline during hypothermia. With this strategy, blood is hypercapnic and acidotic when measured at 37 °C.

The principle of this therapy is based on the effect that body temperature (Table 1.7) exerts on hydrogen ions (H^+) concentration in body compartements. It is well known that temperature influences dissociation constants (pKa) and solubility of CO_2 hence bringing changes in pH. As temperature increases, pH decreases and viceversa in such a way that blood pH changes by 0.0015-0.002 units of pH/°C. These temperature-dependent changes in intracellular as well as in extracellular pHs are thought to be crucial in maintaining a constant $[OH^-]$: $[H^+]$ ratio throughout the body.

The basic difference between the alpha-stat and the pH-stat management is determined by the way in which cold-blooded (ectotherms) and warmed-blooded animals manage their acid-base status: cold-blooded animals experience pH and CO_2 adjustments by natural temperature fluctuations (alpha-stat), whereas in warm-blooded animals, the changes are clinically imposed in patients (pH-strategy) [8].

As mentioned earlier, these strategies have not been applied to animals or humans suffering from hemorrhagic shock. The existing information pertains to studies in cardiovascular surgery and neuro-surgery in which deep hypothermia along with circulatory arrest has been applied.

Controversy exists in reference to which blood gas therapeutic approach is "ideal" during profound hypothermia, particularly with regard to brain protection [178]. Those who advocate the use of the pH-stat hypothesis argue that it is important to maintain a constant pH of 7.40 and a PCO_2 of 40 mm Hg at any temperature. Supporters of the pH-stat strategy realize that if the pH and PCO_2 were kept constant at pH of 7.40 and PCO_2 of 40 mm Hg during hypothermia, the patient would be acidotic, but they argue that pH-stat oriented therapy reduces morbidity [110].

Johnsson and associates [70] assessed cerebral vasoreactivity to CO_2 during cardiopulmonary perfusion at normothermia and hypothermia in patients undergoing coronary artery bypass and reported that cerebral vasoreactivity to changes in PCO_2 was preserved. Hence, the respiratory acidosis during hypothermic cardiopulmonary bypass with the pH-stat therapy results in a CO_2 –mediated hyperemia that endangers autoregulation and uncouples flow and metabolism. They suggested that the alpha-stat therapy was the alternative for hypothermic cardiopulmonary bypass.

Studies in pigs [184] have shown a higher degree of reduction in myocardial and whole body VO_2 with alpha-stat regulation compared to the pH-stat, suggesting that the effect of hypothermia in reducing VO_2 is less pronounced with the pH-stat strategy. Experiments in humans [160] undergoing elective coronary artery bypass surgery have revealed that the pH-stat management results in luxury cerebral perfusion (brain hyperperfusion), loss of cerebral autoregulation, and more neurologic injury.

Work in rabbits [64] using a model of cardiopulmonary bypass has reported that hypothermic (27 °C) acid-base management using both approaches have no quantifiable consequences on cerebral metabolic rate for oxygen. Cerebral metabolic rate for oxygen

is not extraction-limited or dependent on PCO_2 cerebral blood flow, or hemoglobin oxygen affinity differences. According to the authors, even though cerebral blood flow was greater with pH-stat strategy than with alpha-stat strategy, chronic management with pH-stat diminishes cerebrovascular reactivity to PCO_2, while chronic alpha-stat approach better preserves it.

Verhaegen et al, 1993 [172] conducted studies in rats to examine the influence of moderate hypothermia (31 °C) on cerebral autoregulation and showed that if PCO_2 is maintained at 40 mm Hg after correction for temperature (pH-stat) autoregulation is eliminated. In contrast, if PCO_2 is uncorrected (alpha-stat), certain degree of autoregulation is preserved.

Skaryak et al [156] evaluated the two strategies and studied the effects of blood gas management and degree of cooling on cerebral metabolism in piglets before and after deep hypothermic circulatory arrest and found that the use of the pH-stat therapy when the animals were cooled to 14 °C followed by a switch to alpha-stat approach just before arrest, produced a better improvement of cerebral metabolism compared with recovery with either strategy used alone.

Those in favor of the alpha-stat management point out that blood flow to vital organs, mainly cerebral blood flow is pressure-dependent with pH-stat therapy and that normal vasomotor tone (autoregulation) may be compromised [110].

Kurth et al [84] studied cortical oxygen saturation, cortical blood flow, and cortical physiologic recovery in piglets subjected to deep hypothermic cardiopulmonary bypass and found that the pH-stat management produced slower cortical deoxygenation during arrest, increased brain cooling, and increased cerebral blood flow during

reperfusion when compared with the alpha-stat. According to the authors, the decreased cortical deoxygenation was attributed to both increased DO_2 and decreased oxygen metabolic rate.

The alpha-stat management has been criticized [108] because it worsens the already hypothermia-induced alkalosis that shifts the oxyhemoglobin dissociation curve to the left. The consequence is that the affinity of hemoglobin for oxygen is increased resulting in impairment of oxygen delivery to tissues, leading to hypoxia in spite of adequate blood PO_2.

A retrospective study in children [119] who were subjected to deep hypothermic circulatory arrest showed that the pH-stat technique using hyperoxia before deep hypothermic circulatory arrest resulted in lower levels of acid production. They speculated that the reduced acid production is associated with a loading of tissues with higher amounts of oxygen, which enables continuing aerobic metabolism during deep hypothermic circulatory arrest.

There is disagreement regarding the administration of CO_2 and its effects on hemodynamics. Ohmura and his associates [113] working with anesthetized dogs, evaluated the effects of hypocarbia and normocarbia on cardiovascular hemodynamics, cerebral, mesenteric, and renal blood flows, and total body oxygen consumption during surface-induced hypothermia (24 °C). Their results showed that when CO_2 is added to the inspired gases, cardiac index decreases significantly with cooling, compared with dogs with normocarbia. Dogs with hypercarbia show a greater decrease in heart rate and a superior increase in pulmonary vascular resistance.

According to the authors, the addition of CO_2 to the inspired gas to preserve normal PCO_2 during cooling might be beneficial for the brain, but deleterious for the cardiovascular system.

In summary, the alpha-stat and the pH-stat therapeutic approaches have shown to be beneficial in both cardiovascular and brain surgeries. Astonishingly, in the highly frequent clinical condition of hemorrhagic shock these therapies have not been applied to manage the acid-base disturbances that take place in this syndrome.

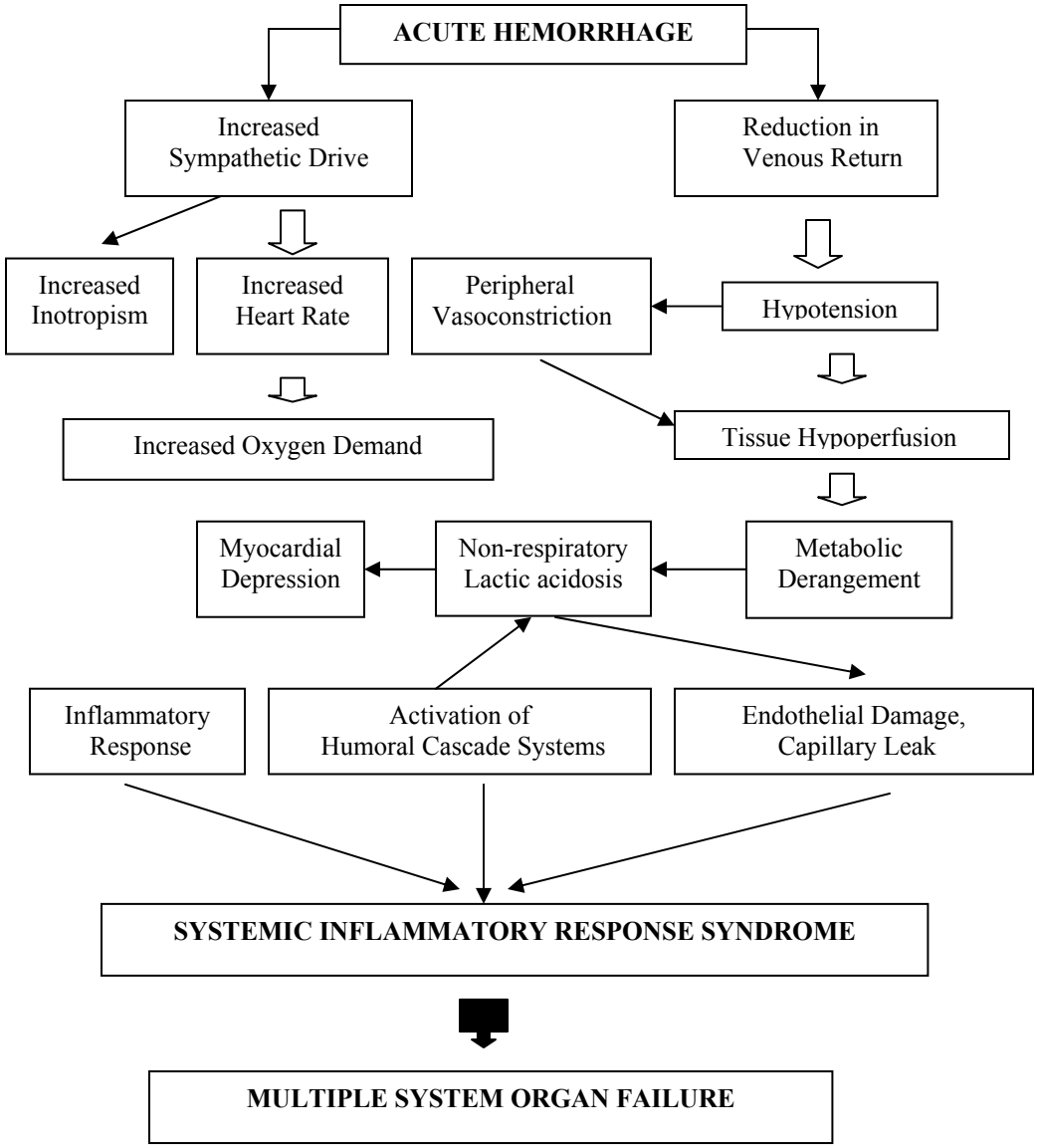

Fig. 1.1: Pathophysiology of Hemorrhagic Shock.

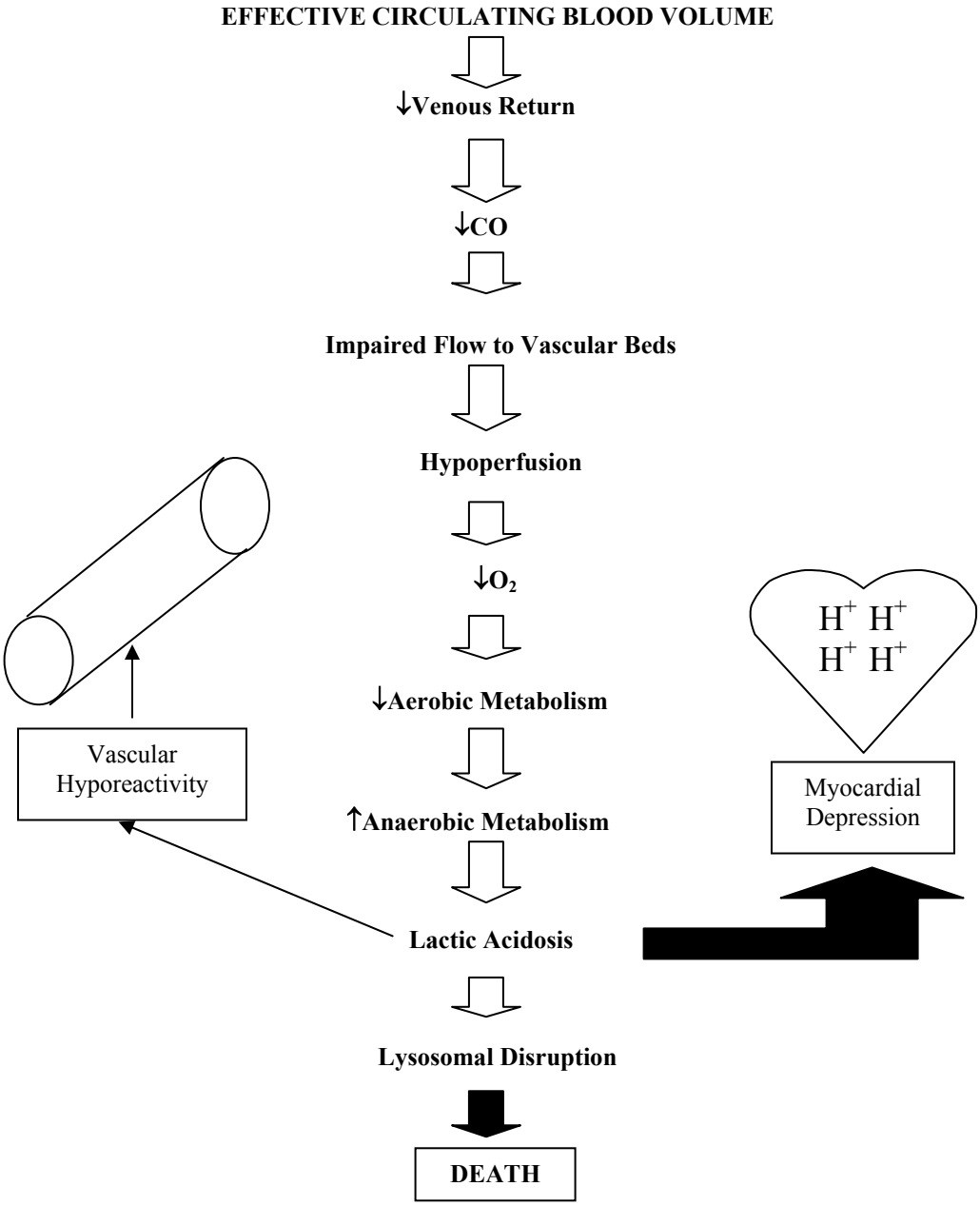

Fig. 1.2: Central role of O_2 in metabolism and consequences of its absence.

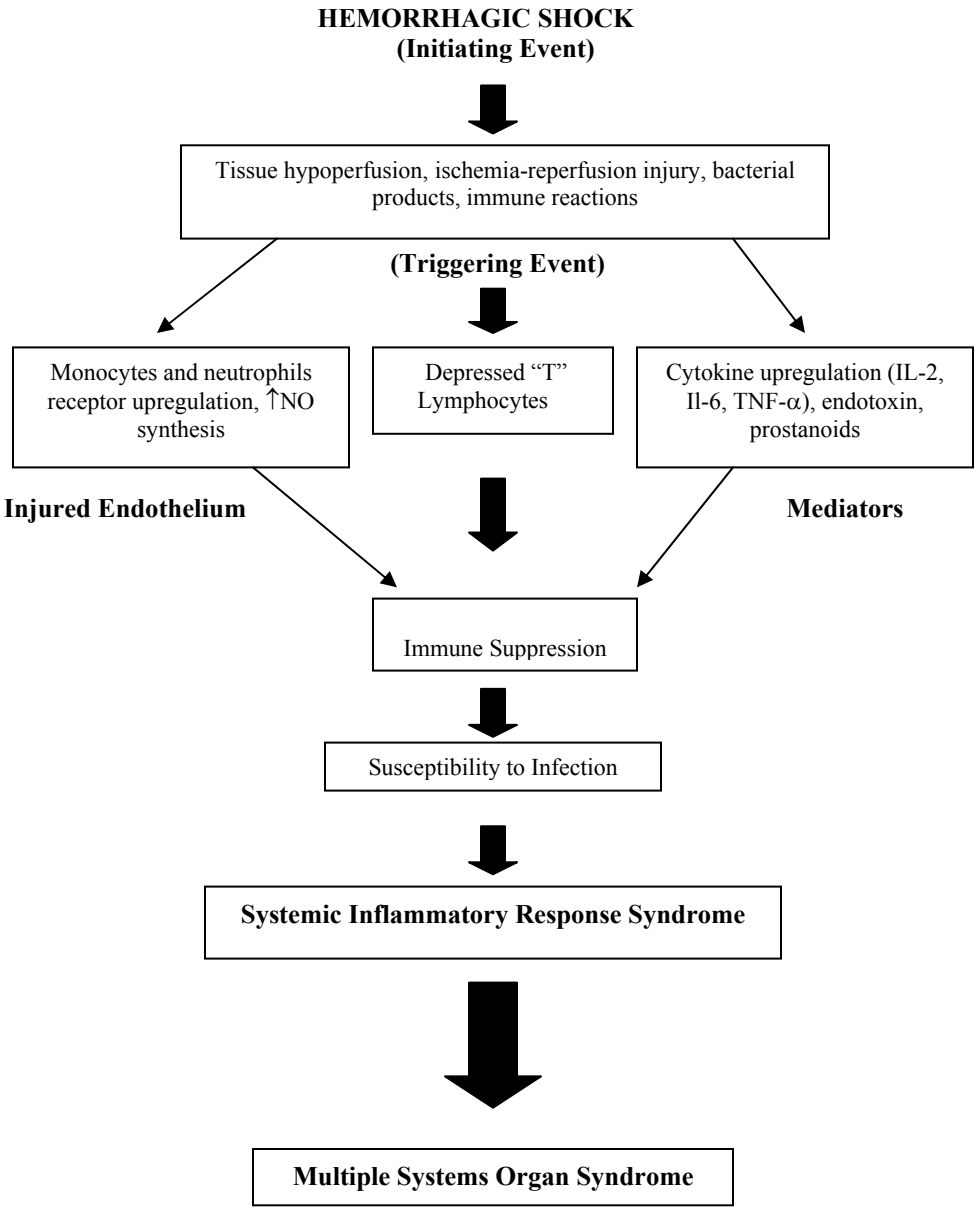

Fig. 1.3: Some events in the inflammatory response to hemorrhagic shock.

VESSEL TYPE	AVERAGE SIZE (μM)*	CHARACTERISTIC RESPONSES DURING HEMORRHAGIC SHOCK
A_1	99.6 (16)	Constriction
A_2	61.5 (25)	Constriction
A_3	38.5 (30)	Progressive constriction
A_4	17.4 (14)	Heterogeneous: Dilatation, followed by constriction
V_1	160.3 (17)	Increased volume
V_2	90.8 (32)	Reduced volume
V_3	53.9 (17)	Reduced volume
V_4	25.0 (20)	Increased volume

Table 1.1: Microvascular responses during hemorrhagic shock in rats. * Number of vessels analyzed given in parenthesis. Modified from Hutchins et al, 1973 and Garrison and Cryer, 1989.

Type of study	Species	Year	Reference
Theories of shock	Man, frog, dog	1879, 1899, 1905	63, 18, 62
Mesenteric circulation	Man, dog	1919, 1957, 1977, 1983, 1987, 1998, 2001	19, 20, 59, 21, 2, 95, 30, 5, 80
Infusion therapies	Man, dog, rat, swine	1990, 1991, 1993, 1995, 1998, 2002	105, 106, 107, 14, 82, 31
Classification of shock	Man, dog	1934	76, 12
Sympathetic system, vasoactive amines, vasomotor changes and vascular reactivity	Dog	1932, 1943, 1950, 1953, 1956, 1957, 1959, 1961, 1963, 1964, 1967, 1968, 1970, 1974, 1977, 1982, 1985	26, 70, 51, 81, 53, 114, 59, 104, 84, 85, 66, 108, 42, 13, 38, 34, 10, 75, 11, 115
Criteria for hemorrhagic shock	Dog	1945, 1950	25, 112
Effects upon microcirculation	Rat, dog, cat	1944, 1962, 1963, 1973, 1976, 1980, 1984, 1985, 1989, 2000	117, 57, 91, 43, 45, 9, 3, 22, 16, 29, 56
Effects of nitric oxide and other dilatory factors on vasculature	Dog, rabbit, rat	1980, 1987, 1989, 1990, 1991, 1992, 1993, 1995, 1999, 2000	27, 44, 72, 1, 28, 78, 102, 52, 58, 97, 116, 49, 100, 50, 60, 33, 93
Inflammatory response	Rat	1984, 1987, 1993, 1995, 1997, 2002	86, 95,, 36, 74, 65, 82, 31

Table 1.2: Chronological summary of some important contributions to the knowledge of hemorrhagic shock.

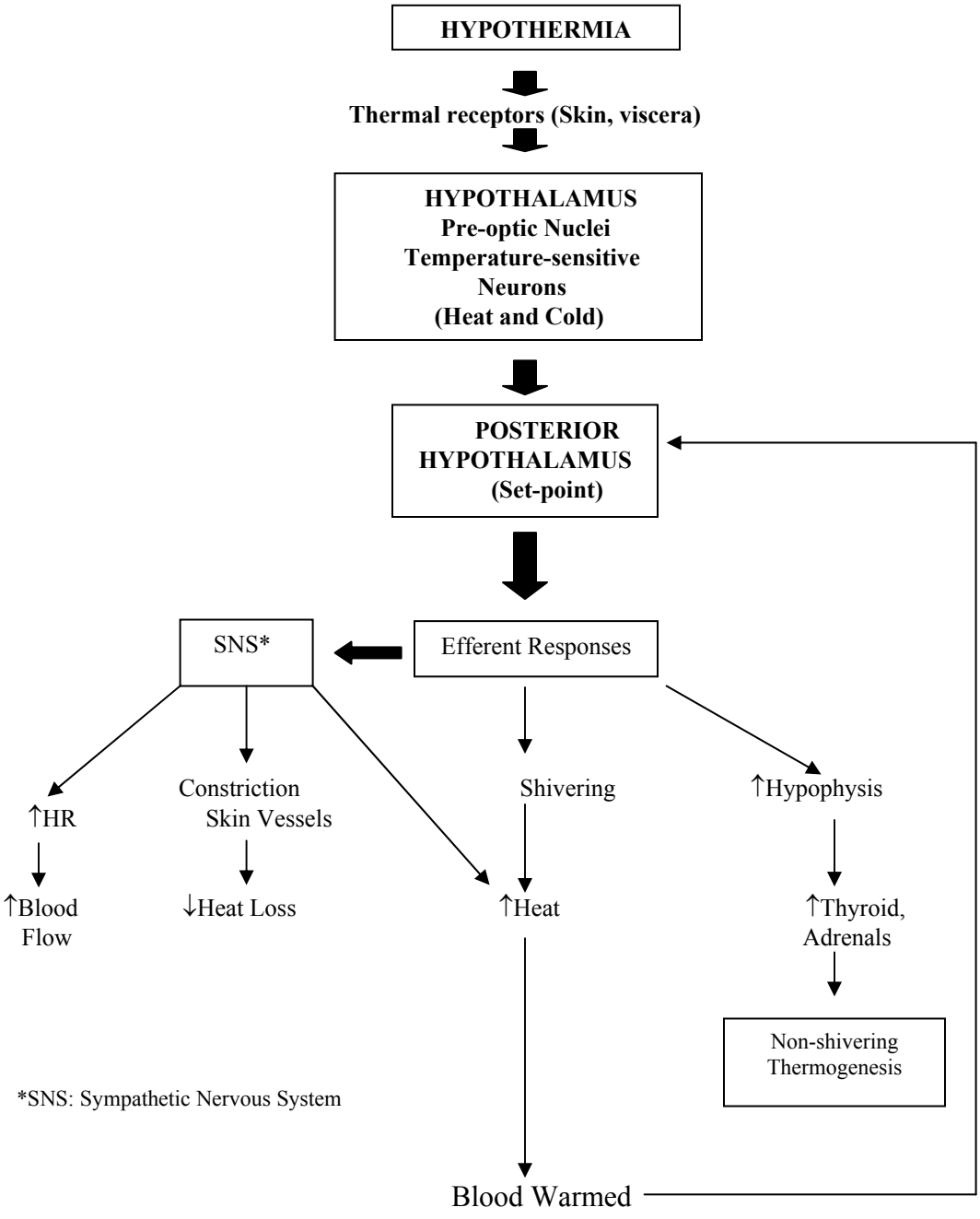

Fig. 1.4: Thermoregulatory responses during hypothermia. Modified from Reuler, 1978 and Buggy and Crossley, 2000.

TYPE	TEMPERATURE RANGE
Primary Hypothermia	
Mild	32 °C-37 °C
Moderate	28 °C-32 °C
Severe	20 °C-28 °C
Profound	< 20 °C
Secondary Hypothermia	
Mild	36.7 °C-37.7 °C
Moderate	35.5 °C-36.7 °C
Severe	33.0 °C-35.5 °C
Critical	< 33.0 °C

Table 1.3: Classification of hypothermia. From: Oncken et al, 2001.

Beneficial Effects	Type of Hypothermia	Reference
Tolerance to hemorrhage and infection resistance	Deep (28 °C)	Friedman et al, 1956
Reduction in metabolic rate, prevention of increases in lactate, lack of cellular aggregation	Moderate (33-36°C)	Schumer, 1966
Decreased metabolic demands; positive inotropism	Moderate (33 °C)	Meyer and Horton, 1988
Increased survival time	Moderate (30°C); mild (33 °C)	Kim et al, 1998; Kawaguchi et al, 1998
Absence of metabolic acidosis, catecholamine reduction	Moderate (30 °C)	Wladis et al, 1998
Increases in blood pressure, prolongation of survival time	Mild (32-36°C and 28-32 °C); moderate (30°C)	Takasu et al, 2000
Reduction in cerebral oxygen requirements	Moderate (32 °C)	Leonov et al, 2002
Reduced VO_2, DO_2 preservation; increases in catecholamines, interleukin 6, K^+, leukocytes	Moderate (30 °C)	Wladis et al, 2002

Table 1.4: Major beneficial effects of different degrees of hypothermia in hemorrhagic shock.

Detrimental Effect	Type of Hypothermia	Reference
Positive relationship between hypothermia and injury severity	Mild (34-36 °C), severe (< 34 °C)	Luna, 1987
Related to irreversible shock and acidosis	Severe (31-34 °C), critical (33-35 °C)	Ferrara et al, 1990; Bernabei et al, 1992
Post-injury coagulopathy	Severe (< 34 °C)	Cosgriff et al, 1997
Decreased CO, prolonged prothrombin and thromboplastin times	Mild (32 °C)	Krause et al, 2000
Rapid acceleration of death	Critical (34.5 °C)	Takasu et al, 2000
Increased heart rate, decreased CO and MAP	Induced (30 °C)	Wladis et al, 2001

Table 1.5: Major detrimental effects of different degrees of hypothermia in hemorrhagic shock.

Concept	Purpose	Total CO_2	pH and PCO_2	Intracellular State	Alpha-Imidazole and Buffering	Enzyme Structure and Function
pH-stat	Constant pH	Increases	Normal corrected values	Acidotic (excess H^+)	Excess (+) charge, buffering decreased	Altered and activity decreased
Alpha-stat	Constant OH^-/ H^+	Constant	Normal uncorrected values	Neutral ($H^+ = OH^-$)	Constant net charge, buffering constant	Normal and activity maximal
pH-stat modified	Constant pH	Increases up to 60 mm Hg	Normal corrected values	Acidotic (excess H^+)	Excess (+) charge, buffering decreased	Altered and activity decreased

Table 1.6: Comparison of pH-stat, alpha-stat, and pH-stat-modified acid-base regulation. Modified from Lumb and Jones, 1996 [27].

TEMPERATURE (°C)	PO_2	PCO_2	pH
39	90	44	7.30
37	80	40	7.40
30	54	30	7.50

Table 1.7: Effect of temperature upon PO_2, PCO_2 and pH. Source: Lumb and Jones, 1996 [27].

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CHAPTER 2

2 THE HEMORRHAGIC SHOCK MODEL

A combination of both the fixed volume model and the fixed pressure model of Wiggers [33] was used. In the first model, a fixed volume of blood is withdrawn over a specified period, despite changes in blood pressure [24, 4]. In the Wiggers' preparation, a certain amount of blood is withdrawn to decrease mean arterial pressure to a predetermined stabilized pressure. What characterizes the Wiggers' model is the marked reduction in cardiac output and impairment of important homeostatic responses to blood loss [4].

Dogs were acutely bled and approximately 40 % of the dog's blood volume was removed from the femoral artery until the mean arterial pressure declined and reached a target of 50 mm Hg in approximately 15-30 minutes. The arterial blood pressure was held constant between 50-55 mm Hg for 60 minutes by removing blood from the artery into a reservoir or adding small amounts from the reservoir [31].

This model allowed us to study the decompensated stage of hemorrhagic shock. However, controversy has existed for years among authors regarding the conceptualization of this stage. Decompensation has been defined as that period of

hemorrhagic shock in which the initial compensatory responses are no longer favorable and the vasculature is refractory (vascular hyporeactivity) to the action of endogenous and exogenous catecholamines, being unable to sustain blood pressure despite fluid resuscitation (blood transfusion, crystalloids) [19].

Wiggers and Werle [32] stated in 1942 *" the state of hypotension which follows severe hemorrhage is not necessarily equivalent to that of shock but that progressive circulatory failure which supervenes after an effective period of such hypotension and the reinfusion of all the withdrawn blood warrants the designation, hemorrhagic shock."* This progressive circulatory failure as described by Wiggers is precisely what characterizes the decompensated phase.

The model used is considered relevant because it examined the persistent deficiency of blood through tissues during protracted hemorrhage. The model was functional in this respect because it is during this period that progressive and significant changes caused by continued hemorrhage lead to a deterioration of homeostasis despite restoration of the blood volume to normovolemia [26]. Therefore, tissue hypop erfusion, which causes non-respiratory lactic acidosis, its effects on the body and the events that lead to circulatory derangement (mainly vascular hyporeactivity), and the response to therapy were addressed using this model.

Species

The dog has been widely used in experimental shock. One basic reason for using this species in conducting these studies was the fact that shock in dogs is a common occurrence. Furthermore, the hemodynamic responses to hemorrhage in man and dogs are similar [3], although the mechanisms involved might not be the same [36].

However, the use of dogs has led to some bias in the design of this type of experiments. For example, the presence of a unique hepatic sphincter tends to exaggerate the splanchnic response under shock conditions [36]. Nonetheless, vascular reactivity in general and not specific visceral responses was measured in these experiments.

Clinical Relevance

It is well known that for an experimental shock model to have clinical application, it has to reproduce significant aspects of shock as seen in humans during or following considerable blood loss. The model simulated as closely as possible, the clinical scenario of acute hemorrhage and resuscitation [3]. Furthermore, it gave the most detailed and useful information such as cardiac output and other hemodynamic indices [36]. Previous work in the lab has confirmed its reproducibility. The model also incorporates essential aspects of refractory shock as seen in humans. These include hypothermia, hypoxia, hypotension, acidosis, coagulopathies [4].

Therapeutic Implications

It has been argued [3] that any experimental model of hemorrhagic shock cannot totally embody the whole range of physiologic compensations that take place during the course of this syndrome. These interactions occur between hemorrhage, the responses to it and the compensations that arise as a result of therapy. But the model was useful for the study of most of the main variables thought to be involved in the generation of vascular hyporeactivity. Therefore, it has therapeutic relevance in predicting patient outcome when the two therapeutic strategies used (the pH-stat and the pH-stat modified) are evaluated.

2.1 THE IMPACT OF ANESTHESIA ON EXPERIMENTAL HEMORRHAGIC SHOCK

Although anesthetics are essential in the execution of experiments and throughout surgical intervention for treatment of hemorrhage and trauma in man as well as in animals, they have important influences on the host response to shock [28].

From the clinical standpoint and considering a first scenario, a patient with hemorrhagic shock may need urgent surgical treatment to manage blood loss. Therefore, the impact of the anesthetic on the cardiovascular system of a hypovolemic patient may be crucial. A second scenario would be the development of hypovolemia intraoperatively due to a failure to control bleeding during a vascular surgical intervention. At this time, anesthesia is already present when hemorrhage develops [28].

It is well known that anesthetics might modify experimental results if not given adequate consideration. Anesthetics affect the distribution of blood cells and body fluids and exert significant influences on the cardiovascular system, mainly cardiac performance, blood pressure control, regional blood flows, pulmonary function, respiration, metabolism, and oxygen consumption. The investigator conducting studies in hemorrhagic shock must be aware that these hemodynamic changes induced by anesthetics may affect the outcome once hemorrhagic shock ensues. If the investigator is not vigilant of the influences of the anesthetics, they may mistakenly interpret an otherwise legitimate experimental work [33, 18].

The selection of an anesthetic agent is an important issue. Wiggers [33] stated that *"the ideal anesthetic for the study of the shock problem is one which can be given intravenously, which produces the least disturbance of natural reflexes, maintains an*

even anesthesia for hours without readministration, and which, of course, does not by its own action produce circulatory states that can be confused with those of shock." The general idea has been that anesthetics increase the susceptibility to hemorrhage. However, work with dogs [33] in which morphine and/or barbital were used has not provided evidence that such alterations affect the resistance to hemorrhage or that qualitative or quantitative differences occur in compensatory reactions in dogs. Wiggers compared the results of different investigators who performed experiments on barbitalized dogs subjected to hemorrhagic shock and suggested that the compensatory movement of water from tissues to the intravascular compartment is just as effective in anesthetized animals.

However, comparisons are rather difficult due to the substantial variability between different animals even under the same experimental conditions. Slight differences have been found in the outcome of hemorrhagic procedures whether the dogs are anesthetized with a combination of morphine-barbital or not. It has been suggested that the type, rate, and level of anesthesia might explain the divergent results among different laboratories [33, 6].

However, Green [6] argues that in some patients, the effect produced by high doses of pentobarbital is difficult to distinguish from shock. The dose size and method of its administration are the most important causes of variation in the response to pentobarbital. According to this author, nearly one of four animals given a dose of pentobarbital of 30 mg/kg develops effects that mimic some phases of shock.

Cardiocirculatory Effects of Pentobarbital

It has been reported [33] that the main and most important action of barbiturates in dogs appears to be a rapid decline in the effective circulating blood volume. This reduction is caused by sequestration of blood in the dilated spleen.

Pentobarbital, amobarbital and thiopental produce dilation of the spleen, which presumably accounts for the decrease in erythrocytes. Maximal dilation occurs 20 to 30 minutes after the injection of the anesthetic [6].

Van Citters et al [29] evaluated left ventricular responses of dogs during anesthesia with alpha-chloralose and pentobarbital and reported that pentobarbital increases heart rate and does not produce changes in total quantity of blood pumped or the amount of work performed. Conversely, alpha-chloralose exaggerates baroreflexes responses.

Priano et al [21] undertook studies in dogs to define in a more precise way, the immediate and prolong alterations induced by pentobarbital anesthesia in intact unanesthetized calm dogs that had not been subjected to any previous surgical procedure. Their data showed depression of systolic blood pressure, myocardial contractility, stroke volume, pulse pressure, central venous pressure and reductions in PO_2, pH and body temperature. Heart rate and PCO_2 increased significantly. Although the authors did not define the precise mechanisms by which pentobarbital brings about these alterations, they speculated from their study that barbiturates make an experimental preparation pathologic rather than physiologic. They also called attention to the implications these alterations may have in the study of cardiovascular and respiratory responses when employing an anesthetized model for physiologic and pharmacologic studies.

Longnecker and associates [16] conducted a comparative study on survival in rats subjected to hemorrhage. They used inhalant anesthetics (fluroxone and halothane), barbiturates (pentobarbital), and ketamine (a dissoaciative anesthetic) and found that the most conspicuous results of their study were the improvement of survival rate and the lack of splachnic pathologic changes following hemorrhage in rats treated with ketamine when compared with the other two anesthetics.

Cox and Bagshaw [5] investigated the systemic hemodynamic responses of pentobarbital, chloralose and halothane to carotid sinus hypotension in trained, chronically instrumented dogs and found that all three anesthetics decreased cardiac output and pressor responses to carotid sinus hypotension. The magnitude of the change in mean and pulsatile carotid sinus pressure with carotid sinus hypotension was larger after anesthesia than before. Their results suggest that the three anesthetics depress the responses of peripheral baroreceptor-mediated reflexes.

Hosomi and Sagawa [10] quantified the effect of pentobarbital on hypotension after mild (10%) and brief (30 seconds) hemorrhage in dogs before and after denervation of the carotid sinus nerve and/or the vagi and found that the commonly used dose of this anesthetic (30 mg/kg) does not significantly impair the responses of the rapidly acting arterial pressure control systems (high-and low-pressure-receptor reflex systems) after acute hemorrhage, when compared to unanesthetized dogs.

Zimpfer et al [34] studied in dogs the effects of three anesthetics (alpha-chloralose, pentobarbital, and halothane) on cardiac and peripheral vascular responses to stimulation of the carotid chemoreceptor reflex. They found that the three anesthetics caused bradychardia in response to carotid chemoreceptor reflex stimulation.

The following year, Zimpfer et al [35] compared the capability of conscious dogs and dogs anesthetized with pentobarbital to maintain arterial pressure in response to progressive hemorrhage and found that pentobarbital alters markedly the capacity to maintain arterial pressure with hemorrhage. Their results suggest that the sympathoadrenal and renin-angiotensin systems act in concert in the response to hemorrhage in the conscious and anesthetized states. In intact dogs, the sympathoadrenal system predominates, while in the anesthetized state the renin-angiotensin system prevails. Consequently, pentobarbital alters the levels of plasma catecholamines to hemorrhage and increases the responses of plasma renin. They suggested that the latter effect could be due to the more severe hypotension sustained by the anesthetized dogs with hemorrhage, as well as differences in responses of renal blood flow.

Their data did not support the concept that animals anesthetized with barbiturates show a high degree of sympathetic tone. They suggested that the high sympathetic tone was probably related to environmental and surgical stress commonly seen in preparations used for physiological studies.

Lindmar et al [14] studied the effects of pentobarbital on heart preparations of chicken and cat and showed that subanesthetic concentrations ($\leq 2 \times 10^4$ M in the perfusate) of pentobarbital produce an increase in heart rate due to reduction in the release of acetylcholine. They concluded that the effect was caused by an action of pentobarbital at a postganglionic level and not on ganglionic transmission. They postulated that the possible mechanism was an interference with the neuronal Ca^{2+} entry.

Seyde et al [25] compared the effects of pentobarbital, chloralose-urethane and decerebration on central and regional hemodynamics in normovolemic and hemorrhaged rats and showed that in unanesthetized normovolemic rats, pentobarbital in particular, alters general hemodynamics and causes respiratory depression, while decerebration modifies cerebral and renal hemodynamics. Renal hemodynamics were not altered by chloralose-urethane, but heart rate and mean arterial pressure were.

However, when responses to hemorrhage were evaluated, the changes in cardiac output and regional blood flows in decerebrated animals were very similar to those in nonanesthetised rats. They concluded that decerebration might be the adequate anesthetic technique if the objective is to induce responses in anesthetized animals that are most comparable to those in awake rats. They called attention that generalizations regarding anesthetic selection do not necessarily apply to specific organs.

Myers et al [20] performed *in vivo* studies on a rat shock model of hemorrhagic shock and resuscitation and compared the effects of two anesthetic agents (methoxyflurane and pentobarbital) on splanchnic arterial blood flow. Their findings revealed that both anesthetics decrease superior mesenteric blood flow in a similar manner in animals with acute hemorrhage. In contrast, during resuscitation, arterial pressure and superior mesenteric blood flow were significantly reduced in the group with pentobarbital while blood pressure returned to baseline values and superior mesenteric artery blood flow significantly improved in rats anesthetized with methoxyflurane.

In a model of uncontrolled hemorrhage in rats, Soucy et al [27] contrasted the effects of pentobarbital vs. droperidol-ketamine and found that the responses (blood loss, mortality) of rats subjected to pentobarbital approximated more closely the responses of

unanesthetized rats, although the mortality rate was higher in the anesthetized rats. Rats anesthetized with the combination of droperidol-ketamine had an excessive rate of blood loss and less survival time.

The Microcirculation during Anesthesia

The microcirculation is not excluded from the action of general anesthetics. Anesthetic agents influence the effective microcirculatory blood flow pattern [2, 7] and modify both the vessel caliber and the responses to stress, such as catecholamine stimulation or hemorrhage [17].

There are relatively few studies of the effects of anesthetics on the microcirculation. Johnson [12] showed that barbiturate anesthesia causes a reduction of the autoregulatory responses of mesenteric arterioles of cats. These responses are manifested by decreases in diameters as well as biphasic responses of the arterioles.

In 1971, in experiments performed on wings of unanesthetized bats, Harris et al [8] studied the vascular responses of the microcirculation to the administration of two thiobarbiturates (thiopental). Pentobarbital caused a statistically significant dilatation of the small arteries (35- 45μ) and veins (70-100μ) whereas thiopental did not have any effect on the diameter of those vessels. They suggested that both anesthetics have different effects on the microcirculation.

Harris et al [9] examined the diameters of small arteries and veins in the cremaster muscle of rats subjected to moderate hypothermia and anesthetized with pentobarbital and observed marked constrictive responses of these vessels. Their findings are in obvious contrast with those of Hutchins et al [11] who found venular dilatation.

According to some authors [17] variations in vessels diameter in conjunction with changes in arterial pressure and cardiac output are accountable for the changes in organ blood flow that take place in the microcirculation during general anesthesia.

Altura et al [1] have provided important *in vivo* and *in vitro* experimental evidence on the depressant action of anesthetic agents on vascular smooth muscle. These investigators have postulated that anesthetics may participate to some extent, in the decreased vasoconstrictor tone and vasodilatation associated with induction of anesthesia in mammals.

The mechanisms that appear to be involved in the depressant action of general anesthetics are linked to the suppression of normal vasomotion dependent on the external Ca^{2+} concentrations and to the inhibition, in a non-specific way, of the contractile responses to neurohumoral substances such as angiotensin II, catecholamines, serotonin, prostaglandins and certain ions (K, $^{+}$ Ba^{2+}) [1].

Opioids in Anesthesia

Opioids are used in balanced anesthesia and conscious sedation for their marked analgesic effect. These agents have no remarkable direct effects on the heart and no major effects on cardiac rhythms with the exception of bradycardia or blood pressure. Generally, opioids maintain blood pressure in patients unless the cardiovascular system is stressed, wherein hypotension may occur. This hypotensive effect is probably the result of peripheral arterial and venous dilatation, which has been attributed to several mechanisms such as depression of vasomotor-stabilizing mechanisms and release of histamine. Opioids do not affect ECG in a significant manner; effect on cardiac output is

not consistent. However, extreme caution should be exercised in hypovolemic patients since the mechanisms described make these patients very vulnerable to hypotension [30].

Opioids can cause marked dose-response respiratory depression by inhibiting brain stem respiratory mechanism. As a result, PCO_2 may rise, but the most consistent indicator of this depression is a reduced response to CO_2 challenge [30].

Opioids are often used for preanesthesic medication reducing by 10% to 20% the amount of general anesthetic required [13].

Wiggers [33] performed numerous studies on hemorrhagic shock using a combination of morphine and barbiturates. Morphine counterbalances the unwanted effects of barbiturates. It prevents cerebral excitement, muscular tremors, and deep respiration. Morphine enhances vagal tone so that tachycardia is not severe.

The hyperpnea currently seen during hemorrhagic shock is less intense in barbitalized than in conscious dogs. This has allowed researchers to separate the cardiovascular from the respiratory effects on the circulation. In addition, in barbitalized animals, oxygen saturation of hemoglobin is also preserved despite the hyperpnea that occurs after severe blood loss.

Fentanyl is a synthetic opioid (a morphine-like opioid) analgesic related to the phenylpiperidines. It is a selective μ agonist with an analgesic potency 50 to 100 times greater than morphine. Fentanyl might cause hemodynamic instability during surgery, partly because it does not cause the release of histamine. Fentanyl can aggravate hypovolemic shock if not used with caution [22].

In summary, unquestionable experimental evidence has shown that anesthetic agents do not have therapeutic effects. They might alter baroreflexes-mediated responses; have an impact on cardiac performance and major hemodynamic variables such as arterial pressure, cardiac output, and heart rate. Anesthetics affect blood flows to different vascular beds, as well as the autonomic nervous system compensatory responses.

The microcirculation does not escape to the action of anesthetics. They can modify both vessel diameters and constrictor responses in different vascular territories. Furthermore, in different species, the behavior of the microcirculation in response to these agents is different.

Investigators should have a clear knowledge of the pathophysiology of shock and the pharmacology of anesthetics to be able to select the suitable agent, which causes the least undesirable effects. They also should be aware of the type, rate, level of anesthesia, and the species. In addition, when conducting hemorrhagic shock experiments, they should take advantage of that combination of anesthetics which counterbalances the undesirable effects, because the choice of anesthetics may considerably influence the results of the experiments.

2.2 MATERIAL AND METHODS

These experiments were approved by the Ohio State University Institutional Laboratory Animal Care and Use Committee (ILACUC, protocol # 02A0037). The studies were in rigorous adherence to current NIH guidelines for the use of experimental animals.

Animals

Twenty-three (23) young, mature, healthy mixed-breed intact dogs of either sex were used. The dogs weighed between 15.5 and 21.6 kg (mean 18.6 kg). The animals were free of heartworms, had normal appetite and temperature, and no abnormal heart sounds and murmurs or gallops were detected. They were fasted for 12 hours prior to the experiments, but allowed water *ad libitum.*

Experimental Design

The dogs were randomly assigned to four (4) groups, as follows: Group I: One (1) dog was included as control (pilot study) in order to provide baseline and control data using the current laboratory and acquisition equipment available in the laboratory. Group II: Seven (7) hemorrhaged, hypothermic (32 °C; approximately 90 °F) dogs received a crystalloid solution of lactated Ringer's (LRS) based on the administration of three (3) times the amount of total blood removed. Group III: Seven (7) hemorrhaged, hypothermic dogs received LRS as in group II and were subjected to the pH-stat therapy; Group IV: Eight (8) hemorrhaged, hypothermic dogs received LRS as in group II and underwent the pH-stat modified treatment. All dogs were splenectomized through a midline laparotomy prior to the experimental procedures.

Instrumentation

Surgical incisions and dissections were made on both sides of the neck and on the hind limbs for the introduction of catheters. The left carotid artery was cannulated with a 7F Millar [a] pressure transducer catheter connected to a recorder, for the determination of

[a] Millar catheters.

aortic systolic pressure, left ventricular systolic pressure, and left ventricular end diastolic pressure. The proximal tip of a balloon thermodilution catheter [b] was inserted via the right external jugular vein to the level of the right atrium for measurement of right atrial pressure; the distal tip of the catheter was positioned in the pulmonary artery for measurement of pulmonary artery pressure, cardiac output, stroke volume, and temperature, using a cardiac output computer. A catheter was placed in the right femoral vein for pH and blood gases determination, and for blood collection. Another catheter was inserted in the right femoral artery for pH and blood gases determination, for bleeding, and for the return of shed blood when needed. The right cephalic vein was used for fluid and drug administration.

An ultrasonic abdominal probe [c] was placed in the cranial mesenteric artery to measure blood flow to the small intestine. A similar probe was inserted in the left femoral artery to monitor blood flow to the hind limb. A pulse oxymeter [d] was placed on the tongue for measuring % SpO_2 and heart rate.

Surgical Procedure

All dogs were anesthetized with a combination of pentobarbital and fentanyl. An intravenous loading dose of pentobarbital sodium [e] (30 mg/kg body weight) and fentanyl citrate [f] (10 μg/kg body weight) was given. Subsequent to the induction of anesthesia, the animals were administered a maintenance dose of pentobarbital (10 mg/kg/hr) and fentanyl (10 μg/kg /hr) to maintain a stable surgical plane of anesthesia for the duration

[b] Edwards Swan-Gantz® thermodilution catheter.
[c] Model T201, Transonic Systems, Inc.
[d] Hallowell EMC.
[e] Nembutal™, Abbott Laboratories.
[f] Sublimaze™, Taylor Pharmaceuticals.

of the experiment. This anesthetic technique has been previously validated in our laboratory to produce satisfactory pain-free anesthesia and clinically relevant hemodynamic data.

The dogs were intubated with a cuffed endotracheal tube and were mechanically ventilated on room air to produce an end tidal CO_2 of 35-40 mm Hg. The dogs initially received an intravenous infusion of LRS (10 ml/kg/hr) to keep them hydrated. This treatment was given until hemorrhage.

Following hemorrhage, the maintenance dose of anesthetic was reduced by 50% and infused as follows: 5 mg/kg/hr of pentobarbital and 5 μg/kg /hr of fentanyl.

At the conclusion of the experiments, all dogs were euthanized, with an excess of anesthetic (pentobarbital), while still under anesthesia.

Induction of Hemorrhagic Shock

Approximately 40 % of the dog's blood volume was removed (blood volume is estimated as 8% of body weight or 90 ml/kg) from the right femoral artery until the mean arterial blood pressure reached a target value of 50 mm Hg. Dogs were hemorrhaged for over 15-30 minutes by removing blood from the femoral artery catheter into a heparinized reservoir [15]. Subsequently, the mean arterial blood pressure was held constant at approximately 50-55 mm Hg for 60 minutes by removing blood from the artery into the reservoir or by adding small amounts of blood from the reservoir into the circulation.

Temperature Control

During the surgical procedure, blood temperature was stabilized at 37.5 °C by means of a heated water circulating [g] placed underneath the animal. After hemorrhage, temperature was allowed to drop spontaneously to approximately 32 °C.

Esophageal and abdominal temperatures were recorded from thermistor probes placed in the esophagus and abdomen, respectively, and connected to temperature measuring devices. [h] Blood temperature was recorded from the pulmonary artery.[i]

Treatments

At the end of the hemorrhage period, all dogs were treated with LRS. All dogs were administered three times the amount of total blood removed given as LRS. Dogs in groups III and IV were then subjected to the pH-stat therapy or the pH-stat modified therapy**.** The pH-stat therapeutic approach maintains the arterial blood pH value at 7.40 and the arterial PCO_2 at 40 mm Hg regardless of body temperature. For this treatment, both arterial and venous blood gases (PaO_2, $PaCO_2$) and pH were corrected to the animal's body temperature. It has been previously determined that dogs subjected to this protocol will develop significant non-respiratory (lactic) acidosis that can be appropriately managed by the administration of sodium bicarbonate ($NaHCO_3$). Dogs from group IV were subjected to the pH-stat modified therapy, which consists of keeping a fixed PCO_2 of 60 mm Hg and a pH of 7.30. The desired values are obtained by manipulating PCO_2 through adjustments in ventilation and by giving sodium bicarbonate to regulate blood pH at 7.30.

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[g] Hallowell EMC.
[h] 2100 Tele-Thermometer, Yellow Spring Inst. Co.
[i] 9520A Cardiac Output Computer, American Edwards Lab.

Experimental Procedures

Blood flow to the hind limb (femoral artery blood flow) and to the small intestine (cranial mesenteric artery blood flow) was determined before (-15 minutes) hemorrhage (baseline), at the end of the 60-minute period of hemorrhage, and at 60, 90, 120, 150, and 180 minutes (every thirty minutes) after resuscitation with LRS and either the pH-stat or the pH-stat modified therapies. After a brief hind limb occlusion (1 minute), HR, SAP, DAP, MAP, mPAP, mRAP, LVSP, LVEDP, LV + dP/dT, LV – dP/dT, TAU, femoral artery blood flow and cranial mesenteric artery blood flow were measured before hemorrhage (baseline), at the end of the 60-minute period of hemorrhage, and at 60, 90,120, 150, and 180 minutes (every thirty minutes) after the end of treatment with crystalloids LRS and either the pH-stat or the pH-stat modified therapies.

Cardiac output was determined (- 15 minutes) before hemorrhage (baseline), at the end of the 60-minute period of hemorrhage, and at 60, 90,120, 150, and 180 minutes (every thirty minutes) after the end of treatment with LRS and either the pH-stat or the pH-stat modified treatments.

Data Base Collection

Dogs were stabilized for 30 minutes. Blood gas data were recorded (-15 minutes)before hemorrhage (baseline), at the end of the 60-minute period of hemorrhage, and at 60, 120, and 180 minutes after the end of treatment with LRS and either the pH-stat or the pH-stat modified therapies.

Vascular reactivity [23] was determined by the vascular response to a norepinephrine infusion challenge in all dogs before hemorrhage (-15 minutes), at the end of the 60-minute period of hemorrhage, and at 60, 90,120, 150, and 180 minutes (every

thirty minutes) after the end of treatment with LRS and either the pH-stat or the pH-modified treatments. A 0.5 μg/kg of norepinephrine was administered and the same dose was repeated after 5 minutes.

After the infusion of norepinephrine, HR, SAP, DAP, MAP, mPAP, mRAP, LVSP, LVEDP, LV + dP/dT, LV – dP/dT, TAU, FABF, and CMABF were measured before hemorrhage (baseline), at the end of the 60-minute period of hemorrhage, and at 60, 120, and 180 minutes post-resuscitation with LRS or either the pH-stat or the pH-stat modified treatments.

Hemodynamic Measurements

Intravascular catheters were connected to the appropriate pressure transducers and subsequently to a physiologic recording system and computer-based data acquisition system.[j] The experimental procedure facilitates the measurement of HR (beats/minute), mean pulmonary artery pressure (mPAP; mm Hg), mean right atrial pressure (mRAP; mm Hg), aortic systolic (SAP; mm Hg), diastolic (DAP; mm Hg) and mean arterial pressures (MAP; mm Hg), left ventricular systolic pressure (LVSP; mm Hg), left ventricular end diastolic pressure (LVEDP; mm Hg), and cardiac output (CO; ml/kg/min). These hemodynamic variables were used to calculate systemic vascular resistance (SVR; dynes.sec/cm^5), the rate of left ventricular pressure rise (+ dP/dt; mm Hg/sec), the rate of left ventricular pressure fall (- LV dP/dT), and the rate pressure product (RPP; heart rate [beats/min] x MAP [mm Hg]. Oxygen delivery (DO_2; L/min), oxygen consumption (VO_2; L/min), and oxygen extraction (O_2ER) were calculated from hemodynamic (CO) arterial and venous oxygen content values. All data were

[j] Data Acquisition System. Gould Instruments Inc.

continuously monitored and periodically recorded using a computer-based data acquisition system for physiologic measurements available in the laboratory (see Fig. 2.1 for a diagram of the experimental preparation).

Blood, Gas, Hematological, and Lactate Measurements.

Samples of anaerobic blood were collected from the right vein and femoral arteries, respectively, and were used to determine venous and arterial pH and blood gas tensions (PO_2, PCO_2), HCO_3^-, arterial and venous base excess (BE), and hemoglobin by means of a blood-gas analyzer. Tubes for collecting arterial blood (0.2 ml) had previously been heparinized (sodium heparin, USP, 1000 units/ml. Elkins-Sinn, Inc, NJ). Immediately after blood gas determinations, blood was centrifuged for 2 minutes at 2000 g for microhematocrit determination. Total proteins were measured by refractometry using 0.5 ml of heparinized arterial blood. Lactate samples were centrifuged for 7 minutes at 3000 rpm at 3°C and kept frozen at -70 °C until further determination. Once thawed, lactate samples were run in duplicates in a lactate analyzer [k] using 5 μl of arterial blood. Plasma colloidosmotic pressure was measured using 0.8 ml of venous blood in a colloid osmometer. [l] A volume of 80 μl of serum was used to run the electrolytes. [m]

Statistical Analysis

All data were expressed as mean ± SD, followed by appropriate statistical analysis for multiple groupings: One-way analysis of variance (ANOVA I) for repeated measures on multiple groups and Tukey's post-tests for comparison of means within and among groups. Differences were considered significant at $P < 0.05$.

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[k] Power Wave X, Bio-TCK Instruments, Inc.
[l] 4420 Colloid Osmometer, Wescor, Inc.
[m] 911 Automatic Analyzer, Hitachi.

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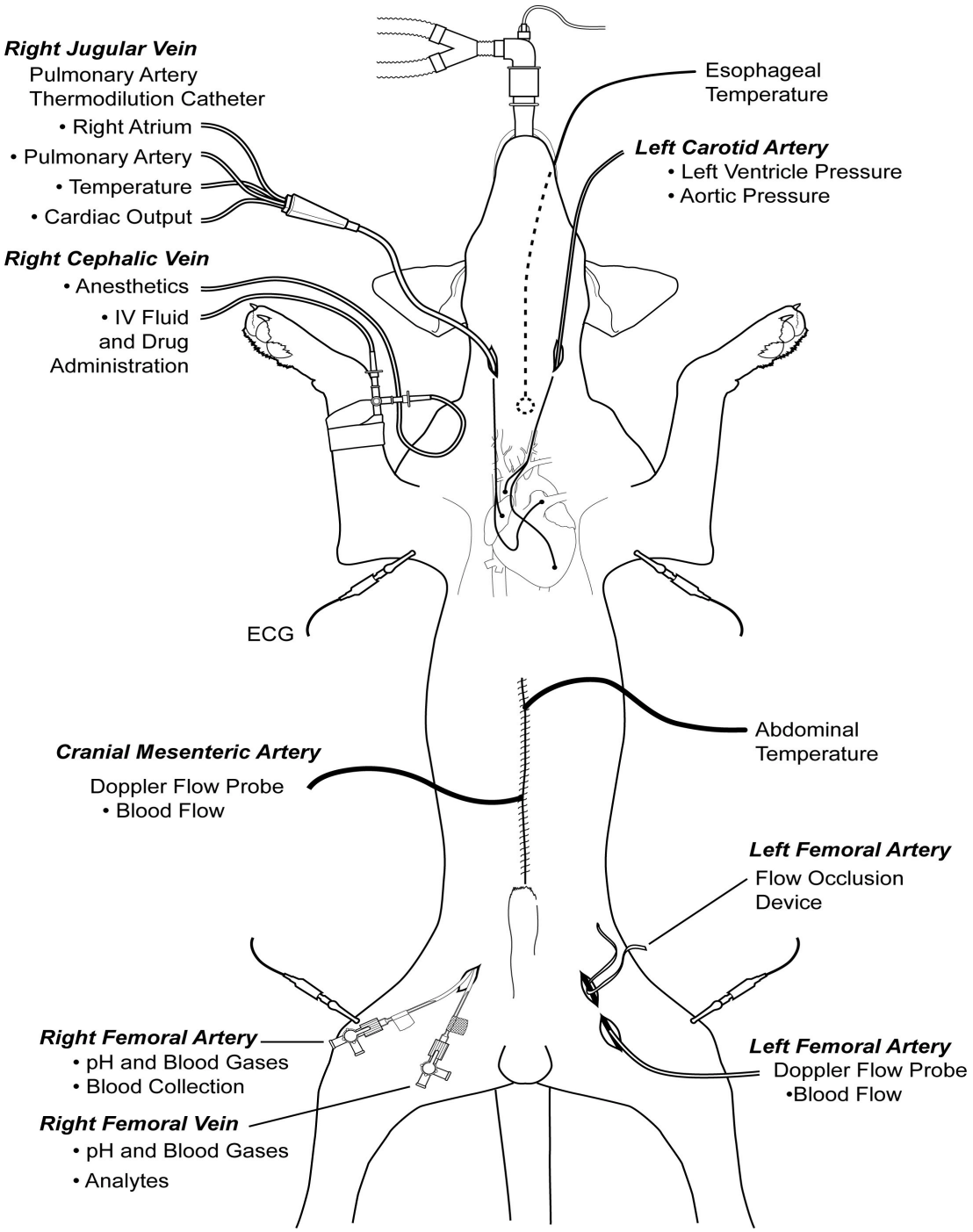

Figure 2.1: Schematic representation of experimental preparation.

CHAPTER 3

3 RESULTS

WITHIN GROUP ANALYSIS FOR LRS GROUP

Hemodynamic Variables

One dog was used in the pilot study. This animal did not receive any treatment. Baseline hemodynamic and blood variables for the pilot study and for all animals receiving different treatments fell within the normal range of values previously reported for dogs [2, 1]. As a result of the acute bleeding, animals in the LRS group insignificantly increased their HR (Fig. 3.1), when compared to baseline values. During hemorrhage, SAP, DAP, MAP, mPAP, mRAP, LVEDP, LV - dP/dt, FABF and CMABF (Figs. 3.2-3.6, 3.8, 3.10, 3.12 and 3.13) significantly declined (see Tables 3.1 and 3.2 for details). LVSP, LV + dP/dt and TAU (Figs. 3.7, 3.9 and 3.11) also decreased, but the change was not significant. At the end of treatment, HR increased, but the elevation was insignificant. LV + dP/dt and FABF showed statistically significant increases (Table 3.2). CMABF was elevated, but the elevation was not statistically significant. mPAP also increased insignificantly. In contrast, DAP and LV – dP/dt significantly declined. SAP, MAP, LVSP, and TAU experienced minor reductions. Both mRAP and LVEDP reached baseline values at this stage of the experiment. At 60 minutes following

resuscitation, HR, LVSP, LV + dP/dt, and TAU exhibited non-significant elevations, when compared to baseline. In contrast, SAP, DAP, mPAP, mRAP, LVEDP, LV – dP/dt, and FABF showed a statistically significant reduction, when compared to baseline values (see Tables 3.1 and 3.2). MAP and CMABF decreased 28 and 29 % of baseline, but the changes were irrelevant. At 120 minutes after treatment, SAP, DAP, MAP, mPAP, LVEDP, FABF, and CMABF were significantly reduced. HR, mRAP and LV – dP/dt were also reduced, but the change was not significant. In contrast, LVSP, LV + dP/dt and TAU experienced non-significant increases. At 180 minutes after treatment, HR, LV + dP/dt and TAU experienced non-significant increases while SAP, DAP, MAP, mPAP, mRAP, LVEDP, and CMABF were significantly reduced. At the same time, LVSP, LV – dP/dt and FABF exhibited non-significant reductions (Tables 3.1 and 3.2 for details). When animals receiving the LRS treatment during hypovolemia were given a norepinephrine infusion (Tables 3.3, 3.4 and 3.16), HR, SAP, DAP, mPAP, mRAP, LVSP, LVEDP, FMAB, and CMABF showed statistically significant pharmacologic responses, when compared to baseline values. HR and LVSP increased and SAP, DAP, mPAP, mRAP, LVEDP, FABF, and CMABF fell**.** There were also non-significant responses to norepinephrine infusion during this period. MAP, LV – dP/dt nd TAU were reduced. In contrast, LV + dP/dt increased insignificantly. At the end of treatment, HR, SAP, DAP, MAP, mPAP, FABF and CMABF increased insignificantly. mRAP, LV – dP/dt and TAU diminished in a non-significant manner, with no change in LVEDP. LVSP and LV + dP/dt were significantly elevated. At 120 minutes following resuscitation, HR, SAP, DAP, MAP, mPAP, mRAP, LVEDP, and LV – dP/dt, respectively, showed non-significant reductions. FABF and CMABF showed significant

reductions**.** LV + dP/dt exhibited the only significant elevation (169 % of baseline), when challenged with norepinephrine. LVSP and TAU augmented, when compared to baseline, but the elevation was not significant. At 180 minutes after treatment, HR, SAP, MAP, LVSP, LV + dP/dt, and TAU went up 10, 3, 2, 50, 130, and 41 % of baseline, respectively, but these changes were not statistically significant. DAP and CMABF were the only parameters which were significantly modified. When compared to baseline, DAP increased 3 % and CMABF dropped 52 %. mPAP, mRAP, LVEDP, LV – dP/dt, and FABF, respectively, were insignificantly reduced 22, 50, 21, 20, and 82 %, respectively, when compared to baseline (see Tables 3.3 and 3.4 for details). The response to occlusion to the hind limb (Table 3.17) throughout hemorrhage was diverse. HR and TAU increased, and LVSP and LV + dP/dt declined, but these changes were not significant. In contrast, SAP, DAP, MAP, mPAP, mRAP, LVEDP, LV – dP/dT, FABF, and CMABF experienced significant reductions of 52, 52, 57, 50, 67, 64, 57, 48, and 70 %, in that order, when compared to baseline At the end of treatment, LV + dP/dt and TAU increased significantly. HR, LVSP, FABF, CMABF were elevated, but the increase was not statistically significant. SAP, DAP, mPAP, mRAP, LVEDP, and LV – dP/dt decreased significantly. MAP was the only variable in which there was a non-significant reduction. At 120 minutes after treatment, HR, LVSP, LV – dP/dt, and FABF decreased 6, 3, 43, and 38 % of baseline, respectively, but the changes were not significant. In contrast, SAP, DAP, MAP, mPAP, mRAP, LVEDP, and CMBF fell 38, 38, 41, 50, 33, 43, and 47 % of baseline respectively, when brief occlusion to the hind limb was applied. The fall was statistically significant. Irrelevant increases (43 and 100 %) occurred in LV + dP/dt and TAU. At 180 minutes after resuscitation, HR, LV + dP/dt, and TAU

increased non-significantly. SAP, DAP, MAP, and mPAP were the only significant parameters in which a reduction was reported. They declined 42, 42, 45, and 50 % of baseline, in that order. mRAP, LVSP, LVEDP, LV – dP/dt, FABF, and CMABF declined 67, 9, 57, 61, 22, and 40 %, respectively, when compared to baseline. The change was not significant.

Derived Hemodynamic Variables

Unsurprisingly, CO (Fig. 3.14) significantly diminished 78, 47, and 58 % of baseline during hemorrhage and at 60 and 120 minutes after treatment, respectively. When compared to baseline, a 67 % increase occurred at the end of treatment. To compensate for the fall in CO, SVR (Fig. 3.15) was markedly elevated during hypovolemia. SVR rose 89, 38, 56, and 98 % of baseline during hemorrhage and at 60, 120, and 180 minutes after treatment, respectively. There was a significant decline (52 % of baseline) in this variable at the end of treatment. RPP (Fig. 3.16) exhibited a 45 and 3 % of baseline reduction in hemorrhage and at the end of treatment, respectively, and a 23, 45, and 35 % at 60, 120, and 180 minutes after treatment, respectively, when compared to baseline values (see Table 3.7 for details). After norepinephrine infusion, RPP significantly fell 28 % throughout hemorrhage. At 120 minutes after resuscitation, RPP diminished 18 % of baseline, but the fall was not significant. RPP rose 8 and 14 % at the end of treatment and at 180 minutes post-treatment, respectively, when compared to baseline, but the changes were not remarkable (Table 3.8). When assessed against occlusion, RPP significantly fell during hypovolemia and at 120 minutes after resuscitation, in that order, when compared to baseline. At the end of treatment and at 180 minutes following resuscitation, RPP decreased, but the changes were not significant (Table 3.9).

Respiratory Variables and Temperatures

Subsequent to the equilibration phase, BT (Fig. 3.19) significantly dropped 2 and 13 % of baseline during hemorrhage and at the end of treatment. There was also a significant reduction of nearly 15 % at 120 and 180 minutes after treatment, respectively. ET (Fig. 3.20) also fell significantly nearly 2, 12 and 15 % of baseline during hemorrhage, at the end of treatment, and at both 120 and 180 minutes after treatment, correspondingly. AT (Fig. 3.21) was insignificantly reduced roughly 5 % during hemorrhage. In contrast, this temperature markedly dropped 14 % below baseline, at the end of treatment and 15 % at 120 and 180 minutes after treatment, respectively, when compared to baseline values (see Table 3.10 for details). Although RR (Fig. 3.17) showed a mild increased during both hemorrhage and at the end of treatment, and a decrease at 120 minutes after treatment, these changes were not significant. RR did not change at 180 minutes post-treatment. Both the infusion of norepinephrine and the occlusion did not bring about relevant changes in RR at any one time (Tables 3.8 and 3.9). When compared to baseline, $ETCO_2$ (Fig. 3.18) was reduced 20 % during hemorrhage and at the end of treatment. It also decreased 37 % at 120 and 180 minutes after treatment. The infusion of norepinephrine as well as the occlusion of the hind limb in animals receiving LRS treatment resulted in statistically significant reductions in $ETCO_2$ at all stages of the experimental observation (Tables 3.8 and 3.9).

Derived Respiratory Variables

The acute bleeding reduced the effective circulating blood volume leading to both a diminished DO_2 and VO_2 (Figs. 3.22-3.23). DO_2 significantly lessened (84 % of baseline) during hemorrhage, but was not significantly reduced at the end of treatment.

However, at 120 and 180 minutes after treatment, DO_2 significantly decreased 77 and 81 % of baseline, respectively. VO_2 decreased 33 and 17 % during hemorrhage and at the end of treatment, when compared to baseline. It also fell 33 and 50 % at 120 and 180 minutes post-treatment, in that order. All the reductions in VO_2 were not statistically significant. As a result of the hypovolemic condition, O_2ER significantly increased 337 and 221 % of baseline during hemorrhage and at 120 minutes post-resuscitation. There was also an insignificant elevation (5 and 163 % of baseline) at the end of treatment and at 180 minutes after resuscitation, correspondingly. The hypoxic condition produced during hemorrhage resulted in an increase in blood lactate levels (Fig. 3.25). Lactate significantly increased 377 and 523 % through hemorrhage and at the end of treatment. At 120 and 180 minutes post-treatment, lactate levels were still above baseline values (215 and 62 %, respectively), but the increase was not significant (see Table 3.11 for details).

Blood Gas Variables at Patient Temperature

In the course of hemorrhage, pHa (Fig. 3.26) experienced a significant reduction (2.86 %) when compared to baseline values. At the end of treatment, pHa also experienced a decline (2.04 % of baseline), but this reduction was not significant. The pHa values increased significantly 0.54 and 1.36 % above baseline at 120 and 180 minutes post-treatment, respectively. When evaluated against baseline, $aPCO_2$ (Fig. 3.27) experienced a progressive reduction at all stages of the experimental observation. It insignificantly decreased 5 and 10 % during hemorrhage and at the end of treatment, but it decreased significantly at 120 and 180 minutes after treatment, respectively. aPO_2 (Fig. 3.28) gradually increased through hemorrhage, and it continued to increase at the end of

treatment and at both 120 and 180 minutes after resuscitation, respectively. The elevation in aPO_2 was not statistically significant for this group during the entire course of the experiment. The $aHCO_3^-$ (Fig. 3.29) showed a significant reduction (41 %) during hemorrhage, remaining below baseline (27 %) values at the end of treatment. It continued to decrease 18 and 5 % at 120 and 180 minutes post-treatment, respectively, when compared to baseline, but this reduction was not statistically significant. aBE (Fig. 3.30) exhibited a statistically significant elevation during the whole experiment. It rose approximately 328, 272, 69 and 28 % during hemorrhage, at the end of treatment and at 120 and 180 minutes after treatment, in that order, when compared to baseline. Even though aBE showed a tendency to significantly decline from the end of treatment up to 180 minutes post-treatment, their values remained above baseline (see Table 3.12 for details). pHv (Fig. 3.31) significantly decreased 4.09 % during hemorrhage, when compared to baseline. At the end of treatment and at 120 minutes following treatment, pHv continue to decrease 1.64 and 1.09 %, respectively. At 180 minutes after treatment, pHv was elevated 0.68 % of baseline. Even though pHv tended to increase from the end of treatment until the end of the experiment, this increase was not statistically significant. When compared to baseline, $vPCO_2$ (Fig. 3.32) showed an important increase (45 %) throughout hemorrhage. $vPCO_2$ values diminished 14 % at the end of treatment and 7 and 16 % at 120 and 180 minutes, respectively, following treatment. vPO_2 (Fig. 3.33) decreased 54, 6 and 56 % of baseline in hemorrhage, end of treatment, and at both 120 and 180 minutes post-treatment, respectively. $vHCO_3^-$ concentration (Fig. 3.34) significantly decreased 26 % in hemorrhage and at the end of treatment, respectively, when compared to baseline. At 120 minutes following resuscitation, the reduction (13 %)

was not statistically significant. At 180 minutes after resuscitation, $vHCO_3^-$ reached baseline levels. When compared to baseline, vBE concentration (Fig. 3.35) markedly increased 430 % during both hypovolemia and at the end of treatment and 245 and 40 % at 120 and 180 minutes following treatment, correspondingly. Even though these last two values showed a tendency to decline, they never reached baseline levels (see Table 3.13 for details).

Chemistry Variables

No significant changes in serum Na^+ (Fig. 3.36) resulted during the length of the experiment. Although serum K^+ (Fig. 3.37) increased throughout hypovolemia and at 120 minutes after treatment, and decreased at 180 minutes following treatment, the change was not statistically significant. Serum Ca^{2+} (Fig. 3.38) concentration was not modified during hemorrhage. In contrast, this electrolyte concentration experienced a significant reduction (18 %), at the end of treatment and at 120 (9 %) and 180 (9 %) minutes following treatment, respectively, when compared to baseline (see Table 3.14). The chemistry variables analysis revealed statistically significant reductions of 23, 56, 42, and 35 % of baseline in PCV (Fig. 3.39) during hemorrhage, end of treatment, and at 120 and 180 minutes after treatment, respectively, when compared to baseline values. TP levels (Fig. 3.40) experienced an insignificant reduction (26 % of baseline) during hypovolemia. It also decreased significantly 60, 54 and 51 % of baseline during hemorrhage, at the end of treatment, and at 120 and 180 minutes after treatment, respectively. COP (Fig. 3.41) significantly decreased 26, 68, 53, and 42 % through hemorrhage, at the end of treatment, and at 120 and 180 minutes after treatment, respectively, when compared to baseline (sees Table 3.15 for details).

WITHIN GROUP ANALYSIS FOR pH-STAT GROUP

Hemodynamic Variables

Animals undergoing the pH-stat treatment experienced a non-significant increase in HR (Fig. 3.1) during hemorrhage. During this period, SAP, DAP, MAP, mPAP, mRAP, LVEDP, LV – dP/dt, FABF, and CMABF (Figs. 3.2-3.6, 3.8, 3.10, 3.12, and 3.13) significantly decreased, when compared to baseline values. LVSP (Fig. 3.7) insignificantly decreased (33 % of baseline) during this phase of the experiment. In contrast, LV + dP/dt (Fig. 3.9) and TAU (Fig. 3.11) increased, but the increase was not statistically significant. At the end of treatment, HR, LVEDP, TAU, FABF, and CMABF increased non-significantly. SAP, DAP, MAP, and LV – dP/dt decreased in a significant manner, when compared to baseline, and LV + dP/dt significantly rose 103 % of baseline. mPAP and LVSP declined insignificantly. mRAP reached baseline levels during this period. At 60 minutes following resuscitation, HR and LV + dP/dt experienced non-significant increases. SAP, DAP, MAP, mPAP, mRAP, LV – dP/dt, and FABF were significantly reduced. TAU augmented in a significant manner, when compared to baseline. LVSP, LVEDP, and CMABF showed non-significant reductions. At 120 minutes after resuscitation, HR, LVSP, LVEDP, and LV + dP/dt exhibited non-significant reductions. SAP, DAP, MAP, mPAP, mRAP, LV – dP/dt, FABF, and CMABF significantly declined, when compared to baseline. TAU was the only variable to significantly increase (150 % of baseline) during this period. At 180 minutes after resuscitation, HR, LVSP, LVEDP, and LV + dP/dt dropped 20, 32, 36, and 27 % of baseline, correspondingly. The reduction was not significant. In contrast, SAP, DAP, MAP, mPAP, mRAP, LV – dP/dt, FABF, and CMABF were significantly reduced 55,

62, 60, 63, 60, 75, 73, and 64 % of baseline, respectively. TAU significantly increased (203 % of baseline) at this stage of the experimental observation (see Tables 3.1 and 3.2 for details). The response to a norepinephrine infusion (Table 3.16) during hemorrhage, revealed that HR was the only hemodynamic variable that significantly increased (27 %) during this period, when compared to baseline values. SAP, DAP, MAP, mPAP, mRAP, LVEDP, FABF, and CMABF declined 48, 53, 53, 68, 60, 36, 82, and 70 % of baseline, respectively. LVSP and LV + dP/dt also rose 13 and 40 % of baseline. Similarly, LV – dP/dt declined 34 % of baseline. TAU was within baseline values during this phase of the experimental observation. At the end of treatment, HR, SAP, TAU, FABF and CMABF increased 8, 5, 17, 16, and 23 %, when compared to baseline. These changes were not significant. LVSP, LVEDP and LV + dP/dt showed significant increments of 44, 27, and 195 % of baseline, correspondingly. Significant reductions of 17 and 26 % of baseline in DAP and mPAP occurred. When compared to baseline, MAP, and LV – dP/dt dropped 6 and 3 %, respectively, but the reduction was insignificant. mRAP remained within baseline values during this period. At 120 minutes after treatment, HR and LVEDP experienced a non-significant decrease of 16 and 27 % of baseline. In contrast, LVSP rose 16 %, when compared to baseline, but this elevation was not significant. SAP, DAP, MAP, mPAP, mRAP, LV – dP/dt, FABF, and CMABF decreased significantly 30, 40, 36, 63, 60, 47, 75 and 67 %, in that order, when compared to baseline. At the same time, LV + dP/dt and TAU rose 47 and 80 % of baseline. These changes were statistically significant. At 180 minutes following resuscitation, HR, SAP, DAP, MAP and LVEDP had non-significant reductions, and LVSP and TAU were insignificantly elevated. mPAP, mRAP, LV – dP/dt, FABF, and CMABF diminished

significantly, when compared to baseline. LV + dP/dt significantly rose 68 % of baseline (see Tables 3.3 and 3.4). During hemorrhage, when occlusion was applied (Table 3.17), animals receiving the pH-stat treatment experienced a significant increase (26 %) in HR, when compared to baseline. SAP, DAP, MAP, mPAP, mRAP, LVEDP, LV – dP/dt, and CMABF showed significant decreases of 56, 60, 60, 68, 60, 45, 54, and 75 % of baseline, correspondingly. TAU increased insignificantly. LVSP, LV + dP/dt, and FABF declined 16, 5, and 44 % of baseline. At the end of treatment, HR, LVSP and CMABF increased 11, 18, and 8 % of baseline, respectively, but the change was not significant. In contrast, SAP, DAP, MAP, mPAP, mRAP, and LV – dP/dt diminished in a significant manner 22, 39, 31, 47, 40, and 32 %, in that order, when compared to baseline values. Also, LV + dP/dt, TAU, and FABF significantly increased 98, 43, and 62 % of baseline. LVEDP was within baseline values at this stage of the experimental observation. At 120 minutes post-resuscitation, HR, LVSP, LVEDP, LV + dP/dt, and FABF declined insignificantly. SAP, DAP, MAP, mPAP, mRAP, LV – dP/dt, and CMABF significantly diminished 51, 61, 57, 63, 60, 71, and 63 %, correspondingly, when compared to baseline. TAU augmented significantly 210 % of baseline. At 180 minutes after treatment, HR, LVSP, LVEDP, LV + dP/dt, and FABF declined 20, 21, 36, 15, and 38 % of baseline, respectively, but the reduction was not significant. SAP, DAP, MAP, mPAP, m RAP, LV – dP/dt, and CMABF were significantly reduced 47, 51, 49, 53, 60, 72, and 56 % of baseline. At the same time, there was a statistically-significant increase (183 % of baseline) in TAU.

Derived Hemodynamic Variables

CO (Fig. 3.14) significantly decreased 72, 46, 57, and 67 % during hemorrhage and at 60, 120, and 180 minutes post-treatment, correspondingly, when compared to baseline. However, CO significantly increased (74 %) at the end of treatment. SVR (Fig. 3.15) experienced a significant elevation (33 % of baseline) through hemorrhage. It continued to increase 6, 7 and 23 % of baseline at 60, 120 and 180 minutes post-resuscitation, respectively. At the end of treatment, there was a significant reduction (54 % of baseline) in this parameter. RPP (Fig. 3.16) declined in a statistically significant manner 50, 35, 55, and 63 % during hemorrhage and at 60, 120, and 180 minutes post-treatment, when compared to baseline. The only non-significant elevation in RPP (1 % of baseline) occurred at the end of treatment (see Table 3.7 for details). When RPP was measured in animals challenged with norepinephrine, a significant reduction of 34 % of baseline resulted through hemorrhage. Non-significant reductions of 41 and 38 % of baseline occurred at 120 and 180 minutes post-resuscitation. In contrast, at the end of treatment, there was an insignificant increase (12 % of baseline) in this variable. When occlusion to the hind limb was applied, animals experienced a 44, 59 and 54 % of baseline reduction during hemorrhage and at 120 and 180 minutes after treatment, correspondingly. This reduction was statistically significant. At the end of treatment, the reduction was 15 % of baseline, but it was not significant (see Tables 3.8 and 3.9 for details).

Respiratory Variables and Temperatures

In animals undergoing the pH-stat treatment, BT (Fig. 3.19) significantly dropped during hemorrhage, end of treatment and at 120 and 180 minutes after resuscitation, respectively. As with BT, ET (Fig. 3.20) fell significantly during the length of the experiment. Similarly, AT (Fig. 3.21) dropped throughout hemorrhage, but the fall was not significant. However, AT fell significantly at the end of treatment, and at 120 and 180 minutes after treatment, correspondingly. The only non-significant change in RR (Fig. 3.17) was evidenced at 120 minutes following treatment (see Table 3.10 for details). Neither norepinephrine infusion nor occlusion resulted in statistically significant adjustments in RR at any one time. $ETCO_2$ (Fig. 3.18) significantly decreased throughout hemorrhage and at 120 minutes following treatment. At the end of treatment, there was a non-significant increase in $ETCO_2$, with no change at 180 minutes after treatment. The infusion of norepinephrine during hemorrhage caused a significant decrease in $ETCO_2$. In contrast, there was an increment in this parameter at the end of treatment and at 120 and 180 minutes post-treatment, respectively. The increment was not significant. When occlusion was applied, $ETCO_2$ significantly diminished during hypovolemia. There was a non-remarkable reduction (5 % of baseline) at the end of treatment and at 180 minutes post-resuscitation. There was also a 5 % of baseline increase at 180 minutes following resuscitation, but this increase was not statistically significant (see Tables 3.8 and 3.9).

Derived Respiratory Variables

Due to the hypovolemic condition, DO_2 (Fig. 3.22) to tissues experienced a reduction. It significantly decreased 80, 36, 80, and 84 % during hemorrhage, end of treatment, and at 120 and 180 minutes after treatment, respectively, when compared to baseline. VO_2 (Fig. 3.23) also resulted in a 20 % reduction of baseline throughout hemorrhage, end of treatment and at 120 minutes after treatment, respectively. VO_2 also declined 40 % of baseline at 180 minutes after treatment. All the reductions were not significant. In general, O_2ER (Fig. 3.24) increased significantly 413, and 313 % during hemorrhage and at both 120 and 180 minutes after treatment, respectively, when values were compared to baseline. It also showed a 25 % increment of baseline at the end of treatment, but the increment was not significant. Blood lactate levels (Fig. 3.25) increased significantly (500 and 507 % of baseline) during hypovolemia and at the end of treatment. At 120 and 180 minutes post-resuscitation, lactate levels declined, but were still above baseline (250 and 307 %). However, these changes were not significant (Tables 3.11).

Blood Gas Variables at Patient Temperature

When compared to baseline values, pHa (Fig. 3.26) significantly fell during the course of hemorrhage. In contrast, pHa increased at the end of treatment, and at 120 and 180 minutes after treatment, in that order. The elevation in pHa for these periods was not statistically significant. $aPCO_2$ (Fig. 3.27) decreased at all times. It exhibited an overall reduction throughout hemorrhage, at the end of treatment and at 120 and 180 minutes following treatment, respectively, when compared to baseline, but none of the changes were statistically significant. aPO_2 (Fig. 3.28) was elevated during the entire course of

the experimental observation, when compared to baseline. Significant elevations from baseline values were seen during hemorrhage, end of treatment and at 180 minutes after resuscitation (24 %). The elevation at 120 minutes post-treatment was not significant. $aHCO_3^-$ concentration (Fig. 3.29) showed a statistically significant reduction during hemorrhage, when compared to baseline. It then increased at the end of treatment and at 120 minutes following treatment, respectively, but the elevation was not significant. At 180 minutes after treatment, a significant elevation occurred. aBE concentration (Fig. 3.30) was elevated during hypovolemia. It then decreased at the end of treatment, but the change was not significant. It continued to decrease at 120 minutes following treatment. At 180 minutes after treatment, the change showed a positive but insignificant elevation [see Table 3.12]. pHv (Fig. 3.31) in a statistically significant manner during hypovolemia. Additional non-significant reductions resulted at the end of treatment, and at 120 and 180 minutes following treatment, in that order. Statistically significant elevations in $vPCO_2$ (Fig. 3.32) occurred during hemorrhage and at 180 minutes after resuscitation. $vPCO_2$ also increased at 120 minutes after treatment, but this increment was not significant. At the end of treatment, $vPCO_2$ declined insignificantly. vPO_2 (Fig. 3.33) decreased throughout the experiment. It exhibited significant reductions during hypovolemia and at 120 and 180 minutes after resuscitation, respectively. At the end of treatment, the reduction was not significant. $vHCO_3^-$ concentration (Fig. 3.34) showed only a significant decrease during the course of the hypovolemic event. $vHCO_3^-$ insignificantly increased at 120 minutes post-treatment. It also augmented significantly at 180 minutes following resuscitation. No change resulted at the end of treatment. When compared to baseline, vBE (Fig. 3.35) undertook a significant increase (1000 %)

during hemorrhage. It was elevated at the end of treatment, when compared to baseline. This last increment was not statistically significant. vBE diminished at 120 and 180 minutes following treatment, respectively. This reduction was not statistically significant (see Table 3.13 for details).

Chemistry Variables

When compared to baseline, the only significant decrease in serum Na^+ concentration (Fig. 3.36) occurred during hemorrhage. Succesive non-significant elevations were reported at the end of treatment and at 120 and 180 minutes following resuscitation, respectively. Serum K^+ (Fig. 3.37) significantly increased during the hypovolemic condition, at the end of treatment, and at 120 minutes following treatment, respectively, when compared to baseline. It was also reduced at 180 minutes after the end of treatment, but this reduction was not significant. Serum calcium (Ca^{2+}) concentration (Fig. 3.38) was significantly diminished during the length of the experiment. All the chemistry values in animals that undertook the pH-stat approach were statistically significant, when compared to baseline values. PCV (Fig. 3.39) decreased during hemorrhage, end of treatment, and at 120 and 180 minutes following treatment, respectively. TP (Fig. 3.40) was reduced likewise. COP (Fig. 3.41) showed reductions during hemorrhage, end of treatment and at both 120 and 180 minutes following treatment (see Tables 3.14 and 3.15 for details).

WITHIN GROUP ANALYSIS FOR pH-STAT MODIFIED GROUP

Hemodynamic Variables

As with the LRS and the pH-stat groups, HR (Fig. 3.1) increased (28 % above baseline) during the hypovolemic period. However, the increase was statistically significant. TAU (Fig. 3.11) significantly went up 7 % of baseline. SAP, DAP, MAP, mPAP, mRAP, LVSP, LV – dP/dt, FABF, and CMABF (Fig. 3.2-3.7, 3.10, 3.12 and 3.13) experienced a significant elevation of 56, 61, 60, 40, 50, 38, 63, 76, and 58 % of baseline, respectively. Non-significant reductions were seen in LVEDP (Fig. 3.8) and LV + dP/dt (Fig. 3.9) during this period. At the end of treatment, HR and LVEDP were also increased, but both changes were not significant. SAP, LVSP and TAU decreased insignificantly. In contrast, DAP, MAP and LV – dP/dt dropped significantly 31, 20 and 23 % of baseline. At the same time, mPAP, mRAP, LV + dP/dt, FABF, and CMABF showed significant increases of 27, 25, 100, 93, and 192 %, when compared to baseline values. At 60 minutes following resuscitation, HR, LV + dP/dt, TAU, and CMABF exhibited non-significant increases. SAP, DAP, MAP, mPAP, mRAP, LVSP, LVEDP, and LV – dP/dt decreased significantly 33, 42, 38, 27, 25, 21, 30, and 42 %, respectively, when compared to baseline. FABF was also reduced (14 % of baseline), but the reduction was not significant. At 120 minutes post-treatment, HR, mPAP, LV + dP/dt, and CMABF declined insignificantly. SAP, DAP, MAP, mRAP, LVSP, LVEDP, LV – dP/dt, and FABF significantly declined 46, 53, 50, 50, 34, 30, 58, and 40 % of baseline, respectively. TAU showed a significant elevation at this stage of the experiment. At 180 minutes following resuscitation, HR and mRAP fell 14 and 50 %, when compared to baseline, but the reduction in these parameters was not significant. SAP, DAP, MAP,

mPAP, LVSP, LVEDP, LV + dP/dt, LV – dP/dt, FABF, and CMABF experienced a significant reduction of 50, 58, 54, 33, 37, 40, 26, 63, 48, and 26 % of baseline. In contrast, TAU was the only parameter which showed a significant elevation (45 %), when compared to baseline values (see Tables 3. 1 and 3.2 for details). The infusion of norepinephrine (Table 3.16) to animals receiving the pH-stat modified treatment during hemorrhage caused a 29 % of baseline increase in HR. This elevation was statistically significant. SAP, DAP, MAP, mPAP, LVEDP, LV – dP/dt, FABF, and CMABF fell significantly 44, 50, 49, 33, 40, 39, 67, and 35 % of baseline. mRAP and LVSP decreased 25 and 15 % of baseline, but these changes were not important. LV + dP/dt and TAU increased insignificantly. At the end of treatment, HR, SAP, and LV – dP/dt increased insignificantly. mPAP, mRAP, LVSP, LVEDP, LV + dP/dt, FABF, and CMABF were significantly elevated 27, 25, 12, 40, 178, 41, and 91 % of baseline, respectively. At the same time, DAP experienced a significant reduction (17 %), when compared to baseline values. MAP and TAU declined insignificantly. At 120 minutes after treatment, HR, SAP, MAP, mPAP, mRAP, LVSP, LVEDP, and CMABF declined insignificantly. TAU increased insignificantly. In contrast, DAP, LV – dP/dt and FABF markedly dropped 25, 28 and 62 %, respectively, when compared to baseline. LV + dP/dt rose 59 % of baseline in a significant manner. At 180 minutes post-resuscitation, HR, DAP, mRAP, LVEDP, LV – dP/dt, FABF, and CMABF decreased 19, 23, 50, 20, 26, 64, and 30 % of baseline. This reduction was statistically significant. LV + dP/dt went up 58 % of baseline in a significant manner. SAP, MAP, mPAP, and LVSP were insignificantly reduced. Similarly, TAU experienced a non-significant elevation (31 % of baseline) [see Table 3.3 and 3.4 for details]. When occlusion to the hind limb was

applied (Table 3.17) during hemorrhage, HR increased significantly 28 % of baseline. SAP, DAP, MAP, mPAP, LVSP, LV – dP/dt, and CMABF experienced statistically significant reductions of 57, 63, 61, 47, 38, 62, and 46 %, respectively, when compared to baseline. mRAP, LVEDP and LV + dP/dt declined insignificantly. In contrast, TAU and FABF insignificantly increased. At the end of treatment, HR exhibited a slight, non-significant increase. SAP, DAP, MAP, LVSP, and LV – dP/dt rose 21, 38, 29, 12, and 32 %, respectively, when compared to baseline. This reduction was statistically significant. LV + dP/dt, FABF and CMABF improved significantly 73, 201 and 83 % of baseline, correspondingly. In contrast, mPAP and TAU diminished insignificantly. mRAP and LVEDP were within baseline levels during this phase of the experiment. At 120 minutes post-resuscitation, HR was still slightly reduced (8 %), when compared to baseline. At the same time, mRAP, LV + dP/dt and CMABF declined 25, 12 and 19 %, respectively, when compared to baseline. These changes were not significant. SAP, DAP, MAP, mPAP, LVSP, LVEDP, and LV – dP/dt decreased in a significant manner 46, 54, 50, 33, 33, 30, and 58 % of baseline, respectively. FABF increased 60 % of baseline. TAU exhibited a non-significant elevation (31 % of baseline). This reduction was not significant. At 180 minutes following treatment, HR and LVEDP remained below baseline values (17 and 20 % of baseline, respectively), but this reduction was not statistically significant. SAP, DAP, MAP, mPAP, mRAP, LVSP, LV + dP/dt, LV – dP/dt, and CMABF declined significantly 51, 58, 55, 33, 50, 37, 23, 64, and 30 % of baseline. At the same time, TAU and FABF increased significantly 76 and 38 %, when compared to baseline values.

Derived Hemodynamic Variables

CO (Fig. 3.14) decreased significantly 64, 42, and 46 % of baseline, respectively, during hemorrhage and at 120 and 180 minutes following treatment, respectively. In contrast, it significantly increased 114 % of baseline at the end of treatment. At 60 minutes after treatment, CO also increased (7 % of baseline), but the change was irrelevant. SVR (Fig. 3.15) decreased during the entire course of the experimental observation. It dropped significantly 69 and 48 % of baseline at the end of treatment and at 60 minutes after treatment. SVR diminished as well (15 and 28 % of baseline) throughout hemorrhage and at both 120 and 180 minutes post-treatment, respectively, but this reduction was not statistically significant. RPP (Fig. 3.16) changed accordingly, but all the changes were statistically significant when compared to baseline. RPP fell 48, 11, 36, 53, and 60 % during hemorrhage, end of treatment, and at 60, 120, and 180 minutes after treatment, respectively, when compared to baseline values (see Table 3.7 for details). The infusion of norepinephrine brought about a significant reduction in RPP of 33, 33 and 36 % of baseline, respectively during hemorrhage and at 120 and 180 minutes following resuscitation. At the end of treatment, there was an insignificant increase (2 % of baseline). Animals receiving the pH-stat modified treatment reacted to occlusion by an overall significant reduction in RPP. This parameter diminished 50, 23, 55 and 62 % of baseline at all stages of the experimental observation (see Table 3. 8 and 3.9 for details).

Respiratory Variables and Temperatures

All temperatures were at a variance in all phases of the experiment. BT (Fig. 3.19) dropped significantly nearly 2, 11, 14, and 15 % of baseline throughout hemorrhage, end of treatment, and at 120 and 180 minutes following treatment, respectively. ET (Fig. 3.20) fell approximately the same proportion during hemorrhage, end of treatment, and at 120 and 180 minutes following treatment, respectively. AT (Fig. 3.21) decreased significantly 4, 12, 14, and 15 % of baseline during hemorrhage, end of treatment, and at 120 and 180 minutes following treatment, respectively (Table 3.10). RR (Fig. 3.17) did not show any change in this group during the length of the experiment. Neither norepinephrine nor occlusion exerted any relevant influence on RR at any one time during the experiment in animals receiving the pH-stat modified treatment. When compared to baseline, the only significant decrease (12 %) in $ETCO_2$ (Fig. 3.18) occurred during hypovolemia. Successive significant increases (59, 54, and 59 %) were seen at the end of treatment and at 120 and 180 minutes after treatment, in that order. The infusion of norepinephrine caused a slight insignificant reduction (2 % of baseline) in $ETCO_2$ in hemorrhage. In contrast, consecutive relevant increases (61, 63 and 61 % of baseline) were seen at the end of treatment and at 120 and 180 minutes post-resuscitation, respectively. Occlusion brought about a significant reduction (12 % of baseline) during hypovolemia. Consecutive important increases in this variable (54, 56 and 59 %) were reported at the end of treatment and at 120 and 180 minutes after resuscitation, respectively, when compared to baseline values (see Tables 3.8 and 3.9).

Derived Respiratory Variables

DO_2 (Fig. 3.22) decreased significantly 67 and 62 % of baseline during hypovolemia and at both 120 and 180 minutes post-treatment, respectively. A non-statistically significant increase (14 % of baseline) occurred at the end of treatment. When compared to baseline, VO_2 (Fig. 3.23) was not modified during hemorrhage as well as at the end of treatment. It decreased 17 % at 120 and at 180 minutes after treatment. All changes were insignificant. O_2ER (Fig. 3.24) increased in a significant manner 183, 97, and 114 % of baseline throughout hemorrhage and at 120 and 180 minutes following treatment, respectively. At the end of treatment, there was a non-significant decrease (7 %) in O_2ER. Blood lactate (Fig. 3.25) showed marked elevation throughout the experiment. The increase in lactate levels was 373, 540, 127, and 107 % of baseline through hemorrhage, end of treatment, and at 120 and 180 minutes following treatment, respectively (see Table 3.11 for details).

Blood Gas Variables at Patient Temperature

All changes in pHa (Fig. 3.26) were statistically significant at all phases of the experimental observation. Quite the opposite of what occurred in the LRS and the pH-stat groups, $aPCO_2$ (Fig. 3.27) was elevated during the length of the experimental observation. During hemorrhage, $aPCO_2$ increased insignificantly. At the end of treatment and at 120 and 180 minutes following treatment, respectively, $aPCO_2$ significantly increased, when compared to baseline. aPO_2 (Fig. 3.28) decreased during hemorrhage and at the end of treatment and increased at 120 and 180 minutes post-treatment, respectively. Neither the decrease nor the increase was statistically significant. $aHCO_3^-$ concentration (Fig. 3.29) was only significantly reduced during hemorrhage. In contrast, a 33 and 43 % increase of

baseline occurred at the end of treatment, and at both 120 and 180 minutes following treatment, respectively. This elevation was significant. When compared to baseline values, aBE concentration (Fig. 3.30) showed a marked elevation (285 % of baseline) during the course of hemorrhage. In contrast, a 124, 177 and 179 % reduction resulted at the end of treatment and at 120 and 180 minutes after treatment, respectively.

The reduction was significant (Table 3.12). pHv (Fig. 3.31) values fell in a similar way as pHa. pHv dropped 3.68, 1.50, 1.36, and 1.50 % of baseline through hemorrhage, end of treatment, and at 120 and 180 minutes after treatment, respectively. These changes in pHv were statistically significant and reflected the acidosis that occurred as a result of the marked bleeding. $vPCO_2$ (Fig. 3.32) showed a continuous significant increase during the course of the experiment. When compared to baseline, it rose 38 % during both hemorrhage and at the end of treatment. It continued to increase 50 and 54 % at 120 as well as at 180 minutes following treatment. vPO_2 (Fig. 3.33) decreased significantly 47, 45 and 49 % of baseline during hemorrhage and at 120 and 180 minutes after treatment, respectively. The reduction (6 %) in vPO_2 at the end of treatment was irrelevant. $vHCO_3^-$ (Fig. 3.34) significantly decreased 25 % of baseline in the course of hemorrhage. It then rose significantly 17, 29 and 33 % of baseline at the end of treatment, and at 120 and 180 minutes post-treatment, respectively. vBE concentration (Fig. 3.35) exhibited a statistically significant increase (1288 % of baseline) during hemorrhage. It went down (125 % of baseline) in a significant manner at the end of treatment. There were also insignificant reductions (500 %) at 120 as well as at 180 minutes following treatment, when compared to baseline (Table 3.13).

Chemistry Variables

When compared to baseline, Na^+ concentration (Fig. 3.36) decreased insignificantly during hemorrhage. Na^+ was significantly elevated (3 %) at the end of treatment and at both 120 and 180 minutes after treatment, respectively. K^+ (Fig. 3.37) significantly rose nearly 11 and 3 % during hemorrhage and at 180 minutes following treatment, respectively, when compared to baseline. This elevation in K^+ concentration was insignificant. An important reduction (approximately 14 % of baseline) in K^+ levels occurred at the end of treatment. No change resulted at 120 minutes post-treatment. Ca^{2+} (Fig. 3.38) diminished in a significant manner throughout the experiment. It was reduced 9 % of baseline during hemorrhage. It also decreased 18 % of baseline at the end of treatment and at 120 and 180 minutes after treatment, respectively (Table 3.14). PCV (Fig. 3.39) was decreased significantly. It experienced a 20, 55, 40, and 38 % of baseline reduction during hemorrhage, end of treatment, and at 120 and 180 minutes after treatment, respectively. TP (Fig. 3.40) dropped significantly nearly 22, 61, 48, and 44 % of baseline during hemorrhage, end of treatment, and at 120 and 180 minutes after treatment, respectively. When compared to baseline values, COP (Fig. 3.41) was considerably reduced as a result of the marked hypovolemia. It diminished 32 and 68 % throughout hemorrhage and at the end of treatment, respectively. It was also reduced 50 % at both 120 and 180 minutes following treatment. All changes were statistically significant (Table 3.15).

AMONG GROUP ANALYSIS

Standard Hemodynamic Variables

After the equilibration phase, the initial hemodynamic response to acute bleeding in animals was an increase in HR (Fig. 3.1) in all groups during hemorrhage. This was probably the result of an autonomic sympathetic compensation. Nonetheless, this increase in HR was not statistically significant among groups during the entire course of the experimental observation. At the end of treatment and at 60 minutes after treatment, in that order, HR showed a tendency to decrease, when compared to the hemorrhage period in all groups, but it was still above baseline. At 120 minutes post-treatment, HR was below baseline in all groups. At 180 minutes post-treatment, HR continued to decline in the pH-stat and the pH-stat modified groups, but not in the LRS group, which exhibited a slight increase throughout hemorrhage. During hemorrhage, SAP, DAP and MAP (Figs. 3.2-3.4) markedly decreased in all groups and continued to decline below baseline for the rest of the experiment. However, the changes were not statistically significant. LV - dP/dt (Fig. 3.10) also dropped in all groups during the experiment with insignificant changes. mPAP (Fig. 3.5) experienced diverse changes among groups. It fell below baseline during hemorrhage and at 60, 120, and 180 minutes following resuscitation, respectively. During hypovolemia, the reduction in mPAP was more noticeable in the pH-stat than in the LRS and the pH-stat modified treatments, respectively. At the end of treatment, however, mPAP rose in the LRS as well as in the pH-stat modified groups. In contrast, it declined in the pH-stat treatment, when compared to baseline values. As in the case of mPAP, mRAP (Fig. 3.6) diminished below baseline levels at all times in all groups except at the end of treatment in which no

changes resulted in both the LRS and the pH-stat treatments. Nevertheless, in the pH-stat modified group, mRAP rose during this period. Again, these changes were not statistically significant. LVSP (Fig. 3.7) dropped below baseline in all groups in the course of the hypovolemic event, at the end of treatment, and at 180 minutes after treatment, respectively. This pressure transiently increased in the LRS group at 60 and 120 minutes following treatment, correspondingly. During these periods, LVSP diminished in both the pH-stat and the pH-stat modified groups. Once more, the changes among groups were not significant. LVEDP (Fig. 3.8) fell in all groups during hemorrhage and at 60, 120, and 180 minutes after resuscitation, respectively. At the end of treatment, this pressure was not modified in the LRS group. In contrast, it increased transiently in the pH-stat and the pH-stat modified treatments. All changes among groups were not significant. LV + dP/dt (Fig. 3.9) did not exhibit statistically significant variations among groups. It was elevated above baseline at the end of treatment and at 60 minutes after treatment, respectively in all groups. In the LRS group, LV + dP/dT declined during hemorrhage and increased at the end of treatment and at 60, 120, and 180 minutes following resuscitation, respectively. In the pH-stat group, it rose above baseline during hemorrhage, end of treatment, and at 60 minutes post-treatment, respectively. In the pH-stat modified group, LV + dP/dt was slightly reduced during hemorrhage. It also diminished at 120 and 180 minutes after treatment, respectively. In contrast, it was elevated above baseline levels at the end of treatment and at 60 minutes after treatment, in that order. TAU (Fig. 3.11) decreased for the LRS group during hypovolemia and increased for both the pH-stat and the pH-stat modified therapies. Nonetheless, the changes among the 3 interventions were not different. At the end of treatment, the three

groups behaved in a similar way. At 60 minutes following resuscitation, TAU increased in all groups, but there were statistically significant differences between LRS and pH-stat modified. Values for LRS group were higher than those of pH-stat modified. At 120 minutes after resuscitation, values for LRS declined and those of pH-stat and pH-stat modified increased, but there were no differences among groups. At 180 minutes following resuscitation, the tendency was similar. FABF (Fig. 3.12) experienced reductions in all groups during hypovolemia, but the differences were not significant. At the end of treatment, an increase in FABF occurred with all interventions, but such an increase was not relevant. Significant changes resulted between LRS and pH-stat modified and between pH-stat and pH-stat modified for the rest of the experimental observation. Better flows were seen for the pH-stat modified approach in the entire course of the experiment. CMABF (Fig. 3.13) behaved in a similar way as FABF through hemorrhage. Significant changes occurred between LRS and pH-stat modified and between pH-stat and pH-stat modified therapies at the end of treatment. At 60 and at 180 minutes after resuscitation, there were also significant changes between pH-stat and pH-stat modified treatments. At 120 minutes following treatment, no changes among groups occurred. Again, flow was superior with the pH-stat modified therapy. When animals were exposed to a pharmacologic challenge with norepinephrine (Table 3.16) HR, SAP, DAP, MAP, mPAP, mRAP, LVSP, LVEDP, LV + dP/dT, LV – dP/dT, and TAU did not show statistical differences among groups any one time. In contrast, FABF exhibited a statistically significant difference between LRS and pH-stat modified and pH-stat and pH-stat modified treatments at 180 minutes post-resuscitation, with pH-stat modified showing a better flow over the other 2 interventions. CMABF experienced a

significant change between LRS and pH-stat modified and pH-stat and pH-stat modified during hemorrhage and at 120 minutes post-resuscitation, respectively. There was also a significant difference between pH-stat and pH-stat modified at 180 minutes following resuscitation. Once more, the flow was better for animals that undertook the pH-stat modified approach. When occlusion to the femoral artery was applied (Table 3.17), HR, SAP, DAP, MAP, mPAP, mRAP, LVSP, LVEDP, LV + dP/dT, LV – dP/dT did not show statistically significant differences among groups at any one time. In contrast, TAU experienced significant changes between LRS and pH-stat modified at the end of treatment. TAU was higher for LRS than for pH-stat modified at this phase of the experiment. Relevant changes were noticed for this variable between pH-stat and pH-stat modified at 120 and 180 minutes post-resuscitation. Values for TAU were higher for pH-stat than for pH-stat modified at these periods. After occlusion, FABF at 120 and 180 minutes following resuscitation was much higher for pH-stat modified than for the other two interventions. During hypovolemia and at 120 minutes after resuscitation, CMABF was superior for the pH-stat modified group, when compared to the other treatments. At the end of treatment, CMABF showed an improvement with LRS and pH-stat modified, when compared with pH-stat treatment.

Derived Hemodynamic Variables

CO (Fig. 3.14) showed significant differences among the LRS and the pH-stat modified treatments during hemorrhage, with a less pronounced reduction in the pH-stat modified group than in the LRS group. There were also significant differences between the pH-stat and the pH-stat modified treatments at 60 minutes post-resuscitation, when cardiac output improved in the pH-stat modified group. The rest of the experimental

observation, all groups showed reductions in CO. SVR (Fig. 3.15) experienced a significant change between the LRS and the pH-stat modified treatments during hemorrhage and at 60 and 180 minutes after treatment, respectively. During these periods, SVR was much higher in the LRS than in the pH-stat modified approach. There were also differences between the LRS and the pH-stat and the pH-stat and the pH-stat modified groups, at 60 minutes after resuscitation, respectively. Again SVR was higher in the LRS than in the other two groups. RPP (Fig. 3.16) did not differ in any of the animal groups studied (Tables 3.7). Neither the pharmacological challenge with norepinephrine nor the occlusion resulted in significant changes in rate pressure product and respiratory rate in all groups (see Tables 3.8 and 3.9 for details).

Respiratory Variables and Temperatures

After the equilibration phase, significant changes in blood, esophageal and abdominal temperatures (Figs. 3.19-3.21) in all groups were not reported at any of the periods except for a statistical difference in ET between the LRS and the pH-stat modified groups, at the end of treatment. At the same time, RR (Fig. 3.17) did not change at any one time among the three groups studied (Table 3.10). Neither the infusion of norepinephrine nor the occlusion of the femoral artery resulted in changes in respiratory rate. $ETCO_2$ (Fig. 3.18) was not different among groups during hemorrhage, but significant differences among the three groups were found over the rest of the observation period. $ETCO_2$ in the pH-stat modified group was always above that of the other groups at all times. Both norepinephrine infusion and occlusion demonstrated statistical differences in $ETCO_2$ in all groups, at the end of treatment and at 120 and 180 minutes following resuscitation, respectively. During these periods, values for $ETCO_2$ in

the pH-stat modified group were superior to the other interventions when animals were challenged with norepinephrine and when occlusion was applied (see Tables 3.8 and 3.9 for details).

Derived Respiratory Variables

None of the changes in DO_2, VO_2, O_2ER, (Figs. 3.22-3.25) and lactate were statistically significant among treatments at any one time. As anticipated, DO_2 and VO_2 were reduced during the entire course of the experimental observation, with the exception of the pH-stat modified group which exhibited a 14 % increase of baseline in DO_2 at the end of treatment. The DO_2 reduction in the pH-stat modified group was less pronounced than that of the other two groups, during the course of the experimental observation. In the pH-stat modified group, VO_2 did not change throughout hemorrhage and at the end of treatment, respectively. Although VO_2 diminished in the pH-stat modified group, the reduction was less pronounced at 120 and 180 minutes after treatment, respectively, when compared to the LRS and the pH-stat groups. In all groups, O_2ER increased above baseline during the hypovolemic event. At the end of treatment, O_2ER in all groups had abruptly decreased, showing a tendency to reach baseline values. However, at 120 and 180 minutes post-resuscitation, the values increased again above baseline in all groups. Blood lactate in all groups reflected the acid-base status derangement. Lactate increased in all stages of the experiment. The average increment in blood lactate for the three groups was 417, 523, 197, and 158 % of baseline during hemorrhage; end of treatment and at 120 and 180 minutes following resuscitation, respectively (see Table 3.11 for details).

Arterial and Venous Blood Gas Variables at Patient Temperature

In the course of hypovolemia, pHa at patient temperature (Fig. 3.26) among groups fell below baseline, but it was not statistically different. Significant changes occurred at the end of treatment and at 120 minutes following resuscitation between the LRS and the pH-stat and the pH-stat and the pH-stat modified groups, respectively. At 120 minutes after treatment, pHa in the LRS group, increased above baseline and that of the pH-stat modified decreased. These changes were statistically significant. At 180 minutes following treatment, all three groups were different. pHa in the LRS treatment fell during hypovolemia. It then started to increase following hemorrhage from the end of treatment to the final stage of the experimental observation reaching values above baseline. In the pH-stat group, pHa increased above baseline at the end of treatment and at 120 and 180 minutes, respectively, following treatment. Although there was a post-hemorrhage increase in pHa in the pH-stat modified group until the end of the experiment, it remained below baseline values. There were not significant changes in $aPCO_2$ (Fig. 3.27) among groups during hemorrhage. In contrast, a significant variation in $aPCO_2$ between the LRS and the pH-stat modified and the pH-stat and the pH-stat modified groups occurred at the end of treatment. $aPCO_2$ decreased in the LRS as well as in the pH-stat group, but the pH-stat modified group, experienced an important elevation. There were significant differences among all groups for the rest of the experimental period. $aPCO_2$ was reduced below baseline in the LRS and the pH-stat groups from hemorrhage to the end of the experiment. In contrast, in the pH-stat modified group, $aPCO_2$ was always elevated above baseline during all phases of the experiment. The only statistically significant variation in aPO_2 (Fig. 3.28) among groups was seen during

hemorrhage between the pH-stat and the pH-stat modified groups. aPO_2 increased above baseline at all periods in the LRS and the pH-stat groups. In the pH-stat modified group, different changes resulted. It diminished below baseline values during hemorrhage and at the end of treatment and increased at 120 and 180 minutes after treatment, respectively. No changes in $aHCO_3^-$ (Fig. 3.29) at patient temperature resulted in all groups during hemorrhage. Significant variations in $aHCO_3^-$ concentration occurred between the LRS and the pH-stat and the LRS and the pH-stat modified treatments through the rest of the experimental observation. The $aHCO_3^-$ concentration in all groups remained below baseline through hemorrhage as a compensation for the non-respiratory (lactic) acidosis that the animals underwent. In the LRS group, $aHCO_3^-$ concentration decreased during hemorrhage and started to increase from the end of treatment, approaching baseline values at 180 minutes post-resuscitation. Animals under the pH-stat treatment showed the same tendency, but the $aHCO_3^-$ reached values above baseline from the end of treatment through 180 minutes after resuscitation. The trend in the animals that underwent the pH-stat modified treatment was as similar as that of the pH-stat group, but the values reached at all phases of the experiment were higher than in the pH-stat group. The aBE concentration (Fig. 3.30) was elevated above baseline during hypovolemia in all groups, but they did not differ statistically. At the end of treatment, animals that underwent the LRS treatment exhibited significantly higher values than animals that received the pH-stat and the pH-stat modified therapies. aBE concentration was also at a variance between the LRS and the pH-stat modified treatments at 120 minutes post-treatment. At 180 minutes after treatment, all groups differed significantly. In the LRS group, the tendency was to a marked increase at all phases of the experiment. In the pH-stat group,

this variable increased during hemorrhage and diminished the rest of the experimental observation. In the pH-stat modified group, the negative aBE concentration was only elevated throughout hemorrhage (Table 3.12). Due to the non-respiratory (lactic) acidosis caused by hemorrhage, pHv at patient temperature (Fig. 3.31) among groups fell during hypovolemia, end of treatment and at 120 minutes after treatment, respectively, but the fall was insignificant. In contrast, pHv only experienced a statistically significant variation at 180 minutes after treatment when all groups differed. In the LRS group, pHv declined during hemorrhage but it started to increase through the rest of the experiment reaching above baseline values at 180 minutes post-resuscitation. The pH-stat group behaved in a similar manner as the LRS except that at 180 minutes post-resuscitation, the pH never reached baseline values. The results of the pH-stat modified treatment were similar to those of the pH-stat group, but the pH reduction was more pronounced (178 %). During hemorrhage, $vPCO_2$ at patient temperature (Fig. 3.32) was not modified among groups. It varied in a significant manner at the end of treatment and at 120 minutes post-treatment between the LRS and the pH-stat and the LRS and the pH-stat modified groups, respectively. At 180 minutes following treatment, all groups showed significant variations in $vPCO_2$. During hemorrhage, $vPCO_2$ increased in an insignificant manner in all groups. In the LRS group, this variable began to decrease at the end of treatment and at both 120 and 180 minutes post-resuscitation, never approaching baseline. At the end of treatment, $vPCO_2$ decreased below baseline in animals that were treated with the pH-stat approach. It then rose above baseline at 120 and 180 minutes after treatment, respectively. $vPCO_2$ values for the pH-stat modified group increased above baseline during all phases of the experimental observation. There were no changes

in vPO_2 among the three groups (Fig. 3.33) at any time period, when compared to baseline values. vPO_2 values in all groups were reduced during the entire period of experimentation, except at the end of treatment where they increased again, but remained below baseline levels. The reduction in vPO_2 was not statistically significant. Quite the opposite, $vHCO_3^-$ concentration (Fig. 3.34) showed differences in all groups at the end of treatment and at 180 minutes after treatment, respectively. At 120 minutes following treatment, there were significant differences between the LRS and the pH-stat and the LRS and the pH-stat modified groups, in that order. However, no statistically significant differences were found between the pH-stat and the pH-stat modified treatments. In the LRS group, $vHCO_3^-$ fell below baseline during hemorrhage, at the end of treatment and at 120 minutes following resuscitation. It reached baseline concentrations at 180 minutes after treatment. In the pH-stat group, $vHCO_3^-$ decreased through hemorrhage, but did not change at the end of treatment. However, it began to increase above baseline levels at 120 and 180 minutes post-resuscitation, respectively. After hemorrhage, $vHCO_3^-$ concentrations in the pH-stat modified group remained elevated for the rest of the experimental period. Although negative vBE concentration (Fig. 3.35) increased during bleeding, it did not vary significantly among groups. However, it changed significantly between the LRS and the pH-stat and the LRS and the pH-stat modified groups, at the end of treatment. It also differed between the LRS and the pH-stat modified groups at 120 minutes after treatment. All groups changed significantly at 180 minutes following the end of treatment. Animals receiving the LRS treatment exhibited an increase in vBE at all times in the experiment. In the pH-stat group, this variable rose during hemorrhage and at the end of treatment, respectively. It lowered considerably at both 120 and 180

minutes post-treatment, coming closer to baseline values. In the animals that undertook the pH-stat modified treatment, the only elevation seen in negative BE concentration was during hemorrhage. In contrast, there was a decrease below baseline, at the end of treatment and at 120 and 180 minutes post resuscitation, respectively (see Tables 3.13 for details).

Chemistry Variables

Regarding electrolytes, no differences were observed in serum Na^+ concentration (Fig. 3.36) during hemorrhage and at 180 minutes post-treatment, respectively. A statistically significant difference between the LRS and the pH-stat and the pH-stat and the pH-stat modified groups was seen at the end of treatment and at 120 minutes after treatment, respectively. No significant changes among groups occurred in serum K^+ concentration (Fig. 3.37). Serum Ca^{2+} concentration (Fig. 3.38) differed between the LRS and the pH-stat groups and the LRS and the pH-stat modified groups through the hypovolemic period and at 180 minutes after treatment, respectively. No differences resulted at the end of treatment and at 120 minutes after treatment, respectively (see Table 3.14 for details). The hemodynamic reaction to the acute blood loss in animals undergoing different interventions resulted in a reduction in PCV (Fig. 3.39). However, the differences were not statistically significant. No group differences in TP (Fig. 3.40) resulted during both hemorrhage and at the end of treatment, respectively. In contrast, changes in TP were found between animals which received the pH-stat and those which received the pH-stat modified treatments at 120 and 180 minutes after treatment, respectively. As with TP, COP (Fig. 3.41) changed in a comparable manner in all phases of the experiment (see Table 3.15 for details).

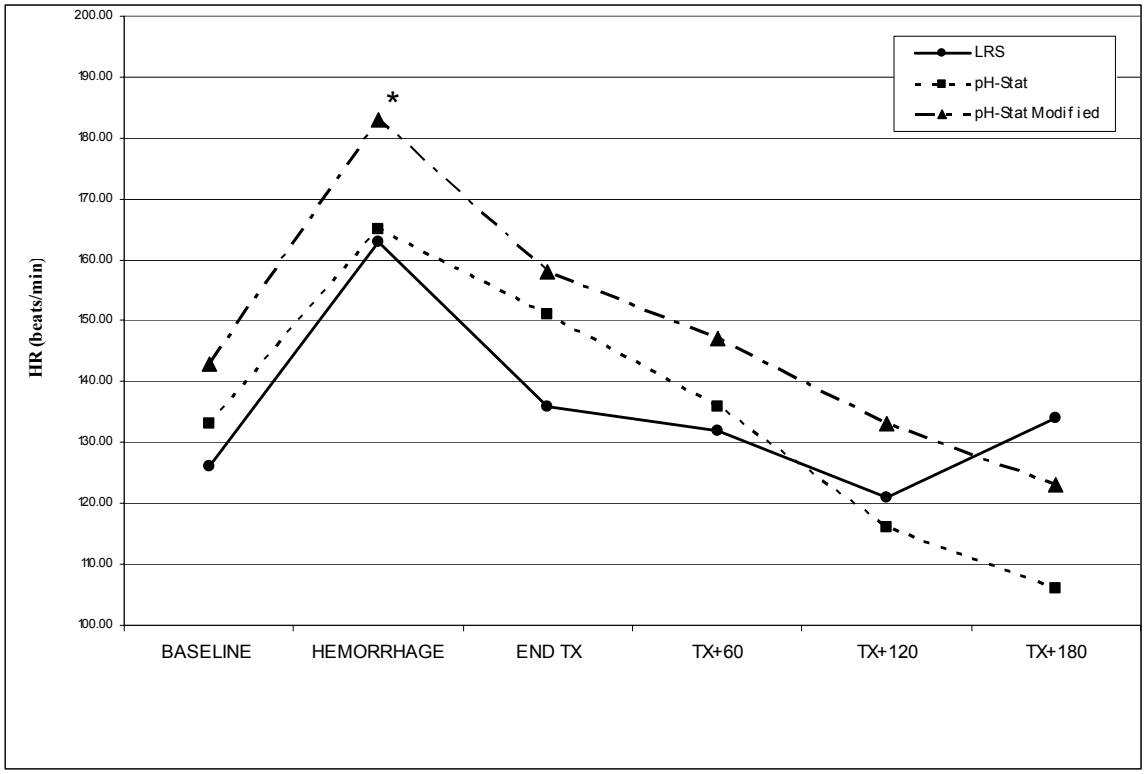

Fig. 3.1: Heart rate in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

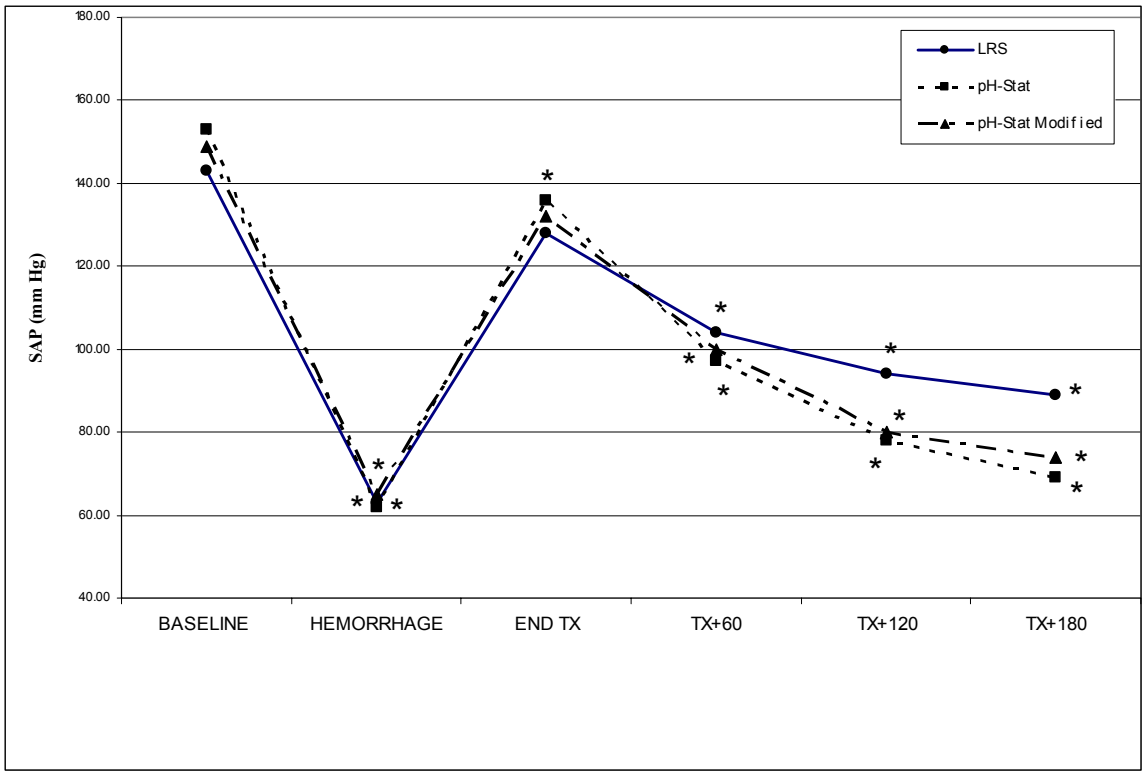

Fig. 3.2: Systolic arterial pressure in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

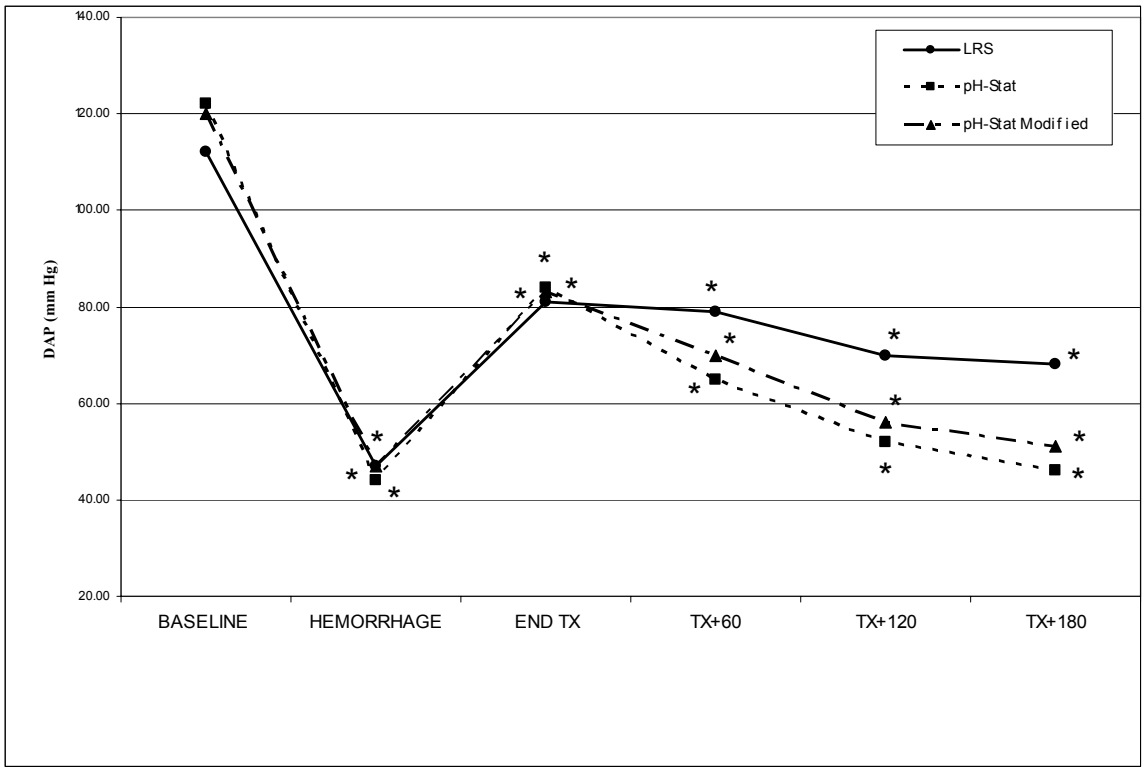

Fig. 3.3: Diastolic arterial pressure in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05

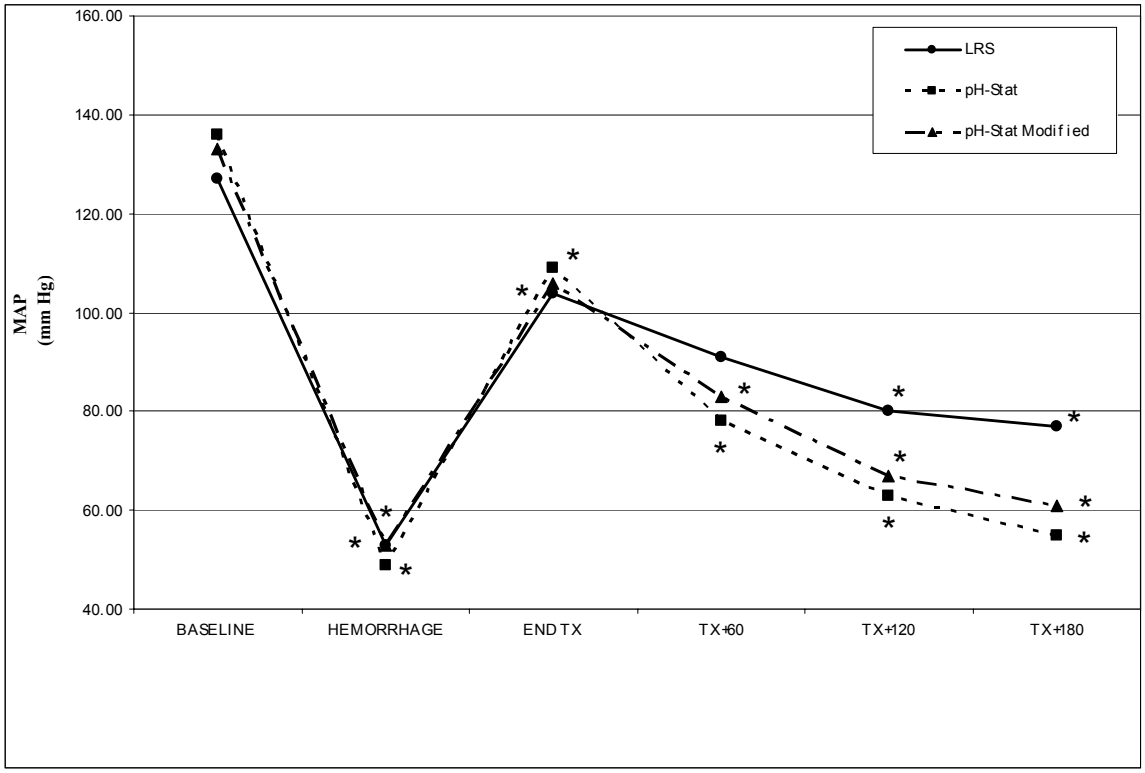

Fig. 3.4: Mean arterial pressure in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

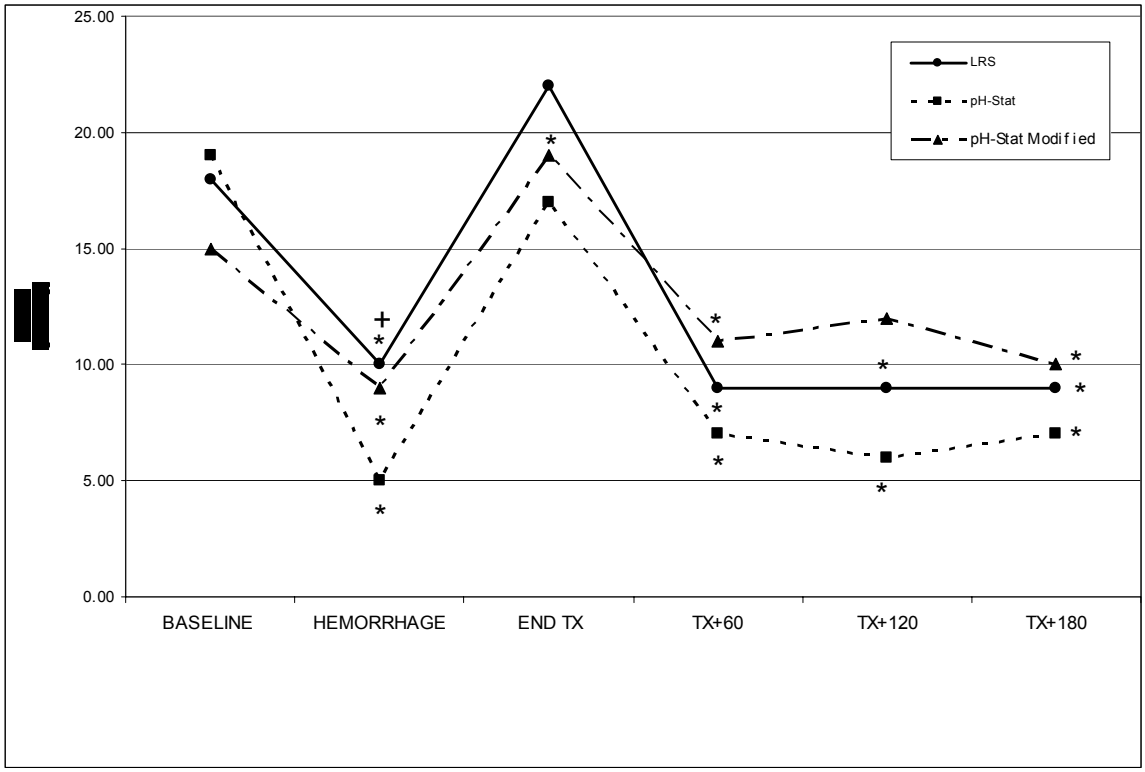

Fig. 3.5: Mean pulmonary arterial pressure in dogs under hemorrhagic shock.Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

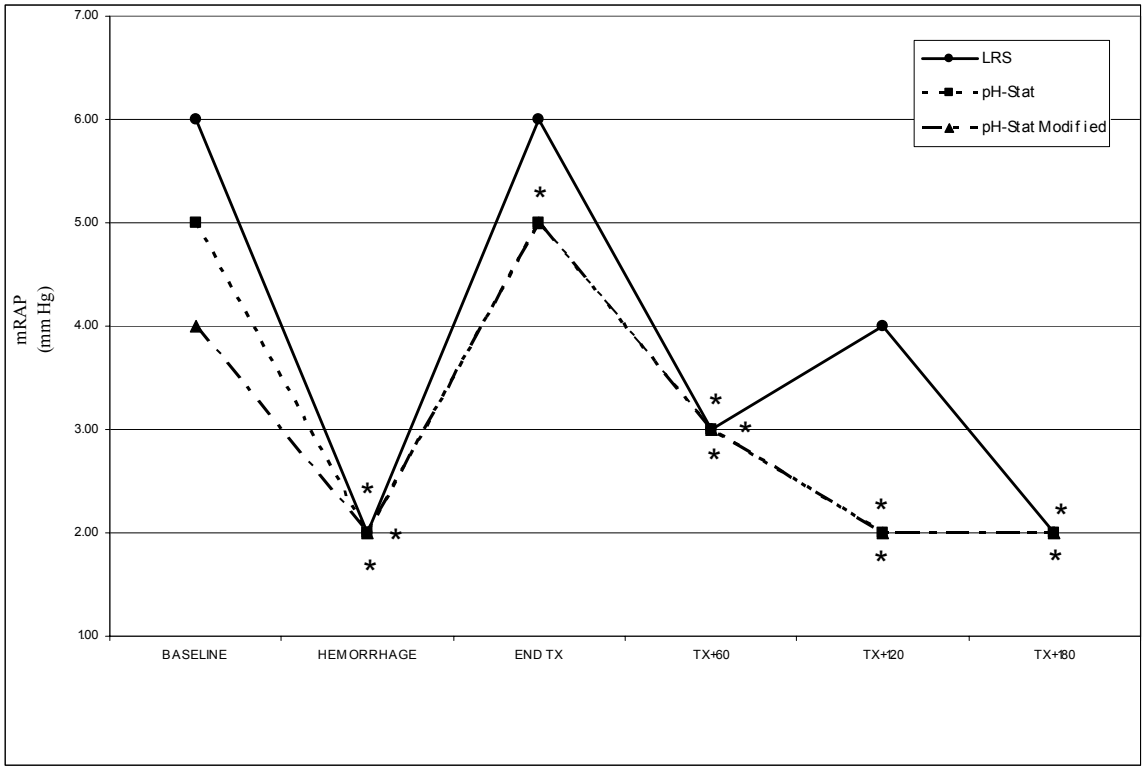

Fig. 3.6: Mean right atrial pressure in dogs under hemorrhagic shock.Significant defferences from baseline values: *P<0.05. +Significant differences between group 1and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

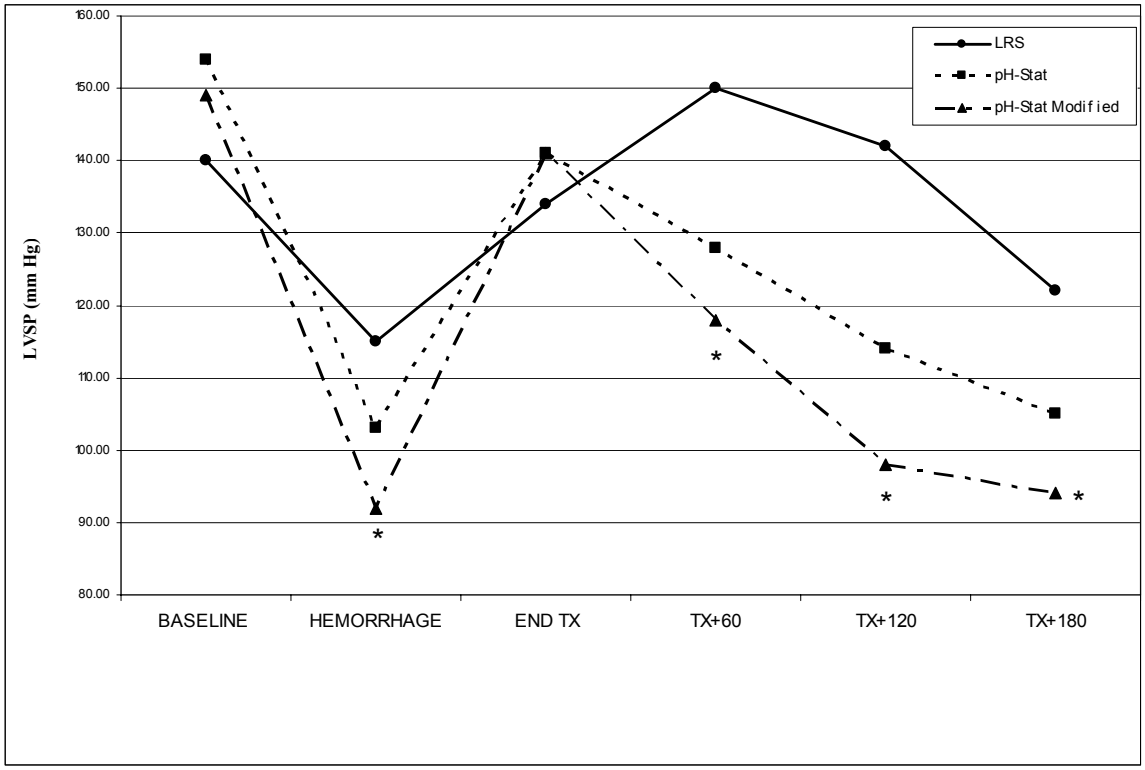

Fig. 3.7: Left ventricular systolic pressure in dogs under hemorrhagic shock. Significant differences from baseline: *P< 0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

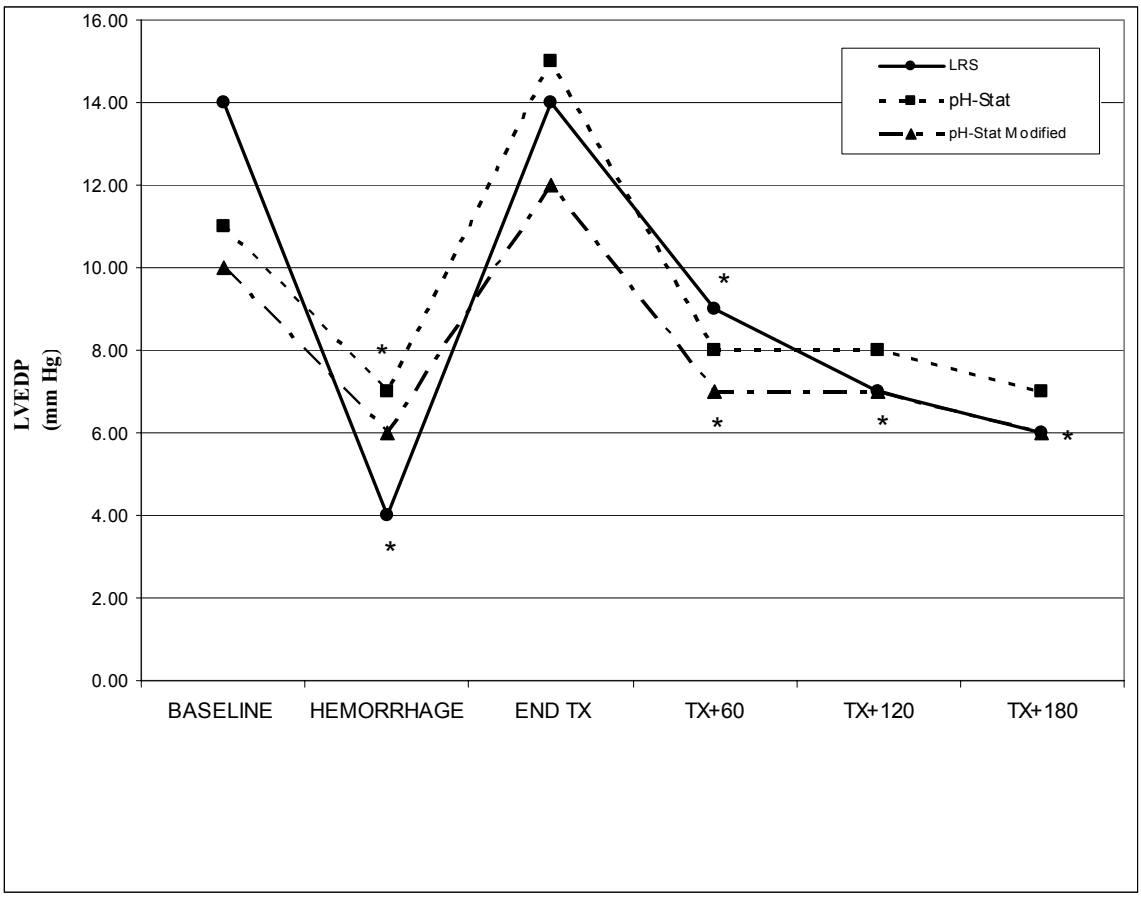

Fig. 3.8: Left ventricular end diastolic pressure in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

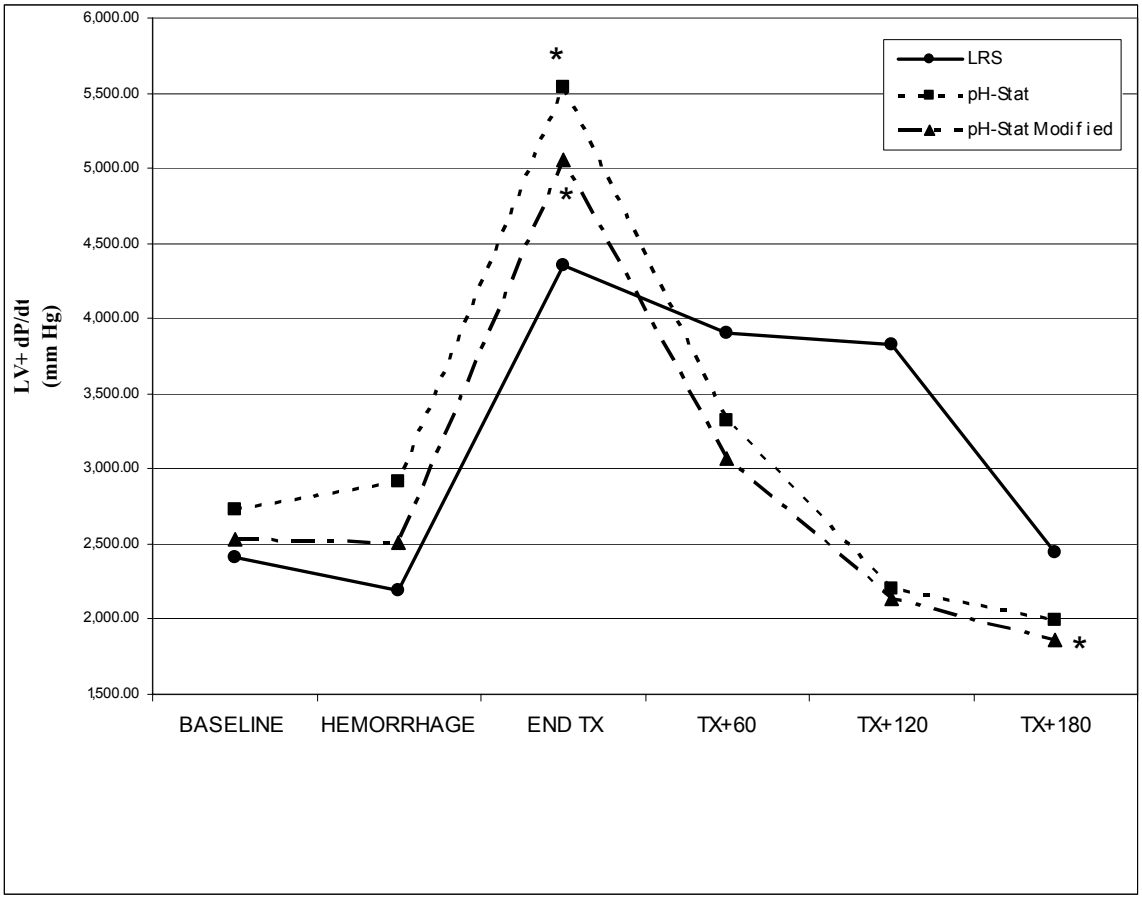

Fig. 3.9: Left ventricular positive dP/dT in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2, x: 1 and 3; ^: 2 and 3, at P< 0.05.

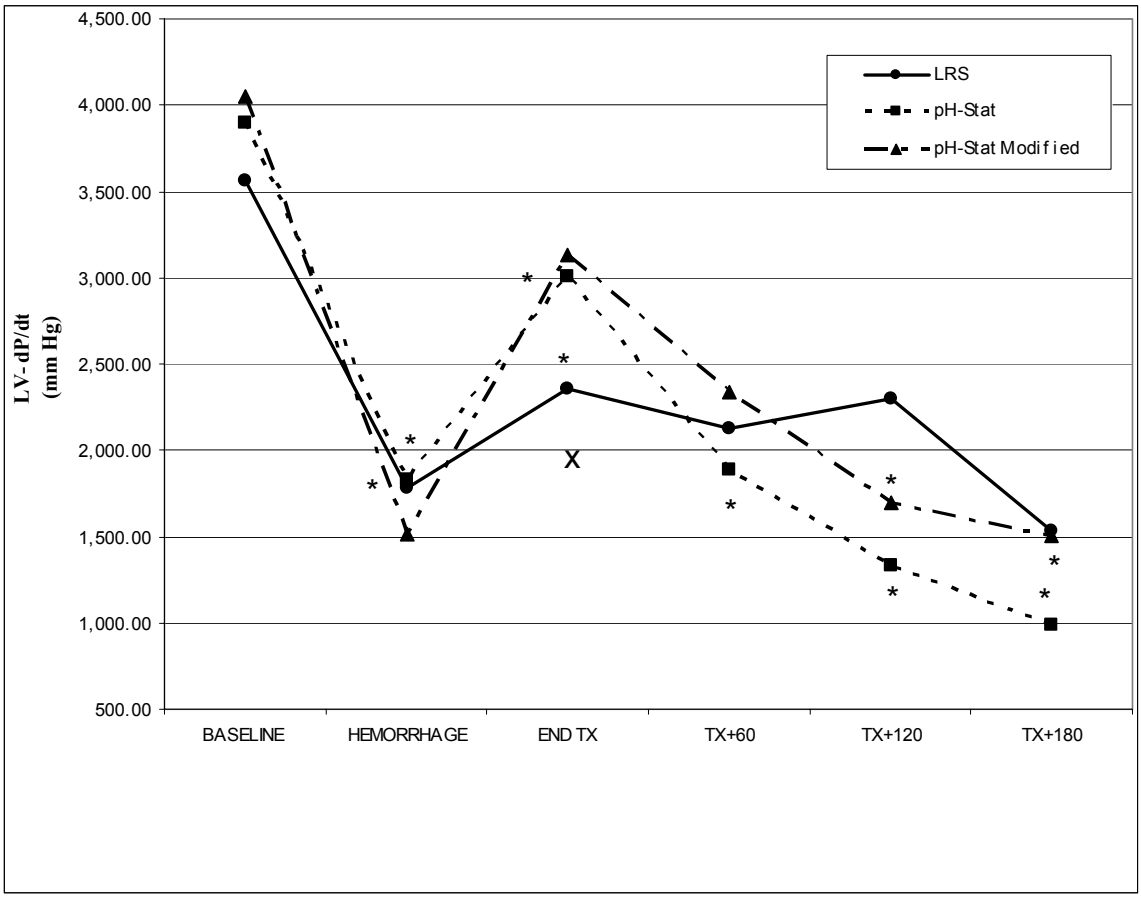

Fig. 3.10: Left ventricular negative dP/dT in dogs under hemorrhagic shock.Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

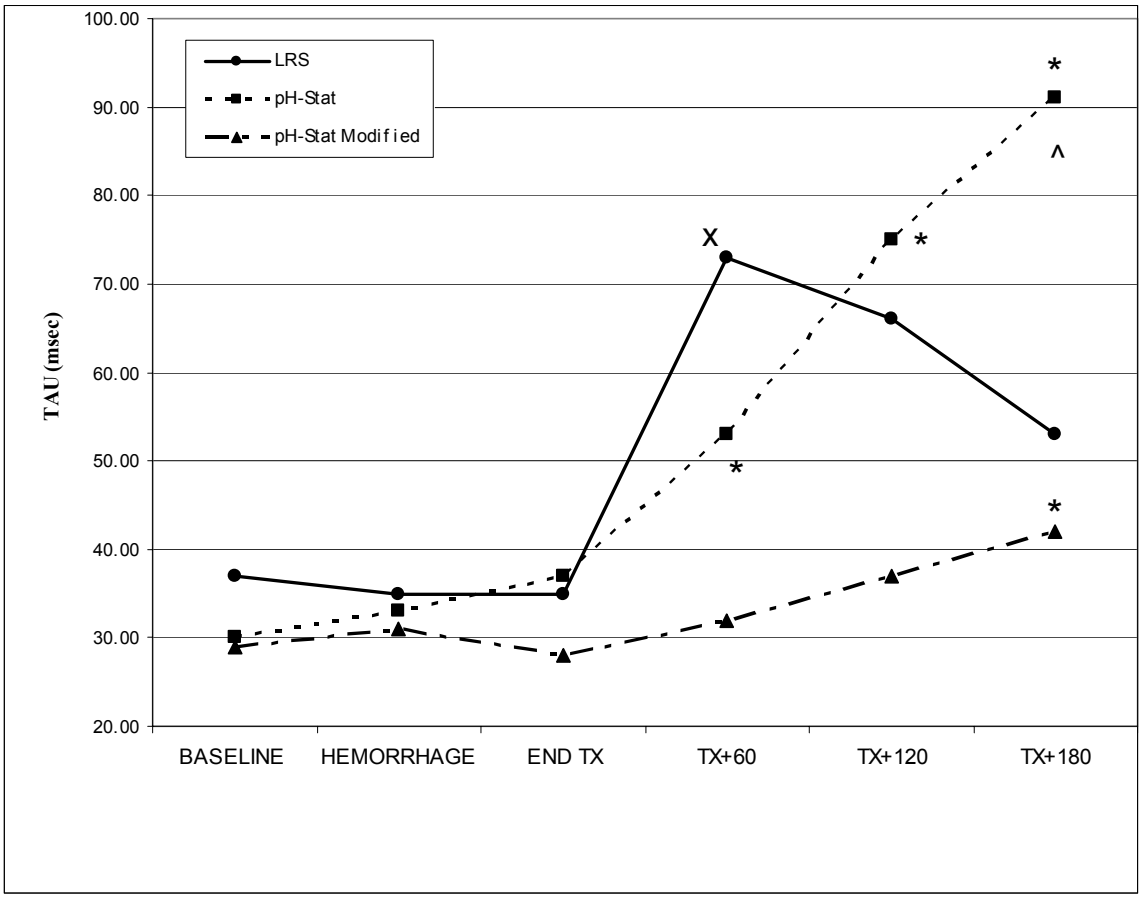

Fig. 3.11: Tau in dogs under hemorrhagic shock. Significant differences from baseline values. *P< 0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

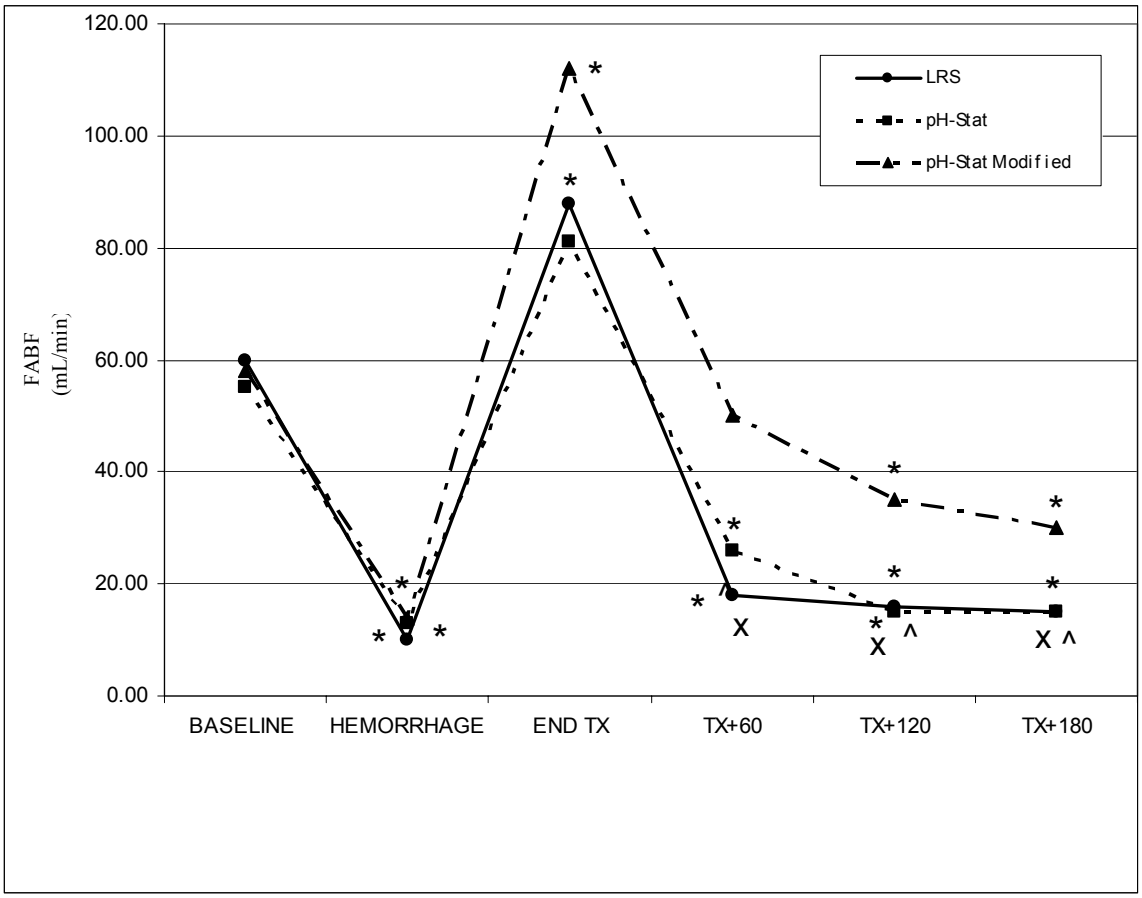

Fig. 3.12: Femoral artery blood flow in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

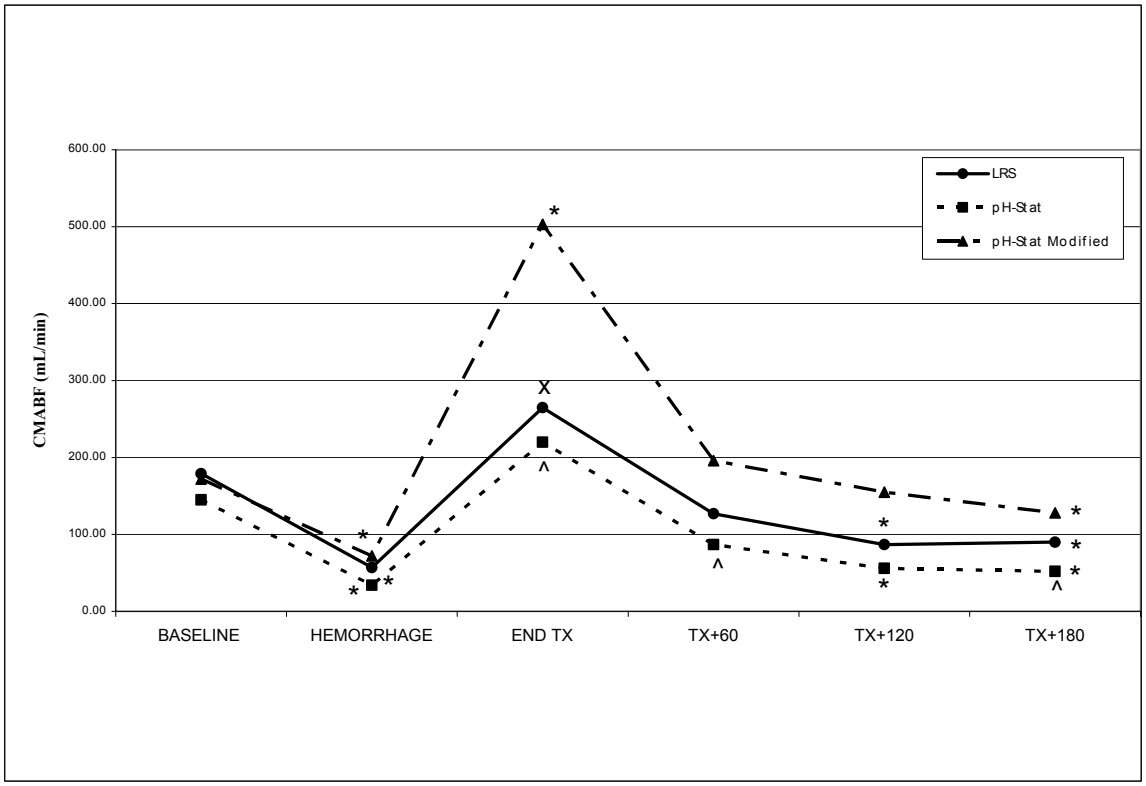

Fig. 3.13: Cranial mesenteric artery blood flow in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

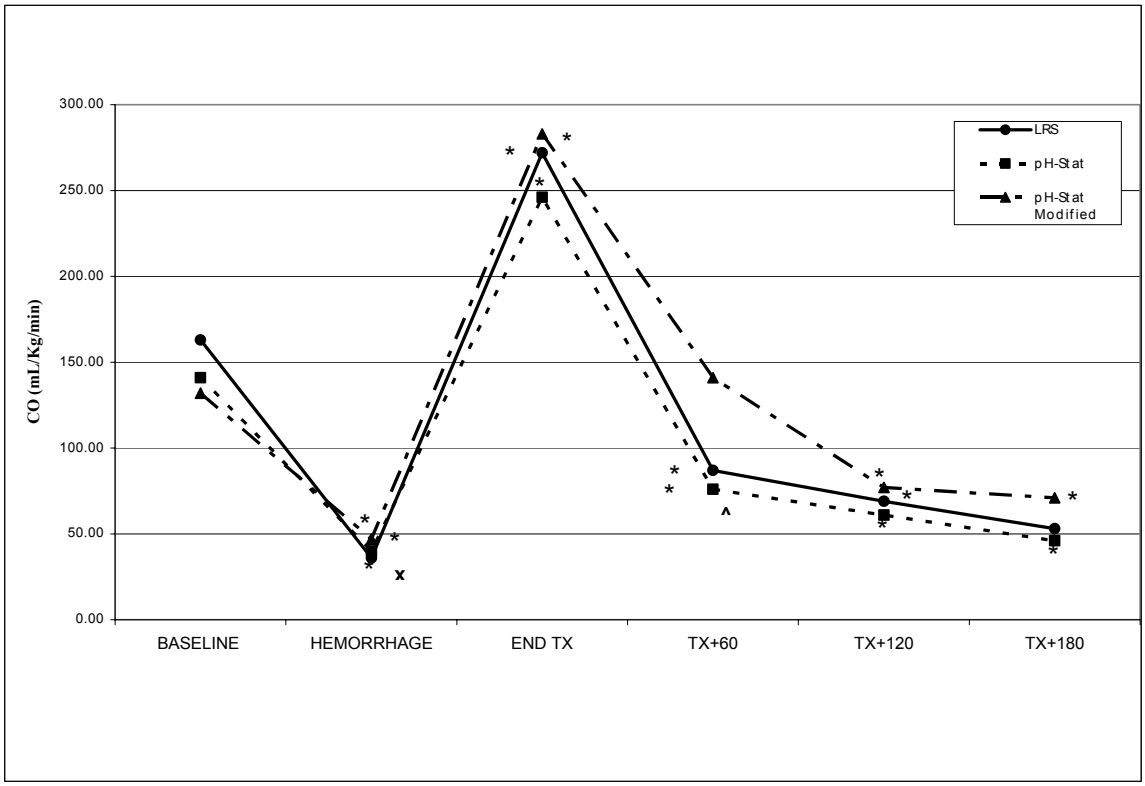

Fig. 3.14: Cardiac output in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between groups 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

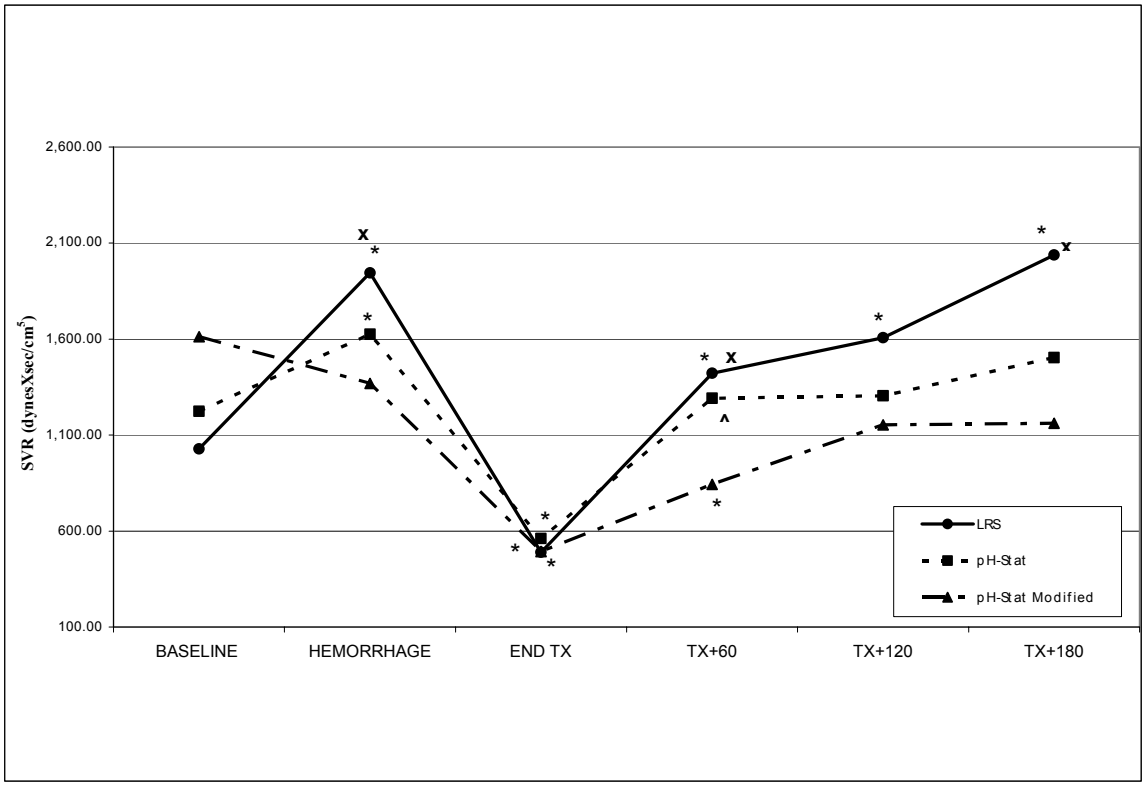

Fig. 3.15. Systemic vascular resistance in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

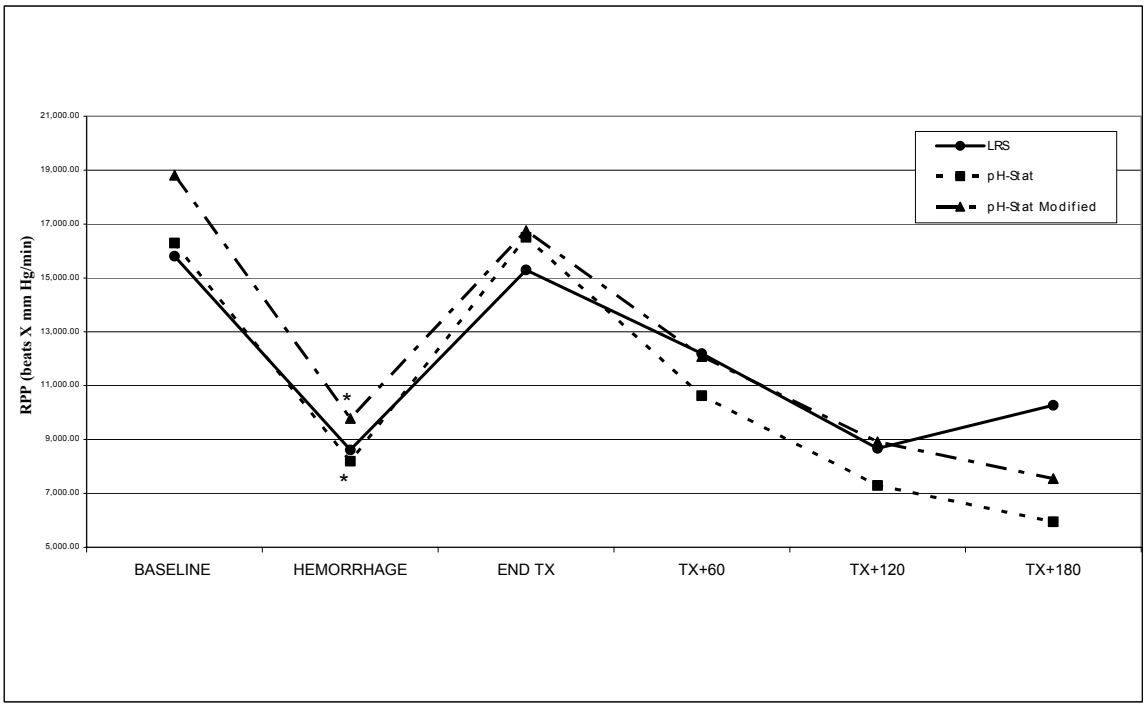

Fig. 3.16: Rate pressure product in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

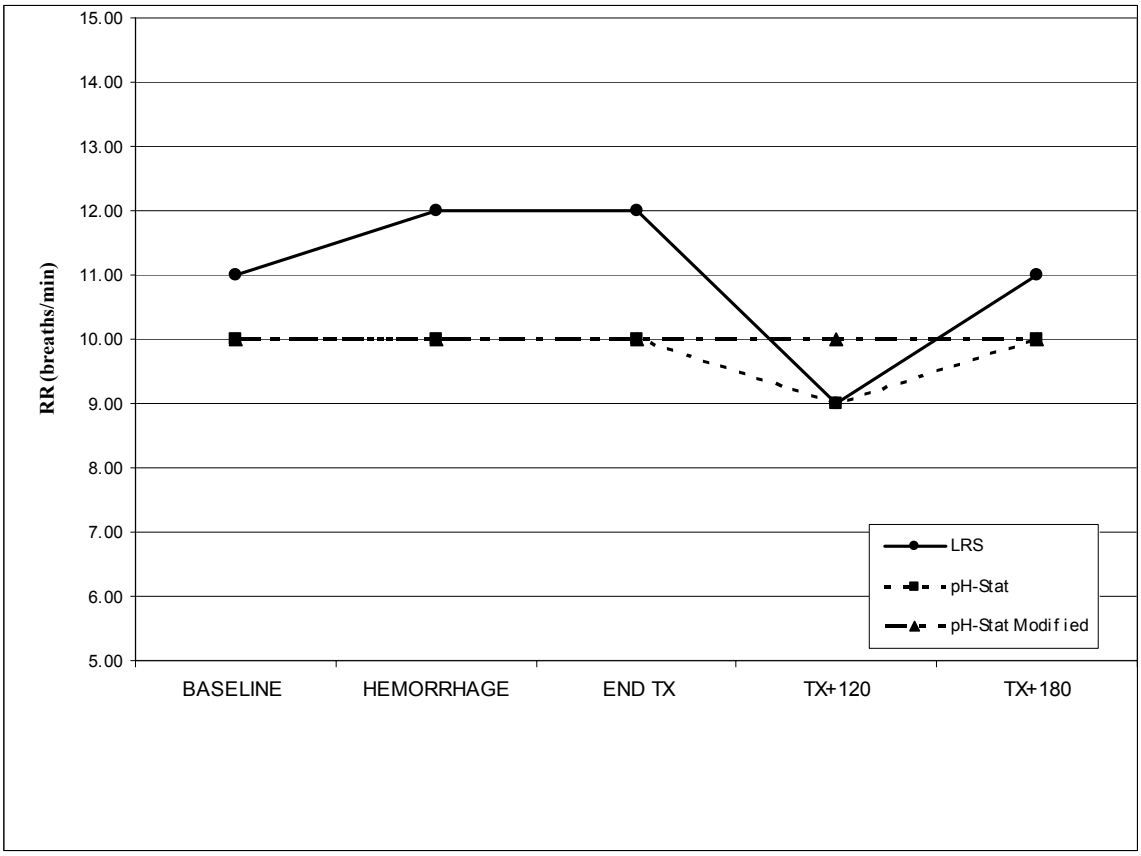

Fig. 3.17: Respiratory rate in dogs under hemorrhagic shock.Significant differences from baseline values: *P>0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

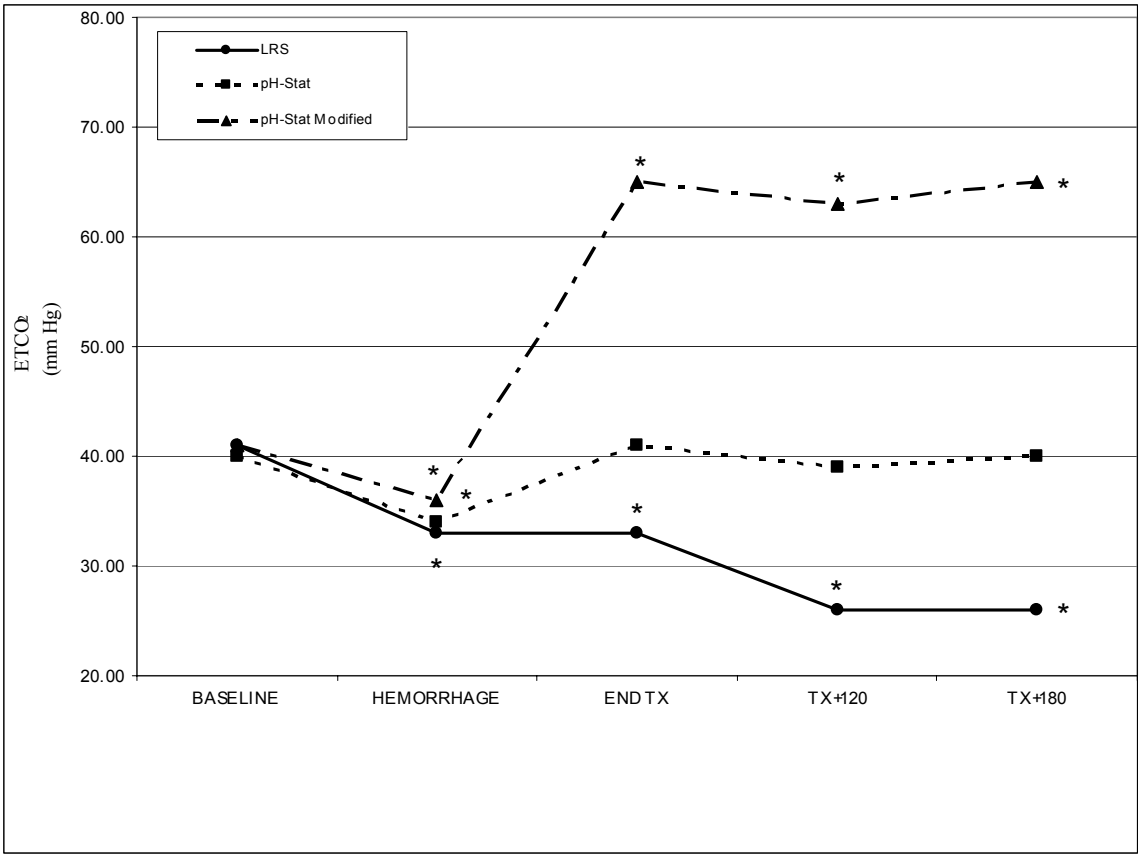

Fig. 3.18: End tidal carbon dioxide in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

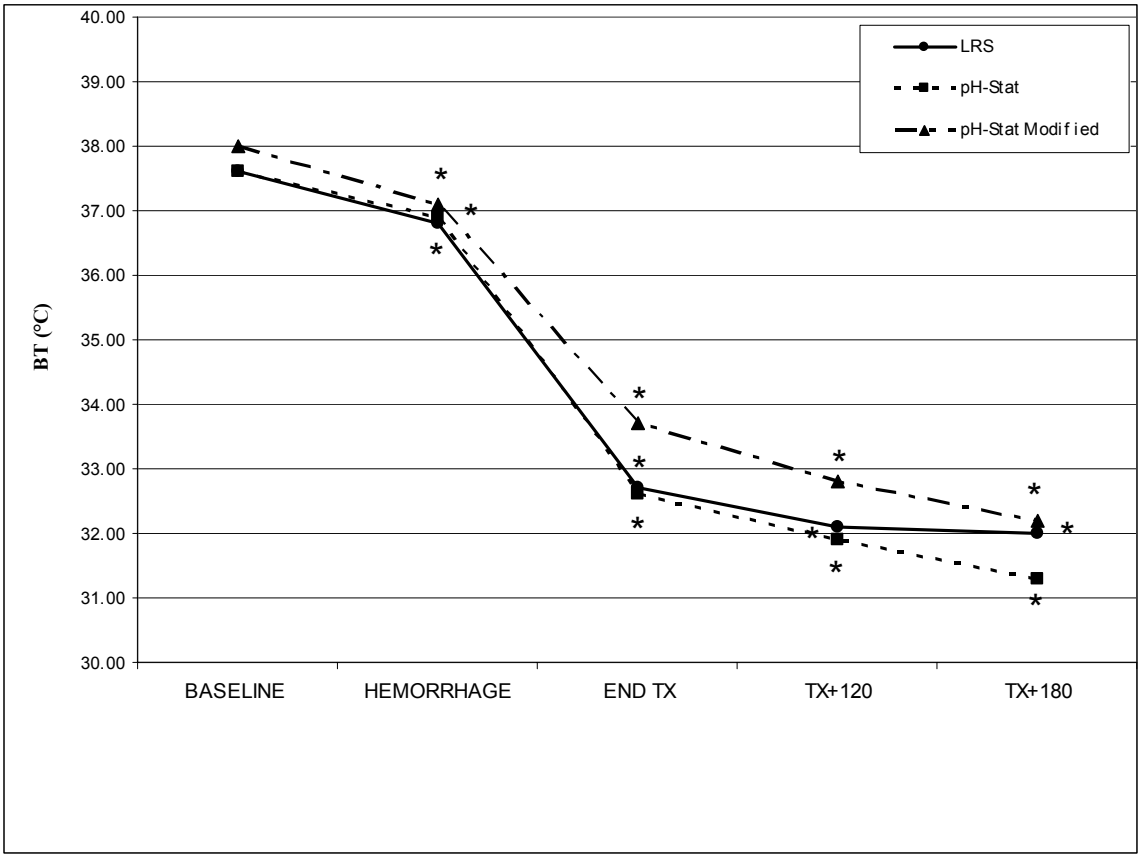

Fig. 3.19: Blood temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

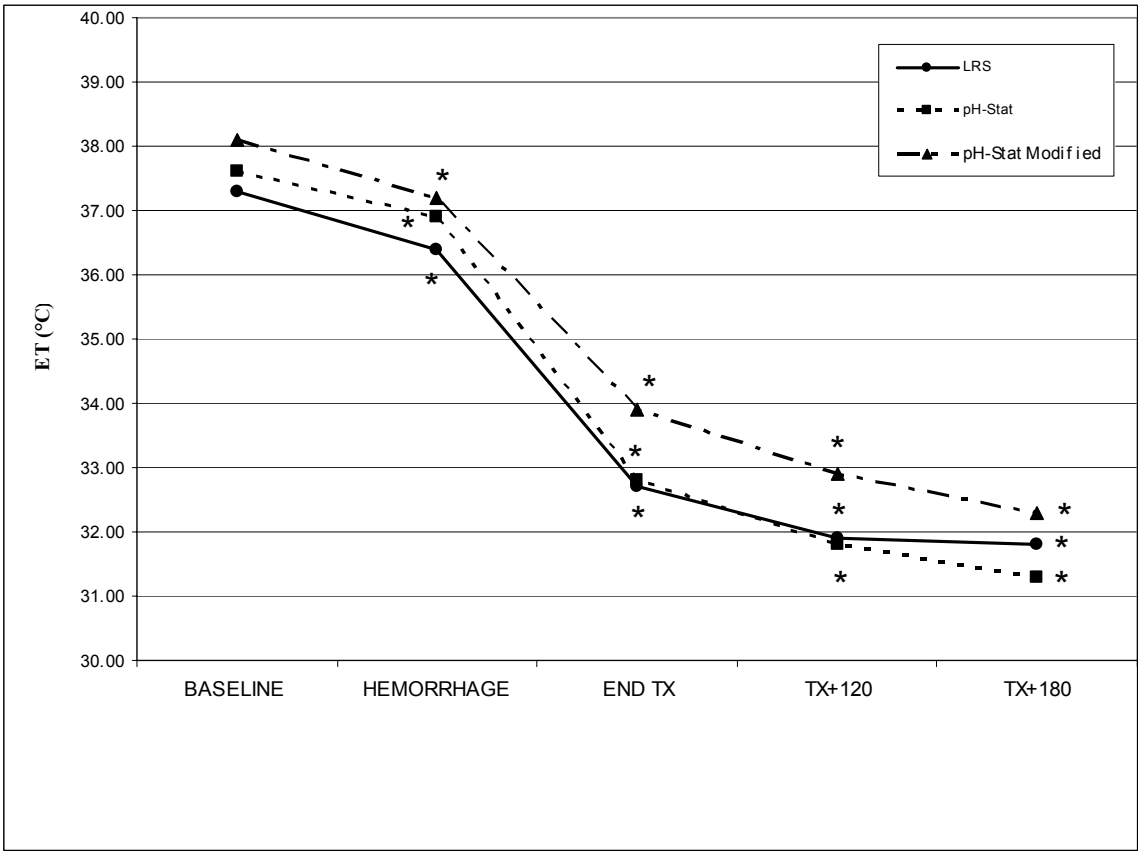

Fig. 3.20: Esophageal temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

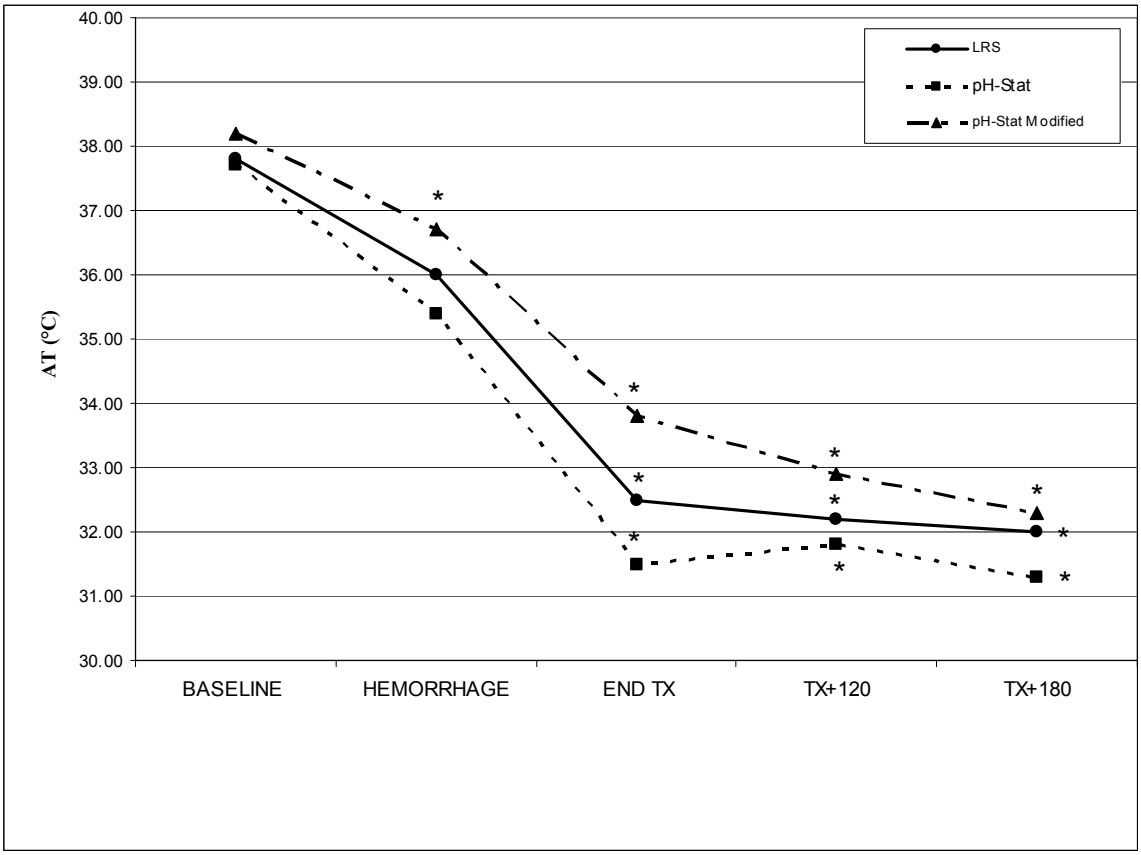

Fig. 3.21: Abdominal temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

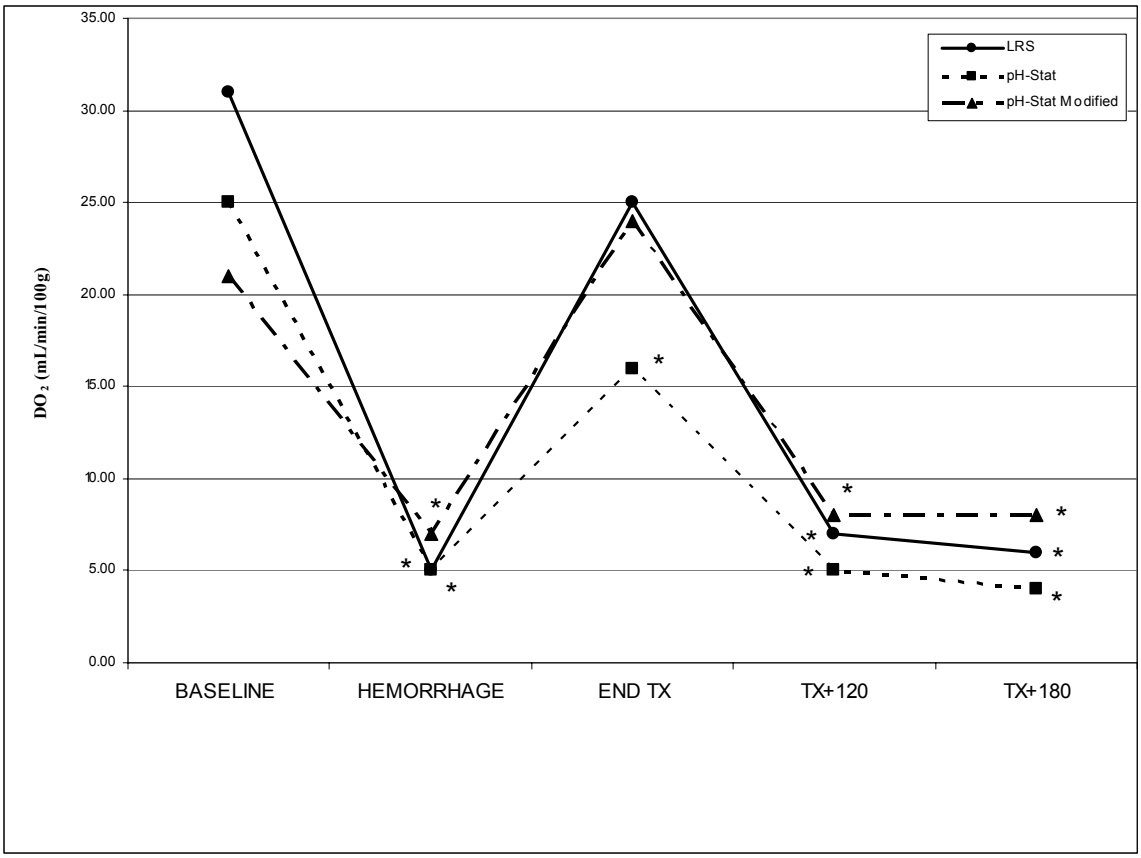

Fig. 3.22: Oxygen delivery in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: between 1 and 3; ^: between 2 and 3, at P< 0.05.

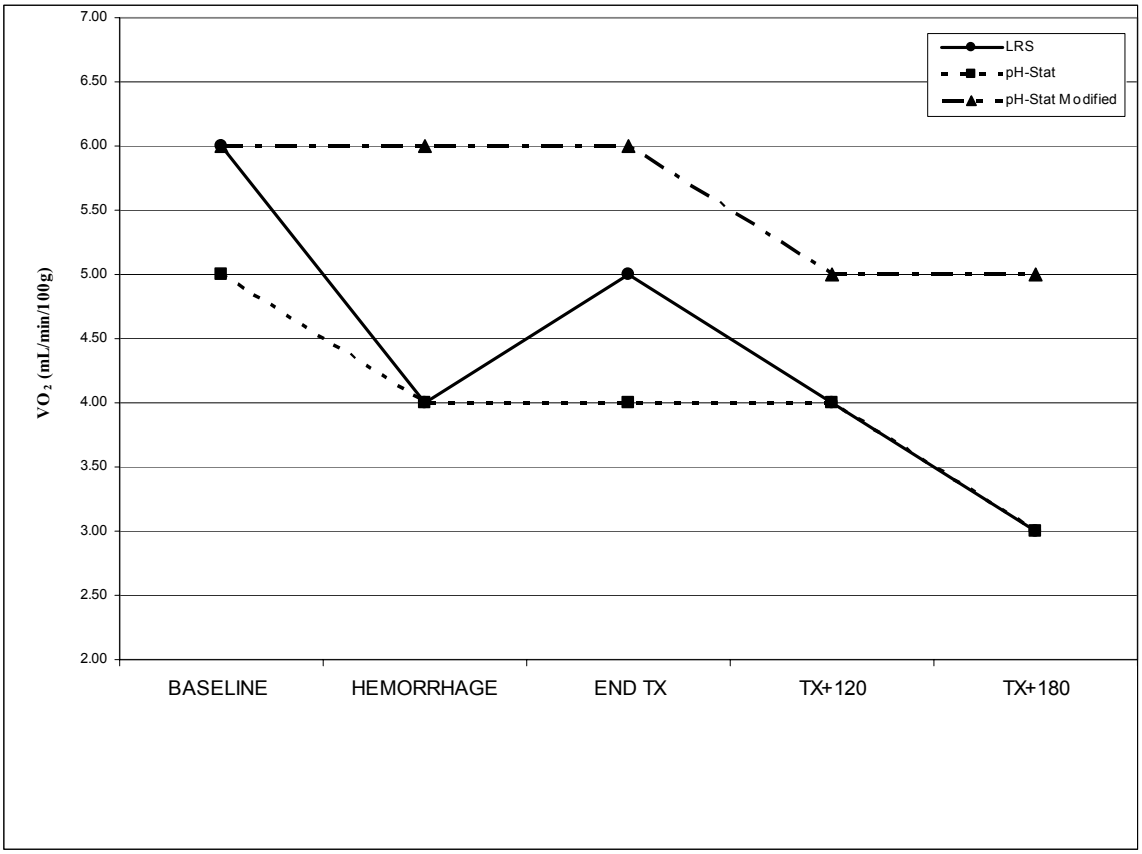

Fig. 3.23: Oxygen consumption in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: between 1 and 3; ^: between 2 and 3, at P< 0.05.

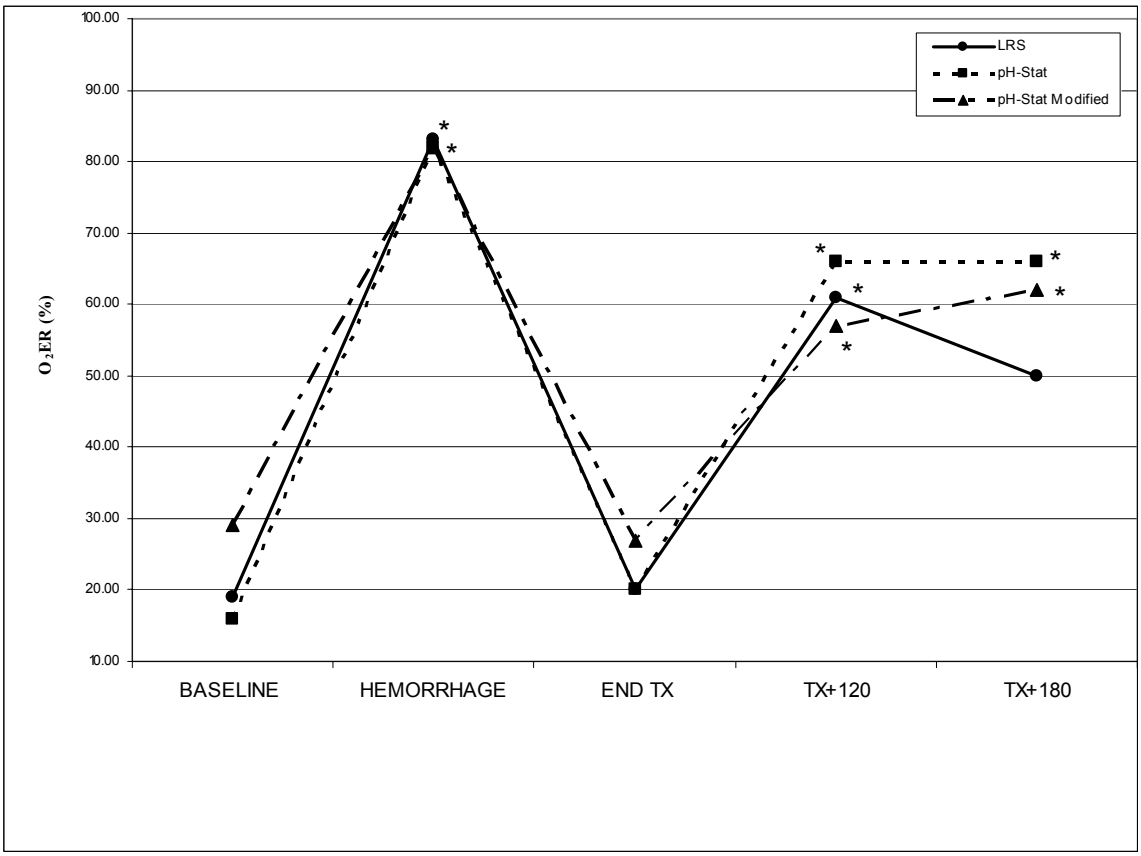

Fig. 3.24: Oxygen extraction ratio in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: between 1 and 3; ^: between 2 and 3, at P< 0.05.

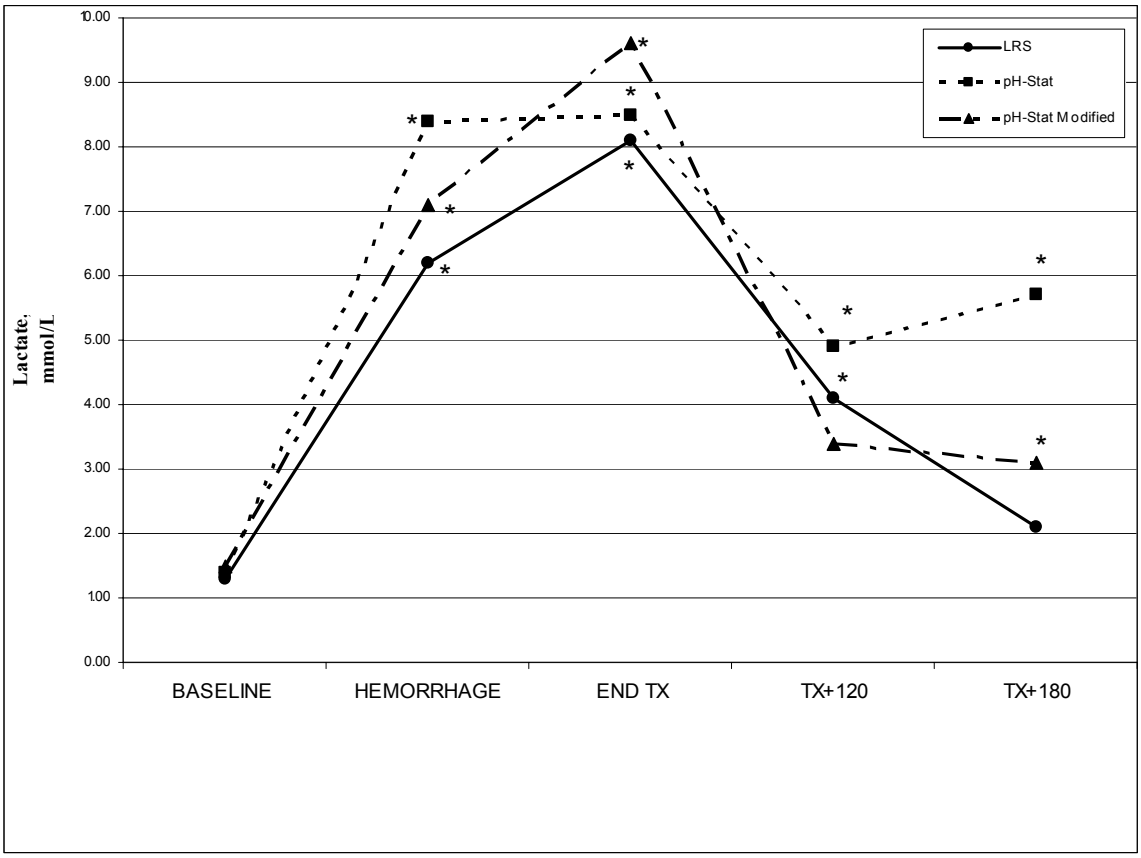

Fig. 3.25: Blood lactate in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

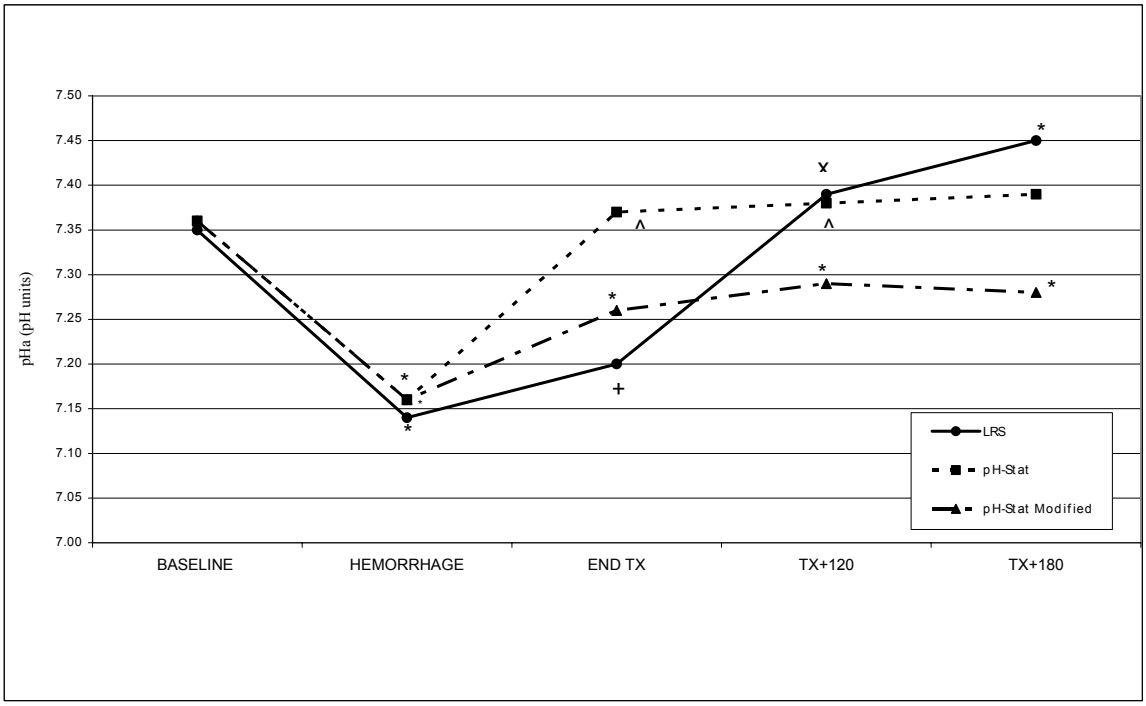

Fig. 3.26: Arterial pH at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between groups: + 1 and 2; x: 1 and 3; ^:2 and 3, at P< 0.05.

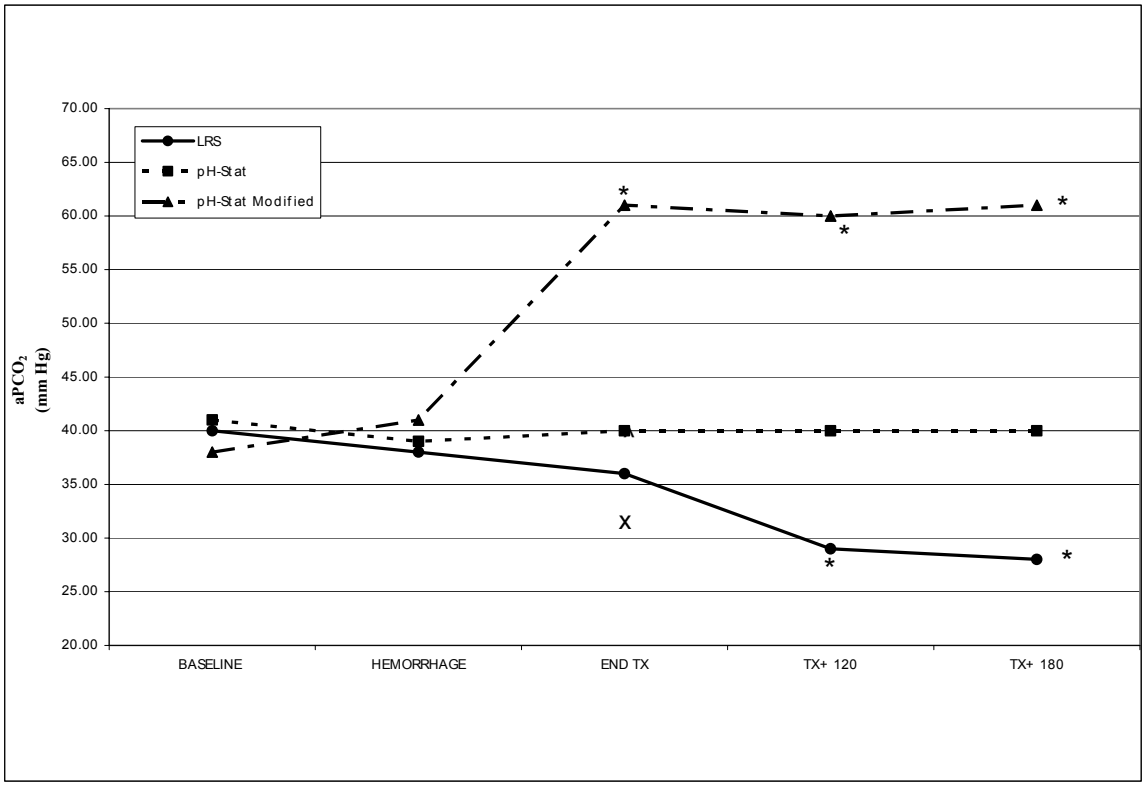

Fig. 3.27: Arterial PCO_2 at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +: Significant differences between groups 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

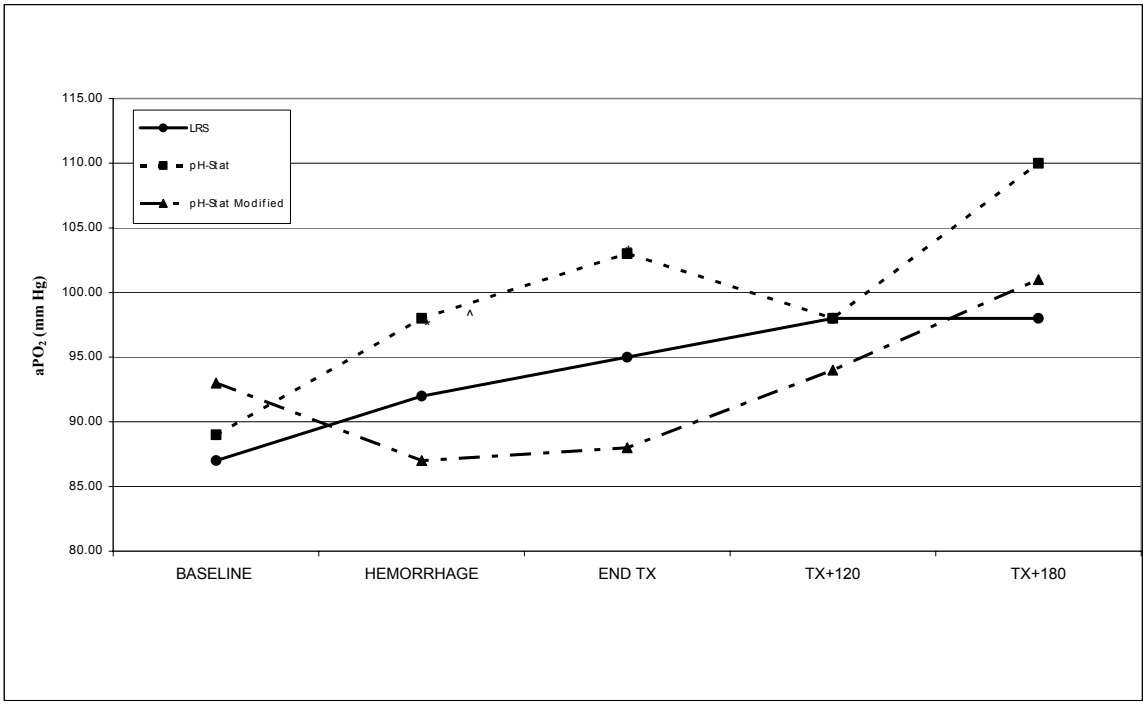

Fig. 3.28: Arterial PO_2 at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +: Significant differences between groups 1and 2; x: 1 and 3; ^: 2 and 3 at P< 0.05.

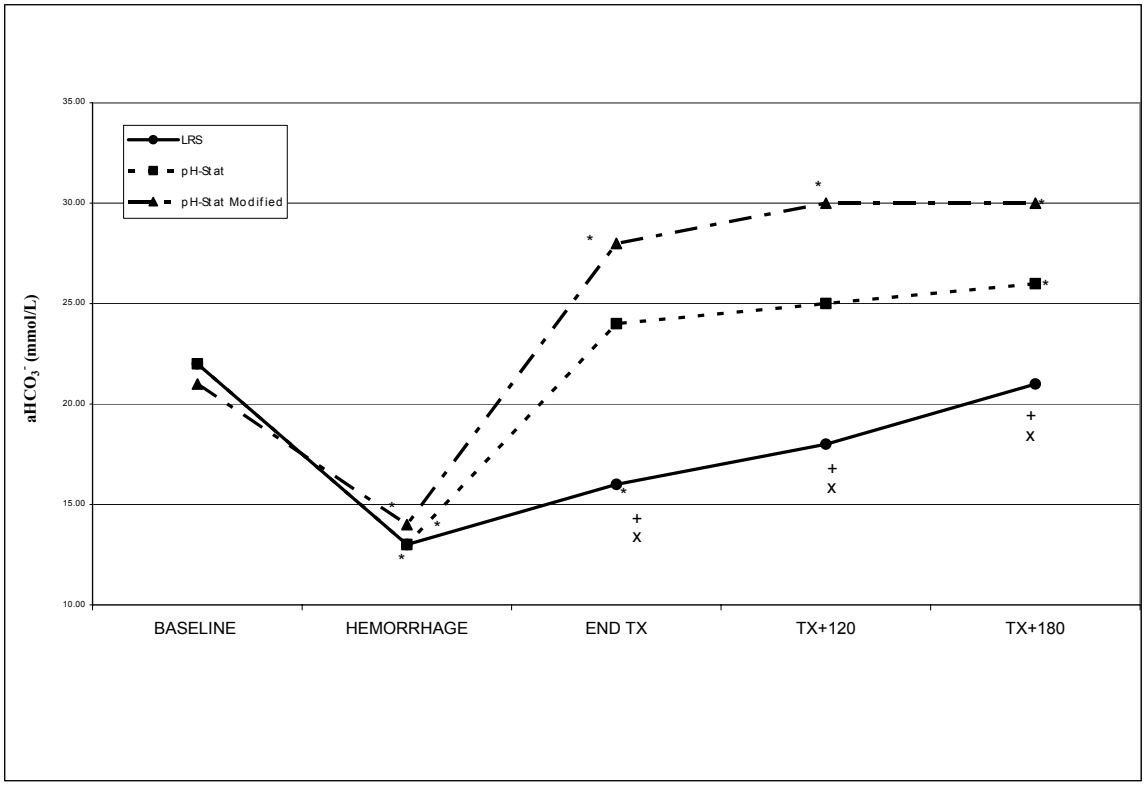

Fig. 3.29: Arterial HCO_3^- at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between groups 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

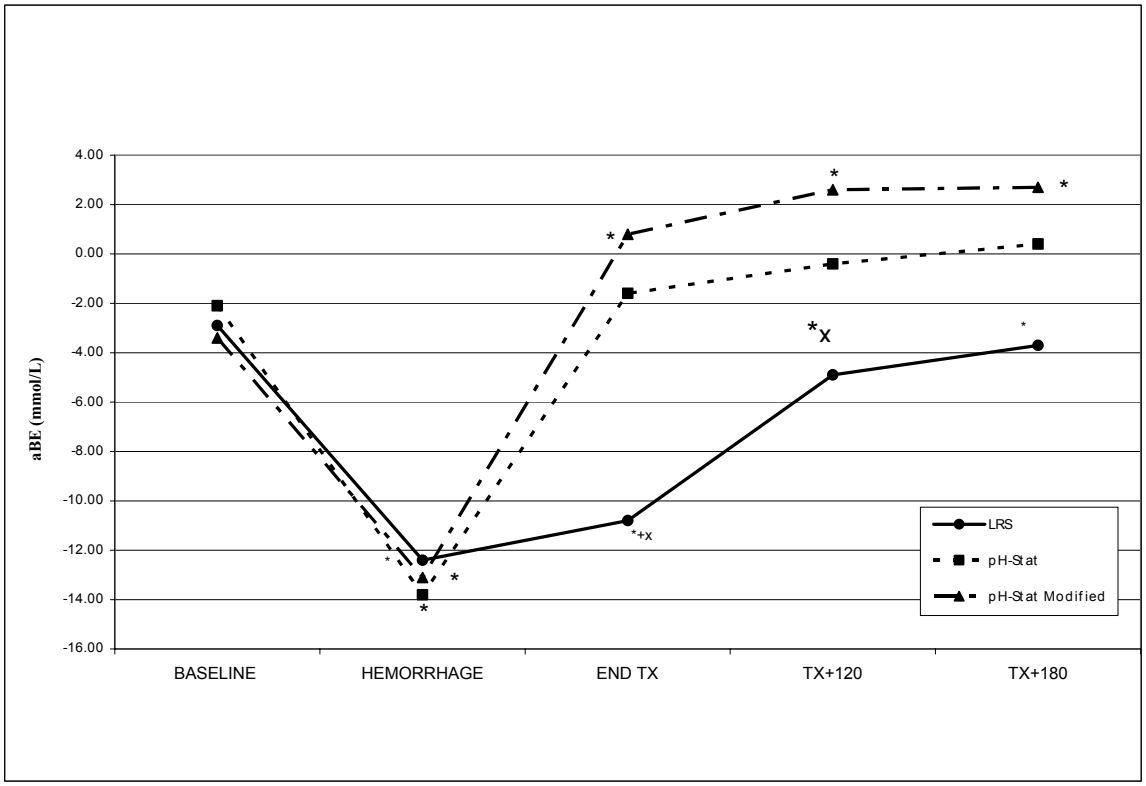

Fig. 3.30: Arterial base excess concentration at patient temperature in dogs under hemorrrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

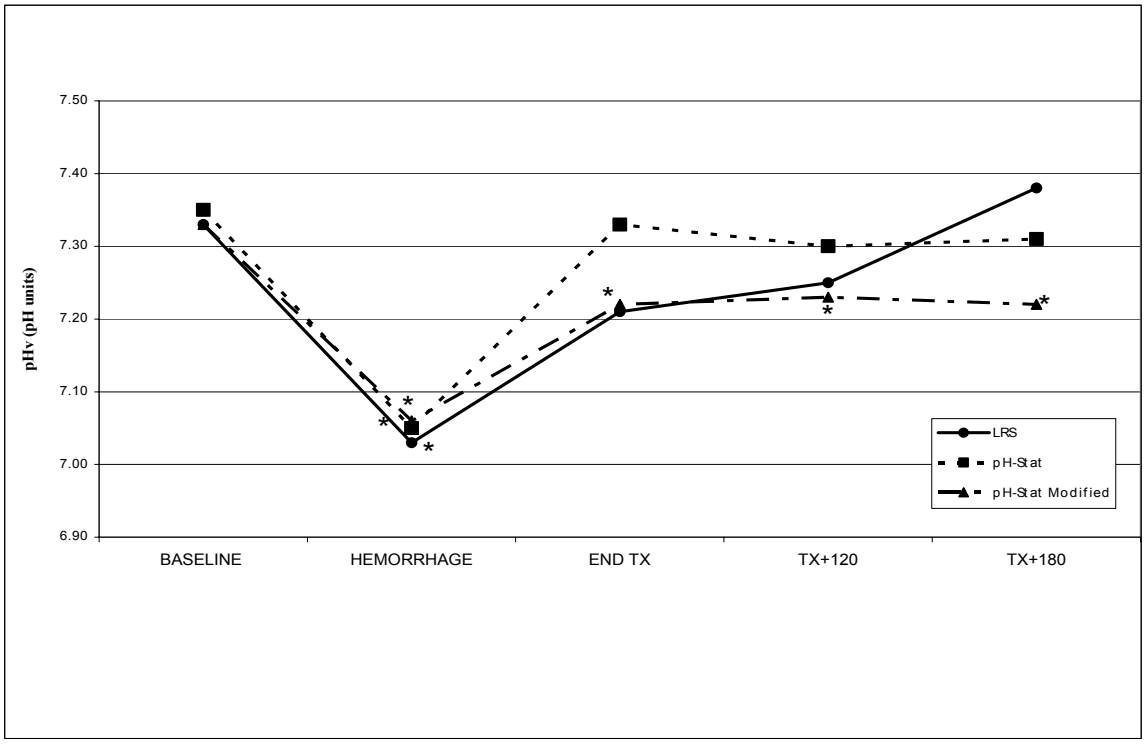

Fig. 3.31: Venous pH at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

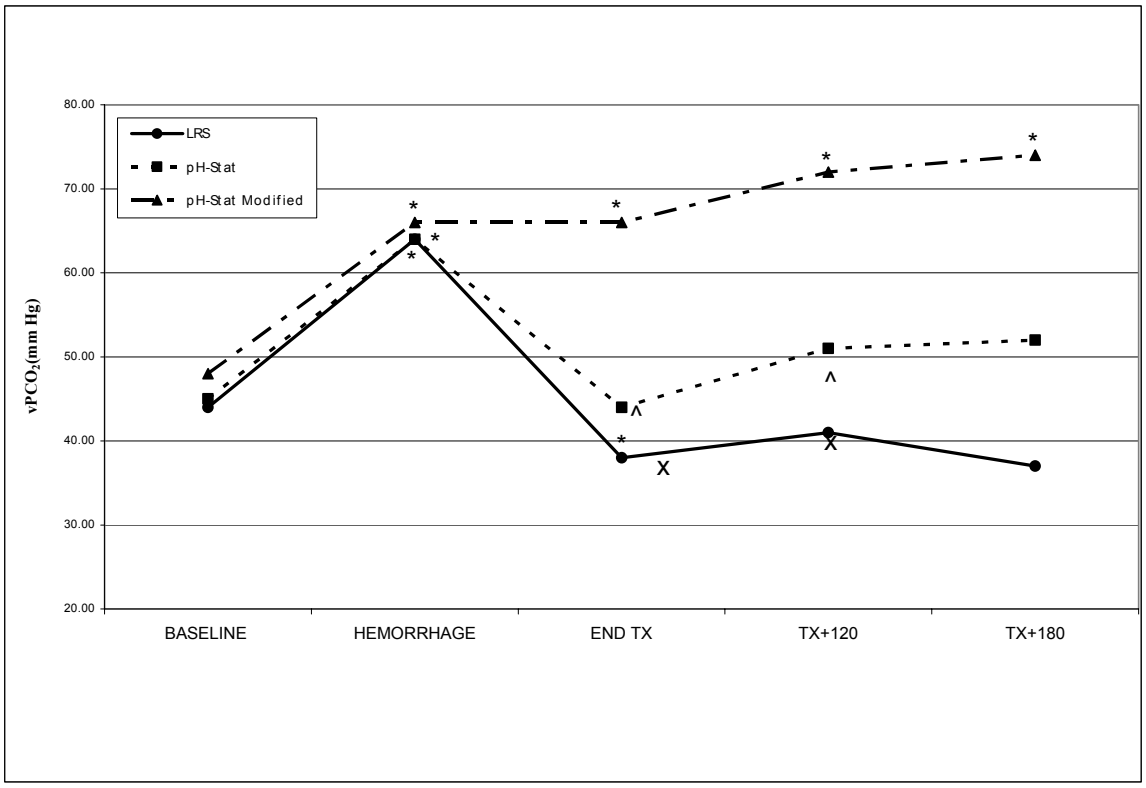

Fig. 3.32: Venous PCO_2 at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

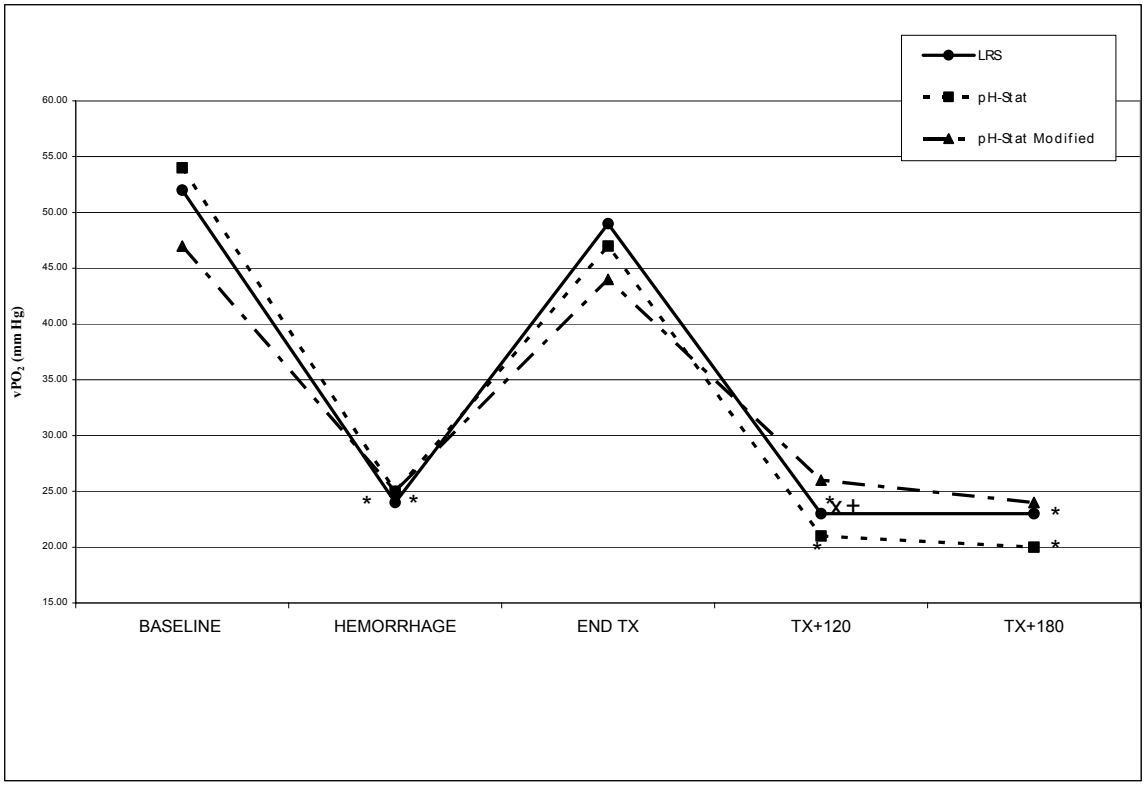

Fig. 3.33: Venous PO_2 at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

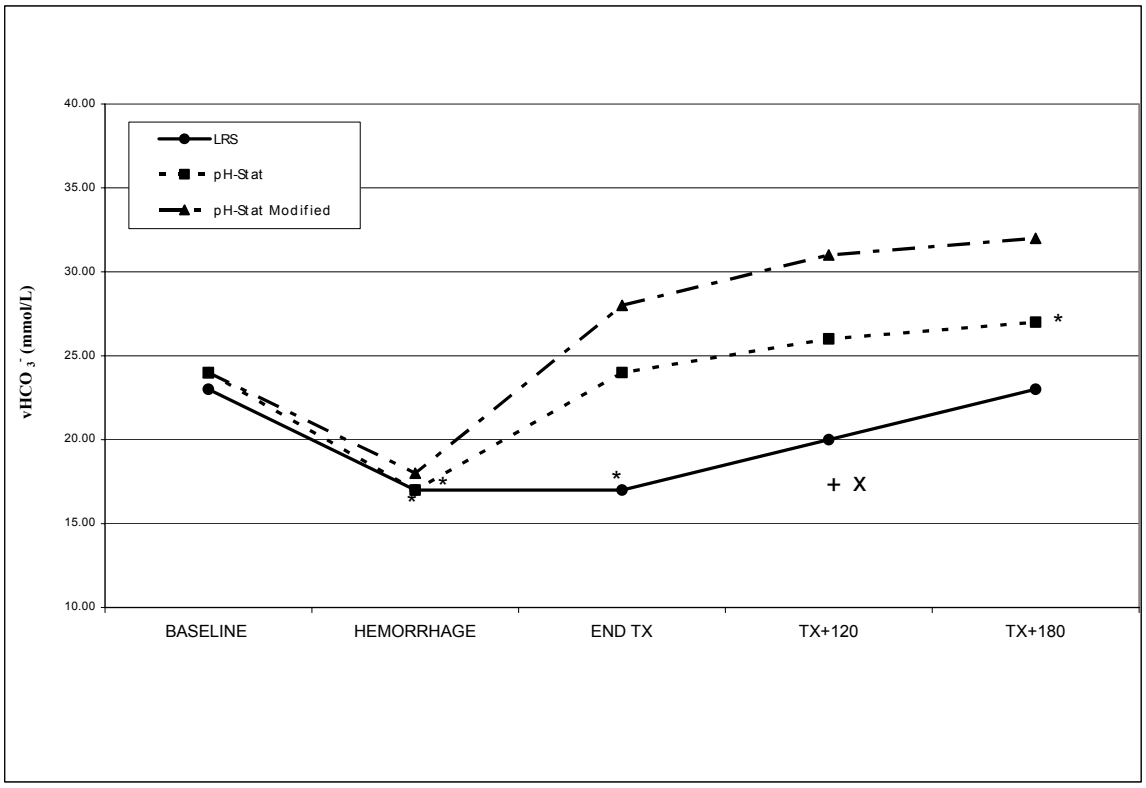

Fig. 3.34: Venous HCO_3^- at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

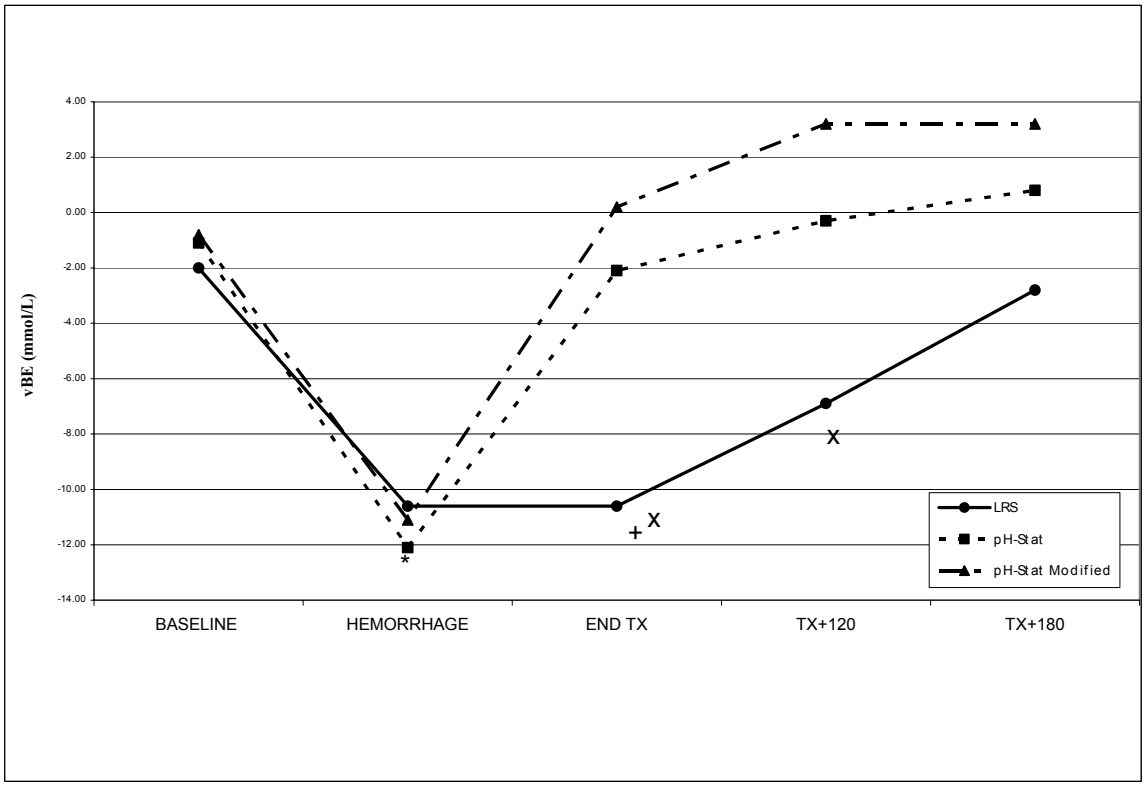

Fig. 3. 35: Venous base excess at patient temperature in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

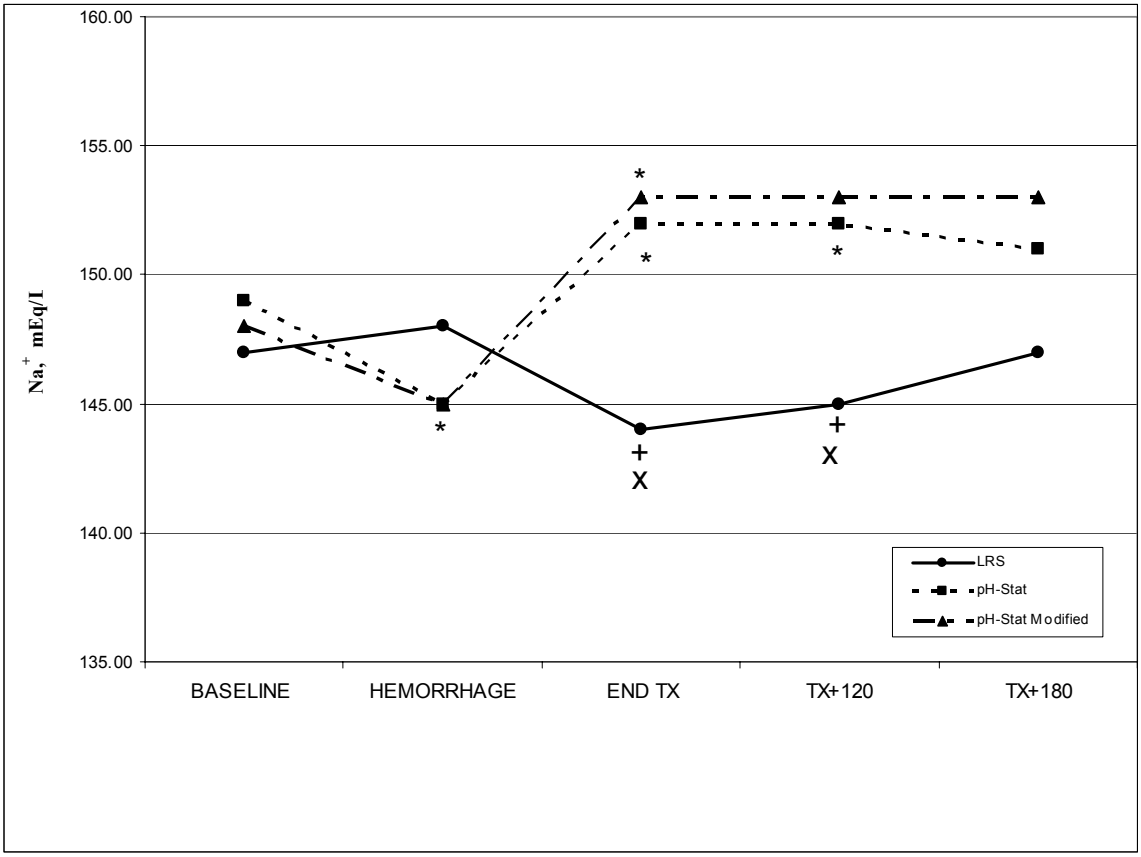

Fig. 3.36: Sodium concentration in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

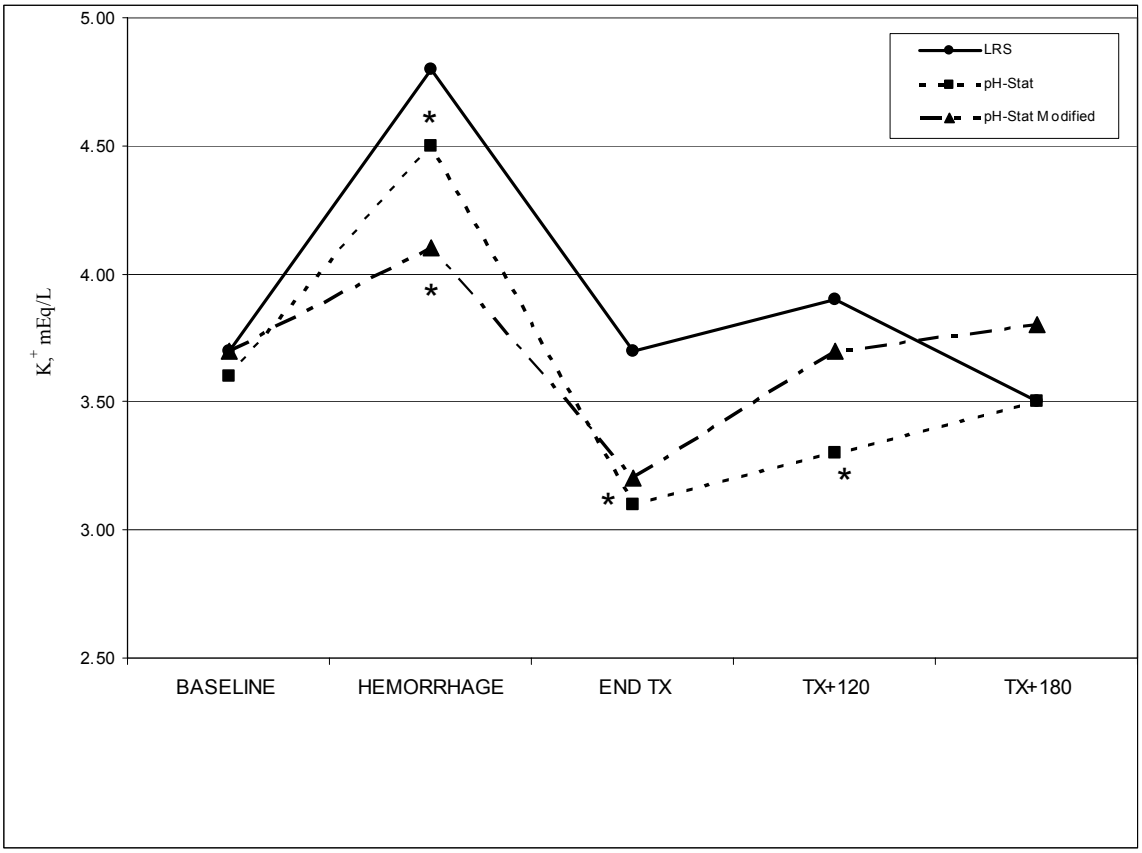

Fig. 3.37: Potassium concentration in dogs under hemorrhagic shock.
Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

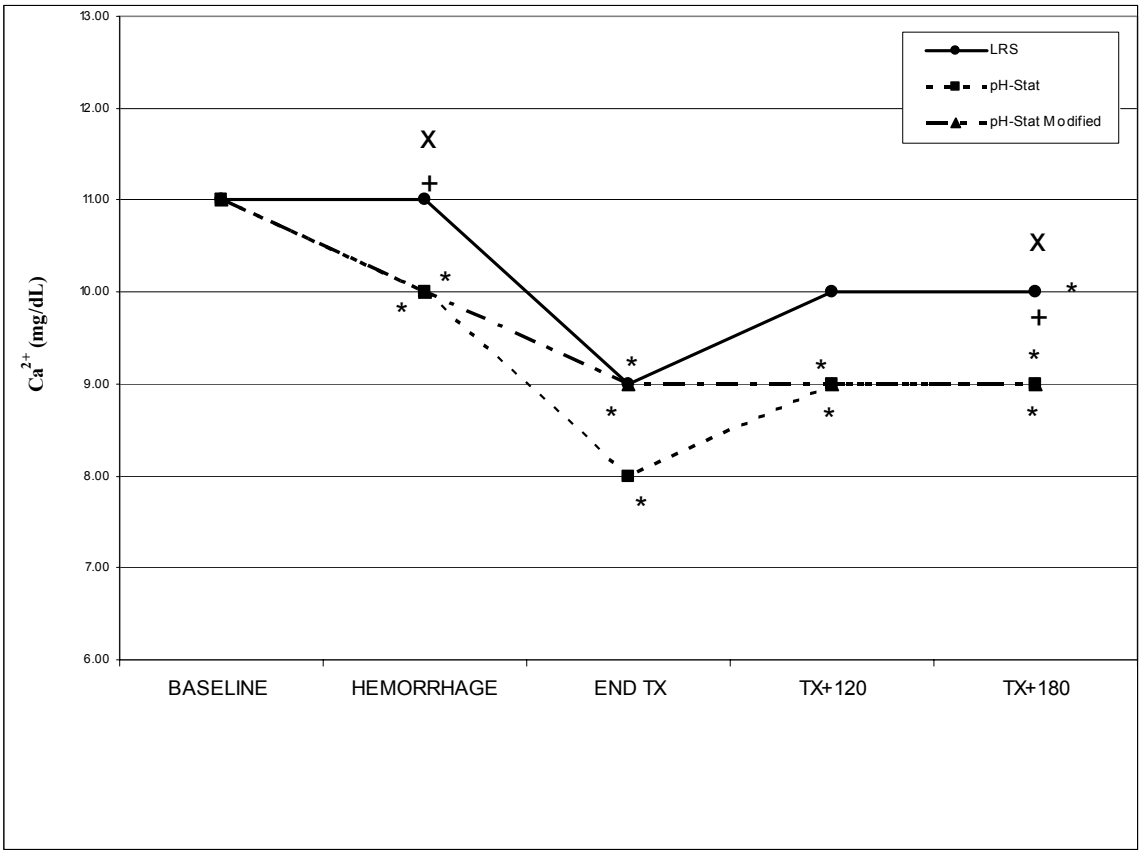

Fig. 3.38: Ionized calcium concentration in dogs under hemorrhagic shock. Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

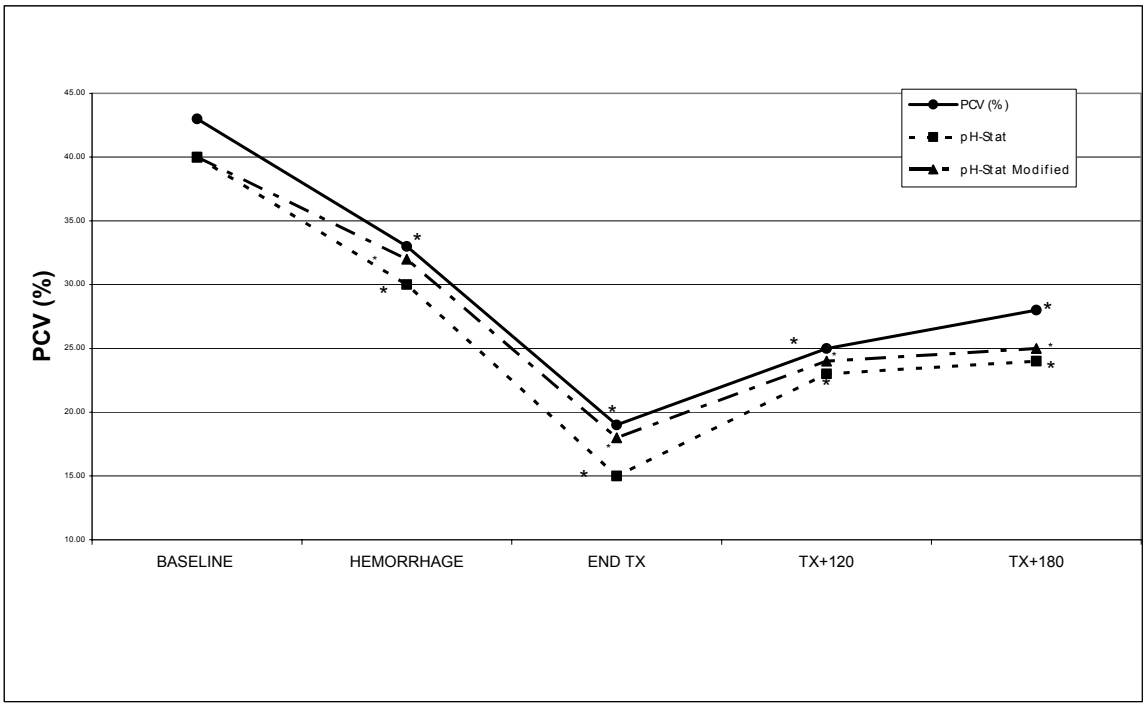

Fig. 3.39: Packed cell volume in dogs under hemorrhagic shock.
Significant differences from baseline values: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

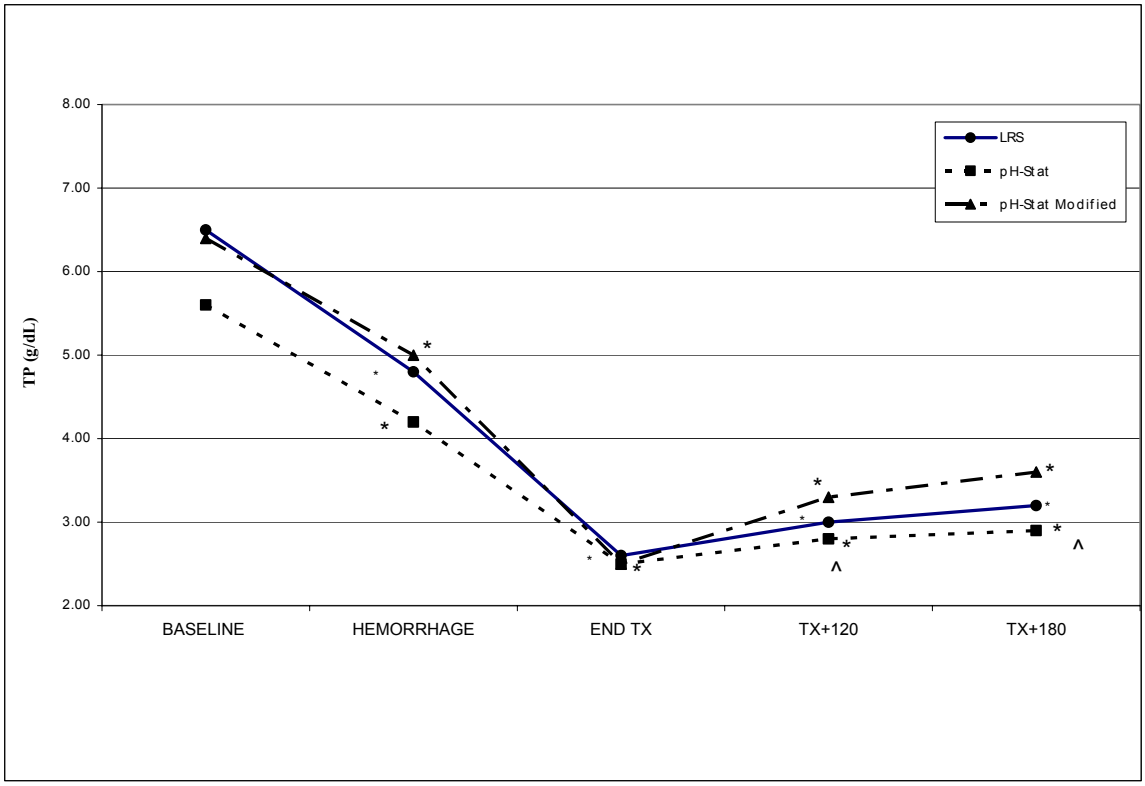

Fig. 3.40: Total proteins in dogs under hemorrhagic shock. Significant differences from baseline: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

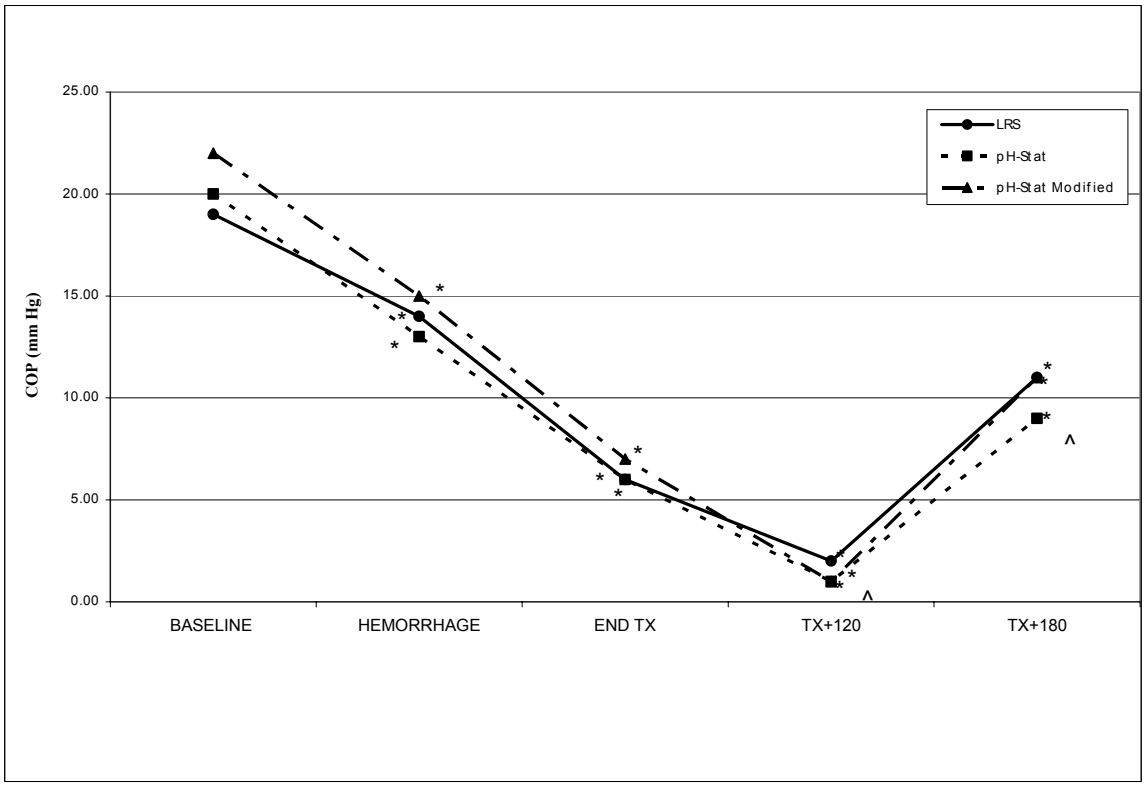

Fig. 3.41: Colloid osmotic pressure on dogs under hemorrhaagic shock. Significant differences from baseline: *P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	BASELINE VALUE	HEMORRHAGE		END TREATMENT		TX+60		TX+120		TX+180	
		VALUE	CHANGE (%)#	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE	VALUE	CHANGE
HR											
LRS	126±19	163±30	29	136±20	8	132±29	5	121±34	-4	134±27	6
pH-Stat	133±33	165±36	24	151±21	14	136±20	2	116±21	-13	106±23	-20
pH-Stat Modified	143±21	183±32	28 *	158±22	10	147±24	3	133±26	-7	123±27	-14
SAP											
LRS	143±19	63±11	-56 *	128±14	-10	104±31	-27 *	94±31	-34 *	89±1	-38 *
pH-Stat	153±13	62±8	-59 *	136±18	-11 *	97±33	-37 *	78±23	-49 *	69±22	-55 *
pH-Stat Modified	149±31	65±4	-56 *	132±16	-11	100±22	-33 *	80±18	-46 *	74±21	-50 *
DAP											
LRS	112±13	47±5	-58 *	81±21	-28 *	79±28	-29 *	70±29	-38 *	68±7	-39 *
pH-Stat	122±12	44±5	-64 *	84±17	-31 *	65±32	-47 *	52±22	-57 *	46±21	-62 *
pH-Stat Modified	120±25	47±3	-61 *	83±21	-31 *	70±22	-42 *	56±13	-53 *	51±14	-58 *
MAP											
LRS	127±15	53±7	-58 *	104±17	-18	91±30	-28	80±31	-37 *	77±5	-39 *
pH-Stat	136±12	49±1	-64 *	109±18	-20 *	78±34	-43 *	63±24	-54 *	55±22	-60 *
pH-Stat Modified	133±28	53±2	-60 *	106±17	-20 *	83±23	-38 *	67±15	-50 *	61±18	-54 *
mPAP											
LRS	18±1	10±4	-44 *+	22±7	22	9±4	-50 *	9±2	-50 *	9±3	-50 *
pH-Stat	19±4	5±4	-74 *	17±9	-11	7±4	-63 *	6±3	-68 *	7±3	-63 *
pH-Stat Modified	15±2	9±3	-40 *	19±2	27 *	11±3	-27 *	12±6	-20	10±4	-33 *
mRAP											
LRS	6±2	2±1	-67 *	6±2	0	3±1	-50 *	4±2	-33	2±1	-67 *
pH-Stat	5±2	2±1	-60 *	5±2	0	3±1	-40 *	2±1	-60 *	2±1	-60 *
pH-Stat Modified	4±1	2±1	-50 *	5±1	25 *	3±1	-25 *	2±1	-50 *	2±1	-50
LVSP											
LRS	140±25	115±45	-18	134±16	-4	150±62	7	142±62	1	122±30	-13
pH-Stat	154±15	103±43	-33	141±27	-8	128±49	-17	114±43	-26	105±54	-32
pH-Stat Modified	149±27	92±22	-38 *	141±13	-5	118±19	-21 *	98±21	-34 *	94±26	-37 *

Table 3.1: Mean ± SD hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05

VARIABLE	TIME OF RECORDING																
	BASELINE	HEMORRHAGE			END TREATMENT			TX+60			TX+120			TX+180		
	VALUE	VALUE	CHANGE (%)#		VALUE	CHANGE		VALUE	CHANGE		VALUE	CHANGE		VALUE	CHANGE	
LVEDP																
LRS	14 ± 2	4 ± 1	-71	*	14 ± 1	0		9 ± 3	-36	*	7 ± 3	-50	*	6 ± 1	-57	*
pH-stat	11 ± 4	7 ± 4	-36	*	15 ± 7	36		8 ± 2	-27		8 ± 1	-27		7 ± 2	-36	
pH-stat modified	10 ± 3	6 ± 4	-40		12 ± 3	20		7 ± 2	-30	*	7 ± 2	-30	*	6 ± 2	-40	*
LV+dP/dT																
LRS	2415 ± 466	2187 ± 739	-9		4351 ± 1349	80	*	3900 ± 2854	61		3823 ± 3361	58		2443 ± 1230	1	
pH-stat	2727 ± 651	2912 ± 916	7		5534 ± 1617	103	*	3324 ± 1396	22		2198 ± 718	-19		1990 ± 814	-27	
pH-stat modified	2527 ± 850	2508 ± 589	-1		5052 ± 1229	100	*	3075 ± 562	22		2136 ± 404	-15		1867 ± 471	-26	*
LV-dP/dT																
LRS	3559 ± 713	1778 ± 605	-50	*	2352 ± 552	-34	*x	2125 ± 1,230	-40	*	2297 ± 1742	-35		1532 ± 319	-57	
pH-stat	3895 ± 583	1833 ± 760	-53	*	3011 ± 556	-23	*	1890 ± 886	-51	*	1328 ± 545	-66	*	985 ± 472	-75	*
pH-stat modified	4047 ± 708	1510 ± 215	-63	*	3129 ± 541	-23	*	2339 ± 651	-42	*	1700 ± 413	-58	*	1505 ± 368	-63	*
TAU																
LRS	37 ± 7	35 ± 12	-5		35 ± 15	-5		73 ± 50	97	x	66 ± 47	78		53 ± 28	43	
pH-stat	30 ± 5	33 ± 8	10		37 ± 13	23		53 ± 19	77	*	75 ± 25	150	*	91 ± 38	203	*^
pH-stat modified	29 ± 5	31 ± 8	7		28 ± 7	-3		32 ± 9	10		37 ± 9	28		42 ± 14	45	*
FABF																
LRS	60 ± 18	10 ± 7	-83	*	88 ± 33	47	*	18 ± 9	-70	*x	16 ± 14	-73	*x	15 ± 5	-75	x
pH-stat	55 ± 16	13 ± 8	-76	*	81 ± 34	47		26 ± 13	-53	*^	15 ± 9	-73	*^	15 ± 6	-73	*^
pH-stat modified	58 ± 21	14 ± 2	-76	*	112 ± 42	93	*	50 ± 19	-14		35 ± 15	-40	*	30 ± 10	-48	*
CMABF																
LRS	179 ± 37	57 ± 38	-68	*	265 ± 109	48	x	127 ± 79	-29		87 ± 55	-51	*	90 ± 0	-50	*
pH-stat	145 ± 35	34 ± 31	-77	*	220 ± 77	52	^	87 ± 53	-40	^	56 ± 34	-61	*	52 ± 29	-64	*^
pH-stat modified	172 ± 55	72 ± 20	-58	*	503 ± 119	192	*	196 ± 73	14		155 ± 64	-10		128 ± 54	-26	*

Table 3.2: Mean ± SD hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	BASELINE VALUE	HEMORRHAGE		END TREATMENT		TX+120		TX+180	
		NOREPINEPHRINE	CHANGE (%)#	NOREPINEPHRINE	CHANGE	NOREPINEPHRINE	CHANGE	NOREPINEPHRINE	CHANGE
HR									
LRS	126 ± 19	168 ± 27	33*	134 ± 16	6	115 ± 40	-8	138 ± 28	10
pH-stat	133 ± 33	169 ± 31	27*	143 ± 22	8	112 ± 24	-16	105 ± 27	-21
pH-stat modified	143 ± 21	185 ± 33	29*	153 ± 24	7	126 ± 27	-12	116 ± 26	-19*
SAP									
LRS	143 ± 19	81 ± 21	-43*	167 ± 40	17	133 ± 58	-7	147 ± 48	3
pH-stat	153 ± 13	79 ± 13	-48*	160 ± 20	5	107 ± 31	-30*	114 ± 21	-25
pH-stat modified	149 ± 31	83 ± 6	-44*	156 ± 17	5	121 ± 35	-19	125 ± 42	-16
DAP									
LRS	112 ± 13	59 ± 11	-43*	110 ± 34	17	99 ± 50	-7	116 ± 49	3
pH-stat	122 ± 12	57 ± 9	-53*	101 ± 18	-17*	73 ± 32	-40*	84 ± 24	-41
pH-stat modified	120 ± 25	60 ± 9	-50*	100 ± 15	-17*	90 ± 25	-25*	93 ± 30	-23*
MAP									
LRS	127 ± 15	67 ± 14	-47	136 ± 37	7	114 ± 55	-10	130 ± 50	2
pH-stat	136 ± 12	64 ± 9	-53*	128 ± 19	-6	87 ± 33	-36*	98 ± 24	-28
pH-stat modified	133 ± 28	68 ± 7	-49*	126 ± 17	-5	104 ± 30	-22	108 ± 36	-18
mPAP									
LRS	18 ± 1	11 ± 4	-39*	20 ± 6	82	12 ± 6	-33	14 ± 9	-22
pH-stat	19 ± 4	6 ± 5	-68*	14 ± 5	-26*	6 ± 3	-63*	8 ± 3	-58*
pH-stat modified	15 ± 2	10 ± 4	-33*	19 ± 3	27*	12 ± 4	-20	13 ± 4	-13
mRAP									
LRS	6 ± 2	2 ± 1	-67*	5 ± 2	-17	4 ± 1	-33	3 ± 1	-50
pH-stat	5 ± 2	2 ± 1	-60*	5 ± 2	NC	2 ± 1	-60*	2 ± 1	-60*
pH-stat modified	4 ± 1	3 ± 2	-25	5 ± 1	25*	3 ± 1	-25	2 ± 2	-50*
LVSP									
LRS	140 ± 25	189 ± 125	35*	186 ± 43	33*	200 ± 69	43	210 ± 17	50
pH-stat	154 ± 15	174 ± 94	13	221 ± 75	44*	178 ± 85	16	186 ± 75	21
pH-stat modified	149 ± 27	127 ± 43	-15	167 ± 22	12*	138 ± 32	-7	140 ± 38	-6

Table 3.3: Effect of an infusion of norepinephrine on hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline: *P< 0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^ 2 and 3, at P< 0.05.

VARIABLE	BASELINE VALUE	HEMORRHAGE		END TREATMENT		TX+120		TX+180	
		NOREPINEPHRINE	CHANGE (%)#	NOREPINEPHRINE	CHANGE	NOREPINEPHRINE	CHANGE	NOREPINEPHRINE	CHANGE
LVEDP									
LRS	14 ± 2	5 ± 2	-64*	14 ± 4	NC	10 ± 5	-29	11 ± 8	-21
pH-Stat	11 ± 4	7 ± 3	-36*	14 ± 4	27*	8 ± 1	-27	9 ± 2	-18
pH-Stat Modified	10 ± 3	6 ± 2	-40*	14 ± 4	40*	8 ± 3	-20	8 ± 3	-20*
LV+dP/dT									
LRS	2415 ± 466	4094 ± 3772	70	7193 ± 1931	198*	6485 ± 3750	169*	5559 ± 1635	130
pH-Stat	2727 ± 656	3819 ± 1786	40	8042 ± 1416	195*	4010 ± 1238	47*	4578 ± 480	68*
pH-Stat Modified	2527 ± 830	4063 ± 1672	61	7018 ± 1192	178*	4020 ± 972	59*	4002 ± 1157	58*
LV-dP/dT									
LRS	3559 ± 713	2897 ± 2272	-19	3531 ± 851	-1	3309 ± 1821	-7	2834 ± 383	-20
pH-stat	3895 ± 583	2586 ± 1293	-34	3769 ± 536	-3	2051 ± 774	-47*	2284 ± 391	-41*
pH-stat modified	4047 ± 708	2453 ± 728	-39*	4279 ± 1097	6	2912 ± 820	-28*	2975 ± 1092	-26*
TAU									
LRS	37 ± 7	32 ± 15	-14	36 ± 13	-3	66 ± 52	78	52 ± 33	41
pH-stat	30 ± 5	30 ± 5	NC	35 ± 16	17	54 ± 18	80*	56 ± 22	87
pH-stat modified	29 ± 5	46 ± 40	59	25 ± 5	-14	34 ± 8	17	38 ± 10	31
FABF									
LRS	60 ± 18	12 ± 7	-80*	70 ± 31	17	14 ± 11	-77*	11 ± 2	-82x
pH-stat	55 ± 16	10 ± 7	-82*	64 ± 32	16	14 ± 10	-75*	9 ± 2	-84*^
pH-stat modified	58 ± 21	19 ± 14	-67*	82 ± 25	41*	22 ± 8	-62*	21 ± 7	-64*
CMABF									
LRS	179 ± 37	51 ± 36	-72*x	270 ± 207	51	67 ± 39	-63*x	86 ± 23	-52*
pH-stat	145 ± 35	43 ± 38	-70*^	179 ± 56	23	56 ± 34	-67*^	57 ± 21	-61*^
pH-stat modified	172 ± 55	111 ± 47	-35*	329 ± 103	91*	136 ± 49	-21	120 ± 43	-30*

Table 3.4: Effect of an infusion of norepinephrine on hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. *P< 0.05: Significant differences from baseline. +Significant differences between group 1 and 2; x: 1 and 3; ^2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																	
	BASELINE VALUE			HEMORRHAGE				END TREATMENT				TX+120				TX+180		
				OCCLUSION			CHANGE (%)#	OCCLUSION			CHANGE	OCCLUSION			CHANGE	OCCLUSION			CHANGE
HR																		
LRS	126	±	19	165	±	31	31	140	±	27	11	118	±	37	-6	127	±	32	1
pH-stat	133	±	33	168	±	21	26*	147	±	18	11	110	±	26	-17	107	±	24	-20
pH-stat modified	143	±	21	183	±	32	28*	156	±	21	9	131	±	26	-8	118	±	27	-17
SAP																		
LRS	143	±	19	68	±	18	-52*	115	±	20	-20*	88	±	31	-38*	83	±	7	-42*
pH-stat	153	±	13	68	±	12	-56*	119	±	19	-22*	75	±	25	-51*	81	±	23	-47*
pH-stat modified	149	±	31	64	±	6	-57*	118	±	19	-21*	80	±	20	-46*	73	±	19	-51*
DAP																		
LRS	112	±	13	49	±	11	-52*	77	±	23	-20*	65	±	28	-38*	61	±	2	-42*
pH-stat	122	±	12	49	±	12	-60*	74	±	19	-39*	48	±	23	-61*	60	±	26	-51*
pH-stat modified	120	±	25	45	±	5	-63*	74	±	17	-38*	55	±	13	-54*	50	±	12	-58*
MAP																		
LRS	127	±	15	55	±	13	-57*	95	±	23	-25	75	±	30	-41*	70	±	2	-45*
pH-stat	136	±	12	55	±	9	-60*	94	±	20	-31*	59	±	25	-57*	69	±	26	-49*
pH-stat modified	133	±	28	52	±	4	-61*	94	±	20	-29*	66	±	16	-50*	60	±	15	-55*
mPAP																		
LRS	18	±	1	9	±	2	-50*	12	±	4	-33*	9	±	2	-50*	9	±	2	-50*
pH-stat	19	±	4	6	±	4	-68*	10	±	4	-47*	7	±	3	-63*	9	±	3	-53*
pH-stat modified	15	±	2	8	±	3	-47*	14	±	4	-7	10	±	3	-33*	10	±	3	-33*
mRAP																		
LRS	6	±	2	2	±	1	-67*	4	±	2	-33*	4	±	1	-33*	2	±	1	-67
pH-stat	5	±	2	2	±	1	-60*	3	±	1	-40*	2	±	1	-60*	2	±	1	-60*
pH-stat modified	4	±	1	3	±	1	-25	4	±	1	NC	3	±	1	-25	2	±	1	-50*
LVSP																		
LRS	140	±	25	107	±	57	-24	153	±	55	9	136	±	70	-3	127	±	43	-9
pH-stat	154	±	15	130	±	63	-16	182	±	91	18	116	±	48	-25	121	±	61	-21
pH-stat modified	149	±	27	92	±	30	-38*	131	±	19	-12*	100	±	23	-33*	94	±	25	-37*

Table 3.5: Effect of occlusion on hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. + Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05. NC: no change.

VARIABLE	TIME OF RECORDING																	
	BASELINE VALUE			HEMORRHAGE				END TREATMENT				TX+120				TX+180		
				OCCLUSION			CHANGE	OCCLUSION			CHANGE	OCCLUSION			CHANGE	OCCLUSION			CHANGE
LVEDP																	±		
LRS	14	±	2	5	±	3	-64*	10	±	1	-29*	8	±	2	-43*	6	±	2	-57
pH-Stat	11	±	4	6	±	3	-45*	11	±	3	NC	7	±	1	-36	7	±	1	-36
pH-Stat Modified	10	±	3	6	±	4	-40	10	±	1	NC	7	±	1	-30*	8	±	4	-20
LV+dP/dT																			
LRS	2415	±	466	1936	±	1090	-20	4276	±	1925	77*	3446	±	3505	43	2518	±	1469	4
pH-Stat	2727	±	651	2603	±	1063	-5	5408	±	2230	98*	2168	±	856	-20	2305	±	761	-15
pH-Stat Modified	2527	±	850	2367	±	625	-6	4377	±	939	73*	2215	±	386	-12	1949	±	373	-23*
LV-dP/dT																			
LRS	3559	±	713	1527	±	899	-57*	2409	±	997	-32*	2039	±	1945	-43	1374	±	592	-61
pH-Stat	3895	±	583	1786	±	909	-54*	2648	±	820	-32*	1149	±	590	-71*	1103	±	432	-72*
pH-Stat Modified	4047	±	708	1548	±	488	-62*	2760	±	630	-32*	1711	±	475	-58*	1465	±	374	-64*
TAU																			
LRS	37	±	7	42	±	20	14	54	±	20	46*x	74	±	57	100	55	±	29	49
pH-Stat	30	±	5	36	±	7	20	43	±	14	43*	93	±	41	210*^	85	±	36	183*^
pH-Stat Modified	29	±	5	43	±	31	48	28	±	6	48	38	±	9	-31	51	±	19	76*
FABF																			
LRS	60	±	18	31	±	22	-48*	72	±	23	20 x	37	±	33	-38 x	47	±	27	-22
pH-Stat	55	±	16	31	±	28	-44	89	±	35	62^	41	±	25	-25^	34	±	12	-38^
pH-Stat Modified	58	±	21	59	±	24	2	175	±	56	201*	93	±	35	60*	80	±	36	38*
CMBF																			
LRS	179	±	37	53	±	51	-70*	352	±	226	97+	94	±	60	-47*	108	±	42	-40
pH-Stat	145	±	35	36	±	37	-75*^	157	±	56	8	53	±	34	-63*^	64	±	21	-56*
pH-Stat Modified	172	±	55	93	±	37	-46*	315	±	94	83*	140	±	60	-19	121	±	53	-30*

Table 3.6: Effect of occlusion on hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline: *P< 0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05. NC: no change.

VARIABLE	TIME OF RECORDING												
	BASELINE VALUE	HEMORRHAGE		END TREATMENT		TX+60		TX+120		TX+180			
		VALUE	CHANGE (%)#		VALUE	CHANGE		VALUE	CHANGE		VALUE	CHANGE	
CO													
LRS	163 ± 28	36 ± 5	-78	*x	272 ± 50	67	*	87 ± 32	-47	*	69 ± 29	-58	*	53 ± 13	-67	ND
pH-Stat	141 ± 21	40 ± 7	-72	*	246 ± 52	74	*	76 ± 19	-46	*^	61 ± 19	-57	*	46 ± 12	-67	*
pH-Stat Modified	132 ± 27	47 ± 7	-64	*	283 ± 73	114	*	141 ± 63	7		77 ± 20	-42	*	71 ± 26	-46	*
RPP													
LRS	15807 ± 1703	8615 ± 2059	-45	*	15295 ± 3875	-3		12191 ± 5049	-23		8675 ± 4999	-45	*	10272 ± 1390	-35	
pH-Stat	16286 ± 413	8192 ± 1932	-50	*	16509 ± 3632	1		10625 ± 5045	-35		7299 ± 2693	-55	*	5949 ± 2860	-63	*
pH-Stat Modified	18809 ± 3279	9780 ± 1417	-48	*	16756 ± 3932	-11	*	12034 ± 3284	-36	*	8916 ± 2132	-53	*	7549 ± 2681	-60	*
SVR													
LRS	1028 ± 249	1945 ± 397	89	*x	490 ± 99	-52	*	1422 ± 323	38	*x	1607 ± 573	56	*	2038 ± 371	98	*x
pH-Stat	1224 ± 240	1625 ± 270	33	*	561 ± 131	-54	*	1292 ± 432	6	^	1305 ± 290	7		1504 ± 294	23	
pH-Stat Modified	1612 ± 711	1369 ± 258	-15		494 ± 102	-69	*	843 ± 250	-48	*	1153 ± 207	-28		1162 ± 309	-28	

Table 3.7: Mean ± SD derived hemodynamic variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05. ND: not determined.

	TIME OF RECORDING																	
VARIABLE	BASELINE VALUE			HEMORRHAGE				END TREATMENT				TX+120				TX+180		
				NOREPINEPHRINE			CHANGE (%)#	NOREPINEPHRINE			CHANGE	NOREPINEPHRINE			CHANGE	NOREPINEPHRINE			CHANGE
RPP																		
LRS	15807	±	1763	11365	±	3520	-28*	17112	±	4809	8	13038	±	8347	-18	18064	±	8488	14
pH-stat	16286	±	4413	10805	±	2595	-34*	18166	±	2829	12	9607	±	3790	-41	10111	±	2735	-38
pH-stat modified	18809	±	3279	12576	±	2561	-33*	19258	±	3479	2	12658	±	2818	-33*	12070	±	3934	-36*
RR																		
LRS	11	±	1	12	±	2	9	11	±	2	NC	10	±	2	-9	10	±	2	-9
pH-stat	10	±	2	10	±	2	NC	10	±	2	NC	9	±	2	-10	10	±	2	NC
pH-stat modified	10	±	1	10	±	2	NC	10	±	1	NC	10	±	2	NC	10	±	2	NC
$ETCO_2$																		
LRS	41	±	3	35	±	5	-15*	35	±	4	-15*	28	±	10	-32*	29	±	1	-29*
pH-stat	40	±	3	35	±	5	-13*	41	±	2	3	41	±	6	3	43	±	2	8
pH-stat modified	41	±	2	40	±	4	-2	66	±	5	61*	67	±	3	63*	66	±	4	61*

Table 3.8: Effect of an infusion of norepinephrine on rate pressure product, respiratory rate and end tidal carbon dioxide in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05. NC: no change.

VARIABLE	TIME OF RECORDING														
	BASELINE VALUE	HEMORRHAGE			END TREATMENT			TX+120			TX+180		
		OCCLUSION		CHANGE (%)#	OCCLUSION		CHANGE	OCCLUSION		CHANGE	OCCLUSION		CHANGE
RPP													
LRS	15837 ± 1763	9531 ± 3335		-40*	13433 ± 4576		-15	9073 ± 4617		-43*	8996 ± 2475		-43
pH-stat	16286 ± 4413	9191 ± 2092		-44*	13816 ± 3637		-15	6749 ± 3501		-59*	7437 ± 3437		-54*
pH-stat modified	18839 ± 3279	9490 ± 1796		-50*	14495 ± 2958		-23*	8476 ± 2162		-55*	7123 ± 2532		-62*
RR													
LRS	11 ± 1	12 ± 2		9	12 ± 2		9	10 ± 2		-9	10 ± 0		-9
pH-stat	10 ± 2	10 ± 2		NC	10 ± 3		NC	9 ± 2		-10	10 ± 2		NC
pH-stat modified	10 ± 1	10 ± 2		NC	10 ± 1		NC	10 ± 2		NC	10 ± 2		NC
$ETCO_2$													
LRS	41 ± 3	34 ± 5		-17*	30 ± 5		-27*	27 ± 10		-34*	28 ± 1		-32*
pH-stat	40 ± 3	32 ± 6		-20*	38 ± 4		-5	38 ± 7		-5	42 ± 4		5
pH-stat modified	41 ± 2	36 ± 4		-12*	63 ± 4		54*	64 ± 2		56*	63 ± 3		59*

Table 3.9: Effect of occlusion on rate pressure product, respiratory rate and end tidal carbon dioxide. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. + Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05. NC: no change.

VARIABLE	TIME OF RECORDING																							
	BASELINE VALUE			HEMORRHAGE						END TREATMENT						TX+120						TX+180				
				VALUE			CHANGE (%)#			VALUE			CHANGE			VALUE			CHANGE			VALUE			CHANGE		
RR																										
LRS	11	±	1	12	±	2	9			12	±	2	9			9	±	2	-18			11	±	1	0		
pH-stat	10	±	2	10	±	2	0			10	±	1	0			9	±	2	-10			10	±	3	0		
pH-stat modified	10	±	1	10	±	1	0			10	±	2	0			10	±	2	0			10	±	2	0		
$ETCO_2$																										
LRS	41	±	3	33	±	5	-20		*	33	±	3	-20		*	26	±	10	-37		*	26	±	2	-37		*
pH-stat	40	±	3	34	±	4	-15		*	41	±	4	3			39	±	6	-3			40	±	3	0		
pH-stat modified	41	±	2	36	±	5	-12		*	65	±	4	59		*	63	±	3	54		*	65	±	3	59		*
BT																										
LRS	37.6	±	0.4	36.8	±	0.7	-2.1		*	32.7	±	0.7	-13.0		*	32.1	±	1.4	-14.6		*	32.0	±	2.0	-14.9		*
pH-stat	37.6	±	0.2	36.9	±	0.6	-1.9		*	32.6	±	0.6	-13.3		*	31.9	±	0.9	-15.2		*	31.3	±	1.1	-16.8		*
pH-stat modified	38.0	±	0.4	37.1	±	0.7	-2.4		*	33.7	±	1.1	-11.3		*	32.8	±	1.6	-13.7		*	32.2	±	1.7	-15.3		*
ET																										
LRS	37.3	±	0.5	36.4	±	0.8	-2.4		*	32.7	±	0.7	-12.3		*x	31.9	±	1.3	-14.5		*	31.8	±	2.1	-14.7		*
pH-stat	37.6	±	0.3	36.9	±	0.8	-1.9		*	32.8	±	0.6	-12.8		*	31.8	±	1.3	-15.4		*	31.3	±	1.4	-16.8		*
pH-stat modified	38.1	±	0.6	37.2	±	0.7	-2.4		*	33.9	±	1.2	-11.0		*	32.9	±	1.5	-13.6		*	32.3	±	1.6	-15.2		*
AT																										
LRS	37.8	±	0.5	36.0	±	2.6	-4.8			32.5	±	1.0	-14.0		*	32.2	±	1.2	-14.8		*	32.0	±	2.1	-15.3		*
pH-stat	37.7	±	0.5	35.4	±	3.3	-6.1			31.5	±	3.7	-16.4		*	31.8	±	1.1	-15.6		*	31.3	±	1.2	-17.0		*
pH-stat modified	38.2	±	0.8	36.7	±	1.2	-3.9		*	33.8	±	1.2	-11.5		*	32.9	±	1.7	-13.9		*	32.3	±	1.9	-15.4		*

Table 3. 10: Mean ± SD respiratory variables and temperatures in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values.Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																			
	BASELINE VALUE			HEMORRHAGE				END TREATMENT					TX+120				TX+180			
				VALUE			CHANGE (%) #		VALUE			CHANGE	VALUE			CHANGE	VALUE			CHANGE
DO_2																				
LRS	31	±	5	5	±	1	-84	*	25	±	6	-19	7	±	4	-77	*	6	±	1	-81	*
pH-stat	25	±	4	5	±	1	-80	*	16	±	3	-36	*	5	±	2	-80	*	4	±	2	-84	*
pH-stat modified	21	±	7	7	±	2	-67	*	24	±	8	14	8	±	3	-62	*	8	±	3	-62	*
VO_2																				
LRS	6	±	3	4	±	1	-33		5	±	3	-17	4	±	2	-33		3	±	0	-50	
pH-stat	5	±	2	4	±	1	-20		4	±	2	-20	4	±	1	-20		3	±	1	-40	
pH-stat modified	6	±	2	6	±	2	0		6	±	2	0	5	±	1	-17		5	±	2	-17	
O_2ER																				
LRS	19	±	8	83	±	8	337	*	20	±	11	5	61	±	16	221	*	50	±	5	163	
pH-stat	16	±	5	82	±	6	413	*	20	±	13	25	66	±	21	313	*	66	±	19	313	*
pH-stat modified	29	±	14	82	±	9	183	*	27	±	12	-7	57	±	14	97	*	62	±	18	114	*
LACTATE																				
LRS	1.3	±	0.6	6.2	±	3.1	377	*	8.1	±	3.2	523	*	4.1	±	3.5	215	*	2.2	±	0.6	69	
pH-stat	1.4	±	0.3	8.6	±	2.6	514	*	8.4	±	1.4	500	*	3.6	±	1.1	157	*	4.3	±	3.1	207	*
pH-stat modified	1.5	±	0.5	7.1	±	2.6	373	*	9.6	±	2.2	540	*	2.4	±	1.0	60		1.1	±	0.6	-27	*

Table 3.11: Mean ± SD derived respiratory variables in dogs under hemorrhagic shock . #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^ 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																			
	BASELINE VALUE			HEMORRHAGE					END TREATMENT					TX+120				TX+180			
				VALUE			CHANGE (%)#		VALUE			CHANGE		VALUE			CHANGE	VALUE			CHANGE	
pHa																						
LRS	7.35	±	0.03	7.14	±	0.18	-3	*	7.20	±	0.16	-2	+	7.39	±	0.10	1	x	7.45	±	0.03	1	*
pH-Stat	7.36	±	0.03	7.16	±	0.04	-3	*	7.37	±	0.06	0	^	7.38	±	0.03	0	^	7.39	±	0.03	0	
pH-Stat Modified	7.36	±	0.03	7.16	±	0.06	-3	*	7.26	±	0.01	-1	*	7.29	±	0.03	-1	*	7.28	±	0.02	-1	*
$aPCO_2$																							
LRS	40	±	2	38	±	4	-5		36	±	4	-10	x	29	±	8	-28	*	28	±	2	-30	*
pH-stat	41	±	4	39	±	3	-5		40	±	4	-2	^	40	±	3	-2		40	±	3	-2	
pH-stat modified	38	±	5	41	±	5	8		61	±	4	61	*	60	±	3	58	*	61	±	3	61	*
aPO_2																							
LRS	87	±	6	92	±	9	6		95	±	15	9		98	±	20	13		98	±	24	13	
pH-stat	89	±	4	98	±	6	10	*^	103	±	11	16	*	98	±	14	10		110	±	13	24	*
pH-stat modified	93	±	16	87	±	8	-6		88	±	14	-5		94	±	13	1		101	±	19	9	
$aHCO_3$																							
LRS	22	±	1	13	±	4	-41	*	16	±	5	-27	*+x	18	±	7	-18	+x	21	±	1	-5	+x
pH-Stat	22	±	2	13	±	2	-41	*	24	±	3	9		25	±	3	14		26	±	2	18	*
pH-stat modified	21	±	3	14	±	1	-33	*	28	±	1	33	*	30	±	2	43	*	30	±	1	43	*
aBE																							
LRS	-3	±	1.3	-12.4	±	4.7	328	*	-11	±	7	272	*x+	-4.9	±	5.4	69	*x	-3.7	±	0.7	28	*
pH-stat	-2	±	1.5	-13.8	±	2.5	557	*	-2	±	4	-24		-0.4	±	2.8	-81		0.4	±	1.8	-119	
pH-stat modified	-3	±	2.9	-13.1	±	1.9	285	*	1	±	1	-124	*	2.6	±	2.0	-176	*	2.7	±	0.9	-179	*

Table 3.12: Mean ± SD arterial blood variables at patient temperature in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																							
	BASELINE VALUE			HEMORRHAGE					END TREATMENT					TX+120					TX+180					
				VALUE			CHANGE (%)#		VALUE			CHANGE		VALUE			CHANGE		VALUE			CHANGE		
pHv																								
LRS	7.33	±	0.03	7.03	±	0.20	-4.09	*	7.21	±	0.18	-1.64		7.25	±	0.19	-1.09		7.38	±	0.05	0.68		
pH-Stat	7.35	±	0.03	7.05	±	0.07	-4.08	*	7.33	±	0.08	-0.27		7.30	±	0.06	-0.68		7.31	±	0.04	-0.54		
pH-Stat Modified	7.33	±	0.04	7.06	±	0.07	-3.68	*	7.22	±	0.02	-1.50	*	7.23	±	0.02	-1.36	*	7.22	±	0.03	-1.50	*	
$vPCO_2$																								
LRS	44	±	2	64	±	13	45	*	38	±	5	-14	*x	41	±	6	-7	x	37	±	5	-16		
pH-Stat	45	±	3	64	±	5	42	*	44	±	7	-2	^	51	±	5	13	^	52	±	4	16	*	
pH-Stat Modified	48	±	5	66	±	9	38	*	66	±	7	38	*	72	±	6	50	*	74	±	8	54	*	
vPO_2																								
LRS	52	±	7	24	±	8	-54	*	49	±	7	-6		23	±	7	-56	*	23	±	4	-56	*	
pH-Stat	54	±	6	25	±	2	-54	*	47	±	13	-13		21	±	7	-61	*	20	±	6	-63	*	
pH-Stat Modified	47	±	7	25	±	5	-47	*	44	±	4	-6		26	±	4	-45	*	24	±	4	-49	*	
$vHCO_3^-$																								
LRS	23	±	1	17	±	4	-26	*	17	±	5	-26	*	20	±	6	-13	+x	23	±	1	0		
pH-Stat	24	±	1	17	±	3	-29	*	24	±	2	0		26	±	2	8		27	±	2	13	*	
pH-Stat Modified	24	±	1	18	±	2	-25	*	28	±	1	17	*	31	±	2	29	*	32	±	1	33	*	
vBE																								
LRS	-2	±	1.2	-10.6	±	5	430	*	-10.6	±	7	430	*+x	-6.9	±	8.5	245	x	-2.8	±	1.2	40		
pH-Stat	-1.1	±	1.0	-12.1	±	3	1000	*	-2.1	±	2.2	91		-0.3	±	2.9	-73		0.8	±	2.1	-173		
pH-Stat Modified	-0.8	±	0.7	-11.1	±	2.4	1288	*	0.2	±	0.8	-125	*	3.2	±	1.8	-500		3.2	±	1.2	-500		

Table 3.13: Mean ± SD venous blood variables at patient temperature in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Signifficant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																						
	BASELINE VALUE			HEMORRHAGE					END TREATMENT					TX+120					TX+180				
				VALUE			CHANGE (%) #		VALUE			CHANGE		VALUE			CHANGE		VALUE			CHANGE	
Na^+																							
LRS	147	±	2	148	±	4	1		144	±	4	-2	+x	145	±	5	-1	+x	147	±	8	0	
pH-stat	149	±	1	145	±	3	-3	*	152	±	3	2	*	152	±	5	2		151	±	6	1	
pH-stat modified	148	±	3	145	±	4	-2		153	±	5	3	*	153	±	4	3	*	153	±	3	3	*
K^+																							
LRS	3.7	±	0.5	4.8	±	1.0	29.7		3.7	±	0.8	0.0		3.9	±	0.9	5.4		3.5	±	0.1	-5.4	
pH-stat	3.6	±	0.4	4.5	±	0.5	25.0	*	3.1	±	0.3	-13.9	*	3.3	±	0.3	-8.3	*	3.5	±	0.5	-2.8	
pH-stat modified	3.7	±	0.3	4.1	±	0.6	10.8		3.2	±	0.4	-13.5	*	3.7	±	0.3	0.0		3.8	±	0.4	2.7	
Ca^{2+}																							
LRS	11	±	0	11	±	0	0	+x	9	±	1	-18	*	10	±	1	-9		10	±	0	-9	*+x
pH-stat	11	±	0	10	±	1	-9	*	8	±	0	-27	*	9	±	0	-18	*	9	±	0	-18	*
pH-stat modified	11	±	0	10	±	1	-9	*	9	±	0	-18	*	9	±	1	-18	*	9	±	0	-18	*

Table 3.14: Mean ± SD serum electrolytes concentration in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING																							
	BASELINE VALUE			HEMORRHAGE						END TREATMENT						TX+120						TX+180				
				VALUE			CHANGE (%)#			VALUE			CHANGE			VALUE			CHANGE			VALUE			CHANGE	
PCV																										
LRS	43	±	6	33	±	7	-23	*		19	±	3	-56	*		25	±	4	-42	*		28	±	4	-35	*
pH-stat	40	±	5	30	±	7	-25	*		15	±	4	-63	*		23	±	5	-43	*		24	±	6	-40	*
pH-stat modified	40	±	5	32	±	7	-20	*		18	±	3	-55	*		24	±	3	-40	*		25	±	5	-38	*
TP																										
LRS	6.5	±	1.8	4.80	±	0.7	-26.2			2.6	±	0.1	-60.0	*		3.0	±	0.4	-53.8	*		3.2	±	0.3	-50.8	*
pH-stat	5.6	±	0.4	4.20	±	0.6	-25.0	*		2.5	±	0.0	-55.4	*		2.8	±	0.2	-50.0	*^		2.9	±	0.2	-48.2	*^
pH-stat modified	6.4	±	0.7	5.00	±	0.7	-21.9	*		2.5	±	0.1	-60.9	*		3.3	±	0.3	-48.4	*		3.6	±	0.3	-43.8	*
COP																										
LRS	19	±	3	14	±	3	-26	*		6	±	1	-68	*		9	±	2	-53	*		11	±	1	-42	*
pH-stat	20	±	2	13	±	2	-35	*		6	±	1	-70	*		9	±	1	-55	*^		9	±	1	-55	*^
pH-stat modified	22	±	3	15	±	3	-32	*		7	±	1	-68	*		11	±	1	-50	*		11	±	1	-50	*

Table 3.15: Mean ± SD chemical variables in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

VARIABLE	TIME OF RECORDING															
	BASELINE VALUE	HEMORRHAGE			END TREATMENT			TX+120			TX+180		
		NOREPINEPHRINE		CHANGE (%) #	NOREPINEPHRINE		CHANGE	NOREPINEPHRINE		CHANGE	NOREPINEPHRINE		CHANGE
FABF													
LRS	60 ± 18	12 ± 7		-80*	70 ± 31		17	14 ± 11		-77*	11 ± 2		-82x
pH-stat	55 ± 16	10 ± 7		-82*	64 ± 32		16	14 ± 10		-75*	9 ± 2		-84*^
pH-stat modified	58 ± 21	19 ± 14		-67*	82 ± 25		41*	22 ± 8		-62*	21 ± 7		-64*
CMABF													
LRS	179 ± 37	51 ± 36		-72*x	270 ± 207		51	67 ± 39		-63*x	86 ± 23		-52*
pH-stat	145 ± 35	43 ± 38		-70*^	179 ± 56		23	56 ± 34		-67*^	57 ± 21		-61*^
pH-stat modified	172 ± 55	111 ± 47		-35*	329 ± 103		91*	136 ± 49		-21	120 ± 43		-30*

Table 3.16: Effect of an infusion of norepinephrine on blood flow to different regions in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: *P< 0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

	TIME OF RECORDING											
VARIABLE	BASELINE VALUE	HEMORRHAGE		END TREATMENT		TX+120		TX+180	
		OCCLUSION	CHANGE (%)#	OCCLUSION	CHANGE	OCCLUSION	CHANGE	OCCLUSION	CHANGE
FABF									
LRS	60 ± 18	31 ± 22	-48*	72 ± 23	20x	37 ± 33	-38x	47 ± 27	-22
pH-stat	55 ± 16	31 ± 28	-44	89 ± 35	62^	41 ± 25	-25^	34 ± 12	-38^
pH-stat modified	58 ± 21	59 ± 24	2	175 ± 56	201*	93 ± 35	60*	80 ± 36	38*
CMABF									
LRS	179 ± 37	53 ± 51	-70*	352 ± 226	97+				
pH-stat	145 ± 35	36 ± 37	-75*^	157 ± 56	8	53 ± 34	-63*^	64 ± 21	-56*
pH-stat modified	172 ± 55	93 ± 37	-46*	315 ± 94	83*	140 ± 60	-19	121 ± 53	-30*

Table 3.17: Effect of occlusion on blood flow to different regions in dogs under hemorrhagic shock. #: Change (%) is given in reference to baseline values. Significant differences from baseline values: * P<0.05. +Significant differences between group 1 and 2; x: 1 and 3; ^: 2 and 3, at P< 0.05.

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CHAPTER 4

4. DISCUSSION

Despite significant progress made in the application of novel therapies and in the development of new treatments, patients still die from hemorrhagic shock.

Two therapeutic approaches used to resolve acid-base disturbances that occur in hypoperfusion states have been developed in conjunction with cardio-pulmonary bypass procedures in human patients: the alpha-stat approach and the pH-stat approach. Unfortunately, these procedures have never been applied to clinical conditions of common occurrence such as hemorrhagic shock.

The purpose of this study was to test if the pH-stat modified treatment is more effective than the pH-stat therapy in treating acid-base derangements and vascular hyporeactivity in hemorrhagic shock. The dog was used as an experimental and clinically-applicable model of hemorrhagic hypovolemic shock. The study compared the effects of three different treatments (the LRS, the pH-stat and the pH-stat modified therapies) on cardiovascular function (hemodynamics, ventricular function, and vascular reactivity), certain parameters of respiratory function, and acid-base derangements.

A total of 23 experiments were conducted, with 7 or 8 animals in each of the 3 groups. Recordings of all physiological variables satisfactory for analysis were obtained in all studies.

Heart Rate

As anticipated from the reduction in blood volume, HR accelerated as high pressure baroreceptors were activated and the baroreceptor reflex was initiated [11, 12] During all 3 of the interventions HR returned to values not different from baseline, and there were no differences of significance among the interventions. It was anticipated that resuscitation with the pH-stat or the pH-stat modified treatment would have been superior to that of LRS, alone, if modification of pH and/or acid-base is important. That there are no differences indicates that return of volume alone is the important factor in resuscitation.

Ventricular Function

Diastolic

As expected from the hypovolemic condition, LVEDP decreased significantly from baseline during hemorrhage, and then returned to values not different from those at baseline at the end of treatment for all groups. However, with time, LVEDP decreased equally for all groups, to values below those of baseline. Since blood volume should have been sustained, the fall in LVEDP must have indicated venodilatation, pooling of blood in veins, and decrease in circulating blood volume. It is clear that none of the 3 therapies was superior to the other in sustaining LVEDP and preload. In the same direction, mRAP "tracked" LVEDP, consistent with a reduction in right ventricular preload initially due to the hypovolemic condition and subsequently to venous pooling [15, 5, 2, 7].

As anticipated, LV - dP/dt decreased after hemorrhage**,** tended to return to baseline at the end of treatment, with all 3 methods of resuscitation, but then decreased with time to levels below those observed during baseline. This reduction may represent a reduced rate of resequestration of Ca^{2+} into the sarcoplasmic reticulum due to a negative lusitropism of hemorrhage or to altered loading conditions. However, the fall in SAP (see following explanation) resulting in the left ventricular isovolumetric pressure falling from a lower level (at the end of ejection), by itself, would be expected to reduce LV - dP/dt; and it is more reasonable to believe that the reduction in LV - dP/dt was an effect of altered loading. Tau, the time-constant of relaxation, is a more load-independent estimate of lusitropy. Tau did not change after hemorrhage. Tau increased 3 hours post-resuscitation for the pH-stat and less so for the LRS and the pH-stat modified treatments. This supports the contention that hemorrhage did not change lusitropy, and that either time alone, as it has been suggested by some authors, [14, 13] or the interventions with LRS, pH-stat or pH-stat modified therapies decreased lusitropy (i.e. lengthened Tau). Alternatively, the increase in Tau could have been a result of altered loading conditions for which Tau imperfectly corrected.

Systolic

Contrary to what might be expected by volume depletion and reduction in preload (reduction in LVEDP), LV + dP/dt did not decrease after hemorrhage, except for the LRS group. This is particularly surprising since SAP fell, the aortic valve should have opened earlier and thus ejection (when LV + dP/dt normally falls) would have begun at a lower intraventricular pressure. Furthermore, with a decrease in LVEDP, preload should have been reduced, according to the Frank-Starling mechanism during the immediate post-

hemorrhage period. The apparent reduction in LV + dP/dt due to hemorrhage is unexplainable, but the increase at the end of volume expansion is perfectly consistent with a Frank-Starling effect and the increase in LVEDP (see above). The negative drift in LV + dP/dt unquestionably indicates the decrease in preload (venous pooling) and invocation of the Frank-Starling mechanism [10].

All systemic arterial pressures (i.e., mean, systolic, diastolic arterial and peak systolic left ventricular) behaved nearly identically during hemorrhage and subsequent fluid restitution [4, 6]. As expected, they fell at the end of hemorrhage, certainly a Frank-Starling effect mediated by reduction in preload, then tended to return to normal at the end of fluid expansion, then drifted to subnormal values consistent with venous pooling and reduction in preload. mPAP followed precisely mRAP pressure, consistent with the Frank-Starling mechanism evoked first by hemorrhage, next by volume replacement, and finally by venous pooling.

Systemic Vascular Resistance

Following hemorrhage, SVR increased significantly for LRS and pH-stat, and did not change for pH-stat modified. There is no reason why intention to resuscitate should change the SVR after hemorrhage, and it is likely that SVR increased in response to the fall in SAP and reflex arteriolar and arterial constriction. SVR decreased for all groups at the end of volume replacement, and then increased in LRS and pH-stat above baseline levels at 180 minutes following resuscitation.

The decrease in SVR at the end of treatment is consistent with increases in CO and SAP, decreased activation of high pressure baroreceptors, and vasodilatation; and the increase with time is consistent with hemodynamic deterioration due to venous pooling and activation of arterial smooth muscle either directly or neurogenically [12].

Cardiac Output and Efficiency

Efficiency of left ventricular contraction can be expressed in terms of the ratio of the product of CO and mean SAP to myocardial oxygen consumption, estimated by the RPP. Following hemorrhage, both CO [3] and arterial pressure fell (a Frank-Starling effect) and the RPP "tracked" nearly identically. Therefore efficiency must not have decreased profoundly, if at all. The statistical difference between the fall in CO between the LRS treatment and the pH-stat modified treatment during hypovolemia is clearly irrelevant, that is, there should not be any reason why, before receiving fluid replacement, CO should have fallen more for one group than for another. The return of CO following all modes of volume replacement was predictable (a Frank-Starling effect). However, following replacement with the pH-stat modified strategy, CO tended to fall inexplicably, more slowly and to a lesser degree. Since this was not translated to loading conditions (i.e. LVEDP, MAP), it probably is of little significance.

Vascular Reactivity to Pharmacological Challenge

The administration of norepinephrine should increase MAP and HR by the Marey reflex (reflex bradycardia), and change RPP in a direction determined by whether the change in HR was greater or lesser than the change in MAP. The ability of norepinephrine to increase MAP was similar for all interventions, that is to say, the average percent change in MAP was approximately 31 % for all states, except at the

recording made at 180 minutes after volume resuscitation when MAP increased approximately 75 % for all interventions. Consequently, the interventions, or the preceding period of hypotension produced by hemorrhage, resulted in an apparent increase of smooth muscle reactivity or up-regulation of adrenergic receptors. The mechanism by which this occurred is unknown. The baroreceptor reflex (monitored by the decrease in HR in response to the increase in MAP) was virtually extinguished by hemorrhage independent of which method of volume resuscitation was employed. This may have resulted from the inability of any of the methods for volume resuscitation to return MAP to a range in which the baroreceptor reflex functions. Alternatively, it is possible that the period of hemorrhage *per se* injured one or more component (s) [receptors, medullary centers, neuroendocrine communications] of the reflex.

Occlusion of an arterial supply should decrease stretch on high pressure baroreceptors and produce a reflex increase in HR, MAP and RPP. In general, occlusion did not cause any substantial increase in HR, MAP and RPP for the 3 treatments during the entire course of the experimental observation. This may also indicate that the reflex was refractory to all the interventions.

Respiratory Function, Blood Gases, and End-Tidal Carbon Dioxide

RR between each period following hemorrhage and volume resuscitation did not change for any of the groups. An increase rate would have been expected due to hemorrhage, since reduced DO_2 to the ventilatory centers should have been a stimulus for increased rate and/or end tidal volume. However, oxygen debt must be relatively extreme (compared with CO_2 excess) and is much less of a stimulus to ventilation than is increased CO_2.

Since aPO_2 did not decrease following hemorrhage, but actually increased significantly in the dogs to be given pH-stat, then there should not have been a stimulus for increased RR.

$aPCO_2$ (and $ETCO_2$, which must and always parallels $aPCO_2$) did not change after hemorrhage; therefore there should have been no stimulus for increased RR. However, $aPCO_2$ increased rather dramatically (but not of statistical significance) for dogs receiving the pH-stat modified therapy. This could represent either a decrease in alveolar ventilation (i.e. a decrease in end tidal volume since frequency did not change) or an increase in metabolic activity producing such an increment in CO_2 that the lung could not eliminate it. Hemorrhagic shock is known to result in increased metabolic activity (a state of hypermetabolism) in terms of a high oxygen demand [8, 16], but the increase in $aPCO_2$ for the pH-stat modified remains inexplicable and is consistent with it not achieving levels of statistical significance. Following all modes of volume resuscitation, aPO_2 increased in dogs receiving the LRS, more dramatically for the pH-stat, and to a lesser extend in the pH-stat modified treatment.

In view of the fact that RR did not increase, the increase in aPO_2 may be explained by an increase in tidal volume or more likely, by a decrease in ventilation-perfusion inequality.

Since there were not statistically significant changes in blood gases and ventilation, in parameters of cardiovascular function, and in an anesthetized dog without changes in muscle activity, VO_2 was not modified. However, Nahas [9] suggested that acidosis limits the increase in VO_2 and might embody an additional interference to oxygen utilization by tissues during severe shock.

DO_2 decreased following hypovolemia and at the end of volume resuscitation, and that may be explained by reduction in oxygen carrying capacity. At the end of the initial period of volume resuscitation, DO_2 returned to normal with pH-stat modified, but for LRS and pH-stat, but then decreased with time up to the end of surveillance for the three interventions.

Without the addition of an oxygen-carrying moiety to blood (Hb), it is difficult to explain why DO_2 should have increased at all, and the apparent increase following volume resuscitation may well have been artifactual. If CO had increased proportionally with the decrease in oxygen carrying capacity, it is possible for DO_2 to have returned toward normal, but the increased flow did not occur.

The increase in O_2ER indicates that with reduced delivery due to decreased Hb, the reduction in VO_2 could have been remediated. Again, there is not a satisfactory explanation as to why the O_2ER decreased to normal immediately after volume resuscitation (without additional Hb). However, the increase during the final 2 periods of surveillance is consistent with the deterioration in cardiovascular function due to venous pooling. Finally, VO_2 remained unchanged during hemorrhage or volume resuscitation because the extraction of oxygen compensated adequately for the reduced Hb.

Immediately following hemorrhage, pHa and $HC0_3^-$, decreased, lactate increased, and $aPCO_2$ did not change. The constancy of $aPCO_2$ is consistent with normal ventilation which excludes respiratory acidosis; the increase in lactate, and decreases in pHa and $HC0_3^-$ indicate that the metabolic (lactic) acidosis was due possibly to inadequate DO_2 to metabolizing tissues, the lack of buffering by scarce Hb, or to increased metabolic activity, the latter a known consequence of hemorrhageic shock.

Previous pilot studies in our laboratory corroborated that the pH-stat therapy is better than the alpha-stat therapy in improving acid-base disturbances in hemorrhagic shock. This was confirmed in this study when animals which received the pH-stat approach enhanced pHa to normal levels, when compared to the other interventions. However, with the pH-stat modified treatment, despite the fact that pHa did not reach baseline levels and animals were still suffering from metabolic (lactic) acidosis, the CO_2 manipulation resulted in flow improvement at the end of the experimental observation. This flow enhancement was superior to the other two interventions even when animals were exposed to a pharmacological challenge with norepinephrine and when occlusion to the hind limb as well as to the small intestine was applied [1].

Blood Chemistries/Analysis

COP, TP concentration, and PCV behaved in a nearly identical manner, and serum Ca^{++} acted similarly but to a lesser degree. All decreased precipitously (Ca^{++} to a lesser degree) with hemorrhage, decreased further after the end of whatever volume expander was used, and then either increased or tended to increase (but never to pre-hemorrhage levels) by the 180 minute observation. The apparent reduced fall in Ca^{++} for dogs destined to receive LSR as a volume expander, must be artifactual, since intention to treat with LRS cannot alter Ca^{++} concentrations. The initial decrease at the end of hemorrhage was due, undoubtedly, to removal of red cells and proteins, and the autoreplacement as fluid was drawn, over the ensuing 60 minutes, from the interstitial and possible even intracellular compartments. The secondary decrease to the end of volume replacement resulted, no doubt, from replacement with the protein-free substances (hemodilution). The increase in COP, PCV and TP that occurred from the end

of fluid replacement to 180 minutes post-resuscitation, must have resulted from sequestration of non-cellular components of blood to a compartment (interstitial, intracellular) where it would allow for the cellular elements to increase in concentration. This is consistent with non-cellular elements transuding out of the vascular system as through leaky capillaries, or possibly with renal loss of water. The alternative, that osmotic particles or red blood cells are somehow taken into the vascular system, is untenable.

One limitation in this study arises from the fact that since this is the first time that both the pH-stat and the pH-stat modified approaches are used in hemorrhagic shock in dogs, there is not a point of reference for comparison purposes. As mentioned in the Introduction, most of the data come from studies with deep hypothermic circulatory arrest in cardiopulmonary bypass and neurosurgery. Extreme care must be exerted not to extrapolate those results into our study. For future studies, it is highly recommended that the period of observation be extended to 24 hours to further study both the hemodynamic and metabolic responses.

Depending on the results, experiments to assess the effect of specific pharmacological therapy on vascular response could be included. It would also be advisable to increase the sample size to improve the statistical power.

4.1 CONCLUSIONS

All of the 3 methods of volume resuscitation produced transient improvements in the physiological variables measured or calculated. These improvements were obvious during recordings at the termination of infusion. However, improvements in parameters did not persist with time for any of the methods, and the values deteriorated within 60 minutes after infusion, asymptotically reaching a steady state at lower levels of function by the 120 minute surveillance.

The main findings of this research were:

1. A superior flow to both the hind limb and the small intestine at all times with the pH-stat modified intervention, compared to the other two groups.
2. In a similar way, for those animals that received the pH-stat modified therapy, the flows to the hind limb and to the small intestine were better than for the other two interventions, when animals were challenged with norepinephrine or when occlusion was applied.
3. The lowest lactate concentration was seen in animals which received the pH-stat modified treatment 3 hours after fluid replacement.
4. There were statistically significant differences in pHa among groups at the end of treatment and at 2 hours post-treatment. Animals treated with the pH-stat
5. modified therapeutic approach exhibited the lowest pHa levels, when compared to the other two groups.

6. The PCO_2 in pH-stat modified intervention showed a constant increase during the length of the experiment. In contrast, the other two treatments exhibited negative changes during the course of the experimental observation.

There did not appear to be substantive differences produced by one volume replacement over another with the exception of flow improvement to tissues in animals treated with the pH-stat modified strategy. This could have potential therapeutic implications since hemorrhagic shock is a state of hypoperfusion and if both blood flow to organs and acid-base disturbances are corrected, oxygenation as well as vascular hyporeactivity will improve and animals might enhance their chance of survival.

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