Incidence of acute lung injury in dogs receiving transfusions

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Objective—To document the existence and incidence of acute lung injury (ie, veterinary acute lung injury [VetALI]) per the 2007 consensus definition in a population of client-owned dogs receiving transfusions for various clinical reasons.

Design—Prospective observational study.

Animals—54 client-owned dogs.

Procedures—Arterial blood gas analysis was performed for dogs receiving a transfusion (blood and plasma products) at 0 to 12 hours before and 24 to 48 hours after transfusion; dogs also underwent thoracic radiography 0 to 24 hours before and 24 to 48 hours after transfusion. The ratio of PaO₂ to fraction of inspired oxygen (FIO₂) was calculated. Dogs with posttransfusion radiographic signs of pulmonary infiltrates, a PaO₂:FIO₂ ratio < 300, or clinical signs of respiratory compromise were suspected of having VetALI and underwent echocardiography to exclude left-sided heart failure. The incidence of VetALI was calculated, and χ² tests were used to compare the incidence in study dogs with the historical reported incidence of acute respiratory distress syndrome (ARDS) in ill dogs (not receiving transfusions) and transfusion-related acute lung injury (TRALI) in humans.

Results—The incidence of VetALI (2/54 [3.7%]; 95% confidence interval, 0% to 8.73%) in study dogs was significantly less than the reported incidence of TRALI in humans (25%) and not significantly different from the reported incidence of ARDS in ill dogs (10%).

Conclusions and Clinical Relevance—VetALI occurred in dogs that received transfusions at a frequency similar to that previously reported for ARDS in ill dogs that did not receive transfusions. (J Am Vet Med Assoc 2014;244:170–174)
These studies14,15 formed the basis of the TRALI definition. Changes in temperature, pulse rate, and respiratory rate can occur with and are ascribed to many other conditions. Respiratory signs resulting from TRALI are commonly mistaken for circulatory overload secondary to the transfusion, pneumonia, or possibly allergic reactions resulting from antigenic stimulation from the blood products.

Although not yet formally recognized in veterinary medicine, the authors believe that TRALI does occur in veterinary patients. In fact, one of the first descriptions of what is now referred to as TRALI was in 1972; findings in studies that used baboons14 and dogs14,15 revealed that transfusion of autologous stored blood (stored for 21 days) could lead to ALI despite filtering of the blood products. This scenario is now referred to as shock lung, and was initially thought to be a condition limited to patients in surgical settings receiving multiple blood products in response to blood loss.15 These studies14,15 formed the basis of the TRALI definition for humans, which suggests that TRALI may also occur in canine patients.

The purpose of the study reported here was to document that VetALI (ie, ALI meeting the veterinary-specific criteria of the 2007 consensus definition based on the definitions for ALI in humans) does occur in dogs receiving transfusions of blood and plasma products within the first 24 to 48 hours after transfusion and to determine the incidence of VetALI in this population of dogs. Our hypotheses were that VetALI does occur in animals receiving transfusions and its incidence would be similar to that of TRALI in humans.

Materials and Methods

Animals and study protocol—Sixty dogs requiring transfusions of blood or plasma-containing products that had not received previous transfusions were planned to be enrolled in the study. All dogs were patients evaluated at the small animal clinic at the University of Wisconsin-Madison Veterinary Medical Teaching Hospital between July 1, 2009, and July 1, 2012. Written or verbal consent was obtained from all owners prior to enrollment in the study, and the study protocol was approved by the University of Wisconsin Animal Care and Use Committee. Information was collected regarding each dog’s signalment, reason for transfusion, type of transfused product, and volume of transfused product.

All dogs were being treated for a variety of clinical conditions, but each received a transfusion of either blood or plasma while hospitalized. Blood products included fresh whole blood, packed RBCs, and fresh frozen plasma. The amount of blood or plasma transfused was determined by the attending clinician. All dogs underwent 3-view (right lateral, left lateral, and ventrodorsal or dorsoventral) thoracic radiography 0 to 24 hours before the transfusion. When possible, each dog had an arterial blood sample obtained for blood gas analysis at 0 to 6 hours before receiving the transfusion. If an arterial blood sample could not be collected from a patient, a pulse oximetry reading was recorded that was repeatable, with a reliable plethysmograph on the display screen of the pulse oximeter.*

Transfusions were administered over 1 to 6 hours in each case, with the type of blood product, rate, and volume of transfusion determined by the attending clinician. Patients were monitored during the transfusion for acute changes in temperature, pulse rate, and respiratory rate and for the presence of urticaria, facial swelling, vomiting, or diarrhea that would be indicative of a transfusion reaction. If signs of a transfusion reaction were observed, interventions were dictated by the primary clinician and typically included stopping the transfusion and administering diphenhydramine (2 mg/kg [0.9 mg/lb], IM) or dexamethasone (0.15 mg/kg [0.068 mg/lb], IV).

If no indications of acute transfusion reaction occurred, thoracic radiography and arterial blood gas analysis (or, when collection of an arterial blood sample was unsuccessful, pulse oximetry) were repeated 24 to 48 hours after the transfusion. All radiographs were initially interpreted by a board-certified veterinary radiologist who was aware of which radiographs were taken before and which were taken after transfusion. A single radiologist was intended to interpret all radiographs, but radiographs from the final third of the cases were interpreted by a second board-certified veterinary radiologist. Later, radiographs of all dogs with low PaO2:FIO2 ratios (< 300) after transfusion were independently interpreted by a separate single board-certified veterinary radiologist blinded to the timing of thoracic radiography. All arterial blood samples were acquired by a licensed veterinary technician or veterinarian; samples were analyzed with a point of care blood gas analyzer. Arterial blood gas analysis results were used to calculate the PaO2:FIO2 ratio. When pulse oximetry measurements were used, they were recorded and later converted to PaO2 on the basis of the relationship depicted in the oxyhemoglobin dissociation curve. The derived PaO2 was then used to calculate the PaO2:FIO2 ratio. All but 2 dogs were breathing room air at the time of sample collection (ie, any oxygen supplementation was turned off for 5 to 10 minutes before sample collection), so 21% was used as the FIO2 in the PaO2:FIO2 ratio. Of the remaining 2 dogs, one was receiving nasal oxygen supplementation (FIO2 of 40% was used in this dog’s calculations) and the other was intubated and receiving 100% oxygen.

If dogs developed clinical signs of respiratory distress at any point during or after the transfusion, thoracic radiography and arterial blood gas analysis (or pulse oximetry if an arterial blood sample could not be collected) were performed sooner than 24 hours after the transfusion. Any patients that developed clinical signs consistent with respiratory distress or respiratory abnormalities (changes in respiratory rate or effort, dyspnea, and increased or decreased lung sounds on auscultation vs baseline) or had new radiographic evidence of lung infiltrates observed in the posttransfusion radiographs were scheduled to undergo echocardiography. Echocardiography was performed by a board-certified veterinary cardiologist to evaluate for evidence of left-sided cardiac failure or circulatory overload. The cardiologist was informed that the patients were in the study.

Dogs were categorized as having VetALI (Appendix 1) on the basis of the appearance of posttransfusion radiographic pulmonary infiltrates (without evidence of congestive heart failure on radiographs or a concurrent echocardiogram) and a low PaO2:FIO2 ratio (< 300). Per the description of TRALI in the human literature (Appendix 2),14,15 patients did not have to have clinical signs of respiratory distress or increased respiratory effort to be categorized as having VetALI.

Statistical analysis—Based on the cumulative incidence of TRALI reported in humans studied during the 72-hour period after transfusion (25% total incidence during
that timeframe\textsuperscript{16}, compared with a historical incidence of 10% of ARDS in ill dogs that did not receive transfusions (19/186 dogs).\textsuperscript{17} A population of 60 dogs was calculated to provide 86% power to detect VetALI if it occurred in dogs receiving transfusions at a similar incidence as TRALI in humans ($P < 0.05$). This study design did not allow assignment of cause and effect between transfusion and the occurrence of VetALI; the study was designed to determine whether further evaluation of the relative incidence of VetALI in dogs receiving a transfusion versus ill dogs not receiving transfusions is warranted.

The total number of dogs with VetALI, compared with the total population of enrolled dogs, was used to determine the incidence of VetALI in study dogs receiving transfusions, and the 95% confidence interval was calculated.\textsuperscript{4} A $\chi^2$ analysis\textsuperscript{6} was then applied to determine whether the incidence of study dogs with VetALI was significantly different than the 10% incidence (19/186 dogs) of ARDS in a population of ill dogs that did not receive transfusions\textsuperscript{11} and to determine whether the incidence of VetALI in the study dogs was similar to that reported for TRALI in humans (23%).\textsuperscript{15}

**Results**

Sixty-six dogs were enrolled in the study, and 54 dogs completed the study. Six were excluded because of death, euthanasia, or discharge from the hospital prior to completion of the posttransfusion data collection. One dog was excluded because of improper record keeping where the patient’s pretransfusion arterial blood gas analysis results were entered as its posttransfusion arterial blood gas analysis results in the permanent computerized medical record, and the actual original results were not available for review. One dog was excluded because of missing pretransfusion radiographs. The remaining 4 dogs were excluded after study completion because of suspicion that either pre- or posttransfusion arterial blood samples were actually venous or mixed arterial-venous blood samples. In each of these dogs, the $\text{Pa}_2$ was between 30 and 40 mm Hg, with no clinical indications of respiratory distress. Two of these excluded dogs had immune-mediated hemolytic anemia, a second had pure RBC aplasia, and the third had a thoracic abscess subsequent to trauma.

Of the 54 dogs included in the study, all but 4 patients had pre- and posttransfusion collection of arterial blood samples. Of these 4 patients that had $\text{Pa}_2$, measurements derived from pulse oximetry, 2 had pulse oximetry for all readings, 1 had only a posttransfusion pulse oximetry reading, and 1 had only a pretransfusion pulse oximetry reading. None of these patients was on supplemental oxygen at the time that the reading was taken. All of these patients had $\text{Pa}_2 \text{:FiO}_2$ ratios > 300 both before and after the transfusion, ruling out the presence of VetALI.

Patients enrolled in the study ranged in age from 1 to 13 years (mean ± SD, 7.4 ± 3.7 years). There were 26 males (26 castrated and 1 sexually intact) and 27 spayed females. The patients received transfusions for a variety of reasons, including immune-mediated hemolytic anemia (n = 16), postoperative anemia (8), perioperative splenectomy with or without hemoabdomen (8), gastrointestinal bleeding (4), prolonged coagulation times (4), pancreatitis (3), idiopathic anemia or anemia of chronic disease (5), immune-mediated or other thrombocytopenia (3), trauma (1), pure RBC aplasia (1), and idiopathic hemorhax (1). Forty-four dogs received packed RBCs, 16 dogs received fresh frozen plasma, and 2 received whole blood. Six of the dogs receiving packed RBCs also received fresh frozen plasma. Two dogs received both packed RBCs and whole blood. Total amounts of transfused packed RBCs ranged from 6.6 to 39 mL/kg (3 to 17.7 mL/lb), whole blood from 5.3 to 36 mL/kg (2.4 to 16.4 mL/lb), and fresh frozen plasma from 9.2 to 36.5 mL/kg (4.2 to 16.6 mL/lb). No patients were observed to have clinical signs consistent with an acute hemolytic transfusion reaction.

To meet the definition of VetALI, patients were required to have a $\text{Pa}_2 \text{:FiO}_2$ ratio < 300 after transfusion with newly visible pulmonary infiltrates on posttransfusion thoracic radiographs. Screening first for a $\text{Pa}_2 \text{:FiO}_2$ ratio < 300 after transfusion, 4 patients met that criterion, with 1 female patient (with immune-mediated hemolytic anemia) actually having a higher $\text{Pa}_2 \text{:FiO}_2$ ratio after transfusion (206) than before transfusion (186). This patient was not considered to have VetALI because its $\text{Pa}_2 \text{:FiO}_2$ ratio improved after the transfusion, and review of radiographs did not reveal the presence of pulmonary infiltrates.

Of the 3 remaining dogs with posttransfusion $\text{Pa}_2 \text{:FiO}_2$ ratios < 300 that decreased from their pretransfusion values, 2 had changes on radiographs after transfusion that could be attributed to ALI. One patient (with pancreatitis) had an unstructured interstitial pattern most prominent in the caudodorsal lung field after transfusion of fresh frozen plasma (13 mL/kg [5.9 mL/lb]) without changes in pulmonary vasculature or cardiac silhouette on posttransfusion radiographs. After transfusion of fresh frozen plasma (22 mL/kg [10 mL/lb]), the other patient (that had undergone a lung lobectomy) had a generalized interstitial pattern, which was more severe in the right lung fields but also in the left caudal lung field, without any changes in pulmonary vasculature or cardiac silhouette on posttransfusion radiographs. Neither of the 2 patients with $\text{Pa}_2 \text{:FiO}_2$ ratios < 300 and radiographic changes that could be attributed to ALI developed dyspnea or tachypnea. Unfortunately, neither of these patients underwent an echocardiogram because radiographic changes were not identified until after discharge from the hospital or after patient death.

The overall incidence of VetALI in this population of patients that received transfusions was 3.7% (2/54; 95% CI, 0% to 8.7%). The incidence of VetALI in the study dogs (3.7%) was significantly ($P < 0.001$) less than the reported incidence of TRALI in humans (23%).\textsuperscript{16} The incidence of VetALI in the study dogs (3.7%), however, was not significantly ($P = 0.16$) different than the reported incidence of VetALI in a population of ill dogs that did not receive transfusions.\textsuperscript{17}

**Discussion**

Of the 54 dogs included in the study, it is believed that 2 dogs developed VetALI (incidence, 3.7%; 95% CI, 0% to 8.7%) within 48 hours after transfusion. This is less than the reported incidence of TRALI in humans (23%).\textsuperscript{2,3,16} but comparable to the incidence of ARDS in a population of ill dogs that did not receive transfusions.\textsuperscript{17} Therefore, it is impossible to definitively say that these 2 patients had VetALI secondary to their transfusions (also known as TRALI) rather than VetALI secondary to their underlying illnesses. In both cases, dogs had underlying inflammatory disease processes (pancreatitis and postsurgical inflammation), which are reported risk factors for VetALI.
At this point, it is impossible to distinguish whether the patients had TRALI or non-transfusion-induced VetALI. One factor that supports that these patients might have had TRALI is that neither of the patients initially had dyspnea or overt signs of respiratory distress despite worsening hypoxemia after transfusion. Acute onset of respiratory distress is expected in acute cases of VetALI but is not commonly seen with TRALI.2–13 On the other hand, the dog with pancreatitis was euthanized because of worsening respiratory effort and elevated respiratory rate 3 days after transfusion. Acute lung injury not induced by transfusion carries a poor prognosis, with a mortality rate of up to 72% in humans48 versus a mortality rate of only 10% for humans with TRALI.2

Our study had several limitations, largely as a result of its observational nature. First, our original power calculation of 86% was based on enrolling 60 dogs. Unfortunately, after all exclusions were taken into account, only 54 dogs remained in the study, which reduced the power to approximately 80%. During enrollment of the dogs, every attempt was made to include all dogs receiving transfusions at our institution during the study. However, in some cases, dogs that unexpectedly received transfusions intraoperatively could not be enrolled because of a lack of the appropriate pretransfusion radiographs and blood gas analysis results. Additionally, at times, dogs admitted to the hospital on an emergency basis were not enrolled as a result of the primary authors not being in the clinic or concerns that delaying a transfusion to collect the pretransfusion samples would be detrimental to the dogs. It is possible that ALI occurred in these patients and was not documented. Additionally, in the 4 dogs that were excluded because of suspicion that their arterial blood samples were venous or mixed arterial-venous samples, we cannot be sure that a case of VetALI was not mistakenly excluded.

Another limitation is that 4 of the patients did not have arterial blood samples for the determination of PaO2:FIO2 ratios. It is accepted that when patients are breathing room air with normal lungs, the conversion between SpO2 to PaO2 can be predicted by the oxyhemoglobin dissociation curve. However, when dogs have diseased lungs, anemia, or other pathological changes, this relationship may not be preserved. In our study, we believe that use of the approximation did not negatively impact our results, considering that none of the 4 dogs in which SpO2 was used to approximate PaO2 fell within the criteria used for VetALI. Three of the patients had PaO2:FIO2 ratios > 400 before and after transfusion with no changes evident on radiographs. The remaining dog (with an unknown etiology for anemia [suspected gastrointestinal bleeding vs non-regenerative anemia]) had a PaO2:FIO2 ratio of 386 prior to transfusion and 312 after transfusion after the conversion of SpO2 to PaO2. This patient had normal findings on thoracic radiographs without respiratory signs prior to transfusion and pleural effusion after transfusion. Echocardiography was performed after transfusion, and results were consistent with mild mitral and tricuspid regurgitation and mild pulmonary hypertension without cardiomegaly (class B1 heart disease). These echocardiographic findings made VetALI an unlikely cause for the worsening PaO2:FIO2 ratio after transfusion in that patient.

A third limitation of our study was that we did not obtain as many echocardiograms as we had originally intended in the design of the study. The original aim was to complete echocardiography on any patients with PaO2:FIO2 ratios < 300 after transfusion or any patients with new changes on radiographs obtained after transfusion. However, because the posttransfusion blood samples and radiographs for many dogs were taken on the weekends or immediately prior to planned discharge from the hospital, it was not always possible to have an official radiographic review completed or to have access to our cardiology service for echocardiography assistance. Therefore, some dogs with subtle radiographic changes and some with low PaO2:FIO2 ratios did not undergo echocardiography. Unfortunately, this included the 2 patients that we believe had VetALI. In each of these patients, there were changes present in the pulmonary parenchyma on radiographs consistent with VetALI, but we were not able to confirm a lack of circulatory overload via echocardiography. However, the patient with suspected VetALI that had pancreatitis did receive a postmortem examination that revealed pulmonary changes consistent with ALL.

Finally, our population of dogs included only 18 dogs that received plasma or plasma-containing products (2 receiving whole blood transfusions and 16 receiving fresh frozen plasma) and only 2 dogs that received functional platelets (as part of a fresh whole blood transfusions). In the human literature, plasma-containing products are much more likely to cause TRALI than are other blood products2–11,16 and there is evidence that transfused platelets specifically play a role in TRALI.16 However, because all of the packed RBCs administered in our hospital were made in-house from donor dogs, a process that is not as streamlined as the process at a commercial blood bank, plasma was present in small amounts in all administered packed RBC units. It has been reported that TRALI can occur even if < 10% of the blood product is made up of plasma16; therefore, it is possible that at least some of the dogs receiving packed RBCs had enough plasma administered to cause TRALI. Of the 2 dogs that received functional platelets as part of a fresh whole blood transfusion, neither developed VetALI. Whether there is dose dependency to the development of TRALI secondary to platelet transfusions or the exact mechanism of why platelets cause TRALI is as yet unknown in the human literature. Therefore, it is possible that the dogs required a larger dose of platelets to induce VetALI or that it must be pure platelet transfusions (as in the human literature) rather than fresh whole blood to cause VetALI.

Despite these limitations, we believe that our study was successful in showing that 2 patients did develop VetALI within the first 24 to 48 hours after transfusion. Given that the incidence of VetALI in this patient population was not significantly different than the incidence of ARDS in critically ill dogs that did not receive transfusions, we are unable to definitively attribute VetALI to transfusions in the study dogs.

References


Appendix 1

Modified definition of VetALI

<table>
<thead>
<tr>
<th>Criterion*</th>
<th>Description</th>
<th>Fulfillment (≥ 1 within a criterion category)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Acute onset</td>
<td>&lt; 72 hours of tachypnea and labored breathing at rest</td>
</tr>
<tr>
<td>2</td>
<td>Known risk factors</td>
<td>Inflammation, Infection, Sepsis, Systemic inflammatory response, Severe trauma, Multiple transfusions, Smoke inhalation, Near drowning, Aspiration of stomach contents</td>
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<tr>
<td>3</td>
<td>Pulmonary capillary leak†</td>
<td>Bilateral and diffuse infiltrates on thoracic radiograph, Bilateral dependent density gradient on CT, Proteinaceous fluid within the conducting airways, or Increased extravascular lung water</td>
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<tr>
<td>4</td>
<td>Inefficient gas exchange</td>
<td>Hypoxemia without positive end-expiratory pressure or continuous positive airway pressure plus known (not estimated) Fio2, as evidenced by: • PaO2:Fio2 ratio ≤ 300, • Increased alveolar-arterial oxygen gradient, or • Venous admixture indicative of a noncardiac shunt, Increased dead space ventilation</td>
</tr>
<tr>
<td>5</td>
<td>Diffuse pulmonary inflammation</td>
<td>Transtracheal wash or bronchoalveolar lavage fluid with neutrophilia, Transtracheal wash or bronchoalveolar lavage fluid with biomarkers of inflammation, or Evidence of inflammation on positron emission tomography</td>
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*Must fulfill the first 4 criteria; fulfillment of criterion 5 is recommended, but optional. †Without an increase in pulmonary capillary pressure and no evidence of cardiogenic edema.

Appendix 2

Definition of human TRALI

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Acute onset of clinical signs in a patient without clinical signs of acute lung injury</td>
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<tr>
<td>2</td>
<td>Hypoxemia (PaO2:Fio2 ratio ≤ 300) or oxygen saturation (SPO2) &lt; 90% on room air</td>
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<td>3</td>
<td>Bilateral lung infiltrates evident on radiographs</td>
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<td>4</td>
<td>No evidence of left atrial hypertension</td>
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<td>5</td>
<td>Occurrence during transfusion or within 6 hours of completion of transfusion</td>
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<tr>
<td>6</td>
<td>No preexisting acute lung injury before transfusion or relationship of clinical signs to another risk factor for acute lung injury other than the transfusion. Such risk factors include sepsis, aspiration or other pneumonia, previous transfusion, near drowning, disseminated intravascular coagulation, pulmonary contusion or other injury, fracture of bones or pelvis, and burns</td>
</tr>
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