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COMPARISON OF EPHEDRINE AND DOPAMINE TO MANAGE HYPOTENSION AND ASSESSMENT OF ARTERIAL PRESSURE WAVEFORM ANALYSIS TO MONITOR CARDIAC OUPUT IN DOGS UNDER ISOFLURANE ANESTHESIA

HUI CHENG CHEN

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ABSTRACT

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Hui Cheng Chen
University of Guelph, 2004

Advisors: Dr. Melissa D. Sinclair
Dr. Doris H. Dyson

The first study compared the cardiovascular responses of ephedrine at 0.2 mg/kg, IV (repeated if inadequate response) and dopamine infusion at 5 μg/kg/min, IV (doubled to 10 μg/kg/min, IV, if inadequate response) to manage hypotension in clinical canine cases during routine anesthetic management. Treatments were randomly assigned to treat hypotension (mean arterial pressure, MAP < 60 mm Hg) in 12 cases. When MAP remained lower than 70 mm Hg at 10 minutes post treatment, the ephedrine bolus was repeated or the dopamine infusion was doubled. The pressure-elevating effect of ephedrine was found to last less than 5 minutes, with improvement in cardiac index (CI), stroke volume index (SVI) and oxygen delivery index (DO_2I), but a decrease in systemic vascular resistance (SVR) at 10 minutes. Repeating the ephedrine did not produce further improvement. The infusion of dopamine at 5 μg/kg/min did not improve blood pressure (BP), CI, DO_2I or SVI within 10 minutes. Increasing the infusion to 10 μg/kg/min improved BP within 5 minutes, and increased CI, DO_2I and SVI by 10 minutes. The ephedrine boluses were less effective than the dopamine infusions to augment BP, but the improvement in CI, DO_2I and SVI by the end of the 20-minute study period was not different between treatments.

The second study validated the use of a commercial system (PulseCO™) that estimates cardiac output (CO) based on arterial pressure waveform analysis (PCO) in anesthetized dogs, and assessed the agreement between PCO and lithium dilution CO (LiD) during variable hemodynamic situations induced by changes in anesthetic depth and administration of inotropes (dopamine and dobutamine). Pressure waveform from the dorsal pedal artery was used to track the CO changes by the PCO monitor following a one-point calibration with LiD. Analysis based on 48 pairs of CO measurements found that PCO always produced higher readings than LiD during deep anesthesia but lower than LiD during dopamine infusions. Differences were not detected during light anesthesia or dobutamine infusions. The coefficient of correlation (r) was 0.6289. Tolerance limits varied according to treatment. Power to detect 30% or more difference between PCO and LiD was 92.5%. It was concluded that PCO can be used to monitor CO when conditions are similar to those during calibration with LiD. Recalibration is recommended for accurate estimation of CO when hemodynamic conditions or pressure waveform change significantly.

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DECLARATION OF WORK PERFORMED

I declare that with the exception of the items listed below, all work reported in this thesis was performed by me.

The designs of the studies were developed in consultation with Dr. Melissa Sinclair and Dr. Doris Dyson (Chapter III), and with Dr. Melissa Sinclair, Dr, Doris Dyson and Dr. Wayne McDonell (Chapter IV).

Assistance with the anesthetic inductions, instrumentation, monitoring and data collection was provided by Dr. Melissa Sinclair, Dr. Doris Dyson, Dr. Kuldip Mirakhur, Tiffany Renwick, Amanda Hathway and Tara Montgomery.

Assistance with obtaining informed clients' consent for the recruitment of clinical cases into the first study was provided by the surgery interns and residents on duty.

Assistance with the statistical analysis was provided by Mr. William Sears.

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CHAPTER I

LITERATURE REVIEW

1.1 HYPOTENSION

1.1.1 Definition

The word 'hypotension' means 'abnormally low blood pressure'. The arterial blood pressures are measured in terms of systolic, diastolic and mean levels. Normal systolic (SAP), mean (MAP) and diastolic (DAP) arterial blood pressure (BP) values for conscious, non-anesthetized small animals are approximately 100–160, 80-120 and 60-100 mm Hg respectively (Haskins, 1996). Hypotension during anesthesia has arbitrarily been defined as a MAP of less than 60 mm Hg, which generally corresponds to a SAP of less than 80 – 90 mm Hg (Wagner and Brodbelt, 1997; Gaynor et al., 1999; Smith, 2002). Although not clearly defined as such, these values are probably based on the lower limit of the BP range in the normal population where vital organs, such as the brain and the kidney could maintain autoregulation of its blood supply. Below this lower limit, the organ blood flow may decline in proportion to the drop in the BP (Guyton and Hall, 2000). Therefore, SAP below 80 mm Hg and MAP below 60 mm Hg are assumed to result in inadequate cerebral and coronary perfusion and may warrant therapy (Haskins, 1996). The exact time required before negative consequences result is not clearly noted, but the extent of damage within these organs is assumed to be proportional to the time of hypotension.

Despite the above general definition, MAP of 50-55 mm Hg has been set as the 'safe' lower limit for the practice of deliberate hypotension during anesthesia in human medicine (more detail in section 1.1.2) (van Aken and Miller, 2000), while a MAP of 70 mm Hg has been recommended as the lower limit to minimize post-anesthetic myopathy in large animals (Smith, 2002). Furthermore, the autoregulation curve may be

shifted to the right in hypertensive patients such that a decrease in vital organ blood flow may occur at a MAP higher than 60 mm Hg and thus, hypotension should be defined at a MAP higher than 60 mm Hg in such patients. Therefore, the definition of hypotension based on 'acceptable' or 'safe' lower limit of BP may somewhat varies depending on disease states, the specific organ system of interest, organ reserve and related outcome measures. The rationale behind setting these lower limits should probably be based on adequacy of organ perfusion and oxygen delivery to meet tissue metabolic demand and maintenance of organ function. Hence, the 'safe' lower limit during anesthesia would also need to consider the alterations in hemodynamics and distribution of cardiac output induced by the various drugs, the patient's hydration and intra-vascular volume status and whether supplemented oxygen is used.

1.1.2 Relationship Between Pressure And Flow

According to Ohm's Law, flow is directly proportional to the pressure difference between two points and inversely proportional to the resistance to the flow (Stoelting, 1999; Cunningham, 2002). This relationship can be expressed mathematically as:

$$\text{Blood Flow (Q)} = \frac{\text{Pressure difference between two points } (\Delta P)}{\text{Resistance to Flow (R)}}$$

Applying this formula to the systemic blood flow, blood pressure and vascular resistance, the formula can be rewritten as:

$$\text{Cardiac output (CO)} = \frac{\text{Mean aortic pressure(MAP) - Right atrial pressure(RAP)}}{\text{Systemic vascular resistance (SVR)}}$$

where;

CO (L/min) is the total amount of blood that flows through the systemic circuit in a defined period
MAP and RAP (mmHg) are the respective pressures measured directly
SVR (dyn/sec/cm^{-5}) is a calculated parameter based on the above formula

Since changes in the RAP are usually negligible compared to that of MAP, changes in MAP could be a reflection of changes in CO or SVR or both. Thus, a decrease in MAP does not necessarily mean a decrease in CO or vice versa; likewise MAP values may be normal despite a low CO when SVR is high. Since CO is a flow parameter, it is more relevant to systemic perfusion than BP (Haskins, 1996).

Applying the formula ($Q = \Delta P/R$) to a particular organ, blood flow to the organ is determined by the perfusion pressure (arterial pressure – venous pressure) and resistance of the blood vessels within that particular organ. Since all the organs of the systemic circulation are exposed to the same perfusion pressure (i.e. similar systemic arterial and venous pressure), differences in distribution of blood to the various organs are result of the differences in vascular resistance of each organ (Cunningham, 2002).

The vascular resistance of an organ is determined mainly by the diameter of its high-resistance arterioles. Arteriolar vasoconstriction and vasodilation are the mechanism that decreases or increases the blood flow to the organ. It is also the mechanism underlying autoregulation of orgam blood flow to maintain a constant blood flow within certain limits. As systemic pressure drops and therefore perfusion pressure, the arterioles vasodilate, up to a certain limit, where further drop in perfusion pressure results in parallel decline in organ blood flow.

The cerebral perfusion pressure is expressed as the difference between MAP and intracranial pressure (ICP), and is more important to cerebral blood flow autoregulation than MAP (van Aken and Miller, 2000). In a normal man, normal cerebral oxygen metabolism can continue in spite of a reduction in cerebral blood flow corresponding to a cerebral perfusion pressure of 30 to 40 mm Hg. This pressure relates to a MAP of 30 to 40 mm Hg, measured at the level of the carotid artery when the skull is opened (i.e., ICP of 0). However, when MAP falls below 50 mm Hg, cerebral blood flow no longer responds to changes in arterial carbon dioxide tension. Therefore, a MAP of

50 –55 mm Hg in normothermic patients represents the lowest MAP where autoregulation of the cerebral blood flow is still in force, and forms the basis for the 'safe' lower limit of deliberate hypotension during anesthesia, utilized to reduce intra-operative blood loss in healthy patients. It is also important to note that this 'safe' lower limit is based on normovolemic patients with supplemented oxygen.

Coronary blood flow fluctuates depending on the state of cardiac contraction, and blood flow through the left heart is maximal during diastole. Therefore, coronary perfusion pressure is more dependent on the diastolic pressure and is defined as the difference between diastolic aortic pressure and left ventricular end-diastolic pressure (Kirk and Sonnenblick, 1982). Coronary blood flow is autoregulated over a perfusion pressure range of 0 to 140 mm Hg, independent of myocardial oxygen demand (Olsson, Bunger and Spaan, 1991)

Autoregulation of renal blood flow and glomerular filtration rate are maintained when MAP is between 60 and 160 mm Hg (Guyton and Hall, 2000). However, when effective circulatory volume decreases, renal blood flow decreases regardless of perfusion pressure or presence of autoregulation (Lote, Harper and Savage, 1996). Therefore, underperfusion of kidneys is possible in face of hypovolemia, even though MAP is within the range for autoregulation of renal blood flow. On the other hand, no significant changes in pre- or post-op (up to 8 days) serum creatinine, blood urea nitrogen, serum or urinary electrolytes were observed following deliberate hypotension at 50 mm Hg for an average of 100 minutes (Thompson et al., 1978). The sensitivity of such measurements to detect tissue damage is questionable, and the impact of such treatment may be detrimental on long-term renal function. The presence of adequate urine output (without use of diuretics) has been equated with sufficient renal perfusion, since glomerular filtration and urine production should cease when there is no renal perfusion (Aronson, 2000). In healthy, normovolemic human patients, significant

reduction in urine output and endogenous creatinine clearance had been shown during periods of hypotension (average MAP of 49 mm Hg, for 55 minutes) (Behnia, Siqueira and Brunner, 1978; Behnia et al., 1982). However, these parameters returned to normal levels within one hour upon restoration of BP.

The pressure-flow autoregulation is limited in the hepatic arterial bed and probably absent in the portal venous circulation (van Aken and Miller, 2000). Extrinsic control of hepatic blood flow occurs primarily through a1-mediated vasoconstriction by the sympathetic nervous system innervation from T3 – T11 (Stoelting, 1999). Change to the hepatic venous compliance plays an essential role in the overall regulation of CO and therefore, liver perfusion may be more dependent on CO and extrinsic control by the sympathetic nervous system. Profound changes in liver perfusion may occur during periods of hypotension (van Aken and Miller, 2000).

Based on the above discussions, it is clear that systemic BP is not an exact indicator of organ blood flow or tissue perfusion. But it is the most practical and least invasive means of cardiovascular monitoring in the clinical setting (Wagner and Brodbelt, 1997). Ideally, CO along with BP should be used to provide an assessment of global cardiovascular function. However, we are limited in our abilities to measure CO in clinical veterinary practice due to technical expertise required, cost of equipment and invasiveness of the methods. Used in conjunction with other clinical assessments such as mentation status, mucous membrane colour, capillary refill time, heart rate and urine output (when available), measurement of BP plays a valid indirect role in our clinical assessment of the cardiovascular function of veterinary patients. Analysis of venous oxygen saturation and partial pressure, and lactate level may also help with determination of adequate supply of whole body oxygen demands. Assessment of the actual end-organ perfusion could be as simple as measuring urine output (as an indirect

indicator of renal perfusion) or as sophisticated as gastric tonometry (in assessment of the splanchnic circulation).

1.1.3 Causes Of Hypotension During Anesthesia

In identifying the causes of hypotension it is useful to consider the determinants of BP and factors that could contribute to hypotension. Based on the relationship between CO, MAP and SVR explained above, and the negligible change in RAP, the formula can be simplified and rearranged as MAP = CO X SVR. Therefore, factors that cause a reduction in CO or SVR can reduce MAP and lead to hypotension. Cardiac output is the function of heart rate (HR) and stroke volume (SV) [CO = HR X SV], and SV can be reduced with reduced preload, increased afterload or reduced cardiac contractility (Muir and Mason, 1996). Thus, drugs or conditions that cause vasodilation will reduce SVR, and drugs or conditions that reduce HR or SV can contribute to decreased CO, and therefore, MAP.

The pathophysiology of hypotension during anesthesia is multifactorial with the major contributing factors related to the cardiovascular effects of the anesthetic agents used and the clinical condition of the patient. While the extreme severity of disease condition in an animal may primarily be responsible, the effects of anesthetic agents on the cardiovascular system are usually partly responsible, hence anesthetic protocols are tailored to the pre-operative condition of the patient. Various injectable and inhalant anesthetic agents can directly affect HR, preload, afterload, myocardial contractility or SVR, resulting in decreased CO and/ or MAP (Mazzaferro and Wagner, 2001). Therefore, balanced anesthesia is preferred to minimize doses and the effects of any one particular agent on the cardiovascular system. However, even with these measures, hypotension under anesthesia can result.

1.1.3.1 Effects Of Anesthetics And Adjuncts

Various classes of anesthetic agents and adjuncts can be used to achieve the varying needs of analgesia, immobilization, unconciousness and muscle relaxation. In a survey of 66 small animal practices in Ontario in 1993, agents that were commonly used in the anesthetic management of a total of 8,087 canine cases included, acepromazine (68%), atropine (59%), butorphanol (37%), meperidine (28%), glycopyrrolate (10%), thiobarbiturate (52%), ketamine-diazepam (26%), halothane (38%) and isoflurane (36%) (Dyson, 1998). All of these agents can affect the cardiovascular system.

Acepromazine is a potent neuroleptic commonly used to calm and sedate an animal prior to anesthesia. Pre-anesthetic administration decreases the amount of general anesthetic required and may offer protection against cardiac dysrhythmias (Dyson and Pettifer, 1997). However, it is a potent α_1 antagonist that can cause peripheral vasodilation resulting in a dose-dependent decrease in BP (Popovic et al., 1972; Muir and Hubbell, 1985).

Atropine and glycopyrrolate are both anticholinergic agents that block the action of acetylcholine on the parasympathetic nervous system. Clinically, they are used to limit salivary secretions, to prevent bradycardia and associated bradyarrhythmias, or to deliberately increase HR (Muir et al. 2000). Their cardiovascular effects will be further discussed in section 1.1.4.1.

Butorphanol (a kappa agonist) and meperidine (a mu agonist) are both opioids that are used mainly for their analgesic and sedative properties. Other mu agonists that are commercially available in North America include morphine, oxymorphone, hydromorphone, fentanyl, alfentanil and sufentanil. In general, opioids cause little cardiovascular depression (Stoelting, 1999) and rarely are causes of hypotension. The advantages of including an opioid in an anesthetic regimen are sedation, pre-, intra- and post-operative analgesia, reduction in the requirement of induction and maintenance

anesthetics, and reversibility of their physiologic effects (Paddleford, 1999). However, depending on the opioid and dose used, they can cause respiratory depression, sinus bradycardia, excitement and emesis (Muir et al, 2000). Opioid-induced bradycardia in the presence of cardio-depressive or vasodilating agents, such as isoflurane (Tyner, Greene and Hartsfield, 1989), halothane (Torske, Dyson and Conlon, 1999), propofol (Smith et al., 1993), or acepromazine (Cornick and Hartsfield, 1992), may decrease CO and thus, MAP. Treatment of the opioid-induced bradycardia with an anticholinergic has been demonstrated to resolve the reduction in CO. Rapid intravenous injection of morphine and meperidine may cause hypotension via histamine release (Patschke, 1977; Muldoon et al, 1987), thus, these opioids are usually administered intramuscularly.

Thiopental is an ultrashort acting thiobarbiturate with a rapid onset and short duration of action. Depending on the level of sedation, an initial 1/2 - 2/3 bolus dose of thiopental may need to be administered to avoid the excitement stage. In humans, rapid administration of thiopental has been associated with a mild and transient fall in BP due to arteriolar dilation. In healthy patients, this decrease in BP could be masked by a compensatory sympathetic response of increased HR (Filner and Karliner, 1976). In healthy dogs, the administration of thiopental caused an initial increase in HR, a decrease in SV, with no change in CO. Blood pressures were elevated transiently while HR was elevated for up to 10 minutes (Turner and Ilkiw, 1990; Quandt et al., 1998). In the absence of compensatory increases in the sympathetic nervous system activity, the negative inotropic effect of thiopental can be demonstrated (Housmans et al., 1995). In hypovolemic dogs, MAP may be maintained or even elevated in some dogs while severe hypotension and death could occur in others (Burstein and Hershey 1943; Ilkiw et al., 1991). The ability to compensate might depend on the degree of sympathetic activity at the time of thiopental administration, with more profound and disastrous effects

developing in dogs that had a high degree of sympathetic activity present following hemorrhage (Ilkiw et al., 1991).

Ketamine as an induction agent in normovolemic or hypovolemic dogs is associated with an increase in HR, BP and CO due to sympathetic stimulation (Haskins et al., 1985; Haskins et al., 1990; Mattson, 2003). In dogs, ketamine is often administered together with diazepam. Diazepam is a benzodiazepine with minimal effects on the cardiovascular system (Haskins et al., 1986; Stoelting, 1999). Cardiovascular stimulation is less apparent when ketamine is administered after diazepam (Haskins et al., 1986). However, when ketamine is administered at large doses (30 mg/kg, IV) to dogs recovering from isoflurane anesthesia, transient decreases in BP, CO and SVR were noted (Muir and Hubbell, 1988). In vitro, ketamine had been demonstrated to have a direct negative inotropic effect (Rusy et al., 1990). Thus, although ketamine is usually used in critically ill patients, profound hypotension may still occur if the endogenous store of catecholamines is depleted or if the sympathetic nervous system is profoundly suppressed (Waxman et al., 1980).

In addition to thiobarbiturates and ketamine, propofol is becoming an increasingly popular injectable anesthetic as it provides rapid and excitement-free induction and recovery in both premedicated and non-premedicated dogs. Duration of anesthesia results in little difference in the recovery characteristics due to the rapid metabolism that occurs even when tissue saturation impairs distribution (Watkins, Hall and Clarke, 1987). However, propofol is relatively expensive and has a limited shelf-life once the ampule is opened. It has been reported to produce dose-dependant cardiopulmonary depression, although in healthy dogs, propofol at 8 mg/kg, IV did not affect cardiovascular parameters significantly (Quandt et al., 1998). In hypovolemic dogs, propofol at 6 mg/kg, IV caused a rapid drop in MAP with no compensatory increase in HR (Ilkiw et al., 1992). Similarly, propofol at 2.5 mg/kg, IV decreased MAP and CO with no effect on HR in dogs

anesthetized under ketamine and fentanyl (Brussel et al., 1989). In another study performed in hypovolemic dogs, induction with propofol and diazepam, followed by tracheal intubation, resulted in an increase in HR while MAP was maintained (Mattson, 2003). The mechanisms underlying the decrease in MAP with propofol include a decrease in preload, vascular resistance, as well as cardiac contractility (Claeys et al., 1988; Goodchild and Serrao, 1989; Brussel et al., 1989).

Inhalation anesthetic agents are often used to maintain general anesthesia. In North America, halothane, enflurane, isoflurane, desflurane and sevoflurane are available for use. Of these, halothane, isoflurane and sevoflurane may be the more commonly used agents in small animals, with isoflurane gaining popularity over the years (Dodman and Lamb, 1992; Dyson et al., 1998; Wagner and Hellyer, 2002). Isoflurane is likely the most commonly used inhalant in small animals. A survey by Wagner and Hellyer (2002) revealed 100% of their respondents used isoflurane while none used halothane or sevoflurane. Isoflurane's advantages over halothane include its low blood solubility, allowing more rapid induction and recovery (Steffey, 1996), and its relative lack of arrhythmogenicity (Hubbell et al., 1984; Pettifer et al., 1997). Both halothane and isoflurane caused dose-dependant decreases in MAP in healthy dogs (Pagel et al., 1991; Mutoh et al., 1997). The decrease in BP produced by halothane is mainly a consequence of decreases in myocardial contractility and CO, whereas with isoflurane, the drop in BP is attributable more to the decrease in SVR (Stoelting, 1999). As the end-tidal isoflurane (Et-iso) concentration was increased from the minimum alveolar concentration (MAC)[1] of 1.3% to 2 times MAC (2.6%) in dogs, MAP and SVR decreased, while CO was sustained by an increase in HR (Steffey and Howland, 1977). When used alone, isoflurane may only result in a MAP of less than 60 mm Hg starting at

[1] MAC is the minimum alveolar concentration of the inhalant that produces immobility in 50% of subjects exposed to a supramaximal noxious stimulus

2 times MAC (Steffey and Howland, 1977), but in combination with other anesthetics, hypotension may develop at a lower concentration. For example, a typical anesthetic protocol in a dog that consists of premedication with acepromazine (0.05 mg/kg, IM) and butorphanol (0.2 mg/kg) IM; induction with propofol (3-6 mg/kg, IV); and maintenance with isoflurane at the typical end-tidal concentration of 1.2 – 1.4% may result in a MAP of ~ 60 mmHg (Vaisanen et al., 2002). Similarly, the administration of butorphanol at 0.2 mg/kg, IV in dogs under 1.7% Et-iso decreased MAP from 90 mm Hg to 61 mm Hg (Tyner, Greene and Hartsfield, 1989). Thus, with the potential additive cardio-depressant effects of various combinations of anesthetics with isoflurane, it is not surprising that hypotension is one of the most common complications that develop during anesthesia in small animals (Hosgood, 1998; Gaynor et al., 1999).

1.1.3.2 Clinical Conditions

In a systemically ill patient, the underlying disease conditions may contribute to the development of hypotension during general anesthesia, making the correctly chosen anesthetic agents and dose even more critical. Examples of clinical conditions in systemically ill patients that can affect CO and SVR, the two determinants of BP, are presented using the background presented by the review by Day (2000) and Smith (2002). For further details on the shock syndrome and its relevance to veterinary medicine, please refer to the review by Day (2000).

Bradycardia associated with hypothermia, electrolyte imbalance and underlying cardiac disease may become worse with the administration of anesthetics. Patients with cardiac disease may have reduced CO as a result of valvular disease, outflow tract obstruction (increased afterload), dilated cardiomyopathy (decreased contractility), pericardial disease (decreased preload) or unsynchronized cardiac rhythm