In the physician or surgeon no quality takes rank with imperturbability ... coolness and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril. *William Osler* 

# FLUID ADMINISTRATION FOR THE TREATMENT OF ISOFLURANE-INDUCED HYPOTENSION IN DOGS

A Thesis

Presented in Partial Fulfillment of the Requirements for

The Degree Master of Science in the

Graduate School of The Ohio State University

By

Turi Kenna Aarnes, BA, BA, DVM

The Ohio State University 2009

Master's Committee:

Dr. Richard M. Bednarski, Advisor

Dr. Phillip Lerche

Dr. John A.E. Hubbell

Dr. Karsten Schober

Approved by

Advisor Graduate Program in Veterinary Clinical Sciences

#### ABSTRACT

Isoflurane is the most commonly used inhalant anesthetic in veterinary practice. Hypotension, a dose-dependent side effect of isoflurane anesthesia, may increase morbidity and mortality. Intravenous fluid therapy is frequently proposed as the first option for correction of anesthetic-induced hypotension, but fluid administration impacts cellular functions. The efficacy of various fluid therapies for the treatment of isofluraneinduced hypotension has not been investigated.

The objective of our study was to determine the effect of the intravenous administration of a crystalloid (Lactated Ringer's Solution, (LRS)) or colloid (Hetastarch, HES) on isoflurane-induced hypotension in dogs. We hypothesized that rapid IV fluid administration would correct isoflurane-induced hypotension and that HES administration would reverse isoflurane-induced hypotension more rapidly, more effectively, and with a smaller volume than with LRS.

Six purpose-bred Beagles were studied. The study was conducted in a nonblinded, random-ordered three-way cross-over design. Isoflurane minimum alveolar concentration (MAC) was determined for each dog. At least one week after individual MAC determination, all dogs underwent each of three treatments separated by a minimum of 7 days: Treatment 1- an infusion of HES, Treatment 2- an infusion of LRS, and Treatment 3- no IV fluid administration (NFA).

Following propofol induction and isoflurane maintenance, dogs were instrumented with thermodilution and arterial catheters. Blood volume change (BV) was measured by a central venous extracorporeal circuit which extended from the left jugular catheter to the left cephalic catheter. Dogs were maintained at 1.3 times their individual isoflurane MAC for an additional 30 minutes following completion of instrumentation. Baseline data were collected and recorded. The isoflurane concentration was then increased to achieve and maintain a systolic arterial blood pressure (SABP) of 80 mmHg for 15 minutes (time 0). The isoflurane concentration required to attain a SABP of 80 mmHg was maintained for the duration of the experiment. Fluid administration in the HES and LRS groups began at time 0 (after measurements and blood samples were completed) at a rate of 80 mL/kg/hr.

Fluid administration was discontinued if SABP returned to within 10% of baseline. If SABP did not return to within 10% of its baseline value, fluid was administered to a pre-determined maximum volume: 40 mL/kg for HES and 80 mL/kg for LRS.

Heart rate (HR), body temperature, SABP, mean arterial blood pressure, diastolic arterial blood pressure, mean pulmonary artery pressure, right atrial pressure, cardiac output, and blood volume change were measured and recorded at baseline, when the SABP had been stabilized at 80 mmHg for 15 minutes (time 0), and at 15, 30, 45, 60, 90, and 120 minutes in all groups, and at 150 and 180 minutes in the fluid treatment groups.

Blood gases, pH, lactate, electrolytes, packed cell volume (PCV), total protein

(TP), albumin, colloid osmotic pressure, and whole blood viscosity were determined at baseline, time 0, 15, 30, 60 and 120 minutes. An additional blood sample was obtained for determination of whole blood viscosity at 180 minutes in the fluid treatment groups. Venous blood was collected 24 hours after recovery from anesthesia for hemogram, PCV, TP, lactate, whole blood viscosity, and chemical profile analysis. Cardiac index, systemic oxygen delivery, and systemic vascular resistance (SVR) were calculated from measured data.

Administration of 80 mL/kg of LRS did not increase SABP in any dog, while administration of 40 mL/kg or less of HES increased SABP in four of six dogs. Systolic arterial blood pressure, DABP, and MABP were significantly increased in dogs that received HES compared with LRS. Cardiac index increased and SVR decreased with fluid administration. Viscosity was significantly lower in dogs that received LRS compared with HES. Packed cell volume and TP decreased with LRS. Colloid osmotic pressure increased with HES.

Hetastarch but not LRS increased SABP despite lower volumes of HES administered. The present study supports the administration of HES over LRS for the treatment of isoflurane-induced hypotension in dogs.

iv

Dedicated to my father and my sisters

#### ACKNOWLEDGMENTS

I would like to thank my resident and research advisor Dr. Richard Bednarski for his encouragement, his innate professionalism, his sense of humor, and for trying to teach me to let go of the little things. I would also like to thank Dr. William Muir for his help and support with this project and beyond. Sincerest thanks to Dr. John Hubbell for giving me a different perspective and trying to teach me patience. Thank you to Dr. Phillip Lerche for always encouraging me to do more and challenging me every step of the way. These four men have been the best examples of what I hope to be: the calmest person in the room.

Thank you to Dr. Karsten Schober for being a member of my thesis committee. Thank you to Dr. Yukie Ueyama and Barb Lang for their technical assistance and to all of the anesthesia technicians: Renee Calvin, Heather Cruea, Chris Duffey, Amanda English, Theresa Weber Hand, Sue Huck, Gladys Karpa, Carl O'Brien, and Zach Schell, for their support during this project and during my residency. Finally, I would like to thank Dr. Jean Powers for her statistical assistance and Tim Vojt for his help with the graphs.

This research was funded by a grant from the Canine Research Fund at The Ohio State University.

# VITA

1996	.BA Psychology, University of Hawaii Manoa
1996	.BA Science and Mathematics, Hawaii Pacific University
2005	.DVM, Atlantic Veterinary College, University of Prince Edward Island, Canada
2005 – 2006	.Intern, Greenbrier Veterinary Referral Center
2006 – 2009	Graduate Research Associate The Ohio State University Department of Veterinary Clinical Sciences
2006 – 2009	Resident, Anesthesia The Ohio State University Department of Veterinary Clinical Sciences

### FIELD OF STUDY

Major Field: Veterinary Clinical Sciences

Area of Emphasis: Veterinary Anesthesia

# TABLE OF CONTENTS

Abstract	ii
Dedication	V
Acknowledgments	vi
Vita	vii
List of Tables	X
List of Figures	xi

# Chapters:

1.	Litera	ture Review1
	1.1	Introduction1
	1.2	Isoflurane anesthesia
	1.3	Isoflurane-induced hypotension and its effect on renal, hepatic, and
		cardiovascular systems
	1.4	Intravenous fluids and the treatment of anesthetic-induced hypotension5
	1.5	Effects of isoflurane and fluid administration on intravascular volume9
	1.6	Other treatments for isoflurane-induced hypotension10
	1.7	Hypothesis11

2.	Expe	Experimental Study							
	2.1	Materials and Methods	13						
	2.2	Results	19						
	2.3	Discussion	23						

List of References		44
--------------------	--	----

# LIST OF TABLES

## Table

# Page

1.1	Fluid constituents
2.1	Isoflurane MAC values
2.2	Body temperature and end-tidal isoflurane concentrations in isoflurane-
	anesthetized dogs
2.3	Hemodynamic values in isoflurane-anesthetized dogs33
2.4	Blood volume change and in-line hematocrit values in isoflurane-
	anesthetized dogs
2.5	Hemorheologic values in isoflurane-anesthetized dogs
2.6	Blood biochemical and oxygen delivery values in isoflurane-anesthetized
	dogs

# LIST OF FIGURES

Figure		Page
1.1	Isoflurane molecule	2
1.2	Hetastarch molecule	6
2.1	Heart rate	
2.2	Systolic arterial blood pressure	37
2.3	Diastolic arterial blood pressure	
2.4	Mean pulmonary artery pressure	
2.5	Right atrial pressure	
2.6	Cardiac index	
2.7	Systemic vascular resistance	40
2.8	Blood volume change	40
2.9	Whole blood viscosity	41
2.10	Packed cell volume	41
2.11	Total protein	42
2.12	Colloid osmotic pressure	42
2.13	Oxygen delivery	43

### CHAPTER 1

### LITERATURE REVIEW

### 1.1 Introduction

Isoflurane is the most commonly used inhalant anesthetic in veterinary practice (Gaynor 1999). Hypotension, a dose-dependent side effect of isoflurane anesthesia, may increase morbidity and mortality as a result of diminished organ perfusion (Mutoh 1997, Gaynor 1999, Tomiyasu 1999). Hypotension is defined as systolic arterial blood pressures (SABP) of 80 mmHg or less (Bijker 2007). The clinical incidence of hypotension that is directly attributed to isoflurane is unknown, but hypotension is estimated to occur in 41% of anesthetized humans, up to 32% of anesthetized dogs, and up to 33% of anesthetized cats (Gaynor 1999, Wager 2003, Gordon 2006, Bijker 2007). The efficacy of various fluid therapies for the treatment of isoflurane-induced hypotension has not been investigated.

### 1.2 Isoflurane anesthesia

Isoflurane is a halogenated ether compound that was introduced to human anesthesia in 1965 (Anderson 1986).



Figure 1.1. Isoflurane Molecule

Isoflurane is resistant to metabolic breakdown and has a blood gas coefficient of 1.4, which results in rapid induction and recovery when compared to other inhalant anesthetics of the time (Anderson 1986). The minimum alveolar concentration (MAC) was initially described as an "index of comparison" of anesthetic agents in 1963 (Quasha 1980). MAC is defined as the minimum alveolar concentration in the alveolus at a pressure of one atmosphere as measured by end-tidal gas concentration required to prevent gross purposeful movement in response to a noxious stimulus. The alveolar concentration is equal to the concentration in the brain (Quasha 1980). MAC of isoflurane in dogs is reported to be between 1.28 and 1.50 (Steffey 1977, Mutoh 1997, Steffey 2007). MAC can be determined using different methods, including application of a tail clamp and electrostimulation of the buccal mucosa (Steffey 2007). Isoflurane MAC is also dependent on other factors, such as atmospheric pressure, lipid solubility, and core body temperature; isoflurane MAC decreases approximately 5% for every degree Celsius decrease of core body temperature (Antognini 1993, Steffey 2007).

The mechanism of action of isoflurane is still debated. It is generally accepted that isoflurane acts at the level of the spinal cord to prevent movement, and that there is also a cerebral cortical effect that results in amnesia (Antognini 1993, Eger 2002).

1.3 Isoflurane-induced hypotension and its effect on renal, hepatic, and cardiovascular systems

Isoflurane causes dose-dependent cardiovascular depression resulting in a decrease in systemic vascular resistance (SVR). At approximately 2 times MAC, systolic arterial blood pressure will decrease to  $86\pm10$  mmHg in dogs (Mutoh 1997). As a result of this, SABP decreases and there is often a compensatory increase in heart rate (Mutoh 1997). Myocardial oxygen consumption decreases because of a decrease in afterload and myocardial contractility (Conzen 1989). Isoflurane induces coronary vasodilation through activation of K<sup>+</sup><sub>ATP</sub> channels (Fujiwara 1999). Cardiac rhythm is stable under isoflurane anesthesia (Anderson 1986). Respiratory depression is also a noted effect of isoflurane anesthesia (Steffey 1977, Anderson 1986).

Isoflurane-induced vasodilation occurs in the skin, heart, brain, muscle, kidneys, and the spleen, and blood flow increases to the brain, stomach, pancreas, intestines, and muscle, while blood flow decreases to the heart and kidneys (Anderson 1986, Lam 1990). Pulmonary circulation is less affected by isoflurane (Cousins 1983, Lessard 1991, Conzen 1992, Mutoh 1997, Fujiwara 1999, Tomiyasu 1999).

Hypotension in awake animals activates a stress response in an attempt to maintain arterial blood pressure (Adams 1975, Wo 1993). This results in activation of several homeostatic mechanisms including activation of the autonomic nervous system, a release of endogenous catecholamines, activation of the renin-angiotensin aldosterone system, and aldosterone release and sodium chloride retention (Adams 1975, Wo 1993). If these compensatory mechanisms are overwhelmed due to prolonged hypotension, blood pressure and flow decrease (Wo 1993). Controlled hypotension (to mean arterial blood pressures between 40 and 60 mmHg) with isoflurane-induced vasodilation does not induce cardiac arrhythmias in people (Manninen 1987), and cardiac output (CO) is unaffected in dogs and people (Lam 1983, Lam 1990, Tomiyasu 1999). Decrease in afterload results in a decrease in myocardial oxygen demand (Lam 1990).

Cerebral blood flow autoregulation does not occur at or below MABP of 50 mmHg; at a MABP of 41 mmHg, a decrease in oxygen uptake and utilization of glucose, and an increase in cerebral lactate production have been demonstrated in dogs (Kovach 1976).

Hypotension can result in potentially life-threatening complications as a result of diminished vital organ perfusion (Gaynor 1999, Tomiyasu 1999). Increasing isoflurane concentrations to reduce MABP to 60 mmHg will increase blood flow to brain, stomach, pancreas, and muscle, while decreasing renal blood flow (Lessard 1991, Tomiyasu 1999).

Isoflurane-induced hypotension results from decreased SVR. During isofluraneinduced hypotension, a normal ratio between renal vascular resistance and SVR is maintained by a compensatory decrease in renal vascular resistance. The reduction in glomerular filtration rate (GFR) and effective renal plasma flow is quickly reversed following a return to normotension, and in fact, GFR increases from preoperative values following recovery from isoflurane-induced hypotension (Lessard 1990, Lessard 1991). General anesthesia and surgery also result in a decreased electrolyte excretion by the kidneys (Cousins 1983). This decrease in renal blood flow is more likely to occur when "hypotension is below the normal lower limit of autoregulation of the renal vasculature in dogs" (Takeda 2002). Reduced renal blood flow and GFR occur when SABP is below 75 mmHg (Newell 1997, Lobetti 2000). During hypotension, a reduction of renal vascular resistance is the normal compensatory mechanism (Lessard 1990).

### 1.4 Intravenous fluids and the treatment of hypotension

Intravenous fluid therapy is frequently proposed as the first option for correction of anesthetic-induced hypotension, but fluids impact cellular functions, including causing an increase in release of free radicals and cytokines, and expression of adhesion molecules on neutrophils (Gaynor 1999, Rhee 2000, Alam 2007). Crystalloids are fluids that contain solutes which are able to enter all body compartments (DiBartola 2006). Most crystalloid fluids are relatively inexpensive and readily available. Balanced electrolyte solutions (solutions that are similar to plasma in electrolyte composition and tonicity, e.g. Lactated Ringer's solution (LRS)), are recommended during anesthesia and surgery (Raffe 1992, Kudnig 2002). LRS is an isotonic electrolyte solution, containing sodium chloride (6 g/L), sodium lactate (3.1 g/L), potassium chloride (0.3 g/L), and calcium chloride (0.2 g/L). LRS contains lactate, which is converted to bicarbonate in the liver by oxidative metabolism (DiBartola 2006). Plasma lactate levels in healthy animals are not affected by LRS administration (Holowaychuk 2006, Pang 2007). LRS has the same osmolality as plasma and rapidly, but temporarily expands the extracellular fluid space, equilibrating in the larger interstitial fluid compartment (Kudnig 2002).

The administration of colloidal solutions for the treatment of hypovolemia and hypotension is becoming increasingly popular in veterinary practice (Kudnig 2002, Hughes 2001). Colloids are solutions that contain large molecules that stay in the vascular space and other smaller molecules that diffuse out of the vasculature (Kudnig 2002). Hetastarch (HES), a colloid with a mean molecular weight of 450 kDa, is formulated as a 6% solution in 0.9% sodium chloride with a colloid osmotic pressure (COP) of 40 mmHg, compared with plasma, which has a COP ranging from 16.9 to 19.3 mmHg (Table 1.1).



The administration of HES usually results in a plasma volume expansion beyond the delivered volume, with estimates of initial plasma volume expansion up to 170 percent (Kudnig 2002). The degree of initial plasma expansion ranges from Hetastarch is degraded by amylase in the liver and has a reported duration of plasma volume expansion between 12 and 24 hours (Kudnig 2002, Grocott 2005).

The choice of crystalloid and colloid administration during anesthesia has been controversial. Many believe that fluids may not be necessary, but may still be administered as standard practice (Chappell 2008). Recently, the controversy has been

associated with which fluid type (e.g., crystalloid or colloid) should be administered because both fluids have collateral effects (Chappell 2008). Both fluids increase intravascular volume in the short term. Crystalloid fluids rapidly leave the intravascular space due to their osmolality and lack of osmotic pressure, with less than twenty percent of crystalloids remaining in the intravascular space after two hours (Kudnig 2002, Table 1.1). They then enter the interstitial space. In the event of large volume administration or in certain disease conditions, this can result in hemodilution and the development of pulmonary edema, respiratory distress, and heart failure (Anderson 1986, Wagner 1986, Lowell 1990, Dyson 1998, Holte 2002). Hemodilution can also impair hemostasis due to the disruption of the coagulation cascade, and decrease oxygen delivery (Singbartl 2003, Dutton 2005, Kimberger 2007). Hemoglobin dilution is often not as pronounced as albumin dilution, and the dilution of albumin results in decreased COP and extravascular fluid accumulation (Norberg 2007). Increased intracranial pressure, ascites, peripheral edema, and disseminated intravascular coagulation have also been reported (Wagner 1986, Dyson 1998). Rapid administration of intravenous fluids can also result in decreased body temperature (Dutton 2005), and LRS administration can result in neutrophil activation (Rhee 1998, Alam 2007). Finally, significant increases in intravascular volume are possible without increasing blood pressure (Rhee 1998).

Administration of large volumes of colloid fluids may be associated with coagulopathies, renal failure, allergic reactions, and worsening pulmonary edema (Ring 1977, Hughes 2001, Cotton 2006). Postulated mechanisms for colloid-induced coagulopathies include: 1) interactions between Factor IIa and Factor I and between Factor XIIIa and fibrin polymers; 2) reduced factor VIII activity; and 3) decreased concentrations of von Willebrand factor (Nielsen 2005, Gandhi 2007). Colloid administration results in hemodilution. In addition, the increased oncotic pressure from colloid administration results in autotransfusion of fluid into the vascular space. This results in further hemodilution. The incidence of anaphylactoid reactions (shock, cardiac and/or respiratory arrest) is dependent on the type of colloid, and for HES was reported as 0.006% in humans (Ring 1977). The mechanism for this reaction is unknown, but has been postulated to be due to non-immunoglobulin E HES-specific antibodies and complement activation (McHugh 1998). Colloid-induced renal failure has been reported in humans, but only in cases of severe sepsis (Chappell 2008). The worsening of pulmonary edema due to colloid administration is a result of an increased pulmonary capillary permeability due to vasculitis, a break in the endothelium, or disruption of the endothelial glycocalyx. Colloid molecules move into pulmonary tissue and cause an increased oncotic gradient, which results in increased fluid accumulation in the lungs.

Intravenous fluid administration also results in a decrease in blood viscosity (Pries 1998, Teyssier 1998). The primary determinants of blood viscosity are hematocrit, RBC aggregability and deformability, plasma viscosity, temperature, and blood flow (Muir 2007). Fluid administration for the treatment of hypotension decreases hematocrit and plasma viscosity, and results in decreased blood viscosity, which results in decreased resistance to blood flow according to the Poiseuille-Hagen law. Blood vessel radius and length also contribute to blood flow resistance (Muir 2007). In the microvascular circulation, viscosity declines with decreasing diameter, termed the Fåhraeus-Lindqvist effect. The decrease in viscosity in small diameter vessels results in a decrease in resistance, however, it is higher than would be expected given a specific viscosity in a larger vessel (Pries 2005). The decrease in shear stress due to lower viscosity may have a greater impact on oxygen delivery by the microvascular circulation than that of a lower hematocrit (Cabrales 2007).

1.5 Effects of isoflurane and fluid administration on intravascular volume

Isoflurane administration alters the distribution of intravenously administered fluids. Isoflurane decreases the rate of excretion of rapidly administered crystalloids by the kidneys and results in fluid accumulation in the interstitium (Norberg 2007). Vasodilation resulting from isoflurane administration promotes expansion of the intravascular compartment, and albumin is more easily extravasated during isoflurane administration, resulting in an increase in the extravascular fluid compartment (Connolly 2003, Norberg 2007). Renal excretion of fluids is also decreased during isoflurane anesthesia (Connolly 2003, Norberg 2007).

While fluid administration results in an increase in intravascular volume, crystalloid fluid administration does not increase blood pressure in isofluraneanesthetized patients (Norberg 2007). In addition, administered crystalloid fluids may accumulate in the splanchnic vessels which may result in an increase in unstressed vascular volume that does not contribute to an increase in venous return or cardiac output (Shoukas 1973, Wang 1995, Scott-Douglas 2002, Gelman 2008). Splanchnic vessels are a reservoir of blood volume that adapt in response to changes in venous pressure (Scott-Douglas 2002). The result is that changes in vascular capacitance are inversely related to changes in SVR (Scott-Douglas 2002). During volume loading, SVR decreases, and vascular capacitance increases. In addition, changes in vascular capacitance buffer changes in CO (Scott-Douglas 2002).

Increasing intravascular volume increases stressed volume, which is the volume of blood within a vein under a transmural pressure greater than zero. This increase in stressed volume results in an increase in mean circulatory filling pressure and an increase in venous return to the heart, and should also increase CO (Gelman 2008). Isoflurane decreases venous resistance, decreases stressed volume, and increases unstressed vascular volume, or the volume of blood in a vein at a transmural pressure equal to zero. The unstressed volume does not directly participate in venous return (Gelman 2008). The result is that fluid administration during isoflurane anesthesia may not result in an increase in CO, even though intravascular volume increases.

Fluid administration during isoflurane anesthesia results in a greater decrease in hemoglobin compared with fluid administration in awake patients (Norberg 2007). In addition, the albumin dilution is more significant than the hemoglobin dilution in isoflurane-anesthetized humans (Norberg 2007).

#### 1.6 Other treatments for isoflurane-induced hypotension

Other strategies for correction of isoflurane-induced hypotension include decreasing or terminating the delivery of isoflurane, administration of anesthetic and analgesic adjuncts in order to reduce the inspired isoflurane concentration, and the administration of positive inotropic drugs and other vasoactive drugs (Curtis 1989, Ewing 1993, Hellyer 2001, Muir 2003, Valverde 2004, Dyson 2006, Machado 2006, Solano 2006). A reduction in the delivered anesthetic concentration can be effective, but may be impractical or inappropriate during surgery or diagnostic procedures because of the animal's return to consciousness. Co-administration of inhalant anesthetic-sparing drugs or anesthetic analgesic adjuncts such as ketamine, opioids, lidocaine, or alpha-2 adrenergic agonists reduce the required inhalant concentration and may restore normotension, but bradycardia and respiratory depression may occur and post-anesthetic return to consciousness may be delayed (Ewing 1993, Hellyer 2001, Muir 2003, Valverde 2004, Machado 2006, Solano 2006). Positive inotropic drugs, such as dopamine or dobutamine, are advocated for the treatment of anesthetic-induced hypotension, but increase myocardial oxygen demand and may induce cardiac arrhythmias (Curtis 1989, Dyson 2006).

### 1.7 Hypothesis

The objective of our study was to determine the effects of a crystalloid (LRS) or colloid (HES) on isoflurane-induced hypotension in dogs. We hypothesized that IV fluid administration would correct isoflurane-induced hypotension and that HES administration would reverse isoflurane-induced hypotension more rapidly, more effectively, and with less volume than LRS.

Solution	Na <sup>+</sup>	$K^+$	Cl	Ca <sup>2+</sup>	$Mg^{2+}$	Buffer	COP	MW
	(mmol/L)	(mmol/L)	(mmol/L)	(mEq/L)	(mEq/L)	(mEq/L)	(mmHg)	(kDa)
Dextrose 5%							<1	
in water								
Dextrose 2.5%	31		31				<1	
in 0.45% Saline								
0.9% Saline	154		154				0	
Lactated Ringer's	131	4	111	3		Lactate 28	0	
Solution								
Normosol-R	140	5	98		3	Acetate 27	0	
						Gluconate 23		
Plasmalyte 148	140	5	98		3	Acetate 27	0	
						Gluconate 23		
Hetastarch 6%	154		154				40	450
(in 0.9% saline)								
Hextend 6%	143	3	124	5	0.9	Lactate 28	38	670
(in LRS)								
6% Dextran 70 in	154		154				62	70
0.9% Saline								
Plasma	145	5	105	5	3	Bicarbonate 24	16.9-19.3	
Albumin	130-160						19.8	69

Table 1.1. Constituents of various intravenous fluids

(Modified from Kudnig 2002, Muir 2004, Grocott 2005, DiBartola 2006, and Wellman 2006.

### CHAPTER 2

### EXPERIMENTAL STUDY

### 2.1 Materials and Methods

#### Animals

Six purpose-bred Beagles (3 females and 3 males) were studied. Dogs ranged in age from 1 to 2 years, and weighed between 12 and 14 kg. The dogs were healthy based on physical examination, fecal flotation, hemogram, and chemical profile analysis. This study was approved by The Ohio State University Institutional Animal Care and Use Committee. The study was conducted in a non-blinded, random-ordered three-way crossover design. Food, but not water, was withheld for approximately 12 hours prior to each experiment. Isoflurane MAC was determined for each dog. At least one week after MAC determination, all dogs underwent each of three treatments separated by a minimum of 7 days: Treatment 1- an infusion of HES, Treatment 2- an infusion of LRS, and Treatment 3- no IV fluid administration (NFA).

#### MAC determination

Determination of isoflurane MAC for each individual dog occurred at least one week prior to the start of the study. An IV catheter was inserted into the right cephalic

vein. All dogs were anesthetized with propofol (6 mg/kg IV), oro-tracheally intubated, and mechanically ventilated using an ascending-bellows, volume-cycled, pressureregulated ventilator (Hallowell EMC 2KIE ventilator, Hallowell EMC, Pittsfield, MA) connected to a circle rebreathing anesthetic circuit. The ventilator was set to deliver a tidal volume of 10 to 15 mL/kg at a rate of 8 to 12 breaths per minute in order to maintain arterial partial pressures of carbon dioxide (PaCO<sub>2</sub>) between 35 and 45 mmHg. Isoflurane in 100% oxygen was delivered using an out-of-circuit precision isoflurane vaporizer (Ohmeda Isotec 3, Madison, WI). The end tidal isoflurane concentration was maintained at 1.5% for the instrumentation period and for an additional 30 minutes. The distal tip of two 24-gauge, 10 mm insulated stimulating electrodes were inserted into the buccal mucosa caudal and dorsal to the incisors of the upper jaw and approximately one cm apart. An electrical stimulating device (Grass SD9 Stimulator, Grass Instruments, Quincy, MA) was connected to the proximal ends of the electrodes and delivered a repeated stimulus of 50V, 5Hz, and 10 ms duration for a period of one minute. The stimulus was discontinued if the dog had a gross purposeful movement before the end of the one minute stimulation. A gross purposeful movement was defined as lifting of the head and/or repeated movement of the limbs. The following were not considered gross purposeful movements (negative response): slight paw movements, back arching, blinking, opening of the eyes, nystagmus, chewing, or swallowing. If no response occurred, the isoflurane concentration was decreased by 20% and maintained for 15 minutes, and the stimulus was then repeated. This procedure was repeated until the dog responded with gross purposeful movement. The inhalant concentration was then

increased by 10%. The dog was allowed a minimum of 15 minutes for isoflurane equilibration before retesting. MAC was taken as the value midway between positive and negative responses, as determined by calculation of the mean of multiple determinations (Muir 2003).

#### Procedures

A 20 gauge, 1.25 inch IV catheter was inserted into the right cephalic vein. Dogs were anesthetized with propofol (6 mg/kg IV), oro-tracheally intubated, and mechanically ventilated using an ascending-bellows, volume-cycled, pressure-regulated ventilator (Hallowell EMC 2KIE ventilator, Hallowell EMC, Pittsfield, MA) connected to a circle rebreathing anesthetic circuit. The ventilator was set to deliver a tidal volume of 10 to 15 mL/kg at a rate of 8 to 12 breaths per minute in order to maintain arterial partial pressures of carbon dioxide (PaCO<sub>2</sub>) between 35 and 45 mmHg. Isoflurane in 100% oxygen was delivered using an out-of-circuit precision vaporizer (Ohmeda Isotec 3, Madison, WI). The end tidal isoflurane concentration (Gas Module SE, Datascope, Montvale, NJ) was initially maintained at 1.3 times the individually determined MAC value. A warm water circulating blanket (T/Pump Heat Therapy Pump model TP-500, Gaymar Industries, Inc., Orchard Park, NY) and a warm air blanket (Thermacare Convective Warming Unit TC3000, Gaymar Industries, Inc., Orchard Park, NY) were used to support body temperature. A lead II ECG was used to determine rhythm and calculate heart rate. All hemodynamic variables were continuously displayed and systematically recorded using a computerized data acquisition system (PO-NE-MAH Digital Acquisition Analysis and Archive Systems, version 1.21f, Gould Instrument

Systems, Simsbury, CT). A pulse oximetry probe (Passport 2, Datascope, Montvale, NJ) was attached to the tongue to determine hemoglobin oxygen saturation ( $SpO_2$ , %). A flow-directed 5Fr 80 cm thermodilution catheter (Thermodilution balloon catheter, Arrow International, Inc., Reading, PA) was introduced into the right jugular or left femoral vein through a 6Fr catheter introducer using Seldinger technique. The thermodilution catheter was advanced until the distal tip was positioned in the pulmonary artery and its location was confirmed by the characteristic pressure waveform. This catheter was used to measure core body temperature (°C), right atrial pressure (RAP, mmHg), mean pulmonary artery pressure (MPAP, mmHg), and cardiac output (CO, L/min) by thermodilution. Three mLs of 0°C 5% dextrose were injected into the proximal port (right atrium) of the thermodilution catheter and cardiac output was measured (9520A Cardiac Output Computer, American Edwards Laboratories, Irvine, CA). CO was determined as the average of three measurements. The pulmonary artery port on the catheter was used for the collection of mixed venous blood samples. A 20 gauge catheter was percutaneously inserted into a dorsal pedal artery or a surgically exposed femoral artery for continuous monitoring of arterial blood pressure and for anaerobic collection of arterial blood samples, which were stored on ice and analyzed within 5 minutes. A 16 gauge catheter was percutaneously introduced into the left jugular vein using Seldinger technique for the continuous removal of blood for analysis of percent blood volume change (BV, %). A central venous extracorporeal circuit containing a volumetric chamber extended from the left jugular catheter to the left cephalic catheter and contained less than 15 ml of blood. Blood flow was maintained using a fluid pump (Heska Vet

IV2.2, Sensor Devices Inc., Waukesha, WI) set to a rate of 720 ml/hr. BV and in-line hematocrit (Hct, %) were measured using a Crit-Line IIR hematocrit monitor, with an optical sensor attached to the volumetric chamber (HemaMetrics, Kaysville, UT). The sensor determined changes in blood volume based on changes in Hct (Silverstein 2005). All instrumentation procedures were accomplished within two hours of general anesthesia induction, after which the dogs were positioned in dorsal recumbency.

Experimental Plan – Dogs were maintained at 1.3 times their individual isoflurane MAC for an additional 30 minutes following completion of instrumentation. Baseline data were collected and recorded. The isoflurane concentration was then increased to achieve and maintain a SABP of 80 mmHg for 15 minutes (time 0). The isoflurane concentration required to attain a SABP of 80 mmHg was maintained for the duration of the experiment. Fluid administration (80 mL/kg/hr) in the HES and LRS groups began at time 0.

Fluid administration was discontinued if SABP returned to within 10% of baseline SABP. If SABP did not return to within 10% of its baseline value, fluid was administered to a pre-determined maximum volume: 40 mL/kg for HES and 80 mL/kg for LRS. Therefore, the maximum duration of fluid administration was 30 minutes for HES and 60 minutes for LRS. The dogs in the HES and LRS groups were awakened from anesthesia after the 180 minute data collection point, while those in the NFA group were awakened after the 120 minute time point. Time to extubation was recorded. Postanesthetic pain was clinically assessed based on heart rate, respiratory rate, vocalization, and behavior. Pain was treated, when necessary, using parenterally-administered hydromorphone and acepromazine.

Data Collection – Heart rate (HR), temperature, SABP, MABP, DABP, MPAP, RAP, CO, and BV were measured and recorded at baseline, when the SABP had been stabilized at 80 mmHg for 15 minutes (time 0), and at 15, 30, 45, 60, 90, and 120 minutes in all groups, and at 150 and 180 minutes in the fluid treatment groups.

Anaerobically collected samples of arterial and venous blood were analyzed within five minutes at baseline, time 0, and at 15, 30, 60 and 120 minutes for packed cell volume (PCV) (%), total protein (TP) (g/dL), COP (mmHg), albumin (mg/dL), sodium (mmol/L), potassium (mmol/L), chloride (mmol/L), ionized calcium (meq/L), lactate (mmol/L), arterial oxygen saturation (SaO<sub>2</sub>) (%), hemoglobin (Hb) (g/dL), pH, arterial oxygen tension (PaO<sub>2</sub>), and arterial carbon dioxide tension (PaCO<sub>2</sub>). An additional blood sample was obtained for determination of whole blood viscosity at 180 minutes in the fluid treatment groups. Venous blood was collected 24 hours after recovery from anesthesia for hemogram, PCV, TP, lactate, whole blood viscosity, and chemical profile analysis.

PCV was determined by centrifugation and TP by refractometry. Whole blood viscosity was measured within 15 minutes of sampling using a DV-II+ Viscometer (Brookfield Engineering Laboratories, Middleboro, MA) at a shear rate of 150 s<sup>-1</sup> and temperature of 37 °C. COP was measured using a colloid osmometer (model 4420, Wescor, Logan, UT). Albumin was measured using a Roche Hitachi 911 (Indianapolis, IN). Sodium, potassium, chloride, ionized calcium, lactate, SaO<sub>2</sub>, Hb, pH, PaO<sub>2</sub>, and PaCO<sub>2</sub> were measured using a blood gas analyzer (ABL 725 Radiometer America,

Westlake, OH).

### Calculated Values

Cardiac index (CI), systemic oxygen delivery (DO<sub>2</sub>), and systemic vascular resistance (SVR) were calculated from measured data. Values were calculated according to the following equations:

CI (mL/kg/min): (CO/body weight)\*1000

DO<sub>2</sub> (mL O<sub>2</sub>/min):  $10*CO*(1.34*Hb*S_aO_2 + 0.003P_aO_2)$ 

SVR (dyne sec/cm<sup>5</sup>): (MABP-RAP)/CO\*80

#### Statistical Analyses

All data are presented as mean  $\pm$  standard deviation. A two-way analysis of variance (ANOVA) with repeated measures was used to test for main effects and interaction over time and between groups. The Bonferroni post test was performed to identify differences within each group comparing back to both baseline and time 0, and to identify differences between the 3 groups at each time point. Values of *p* <0.05 were considered significant.

#### 2.2 Results

Isoflurane MAC ranged from 1.2 to 1.3% (Table 2.1). End-tidal isoflurane concentrations were not different among groups at baseline or at time 0 (Table 2.2). Body temperature ranged from 36.9 to 38.3 °C in all dogs (Table 2.1).

Administration of 80 mL/kg of LRS did not result in an increase in SABP to within 10% of baseline in any dog. SABP increased to within 10% of baseline in four of

six dogs administered HES. The volume of HES required to increase SABP to within 10% of baseline in four dogs ranged from 4.3 to 40 mL/kg, with the time to endpoint ranging from 5 to 46 minutes. The mean volume in these four dogs was 21.2 mL/kg.

There were no differences among groups at baseline or time zero for HR, SABP, DABP, MABP, MPAP, RAP, CI, and BV (Tables 2.3 and 2.4). Systolic arterial blood pressure, DABP, and MABP significantly decreased from baseline to time 0 in all dogs, and MPAP and RAP remained the same. CI decreased significantly from baseline to time 0 in the LRS and NFA groups. HR significantly increased after 45 minutes in the HES group. Systolic arterial blood pressure was significantly greater during HES administration compared to NFA or LRS (Table 2.3, Figure 2.2). Systolic arterial blood pressure significantly increased and returned to baseline at 120 minutes in the HES group. Systolic ABP did not change during LRS administration or in the NFA group. Diastolic arterial blood pressure in the NFA group was the same as DABP in the HES or LRS groups (Table 2.3, Figure 2.3). Diastolic arterial blood pressure in the HES group was significantly greater than in the LRS group. Diastolic arterial blood pressure in the HES group. Diastolic arterial blood pressure in the HES group. Diastolic arterial blood pressure in the LRS group. Diastolic arterial blood pressure in the HES group was significantly greater than in the LRS group. Diastolic arterial blood pressure increased at 15 minutes in dogs that received LRS. Mean arterial blood pressure increased over time in the HES group, but not in the LRS or NFA groups (Table 2.3).

Mean pulmonary artery pressure and RAP increased significantly in the LRS and HES groups, but not in the NFA group (Table 2.3, Figures 2.4 and 2.5). Cardiac index increased in the LRS and HES groups at some time points, but did not increase in the NFA group (Figure 2.6). Systemic vascular resistance trended down with HES administration, and was significantly decreased with LRS administration, but there was

no difference in SVR between the two fluids (Table 2.3, Figure 2.7). Systemic vascular resistance was significantly greater in the NFA group than in dogs that received LRS. Blood viscosity decreased significantly during fluid administration, and was significantly less in dogs that received LRS compared with HES (Figure 2.9). Viscosity did not change in NFA dogs during the experiment, compared to both baseline and time 0. Blood viscosity was increased in LRS and NFA dogs at 24 hours compared with time 0, and was significantly higher in the LRS groups compared with baseline (Table 2.5). There was a trend for PCV to decrease in the NFA and HES groups, and PCV was significantly decreased in dogs administered LRS (Figure 2.10). Packed cell volume was significantly increased compared to baseline values at time 24 hours in the HES groups, and was significantly increased compared with time 0 in all groups (Table 2.5).

Total protein was significantly decreased in dogs that received LRS compared to dogs that received HES or NFA (Table 2.5, Figure 2.11). Total protein was significantly increased in all groups at 24 hours compared to baseline and time 0. Albumin concentrations were significantly less in dogs receiving LRS compared with NFA dogs, and, compared with baseline, decreased significantly at each time point until fluid administration was discontinued (Table 2.5). Colloid osmotic pressure decreased significantly compared with time 0 starting at 15 minutes until LRS administration was discontinued. COP was significantly less in the LRS dogs than in NFA dogs from 15 minutes through 120 minutes (Table 2.5, Figure 2.12). Colloid osmotic pressure was significantly increased in dogs that received HES compared with dogs that received LRS at 15 minutes through 120 minutes. Colloid osmotic pressure was significantly increased in dogs that received HES after 24 hours compared with both baseline and time 0.

There was no difference in PaO<sub>2</sub> between groups, no difference in PaCO<sub>2</sub> over time or between groups, and pH did not change over time for any group (Table 2.6). Lactate decreased over time in dogs that did not receive fluids, trended downward during HES administration, and trended upward during LRS administration (Table 2.6). Systemic oxygen delivery in the HES groups was significantly higher than the NFA group at 15 minutes, and was higher in the LRS group compared with NFA at 30 minutes (Table 2.6, Figure 2.13). Systemic oxygen delivery was significantly lower than baseline at time 0 and 15 minutes for the LRS group and was significantly lower at 30 minutes and 60 minutes in the NFA group (Table 2.6, Figure 2.13).

Potassium in all groups increased compared to baseline during induction of hypotension, and then returned to baseline values by 30 minutes (Table 2.6). Sodium decreased over time only when dogs received LRS and chloride was not different between groups (Table 2.6). Ionized calcium was significantly decreased from baseline until 120 minutes in the HES group, and was significantly lower than time 0 at 15 and 30 minutes. Ionized calcium was significantly decreased from baseline at time 0, 60, and 90 minutes in the LRS group (Table 2.6).

One dog had diarrhea 24 hours following HES administration. Three dogs administered LRS had fluid dripping from their noses, 5 had chemosis, and 3 vomited in the immediate recovery phase from anesthesia. Chemosis resolved within 4 hours and no further episodes of vomiting were observed.

### 2.3 Discussion

The data demonstrate that: 1) In contrast to LRS, HES increases SABP in dogs with isoflurane-induced hypotension; 2) DABP decreases in dogs administered LRS; 3) cardiac index and DO<sub>2</sub> increase after administration of HES or LRS; and 4) arterial blood pressure may not be the single best indicator of successful fluid resuscitation. These data indicate that treatment of isoflurane-induced hypotension with HES is more effective than LRS.

The administration of HES and LRS increased BV, but HES increased BV more quickly, for a longer duration, and with significantly less volume than LRS (Figure 2.7). The volume and duration of LRS administration was twice that of HES. In addition, the large volume administration of LRS resulted in hemodilution and decreased oncotic pressure. Previous studies have demonstrated this may disrupt the endothelial glycocalyx leading to decreased flow resistance and loss of fluid into the interstitium (Pries 1998, Chappell 2008). The effects of isoflurane on crystalloid fluid accumulation in the extravascular space would also explain the loss of intravascular volume in dogs with isoflurane-induced hypotension (Connolly 2003, Norberg 2007). Blood volume in the NFA group most likely resulted in a decreased capillary hydrostatic pressure that caused a fluid shift from the interstitium into the vasculature (Wright 2008). Auto-transfusion of fluid from the interstitium to the vasculature would account for the increase in BV and decrease in albumin we observed in the NFA group.

Systolic arterial blood pressure, MABP, and DABP increased only with HES administration, but CI increased with LRS and HES administration. CI in the HES group was not statistically different from the LRS group at any time point. Systemic vascular resistance decreased in all groups, but to a lesser extent during NFA, possibly indicating that isoflurane-induced vasodilation persisted to a greater degree during fluid administration, compared with NFA.

There was no difference in HR between groups. Heart rate in the HES group increased significantly at 45 minutes compared with time 0, but this was not significant. The lack of significant difference between the treatment groups may be due to the small sample size and the statistical method chosen. However, the baroreceptor reflex is blunted during inhalant anesthesia and this could possibly explain the lack of an HR increase in all dogs during isoflurane-induced hypotension (Muir 2007).

Blood pressure may not be the single best indicator of successful fluid resuscitation. In the present study although ABP did not increase with LRS administration, other indices of cardiovascular performance such as CI (which increased), SVR, and DO<sub>2</sub>, were not different between HES and LRS. Previous studies in humans demonstrated that although LRS was ineffective in maintaining arterial blood pressure, CI increased (Wo 1993, Kamenik 2001, Dyer 2008). An increase in CI with little or no increase in SABP during LRS administration is likely due to factors that decrease SVR. In addition, studies in septic people suggest that CI and DO<sub>2</sub> should be determined and used in conjunction with arterial blood pressure as indices of successful fluid resuscitation (Hayes 1994). In the present study, there was no significant difference in DO<sub>2</sub> between the HES and LRS groups.

Other factors including vessel diameter and length, organization of vascular beds, and the physical properties of blood (density, viscosity) also influence resistance to blood flow, and therefore tissue perfusion (Whittaker 1933, Muir 2007). A decrease in viscosity during hemodilution results in an increase in blood flow and CO without a concurrent increase in ABP (Pries 1998, Teyssier 1998). This could, in part, explain the increase in CI we observed during LRS administration since BV increased during LRS administration and blood viscosity, TP, PCV, albumin, and COP all decreased. Blood flow increases with a decrease in vessel resistance according to the Poiseuille-Hagen equation (Sirs 1991, Muir 2007). This same equation also predicts that arterial blood pressure decreases as blood viscosity decreases. Fluid administration can result in an increase in vascular capacitance, a decrease in SVR, and little to no change in CO (Scott-Douglas 2002). The net result of these effects upon tissue blood flow may be an increase in tissue perfusion providing adequate tissue perfusion can be maintained.

Blood viscosity, PCV, TP, albumin, and COP decreased during LRS administration indicating hemodilution. Viscosity also decreased during HES administration, though not to the same degree as with LRS administration. Hemodilution can impair autoregulation and decrease cerebral perfusion (Shoemaker 2007). Excessive fluid administration resulting in extreme hemodilution (PCV 50% less than baseline value) decreases blood viscosity and vessel wall shear stress (Martini 2006, Muir 2007). Shear stress in the cardiovascular system describes the stress against vascular endothelium, and is influenced by blood viscosity and flow (Windberger 2003). If shear stress is reduced, tissue oxygenation is reduced (Martini 2006). However, decreased blood (plasma) viscosity promotes blood flow and has been demonstrated to increase CO (Martini 2006, Muir 2007). Maintaining plasma viscosity above 2.2 cP has been recommended in order to provide adequate vessel wall shear stress for nitric oxide production, vasodilation and DO<sub>2</sub> (Martini 2006). Viscosity reached a nadir of 2.9 cP at 60 minutes in the LRS group, which was also when the maximum volume of LRS had been administered and fluids were discontinued. Viscosity returned to 3.4 cP within one hour of terminating LRS administration. The effects of LRS on viscosity in this study were related to dose and duration, and were short-lived. Hetastarch was discontinued at 30 minutes, while LRS was discontinued at 60 minutes. However, at 30 minutes the viscosity in the HES group was significantly higher than in the LRS group. The COP was significantly higher in the HES group compared with the LRS group, and returned to baseline within 24 hours in both groups. Dogs in the NFA group had a decrease in COP one hour after time 0, but returned to baseline 24 hours post experiment. Viscosity in the LRS group, TP in all groups, and PCV in the HES group were all significantly higher at 24 hours than at baseline, which may indicate increased urine production and/or decreased oral fluid intake during the 24 hours following the experiment, as these parameters are indicators of hemoconcentration. In this experiment, normovolemic dogs received fluids. As a result, hydration status was increased, leading to decreased intake of fluids and increased urination. The stress of anesthesia may have also contributed to hemoconcentration in the 24-hours post experiment due to decreased oral intake of fluids (Muir 2007).

Packed cell volume, TP, and albumin tended to decrease during HES administration, but were not significantly lower than baseline values. HES administration impacts TP values when measured by refractometry. As an increasing volume of HES is administered, the TP value approaches 4.5 g/dL, the refractometer reading for HES itself (Hughes 2006). This may have impacted the total protein values for the HES samples.

There were no unexpected or clinically-relevant changes in pH, PaCO<sub>2</sub>, PaO<sub>2</sub>, sodium, calcium, or chloride in any of the three groups. No hyperchloremic acidosis occurred during HES administration, most likely due to the small volume of chloride administered (HES dose was a maximum of 40 mL/kg). The decreased albumin concentrations in the HES and LRS groups did not result in a significant increase in pH in this study, despite the fact that hypoalbuminemia is associated with an alkalosis (Constable 2005). It is likely that a hypoalbuminemic acidosis was not seen in this study because an albumin decrease of 1-g/dL results in a pH increase of 0.047, which is within the standard deviation (Constable 2005). In all treatment groups, potassium increased slightly for a short time during hypotension. Potassium may have been released from within cells during the initial period of hypotension, but was either eliminated by the kidneys or returned to cells when intravascular volume was increased, either by fluid administration or fluid redistribution from the interstitium (Chappell 2008).

Five of six dogs that received LRS exhibited one or more clinical signs associated with fluid overload, including serous nasal discharge, chemosis, and vomiting (Cornelius 1978). None of the side effects were considered serious, and all resolved within 24 hours. Fluid retention increases during isoflurane anesthesia as a result of reduced clearance and slower distribution into the interstitium (Norberg 2007). Large volume colloid administration is associated with coagulopathies due to an unknown mechanism, while large volume crystalloid administration can induce a hemodilution-induced coagulopathy (Hughes 2001, Cotton 2006). There were no clinical signs in any of the dogs that would indicate development of a coagulopathy, despite the dose of HES being twice the recommended daily dose of 20 mL/kg and the hemodilution resulting from LRS administration (Kudnig 2002). However, no objective tests of coagulation were performed. The HES dosage in this study was based on pilot data in anesthetized dogs that revealed no observable adverse effects.

There are several limitations of the study. The investigators were not blinded to the treatments and this could have attributed to bias. The isoflurane concentration was not reduced after inducing hypotension. Common clinical practice during hypotension is to administer fluids and decrease the isoflurane concentration. However, the goal of the study was to determine the effects of fluid administration on blood pressure during isoflurane-induced hypotension. Urine output and urine specific gravity were not measured and may have provided additional information regarding renal perfusion and function during isoflurane-induced hypotension and fluid administration. Reduced perfusion due to hypotension and fluid overload can lead to renal failure (Chappell 2008). Blood volume in the splanchnic circulation and microvascular blood flow were not measured and would have been affected by volume loading and isoflurane anesthesia. Hetastarch and LRS were chosen because they are commonly available fluids in most veterinary practices. The electrolyte and ionic composition of the two fluids is different. The carrier for HES is 0.9% saline, while LRS is a balanced electrolyte solution that contains other ions in addition to sodium and chloride. Although there were no changes in measured electrolytes between the three groups, the differences in electrolyte composition, presence of lactate in LRS, and the differences in pH of the fluids may have influenced our results.

In conclusion, HES but not LRS increased SABP despite the relatively lower volume of HES administered. Both fluids increased CI, and DO<sub>2</sub> decreased slightly in the LRS group. The ideal resuscitation fluid for isoflurane-induced hypotension should address the condition of the whole patient, the reason for anesthesia and/or surgery, and sensible and insensible fluid losses (Chappell 2008). In the non-anesthetized patient the choice of crystalloid or colloid depends on the cause of hypotension. A crystalloid is more appropriate during interstitial fluid loss such as that seen during dehydration. A colloid is more effective to replace the loss of intravascular volume as seen in acute hemorrhage. The correct fluid choice for isoflurane-induced hypotension is unclear. If the end-point of resuscitation is a relatively rapid return to normal ABP then our study indicates that HES is the better fluid choice. If the choice is based on improvement in CI and minimal changes in DO<sub>2</sub>, then either fluid is effective. However, HES but not LRS improved all 3 indices. Interestingly, no dog in the NFA group appeared to suffer any long term consequences as a result of 120 minutes of isoflurane-induced hypotension. Mean arterial blood pressures in all dogs stayed between 40 and 60 mmHg, and as a result, CI was unaffected (Lam 1983, Lam 1990, Tomiyasu 1999), and DO<sub>2</sub> was

minimally decreased. The present study supports HES over LRS for the treatment of isoflurane-induced hypotension in healthy dogs.

Dog	Isoflurane MAC (%)
1	1.2
2	1.3
3	1.3
4	1.3
5	1.2
6	1.3

Table 2.1. Isoflurane MAC values

Parameter	Group	Baseline	0 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min	180 min
_	Hetastarch	$37.5\pm0.5^{\diamond}$	$37.9\pm0.6$	$37.5 \pm 0.5^{\ddagger}$	$37.5 \pm 0.4$	$37.5\pm0.4$	$37.8\pm0.3^{\diamond}$	$38.0\pm0.4^{\diamond}$	$38.2\pm0.4^{\Diamond}$	$38.3\pm0.4^\dagger$	$38.3\pm0.2^\dagger$
1  emp	LRS	$36.9\pm0.3$	$38.0\pm0.4^{\dagger}$	$37.8\pm0.3^{\dagger\ddagger}$	$37.5\pm0.3^{\dagger\ddagger}$	$37.3 \pm 0.3^{\ddagger}$	$37.2\pm0.4^{\ddagger}$	$37.2 \pm 0.4^{\ddagger*}$	$37.6\pm0.3^\dagger$	$37.8\pm0.3^\dagger$	$38.2\pm0.3^\dagger$
(°C)	No fluids	$37.3\pm0.2$	$38.0\pm0.6^{\dagger}$	$38.0\pm0.4$	$37.9\pm0.4$	$37.9\pm0.5$	$37.9\pm0.4$	$37.8\pm0.3$	$37.9\pm0.3$		
EtIso (%)	Hetastarch	$1.9 \pm 0.4$	$3.2\pm0.6^{\dagger}$	$3.1 \pm 0.6$	$3.1 \pm 0.6$	$3.0\pm0.5^{\dagger}$	$3.1\pm0.5^{\dagger}$	$3.1\pm0.6^{\dagger}$	$3.1\pm0.6^{\dagger}$	$3.1 \pm 0.5$	$3.1 \pm 0.5$
	LRS	$1.8 \pm 0.2$	$3.2\pm0.3^{\dagger}$	$3.2\pm0.3^\dagger$	$3.2\pm0.3^\dagger$	$3.2\pm0.4^\dagger$	$3.2\pm0.3^\dagger$	$3.3\pm0.3^\dagger$	$3.3\pm0.3^{\dagger}$	$3.4\pm0.3^{\dagger}$	$3.4\pm0.4^{\dagger}$
	No fluids	$1.9\pm0.3$	$3.0\pm0.4^\dagger$	$3.1\pm0.4^\dagger$	$3.1\pm0.4^\dagger$	$3.1\pm0.4^\dagger$	$3.1\pm0.4^{\dagger}$	$3.1\pm0.4^\dagger$	$3.2\pm0.4^\dagger$		

Table 2.2. Body temperature and end-tidal isoflurane concentrations in isoflurane-anesthetized dogs.

Data are presented as mean ± standard deviation. Temp, body temperature; EtIso, end-tidal isoflurane.

<sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group \* = Significant difference (p < 0.05) from LRS group

	Parameter	Group	Baseline	0 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min	180 min
	HR	Hetastarch	$114\pm26$	$118\pm19$	$121 \pm 14$	$124 \pm 13$	$128\pm20^{\ddagger}$	$133\pm19^{\ddagger}$	$135\pm18^\ddagger$	$135\pm17^{\ddagger}$	$135\pm17^{\ddagger}$	$135\pm15^{\ddagger}$
	(beats/	LRS	$112 \pm 17$	$118\pm12$	$116 \pm 10$	$122 \pm 9$	$124 \pm 10$	$124 \pm 11$	$121\pm14$	$117\pm13$	$117\pm14$	$119\pm12$
	min)	No fluids	$123\pm19$	$125\pm10$	$123\pm10$	$123\pm12$	$122 \pm 12$	$121 \pm 12$	$123\pm10$	$123\pm10$		
		Hetastarch	$110\pm9$	$80\pm0^{\dagger}$	$93\pm10^{\dagger\ddagger \ast\diamond}$	$92\pm7^{\dagger\ddagger\ast\Diamond}$	$95\pm7^{\dagger\ddagger^{*\diamond}}$	$99 \pm 11^{\ddagger \ast \Diamond}$	$97\pm9^{\dagger\ddagger\ast\diamond}$	$98 \pm 13^{\ddagger * \diamond}$	$101\pm16^{\ddagger\Diamond}$	$99\pm16^{\ddagger\Diamond}$
	SABP	LRS	$120 \pm 24$	$80\pm0^{\dagger}$	$79\pm7^\dagger$	$82\pm6^\dagger$	$79\pm8^\dagger$	$78\pm8^\dagger$	$75\pm9^\dagger$	$73\pm6^{\dagger\ddagger}$	$72\pm8^\dagger$	$71\pm12^\dagger$
	(mmHg)	No fluids	$116\pm18$	$80\pm1^\dagger$	$77\pm 6$	$76 \pm 4$	$77\pm8^\dagger$	$75\pm8^\dagger$	$73\pm13^\dagger$	$73\pm11^{\dagger}$		
	5 . 55	Hetastarch	65 ± 11	$43\pm5^\dagger$	$46\pm7^\dagger$	$45\pm9^\dagger$	$47 \pm 7^{\uparrow \Diamond}$	49 ± 11	$47\pm6^{\dagger\Diamond}$	$47\pm9^{\dagger\Diamond}$	$48\pm9$	$46\pm9^{\Diamond}$
	DABP	LRS	$65\pm8$	$45\pm9^\dagger$	$40\pm6^{\dagger\ddagger}$	$39\pm6^{\dagger\ddagger}$	$38 \pm 6^{\dagger\ddagger}$	$38\pm6^\dagger$	$36\pm6^{\dagger\ddagger}$	$37\pm5^{\dagger\ddagger}$	$39\pm8^{\dagger}$	$36\pm6^{\dagger\ddagger}$
	(mmHg)	No fluids	$69\pm9$	$45\pm6^\dagger$	$44\pm 8$	$42\pm7$	$42\pm7^\dagger$	$41\pm6^\dagger$	$40\pm7^\dagger$	$39\pm6^\dagger$		
		Hetastarch	$78 \pm 12$	$54\pm4^\dagger$	$61\pm5^{\dagger\ddagger\Diamond}$	$60\pm9^\dagger$	$62 \pm 6^{\dagger \ddagger \Diamond}$	$65 \pm 9^{\ddagger \Diamond}$	$63\pm5^{\dagger\ddagger\ast\Diamond}$	$63 \pm 9^{\ddagger 0}$	$65\pm10^{\ddagger\Diamond}$	$63 \pm 9^{\ddagger 0}$
	MABP	LRS	$82 \pm 12$	$53\pm4^\dagger$	$53\pm5^\dagger$	$53\pm7^\dagger$	$52\pm7^\dagger$	$52\pm8^\dagger$	$50\pm8^\dagger$	$49\pm7^{\dagger}$	$50\pm8^\dagger$	$50\pm8^\dagger$
	(mmHg)	No fluids	$84 \pm 12$	$57\pm4^\dagger$	$55\pm7$	$53\pm7$	$53 \pm 7$	$52\pm6^\dagger$	$52\pm7^\dagger$	$51\pm7^\dagger$		
	MDAD	Hetastarch	$16.7\pm2.9$	$17.2\pm2.7$	$21.1\pm4.3^{\dagger\ddagger}$	$23.8\pm4.9^{\dagger\ddagger*}$	$24.9\pm5.9^{\dagger^{\star\ast}_{\star}}$	$24.3\pm5.2^{\dagger\ddagger\ast}$	$22.7\pm4.9^{\dagger\ddagger}$	$22.0\pm4.5^{\dagger\ddagger}$	$22.0\pm4.9^{\dagger\ddagger}$	$21.8\pm4.9^{\dagger\ddagger}$
	MPAP	LRS	$17.3\pm2.4$	$16.9\pm2.8$	$21.7 \pm 3.6^{\dagger \ddagger *}$	$24.3\pm4.0^{\dagger \ddagger *}$	$25.3\pm3.8^{\dagger^{\star\ast}_{\star}}$	$25.4\pm3.7^{\dagger\ddagger\ast}$	$21.6\pm3.6^{\dagger\ddagger}$	$19.3\pm2.7^{\dagger\ddagger}$	$19.8\pm3.1^{\dagger\ddagger}$	$20.9\pm4.7^{\dagger}$
	(IIIIIHg)	No fluids	$15.4 \pm 4.0$	$15.7\pm3.6$	$15.6\pm2.9$	$15.8\pm3.4$	$15.9\pm3.2$	$15.8\pm3.2$	$16.2\pm4.3$	$16.6\pm3.6$		
33	D 4 D	Hetastarch	$4.2 \pm 1.4$	$5.1\pm2.0$	$7.2\pm3.0^{\dagger\ddagger}$	$9.3\pm4.2^{\dagger\ddagger}$	$9.6\pm3.9^{\dagger\ddagger}$	$8.7\pm3.6^{\dagger\ddagger}$	$7.9 \pm 2.6^{\dagger \ddagger *}$	$7.3\pm2.5^{\dagger\ddagger}$	$6.9\pm2.5^\dagger$	$6.8\pm2.4^\dagger$
	KAP (mmHa)	LRS	$2.8 \pm 1.6$	$3.9\pm1.5^\dagger$	$6.2\pm2.0^{\dagger\ddagger}$	$7.4\pm2.5^{\dagger\ddagger}$	$8.6 \pm 2.3^{\dagger \ddagger *}$	$9.0 \pm 2.4^{\dagger \ddagger *}$	$7.3\pm2.8^{\dagger\ddagger}$	$6.4\pm1.7^{\dagger\ddagger}$	$5.9\pm1.6^{\dagger\ddagger}$	$5.5\pm1.6^{\dagger\ddagger}$
	(mmig)	No fluids	$3.0\pm1.6$	$4.3\pm1.5^{\dagger}$	$4.3 \pm 1.4$	$4.4 \pm 1.4$	$4.2 \pm 1.4$	$4.3 \pm 1.4$	$4.0 \pm 1.4$	$4.0 \pm 1.4$		
	CI	Hetastarch	$147\pm47$	$106\pm27$	$158\pm28^{\ddagger\ast}$	$167\pm54$	$200\pm84$	$209\pm95$	$215\pm91$	$208\pm96$	$212\pm99$	$217\pm102$
	(mL/kg/	LRS	$165\pm27$	$113\pm16^\dagger$	$152\pm28^*$	$196\pm 39^{\ddagger\ast}$	$202\pm46^{*}$	$198\pm 53^*$	$179\pm55$	$151\pm39$	$160\pm55$	$168\pm53$
	min)	No fluids	$155\pm28$	$108\pm24^\dagger$	$110 \pm 24$	$117\pm26$	$119\pm27$	$124\pm25$	$129 \pm 25$	$125\pm18$		
	SVR	Hetastarch	$3200\pm777$	$2943 \pm 976$	$2092\pm495$	$2046\pm967^\ddagger$	$1905\pm989$	$2032 \pm 1240$	$1841\pm948^{\ddagger}$	$1939\pm978^\ddagger$	$1958 \pm 930$	$1874\pm962^\ddagger$
	(dyn sec	LRS	$2912\pm515$	$2632\pm515$	$1886\pm311^*$	$1438\pm277^{\dagger\ddagger\ast}$	$1332\pm305^{\dagger\ddagger\ast}$	$1360\pm341^{\dagger\ddagger\ast}$	$1503 \pm 363^{\dagger *}$	$1730\pm363^{\dagger\ddagger\ast}$	$1743\pm438^{\dagger\ddagger}$	$1627\pm278^\dagger$
	cm <sup>-5</sup> )	No fluids	$3175\pm555$	$3028\pm790$	$2856\pm836$	$2598 \pm 664$	$2556\pm 640$	$2380\pm557^\dagger$	$2262\pm480^\dagger$	$2268\pm376^\dagger$		

Table 2.3. Hemodynamic values in isoflurane-anesthetized dogs

Data are presented as mean ± standard deviation. HR, heart rate; SABP, systolic arterial blood pressure; DABP, diastolic arterial blood pressure; MABP, mean arterial blood pressure; MPAP, mean pulmonary artery pressure; RAP, right atrial pressure; CI, cardiac index; SVR, systemic vascular resistance.  $^{\dagger}$  = Significant difference (p < 0.05) from baseline value for same treatment group  $^{\ddagger}$  = Significant difference (p < 0.05) from time 0 value for same treatment group  $^{\ddagger}$  = Significant difference (p < 0.05) from No fluids group

 $^{\circ}$  = Significant difference (p < 0.05) from LRS group

Parameter	Group	Baseline	0 min	15 min	30 min	45 min	60 min	90 min	120 min	150 min	180 min
	Hetastarch	$40 \pm 3$	$40 \pm 3$	$32\pm4^{\dagger\ddagger}$	$27\pm5^{\dagger\ddagger}$	$27\pm5^{\dagger\ddagger}$	$29\pm4^{\dagger\ddagger}$	$29\pm4^{\dagger\ddagger}$	$30\pm4^{\dagger\ddagger}$	$31 \pm 4^{\dagger\ddagger}$	$32\pm4^{\dagger\ddagger}$
Hct	LRS	$41 \pm 1$	$38\pm 6$	$31\pm5^{\dagger\ddagger}$	$29\pm4^{\dagger\ddagger}$	$29\pm4^{\dagger\ddagger}$	$28\pm3^{\dagger\ddagger}$	$30\pm4^{\dagger\ddagger}$	$30\pm3^{\dagger\ddagger}$	$29\pm6^{\dagger\ddagger}$	$33\pm8^\dagger$
(%)	No fluids	$40 \pm 2$	$34\pm 6$	$34 \pm 7$	33 ± 7	$32 \pm 6$	$32\pm 6$	$32 \pm 10$	30 ± 12		
	Hetastarch	$0.1 \pm 4.9$	$0.1 \pm 9.0$	$23.9\pm16.3^{\dagger\ddagger}$	$51.6\pm27.8^{\dagger\ddagger}$	$54.1\pm27.4^{\dagger\ddagger}$	$44.4\pm26.2^{\dagger\ddagger}$	$40.2\pm23.2^{\dagger\ddagger}$	$35.9\pm21.1^{\dagger\ddagger}$	$30.5\pm21.1^{\dagger\ddagger}$	$26.5\pm20.0^{\dagger\ddagger}$
BV	LRS	$-0.7 \pm 1.4$	$9.8\pm21.3$	$35.4\pm27.4$	$42.6\pm22.3^{\dagger\ddagger}$	$46.2\pm19.0^{\dagger\ddagger}$	$47.1\pm17.2^{\dagger\ddagger}$	$41.1\pm16.0^{\dagger\ddagger}$	$39.6\pm12.7^{\dagger\ddagger}$	$43.0\pm24.8^{\dagger\ddagger}$	$31.6\pm34.0$
(%)	No fluids	$1.4 \pm 1.4$	$19.0\pm21.0$	$23.6\pm24.6$	$25.8\pm26.5$	$23.7\pm19.3$	$28.4\pm22.5$	$25.7\pm34.0$	$36.1\pm42.7$		

Table 2.4. Blood volume change and in-line hematocrit values in isoflurane-anesthetized dogs

Data are presented as mean  $\pm$  standard deviation. BV, blood volume change, Hct, in-line hematocrit. <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group <sup>\*</sup> = Significant difference (p < 0.05) from No fluids group <sup>◊</sup> = Significant difference (p < 0.05) from LRS group

Parameter	Group	Baseline	0 min	15 min	30 min	60 min	120 min	180 min	24 hours
Visc (cP)	Hetastarch	$4.7 \pm 0.3$	$4.8 \pm 0.3$	$4.3 \pm 0.3$	$4.0\pm0.2^{\dagger\ddagger\diamond}$	$3.9\pm0.3^{\dagger\ddagger\diamond}$	$3.8\pm0.2^{\dagger\ddagger}$	$4.2\pm0.2^{\dagger\ddagger\diamond}$	$5.6 \pm 0.9$
	LRS	$4.2 \pm 1.0$	$4.2 \pm 0.4$	$3.4 \pm 0.4^{\ddagger}$	$3.1 \pm 0.2^{\ddagger*}$	$2.9 \pm 0.3^{\dagger \ddagger *}$	$3.4 \pm 0.4^{\ddagger}$	$3.6\pm0.2^{\dagger\ddagger\diamond}$	$5.7\pm0.4^{\dagger\ddagger}$
	No fluids	$4.5\pm0.4$	$4.5 \pm 0.1$	$4.3\pm0.2$	$4.3 \pm 0.2$	$4.5 \pm 0.4$	$4.4 \pm 0.6$		$5.5\pm0.2^{\ddagger}$
PCV (%)	Hetastarch	$39 \pm 2$	37 ± 2	30 ± 5	$26 \pm 7$	$28 \pm 5$	29 ± 5		$46 \pm 2^{\dagger\ddagger}$
	LRS	$38 \pm 3$	37 ± 2	$31 \pm 3^{\dagger}$	$28\pm4^{\ddagger^*}$	$27 \pm 3^{\dagger \ddagger *}$	$30 \pm 2^{\ddagger*}$		$47 \pm 3^{\ddagger}$
	No fluids	$37 \pm 2$	36 ± 1	35 ± 3	$36 \pm 2$	36 ± 2	$36 \pm 2$		$46 \pm 4^{\ddagger}$
TP (g/dL)	Hetastarch	$5.0 \pm 0.4$	$4.9 \pm 0.5$	$4.8\pm0.3^{\diamond}$	$4.5\pm0.4^{\diamond}$	$4.5\pm0.5^{\diamond}$	$4.4\pm0.4^{\diamond}$		$6.5\pm0.7^{\dagger\ddagger}$
	LRS	$5.2 \pm 0.4$	$5.0 \pm 0.3$	$3.7\pm0.6^{\dagger*}$	$3.4 \pm 0.5^{\dagger \ddagger *}$	$3.1 \pm 0.5^{\dagger \ddagger *}$	$3.5 \pm 0.2^{\dagger \ddagger *}$		$6.4 \pm 0.5^{\dagger \ddagger}$
	No fluids	$4.8 \pm 0.2$	$4.9 \pm 0.3$	$4.6 \pm 0.3$	$4.7 \pm 0.3$	$4.8 \pm 0.2$	$4.8 \pm 0.3$		$6.3\pm0.5^{\dagger\ddagger}$
Albumin (g/dL)	Hetastarch	$3.2 \pm 0.1$	$3.1 \pm 0.1$	$2.2 \pm 0.5$	$2.0 \pm 0.6$	$2.1\pm0.5^{\dagger}$	$2.1 \pm 0.6$		$3.0 \pm 0.4$
	LRS	$3.2 \pm 0.1$	$3.1\pm0.1^\dagger$	$2.4 \pm 0.2^{\dagger \ddagger *}$	$2.1 \pm 0.2^{\dagger \ddagger *}$	$1.9 \pm 0.2^{\dagger \ddagger *}$	$2.3 \pm 0.1^{\dagger \ddagger *}$		$3.3 \pm 0.2$
	No fluids	$3.1 \pm 0.1$	$3.0 \pm 0.1$	$2.9\pm0.1^\dagger$	$2.9 \pm 0.1$	$2.9 \pm 0.2$	$2.9 \pm 0.1$		$3.3 \pm 0.3$
COP (mmHg)	Hetastarch	$17.3 \pm 1.2$	$17.5 \pm 1.8$	$22.2\pm3.5^{*\Diamond}$	$23.1\pm4.2^{\diamond}$	$20.3\pm3.2^{\diamond}$	$18.7\pm3.0^{\diamond}$		$23.6 \pm 2.7^{\dagger\ddagger}$
	LRS	$18.4 \pm 1.4$	$17.3 \pm 1.0^{\dagger}$	$11.6 \pm 1.9^{\dagger \ddagger *}$	$10.0 \pm 1.3^{\dagger \ddagger *}$	$8.0 \pm 1.8^{\dagger \ddagger *}$	$10.8 \pm 1.5^{\dagger \ddagger *}$		$20.4 \pm 2.4$
	No fluids	$17.1 \pm 1.0$	$16.1 \pm 1.0$	$15.9\pm1.3$	$16.4 \pm 1.2$	$15.8\pm1.2^\dagger$	$16.1 \pm 1.6$		$19.7 \pm 2.9$

35 Table 2.5. Hemorheologic values in isoflurane-anesthetized dogs Data are presented as mean ± standard deviation. Visc, whole blood viscosity; PCV, packed cell volume; TP, total protein; COP, colloid osmotic pressure.

The solution is the pressure.  $^{\dagger}$  = Significant difference (p < 0.05) from baseline value for same treatment group  $^{\ddagger}$  = Significant difference (p < 0.05) from time 0 value for same treatment group  $^{\ast}$  = Significant difference (p < 0.05) from No fluids group  $^{\diamond}$  = Significant difference (p < 0.05) from LRS group

Parameter	Group	Baseline	0 min	15 min	30 min	60 min	120 min	24 hours
рН	Hetastarch	$7.33 \pm 0.05$	$7.31\pm0.03$	$7.29\pm0.04$	$7.32\pm0.04$	$7.32\pm0.03$	$7.33 \pm 0.03$	
	LRS	$7.34\pm0.02$	$7.32\pm0.03$	$7.31\pm0.05$	$7.32\pm0.04$	$7.36\pm0.04$	$7.36 \pm 0.03^{*}$	
	No fluids	$7.33 \pm 0.02$	$7.33\pm0.02$	$7.33\pm0.02$	$7.32\pm0.03$	$7.31\pm0.04$	$7.31\pm0.02$	
PaO <sub>2</sub> (mmHg)	Hetastarch	$622 \pm 13$	$602 \pm 14$	$588 \pm 38$	$596 \pm 20$	591 ± 30	$596 \pm 14$	
	LRS	$608 \pm 51$	$578\pm41^{\dagger}$	$566 \pm 64$	$565 \pm 44$	$571 \pm 50$	$582 \pm 38$	
	No fluids	$599\pm40$	$586\pm28$	$584 \pm 32$	$582 \pm 32$	$552 \pm 40$	$540 \pm 46$	
PaCO <sub>2</sub> (mmHg)	Hetastarch	$40.8 \pm 2.2$	$40.3\pm3.6$	$42.3\pm4.2$	$38.4 \pm 3.1$	$39.3 \pm 2.1$	$38.0 \pm 3.0$	
	LRS	$39.3\pm2.0$	$40.9\pm3.7$	$40.4\pm4.0$	$40.2 \pm 3.5$	$36.8\pm2.9$	$38.2 \pm 3.6$	
	No fluids	$39.3 \pm 1.6$	$39.0\pm2.2$	$37.7\pm3.2$	$39.1\pm2.7$	$38.6\pm4.7$	$39.1\pm3.3$	
Lactate (mmol/L)	Hetastarch	$2.5 \pm 0.9$	$2.4 \pm 0.7$	$1.8 \pm 0.6$	$1.6 \pm 0.4$	$1.8 \pm 0.4$	$1.8 \pm 0.5$	$1.9\pm0.8$
	LRS	$2.1 \pm 0.4$	$2.3\pm0.5$	$4.8\pm2.5$	$4.7\pm2.2$	$4.6\pm1.9$	$2.2 \pm 0.3^{*}$	$1.5 \pm 0.3$
	No fluids	$2.3\pm0.2$	$2.2\pm0.2$	$2.0 \pm 0.3$	$1.9\pm0.1^{\ddagger}$	$1.8\pm0.2^{\ddagger}$	$1.7\pm0.2^{\dagger\ddagger}$	$2.0 \pm 0.4$
Potassium (mmol/L)	Hetastarch	$3.9 \pm 0.2$	$4.9\pm0.7^{\dagger}$	$4.4 \pm 0.7^{\ddagger}$	$4.5\pm0.5$	$4.7 \pm 0.6$	$4.8 \pm 0.9$	
	LRS	$3.9 \pm 0.4$	$4.8\pm0.9^\dagger$	$4.4 \pm 1.0^{\ddagger}$	$4.4\pm0.9^{\ddagger}$	$4.5 \pm 0.9$	$4.6 \pm 0.8$	
	No fluids	$3.9\pm0.4$	$4.7\pm0.7^{\dagger}$	$4.4\pm0.8^{\ddagger}$	$4.6\pm0.8$	$4.4\pm0.6$	$5.0\pm0.8$	
Sodium (mmol/L)	Hetastarch	$144 \pm 2$	$143 \pm 2$	$143 \pm 2$	$143 \pm 2$	141 ± 3	$141 \pm 2$	
	LRS	$144 \pm 2$	$143 \pm 2^{\dagger}$	$143 \pm 3$	$142 \pm 2^{\dagger}$	$140\pm2^{\dagger\ddagger}$	$139\pm2^{\dagger}$	
	No fluids	$144 \pm 3$	$142\pm3^\dagger$	$143 \pm 3$	$142 \pm 3^{\dagger}$	$140 \pm 4$	$143 \pm 4$	
Calcium (meq/L)	Hetastarch	$2.7 \pm 0.1$	$2.5\pm0.1^\dagger$	$2.4\pm0.1^{\dagger\ddagger}$	$2.3\pm0.1^{\dagger\ddagger}$	$2.4\pm0.2^\dagger$	$2.4 \pm 0.1^{\dagger}$	
	LRS	$2.7 \pm 0.1$	$2.5\pm0.2^\dagger$	$2.4\pm0.2$	$2.4\pm0.2$	$2.4\pm0.1^{\dagger}$	$2.4\pm0.2^{\dagger}$	
	No fluids	$2.6 \pm 0.1$	$2.6\pm0.1$	$2.5\pm0.2$	$2.5\pm0.1$	$2.3 \pm 0.3$	$2.3 \pm 0.4$	
Chloride (mmol/L)	Hetastarch	$114 \pm 2$	$115 \pm 4$	$117 \pm 4$	$120 \pm 5^{\ddagger}$	$119 \pm 7$	$120 \pm 6$	
	LRS	115 ± 3	$116 \pm 3$	116 ± 3	$116 \pm 2$	$115 \pm 2$	$117 \pm 7$	
	No fluids	$115 \pm 4$	$115 \pm 3$	$117 \pm 7$	$115 \pm 4$	$121 \pm 9$	$117 \pm 3$	
DO <sub>2</sub> (mL/min)	Hetastarch	$403 \pm 134$	$284 \pm 70$	$371 \pm 63^*$	$342 \pm 102$	$416 \pm 174$	430 ±182	
	LRS	$449 \pm 72$	$294\pm43^\dagger$	$341\pm 62^\dagger$	$411 \pm 71^{*}$	$394\pm93$	$325 \pm 81$	
	No fluids	409 ± 83	$278\pm72^{\dagger}$	$277 \pm 73^{\dagger}$	$294 \pm 78$	$295\pm74^\dagger$	$304 \pm 67$	

Table 2.6. Blood biochemical and oxygen delivery values in isoflurane-anesthetized dogs Data are presented as mean  $\pm$  standard deviation. PaO<sub>2</sub>, arterial partial pressure of oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; DO<sub>2</sub>, systemic oxygen delivery. <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group <sup>\*</sup> = Significant difference (p < 0.05) from No fluids group <sup>◊</sup> = Significant difference (p < 0.05) from LRS group

36



Figure 2.1. Heart Rate (beats per minute) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes.

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group Error bars indicate standard error of the mean (SEM).





- <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group
- <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group
- \* = Significant difference (p < 0.05) from No fluids group
- $^{\diamond}$  = Significant difference (p < 0.05) from LRS group



Figure 2.3. Diastolic arterial blood pressure (mmHg) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes. <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group

 $^{\circ}$  = Significant difference (p < 0.05) from LRS group

Error bars indicate SEM.



Figure 2.4. Mean pulmonary arterial pressure (mmHg) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes. <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group



Figure 2.5. Right atrial pressure (mmHg) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes. <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group <sup>\*</sup> = Significant difference (p < 0.05) from No fluids group Error bars indicate SEM.





- <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group
- <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group Error bars indicate SEM.



Figure 2.7. Systemic vascular resistance (dyne sec cm<sup>-5</sup>) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes.

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group

Error bars indicate SEM.



Figure 2.8. Blood volume change (%) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 45, 60, 90, 120, 150, and 180 minutes.

<sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group Error bars indicate SEM.



Figure 2.9. Viscosity (cP) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 60, 120, and 180 minutes, and 24 hours.

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group

 $^{\circ}$  = Significant difference (p < 0.05) from LRS group

Error bars indicate SEM.



Figure 2.10. Packed cell volume (%) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 60, and 120 minutes, and 24 hours.

<sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group



Figure 2.11. Total protein (g/dL) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 60, and 120 minutes, and 24 hours.

<sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group

\* = Significant difference (p < 0.05) from No fluids group

 $^{\circ}$  = Significant difference (p < 0.05) from LRS group

Error bars indicate SEM.



Figure 2.12. Colloid osmotic pressure (mmHg) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 60, and 120 minutes, and 24 hours.

- <sup>†</sup> = Significant difference (p < 0.05) from baseline value for same treatment group
- <sup>‡</sup> = Significant difference (p < 0.05) from time 0 value for same treatment group
- \* = Significant difference (p < 0.05) from No fluids group
- $^{\circ}$  = Significant difference (*p* < 0.05) from LRS group



Figure 2.13. Oxygen Delivery (mL  $O_2$ /min) at baseline, time 0 (SABP 80 mmHg), time 15, 30, 60, and 120 minutes.

\* = Significant difference (p < 0.05) from No fluids group

#### REFERENCES

1. Adams AP. Techniques of vascular control for deliberate hypotension during anaesthesia. *Br J Anaesth* 1975;47(7):777-792.

2. Alam H, Rhee P. New developments in fluid resuscitation. *Surg Clin North Am* 2007;87:55.

3. Anderson JA. Deliberate hypotensive anesthesia for orthognathic surgery: controlled pharmacologic manipulation of cardiovascular physiology. *Int J Adult Orthodontics Orthognathic Surg* 1986;1:133-159.

4. Antognini JF. Hypothermia eliminates isoflurane requirements at 20°C.

Anesthesiology 1993;78:1152-1156.

5. Antognini JF, Schwartz K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. *Anesthesiology* 1993;79:1244-1249.

6. Bijker JB, van Klei WA, Kappen TH, et al. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007;107:213-220.

7. Cabrales P, Tsai AG, Intaglietta M. Is resuscitation from hemorrhagic shock limited by blood oxygen-carrying capacity or blood viscosity? *Shock* 2007;27:380-389.

8. Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology* 2008;109:723-740.

 Connolly CM, Kramer GC, Hahn RG, et al. Isoflurane but not mechanical ventilation promotes extravascular fluid accumulation during crystalloid volume loading. *Anesthesiology* 2003;98:670-681.

10. Conzen PF, Hobbhahn J, Goetz AE, et al. Regional blood flow and tissue oxygen pressures of the collateral-dependent myocardium during isoflurane anesthesia in dogs. *Anesthesiology* 1989;70:442-452.

Constable PD, Stämpfli HR. Experimental determination of net protein charge and A<sub>tot</sub> and K<sub>a</sub> of nonvolatile buffers in canine plasma. *J Vet Intern Med* 2005;19:507-514.
 Conzen, PF, Habazetti H, Vollmar B, et al. Coronary microcirculation during halothane, enflurane, isoflurane, and adenosine in dogs. *Anesthesiology* 1992;76:261-270.

13. Cornelius LM, Finco DR, Culver DH. Physiologic effects of rapid infusion of Ringer's lactate solution into dogs. *Am J Vet Res* 1978;39:1185-1190.

Cotton BA, Guy JS, Morris JA, et al. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock* 2006;26:115-121.
 Cousins MJ, Skowronski G, Plummer JL. Anaesthesia and the kidney. *Anaesth Intens Care* 1983;11:292-317.

 Curtis MB, Bednarski RM, Majors L. Cardiovascular effects of vasopressors in isoflurane-anesthetized dogs before and after hemorrhage. *Am J Vet Res* 1989;50:1866-1871. 17. DiBartola SP, Bateman S. Introduction to fluid therapy. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*. 3<sup>rd</sup> ed. St. Louis:
Elsevier Inc., 2006;325-344.

18. Dutton RP. The role of deliberate hypotension. Hospital Med 2005;66:72-73.

 Dyer RA, Piercy JL, Reed AR, et al. Hemodynamic changes associated with spinal anesthesia for cesarean delivery in sever preeclampsia. *Anesthesiology* 2008;802-811.
 Dyson D, Sinclair M. Impact of dopamine or dobutamine infusions on cardiovascular variables after rapid blood loss and volume replacement during isofluraneinduced anesthesia in dogs. *Am J Vet Res* 2006;67:1121-1130.

21. Dyson DH, Marie MG, Schnurr D. Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. *J Am Anim Hosp Assoc* 1998;34:325-335.

22. Eger EI, Weiskopf RB, Eisenkraft JB. Mechanisms of Inhaled Anesthetic Actions.In: Eger EI, ed. *The Pharmacology of Inhaled Anesthetics*. United States: Dannemiller Memorial Educational Foundation, 2002;33-42.

23. Ewing KK, Mohammed HO, Scarlett JM, et al. Reduction of isoflurane anesthetic requirement by medetomidine and its restoration by atipamezole in dogs. *Am J Vet Res* 1993;54:294-299.

24. Fujiwara Y, Murray P. Effects of isoflurane anesthesia on pulmonary vascular response to K ATP channel activation and circulatory hypotension in chronically instrumented dogs. *Anesthesiology* 1999;90(3):799.

25. Gandhi SD, Weiskopf RB, Jungheinrich C, et al. Volume replacement therapy during major orthopedic surgery using voluven (hydroxyethyl starch 130/0.4) or hetastarch. *Anesthesiology* 2007;106:1120-1127.

26. Gaynor JS, Dunlop CI, Wagner AE, et al. Complications and mortality associated with anesthesia in dogs and cats. *J Am Anim Hosp Assoc* 1999;35:13-17.

27. Gelman, S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008;108:735-748.

28. Gordon AM, Wagner AE. Anesthesia-related hypotension in a small-animal practice. *Vet Med* 2006;101:22-26.

29. Grocott MPW, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesth Analg* 2005;100:1093-106.

30. Hayes MA, Timmins AC, Yau E, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New Eng J Med* 1994;330:1717-1722.

31. Hellyer PW, Mama KR, Shafford HL, et al. Effects of diazepam and flumazenil on minimum alveolar concentrations for dogs anesthetized with isoflurane or a combination of isoflurane and fentanyl. *Am J Vet Res* 2001;62:555-560.

32. Holowaychuk MK, Martin LG. Misconceptions about emergency and critical care: cardiopulmonary cerebral resuscitation, fluid therapy, shock, and trauma. *Compendium* 2006;28:420-431.

33. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* 2002;89:622-632.

34. Hughes D. Fluid therapy with artificial colloids: complications and controversies. *Vet Anaesth Analg* 2001;28:111-118.

35. Hughes D, Boag AK. Fluid therapy with macromolecular plasma volume expanders.
In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice.* 3<sup>rd</sup> ed. St. Louis: Elsevier Inc., 2006;621-634.

36. Kamenik M, Paver-Erzen V. The effects of lactated Ringer's solution infusion on cardiac output changes after spinal anesthesia. *Anesth Analg* 2001;92:710-714.

37. Kimberger O, Fleischmann E, Brandt S, et al. Supplemental oxygen, but not supplemental crystalloid fluid, increases tissue oxygen tension in healthy and anastomotic colon in pigs. *Anesth Analg* 2007;105:773-779.

38. Kovach AG, Sandor P. Cerebral blood flow and brain function during hypotension and shock. *Ann Rev Physiol* 1976;38:571-596.

39. Kudnig ST, Mama K. Perioperative fluid therapy. *J Am Vet Med Assoc* 2002;221:1112-1121.

40. Lam A. The choice of controlled hypotension during repair of intracranial aneurysms: techniques and complications. *Agressologie: revue internationale de physiobiologie et de pharmacologie appliquees aux effets de l'agression*. 1990;31(6):357.

41. Lam AM, Gelb AW. Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesth Analg* 1983;62:742-748.

42. Lee LA, Deem S, Glenny RW, et al. Effects of anemia and hypotension on porcine optic nerve blood flow and oxygen delivery. *Anesthesiology* 2008;108:864-862.

43. Lessard MR, Trepanier CA. Renal function and hemodynamics during prolonged isoflurane-induced hypotension in humans. *Anesthesiology* 1991;74:860-865.

44. Lessard M, Trepanier C, Brochu J, et al. Effects of isoflurane-induced hypotension on renal function and hemodynamics. *Can J Anesth* 1990;37(4 Pt 2):S42.

45. Lobetti R, Lambrechts N. Effects of general anesthesia and surgery on renal function in healthy dogs. *Am J Vet Res* 2000;61:121-124.

46. Lowell JA, Schifferdecker C, Driscoll DF, et al. Postoperative fluid overload: not a benign problem. *Crit Care Med* 1990;18:728-733.

47. Machado CEG, Dyson DH, Maxie MG. Effects of oxymorphone and hydromorphone on the minimum alveolar concentration of isoflurane in dogs. *Vet Anaesth Analg* 2006;33:70-77.

48. Manninen PH, Lam AM, Gelb AW. Electrocardiographic changes during and after isoflurane-induced hypotension for neurovascular surgery. *Can J Anesth* 1987;34(6):549-554.

49. Martini J, Cabrales P, Tsai AG, et al. Mechanotransduction and the homeostatic significance of maintaining blood viscosity in hypotension, hypertension and haemorrhage. *J Intern Med* 2006;259:364-372.

 McHugh GJ. Anaphylactoid reaction to pentastarch. *Can J Anaesth* 1998;45(3):270-272.

51. Muir WW. Cardiovascular system. In: Tranquilli WJ, Thurman JC, Grimm KA, eds. *Lumb and Jones' Veterinary Anesthesia and Analgesia*. 4<sup>th</sup> ed. Ames: Blackwell Publishing, 2007;61-116.

52. Muir WW. Considerations for general anesthesia. In: Tranquilli WJ, Thurman JC, Grimm KA, eds. *Lumb and Jones' Veterinary Anesthesia and Analgesia*. 4<sup>th</sup> ed. Ames: Blackwell Publishing, 2007;7-30.

53. Muir WW, Wiese AJ. Comparison of lactated Ringer's solution and a physiologically balanced 6% hetastarch plasma expander for the treatment of hypotension induced via blood withdrawal in isoflurane-anesthetized dogs. *Am J Vet Res* 2004;65(9):1189-1194.

54. Muir WW, Wiese AJ, March PA. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. *Am J Vet Res* 2003;64:1155-1160.

55. Mutoh T, Nishimura R, Kim H, et al. Cardiopulmonary effects of sevoflurane, compared with halothane, enflurane, and isoflurane, in dogs. *Am J Vet Res* 1997;58:885-890.

56. Newell S, Ko J, Ginn P, et al. Effects of three sedative protocols on glomerular filtration rate in clinically normal dogs. *Am J Vet Res* 1997;58(5):446.

57. Nielsen VG. Colloids decrease clot propagation and strength: role of factor XIIIfibrin polymer and thrombin-fibrinogen interactions. *Acta Anaesthesiol Scand* 2005;49:1163-1171.

58. Norberg A, Hahn RG, Li H, et al. Population volume kinetics predicts retention of 0.9% saline infused in awake and isoflurane-anesthetized volunteers. *Anesthesiology* 2007;107:24-32.

59. Pang DS, Boysen S. Lactate in veterinary critical care: pathophysiology and management. *J Am Anim Hosp Assoc* 2007;43:270-279.

60. Pries AR, Secomb TW. Microvascular blood viscosity in vivo and the endothelial surface layer. *Am J Physiol Heart Circ Physiol* 2005;289:H2657-H2664.

61. Pries AR, Secomb TW, Sperandio M, et al. Blood flow resistance during hemodilution: effect of plasma composition. *Cardiovasc Res* 1998;37:225-235.

62. Quasha AL, Eger EI, Tinker JH. Determination and applications of MAC. *Anesthesiology* 1980;55:315-334.

63. Raffe MR. The case for routine fluid administration. *Vet Clin N Am* 1992;22:447-448.

64. Rhee P, Burris D, Kaufmann C, et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. *J Trauma* 1998;44:313-319.

65. Rhee P, Wang D, Ruff P, et al. Human neutrophil activation and increased adhesion by various resuscitation fluids. *Crit Care Med* 2000;28;74-78.

66. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;467-469.

67. Ruta T, Mutch W. Organ perfusion during deliberate hypotension and superimposed hemorrhage. *Anesthesiology* 1993;79(1):188.

68. Scott-Douglas NW, Robinson VJB, Smiseth OA, et al. Effects of acute volume loading and hemorrhage on intestinal vascular capacitance: A mechanism whereby capacitance modulates cardiac output. *Can J Cardiol* 2002;18:515-522.

69. Shoemaker JK. Hemodilution impairs cerebral autoregulation, demonstrating the complexity of integrative physiology. *Anesth Analg* 2007;105:1179-1181.

70. Shoukas AA, Sagawa K. Control of total systemic capacity by the carotid sinus baroreceptor reflex. *Circ Res* 1973;33:22-33.

71. Silverstein DC, Aldrich J, Haskins SC. Assessment of changes in blood volume in response to resuscitative fluid administration in dogs. *J Vet Emerg Crit Care* 2005;15:185-192.

72. Singbartl K, Innerhofer P, Radvan J, et al. Hemostasis and hemodilution: a quantitative mathematical guide for clinical practice. *Anesth Analg* 2003;96:929.

73. Sirs J. The flow of human blood through capillary tubes. *J Physiol* 1991;442:569-583.

74. Solano AM, Pypendop BH, Boscan PL, et al. Effect of intravenous administration of ketamine on the minimum alveolar concentration of isoflurane in anesthetized dogs. *Am J Vet Res* 2006;67:21-25.

75. Steffey EP, Howland DJ. Isoflurane potency in the dog and cat. *Am J Vet Res* 1977;38(11):1833-1836.

76. Steffey EP, Mama KR. Inhalation Anesthetics. In: Tranquilli WJ, Thurman JC,
Grimm KA, eds. *Lumb and Jones' Veterinary Anesthesia and Analgesia*. 4<sup>th</sup> ed. Ames:
Blackwell Publishing, 2007;355-394.

77. Takeda S, Sato N, Tomaru T. Haemodynamic and splanchnic organ blood flow responses during sevoflurane-induced hypotension in dogs. *Eur J Anaesthesiol* 2002;19:442-446.

78. Teyssier G, Fouron JC, Sonesson SE, et al. Circulatory changes induced by isovolumic increase in red cell mass in fetal lambs. *Arch Dis Child Fetal Neonatal Ed* 1998;79:F180-F184.

79. Tomiyasu S, Hara T, Hasuo H, et al. Comparative analysis of systemic and coronary hemodynamics during sevoflurane- and isoflurane-induced hypotension in dogs. *J Cardiovascular Pharm* 1999;33:741-747.

80. Valverde A, Doherty T, Hernandez J, et al. Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. *Vet Anaesth Analg* 2004;31:264-271.

81. Wagner AE, Wright BD, Hellyer PW. Myths and misconceptions in small animal anesthesia. *J Am Vet Med Assoc* 2003;223:1426-1432.

82. Wagner EM, Trastman RJ. Hydrostatic determinants of cerebral perfusion. *Crit Care Med* 1986;14:484-490.

83. Wang SW, Manyari DE, Scott-Douglas N, et al. Valvular heart disease/ventricular hypertrophy/heart failure: Splanchnic venous pressure volume relation during experimental acute ischemic heart failure: Differential effects of hydralazine, enalaprilat, and nitroglycerin. *Circulation* 1995;91:1205-1212.

84. Wellman ML, DiBartola SP, Kohn CW. Applied physiology of body fluids in dogs and cats. In: DiBartola SP, ed. *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*. 3<sup>rd</sup> ed. St. Louis: Elsevier Inc., 2006;3-26.

85. Whittaker SRF, Winton FR. The apparent viscosity of blood flowing in the isolated hindlimb of the dog, and its variation with corpuscular concentration. *J Physiol* 1933;78:339-369.

86. Wo CCJ, Shoemaker WC, Appel PL. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med* 1993;21:218-223.

87. Wright BD, Hopkins A. Changes in colloid osmotic pressure as a function of anesthesia and surgery in the presence and absence of isotonic fluid administration in dogs. *Vet Anaesth Analg* 2008;35:282-288.