# Transfusion related acute lung injury and associated transient pulmonary hypertension in a dog

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## Akuter Lungeninsult und assoziierte transiente pulmonäre Hypertonie bei einem Hund

Die Gabe von Bluttransfusionen ist zu einer sehr wichtigen unterstützenden Behandlung von anämischen Patienten in der Veterinärmedizin geworden. Jedoch sind Blutprodukte keine harmlosen Substanzen, auch wenn vor der Gabe das Blut typisiert und die Kompatibilität von Spender und Empfänger geprüft werden. Verschiedenste unerwünschte Reaktionen sind möglich und das Risiko einer Nebenwirkung steigt bei bereits kritisch kranken Patienten. Eines der potenziell betroffenen Organsysteme ist der Respirationsapparat, wo eine sogenannte transfusionsassoziierte akute Lungenschädigung (transfusion related acute lung injury, TRALI) auftreten kann. Der vorliegende Fall beschreibt detailliert die Entwicklung eines akuten nicht-kardiogenen Lungenödems mit begleitender hochgradiger pulmonärer Hypertonie wenige Stunden nach der Gabe eines Erythrozytenkonzentrats. Mittels unterstützender Behandlung erholte sich der Hund klinisch, radiologisch und echokardiographisch innerhalb von Tagen. TRALI wird in der Veterinärmedizin zwar nur selten beschrieben, stellt jedoch eine wichtige potenzielle Komplikation bei der Verabreichung von Blutprodukten dar.

**Schlüsselwörter:** Anämie, nicht-kardiogenes Lungenödem, Erythrozytenkonzentrat

## Summary

Blood transfusions have become very important for supportive treatment of anemic animals. However, blood products are not innocuous substances, even if blood is typed and compatibility evaluated before transfusion. Multiple adverse reactions are possible, and the risk is markedly increased in already critically ill patients. One of the organ systems potentially affected by a blood transfusion is the respiratory tract, including transfusion related acute lung injury (TRALI). The present case report describes in detail the development of acute non-cardiogenic pulmonary edema and associated severe pulmonary hypertension a few hours after a packed red blood cell transfusion. With supportive care the dog recovered clinically, radiographically, and echocardiographically within days. Though considered rare in veterinary medicine, TRALI is an important potential complication of transfusion of blood products.

**Keywords:** anemia, non-cardiogenic pulmonary edema, packed red blood cells

## Introduction

Blood transfusions have become increasingly common in veterinary small animal medicine.[17] Although often lifesaving, blood transfusions have the potential to harm the recipient. Large retrospective studies found that 3 %-28 % of blood transfusions are associated with transfusion reactions in dogs.[4,6,10,15,16,18,20] Transfusion reactions can occur during, within a few hours, or several days post-transfusion. The clinical manifestations vary from very mild to life-threatening.[8,19,29]

Respiratory reactions are among the most common complications of blood transfusions. They include Transfusion Associated Dyspnea (TAD), Transfusion Associated Cardiac Overload (TACO), and Transfusion Related Acute Lung Injury (TRALI). TRALI is characterized by acute hypoxemia with clear evidence of non-cardiogenic pulmonary edema during or within 6 hours of blood transfusion. Classically, patients diagnosed with TRALI have no prior lung injury, no evidence of left atrial hypertension, and no temporal relationship to an alternative risk factor for Acute Respiratory Distress Syndrome (ARDS).[9]

In human medicine, the incidence of TRALI varies between 0,08–19,7 % per transfused patient and 0,01–1,12 % per transfused product.[13,26,31,36,37] In veterinary medicine, TRALI appears to be rare. A prospective observational study investigating the incidence of TRALI in dogs receiving transfusions for various clinical reasons reported an occurrence of 3,7 % (2 of 54 dogs).[28] A retrospective study to determine the prevalence and risk factors for ARDS in dogs admitted to the intensive care unit reported 4 cases of TRALI per 1,000 dogs.[2] Finally, a case report described the case of a dog that developed possible TRALI after a forelimb amputation and a whole blood transfusion.[1] Supportive care, including the use of oxygen and, if necessary, mechanical ventilation (ideally using lung-protective settings with low tidal settings with low tidal volumes) is the mainstay of therapy for patients with TRALI.[21] The incidence of TRALI in dogs is actually too low to draw any conclusions about its prognosis in this species, but the mortality rate in human medicine is 5–10 %.[9]

The paucity of literature on TRALI in dogs, and particularly of detailed case descriptions, encouraged us to report this case of acute non-cardiogenic pulmonary edema associated with severe pulmonary hypertension following a packed red blood cell (PRBC) transfusion, diagnosed as TRALI.

## Case report

An 8-year-old male intact Chihuahua, body weight 2,55 kg, was presented because of a severe, non-regenerative anemia. At admission, the dog had a 5-day history of lethargy and hyporexia and had been pre-treated with a non-steroidal anti-inflammatory drug (robenacoxib 2,5 mg/kg SID orally on day 1 and 2) as well as steroids (a single intramuscular dexamethasone-injection of unknown dosage on day 2 and prednisolone 0,7 mg/kg SID orally on day 2, 3, 4 and 5). On physical examination pale mucous membranes, hypothermia (36,3°C), tachypnoea (48 breaths per minute), a soft left systolic heart murmur (grade III/VI), and a bounding pulse were identified. The heart rate was normal (100 beats per minute). Laboratory abnormalities on the day before admission included severe anemia (hematocrit of 13,6 %, reference interval: 37–61 %) and mild thrombocytosis (670'000/µl, reference interval: 148'000–484'000/µl). On admission, a microhematocrit was performed and confirmed progressive severe anemia (packed cell volume 10 %). A point-of-care ultrasound examination did not reveal any intraperitoneal or intrathoracic free fluid and no B-lines.

As emergency treatment the dog was transfused with 55 ml (21,5 ml/kg) of DEA 1.1 negative PRBCs[a] over 6 hours (0,4 ml/kg/h for the first 30 minutes, then 3,3 ml/kg/h until completion; overall transfusion time 390 minutes) to obtain a hematocrit of around 25 % (*volume to be transfused [ml] = 1,5 x desired rise in PCV x kg body weight*)[25] and treated with gastrointestinal protectants (esomeprazole[b] 1 mg/kg BID intravenously, sucralfate[c] 40 mg/kg TID orally). Two hours after the transfusion was completed, the dog developed cough, dyspnea, cyanosis and bilateral crackles on lung auscultation. At this time, a complete blood count and serum biochemistry were repeated and showed a hematocrit of 42 %, a marked left shift with toxic changes, a mild increase in urea and bilirubin, and a markedly increased CRP (table 1). Chest radiographs revealed bilateral mild pleural effusion, moderate right sided cardiomegaly, severe bilateral diffuse interstitial lung pattern, and moderate aerophagia (figure 1). In the absence of left atrial enlargement, non-cardiogenic pulmonary edema with secondary cor pulmonale was suspected. The primary rule-outs for this new development were TRALI or TACO; also considered was ARDS associated with an underlying disease causing the severe anemia, maybe precipitated by the transfusion; acute pneumonia or pulmonary hemorrhage were considered less likely; pre-existing pulmonary fibrosis and infiltrative neoplasia were excluded due to the acute onset of respiratory symptoms, and the absence of B-lines at admission. To rule-out plausible infectious diseases possibly causing pulmonary hemorrhage and anemia, an IDEXX SNAP Lepto-Test[f] and an IDEXX Angio Detect-Test[g] were performed, both of which were negative. Further

examinations to elucidate the cause of the anemia were PCR for *Babesia canis*, *Anaplasma phagocytophilum*, *Mycoplasma haemocanis*, *Candidatus* Mycoplasma haematoparvum and serology for antibodies to *Ehrlichia canis*; all results were negative. The sonographic examination of the abdomen showed a mild enlargement of the liver with slightly congested hepatic veins. Numerous B-lines were observed in the lungs.

The patient was placed in an oxygen chamber for supportive treatment and received four-quadrant antibiotic coverage (ampicillin-sulbactam[h] 20 mg/kg TID intravenously and marbofloxacin[i] 2,5 mg/kg SID intravenously) and butorphanol[j] as needed. When the dog was considered stable enough, an echocardiographic examination was performed which revealed left-sided hypovolemia and mild

**Table 1:** Blood results on day 2 post blood transfusion (55 ml = 21,5 ml/kg PRCBs) in an 8-year-old male intact Chihuahua (2,55 kg) with transfusion associated lung injury and associated transient pulmonary hypertension.

| Complete Blood Count[d] | Value | Normal Range |
|---|---|---|
| Hematocrit (%) | 42 | 42–55 |
| Hemoglobin (g/l) | 15,1 | 14,4–19,1 |
| Red blood cells (*10E6/ul) | 6,98 | 6,1–8,1 |
| MCH (pg) | 22 | 23–26 |
| MCHC (g/dl) | 36 | 34–36 |
| MCV (fl) | 61 | 64–73 |
| Reticulocytes (/ul) | 51'652 | |
| Platelets (*10E3/ul) | 407 | 130–394 |
| White blood cells (*10E3/ul) | 8,8 | 4,7–11,3 |
| Segmented neutrophils (*10E3/ul) | 6,27 | 2,6–7,44 |
| Band neutrophils (*10E3/ul) | 1,62 | 0–0,08 |
| Lymphocytes (*10E3/ul) | 0,61 | 1,15–3,4 |
| Monocytes (*10E3/ul) | 0,22 | 0,2–0,92 |
| Eosinophils (*10E3/ul) | 0,04 | 0,12–1,29 |
| Basophils (*10E3/ul) | - | 0–0,08 |
| Toxic neutrophils | >30 % | |
| Degree of toxicity | 1+ | |
| Biochemistry[e] | Value | Normal Range |
| Bilirubin (umol/l) | 13,2 | 0,1–3,5 |
| Glucose (mmol/l) | 5,5 | 4,1–5,9 |
| BUN (mmol/l) | 11,1 | 3,8–9,4 |
| Creatinine (umol/l) | 31 | 50–119 |
| Total protein (g/l) | 71 | 56–71 |
| Albumin (g/l) | 31 | 29–37 |
| Globulins, calculated (g/l) | 40 | |
| Cholesterol (mmol/l) | 5,2 | 3,5–8,6 |
| Triglycerides (mmol/l) | 1,1 | 0,4–1,5 |
| ALP (U/l) | Interference | 20–98 |
| DGGR-lipase (U/l) | 60 | 17–156 |
| ALT (U/l) | Interference | 20–93 |
| CK (U/l) | Interference | 51–191 |
| Sodium (mmol/l) | 149 | 145–152 |
| Potassium (mmol/l) | Interference | 4,3–5,3 |
| Chloride (mmol/l) | 113 | 107–118 |
| Calcium (mmol/l) | 1,89 | 2,4–2,8 |
| Phosphate (mmol/l) | 1,31 | 1–1,6 |
| CRP (mg/l) | 104,5 | <10,2 |

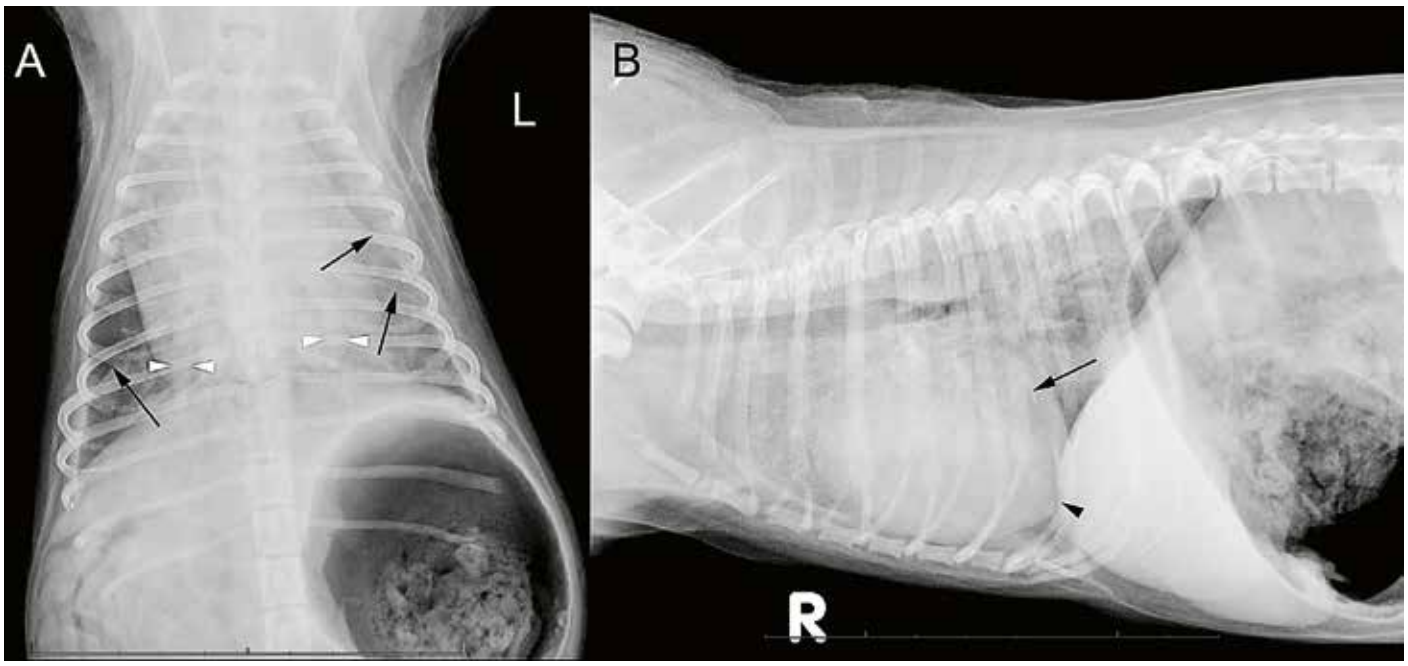


**Figure 1:** Thoracic radiographs of an 8-year-old intact male Chihuahua in two projections (A: ventrodorsal, B: left to right lateral projection). The images were taken at the onset of dyspnea two hours after a blood transfusion. A small amount of fluid accumulates in the pleural space, separating the lung surface from the parietal pleura and causing thin pleural fissure lines (small black arrows). The cardiac silhouette is moderately enlarged. It has a broad sternal contact and a rounded right side that slightly elevates the cardiac apex (small black arrow head) from the sternum. The left side of the heart appears small in volume. The caudal pulmonary arteries have a large diameter (white arrow heads). The pulmonary veins are largely masked by a generalized severe unstructured interstitial lung pattern. The liver has an increased volume and the stomach contains a large amount of gas. The findings were interpreted as non-cardiogenic edema with pressure overload on the right side of the heart, mild secondary pleural effusion and aerophagia.

right-sided volume overload associated with severe pulmonary hypertension (table 2: tricuspid regurgitation peak gradient of around 80 mmHg; pulmonary regurgitation peak gradient of 44 mmHg; peak gradient of pulmonary regurgitation at end diastole of 20 mmHg), but no primary cardiac abnormalities. To support the circulation by increasing blood flow to the left ventricle, sildenafil[k] (2,5 mg/kg TID orally) was added to the treatment.

The dog gradually recovered clinically from the acute respiratory distress. Repeated thoracic radiographic examination revealed partial resolution of the lung changes, right-sided cardiac enlargement, and pleural effusion on day 5 (figure 2). Echocardiography on day 6 showed improvement of pulmonary hypertension based on lower tricuspid regurgitation peak gradient of 30 mmHg and improved left ventricular filling (table 2). On day 7 the patient was discharged from the hospital; amoxicillin-clavulanic acid[l] (20 mg/kg BID orally) was continued for one week, sildenafil (2,5 mg/kg BID orally) for two weeks, and omeprazole[m] (1 mg/kg BID orally) for six weeks. The echocardiogram performed 3 weeks after discharge was unremarkable (table 2).

No definitive cause for the severe anemia could be identified. Based on the course of disease and the initial blood values, the anemia was thought to be due to gastrointestinal blood loss caused by the use of glucocorticoids in combination with non-steroidal anti-inflammatory drugs. The anemia did not recur over a follow-up period of 9 months.

## Discussion

This case report describes in detail the acute onset and course of pulmonary injury (TRALI elicited by the transfusion of PRBCs. The cause-and-effect relationship are supported by the following observations: 1) the absence of clinical respiratory signs and B-lines at admission, but severe dyspnea and severe generalized pulmonary infiltrates on radiographs suggestive of non-cardiogenic pulmonary edema a few hours after transfusion; 2) the absence of any underlying cardiac disease that could cause congestion or predispose to fluid overload; 3) the absence of any underlying disease that could cause ARDS; and finally, 4) the fast resolution of all respiratory tract abnormalities, clinically as well as on diagnostic imaging.

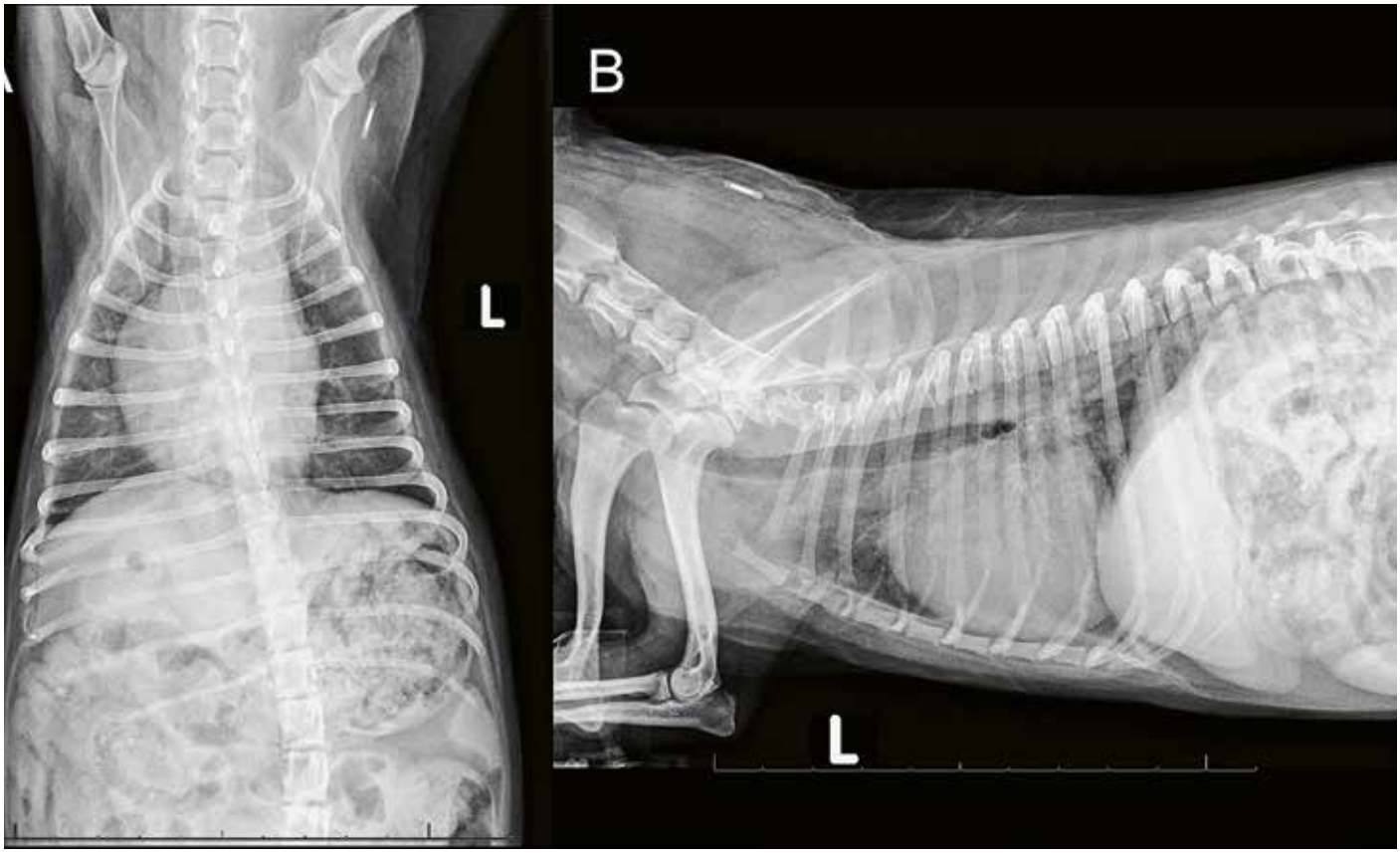


**Figure 2:** Follow up radiographs of the chest of an 8-year-old intact male Chihuahua in two projections (A: ventrodorsal and B: right to left lateral projection). The images were taken five days after blood transfusion and improvement of the dyspnea. The pleural effusion disappeared. The right side of the heart has normalized and the left side appears more voluminous again. The unstructured interstitial lung pattern has normalized with the exception of irregularly distributed ill-defined mild pulmonary opacifications. A portion of food replaces the aerophagia.

**Table 2:** Selective echocardiographic parameters in a Chihuahua (2,55 kg) with transfusion associated lung injury and associated transient pulmonary hypertension.

| | Day 2 | Day 6 | Day 28 |
|---|---|---|---|
| **RVDd** | 1,5 cm | 1,0 | 0,8 |
| **LVDd** | 1,5 cm | 1,8 | 1,8 |
| **LVDDN** | 1,14 | 1,37 | 1,37 |
| **LVDs** | 1,0 | 1,1 | 0,9 |
| **TR Vmax** | 4,6 | 2,8 m/s | na |
| **TR PG** | 85 mmHg | 30 mmHg | na |
| **PR Vmax** | 3,3 m/s | na | na |
| **PR PG** | 44 mmHg | na | na |
| **PRend V** | 2,2 m/s | na | na |
| **PRendPG** | 20 mmHg | na | na |

RVDd, right ventricular diameter in diastole;
LVDd / LVDDN / LVDs, left ventricular dimension in diastole / normalized to body weight / in systole;
TR Vmax peak maximum velocity of tricuspid regurgitation; PG, peak gradient (estimate of systolic pulmonary artery pressure (PAP);
PR Vmax, early diastolic peak velocity of pulmonary valve regurgitation; PR PG, calculated peak gradient of pulmonary regurgitation (estimate of mean pulmonary artery pressure)
PRend V (PG), velocity (peak gradient) of pulmonary valve regurgitation at end diastole (estimate of diastolic pulmonary artery pressure);
na, not assessable due to lack of measurable insufficiency

TRALI seems to be rare in dogs. One aspect that may explain the low incidence is the origin of administered blood products. In human medicine, blood products with high plasma content from multiparous women carry the highest risk of TRALI.[11,13,22,23,31,32] This is supported by the observation that the incidence has decreased significantly since several countries implemented a strategy of providing male-only or male-predominant plasma.[7,12,38] It is unknown how often multiparous female dogs are used as blood donors, but it has been suggested that a high proportion of neutered and nulliparous female canine donors might theoretically contribute to the low incidence of reported TRALI in veterinary patients.[9] However, one study in dogs demonstrated the absence of pregnancy-induced alloantibodies. Exclusion of multiparous female dogs is therefore not warranted.[3]

In the reports of dogs that developed TRALI, two had received fresh frozen plasma (13 ml/kg and 22 ml/kg), one a whole blood transfusion (20 ml/kg), and four unspecified multiple transfusions.[1,2,28] Ours is the first case of TRALI in a dog after transfusion of a single PRBC unit (21,5 ml/kg). Even though in human medicine, blood products with high plasma content have been associated with the greatest risk of TRALI, all blood components have been shown to be capable of inducing TRALI, and PRBCs containing as little as 10–20 mL of residual plasma were capable of inducing antibody-mediated TRALI.[11,13,22,23,31,32,39]

The exact pathophysiology of TRALI remains uncertain and various hypotheses have been proposed in human medicine. In the "two-hit" neutrophil-mediated model, TRALI is brought on by two distinct events.[27] The "first hit" consists of an underlying disease activating the pulmonary endothelium, resulting in priming of the pulmonary neutrophils. Antibodies (e.g. human leucocyte antigen (HLA) and human neutrophil antigen (HNA) antibodies) present in the transfused blood product or non-antibody biological response modifiers accumulated during blood storage (e.g. lipids) represent the "second hit" and activate the primed neutrophils. Activated neutrophils release reactive oxygen species (ROS) that cause endothelial damage leading to fluid leakage into the pulmonary interstitium and alveoli. The potentially fatal consequence is acute respiratory failure.[5,27,30,31,34,35,37] Various studies have shown that the second insult can have a number of cellular targets other than neutrophils, including monocytes, lymphocytes, and the pulmonary endothelium.[34] These then induce neutrophil activation and ROS release. There is also evidence for neutrophil-independent pathways for the development of TRALI.[34] Finally, there is the threshold hypothesis, in which mediators in donor and recipient blood act additively and must reach a threshold together.[5] This model not only highlights why a critically ill patient is more susceptible to TRALI than a non-critically ill patient, but also explains why even healthy individuals can develop TRALI in the presence of a strong transfusion stimulus.

Storage of blood products and the gradual accumulation of non-antibody biological response modifiers may contribute to the development of TRALI. In the dog of this report, the leukoreduced (based on the information provided by the supplier) PRBCs were purchased 2 weeks before transfusion. In a retrospective study, although the risk of transfusion-related complications in dogs increased with each day of storage, transfusion-related hemolysis was the only significant complication.[20] However, in an experimental animal model, the age of blood played a role in the onset TRALI.[33]

The transient marked pulmonary hypertension in our dog was thought to be due to acute alveolar hypoxia with resulting vasoconstriction of pulmonary arteries, i.e. group 3 of the WHO, respectively ACVIM consensus classification.[14,24] According to our literature search, this is the first report of pulmonary hypertension associated with TRALI in dogs.

The reason for the high hematocrit of 42 % after the transfusion is unresolved. Even if we had used a donor with a hematocrit of 100 %, which is obviously impossible, the transfusion of 55 ml of PRCBs would have resulted in a hematocrit of 34 % (*volume to be transfused [ml] = (desired rise in PCV/PCV donor) x 90 x kg body weight*[25]). According to our protocol, over-transfusion, i.e. administration of more than 55 ml, had not occurred. A possible explanation for the unexpectedly high hematocrit could be a TRALI-induced loss of intravascular volume into the pulmonary interstitium and alveoli with consequent hemoconcentration. This hypothesis is supported by the progression of the hematocrit over the course of the hospitalization: as long as the dog showed respiratory symptoms, the hematocrit remained high (42 % immediately after transfusion, 41 % the next day); as the respiratory symptoms and the radiological and echocardiographic abnormalities resolved, the hematocrit decreased (29 % the day before and the day of discharge). However, the fall in hematocrit could also have been a consequence of continuing gastrointestinal bleeding or hemolysis of the transfused blood.

In summary, we described TRALI and associated pulmonary hypertension in a dog after PRBC transfusion. Supportive care addressing the hypoxia as well as the pulmonary hypertension and time led to a complete recovery without permanent sequelae.

## Footnotes

a) The blood product was purchased from an authorized animal blood bank (BSA, Banco de Sangue Animal Lda, Porto, Portugal).
b) Esomep®, Grünenthal Pharma AG, Glarus Süd, Switzerland.

c) Sucralan®, G.L. Pharma, Lannach, Austria.
d) Sysmex XN-1000, Sysmex Corporation, Kobe, Japan.
e) Cobas c 501, Roche Diagnostics AG, Rotkreuz, Switzerland.
f) SNAP® Lepto, IDEXX Laboratories, Westbrook, Maine, USA.
g) Angio Detect®, IDEXX Laboratories, Westbrook, Maine, USA.
h) Ampicillin plus Sulbactam Eberth®, Dr. Friedrich Eberth Arzneimittel GmbH, Ursensollen, Germany.
i) Marbocyl FD®, Vetoquinol AG, Bern, Switzerland.
j) Butomidor®, Streuli, Uznach, Switzerland.
k) Sildenafil-Mepha®, Mepha Pharma AG, Basel, Switzerland.
l) Clavaseptin®, Vetoquinol AG, Bern, Switzerland.
m) Omeprazol, Formula Labor, Schaffhausen, Switzerland.

## Syndrome respiratoire aigu post-transfusionnel avec hypertension pulmonaire transitoire chez un chien

Dans les cas d'anémie sévère, les soins de support par transfusion sanguine sont de plus en plus courant en médecine vétérinaire. Néanmoins, les produits sanguins ne sont pas des substances inoffensives, même si le sang est typé et la compatibilité entre donneur et transfusé examinée avant la transfusion. De multiples réactions indésirables sont possibles et le risque d'effet secondaire augmente encore lorsque le patient est dans un état critique. Le tractus respiratoire est un des systèmes organiques potentiellement concerné, par exemple par le syndrome respiratoire aigu post-transfusionnel (transfusion related acute lung injury, TRALI). Le présent cas détaille le développement d'un oedème pulmonaire non-cardiogénique avec une hypertension pulmonaire sévère quelques heures après l'administration d'un concentré érythrocytaire. Avec des soins de support, le chien a pu récupérer cliniquement, radiologiquement et échocardiographiquement en quelques jours. Bien que les TRALI soient rares en médecine vétérinaire, ils représentent une complication importante et sévère de l'administration de produits sanguins.

**Mots clés:** Anémie, oedème pulmonaire non-cardiogénique, concentré érythrocytaire

## Lesione polmonare acuta legata alla trasfusione con ipertensione polmonare transitoria in un cane

Le trasfusioni di sangue e dei suoi componenti sono diventate un trattamento molto comune in medicina veterinaria. Tuttavia, la somministrazione di prodotti sanguigni presenta dei rischi per il ricevente. Anche se un'incompatibilità tra il sangue del paziente e quello del donatore può essere evitata grazie a test pretrasfusionali, sono comunque possibili diverse reazioni trasfusionali, soprattutto in pazienti già gravemente malati. Tra le complicanze trasfusionali gravi vi sono reazioni respiratorie come la cosiddetta lesione polmonare acuta legata alla trasfusione (TRALI). Il presente caso descrive in dettaglio l'insorgenza acuta di edema polmonare non cardiogeno con concomitante grave ipertensione polmonare poche ore dopo la somministrazione di un concentrato di eritrociti. Grazie alle cure somministrate, il cane si è ripreso clinicamente, radiologicamente ed ecocardiograficamente nell'arco di pochi giorni. Sebbene la TRALI sia raramente descritta in medicina veterinaria, è un'importante complicanza potenziale a seguito della somministrazione di prodotti sanguigni.

**Parole chiave:** Anemia, edema polmonare non cardiogenico, concentrato di eritrociti

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