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Trans-diaphragmatic pressure measurement as a prognostic factor in the Intensive Care Unit in dogs

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ABSTRACT. In the last decade, attempts to improve the quality of the services provided to the critically ill patients in the Intensive Care Unit (ICU) are of great interest in human medicine. The aim of the majority of the clinical studies is the correlation of the survival rate of a critically ill patient with specific prognostic factors at the time of admission. The detailed assessment of a patient at admission in the ICU and during hospitalization seems to affect the management and the outcome. The main aim of this study was to evaluate if the trans-diaphragmatic pressure measurement can be a prognostic factor of the outcome in the ICU in dogs. Thirty-one dogs, 21 male and 10 female was included in this prospective, cohort study. Age, breed, sex, body weight and clinical diagnosis were recorded. The type of admission, the mentation status, physiological and biochemical parameters were measured at the admission of the dog in the ICU. All the variables were assessed over the first 24 hours following ICU admission. The animals were allocated into six groups: peritonitis/intra-abdominal surgery, intra-thoracic surgery, respiratory disease, neurologic disease, neoplasia, and systematic disease. The trans-diaphragmatic pressure (P_{di}) was measured under the same anesthetic level in all animals with two oesophageal balloon catheters. The most frequent problem for admission in ICU was peritonitis (5/31). Seventeen out of 31 were admitted in acute status while 14/31 had a chronic problem. Mean±standard deviation of P_{di} was 10.7±5.6 mmHg and of lactate concentration 2.3±1.2 mmol/L. Both, they can predict outcome (p=0.071 and p=0.076, respectively). Seven out of 31 dogs died, 2 were euthanized and 22 were discharged from the ICU after hospitalization. The technique of P_{di} measurement with balloon catheters can be successfully applied in dogs in the ICU. P_{di} measurement, as well as lactate concentration may be used as prognostic indicators for the outcome, in dogs in the ICU. However, a bigger sample size is need to support these findings.

Keywords: trans-diaphragmatic pressure, outcome, prediction, dog, ICU

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INTRODUCTION

In the last decade, attempts to improve the quality of the services provided to the critically ill patients in the Intensive Care Unit (ICU) are of great interest in human medicine (Kuzniewicz et al., 2008; Kvåle and Flaatten, 2002). The aim of the majority of the clinical studies is the correlation of the survival rate of a critically ill patient with specific prognostic factors at the time of admission. The detailed assessment of a patient at admission in the ICU and during hospitalization seems to affect the management and the outcome. In human medicine, the clinical condition of a patient in the ICU is assessed according to particular objective risk models. Scoring systems for illness severity are based on a number of clinical variables that predict mortality risk, and provide an objective basis for patient triage. These systems should be based on objective criteria, be accurate and easy to use (Gunning and Rowan, 1999). According to the human literature, the most used objective risk model that is applied in the ICU is the APACHE II (Acute Physiology and Chronic Health Evaluation System). The basis for the APACHE development was the hypothesis that the severity of acute disease can be measured by quantifying the degree of abnormality of multiple physiological parameters. In particular, the APACHE II is formed based on three parameters: the assessment of 12 physiological parameters (e.g. heart rate, respiratory rate, mean arterial pressure, temperature, oxygenation, arterial pH, hematocrit), the age of the patient and the presence of chronic surgical disease (Knaus et al., 1985; Niewiński, 2014).

The physiological status of the critical ill patients is characterized by rapid and frequent life-threatening alterations in organ function. The respiratory function is often affected during the hospitalization of a patient in the ICU. Respiratory muscle fatigue may develop, either in primary or secondary respiratory disease, or as a complication during the hospitalization. According to the literature, the majority of the cases in the ICU involve the respiratory system (Eng et al., 1992). Despite the evidence that respiratory muscle dysfunction develops in critically ill patients which contributes to weaning failure, the respiratory muscles are poorly monitored in the ICU (Hermans et al., 2010; Jaber et al., 2011; Laghi et al., 2003). Three factors may contribute to this: 1. the limited knowledge on the effects of critical illness on respiratory muscle function, 2. the lack of knowledge and availability of tools to monitor respiratory muscle function, and 3. the perception that the monitoring of respiratory function has no clinical consequences (Doorduin et al., 2013).

The diaphragm is the main respiratory muscle and it is thought to be very sensitive to respiratory muscle fatigue (Jonville et al., 2002; Moxham et al., 1981b, Moxhman et al., 1981a; Zakynthinos and Roussos, 2005). As respiratory muscle fatigue is defined the inability of the muscle to produce pressure in order to maintain the alveolar ventilation, and it is reversible during rest (Lumb, 2010; Zakynthinos and Roussos, 2005). The effects of critical illness on respiratory function are often part of a generalized phenomenon which is known as "ICU-acquired weakness". The main causes of this phenomenon may be systemic inflammation, drugs, electrolyte disturbances and immobility (Jolley and Bunnell, 2016). Additionally, the prolonged mechanical ventilation in the ICU patients leads to decreased diaphragmatic strength, known as "ventilator-induced diaphragmatic dysfunction" (Vassilakopoulos, 2012).

There are many methods to monitor the respiratory muscle function. Pressure and flow recordings, electromyography, ultrasonography, circulatory biomarkers, computed tomography (CT) and magnetic resonance imaging (MRI) (Doorduin et al., 2013). However, the best indicator of diaphragmatic contractility seems to be the trans-diaphragmatic pressure (P_{di}) measurement. Specifically, the measurement of P_{di} during a maximum inspiratory effort ($P_{di\ max}$) is an indicator of the strength of the diaphragm and it helps to assess patients with respiratory muscle weakness (Chen et al., 2000; Ferguson, 1994; Man et al., 2004; Man et al., 2002).

P_{di} is defined as the difference between the intra-abdominal pressure (P_{abd}) and the intra-pleural pressure (P_{pl}) (Adams et al., 1988; Gilbert et al., 1979; Hubmayr et al., 1990). However, the measurement of P_{abd} and P_{pl} is not straightforward under clinical conditions and therefore alternative, less invasive techniques have been proposed, replacing the measurement of P_{abd} and P_{pl} by the measurement of the intra-gastric pressure (P_{gast}) and the intra-oesophageal pressure (P_{oes}), respectively (Benditt, 2005). This approach has been adapted for use in dogs allowing the monitoring of P_{di} in a clinical setting (Pavlidou et al., 2014). In experimental studies in humans and in animals, the maximum inspiratory pressure is achieved by the electrical stimulation of the phrenic nerves (Hubmayr et al., 1990; Leduc et al., 2008) However, non-invasive methods (Mueller's manoeuvre) have been used in co-operative patients for the measurement of $P_{di\ max}$.

With this method, the maximum P_{gast}, P_{oes} and P_{di} can be measured in one respiratory cycle (De Troyer and Estenne, 1981).

In human medicine, there is an effort to apply P_{di} measurement in the ICU in a routine setting in order to assess the critical ill patients. Recent studies have shown that respiratory muscle fatigue can develop in mechanically ventilated patients in the ICU and this can result in respiratory failure (Demoule et al., 2013; Hermans et al., 2010; Supinski and Ann Callahan, 2013). The respiratory muscle weakness is the result of the absence of diaphragmatic activity, because of the application of mechanical ventilation, and it is worsened with the prolongation of the mechanical ventilation (Petrof, 2013). However, other factors such as hyperglycemia, azotemia and hypoalbuminemia can cause respiratory muscle weakness in critically ill patients in the ICU (Hermans et al., 2007; Modawal et al., 2002; Wu et al., 2009).

Recently, in veterinary clinical practice, the detailed assessment of the critical ill patients in the ICU has been studied. The APPLE (Acute Patient Physiologic and Laboratory Evaluation) score system is the risk model that can be used in the veterinary ICU. Physiological parameters (e.g. sex, age, weight), hematological and biochemical profile, chronic diseases, previous surgical procedures and therapeutic treatments are some of the factors that are assessed in the APPLE score system (Hayes et al., 2010b). Although, critically ill dogs are monitored carefully in the ICU, the evaluation of the respiratory function is not a routine procedure in a clinical setting in these patients. There are few available data for the measurement of P_{di} in veterinary practice, as the most studies were "*in vitro*" and the diaphragmatic contractility was evaluated after the electrical stimulation of the phrenic nerves. However, there are two recent clinical studies in dogs where the modified Mueller's manoeuvre was applied for the P_{di} measurement, with the placement of two oesophageal balloon catheters, one in the oesophagus and one into the stomach, and the effect of different anesthetic protocols on diaphragmatic contractility was studied (Pavlidou et al., 2014, Pavlidou et al., 2013).

To our knowledge, there is no clinical study in veterinary medicine on the measurement of P_{di} as a prognostic factor for the outcome of a clinical case in critically ill dogs. The aim of this study was the evaluation of the P_{di} measurement in animals admitted and hospitalized in the ICU as prognostic factor for the outcome, among other clinical measurements, in a clinical setting.

MATERIALS AND METHODS

Approval from the Ethics Committee of the Aristotle University of Thessaloniki was obtained (2016-050-0503-8401). All the dog owners were informed in detail about the study protocol and a signed written consent was obtained. The study population was dogs admitted to the Intensive Care Unit of Companion Animal Clinic of Aristotle University. The animals were excluded from the study when the collection of the data was impossible (e.g. ineffective measurement of P_{di}). Another exclusion criterion was obesity which has been shown to decrease diaphragmatic contractility (De Keulenaer et al., 2009; Lambert et al., 2005; Ora et al., 2011).

Thirty-one client-owned dogs were enrolled in this observational prospective cohort study. In each dog, age, breed, sex, body weight, clinical diagnosis, and the acute or chronic onset of illness were recorded within the first 24 hours following ICU admission; mentation score was assessed at admission in order to estimate the true baseline mental status before the administration of any analgesia or sedation (Hayes et al., 2010a).

The primary system affected at admission was identified and the dogs were allocated to six groups: peritonitis/intra-abdominal surgery, intra-thoracic surgery, respiratory disease, neurologic disease, neoplasia and systematic disease.

Physiological and biochemical parameters were measured at the admission of the dog in the ICU. Full clinical examination and estimation of consciousness status were performed. The dogs were assigned to one of five levels of consciousness: normal mentation, depression, lethargy, coma and excitement (Hayes et al., 2010b). Heart rate (HR), auscultation of the thorax, electrocardiography (ECG), mucous membrane color, pulse quality and invasive arterial blood pressure (systolic/SAP, diastolic/DAP and mean/MAP) were measured (Mindray, iPMI 12 Vet, Shenzen Mindray Bio-Medical Electronics CO, LTD, Nanshan, China). Respiratory rate (RR) was measured by observation and capnography (Datex-Ohmeda S/5, GE Healthcare, Finland) and the end-tidal carbon dioxide concentration ($ETCO_2$) was estimated also by capnography. Oxyhemoglobin saturation (O_2SAT) was estimated indirectly by pulse oximetry (Mindray, iPMI 12 Vet, Shenzen Mindray Bio-Medical Electronics CO, LTD, Nanshan, China) and calculated from the oxygen partial pressure measured by arterial blood gases analysis (Siemens RapidPoint 500, Siemens Healthcare Diagnostics, New York, USA). The laboratory parameters were hematocrit (HCT), white blood cells (WBC) and platelets (PLT) count, total solids (TS), urea, creatinine (Crea), alanine aminotransferase (ALT), alkaline phosphatase (ALP), glucose (Glu) and electrolytes (K^+, Na^+, Ca^{+2}). Lactate concentration was also measured at the time of admission (Accutrend Plus System, Roche Hellas, Greece). The arterial blood gases analysis gave information about the pH, oxygen partial pressure (PO_2), carbon dioxide partial pressure (PCO_2), bicarbonate concentration (HCO_3^-), O_2SAT and the ratio oxygen partial pressure/fraction of inspired oxygen (PO_2/FiO_2) (Siemens RapidPoint 500, Siemens Healthcare Diagnostics, New York, USA).

The trans-diaphragmatic pressure was measured under the same anesthetic level in all animals. When the anesthetic level was deep (lack of reflexes, adequate muscle relaxation, lack of response to surgical stimulation), two 90 cm long oesophageal balloon catheters with guide wires (Esophageal Balloon Catheter Set; Coopersurgical Company, CT, USA) were introduced orally. Using the landmarks that have been described (Pavlidou et al., 2014; Waterman and Hashim, 1991), the balloon of the first catheter was introduced into the stomach for the measurement of P_{gast} and the distal end of the second catheter was positioned in the mid-third of the oesophagus for the measurement of P_{oes}. The correct positioning of the balloon catheters was confirmed by the observation of positive and negative pressure tracings of P_{gast} and P_{oes}, respectively on a computer screen. The catheters were secured in place by fixing them on the endotracheal tube. The guide wires were removed, the catheters were connected to the pressure transducers and the balloons were inflated with 0.5-1 ml of air. The electrical connections from the transducers were attached to a pressure monitoring device with the appropriate software (Pressure Monitoring system Buzzer-II; Michael Roehrich, Austria) and then to a computer. The pressure transducers were zeroed to the atmospheric pressure prior to each measurement.

In order to obtain the maximum P_{oes}, P_{gast} and P_{di}, a modified Mueller's manoeuvre was applied. Particularly, the endotracheal tube was disconnected from the anaesthetic circuit and the proximal end of the tube was tightly closed with a thumb during the respiratory pause after the end of expiration, and thus forcing the dog to breath against the obstructed airway (modified Mueller's manoeuvre (Pavlidou et al., 2014).

As the animals were critically ill patients, the anaesthetic protocol could not be the same for all of them. In each case, the anaesthetic protocol was based on the clinical condition of the animal and it was selected in a way to minimally affect the P_{di} (Pavlidou et al., 2013). Specifically, the premedication differed among the animals, whereas the induction and the maintenance of anaesthesia was the same in all animals. Anaesthesia was induced with propofol (Propofol MCT/LCT, Fresenius, Fresenius Kabi, Greece) intravenously to effect. An initial dose 1-2 mg/kg was given followed, if needed, by incremental doses of 0.5-1 mg/kg until endotracheal intubation could be easily performed. Anaesthesia was maintained with isoflurane (Isoflurane, Merial, Italy) in oxygen. All animals were breathing spontaneously. Fresh gas (100% oxygen) flow was delivered at 1.5 L/min through a circle rebreathing system. The days of the hospitalization were recorded in all animals and the outcome was assessed as alive, dead or euthanized.

The recorded data of the P_{di} were saved in as spreadsheet and analyzed with a signal analysis software (Qtiplot, MicroCal, Northampton, Massachussets, USA). A positive curve of the gastric pressure and a negative curve of the oesophageal pressure, were drawn. The baseline of gastric and oesophageal curves was zeroed and the P_{di} value was calculated (difference between P_{gast} and P_{oes}). Binary Logistic Regression Analysis was used to evaluate the effect of the predictive variable on the patient outcome. Predictive variables included in the model were group, problem, admission, mental status, lactate concentration, and P_{di} value. The designed model was: log(p/1-p) = constant + b1 x problem + b2 x admission + b3 x mental status + b4 x lactate concentration + b5 x P_{di}., where p is the probability of a dog to be alive.

RESULTS

Thirty-one dogs (21 male, 10 female), 1-15 (6.7±4) years (mean±standard deviation) old, weighing 3-40 kg (16.8±12.3) were included in the study. The most frequent problem for the hospitalization in the ICU was peritonitis (5/31), followed by brachycephalic upper airway syndrome, Wobbler syndrome and status epilepticus (Table 1). Seventeen out of 31 were admitted after an acute onset, while 14/31 had a chronic problem. Moreover, 51.6% were in normal mentation and 48.4% were in depression.

Table 1. The causes for admission in ICU

Problem	Frequency
peritonitis/intra-abdominal surgery	**11**
ileus	1
laparotomy	1
peritonitis	5
pyometra	1
splenectomy	1
gastric dilation/volvulus	2
intra-thoracic surgery	**5**
pericardiectomy	1
patent ductus arteriosus	2
diaphragmatic hernia	2
respiratory	**5**
Brachycephalic upper airway syndrome	3
dyspnoea	1
laryngeal paralysis	1
neurologic	**6**
Wobbler syndrome	3
status epilepticus	3
neoplasia	**3**
lung tumor	1
other	2
systematic	**1**
sepsis	1

Ten dogs were premedicated with dexmedetomidine (Dexdomitor, Pfizer, Greece) at 175 μg/m^2 intramuscularly (IM) alone or in combination with methadone (Synthadon, LeVet, The Nederlands) at 0.1 mg/kg IM, 5 dogs with acepromazine (Acepromazine, Alfasan, The Nederlands) at 0.05 mg/kg IM and methadone at 0.1 mg/kg IM, 12 dogs with fentanyl (Fentanyl, Jansseg-Cilag, Greece) at 1 μg/kg and midazolam (Dormipnol, Viofar, Greece) at 0.5 mg/kg intravenously, and finally 4 dogs were not premedicated at all.

Descriptive statistics for the hemodynamic, respiratory and biochemical parameters are shown in Table 2. P_{di_mean} was 10.7±5.6 mmHg and the PO_2/FiO_2 ration was 348.5±145.4 mmHg. The lactate concentration was 2.3±1.2 mmol/L. The duration of hospitalization was 2±1.8 days. Seven dogs died, 2 were euthanized and 22 were discharged from the ICU after hospitalization. In this clinical study, 16/31 dogs had a normal ratio, ARDS was developed in 5 animals and ALI in one. Eleven out of 16 dogs were discharged, while 3/5 with ARDS and 1/1 with ALI died.

The binary regression analysis results are shown in Table 3. Lactate concentration and P_{di} can both predict outcome with a good probability.

Table 2. Mean±standard deviation for the hemodynamic, respiratory and biochemical parameters

Variable	Mean±standard deviation	Variable	Mean±standard deviation
HR (min^{-1})	122±27.3	pH	7.3±0.12
MAP (mmHg)	61±17.4	PO_2 (mmHg)	346.4±159.3
RR (min^{-1})	15.3±6.4	PCO_2 (mmHg)	48.8±14.1
HCT (%)	36.3±8.1	HCO_3^- (mmHg)	21.8±2.8
GLU (mg/dL)	105.7±18.8	$ETCO_2$ (mmHg)	46.5±11.5
K^+(mmol)	4±0.8	P_{di} (mmHg)	10.7±5.6
Lactate (mmol)	2.3±1.2	PO_2/FiO_2	348.5±145.4

Table 3. Binary logistic regression analysis for outcome with predictive variables in the model: group, problem, admission, mental status, lactate concentration, and P_{di} value (b=coefficient, p=observed probability). The value "respiratory problem" has been defined as baseline value for the analysis.

Variable	b	p	Odds ratio
admission	-3.640	0.149	0.026
mental status	0.215	0.863	1.240
lactate	-0.935	0.071	0.393
P_{di}	-0.354	0.076	0.702
problem		0.602	
peritonitis/intra-abdominal surgery	28.139	0.999	1.66×10^{12}
intra-thoracic surgery	26.284	0.999	2.59×10^{11}
neurologic	31.662	0.999	5.63×10^{13}
neoplasia	32.787	0.999	1.73×10^{14}
systematic	23.926	1.000	2.46×10^{10}
constant	-19.343	1.000	0

DISCUSSION

The aim of this clinical cohort study was the evaluation of the P_{di} measurement in animals admitted and hospitalized in the ICU as prognostic factor for the outcome, among other clinical measurements, in a clinical setting. The evaluation of diaphragmatic contractility was based on P_{di} measurement with balloon catheters. To the best of the authors' knowledge, this is the first application of the P_{di} measurement in a non-fatigued diaphragm in dogs in the ICU. Diaphragmatic contractility and P_{di} measurement with balloon catheters has been studied in fatigued, intact diaphragm after phrenic nerve stimulation in healthy (Araujo and Milic-Emili, 2005; Gilbert et al., 1979; Higgs et al., 1983) and critically ill human patients (Watson et al., 2001). The mean value of P_{di} in critically ill patients after phrenic nerve stimulation has been reported to be 7.87 mmHg, (Watson et al., 2001) which is lower than the mean values in the present study.

In a study in dogs, (Pavlidou et al., 2014) the Mueller's manoeuvre, the most commonly used manoeuvre for the measurement of P_{di} in human medicine, has been modified and applied for three consecutive respiratory cycles for the P_{di} measurement. The same manoeuvre was applied in the present study. Post-obstructive pulmonary edema (POPE) may occur as a complication of the Mueller's manoeuvre. However, there is no reference to the development of POPE in dogs and in awake humans in a clinical setting (Pavlidou et al., 2014). In our clinical study, clinical signs of POPE have not been observed in any animal.

The premedication could not have been the same in all the critically ill patients, because of their different clinical situation. This is a limitation of the study, as the different premedications may have variably affected the diaphragmatic contractility. However, the protocol for the induction and the maintenance of anaesthesia was the same in all animals. According to a previous study, fentanyl and propofol seem to reduce diaphragmatic contractility, as P_{di} values were 12.0±5.9 mmHg and 12.2±3.2 mmHg respectively, in comparison with isoflurane (14.9±4.7 mmHg) in dogs under anaesthesia (Pavlidou et al., 2013).

Lactate concentration is considered to be a useful tool in human and veterinary clinical practice. Hyperlactatemia and lactic acidosis occur frequently in veterinary ICU patients with shock, low cardiac output, acute liver failure, sepsis, neoplasia, peritonitis, poisoning and drug therapy (de Papp et al., 1999; Lagutchik et al., 1998, Lagutchik et al.,1996). In healthy adult dogs at rest, lactate concentration is <2.0 mmol/L, but it may be measured as high as 3.5 mmol/L (Lagutchik et al., 1996). In humans, many studies have estimated the prognostic values of lactate concentration levels. It has been shown that a single measurement of lactate concentration is associated with the prognosis of survival (Bernardin, 1996; Cerović et al., 2003). In veterinary medicine, there seems to be a relationship between lactate concentration and outcome in dogs. According to Lagutchik et al., dogs admitted to the ICU with various underlying diseases, having high blood lactate levels at admission were more likely to die (Lagutchik et al., 1998). Animals with high blood lactate levels (>4-5 mmol/L) have a very poor prognosis after 24 hours of the admission. Gastric dilation/volvulus and peritonitis are two pathological conditions where lactate concentration is considered to be a good prognostic factor in dogs (Cortellini et al., 2015; de Papp et al., 1999).

In the present study, lactate concentration along with P_{di} measurement, may predict outcome, with low p values (0.071 and 0.076, respectively). The combination of these two measurements at admission may be of clinically good prognostic value, in dogs and in an animal hospital setting.

Recently, the study of the PO_2/FiO_2 ratio has gained a lot of interest in human and veterinary medicine. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are two life-threatening syndromes with high morbidity and mortality (Matthay et al., 2012; Rubenfeld et al., 2005). According to the American European Consensus Conference (AECC),(Bernard et al., 1994) in humans, a mean value of PO_2/FiO_2 <300 mmHg indicates ALI and <200 mmHg ARDS. As there are no reference values for ARDS and ALI in dogs, the same normal values of PO_2/FiO_2 has been suggested for dogs (Calabro et al., 2013).

The cause of admission could be another prognostic factor for the outcome of the dogs in the ICU. Intra-abdominal infections are an important cause of ICU morbidity and mortality. Peritonitis develops as complication in 30% of the human patients with intra-abdominal infection in the ICU, increasing the mortality rates up to 50% (Delibegovic et al., 2011; Marshall and Innes, 2003). In veterinary medicine, peritonitis is a major problem in the ICU but there is no study to correlate this with the outcome of a case.

Limitations of the study include all those factors that affect the P_{di} measurement. First of all, the P_{di} measurement with balloon catheters is feasible only under general anaesthesia in dogs. Because of this, it cannot be applied to all animals in the ICU. Thus, in our study, the measurement of P_{di} was not applicable in all cases. Moreover, the return of the diaphragmatic contractility back to its normal function after the hospitalization in the ICU is not always applicable, for the same reason. Another limitation of the study was that the insertion of the balloon catheter was impossible in some cases, because the catheter could not pass through the lower esophageal sphincter.

In summary, the technique of P_{di} measurement with balloon catheters can be successfully applied in dogs in the ICU, although there are some limitations. P_{di} measurement with lactate concentration at admission may also be good prognostic indicators for the outcome, although a larger sample size to support this is needed.

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CONFLICT OF INTEREST

None declared by the authors.

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