Protein C activity in dogs with gastric dilatation and volvulus

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Abstract

Protein C activity, a novel prognostic marker, was evaluated in patients with gastric dilatation and volvulus in relation to mortality and severity of the disease. Data on the mortality, duration of clinical signs, degree of gastric torsion, gastric necrosis, splenectomy and occurrence of disseminated intravascular coagulopathy were recorded. Blood samples were obtained at selected time periods: T0 = no longer than 30 min before surgery; T1 = first day after surgery; T2 = second day after surgery. In addition to protein C activity assessment, haematological and haemostaseological analysis was also performed. The mean protein C activity was the lowest at T1 and the highest at T2. No significant relationship between protein C activity and mortality, duration of clinical signs, degree of gastric torsion, gastric necrosis, splenectomy and disseminated intravascular coagulopathy was found in patients with gastric dilatation and volvulus. All patients that died during hospitalisation after surgery were patients with decreased protein C activity at T1. Although protein C activity was not found to be a reliable preoperative prognostic marker in patients with gastric dilatation and volvulus, the study results show it might be a promising marker in postoperative monitoring of these patients.

GDV, DIC, gastric necrosis, prognostic marker

Gastric dilatation and volvulus syndrome (GDV) is a life-threatening disease that affects mainly large and giant breeds of dogs (Beck et al. 2006; Mackenzie et al. 2010; Beer et al. 2013; Bell 2014; Spinella et al. 2018; Song et al. 2020). Although some predisposing and prognostic factors of the syndrome occurrence such as C-reactive protein (CRP), high mobility group box 1 (HMGB1), lactate, acid-base parameters, haemostatic indices, lipase activity, canine pancreatic lipase immunoreactivity or myoglobin have been found (Adamik et al. 2009; Beer et al. 2013; Mooney et al. 2014; Uhrikova et al. 2015; Verschoof et al. 2015; Spinella et al. 2018), the exact cause of the syndrome remains unclear. In the case of GDV development, a gold standard of GDV therapy is surgical treatment (Glickman et al. 1998). A broadly recognized method of GDV prevention is gastropexy, most often as part of proper surgical treatment of the GDV syndrome, or as a preventive mini-invasive laparoscopic assisted gastropexy (Rawlings 2002; Urbanová et al. 2011). Mortality in surgically treated patients with GDV ranges between 10.0–35.0% (Zatloukal et al. 2005; Beck et al. 2006; Mackenzie et al. 2010; Beer et al. 2013; Verschoof et al. 2015; Spinella et al. 2018; Rauserova-Lexmaulova et al. 2020; Song et al. 2020). Due to the acute and severe condition in patients with GDV, urgency for a radical therapeutic decision and non-negligible amount of preoperative and postoperative risks, every prognostic marker is highly valued.

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As one of the participants of the coagulation pathway, protein C (PC) is a vitamin K-dependent serine protease of activated PC which has antithrombotic, profibrinolytic and anti-inflammatory activities (Yan and Dhainaut 2001). In humans it is considered as a negative acute phase protein (Dhainaut et al. 2001) and a negative prognostic factor in septic patients (Fisher and Yan 2000). Yet, there are only a few studies on this indicator in veterinary emergency medicine; so far, a decrease in PC activity has been found in dogs with disseminated intravascular coagulopathy (DIC) and with sepsis (Madden et. al 1989; De Laforcade et al. 2003), whereas decreased PC activity in septic dogs has been associated with mortality (De Laforcade et al. 2008). Patients with GDV are at high risk of DIC and sepsis development (Millis et al. 1993; Beck et al. 2006; Uhrikova et al. 2015; Verschoof et al. 2015). Verschoof et al. (2015) found PC activity in dogs with GDV to be significantly lower in non-survivors compared to survivors, although only plasma lactate concentration was considered to be of prognostic value for overall survival (Verschoof et al. 2015). Nevertheless, PC activity analysis might represent a valuable preoperative prognostic marker which can aid with subsequent treatment decision making. Therefore, we aimed to further evaluate this indicator and to determine a possible relationship between PC activity and the severity of the disease.

The aim of the study was to evaluate the role of PC as a prognostic marker in patients with GDV and to determine the relationship between PC activity and mortality, duration of clinical signs of GDV, degree of gastric torsion, gastric necrosis occurrence, the need to perform splenectomy and occurrence of DIC. We hypothesized that low PC activity may serve as an unfavourable prognostic factor in patients with GDV in both preoperative and postoperative periods and that it could potentially predict the severity of the disease.

Materials and Methods

Patients with GDV presented to the Department of Surgery & Orthopaedics at the Small Animal Clinic, Faculty of Veterinary Medicine, University of Veterinary Sciences Brno, Czech Republic from January to December 2020, that were treated surgically and in which blood samples were obtained according to the study description, were enrolled in the study. Preoperative stabilisation consisting of gastric decompression (percutaneous gastrocentesis and/or orogastric tube passage) and cannulation into v. cephalica antebrachii and subsequent fluid therapy administration using crystalloids was performed in each treated patient. Surgical treatment included gastric reposition and incisional gastropexy in all cases. Patients were hospitalized for several days after surgery until completely recovered. The following patient data were recorded: duration of clinical signs before presented to the clinic, degree of gastric torsion, gastric necrosis occurrence, the need to perform splenectomy, and mortality. The degree of gastric torsion and gastric necrosis occurrence were evaluated during surgery by a specialist surgeon. The degree of gastric torsion was classified into four categories: 90° torsion, 180° torsion, 270° torsion, and 360° torsion. In the case of gastric necrosis occurrence, partial gastrectomy of the affected gastric area was performed or, in the cases of excessive inoperable necrosis, euthanasia was elected. Splenectomy was performed in the cases of splenic vasculature damage (splenic and/or short gastric vessels thrombosis or avulsion), splenic rupture or torsion. Patients discharged from the clinic were assessed as survivals.

Blood was obtained during a routine preoperative and postoperative examination in the following time periods: T0 = no longer than 30 min before surgery, T1 = first day after surgery, T2 = second day after surgery. Following indicators were analysed: functional PC activity, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), D-dimers (DD) and platelet count. Functional PC activity, PT, APTT, TT, FIB and DD were analysed using STA Satellite Max (Diagnostica Stago, S.A.S., Asnières sur Seine, France) and platelet count was analysed using Sysmex XT-2000iV (Sysmex Corporation, Kobe, Japan). During emergency hours, some platelet count analysis was performed using in-house analyser IDEXX ProCyte Dx Hematology Analyzer (Sysmex Corporation, Kobe, Japan). The reference range for functional PC activity was 75–135%.

Blood was collected into citrated and EDTA tubes. EDTA blood samples were used for platelet count analysis and were analysed either within one hour after sampling or after being stored at 4 °C, but not later than 12 h after sampling. Citrated blood samples were centrifuged (2,250 *g* for 15 min) within one hour after sampling and the citrated plasma was used for PC, PT, APTT, TT, FIB and DD analysis. Citrated plasma used for PC activity analysis was frozen at −80 °C until analysed, with a maximum storage time of 6 months. Citrated plasma used for PT, APTT, TT, FIB and DD was analysed either within one hour after sampling or after being stored at −20 °C, but not later than three days after sampling.

Patients were evaluated as patients with DIC if they showed at least three of the following signs: thrombocytopaenia, prolonged PT, prolonged APTT, low FIB concentration or high DD concentration, as described previously (Beck et al. 2006; Verschoof et al. 2015).

Statistical analysis of collected data was performed using the statistical software Statistica 12 (StatSoft CR s.r.o., Praha, Czech Republic) and Unistat 6.5 (Unistat Ltd, London, United Kingdom). Pearson χ^2-test was used to analyse statistical relationships between the breed, age, sex and mortality, between PC activity and the presence of DIC in the selected time periods, between the presence of DIC in the selected time periods and mortality and between PC activity in the selected time periods and mortality. *T*-test was used to analyse the statistical relationship between decreased PC activity at T0 and the need to perform splenectomy. ANOVA analysis was performed to evaluate the statistical relationship between decreased PC activity at T0 and gastric necrosis, degree of gastric torsion and duration of clinical signs. Gastric necrosis occurrence was also evaluated using logistic regression. Linear regression analysis was used to evaluate the statistical relationship between decreased PC activity at T0 and duration of clinical signs and degree of gastric torsion. The level of significance was set at $P = 0.05$.

Results

A total of 26 dogs were enrolled in the study, 14 females (of which 7 were spayed) and 12 males (none of which was neutered). The most commonly represented breeds were German Shepherd (n = 6), Greater Swiss Mountain Dog (n = 3), Rhodesian Ridgeback (n = 2), Weimaraner (n = 2), Golden Retriever (n = 2). One dog of each of the following breeds was also represented: Anatolian Shepherd Dog, Old English Sheepdog, Brazilian Mastiff, Bullmastiff, Cane Corso, Doberman Pinscher, Flat Coated Retriever, Hovawart, Rottweiler, Chow Chow and a crossbreed. The mean body weight was 41.68 kg (SD 9.85) and the mean age was 8.21 years (SD 2.52).

The mean duration time of clinical signs was 2.47 h (SD 2.35). The degree of gastric torsion was assessed as 90° in 3 dogs (11.54%), as 180° in 17 dogs (65.38%), as 270° in 5 dogs (19.23%) and as 360° in 1 dog (3.85%). Gastric necrosis was found in 4 patients (15.38%). Splenectomy was performed in 12 patients (46.15%). Five of the 26 patients died (19.23%) during the study period. Two patients died during surgery – one of them due to heart failure, the other one was euthanised due to massive gastric necrosis with gastric perforation in the cardiac area of the stomach. Other 3 patients died during the postoperative period. The mean hospitalisation time was 1.92 days (SD 1.44).

Twenty-six samples were obtained at T0, 23 samples at T1, and 10 samples at T2 (samples were not obtained from patients that died during hospitalisation or were discharged from hospitalisation). Protein C activity was decreased in 6 patients (23.08%) at T0, in 12 patients (52.17%) at T1, and in 4 patients (40.00%) at T2. Protein C activity in the selected time periods is shown in Fig. 1. Disseminated intravascular coagulopathy occurred in 4 patients at T0, in 6 patients at T1, and in 1 patient at T2, a total of 8 patients (30.77%) developed DIC during the study period.

No significant difference was found between survivors and non-survivors with regard to breed ($P = 0.51$), sex ($P = 0.76$) or age ($P = 0.748$). No significant relationship was found between decreased PC activity and mortality at T0 ($P = 0.855$), T1 ($P = 0.156$) or T2 ($P = 0.389$), although all patients that died during hospitalisation were patients with decreased PC activity at T1 (Fig. 2). No significant relationship was found between decreased PC activity at T0 and duration of clinical signs ($P = 0.602$), degree of gastric torsion ($P = 0.752$), gastric necrosis ($P = 0.23$) or splenectomy ($P = 0.47$). Also, no significant relationship was found between decreased PC activity at T0 and DIC at T0 ($P = 0.16$), T1 ($P = 0.496$) or T2 ($P = 0.520$), or between decreased PC activity at T1 and DIC at T1 ($P = 0.076$) or decreased PC activity at T2 and DIC at T2 ($P = 0.389$). A significant relationship was found between DIC at T2 and mortality ($P = 0.0009$, Cramer's V=1).

No significant relationship was found between the duration of clinical signs and mortality ($P = 0.186$). Although no significant relationship was found between gastric necrosis and mortality, when logistic regression analysis was performed it was found that gastric

necrosis occurrence increases the risk of death 11 times (Fig. 3). This risk can be calculated after substitution of selected variables into this equation:

Death risk = − 0.126*duration of clinical signs + 0.00438*degree of gastric torsion − 0.64*splenectomy + 2.4*gastric necrosis + 0.0066*patient's age − 0.056*patient's body weight

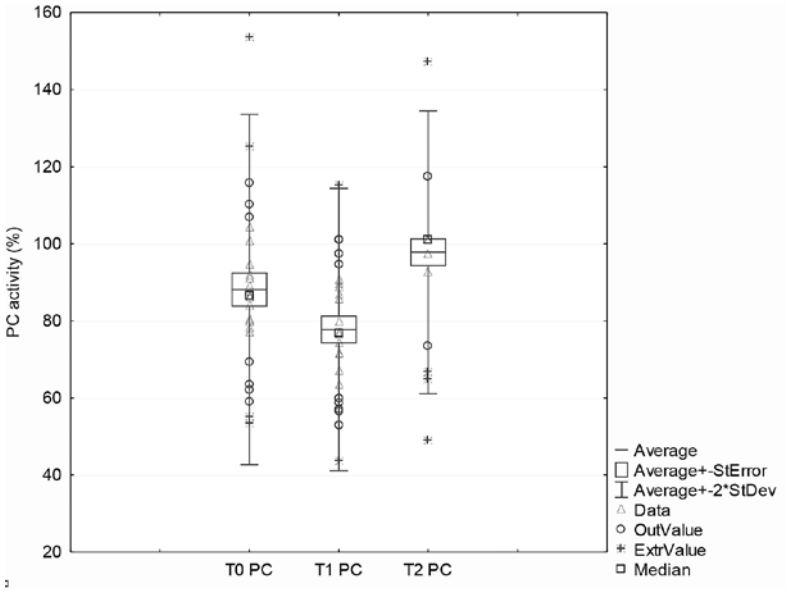

Fig. 1: Protein C activity in selected time periods.
(PC = protein C activity, T0 = no longer than 30 minutes before surgery, T1 = first day after surgery, T2 = second day after surgery)

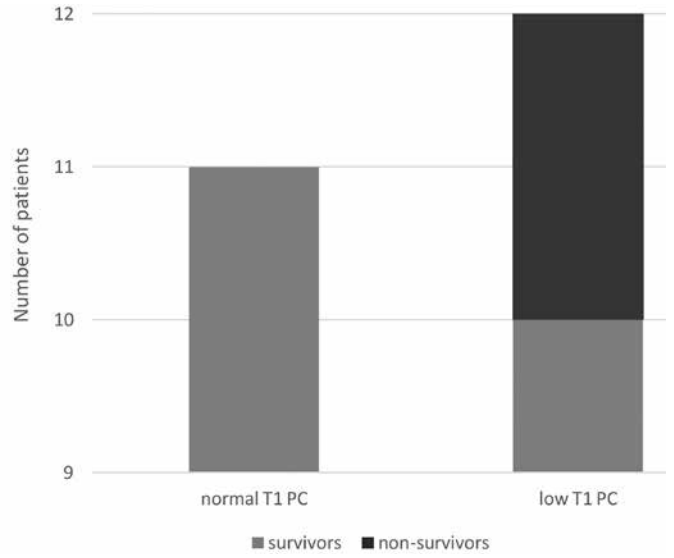

Fig. 2: The effect of protein C activity on mortality of patients with gastric dilatation and volvulus
(T1 = first day after surgery, PC = protein C activity)

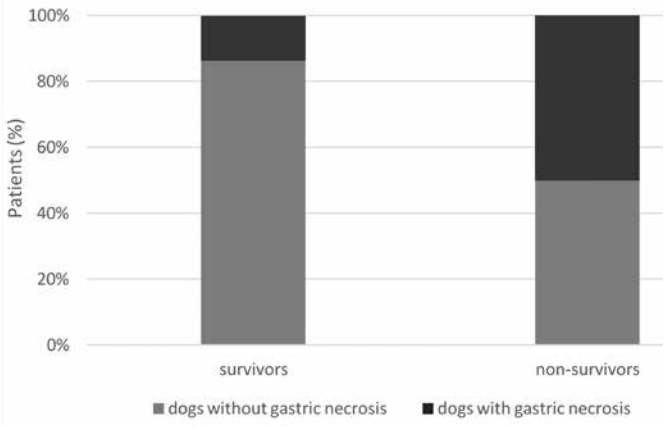

Fig. 3: The effect of gastric necrosis on mortality of patients with gastric dilatation and volvulus (association graph).

Discussion

Different prognostic factors such as CRP, HMGB1, lactate, acid-base parameters, haemostatic indicators, lipase activity, canine pancreatic lipase immunoreactivity or myoglobin have been evaluated in dogs with GDV (Adamik et al. 2009; Beer et al. 2013; Mooney et al. 2014; Uhrikova et al. 2015; Verschoof et al. 2015; Spinella et al. 2018; Rauserova-Lexmaulova et al. 2020). However, a reliable prognostic factor that would facilitate decision making before surgical therapy in a specific patient with GDV is yet to be found. The factor that is of highest benefit so far is the preoperative plasma lactate concentration, although not even lactate has a 100% predictive value (Beer et al. 2013; Mooney et al. 2014; Verschoof et al. 2015; Rauserova-Lexmaulova et al. 2020). Protein C activity evaluated in our study did not show to be a prognostic factor in these patients in terms of either mortality or severity of the disease (duration of clinical signs, degree of gastric torsion, gastric necrosis, splenectomy, DIC).

Although PC activity does not seem to be a suitable preoperative prognostic marker in dogs with GDV, our study results suggest its possible value in postoperative monitoring. Despite no significant relationship was found between decreased PC activity and mortality of patients in the selected time periods, all patients that died during hospitalisation were patients with low PC activity at T1. It is possible that a significant relationship would be found in a larger study population. Similar findings in dogs with GDV were described by Verschoof et al. (2015), who found significantly lower PC activity in non-survivors than in survivors, even though they were evaluating a smaller study population (a total of 20 dogs) than we did in our study. Higher mortality (7 out of 20 dogs) was found by Verschoof et al. (2015) compared to our study, which could have affected the results of statistical analysis given there were more patients in each compared group (survivors vs non-survivors).

Due to enhanced procoagulant processes, a septic state can lead to the development of DIC, which is why these two syndromes often occur together (Madden et al. 1989; Lorente et al. 1993; Fisher and Yan 2000; Yan and Dhainaut 2001; Dhainaut et al. 2001; De Laforcade et al. 2003). A significant difference in PC activity was found between survivors and non-survivors in human septic patients (Lorente et al. 1993). This difference was found after serial measurements during the hospitalisation period –

although plasma PC activity levels were decreased in both groups, on days 4 and 7 levels of PC activity became significantly different between survivors and non-survivors. In non-survivors, levels of PC activity on day 7 were even lower compared to day 1, contrary to survivors in which the levels of PC activity tended to rise (Lorente et al. 1993). Similar results were found in veterinary medicine. De Laforcade et al. (2003) found decreased PC and antithrombin activities in dogs with sepsis compared to healthy control dogs. De Laforcade et al. (2008) also found decreased PC and antithrombin activities to be significantly associated with the outcome in dogs with sepsis, with non-survivors having lower PC and antithrombin activities in comparison to survivors. Although we did not evaluate the occurrence of sepsis in our study patients, we can assume that it did not occur in majority of them, due to a minimum of observed complications during the hospitalisation period and due to their rapid discharge from the clinic. Due to the rapid patients' discharge we were not able to evaluate PC activity for a longer time period, like De Laforcade et al. (2008) did in their study. Nevertheless, we observed a similar tendency in PC activity development in time – a prime decrease was followed by an increase and the lowest PC activity was observed in non-survivors, although this finding was not significant. According to these results, evaluation of PC activity seems to be a promising postoperative prognostic marker in dogs after surgical treatment of GDV, which could ease further treatment decision making in these patients.

Previously, the duration of clinical signs was found to be associated with mortality in patients with GDV (Zatloukal et al. 2005; Beck et al. 2006; Rauserova-Lexmaulova et al. 2020). Longer duration time negatively affects the stomach wall (Lantz et al. 1984). The presence of gastric necrosis in patients with GDV ranges from 18.24% to 28.0% (Zatloukal et al. 2005; Beer et al. 2013; Rauserova-Lexmaulova et al. 2020; Song et al. 2020). A reliable predictive factor for gastric necrosis in dogs with GDV is yet to be found. Previous studies showed that preoperative lactate concentration > 6 mmol/l in dogs presented with GDV poses a higher chance of gastric necrosis occurrence and subsequent complications, although a normal or mildly elevated lactate concentration (2–4 mmol/l) shows only that complications are less likely to occur (de Papp et al. 1999; Mooney et al. 2014). Beer et al. (2013) found a cut-off plasma lactate concentration of 7.4 mmol/l to be 82% accurate for predicting gastric necrosis and 88% accurate for predicting the outcome in patients with GDV. Millis et al. (1993) created a linear regression equation for gastric necrosis prediction based on fibrin degradation product concentration, APTT and antithrombin III activity. Also, pH, bicarbonate, base excess, anion gap and anorganic phosphorus concentration were significantly associated with gastric necrosis in dogs with GDV (Beer et al. 2013; Rauserova-Lexmaulova et al. 2020). Not only the stomach is in danger of damage during GDV but there is also a risk of damage to the spleen due to its anatomical localisation, its common blood supply with the stomach and its passive movement together with the stomach during GDV (Lantz et al. 1984), which is why splenectomy is often performed in surgically treated patients with GDV (Zatloukal et al. 2005; Beck et al. 2006; Mackenzie et al. 2010; Song et al. 2020). To the authors' knowledge, no prior study evaluated correlation between PC activity and duration of clinical signs and the degree of abdominal organ damage in patients with GDV. We hypothesized that the longer the GDV lasts, the bigger the damage of abdominal organs, and the lower the PC activity will be which was observed e.g. by Madden et al. (1989) in dogs after intradermal endotoxin application and DIC induction. Our aim to show a relationship between the duration of clinical signs of GDV and decreased PC activity before surgery was not fulfilled. We also did not find any relationship between low PC activity before surgery and the degree of gastric torsion, gastric necrosis occurrence, and the need to perform splenectomy. According to our results, PC activity is not affected by the degree of abdominal organs damage during GDV.

Madden et al. (1989) showed a steady decrease in PC activity within 24 h after endotoxin-induced DIC in dogs. We observed a similar trend in our group of patients with GDV, although the DIC did not occur in all of them. No significant relationship was found between decreased PC activity and development of DIC in the selected time periods. Also, Beck et al. (2006) did not find a relationship between fibrin degradation products, PT, APTT and the platelet count and development of DIC in dogs with GDV. In our study, DIC developed in 8 patients (30.76%), similar as in patients with GDV in the study by Verschoof et al. (2015) where it developed in a total of 7 of 20 patients (35%) and it was the cause of death in 57% of them. Although we found DIC occurrence in T2 to be significantly associated with mortality, it is important to mention that there was only one patient with DIC that died in this time period, which is a small sample number for statistical analysis and it could have affected the result. This result of our study therefore needs to be confirmed in a larger study population.

We found several variables of apparent importance in our study which can be seen in the death risk equation – duration of clinical signs, degree of gastric torsion, the need to perform splenectomy, gastric necrosis, but also the patient's age and weight, of which the gastric necrosis increases the risk of death in patients with GDV 11 times. The individual variables are closely related and the majority of them were also found to be of risk for the patient in other studies. The severity of gastric damage worsens with time (Lantz et al. 1984). Longer ongoing GDV can further compromise the blood supply of the stomach and the spleen which not only poses a higher risk of gastric necrosis but also of splenic blood supply damage and the need to perform splenectomy (Zatloukal et al. 2005; Rauserova-Lexmaulova et al. 2020). Gastric necrosis is associated with mortality in patients with GDV, same as splenectomy, whether it is splenectomy alone or in combination with partial gastrectomy (Zatloukal et al. 2005; Beck et al. 2006; Mackenzie et al. 2010; Beer et al. 2013; Rauserova-Lexmaulova et al. 2020). Gastric necrosis was also found more often in older dogs and in dogs with a longer duration of clinical signs of GDV (Rauserova-Lexmaulova et al. 2020). The patient's age also plays a role in survival. Zatloukal et al. (2005) observed up to 4 times lower survival rate in dogs with GDV that were ≥ 9 years old compared to dogs under 4 years of age. Similar to our results, Beer et al. (2013) found that dogs with gastric necrosis were 7.1 times more likely to die compared to dogs without gastric necrosis. Our results are in an agreement with previous studies and show that the duration of the disease and the degree of abdominal organ damage play a big role in the prognosis in patients with GDV.

The main limitation of the study is a relatively small study population. Our results suggest that a significance between some of the evaluated indices may have been proved if a larger study population had been evaluated. It would be appropriate to further evaluate our observations in a bigger study group. Another limitation is the fact that it was not possible to compare a similar number of samples for each selected time period due to the patients' death or discharge from the clinic.

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