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A DISSERTATION
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

Development and Evaluation of Intra-abdominal Hypertension Model in Conscious Dogs

의식이 있는 개에서 복강내압 향전증 모델의 개발 및 평가

by

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Development and Evaluation of Intra-abdominal Hypertension Model in Conscious Dogs

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Supervised by
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ABSTRACT

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) have been increasingly recognized as a cause of significant mortality in critically ill patients. The reference interval for intra-abdominal pressure (IAP) in the dog ranges from 0 to 7.4 mmHg, and is affected by body position, abdominal wall tone, ascites, peritonitis, trauma, and gastrointestinal disease. IAH can cause significant dysfunction of cardiovascular, respiratory, renal and gastrointestinal systems. Because existing animal models have been designed to increase IAP under general anesthesia, there is little information whether anesthetic agents have
significant impacts on research findings. Therefore, the purpose of the present study was to develop an IAH model in conscious dogs and to evaluate the effect of IAH on the renal system in anesthetized dogs. In addition, this study described the computed tomography (CT) features of IAH in dogs with abdominal distension.

In chapter I, a new balloon device using a Foley urinary catheter and latex balloon was placed in the intra-abdominal cavity. Consecutive measurements of IAP were made by measuring the intravesicular pressure. The air insufflated into the intra-abdominal balloon device significantly increased the IAP and sustained the IAH without general anesthesia. An acute increase in IAP using the balloon device in normal conscious dogs induced discomfort and gastrointestinal disturbance, as well as increased respiratory effort.

In chapter II, the effect of increased IAP on plasma exogenous creatinine clearance was evaluated in IAH dogs. Plasma exogenous creatinine clearance was compared after intravenous administration of exogenous creatinine solution at 80 mg/kg under four different treatment conditions as follows: control in conscious dogs (CC), IAP levels of 25 mmHg in conscious dogs (C25), control in anesthetized dogs (AC), and IAP levels of 25 mmHg in anesthetized dogs (A25). There were no significant differences in plasma creatinine concentration for CC, AC, and C25 during the treatment period. However, in the A25 treatment condition, the plasma creatinine clearance significantly decreased at 10, 20, 30, 60, 90 and 120 minutes after administration of creatinine.

In chapter III, the CT features of IAH were described in three dogs with abdominal distension. Compression of the caudal vena cava and elevation of the
diaphragm in the seven CT features were observed in all three dogs, while inguinal herniation and renal compression were seen in a dog with an IAP of 26 mmHg. The presence of compression of the caudal vena cava and direct renal compression on the CT images in IAH dogs could induce direct compression of the renal vessels and/or renal parenchyma, increased renal vascular resistance, and renal dysfunction when IAP was elevated.

Based on the results of the present studies, this conscious IAH dog model demonstrated various effects of increased IAP on cardiovascular, respiratory and renal function and was considered as a useful method to induce IAH in conscious dogs. Since increasing awareness of the detrimental effects of IAH has led clinicians to understand the pathobiology and treat IAH in critically ill patients, this conscious IAH dog model could be used to further enhance IAH and ACS researches.

Keywords: intra-abdominal hypertension, intra-abdominal pressure, abdominal compartment syndrome, dog, model

Student number: 2011-23715
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LIST OF ABBREVIATIONS

ABG  Arterial blood gas analysis
ACS  Abdominal compartment syndrome
ANOVA Analysis of variance
AUC  Area under the curve
BCS  Body condition score
CBC  Complete blood count
CO₂  Carbon dioxide
CT  Computed tomography
ECG  Electrocardiogram
GFR  Glomerular filtration rate
HR  Heart rate
IAH  Intra-abdominal hypertension
IAP  Intra-abdominal pressure
IV  Intravenous
IVP  Intravesicular pressure
PO₂  Oxygen partial pressure
**LIST OF ABBREVIATIONS (cont’d)**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>PCO₂</td>
<td>Carbon dioxide partial pressure</td>
</tr>
<tr>
<td>RBS</td>
<td>Round belly sign</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>SAP</td>
<td>Systolic arterial blood pressure</td>
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GENERAL INTRODUCTION

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are defined as states of increased intra-abdominal pressure (IAP) within the confined space of the abdominal cavity, and have been increasingly recognized as a cause of significant morbidity and mortality in critically ill patients (Cheatham et al., 2000). IAP is the steady state of pressure within the closed abdominal cavity. The reference interval for IAP in the dog ranges from 0 to 7.4 mmHg, and varies with the respiratory cycle (Smith and Sande, 2012). The elevated IAP within the compartment cavity limits the blood supply resulting in reduced or absent perfusion to surrounding tissues. Although this restricted perfusion initiates at a microvascular level, it will eventually lead to irreversible tissue damage, and in some cases, death (Nielsen and Whelan, 2012).

IAH can cause significant dysfunction of cardiovascular, respiratory, renal and gastrointestinal systems (Hunter and Damani, 2004). However, most of the studies on this topic have been performed in animal models and abdominal surgical settings under general anesthesia (Schachtrupp et al., 2007). In experimental settings, it has been suggested that cardiovascular and renal hemodynamics are highly sensitive, even to moderate increases in IAP, with remarkable impairments (Dalfino et al., 2008).

In experimental research, multiple animal models have been designed to resemble IAH and ACS (Schachtrupp et al., 2007). In current animal models
developed to induce IAH, gas (air, CO₂ or helium) and fluids (saline, polyethylene glycol solution, and corn oil) were administered intra-abdominally or into an intra-abdominal bag under general anesthesia (McDougall et al., 1996; Meier et al., 2007; Schachtrupp et al., 2007). However, because these IAH/ACS animal models had been designed to elevate IAP under surgical and general anesthesia settings, it was not clear whether different anesthetic agents had significant impacts on research findings.

Therefore, this study was performed 1) to develop a new balloon technique for IAH and ACS in a conscious dog model and its effects on heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP), and arterial blood gas (ABG) values (Chapter I), 2) to determine the effect of increased IAP on plasma exogenous creatinine clearance in conscious and anesthetized dogs (Chapter II), and 3) to examine computed tomography (CT) features of IAH in three dogs with abdominal distension (Chapter III).
CHAPTER I.

Balloon Technique of the Intra-abdominal Hypertension in Conscious Dog Model

Abstract

This study was performed to evaluate the effect of intra-abdominal pressure (IAP) on cardiovascular, respiratory, and arterial blood gas values in a conscious dog model that used a balloon technique to generate intra-abdominal hypertension (IAH).

A new balloon device using a Foley urinary catheter and latex balloon was placed in the intra-abdominal cavity in six healthy beagle dogs. Consecutive measurements of IAP were made by measuring the intravesicular pressure. The abdomen was inflated with air to IAP levels of 10, 15, 20 and 25 mmHg. Heart rate, respiratory rate, systolic arterial blood pressure, and arterial blood gas were evaluated at baseline and at 15, 30, 45, 60, 120, 240, and 300 minutes after IAP elevation.

The air insufflated into the intra-abdominal balloon device significantly increased the IAP and sustained the IAH. The respiratory rate increased significantly ($p<0.05$) when IAP was increased to 15, 20, and 25 mmHg. Although heart rate, systolic arterial blood pressure, oxygen partial pressure ($\text{PaO}_2$) and
carbon dioxide partial pressure (PaCO₂) did not show statistically significant differences between baseline and post-treatment values over time, the dogs with increased IAP showed a distended abdomen, discomfort, and 4/6 (67%) vomited. After measurement of IAP, air was removed. There were no side effects after removal of the balloon device.

The balloon device was successfully insufflated and sustained IAH in conscious dogs. This balloon technique does not require general anesthesia for instillation or removal of gas after installment. An acute IAP increase in normal conscious dogs induced discomfort and vomiting, as well as increased respiratory effort.
Introduction

Awareness of the importance of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) as causes of significant morbidity and mortality among critically ill patients has increased in human and veterinary medicine (Parsak et al., 2008; Malbrain and de Laet, 2009; Nielsen and Whelan, 2012). Intra-abdominal pressure (IAP) within the abdominal cavity limits the blood supply, resulting in reduced or absent normal perfusion to surrounding tissues (Smith and Sande, 2012). Sustained IAH can eventually cause physiologic dysfunction of tissue, initially at the microvascular level, leading to irreversible damage and multiple organ failure (Hunter and Damani, 2004). A better understanding of IAH/ACS will lead to better management in critically ill veterinary patients (Nielsen and Whelan, 2012).

The IAP can be measured by various direct and indirect methods, such as via the peritoneal cavity, urinary bladder, and intragastric and central venous catheters (Engum et al., 2002; Malbrain, 2004; Kimball et al., 2007). Intravesicular methods of IAP measurement are performed using a Foley catheter inserted into the urinary bladder and instillation of saline (Kron et al., 1984; Iberti et al., 1987). In veterinary medicine, the intravesicular pressure (IVP) method is the most widely used in small animals and provides consistent and accurate measurements (Smith and Sande, 2012; Way and Monnet, 2014).
The *in vivo* animal model is an important tool in veterinary IAH and ACS researches (Schachtrupp *et al.*, 2007; Nielsen and Whelan, 2012). Experimental research has been performed in rats, rabbits, dogs, and pigs with a body weight from 200 g to 70 kg (Schachtrupp *et al.*, 2007). Different fluids and gases can be administered intra-abdominally or into an intra-abdominal bag to elevate IAP (Moore-Olufemi *et al.*, 2005; Vivier *et al.*, 2006; Schachtrupp *et al.*, 2007). However, because these multiple animal models have been designed to increase IAP under general anesthesia (Rosenthal *et al.*, 1998; Moore-Olufemi *et al.*, 2005; Vivier *et al.*, 2006), it is not clear whether anesthetic agents have a significant impact on research findings.

A novel device comprising a Foley urinary catheter and latex balloon was designed for use in this study. This technique does not require general anesthesia for instillation or removal of gas after installation. The objectives of this study were to: evaluate a new balloon technique for IAH and ACS in a conscious dog model; determine whether the increased IAP can be sustained in conscious dogs; and determine whether the increased IAP affects heart rate (HR), respiratory rate (RR), systolic arterial blood pressure (SAP), and arterial blood gas (ABG) values.
Materials and Methods

1. Animals

Six clinically healthy Beagle dogs (four male and two female, mean ± SD age 2.0 ± 1.0 years) were used after approval by the Institutional Animal Care and Use Committee of Seoul National University (SNU-150624-8). Body condition score (BCS) was evaluated on a 9-point scale based on methods described previously (Mawby et al., 2004). Mean body weight was 9.7 ± 1.5 kg and the median body condition score was 5 (range 5–6). Prior to the study, all animals were examined and considered to be clinically healthy based on complete physical examination, complete blood count (CBC), blood chemistry analysis, ABG, and thoracic and abdominal radiographs.
2. Preparation of latex balloon device in vitro

This device consists of the plasma-sterilized 20 cm latex balloon, with its open end tied with PDS 3-0 (PDS®, Ethicon, USA) onto the balloon of an 8-Fr Foley urinary catheter (Foley urinary catheter, Yushin Medical Corporation, Korea) (Fig. 1). The balloon of the urinary catheter was inflated with 0.9% sodium chloride solution. A three-way stopcock extension set was connected to the aspiration port of the urinary catheter after stylet removal. A 50 mL syringe was connected to the stopcock. The stopcock was then turned “on” to the balloon and air was insufflated into the latex balloon through the urinary catheter. This process was repeated until balloon pressure reached 45 mmHg in 500 mL of water added to a 5 L plastic box. The pressure of four balloon devices were measured using a cuff manometer (Cuff manometer, VBM, Germany) and recorded after allowing a stabilization period of 1 hour, during which air was repeatedly insufflated until a pressure of 45 mmHg was sustained. Measurements were repeated after a stabilization period of 1 hour, and balloon pressure was recorded until 1, 2, 4, and 8 hours after insufflation with air.
Fig. 1. A schematic drawing of the latex balloon device. A latex balloon, with its open end tied with PDS 3-0 on the balloon of a Foley urinary catheter. A three-way stopcock extension set was connected into the aspiration port of the urinary catheter and a 50 mL syringe was connected to the stopcock.
3. Anesthesia and surgical preparation in vivo

Food was withheld for 8 hours before anesthesia but free access to water was allowed. An intravenous catheter was placed in the cephalic vein and the dog was premedicated with 10 μg/kg medetomidine (Medetomidine, Zoetis, USA) intravenously (IV) and tramadol (Tramadol, Yuhan Corporation, Korea) 4 mg/kg intramuscularly. Anesthesia was induced with 2 mg/kg alfaxalone (Alfaxalone, Jurox Pty Ltd, AUS) IV. After intubation, anesthesia was maintained with 2% isoflurane (Isoflurane, Hana Pharma Corporation, Korea) in 2 L/minute oxygen delivered through a semiclosed circle system. The 0.9% sodium chloride solution was administered at a rate of 5 mL/kg/hour. Electrocardiogram (ECG), hemoglobin oxygen saturation by pulse oximetry, RR, end-tidal carbon dioxide tension, and oscillometric arterial blood pressure were monitored (Carescape Monitor® B650, GE Healthcare, Finland).

The abdominal region was clipped and aseptically prepared. The dog was placed in dorsal recumbency, and the abdomen was prepared for laparotomy. The aseptic latex balloon device designed for this study was placed into the abdominal cavity through a 2 cm ventral midline incision between the umbilicus and pubis (Fig. 2). The abdominal wall musculature was sutured with 2-0 PDS in a simple interrupted pattern, leaving only the urinary catheter port of the device accessible from outside of the abdominal cavity. The subcutis was sutured with 3-0 PDS in a simple continuous pattern and the skin was closed using 3-0 Nylon sutures. A Chinese finger trap suture was used to secure the device’s urinary catheter at the abdominal wall. At the end of the procedure, the animals were allowed to recover.
from anesthesia and each dog received a single dose of cefovecin sodium (Cefovecin sodium, Zoetis, USA) 8 mg/kg subcutaneously. The dogs were observed for dislodgement of the latex balloon device or any complication for 48 hours.
Fig. 2. Schematic drawing of the latex balloon technique used for measurement of intra-abdominal pressure (IAP) in a conscious dog. Consecutive IAP was measured through intravesicular pressure. A 50 mL syringe was connected to the balloon device stopcock and air was insufflated into the balloon through the catheter.
4. Blood pressure measurements

Indirect SAP measurements were conducted using a Doppler ultrasonic flow detector (Model 811-B®, Parks Medical Electronics Inc, USA). The Doppler probe was placed over the palmar digital artery and a cuff (approximately 40% of the limb circumference) with a sphygmomanometer was placed above the carpus. The cuff was inflated until the pulse sound disappeared, then gradually deflated until first audible sounds were detected. The first measurement was discarded and the average of three consecutive readings was recorded.
5. IAP measurement and IAH induction

The Malbrain technique was used to obtain transvesical IAP measurements. The bladder was emptied of urine and 1 mL/kg of 0.9% sodium chloride was instilled into the bladder. The pressure transducer (Auto Transducer®, Acemedical Co., Korea) was calibrated against a mercury manometer and zeroed at the level of the symphysis pubis before measurement. All IAP measurements were obtained with the animals in a standing position and using the pressure transducer. The IAP was continuously monitored, and consecutive IAP measurements were obtained. Baseline IAP was defined as the IAP measured before air insufflation. The stopcock was then turned “on” to the balloon and air was insufflated into the latex balloon through the urinary catheter (Fig. 2). Thereafter, the mean IAP was gradually increased to 10, 15, 20, and 25 mmHg by inflating the latex balloon. Measurements were repeated after a stabilization period of 5 minutes, and air insufflation was repeated until the target IAP was sustained.
6. Experimental protocol

Two days was allowed after installation of the balloon device to avoid the residual effects of anesthetic drugs. Bupivacaine was infiltrated at the site of catheter placement, and a dorsal pedal artery was cannulated with a 22 G sterile catheter for collection of consecutive ABG samples. Body temperature was measured by a thermometer placed in the rectum and used for accurate blood gas results. Repeated arterial blood samples were collected using a heparinized syringe and blood samples were analyzed immediately using a blood gas analyzer (ABL-80 Flex®, Radiometer America, USA). The pH, PaCO₂, PaO₂, base excess, HCO₃⁻, total carbon dioxide, sodium (Na⁺), potassium (K⁺), chloride (Cl⁻), ionized calcium (Ca²⁺), and hematocrit were measured. The HR, RR, SAP, and ABG were measured at baseline before insufflation of air. Consecutive IAP recordings were obtained by measurement of IVP. The abdomen was then insufflated to IAP levels of 10, 15, 20, and 25 mmHg using the balloon device, and mean IAP levels were sustained at 15-minute intervals (Fig. 3). All previously mentioned measurements were repeated at each increment of IAP. If vomiting occurred, IAP measurements were obtained after a stabilization period of 5 minutes. After the first 60 minutes with a 15-minute interval, measurements of IAP and the previously mentioned parameters were restarted at 120 and 240 minutes without additional air insufflation. Thereafter, the balloon device was deflated and removed, with measurement of the air volume. After a stabilization period of 60 minutes, IAP and all other measurements were repeated at 300 minutes.
Fig. 3. Chronological order of experimental procedures. Baseline measurements (▼) were taken before air insufflation. After air insufflation, all measurements were repeated at each increment of intra-abdominal pressure. After 60 minutes, air insufflation was stopped and all measurements were repeated at 120, 240, and 300 minutes. Measurement included heart rate, respiratory rate, systolic arterial blood pressure, rectal temperature, arterial blood gas analysis, and intra-abdominal pressure.
7. Statistical analyses

The data were analyzed using statistical package for the social sciences version 22 software for Windows (SPSS, version 22, SPSS, Inc, USA). One-way analysis of variance (ANOVA) with repeated measures using Bonferroni’s post hoc method was used to evaluate within-group changes in IAP, HR, RR, SAP, and ABG values over time. A $p$-value <0.05 was considered to be statistically significant.
Results

The relationship between balloon device pressure and insufflated air volume in the plastic box was shown in Fig. 4A. After 8 hours, the balloon device pressure gradually decreased from baseline by a mean of 45.0 ± 0.0 to 38.7 ± 1.2 mmHg (Fig. 4B).

Baseline IAP, HR, SAP, and RR at each time point were shown in Table 1. Relative to the baseline measurements, RR increased significantly at 30, 45, and 60 minutes after IAP elevation. Although there were no statistically significant changes in HR and SAP during the treatment periods, a slight increase was observed after induction of IAH. At 60 minutes after induction of an IAP of 25 mmHg, the HR and SAP increased from baseline by a mean of 4.2 ± 9.4 beats per minute and 24.2 ± 8.3 mmHg, respectively.

The baseline ABG values at each time point were shown in Table 2. Relative to baseline measurements, pH decreased significantly at 60 minutes after elevation of IAP. At 60 minutes after induction of an IAP of 25 mmHg, the pH decreased from baseline by a mean of 0.093 ± 0.001. There were no significant differences in PaCO₂, PaO₂, HCO₃⁻, base excess, total carbon dioxide, Na⁺, K⁺, Cl⁻, Ca²⁺, anion gap or hematocrit during the treatment period. At 60 minutes after induction of an IAP of 25 mmHg, the PaCO₂ and base excess increased from baseline by a mean of 7.0 ± 2.3 mmHg and 1.55 ± 1.28 mEq/L, respectively, although these changes were not significant.
The relationship between balloon device pressure and IAP was shown in Fig. 5. After 1 hour of air insufflation, the balloon device pressure and IAP significantly decreased at 240 minutes from 39.3 ± 2.1 to 25.3 ± 2.4, and 25.0 ± 0.0 to 18.5 ± 1.5 mmHg, respectively. The total insufflation air volume was 3405.0 ± 193.3 mL in the balloon device. All dogs with increased IAP showed a distended abdomen, tachypnea and labored breathing. Four of the six dogs vomited and three defecated after elevation of IAP. There were no side effects after removal of the balloon device. No other side-effects were observed during a follow-up period of 3 months.
Fig. 4. Relationship between balloon device pressure and insufflated air volume (A) and balloon device pressure (B) throughout 8 hours in vitro.
Table 1. Consecutive IAP, HR, SAP and RR changes from baseline, at 15, 30, 45, 60, 120, 240 and 300 minutes after IAP elevation in conscious dogs

<table>
<thead>
<tr>
<th>Time after air insufflation into the intra-abdominal balloon devices (minutes)</th>
<th>Baseline</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAP (mmHg)</td>
<td>6.3 ± 1.0</td>
<td>10.0 ± 0.0</td>
<td>15.0 ± 0.0</td>
<td>20.0 ± 0.0</td>
<td>25.0 ± 0.0</td>
<td>21.2 ± 1.8*</td>
<td>18.5 ± 1.4†</td>
<td>4.2 ± 1.0†</td>
</tr>
<tr>
<td>HR (beats)</td>
<td>106.2 ± 17.6</td>
<td>114.5 ± 22.7</td>
<td>131.2 ± 38.0</td>
<td>116.0 ± 28.2</td>
<td>110.3 ± 30.7</td>
<td>113.8 ± 24.5</td>
<td>99.3 ± 20.5</td>
<td>100.7 ± 18.1</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>147.5 ± 15.4</td>
<td>172.5 ± 11.3</td>
<td>170.8 ± 10.2</td>
<td>170.0 ± 10.5</td>
<td>171.7 ± 12.9</td>
<td>169.2 ± 15.6</td>
<td>163.3 ± 11.7</td>
<td>145.0 ± 13.1**</td>
</tr>
<tr>
<td>RR (rates)</td>
<td>28.7 ± 2.5</td>
<td>40.3 ± 3.7</td>
<td>55.0 ± 10.9*</td>
<td>75.0 ± 16.5*</td>
<td>77.0 ± 18.6*</td>
<td>54.0 ± 12.6</td>
<td>39.2 ± 8.7</td>
<td>32.0 ± 6.3***†</td>
</tr>
</tbody>
</table>

IAP, intra-abdominal pressures; HR, heart rate; SAP, systolic arterial blood pressure; RR, respiratory rate; *Significant difference from baseline; **Significant difference from 45 minutes; †Significant difference from 60 minutes.
Table 2. Consecutive arterial blood gas values changes from baseline values, at 15, 30, 45, 60, 120, 240 and 300 minutes after IAP elevation in conscious dogs.

<table>
<thead>
<tr>
<th>Time after air insufflation into the intra-abdominal balloon devices (minutes)</th>
<th>Baseline</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>120</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.368 ± 0.086</td>
<td>7.352 ± 0.037</td>
<td>7.308 ± 0.060</td>
<td>7.295 ± 0.056</td>
<td>7.275 ± 0.085*</td>
<td>7.313 ± 0.080</td>
<td>7.327 ± 0.064</td>
<td>7.367 ± 0.061</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>31.23 ± 7.25</td>
<td>31.35 ± 2.13</td>
<td>36.22 ± 5.50</td>
<td>37.77 ± 3.85</td>
<td>38.23 ± 6.59</td>
<td>32.07 ± 2.91</td>
<td>35.82 ± 4.20</td>
<td>32.48 ± 2.55</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>110.5 ± 6.4</td>
<td>110.0 ± 13.0</td>
<td>101.3 ± 11.2</td>
<td>102.3 ± 14.1</td>
<td>105.8 ± 9.3</td>
<td>104.8 ± 8.8</td>
<td>85.3 ± 37.1</td>
<td>102.3 ± 5.1</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>97.83 ± 0.91</td>
<td>97.73 ± 0.85</td>
<td>96.48 ± 1.94</td>
<td>96.45 ± 1.48</td>
<td>96.73 ± 1.13</td>
<td>97.32 ± 0.76</td>
<td>97.18 ± 0.99</td>
<td>97.68 ± 0.49</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>19.29 ± 1.97</td>
<td>18.78 ± 1.56</td>
<td>18.35 ± 1.74</td>
<td>18.27 ± 1.75</td>
<td>17.53 ± 2.04</td>
<td>17.37 ± 2.60</td>
<td>19.02 ± 2.17</td>
<td>19.33 ± 2.51</td>
</tr>
<tr>
<td>Base excess (mEq/L)</td>
<td>-7.03 ± 2.39</td>
<td>-7.53 ± 1.98</td>
<td>-7.68 ± 2.33</td>
<td>-7.67 ± 2.22</td>
<td>-8.53 ± 2.29</td>
<td>-9.28 ± 3.23</td>
<td>-6.78 ± 2.63</td>
<td>-5.88 ± 3.22</td>
</tr>
<tr>
<td>tCO₂ (mmol/L)</td>
<td>17.95 ± 2.16</td>
<td>17.63 ± 1.75</td>
<td>18.28 ± 2.10</td>
<td>18.52 ± 1.76</td>
<td>17.85 ± 1.56</td>
<td>16.62 ± 2.27</td>
<td>19.13 ± 2.22</td>
<td>17.98 ± 2.61</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>152.3 ± 1.2</td>
<td>151.7 ± 1.6</td>
<td>151.2 ± 1.6</td>
<td>150.8 ± 1.8</td>
<td>150.8 ± 1.8</td>
<td>151.3 ± 1.9</td>
<td>150.8 ± 2.1</td>
<td>151.0 ± 2.6</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>3.751 ± 0.360</td>
<td>3.683 ± 0.326</td>
<td>3.828 ± 0.615</td>
<td>3.932 ± 0.433</td>
<td>3.820 ± 0.515</td>
<td>3.872 ± 0.631</td>
<td>4.038 ± 0.499</td>
<td>3.960 ± 0.478</td>
</tr>
<tr>
<td>Cl⁻ (mmol/L)</td>
<td>113.0 ± 3.7</td>
<td>114.0 ± 2.4</td>
<td>113.2 ± 3.3</td>
<td>112.7 ± 1.8</td>
<td>112.8 ± 3.0</td>
<td>114.0 ± 2.0</td>
<td>112.0 ± 1.9</td>
<td>113.2 ± 2.9</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/L)</td>
<td>1.353 ± 0.028</td>
<td>1.267 ± 0.078</td>
<td>1.361 ± 0.084</td>
<td>1.372 ± 0.057</td>
<td>1.370 ± 0.118</td>
<td>1.323 ± 0.090</td>
<td>1.312 ± 0.088</td>
<td>1.328 ± 0.009</td>
</tr>
<tr>
<td>Anion gap (mmol/L)</td>
<td>22.1 ± 3.0</td>
<td>20.9 ± 3.0</td>
<td>20.8 ± 2.5</td>
<td>20.7 ± 2.7</td>
<td>21.6 ± 3.2</td>
<td>21.7 ± 3.5</td>
<td>21.0 ± 4.6</td>
<td>20.1 ± 3.5</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>39.2 ± 9.2</td>
<td>38.2 ± 6.9</td>
<td>40.2 ± 8.0</td>
<td>40.7 ± 7.4</td>
<td>42.2 ± 8.0</td>
<td>42.5 ± 10.6</td>
<td>41.3 ± 8.5</td>
<td>37.7 ± 7.8</td>
</tr>
</tbody>
</table>

PaCO₂, carbon dioxide partial pressure; PaO₂, oxygen partial pressure; SaO₂, oxygen saturation; tCO₂, total carbon dioxide; Na⁺, sodium; K⁺, potassium; Ca²⁺, calcium; *Significant difference from baseline

PaCO₂, carbon dioxide partial pressure; PaO₂, oxygen partial pressure; SaO₂, oxygen saturation; tCO₂, total carbon dioxide; Na⁺, sodium; K⁺, potassium; Ca²⁺, calcium; *Significant difference from baseline
Fig. 5. Relationship between balloon device pressure (black squares) and intra-abdominal pressure (white squares) in conscious dogs. *$P < 0.05$ versus corresponding from 60 minutes value.
Discussion

Multiple IAH/ACS animal models have been designed to increase IAP artificially and have been able to cause circulatory, respiratory, and renal insufficiency (Rosenthal et al., 1998; Moore-Olufemi et al., 2005; Yagci et al., 2005; Vivier et al., 2006). In human and veterinary medicine, studies in animal models provided valuable supplemental information for patients with IAH and ACS (Schachtrupp et al., 2007; Nielsen and Whelan, 2012). In human medicine, ACS is defined as a sustained IAP >20 mmHg associated with organ dysfunction, and significant alterations in organ function were reported even at a relatively low IAP of 10–15 mmHg (Hunter and Damani, 2004; Cheatham et al., 2007). Although ACS has not been extensively investigated in veterinary medicine, IAH is defined as sustained elevated IAP; 0–7.4 mmHg should be considered normal in a dog, 7.4–14.7 mmHg should be considered mild IAH, 14.7–25.7 mmHg would constitute moderate to severe IAH, and an IAP >25.7 mmHg would necessitate surgical decompression (Fetner and Prittie, 2012; Smith and Sande, 2012).

Several research groups in human and veterinary medicine have evaluated the effects of IAH/ACS in rat, rabbit, dog, and pig models (Rosenthal et al., 1998; Moore-Olufemi et al., 2005; Vivier et al., 2006; Schachtrupp et al., 2007). In these studies, IAH caused significant organ hypoperfusion, ischemic organ damage, and multiple organ failure. However, these animal models involved instillation of fluid and/or gas into the abdomen in order to sustain IAH under general anesthesia.
(Schachtrupp et al., 2007). Although there is sparse information on the effect of different anesthetics in an ACS research model, minimal or no administration (if possible) of anesthetic drugs may be helpful for predicting the effects of IAH in conscious patients.

Regarding the method of induction of IAH, different fluids (saline, polyethylene glycol solution, and corn oil) and gases (air, CO$_2$, or helium) have been directly administered into the abdominal cavity (Rosenthal et al., 1998; Moore-Olufemi et al., 2005; Vivier et al., 2006; Schachtrupp et al., 2007). However, it is not clear whether direct gases and fluid insufflation into the abdominal cavity have systemic effects or a particularly significant impact on research. In addition, the animals in these models sometimes need saline bags or specific insufflators in order to increase IAP (Moore-Olufemi et al., 2005; Vivier et al., 2006; Yagci et al., 2005).

In the present study, a balloon device was aseptically inserted into the abdominal cavity for control of insufflation and desufflation throughout the experimental procedure. The abdomen was successfully insufflated and IAH was maintained in conscious dogs. Although a special insufflator was needed to increase IAP in previous animal models (Rosenthal et al., 1998), this balloon technique was able to inject air into the abdominal balloon with a 50-mL syringe. The authors insufflated air into the latex balloon to induce IAP because instillation of saline into the latex balloon induced balloon rupture in an in vitro pilot study. The IAP was continuously evaluated, and the procedure did not require general anesthesia for injection or removal of air. In addition, insufflation of air into the
latex balloon to induce IAH did not induce peritoneal absorption, resulting in minimal systemic effects on the respiratory and gastrointestinal systems.

Conflicting results have been reported with regard to the effects of sustained IAH on the circulation (Hunter and Damani, 2004; Vivier et al., 2006). Some studies have shown that sustained IAH has a profound effect on the cardiovascular system (Barnes et al., 1985; Hunter and Damani, 2004; Cheatham et al., 2007). A decrease in cardiac output and compensatory tachycardia were observed in response to an increase in intrathoracic pressure and a decrease in stroke volume (Hunter and Damani, 2004), whereas other studies showed IAH to have a minimal effect on cardiac output (Dorsay et al., 1995; Klopfenstein et al., 1998; Greim et al., 2003). In the current study, an increase in IAP to 10, 15, 20, or 25 mmHg caused a slight but statistically insignificant increase in HR and SAP in conscious dogs.

In human medicine, several studies have been performed to evaluate the effect of IAH on respiratory function (Hunter and Damani, 2004). Increased IAP acts directly on the cephalad deviation of the diaphragm and chest wall compliance (Kron et al., 1984). These changes lead to a decrease in total lung capacity and an increase in the ventilation/perfusion mismatch relationship, with subsequent hypoxia and hypercapnia (Ridings et al., 1995; Hunter and Damani, 2004). However, these studies proceeded under general anesthesia. Since respiratory function frequently can be diminished by use of anesthetics (Steffey and Howland, 1977; Pypendop and Verstegen, 1999; Maney et al., 2013), increased IAP may impair ventilation even further. In this study, an increase in IAP to 15, 20, and 25 mmHg significantly increased RR in dogs, but did not induce hypoxia; although
the increase in IAP made respiration increasingly difficult, there were no statistically significant differences in PaCO\(_2\) and PaO\(_2\).

Metabolic and respiratory disturbances associated with IAH have been reported in pediatric patients and animals (Beck et al., 2001; Meier et al., 2007). In this study, an increase in IAP to 25 mmHg significantly decreased pH in dogs, and mild acidosis was observed. As the PaCO\(_2\) was within normal limits but mildly increased, mild metabolic acidosis occurred after the increase in IAP in these conscious dogs.

This study had several limitations. First, IAP slightly decreased after installation of the device when there was no additional air insufflation. A possible explanation might be that a decrease in balloon device tension and adaptation of the abdominal wall to increased IAP might have had effects on the pressure read by the IVP method because additional air insufflation was needed to maintain IAP. The respiratory cycle (increase in inspiration and decrease in expiration) also could have influenced the IAP (Smith and Sande, 2012; Way and Monnet, 2014). In the current study, the pressure monitor was able to adjust its pressure reading to measure rapid variation in respiratory cycles, but mean IAP measured by this method might not be accurate. Finally, an intra-abdominal balloon was used to increase IAP. It has been debatable whether this balloon technique results in a homogenous increase in IAP (Meier et al., 2007; Schachtrupp et al., 2007). However, several studies have evaluated the effects of a balloon and a saline bag as induction methods in IAH (Engum et al., 2002; Yagci et al., 2005). In this study, the balloon device successfully insufflated and maintained IAH in conscious dogs,
and all dogs with increased IAP showed a distended abdomen, respiratory discomfort, and gastrointestinal disturbance.
Conclusions

The new balloon device described here successfully increased IAP in conscious dogs. Because this balloon technique did not require general anesthesia or special insufflators to induce IAH, it could be considered as accurate, repeatable, and useful method. Although more research would be needed to determine the efficacy of this balloon technique in a conscious dog model, it could be considered an appropriate method for animal IAH and ACS researches when an anesthetic effect is undesirable.
CHAPTER II.

Effect of Intra-abdominal Hypertension on Plasma Exogenous Creatinine Clearance in Conscious and Anesthetized Dogs

Abstract

This study was performed to evaluate the effect of intra-abdominal pressure (IAP) on plasma exogenous creatinine clearance in both conscious and anesthetized dog models using a balloon technique to generate intra-abdominal hypertension (IAH).

A balloon device comprising a Foley urinary catheter and latex balloon was placed in the intra-abdominal cavity in six dogs. Plasma exogenous creatinine clearance was compared after intravenous administration of exogenous creatinine solution at 80 mg/kg under four different treatment conditions as follows: control in conscious dogs (CC), IAP levels of 25 mmHg in conscious dogs (C25), control in anesthetized dogs (AC), and IAP levels of 25 mmHg in anesthetized dogs (A25). Samples were obtained before (T0) and 10, 20, 30, 60, 90, 120, 240, 360, 480, and 600 minutes after administration of creatinine in all treatment groups.

There were no significant differences in plasma creatinine concentration for CC, AC, and C25 during the treatment period. However, in the A25 treatment
condition, the plasma creatinine concentration increased significantly at 10, 20, 30, 60, 90, and 120 minutes after administration of creatinine ($p<0.05$). Plasma creatinine clearances were $5.0 \pm 0.5$, $4.7 \pm 1.2$, $5.5 \pm 0.9$, and $2.5 \pm 0.5$ mL/kg/min for 600 minutes (CC, AC, C25, and A25, respectively). After decompression of the abdomen, plasma creatinine concentrations declined rapidly and returned to basal concentrations.

An increase in IAP of 25 mmHg markedly reduced plasma exogenous creatinine clearance in anesthetized dogs but not in conscious dogs. An acute increase in IAP might be critical for renal perfusion and function under general anesthesia in healthy dogs. Timely decompression may improve the outcome of acutely increased IAP when surgery and/or general anesthesia is required in canine patients.
Introduction

A sustained increase in intra-abdominal pressure (IAP) can cause intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS), which contributes significantly to increased morbidity and mortality in critically ill people (Parsak et al., 2008; Malbrain and de Laet, 2009). The increased pressure within the abdominal cavity can adversely affect normal perfusion and function in the surrounding tissues (Nielsen and Whelan, 2012), and eventually this process can lead to physiologic dysfunction and multiple organ failure (Hunter and Damani, 2004). In veterinary medicine, there have been a few reports of IAH and ACS having multiple negative systemic effects (Brosnahan et al., 2009; Rader and Johnson, 2010; Fetner and Prittie, 2012). Awareness of IAP in veterinary patients with critical abdominal disease is essential for optimal patient management (Conzemius et al., 1995; Nielsen and Whelan, 2012).

Increased IAP can lead to renal dysfunction (Richards et al., 1983; Sugrue et al., 1995). In critically ill patients, IAH is associated with acute renal failure. Oliguria is observed at IAPs in the range of 15–20 mmHg, and can progress to anuria when IAP exceeds 30 mmHg (Sugrue et al., 1995; Biancofiore et al., 2003; Dalfino et al., 2008). Relevant studies have been performed in the abdominal surgical and postoperative care setting, where IAH has been identified as critical for occurrence of renal failure. In animal models, renal function is highly sensitive
to even moderate increases in IAP, with marked impairment seen at 10–15 mmHg (Chiu et al., 1994; Dalfino et al., 2008).

Glomerular filtration rate (GFR) is considered to be a sensitive and reliable index of renal perfusion in both health and disease (Finco DR, 2005). Plasma clearance of creatinine administered by bolus IV injection has been used to assess renal function in dogs (Watson et al., 2002; Von Hendy-Willson and Pressler, 2011). This simple method of measuring plasma exogenous creatinine clearance is an accurate indicator of GFR in healthy dogs and in dogs with a 60% decrease in GFR (Watson et al., 2002).

Several studies in both human and veterinary medicine have shown the effects of IAH/ACS in animal models (Schachtrupp et al., 2007). In these studies, elevation of IAP caused significant organ hypoperfusion and multiple organ dysfunction (Rosenthal et al., 1998; Vivier et al., 2006). Most of the studies on IAH/ACS have been performed in the abdominal surgical and general anesthesia setting (McDougall et al., 1996; Sugrue et al., 1999; Vivier et al., 2006; Dalfino et al., 2008). In a previous study, the authors developed a balloon device to induce IAH in conscious dogs and the balloon device successfully increased IAP without general anesthesia in conscious dogs. This IAH dog model may be helpful for predicting renal function in conscious patients because anesthetic agents can decrease cardiac output and reduce renal blood flow, which in turn decreases the GFR (Kongara et al., 2009).
The purpose of this study was to evaluate the effect of increased IAP on plasma exogenous creatinine clearance in conscious and anesthetized dogs.
Materials and Methods

1. Animals

Six clinically healthy male Beagle dogs (mean age 2.0 ± 1.0 years and body weight 9.3 ± 0.8 kg) were used after approval by the Institutional Animal Care and Use Committee of Seoul National University (SNU-150211-1). BCS was 5 (range 5-6) on a 9-point scale. The physical examination, complete blood count, blood chemistry analysis, and urinalysis were within reference ranges for all dogs. All dogs were acclimated to the experimental conditions (including to food and water) and placed in individual cages 30 days before beginning the experiment. During the experimental studies, commercially available dry dog food was fed and water was available *ad libitum.*
2. Preparation of the IAH dog model

The dog model using the balloon technique was prepared using a method previously described in chapter I. The dogs were premedicated with medetomidine 10 µg/kg IV and tramadol 4 mg/kg intramuscularly. Anesthesia was induced with alfaxalone 2 mg/kg and maintained with isoflurane in oxygen. The abdominal region was prepared aseptically and the balloon device for induction of IAH was placed in the abdominal cavity through a ventral midline incision. The abdominal wall was sutured, leaving only the urinary catheter port of the device accessible from the outside of the abdominal cavity. A Chinese finger trap suture was used to secure the device to the abdominal wall and the animals were allowed to recover from anesthesia. All dogs received a single dose of cefovecin sodium 8 mg/kg subcutaneously and observed for dislodgement of the device and any complications for 24 hours.
3. Measurement of IAP and induction of IAH

A Foley urinary catheter was placed and the bladder was emptied of urine, after which 1 mL/kg of 0.9% sodium chloride was instilled into the bladder (Way and Monnet, 2014). The Malbrain IAP monitoring technique was used to measure transvesical IAP (Malbrain, 2004). The pressure was zeroed at the level of the symphysis pubis before measurement. The IAP measurements were obtained with the conscious dogs in a standing position and the anesthetized dogs in the dorsal recumbent position. The IAP was continuously measured using the pressure transducer. To induce IAH, the abdomen was insufflated to an IAP level of 25 mmHg using the balloon device, and mean IAP levels were sustained during treatment.
4. Experimental design

The study was carried out as a cross-over experimental trial, with a 24-hour interval between treatments to avoid residual effects of the anesthetic drugs. Food but not water was withheld for 8 hours prior to treatment. On the day of the study, each dog was weighed and a cephalic vein catheter was inserted. An aqueous creatinine solution (80 mg/mL) was prepared using anhydrous creatinine (Anhydrous creatinine, Sigma Chemical Corporation, USA) and distilled water and administered at 80 mg/kg IV (Watson et al., 2002). Plasma exogenous creatinine clearance was compared after IV administration of exogenous creatinine solution at 80 mg/kg via the cephalic vein under four different treatment conditions as follows: control in conscious dogs (CC), IAP levels of 25 mmHg in conscious dogs (C25), control in anesthetized dogs (AC), and IAP levels of 25 mmHg in anesthetized dogs (A25).

Blood samples (1 mL) were obtained from the jugular vein before (T0) and 10, 20, 30, 60, 90, 120, 240, 360, 480, and 600 minutes after administration of creatinine solution at 80 mg/kg in all treatment conditions. The samples were collected into heparinized tubes and centrifuged at 1,000×g for 10 minutes. The plasma creatinine concentration was measured using an automated analyzer (Dri-Chem 4000i, Fuji Film Corporation, Japan). Washout periods of 24 hours were allowed between treatments and the dogs had access to drinking water *ad libitum* for the remainder of the experiment.
5. Experimental procedures

1) Group CC

Twenty-four hours was allowed after installation of the balloon device before starting measurements in dogs. Plasma creatinine clearance was evaluated for 600 minutes in the standing conscious dogs (Fig. 6). The dogs had free access to water for the duration of the study.

2) Group AC

Induction of anesthesia was performed using alfaxalone 2 mg/kg IV and maintained with 2% isoflurane in 2 L/minute oxygen delivered through a semiclosed circle system. A 0.9% sodium chloride solution was administered at a rate of 2 mL/kg/hour. ECG, hemoglobin oxygen saturation (by pulse oximetry), respiration rate, end-tidal carbon dioxide tension, and oscillometric arterial blood pressure were monitored (Carescape Monitor B650®, GE Healthcare, Finland). The dogs were positioned in dorsal recumbency and the plasma clearance of creatinine was evaluated after a stabilization period of 60 minutes under anesthesia. Samples were obtained before (T0) and at 10, 20, 30, 60, 90 and 120 minutes under anesthesia (Fig. 6). After discontinuation of anesthesia, the dogs were allowed to recover and further samples were obtained at 240, 360, 480 and 600 minutes. After anesthesia, the 0.9% sodium chloride solution was discontinued and water was offered *ad libitum*. 
3) **Group C25**

The abdomen was insufflated to an IAP level of 25 mmHg using the balloon device, and the target IAP became sustained after a stabilization period of 60 minutes. The IAP measurements were repeated during an IAH induction period of 120 minutes. Samples were obtained before (T0) and 10, 20, 30, 60, 90 and 120 minutes under IAH (Fig. 6). Thereafter, the balloon device was deflated and the samples were obtained at 240, 360, 480 and 600 minutes. During the studies, water was offered *ad libitum*.

4) **Group A25**

Induction of anesthesia was performed using alfaxalone 2 mg/kg IV and maintained with 2% isoflurane. The 0.9% sodium chloride solution was administered at a rate of 2 mL/kg/hour. The dogs were positioned in dorsal recumbency and the abdomen was then insufflated to an IAP level of 25 mmHg using the balloon device, and the target IAP became sustained after a stabilization period of 60 minutes. The IAP measurements were repeated during the IAH induction period of 120 minutes. Blood samples were obtained before (T0) and 10, 20, 30, 60, 90 and 120 minutes under IAH with anesthesia (Fig. 6). After discontinuation of anesthesia, the balloon device was deflated. The dogs were then allowed to recover and further blood samples were obtained at 240, 360, 480 and 600 minutes. After anesthesia, the 0.9% sodium chloride solution was discontinued and water was offered *ad libitum*. 
<table>
<thead>
<tr>
<th>Groups</th>
<th>Stabil</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>CC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td></td>
<td>Anesth I</td>
</tr>
<tr>
<td>C25</td>
<td></td>
<td>IAH I</td>
</tr>
<tr>
<td>A25</td>
<td></td>
<td>Anesth &amp; IAH I</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>IV creatinine at 80 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60</td>
<td>▼</td>
</tr>
<tr>
<td>0</td>
<td>▼</td>
</tr>
<tr>
<td>30</td>
<td>▼</td>
</tr>
<tr>
<td>60</td>
<td>▼</td>
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<td>▼</td>
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<td>120</td>
<td>▼</td>
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<td>240</td>
<td>▼</td>
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<tr>
<td>360</td>
<td>▼</td>
</tr>
<tr>
<td>480</td>
<td>▼</td>
</tr>
<tr>
<td>600</td>
<td>▼</td>
</tr>
</tbody>
</table>

Fig. 6. Chronological order of the experimental procedure. In the CC, AC, C25, and A25 treatment condition, plasma clearance of creatinine was evaluated for 600 minutes. CC, conscious control; AC, anesthesia control; C25, IAP level of 25 mmHg in conscious dogs; A25, IAP level of 25 mmHg in anesthetized dogs; Stabil, stabilization; Anesth, anesthesia; IAH, intra-abdominal hypertension; I, induction; ▼, measurement of serum creatinine.
6. Analyses of plasma exogenous creatinine clearance

Plasma concentrations of creatinine were analyzed statistically using the method of moments approach. The area under the plasma concentration versus time curve (AUC) was calculated using the trapezoidal rule with extrapolation according to the method (Watson et al., 2002). Blood samples at the ten time points of 10, 20, 30, 60, 90, 120, 240, 360, 480, and 600 minutes were used to evaluate plasma creatinine clearance. The basal concentration was subtracted from each plasma concentration value and the AUC was calculated using the trapezoidal rule. The AUC between each time point were estimated by a rectangular area and the total AUC was equal to the sum of the 10 trapezoids. The plasma creatinine clearance (mL/kg/min) was equal to the dose divided by the AUC.
7. Statistical analyses

The data were analyzed using statistical package for the social sciences version 22 software for Windows. One-way ANOVA was used to evaluate changes in the plasma creatinine concentration over time (using the ten time points), followed by one-way ANOVA with repeated measures to compare each group at each measurement using Bonferroni’s post hoc method. The plasma exogenous creatinine clearance under each treatment condition was analyzed using a one-way ANOVA. A $p$-value <0.05 was considered to be statistically significant.
Results

The mean (± SD) baseline plasma creatinine concentrations were within the reference ranges of 0.4 ± 0.1, 0.5 ± 0.1, 0.3 ± 0.1, and 0.4 ± 0.1 mg/dL (CC, AC, C25, and A25, respectively). The mean peak plasma creatinine concentrations were 16.1 ± 1.3, 16.8 ± 1.1, 17.1 ± 1.6, and 26.4 ± 3.5 mg/dL (CC, AC, C25, and A25, respectively) at 10 minutes after administration; and all declined rapidly and returned to basal concentrations 10 hours after administration of creatinine.

There were no significant differences in plasma creatinine concentrations for the CC, AC, and C25 treatment conditions during the study. However, in the A25 treatment condition, the plasma creatinine concentration increased significantly at 10, 20, 30, 60, 90 and 120 minutes after administration of creatinine (Fig. 7). The area under the plasma creatinine concentration curve was calculated by the trapezoidal rule between time points in table 3. Mean plasma creatinine clearances were 9.2 ± 0.3, 8.8 ± 1.0, 9.4 ± 1.2, and 5.1 ± 0.9 mL/kg/min at 120 minutes and 5.0 ± 0.5, 4.7 ± 1.2, 5.5 ± 0.9, and 2.5 ± 0.5 mL/kg/min at 600 minutes (CC, AC, C25, and A25, respectively). In the A25 treatment condition, the plasma exogenous creatinine clearance decreased significantly to 50% and 54% of those for the control conditions (CC and AC, respectively).
Fig. 7. Plasma creatinine concentration profiles of after administration of an IV bolus of exogenous creatinine at 80 mg/kg under four treatment conditions as follows: control in conscious dogs (CC), IAP levels of 25 mmHg in conscious dogs (C25), control in anesthetized dogs (AC), and IAP levels of 25 mmHg in anesthetized dogs (A25). *significantly different from the CC, AC and C25 treatments; †significantly different from the CC and C25 treatment.
Table 3. The area under the curve between time points were estimated by a rectangle area in four treatment conditions.

<table>
<thead>
<tr>
<th>Between time points (minutes)</th>
<th>Area under the curve was calculated by the trapezoidal rule (mg min/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC</td>
</tr>
<tr>
<td>0-10</td>
<td>78.3 ± 6.5</td>
</tr>
<tr>
<td>10-20</td>
<td>135.5 ± 6.5</td>
</tr>
<tr>
<td>20-30</td>
<td>103.9 ± 3.9</td>
</tr>
<tr>
<td>30-60</td>
<td>239.0 ± 9.9</td>
</tr>
<tr>
<td>60-90</td>
<td>173.8 ± 12.2</td>
</tr>
<tr>
<td>90-120</td>
<td>138.5 ± 13.9</td>
</tr>
<tr>
<td>120-240</td>
<td>387.0 ± 54.4</td>
</tr>
<tr>
<td>240-360</td>
<td>198.0 ± 46.2</td>
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<tr>
<td>360-480</td>
<td>100.0 ± 34.7</td>
</tr>
<tr>
<td>480-600</td>
<td>48.0 ± 11.4</td>
</tr>
</tbody>
</table>

CC, control in conscious dogs; AC, control in anesthetized dogs; C25, IAP levels of 25 mmHg in conscious dogs; A25, IAP levels of 25 mmHg in anesthetized dogs.
Discussion

Recently, measurement of IAP has become important in the management of critically ill people and animals. Based on a canine study in veterinary medicine, a grading system had been suggested whereby IAH was defined as sustained elevation of IAP: 0–7.4 mmHg was considered normal; 7.4–14.7 mmHg is considered mild IAH; 14.7–25.7 mmHg was considered moderate to severe IAH; and an IAP >25.7 mmHg was considered very severe and would necessitate surgical decompression (Smith and Sande, 2012). In critically ill patients, IAH was associated with acute renal failure, and increased IAP could lead to renal dysfunction (Richards et al., 1983; Dalfino et al., 2008).

The current study found that an IAP of 25 mmHg under general anesthesia markedly increased the plasma creatinine concentration by reducing plasma exogenous creatinine clearance. In the A25 treatment condition, plasma exogenous creatinine clearance decreased to 50% and 54% of the control treatment condition (CC and AC, respectively). These results were consistent with data obtained in earlier studies showing that increased IAP decreased the GFR (Harman et al., 1982; Cullen et al., 1989; Sugrue et al., 1995; Dalfino et al., 2008). The pathophysiology of renal dysfunction was likely to be multifactorial, and changes in cardiac output, direct compression of the renal vessels with decreased renal blood flow, and an increase in renal vascular resistance together contribute to a decrease in GFR (Hunter and Damani, 2004).
One interesting finding was that increased IAP of 25 mmHg in conscious dogs did not cause a significant decrease in plasma exogenous creatinine clearance. This was an unexpected finding because several research groups had evaluated the effects of IAH on renal dysfunction (Sugrue et al., 1995; Hunter and Damani, 2004). A possible explanation for this contrasting result was that most of the studies on this topic have been performed in the abdominal surgical and anesthesia setting (Dalfino et al., 2008). These experimental studies have suggested that renal hemodynamics and function were highly sensitive to even a moderate increase in IAP (10–15 mmHg), with marked renal impairment (Chiu et al., 1994; Sugrue et al., 1999; Biancofiore et al., 2003). However, in this study, there were no statistically significant differences in plasma exogenous creatinine clearance when IAP was increased to 25 mmHg in conscious dogs. Although more research would be needed to determine the effect of IAH on renal function in conscious healthy dogs, the acute increase in IAP in conscious healthy dog results had a minimal effect on renal function.

General anesthesia can cause systemic hypotension, especially when deep, and a decrease in the circulating blood volume with significant vasoconstriction results in reduced renal blood flow, which in turn decreases the GFR (Kongara et al., 2009). In the AC treatment condition, there were no significant differences in plasma creatinine clearance for CC treatment. This finding indicated that light planes of general anesthesia preserved renal blood flow, with little direct effects on GFR (Clark-Price and Grauer, 2015). However, when the IAP was increased to 25 mmHg under light planes of general anesthesia, the plasma exogenous creatinine
clearance decreased significantly to 54% of that in the AC treatment condition. This finding suggests that renal function could be diminished by use of anesthetic agents (Kongara et al., 2009), such that an increase in IAP to 25 mmHg under general anesthesia markedly impairs renal function, thereby reducing GFR.

An increase in IAP to >20 mmHg had a profound effect on cardiac output and urinary output, and it has been assumed that the decrease in urinary output is due to a decrease in cardiac output, which in turn results from decreased venous return (Harman et al., 1982; Hunter and Damani, 2004). However, the maintenance of cardiac output at a normal level did not appear to prevent renal failure (Harman et al., 1982). Similarly, although the mean arterial pressure was maintained (≥80 mmHg) through the treatment period in the A25 condition (results not shown), the plasma exogenous creatinine clearance decreased significantly in this study. This result might be explained by the fact that direct compression of the renal vessels or renal parenchyma with renal blood flow, increased renal vascular resistance, and a redistribution of blood from the renal cortex to the medulla cause renal dysfunction when IAP was elevated (Harman et al., 1982; Hunter and Damani, 2004; Dalfino et al., 2008).

Decompression of the abdomen with a decrease in IAP has been shown to improve oxygenation, cardiac output, and urine output, and usually results in a diuresis (Cullen et al., 1989; Hunter and Damani, 2004). In this study, an increase in IAP to 25 mmHg significantly decreased plasma exogenous creatinine clearance in anesthetized dogs, and plasma creatinine concentrations declined rapidly and returned to basal levels 8 hours after decompression of the abdomen.
This study had several limitations. Firstly, in the CC and C25 treatment conditions, all IAP measurements and blood samples were obtained from the dogs in a standing position. However, in the AC and A25 treatment conditions, all IAP measurements and blood samples were obtained with the dogs positioned in dorsal recumbency during anesthesia. An effect of body position on IAP had been reported in human and veterinary medicine (Cheatham et al., 2009; Scott et al., 2014). Although body position did not affect plasma exogenous creatinine clearance under the CC and AC treatment conditions, it might have influenced the results for the C25 and A25 treatment conditions. Secondly, several studies had shown that renal hemodynamics decrease in response to even a moderate increase in IAP (10–15 mmHg), with remarkable renal impairment (Richards et al., 1983; Sugrue et al., 1995; Dalfino et al., 2008). In this study, the IAP was increased to only 25 mmHg because an increase to 15 mmHg under light general anesthesia did not have an effect on plasma exogenous creatinine clearance in the pilot study (data not shown). Possible explanations for this lack of effect were that the previous experiments were conducted in different anesthesia/surgical setting and/or the methods used to induce IAH might have affected on these results (Chiu et al., 1994; Sugrue et al., 1999; Biancofiore et al., 2003; Schachtrupp et al., 2007). Finally, the plasma exogenous creatinine clearance test was used to evaluate renal function. Determinations of urine clearance of endogenous and exogenous creatinine or an inulin test have been valuable in the research setting, but were not feasible in this type of study because they require accurate collection of urine samples (Watson et al., 2002). The technique used to measure IAP involves infusion of saline into the
bladder, so the plasma exogenous creatinine clearance test was used to evaluate renal function in this study.
Conclusions

In conclusion, an increase of IAP to 25 mmHg markedly reduced plasma exogenous creatinine clearance in anesthetized dogs. An acute increase in IAP might be critical for development of renal failure, although induction of IAH was performed under a light plane of general anesthesia in healthy dogs. These findings suggested that timely decompression of an acutely increased IAP could potentially improve the outcome in canine patients when surgery and/or general anesthesia was required.
CHAPTER III.

Computed Tomography Features of Intra-abdominal Hypertension in Three Dogs with Spontaneous Abdominal Tumor

Abstract

This study was performed to describe the computed tomography (CT) features of intra-abdominal hypertension (IAH) in three dogs with abdominal distension. Three dogs were presented to the diagnostic imaging center for performing CT. Physical examination findings were consistent with anorexia, distended abdomen, and/or labored breathing. All three dogs were premedicated with IV butorphanol (0.2 mg/kg). A Foley urinary catheter was aseptically placed and the transvesical technique was used to obtain intra-abdominal pressure (IAP). The IAP measurements were obtained with the dogs in a standing position after a stabilization period of 5 minutes. The mean IAP values for the three dogs were 26 mmHg, 12 mmHg, and 13 mmHg. Anesthesia was induced with IV propofol (2-4 mg/kg, to effect) for performing CT scan in three dogs and maintained with sevoflurane in two dogs.
Compression of the caudal vena cava and elevation of the diaphragm in the seven CT features were observed in all three dogs, while inguinal herniation and renal compression was seen in a dog with an increase in IAP to 26 mmHg.

The presence of compression of the caudal vena cava, direct renal compression, and inguinal herniation on the CT images of critically ill dogs should alert clinicians to the possibility of IAH. CT features suggestive of IAH should be communicated and prompt clinicians to measure IAP and consider suitable interventions to reduce IAH.
Introduction

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) is defined as a state of increased intra-abdominal pressure (IAP) within the abdominal cavity (Parsak et al., 2008; Nielsen and Whelan, 2012). Increased IAP, also known as IAH, can adversely affect hemodynamic instability, visceral organ perfusion, and pulmonary and thoracic wall compliance, which lead to significantly increased morbidity and mortality in critically ill people (Hunter and Damani, 2004; Malbrain et al., 2006; Kimball et al., 2007). In veterinary medicine, normal IAP ranges between 0 mmHg and 7.4 mmHg, and IAH is defined as sustained increased IAP (7.4–14.7 mmHg, mild IAH; 14.7–25.7 mmHg, moderate to severe IAH; and >25.7 mmHg, severe IAH) (Smith and Sande, 2012). Although IAP is not routinely measured in critical ill patients, IAH is clinically important, as it may lead to multiple organ failure, and timely surgical decompression of the abdomen may improve the outcome (Hunter and Damani, 2004; Al-Bahrani et al., 2007; Rader and Johnson, 2010).

The diagnosis of IAH or ACS is dependent on measurement of IAP (Smith and Sande, 2012). The method of measuring intra-vesicular pressure (IVP) by placement of a urinary catheter is currently accepted as the gold standard method (Engum et al., 2002; Malbrain, 2004). Although IAH and ACS can be diagnosed clinically, a number of CT findings have been reported to help the diagnosis of IAH and ACS in humans (Pickhardt et al., 1999; Epelman et al., 2002; Al-Bahrani et al., 2007). However, despite considerable attention accorded to IAH and ACS in
the veterinary literature (Brosnahan et al., 2009; Rader and Johnson, 2010; Fetner and Prittie, 2012), there is little information about CT findings with regard to IAH/ACS in dogs. This report described the CT findings in three dogs with IAH.
Case series

1) Case 1

A 13–year-old, 4.0 kg, male Maltese was presented for evaluation of an abdominal tumor and effusion. One day prior to referral, the dog was presented to his primary care veterinarian for anorexia, a distended abdomen, and labored breathing. A full blood count was performed and no significant abnormalities were detected. A serum biochemistry profile was performed and abnormalities included increased alkaline phosphatase activity (326 U/L; reference interval, 47–254 U/L), gamma-glutamyl transpeptidase (26 U/L; reference interval, 5–14 U/L). Decreased albumin (2.5 g/dL; reference interval, 2.6–4.0 g/dL), blood urea nitrogen (8.3 mg/dL; reference interval, 9.2–29.2 mg/dL), and creatinine (0.2 mg/dL; reference interval, 0.4–1.4 mg/dL) levels were revealed. The referring right lateral and ventrodorsal abdominal radiographs revealed a complete effacement of serosal detail throughout the distended abdomen.

A physical examination was performed on presentation. Heart rate was 114 beats per minute and respiratory rate was 48 breaths per minute with mild respiratory effort. SAP was 140 mmHg via indirect doppler measurement. Supplemental oxygen was administered via a face mask at a flow rate of 5 L/min, and a 24-gauge catheter was placed in the right cephalic vein. The dog was premedicated with 0.2 mg/kg butorphanol (Butorphanol®, Myungmoon Pharm, Korea) intravenously (IV). The prepuce was clipped and a 6-French Foley urinary catheter was aseptically placed by the veterinarian. The Malbrain technique was
used to obtain transvesical IAP measurements (Malbrain, 2004). A sterile urinary collection system with three three-way stopcocks was connected and a 500 mL bag of 0.9% sodium chloride solution was attached to the first stopcock. A 30 mL syringe and the pressure transducer were connected to the second and third stopcock each. The bladder was emptied of urine and 1 mL/kg of 0.9% sodium chloride was instilled into the bladder (Way and Monnet, 2014). The pressure transducer was zeroed at the level of the symphysis pubis before measurement and IAP measurements were obtained with the animals in a standing position and using the pressure transducer. A mean IAP of 26 mmHg was recorded after a stabilization period of 5 minutes. Anesthesia was induced with 2 mg/kg propofol (Propofol, Myungmoon Pharm, Korea) IV for CT and the urinary catheter was removed. After intubation, anesthesia was maintained with propofol (1 mg/kg, IV) in 2 L/minute oxygen delivered through a semi-closed circle system. Initial readings during CT examination included a heart rate of 93 beats per minute, an indirect mean arterial pressure of 53 mmHg, a respiratory rate of 22 breaths per minute, an end-tidal CO\textsubscript{2} partial pressure of 46 mmHg, and pulse oximetry of 98% as recorded by a monitor (Datex-Ohmeda® S/5, GE Healthcare, Finland).

A thoracic and abdominal CT examination was performed in sternal recumbency by using a 6-slice scanner (Somatom Emotion® 6, Siemens, Germany). Post-contrast dual-phase scanning of the abdomen after pre-contrast CT scanning of the thorax and abdomen was conducted using a bolus-tracking system (CARE-Bolus®, Siemens, Germany). Scan parameters were 130 kVp, 120 mAs, 2.5 mm slice thickness, 0.75 second rotation time, and 1.0 helical pitch. A non-ionic
iodinated contrast medium (Omnipaque®, GE healthcare, Ireland), iohexol (750–850 mg iodine/kg), was administered by automatic power injector (CT 9000™ ADV®, Liebel-Flarsheim, USA) over 10 seconds via the cephalic vein. Arterial and portal phase CT scans were started after injection of the contrast medium with diagnostic delays of 5 and 30 seconds after trigger at the abdominal aorta, respectively. In sequence, thoracic CT scanning was conducted immediately after post-contrast scanning of the abdomen. All images were reconstructed using 1.5 mm intervals and the standard algorithm.

A large amount of peritoneal fluid was identified on the CT images. A large, irregular contouring hepatic mass was seen in the quadrate lobe. The mass was heterogeneous, with attenuation appearing lower than the liver on pre-contrast CT images, and showed marked, heterogeneous, generalized enhancement on both arterial and portal phase images. The hepatic mass was 7 cm in maximal diameter and included a large cavitated lesion of homogenous fluid attenuation. Multiple hypoattenuating nodules from the residual liver lobes were also observed on post-contrast images, along with multiple pulmonary nodules. Interestingly, horizontal compression of the intra-abdominal caudal vena cava, a flattened ventral renal surface, accumulation of fluid around the left spermatic cord suggestive of cryptorchidism, and a raised diaphragm were found, similar to the CT features described in human patients with ACS (Pickhardt et al., 1999; Al-Bahrani et al., 2007). Enlargement of the deep circumflex iliac vein and the caudal epigastric vein was also observed (Fig. 8 and Fig. 9A).
The post-extubation recovery was uneventful. Abdominocentesis was performed by the primary care veterinarian. Unfortunately, ascites returned after 1 week and was accompanied by severe anorexia, so the dog was euthanized.
Fig. 8. Post-contrast CT images for Case 1 with IAP of 26 mmHg, indicating severe IAH. Transverse images (A-C) show a large liver mass (long arrow) with a cavitated lesion (asterisk), renal compression (short arrow), and fluid accumulation (arrow head) surrounding the left spermatic cord and testis. Elevation of the diaphragm and a dilated caudal epigastric vein (black arrow) are observed on the dorsal (D) and volume rendering (E) images.
Fig. 9. Compressed caudal vena cava in all three dogs. The horizontal narrowing of the caudal vena cava in Case 1 with an IAP of 26 mmHg (A) comparing with vertical compression in Case 2 with an IAP of 12 mmHg (B) and in Case 3 with an IAP of 13 mmHg (C) are shown.
2) Case 2

A 12–year-old, 5.0 kg, neutered female Poodle was presented for evaluation of an abdominal tumor. One day prior to referral, the dog was presented to a primary care veterinarian for abdominal distension. A CBC was reportedly normal. Abnormalities on serum biochemistry profile included increased alanine aminotransferase (1100 U/L; reference interval, 17–78 U/L) and alkaline phosphatase activity (1525 U/L; reference interval, 47–254 U/L). The referring right lateral and ventrodorsal abdominal radiographs showed a large, round mass with soft tissue opacity in the central and ventral portion of the middle abdomen, resulting in dorsal deviation of the stomach and caudal displacement of the small bowel.

On presentation to the diagnostic imaging center, physical examination was unremarkable. The dog was premedicated with butorphanol (0.2 mg/kg, IV). The vulva was clipped and aseptically prepared, and a 6-French Foley urinary catheter was aseptically placed by the veterinarian. The Malbrain technique was used to obtain the intravesicular pressure (Malbrain, 2004), and a sterile IAP measurement system was placed with three three-way stopcocks with a pressure transducer. A mean IAP of 12 mmHg was measured after a stabilization period of 5 minutes. Anesthesia was then induced with propofol (4 mg/kg, IV to effect) for CT and the urinary catheter was removed. After intubation, anesthesia was maintained with 2.5% sevoflurane (Sevoflurane®, Piramal Critical Care, Inc., USA) in 2 L/minute oxygen delivered through a semi-closed circle system.
On the CT images obtained, the abdominal mass was identified as a large, round, heterogeneous soft tissue attenuating mass with a maximal diameter of 10 cm and originating in the left lateral liver lobe. The lesion was isoattenuated on arterial phase and hypoattenuated on portal phase when compared with the surrounding hepatic parenchyma. The stomach and pancreas were displaced dorsally, resulting in ventral compression of the caudal vena cava at the level of the right adrenal gland, and the diaphragm was mildly raised (Fig. 9B).

The post anesthesia recovery was uneventful, but follow-up information could not be obtained.
3) Case 3

A 9-year-old, 11.5 kg, neutered male mixed breed dog was presented to our diagnostic imaging center for evaluation of an abdominal tumor. One day prior to referral, the dog was presented to a primary care veterinarian for abdominal distension. A complete blood count was reportedly normal. Abnormalities on the serum biochemistry profile included increased aspartate aminotransferase (57 U/L; reference interval, 17–44 U/L). A large soft tissue opacity mass occupying the ventral portion of the left middle abdomen was revealed on right lateral and ventrodorsal abdominal radiographs.

The physical examination was unremarkable on presentation. The dog was premedicated with butorphanol (0.2 mg/kg, IV). The prepuce was clipped and aseptically prepared. An 8-French Foley urinary catheter was aseptically placed by the veterinarian and the Malbrain technique was used to measure intravesicular pressure. The sterile IAP measuring system was placed and IAP measurements were obtained with the dog in a standing position. A mean IAP of 13 mmHg was measured after a stabilization period of 5 minutes. Anesthesia was then induced with propofol (4 mg/kg, IV to effect) for CT and the urinary catheter was removed. After intubation, anesthesia was maintained with sevoflurane in 2 L/minute oxygen delivered through a semi-closed circle system.

On CT images, the origin of a large, oval-shaped, soft tissue attenuating mass with heterogeneous contrast enhancement was unclear. Free fluid was detected caudally to the mass, and the small and large intestines were displaced laterally and
caudally. The caudal vena cava was compressed ventrally by the mass, and the diaphragm was mildly raised (Fig. 9C).

The dog recovered from anesthesia uneventfully. The tumor was resected by the primary care veterinarian and was diagnosed as sarcoma of unknown primary origin. No clinical or pathological abnormalities were found on follow-up examination 8 months postoperatively.
Discussion

IAH has profound systemic effects, and primarily affects the cardiovascular, respiratory, renal, gastrointestinal, and neurological systems (Parsak et al, 2008). These physiological dysfunctions become more pronounced and clinically significant when IAP is greater than 20 mmHg (Hunter and Damani, 2004). Clinical presentation usually included decreasing cardiac output and urine output and increasing ventilation-perfusion mismatch in the setting of massive abdominal distention (Malbrain and de Laet, 2009; Nielsen and Whelan, 2012). The clinical diagnosis was typically confirmed by measurement of intravesicular pressure, which closely reflects IAP (Smith and Sande, 2012).

In human medicine, a number of radiological features seen on CT could provide evidence of increased IAP in patients at risk for developing ACS (Pickhardt et al, 1999; Epelman et al., 2002; Al-Bahrani et al., 2007). In these studies, seven CT features were reported in patients with IAH and ACS, including compression of the inferior vena cava, the round belly sign (RBS), direct renal compression or displacement, bowel wall thickening with contrast enhancement, solid organ compression, bilateral inguinal herniation, and elevation of the diaphragm. Of these seven CT features, compression of the caudal vena cava and elevation of the diaphragm were observed in all three dogs, while inguinal herniation and renal compression was seen in Case 1, which had an IAP of 26 mmHg. The others three features were not found in any of the dogs.
Interestingly, the dog with severe IAH reported in Case 1 had horizontal compression of the caudal vena cava, whereas vertical compression by a large abdominal mass was present in the other two dogs. In human medicine, a narrowing of the inferior vena cava seen on CT is characteristic of patients with IAH; this was defined as a slit-like appearance less than 3 mm in width and accepted to be the result of retroperitoneal infiltration (Pickhardt et al., 1999). Narrowing of the inferior vena cava was detected in 16 of 32 patients with IAH in the human studies (Wachsberg et al., 1998; Pickhardt et al., 1999; Epelman et al., 2002). Narrowing of the caudal vena cava as a CT sign of IAH was only observed in the dog with severe IAH (Case 1). Furthermore, the deep circumflex iliac vein and caudal epigastric vein were enlarged in the dog with severe IAH, and these vessels were described as a collateral venous pathway for obstruction of the caudal vena cava in dogs (Specchi et al., 2014). Narrowing of the caudal vena cava and formation of a collateral venous circulation as CT signs of severe IAH is worth noting in dogs.

Elevation of the diaphragm was consistent with the CT evaluation of IAH, but was not independently predictive of IAH in human medicine (Al-Bahrani et al., 2007). Radiographically, it had been evaluated subjectively as the distance between the diaphragm and the cardiac silhouette or costodiaphragmatic angle in dogs, and was also observed in various conditions, including obesity, excessive gastric gas or food content, severe pain, and lung collapse in dogs (Llabrés-Díaz F et al., 2008). Therefore, CT evaluation of the diaphragm might not be helpful for predicting IAH in dogs. Unilateral fluid accumulation surrounding the spermatic cord in a dog with
severe IAH was similar to bilateral inguinal hernia in human patients with ACS (Pickhardt et al., 1999). However, this sign was not found in a prospective study of 48 CT examinations in human medicine (Al-Bahrani et al., 2007). Renal compression was related to oliguria in ACS (Harman et al., 1982; Pickhardt et al., 1999). As in the present report, inguinal hernia and renal compression might occasionally be found in dogs with severe IAH.

RBS and bowel wall thickening with contrast enhancement has been found to have a significant relationship with IAH in some human studies (Pickhardt et al, 1999; Al-Bahrani et al., 2007). RBS has been defined as an anteroposterior to transverse diameter ratio of more than 0.8 in humans (Pickhardt et al, 1999). It has not been reported in dogs, and it might be difficult to evaluate the grade of abdominal distension for IAH or ACS because of various chest conformations and the wide range of size in dogs. Bowel wall thickening with contrast enhancement was accepted to be an independent predictor of the presence of IAH in human medicine (Al-Bahrani et al., 2007), but was not found in the present canine cases in spite of dual-phase images. The spatial resolution of CT images in small canine breeds might be not enough to evaluate the signs of IAH, and further study would be required in large numbers of dogs with IAH or ACS.

In human medicine, the management of patients with established IAH and ACS required timely recognition and decompression, because the adverse effects of IAH were reversible if the IAP was promptly decreased (Hunter and Damani, 2004). Although the appropriate timing and indications for surgical decompression were controversial, a grading system based on intravesical measurement of IAP
and recommended surgical decompression when IAP was >25 mmHg, given that sustained IAH could lead to physiologic dysfunction and multiple organ failure (Burch et al., 1996; Pickhardt et al, 1999). In these reports, best management of these complex patients required very close cooperation between surgeons, radiologists and criticalists.

One limitation of this study was the small patient population with IAH referred to our diagnostic imaging center for CT evaluation. However, reporting the above CT features will increase awareness of IAH in dogs among veterinary radiologists and prompt clinicians to measure IAP to determine whether IAH is present (Pickhardt et al, 1999; Al-Bahrani et al., 2007). Detection of these features at an earlier stage could potentially prevent and improve the outcome of IAH and ACS in veterinary patients.
Conclusions

Severe IAH was a life-threatening condition that requires prompt diagnosis and timely intervention. The presence of compression of the caudal vena cava, direct renal compression, and inguinal herniation on CT images of critically ill dogs should alert clinicians to the possibility of IAH. CT features suggestive of IAH should be discussed among radiologists, surgeons and criticalists, and should prompt clinicians to measure IAP and consider suitable interventions to reduce IAH.
GENERAL CONCLUSIONS

This study was designed to develop and evaluate of an IAH model in conscious dogs.

In chapter I, the new balloon device designed for this study was successfully insufflated and sustained IAH in the conscious dogs. Because this balloon technique did not require general anesthesia or special insufflaters to induce IAH, it could be considered as accurate, repeatable, and useful method. An acute IAP increase in normal conscious dogs induced discomfort and vomiting, as well as increased respiratory effort.

In chapter II, the effect of IAP on plasma exogenous creatinine clearance was investigated in both conscious and anesthetized dogs using a balloon technique to generate IAH. Although an increase of IAP to 25 mmHg did not cause a significant decrease in plasma exogenous creatinine clearance in conscious dogs, it significantly reduced plasma exogenous creatinine clearance in the anesthetized IAH dogs.

In chapter III, the dog with severe IAH had compression of the caudal vena cava, direct renal compression, and inguinal herniation on CT images. Intra-abdominal features and hemodynamics might be altered according to increase of IAP. These CT features suggestive of IAH should be discussed among radiologists, surgeons and criticalists, and should prompt clinicians to measure IAP and consider suitable interventions to reduce IAH.
The present study demonstrated that the conscious IAH dog model had deleterious effects on cardiovascular, respiratory, and renal function. Although more research would be needed to determine the efficacy of the current IAH dog model, it could be considered an appropriate method for animal IAH and ACS researches.
REFERENCES


국 문 초 록

의식이 있는 개에서 복강내압 항진증 모델의
개발 및 평가

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장 민

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복강내압 항진증과 복강구획증후군은 중환자에서 사망률을 증가시키는 중요한 요인으로 인식되고 있다. 개에서 정상적인 복강내압은 0-7.4 mmHg 로 알려져 있으며 체중, 자세, 복벽의 긴장도, 복수, 복막염, 외상, 위장관 질환 등에 의해 영향을 받는다. 복강내압의 지속적인 증가는 심혈관계, 호흡기계, 신장계, 소화기계로 공급되는 혈류량을 감소시켜 장기의 기능부전을 유발한다. 기존의 복강내압 항진증 연구는 전신마취상태에서 실시되었으며, 더욱이 이러한 마취가
복강내압 항진증에 미치는 영향에 대하여 연구된 바가 없다. 그러므로 본 연구는 의식있는 개에서 복강내압 항진증 모델을 개발하고, 마취가 복강내압 항진증 모델에 미치는 영향을 평가하였다. 또한 복부팽만을 지닌 환경에서 복강내압 항진증의 컴퓨터단층촬영 소견을 살펴보았다.

제 1 장에서는 새롭게 고안된 요도카테터를 이용한 balloon 장치를 외과적으로 개의 복강 내에 장착하였으며, 방광내압 측정법을 이용하여 간접적으로 복강내압을 측정하였다. 본 모델에서는 의식이 있는 개에서 공기 주입으로 상승된 복강내압이 지속적으로 유지되었으며, 이러한 복강내압의 항진으로 불편함, 소화기 장애, 노력성 호흡이 유도됨을 확인하였다.

제 2 장에서는 복강내압의 상승이 외인성 혈장 creatinine 청소율에 미치는 영향을 검토하였다. 정맥으로 80 mg/kg의 creatinine 을 투여한 후 비마취-대조군, 비마취-복강내압항진군(25 mmHg), 마취-대조군, 마취-복강내압항진군(25 mmHg)에서 외인성 혈장 creatinine 청소율을 평가하였다. 비마취-대조군, 비마취-복강내압항진군, 마취-대조군에서는 혈장 creatinine 청소율에서 유의적인 차이가 확인되지 않았으나, 마취-복강내압항진군에서는 10, 20, 30, 60, 90, 120 분에서 유의적인 청소율의 감소를 확인하였다.

제 3 장에서는 복부팽만을 동반한 복강내압 항진증이 있는 세 마리의 증례에서 컴퓨터단층촬영의 영상학적 특징을 확인하였다. 복강내압이
상승한 3 증례 모두에서 후대정맥 압박 및 횡격막 상승을 보였고, 복강내압이 26 mmHg 로 상승한 1 증례에서 시해부 탈장 및 신장 압박 소견을 추가적으로 확인하였다. 본 증례를 통하여 복강내압의 상승이 후대정맥, 신장혈관, 신장실질에 미치는 압박을 영상학적으로 확인하였으며, 이로 인한 신장 혈관저항의 증가가 신장기능 부전의 원인임을 확인하였다.

이상의 연구결과를 바탕으로 본 연구에서 개발된 모델은 의식이 있는 개에서 복강내압의 항진을 효과적으로 유도하여 심맥관계, 호흡기계 및 비뇨기계에 미치는 영향을 평가할 수 있는 유용한 방법임을 확인하였다. 중환자에서 복강내압 항진증의 유해한 작용에 대한 인식의 증가로 복강내압 항진증의 병태생리적 이해와 치료대책이 개발되고 있으며, 본 모델은 복강내압 항진증과 복강구획증후군 연구분야에서 유용한 동물모델로서 활용할 수 있을 것으로 기대된다.

주요어: 복강내압항진증, 복강내압, 복강구획증후군, 개, 모델
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