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COMMENTARY

TRANSFUSION

Plasma as a resuscitation fluid for volume-depleted shock: Potential benefits and risks

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1 | INTRODUCTION

The clinical state of shock constitutes a relative or absolute deficiency of circulating volume for adequate oxygen delivery to meet the metabolic demands.[1] Although shock states differ in epidemiology, etiology, and pathophysiologic pathways, a common denominator of shock is endothelial barrier dysfunction.[2,3] Different kinds of shock states, such as occurring after major surgery, trauma, and in sepsis, can result in strong pro-inflammatory host responses with ensuing endothelial hyperpermeability.[4–6] Loss of endothelial barrier results in leakage of fluid into surrounding tissue, contributing to edema, tissue hypoxia, and organ failure.[6] This loss of fluids further aggravates the intravascular circulatory volume deficiency during shock. Obviously, septic and traumatic shock are different entities, with different etiologies and differences in initiation of host response and coagulation response. However, endothelial activation with loss of endothelial barrier integrity is a common finding in both shock states.

In trauma-induced shock, current resuscitation strategies consist of the early transfusion of whole blood or a balanced ratio of plasma, platelets, and red blood cells.[7,8] The aim of resuscitation is to ensure adequate oxygen delivery and to correct coagulopathy. Plasma transfusion may play a key role, as trials point toward improved survival with high dose or early use of plasma transfusion compared to standard care.[9–11] Upon reaching surgical hemostasis, it is general practice to stop transfusion. However, as a result of ongoing inflammation and endothelial activation, patients can continue to be fluid dependent, which is often responded to with crystalloids. However, liberal use of crystalloids in traumatic

hemorrhagic shock is associated with increased mortality and increased endothelial permeability, inflammation, and reduced perfusion of vital organs.[12–14]

In septic shock, the primary treatment of shock is volume resuscitation with crystalloid or colloids, as advocated in guidelines.[15] However, comparable to traumatic hemorrhagic shock, use of a restrictive fluid balance reduces the occurrence of organ failure as well as mortality in sepsis.[16–18] most likely, the association between the amount of infused volume and adverse outcome in shock states is related to increased shedding of the glycocalix, breakdown of adherent junctions, and tight junctions resulting in an increased gradient of leakage over the hyper permeable endothelium.[19]

Taken together, due to a relative or absolute deficiency of intravascular volume, patients with shock are likely to need volume expansion to maintain perfusion pressure. This poses a challenge to the treatment of shock, as fluid therapy is both a cornerstone of therapy as well as a foe. Different fluids may have differential effects on endothelial integrity. Low-protein-content fluids seem to aggravate shedding of glycocalix,[20] whereas protein-rich fluids such as plasma may be superior to normal saline in protecting the glycocalix and endothelial barrier function.[21]

Transfusion with plasma as a volume expander in shock may seem controversial at first, but one needs to consider that despite the fact that plasma is transfused in millions of patients annually, there currently is limited understanding of its mechanisms of action. In traumatic blood loss, transfusion of plasma may improve survival by decreasing exsanguination.[7,10] The common perception is that plasma is a pro-coagulant blood product, by replenishing coagulation factors. However, as plasma contains coagulation factors but also anticoagulant proteins, the net effect of plasma on coagulation may be neutral. In line with this, plasma transfusion increases the amount of coagulation factors as well as levels of anticoagulant proteins,[22] resulting in unchanged thrombin generation, at least in non-bleeding critically ill patients with an inflammatory-driven consumption coagulopathy. In patients with traumatic hemorrhagic shock, it is not apparent whether the mechanism of effect of plasma is directly related to the correction of coagulopathy.[23] In rats with hemorrhagic shock, deranged thrombin formation was somewhat restored with resuscitation with plasma but not with crystalloids, but whether this relates to prevention of dilutional coagulopathy or to a specific pro-coagulant effect of plasma is not clear.[24,25] Other mechanisms of the protective effect of plasma may be at hand. These may include preservation of the glycocalix, decreasing inflammation and decreasing endothelial leak. This review aims to discuss the potential of plasma as a resuscitation fluid in shock, with an emphasis on possible mechanisms of benefit on the activated endothelium. Studies comparing plasma with other fluids on (markers of) endothelial integrity have found effects both in (models of) trauma-induced shock and in septic shock. As loss of endothelial integrity may be a common denominator of shock, we will discuss both these shock states.

2 | THE EFFECT OF PLASMA ON THE ENDOTHELIAL GLYCOCALIX

The glycocalix is a luminal endothelial carbohydrate-rich gel-like layer, anchored to glycosaminoglycans, proteoglycans, and other glycoproteins.[26] Together with endothelial intercellular connections, the glycocalix regulates endothelial barrier integrity. In shock states, shedding of constituents of the glycocalix, such as syndecan-1 and heparan sulfate, results in endothelial permeability.[27–29] Proof that syndecan-1 plays a role in preservation of endothelial barrier integrity was shown in a murine model, in which syndecan-1 knockout mice challenged with lipopolysaccharide had more lung edema, organ failure, and mortality compared to wild types.[30]

2.1 | Trauma

In patients with trauma, circulating levels of glycocalix constituents are associated with adverse outcome.[28] In a trial evaluating the effect of prehospital plasma,[10] use of early plasma compared to standard care, was associated with a reduction on markers of glycocalix shedding, as well as with a reduction in inflammatory cytokines and vascular endothelial growth factor.[31] As these markers were reduced long after the resuscitation had ceased, preservation of the glycocalix seems a likely mechanism of the beneficial effects of prehospital plasma. Of interest, the benefit of prehospital plasma was also shown for the subgroup of TBI patients.[32] Although mechanisms are not clear, benefits of plasma in the specific setting of TBI may not be related to volume expansion but again to a reduction of endothelial dysfunction,[31] which may have contributed to preservation of the blood brain barrier. The benefit of plasma may also relate to the duration of shock and hence the severity of endothelial injury, given that plasma may be particularly beneficial in patients with long transport times to the hospital.[11] Further proof-of-concept is provided in experimental trauma models, in which plasma compared to crystalloid resuscitation improved oxygenation, and reduced inflammation, endothelial injury, capillary leakage, and hence, tissue

edema,[24,33–35] associated with restoration of the thickness of the glycocalix layer in organs.[25]

2.2 | Sepsis

In patients with septic shock, the endothelial glycocalix is also degraded,[29] the severity of which is associated with organ failure and mortality.[36] Although confounding by disease severity cannot be ruled out, it appears that the amount of crystalloid fluids during resuscitation of septic shock is associated with the amount of degradation, as evidenced by high-circulating heparin sulfate.[36] In contrast to crystalloids, in a rodent sepsis model, transfusion of plasma was associated with reduced mortality, associated with reduced endothelial injury and lung edema.[37] In an observational study in critically ill patients, plasma infusion is associated with reduced circulating syndecan-1 levels.[38] Of note, studies which have applied plasma exchange as a last resort for refractory septic shock have noted a decreased mortality and improved organ failure compared to either historic controls or in a propensity-matched analysis in children and adults.[39–41]

Taken together, shock results in glycocalix shedding. Compared to crystalloids, use of plasma may be superior in preserving the glycocalix.

3 | POTENTIAL COMPONENTS IN PLASMA THAT MAY MEDIATE PROTECTIVE EFFECTS IN SHOCK

3.1 | Albumin

Circulating proteins are of significant importance for endothelial stability and health. The most abundant protein in plasma is albumin, with an average protein level ranging between 30 and 50 g/dL. The major functions of albumin are maintaining plasma colloid oncotic pressure,[42] and regulating endothelial permeability.[43,44] Hypoalbuminemia occurs commonly in shock patients and is associated with mortality.[45] In vitro, removing albumin causes glycocalix degradation, most likely due to cleaving of the endothelial glycocalix components from the underlying endothelium by matrix metalloproteinases (MMPs).[44] In vivo, albumin restores the endothelial glycocalix, an effect that appears to be independent of osmotic pressure, because at the same osmotic pressure, colloids do not have this restorative effect.[46] In a rodent model of hemorrhagic shock, resuscitation with albumin 5%, which resembles protein content of the body, restored glycocalix thickness as compared to crystalloids, associated with less shedding of syndecan-1.[34] In a rat endotoxemia model, albumin infusion reduced endothelial dysfunction while reducing inflammation and oxidative stress.[47]

The mechanism by which albumin (or plasma) is protective is not known but may involve lipid mediator sphingosine-1-phosphate (S1P, Figure 1). Infusion of plasma or plasma-derived albumin stimulates the release of S1P from its major source, which are red blood cells and platelets. In shock states, S1P protects endothelial barrier function by reduction of oxidative stress and cytokine secretion,[48] by strengthening endothelial cell tight junctions,[44,49] and by inhibiting MMPs.[44,50] In septic shock patients, low S1P levels are associated with organ failure and mortality.[51] To our knowledge, there is a lack of data on S1P levels in hemorrhagic shock patients.

Trials on albumin infusion in septic shock patients predominantly show no effect[52–54] on mortality and organ failure.[52,54] However, post-hoc analysis showed a potential benefit in the subgroup of septic shock patients.[54] Also, in patients with hypoalbuminemia, albumin reduced organ failure when compared to crystalloids.[53] Meta-analyses of studies have also yielded conflicting results, although pooled data from the more robust large-scale studies suggest a benefit of albumin.[55] Endothelial dysfunction has not been used as a primary outcome in these studies. Thereby, whether plasma confers a benefit due to albumin content is not known. Besides albumin, other proteins may play a role in preservation of the glycocalix during shock.

3.2 | Adiponectin

Adiponectin is a cytokine that is produced in adipose tissue. Its circulating plasma levels range from 2 to 30 μg/ml, making up around 0.01% of the plasma protein content.[56–58] Adiponectin has widespread physiological functions, including glucose and lipid metabolism. Furthermore, adiponectin has broad anti-inflammatory and vasoprotective effects.[59] (Figure 1). The role of adiponectin in preserving endothelial barrier function was shown in mouse sepsis models, in which adiponectin knock-out compared to wild-type animals showed upregulation of vascular adhesion molecules, pro-inflammatory cytokine production and more severe organ failure.[60,61] In vitro, adiponectin-reduced TNF-a induced endothelial permeability.[62]

On the one hand, patients with septic shock have decreased plasma levels of adiponectin,[63–67] associated with organ failure and mortality.[65,66] On the other hand,

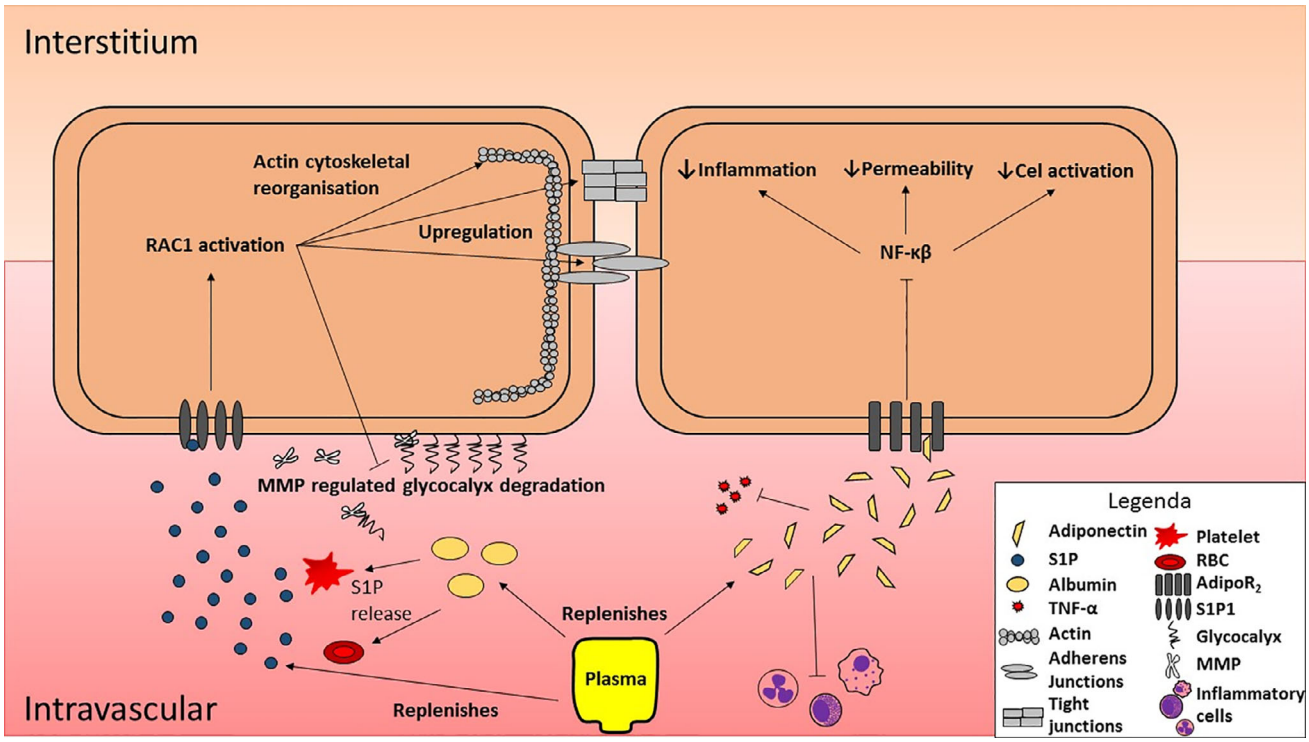

FIGURE 1 Proposed mechanisms of albumin, S1P and adiponectin on endothelial barrier function. In shock, adiponectin, albumin and S1P levels are commonly low. Plasma transfusion can replenish these components. Moreover, albumin also stimulates red blood cells and platelets to release S1P. S1P binds to S1P1 receptors activating Rac1. Rac1 activation has widespread physiological functions in the endothelial cell. It upregulates both endothelial tight junctions and adherent junctions and induces actin cytoskeletal reorganization strengthening endothelial barrier function, reducing endothelial permeability. Also, RAC1 inhibits MMP function resulting in reduced glycocalyx breakdown further retaining endothelial function. By replenishing adiponectin, inflammation is reduced by adiponectin-mediated inhibition of TNF-α and reduction of inflammatory cell response. By binding of adiponectin to AdipoR2, NF-κβ signaling is inhibited leading to reduced inflammation, endothelial permeability, and activation. $AdipoR_2$, adiponectin receptor 2; MMP, matrix metalloproteinase; Rac1, Ras-related C3 botulinum toxin substrate 1; RBC, red blood cell; S1P, Sphingosine-1-Phosphate; S1P1, sphingosine-1-Phosphate receptor 1; TNF-α, tumor necrosis factor-α

higher levels of plasma adiponectin[68,69] are also linked to mortality.[68] These contradictory data suggest a dual regulatory role of adiponectin. In patients with traumatic hemorrhagic shock, low levels of adiponectin are found.[70] In a mouse model of hemorrhagic shock, low adiponectin levels were replenished following resuscitation with plasma as well as following adiponectin infusion, thereby preventing endothelial permeability.[70] As plasma depleted from adiponectin did not prevent permeability, adiponectin appears to mediate the protective effects of plasma resuscitation.[70]

3.3 | Antithrombin

Antithrombin (AT) is a glycoprotein produced by the liver, and has anticoagulant properties (Figures 2 and 3). In both traumatic hemorrhagic and septic shock, AT levels are decreased, associated with organ failure.[71,72] In a preclinical model of hemorrhagic shock, resuscitation with plasma increased syndecan-1 expression in the lung compared to controls, indicating an intact glycocalix.[73] A role for AT in restoring glycocalix was demonstrated, as AT-deficient plasma did not restore syndecan-1 expression, while AT-deficient plasma supplemented with purified AT maintained syndecan-1 expression.[73] In sepsis trials, supplementing AT have failed to demonstrate reduction of mortality.[74] Some observational studies do however show a mortality benefit when supplementing AT in patients with sepsis-induced disseminated intravascular coagulation.[75,76]

3.4 | ADAMTS13

Upon activation, endothelial cells secrete von Willebrand Factor (VWF),[77] which can form larger multimers (ULVWF) with high platelet-binding potential. In normal conditions,

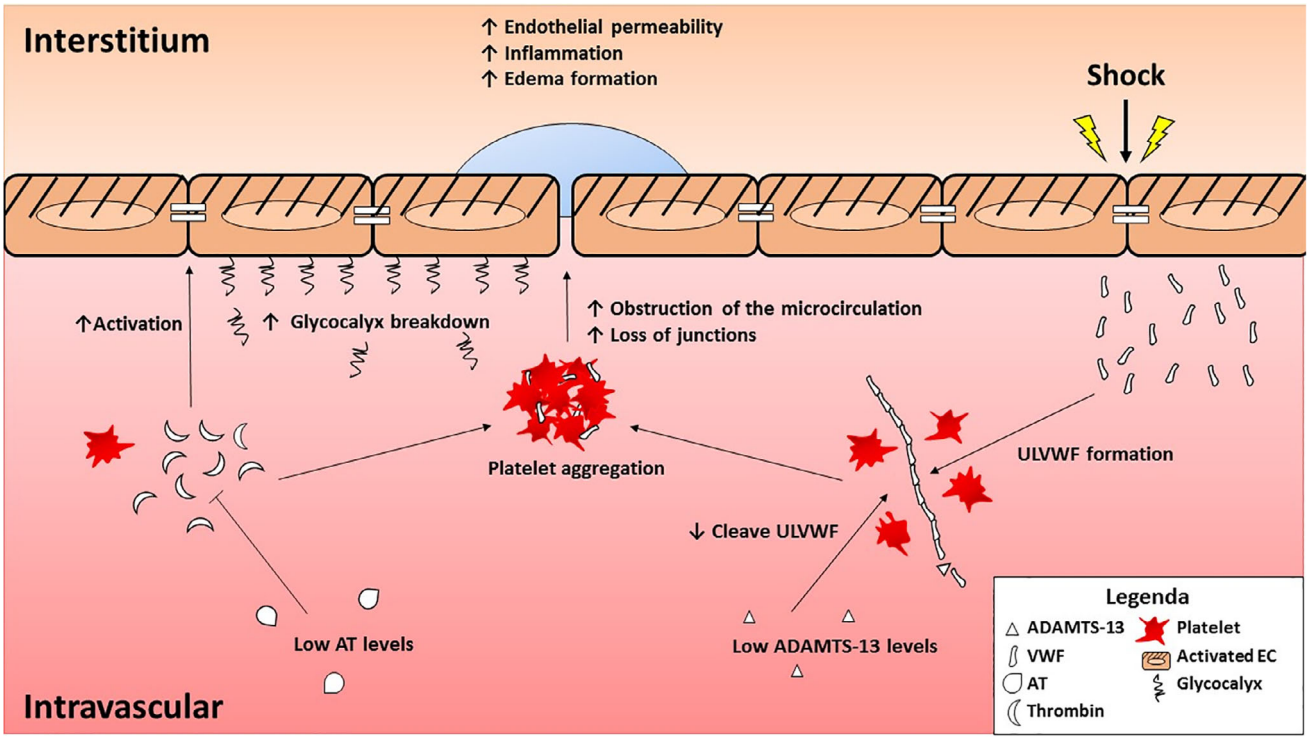

FIGURE 2 Proposed mechanisms of shock-induced microthrombi formation. Shock results in inflammation-mediated activation of the endothelial cells with release of VWF. High amounts of VWF will multimerize and form prothrombotic ULVWF multimers with high platelet-binding affinity. In normal conditions, ULVWF multimers are cleaved by ADAMTS13 into smaller, less prothrombotic VWF monomers. However, as ADAMTS13 levels are decreased during shock, the ULVWF multimers will promote platelet aggregation, resulting in microthrombi formation. This process may result in obstruction of microcirculation, inflammation, increased endothelial permeability, edema which leads to organ damage. Furthermore, the thrombin burst in shock is not counterbalanced by antithrombin. Antithrombin levels and activity are low in shock, further fueling thrombin-induced platelet aggregation and microthrombi formation. ADAMTS13, a desintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13; AT, antithrombin; ULVWF, ultra-large von Willebrand Factor multimers; VWF, von Willebrand Factor

ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13) cleaves ULVWF multimers into smaller fragments, reducing its prothrombotic activity. In multiple shock states such as traumatic and septic, there is increased VWF release, multimerisation, and a simultaneous reduction in ADAMTS13 (Figures 2 and 3).[78–80] This ADAMTS13-ULVWF imbalance is associated with organ failure in patients with sepsis or trauma.[78–80] Plasma contains normal levels of ADAMTS13. We showed in sepsis patients that plasma transfusion replenishes low ADAMTS13 levels, associated with reduced release of VWF into the circulation.[38] Plasma exchange improves the ADAMTS13-ULVWF imbalance in thrombotic thrombocytopenic purpura by removing inhibitory antibodies and ULVWF from the circulation in addition to replenishing functional deficiency in ADAMTS13.[81] In severe COVID-19 infection, plasma exchange decreased the incidence of acute kidney injury, associated with an improved ADAMTS13-VWF disbalance.[82]

In trauma, clinical studies are sparse, but in trauma models it has been shown that replenishing ADAMTS13 was associated with decreased endothelial permeability and organ failure.[83–85]

Taken together, we highlighted some potential pathways of benefit of plasma, although most likely not reaching full comprehension. Alternatively though, plasma may just be not as bad as crystalloids in terms of glycocalix shedding, and no specific pathway is present. Which component in plasma mediates benefit remains an important research question.

4 | A POTENTIAL OVERARCHING BENEFIT OF PLASMA ON THE ENDOTHELIAL SURFACE

In addition to the effect that specific proteins or peptides circulating in plasma may have on the endothelial cell wall, there may also be an overarching benefit of plasma. Approximately 1/3 of circulating blood volume is not flowing, but remains in close proximity to the endothelial surface layer. This fixed plasma is in balance with

proteins on the glycocalix and the endothelial surface, and is also in balance with the dynamic equilibrium of the flowing circulating plasma volume. Although data are sparse, we speculate that plasma is superior to clear fluids in preserving this natural balance between fixed versus circulating plasma volumes.

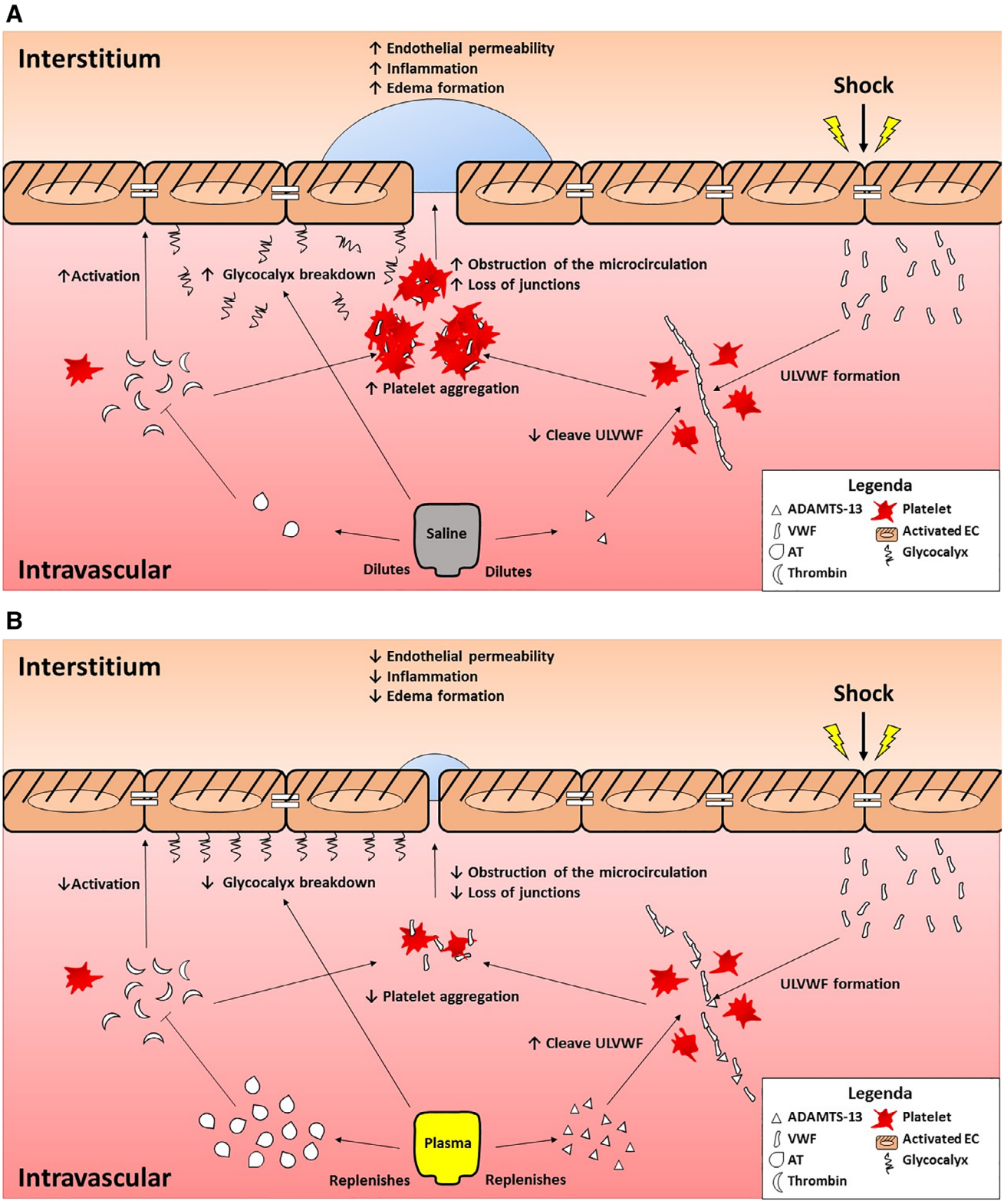

FIGURE 3 Legend on next page.

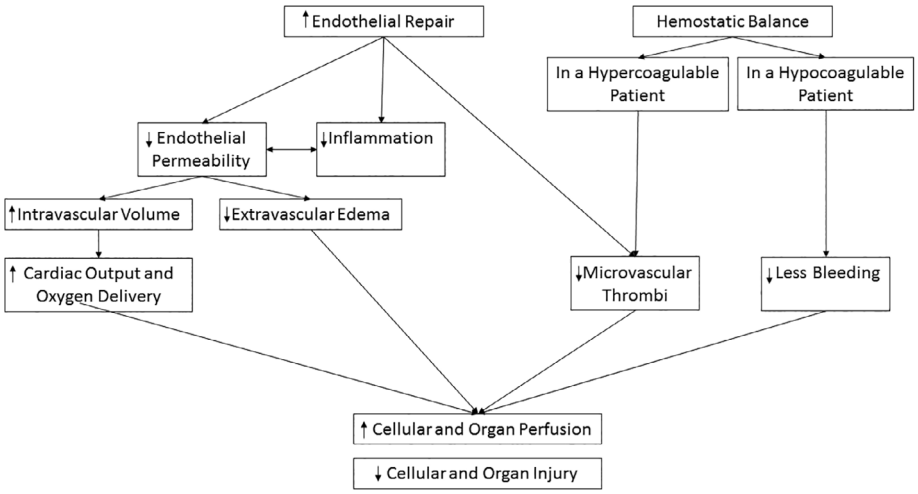

FIGURE 4 Effects of plasma relative to crystalloids for patients in intravascular volume-dependent shock

5 | POTENTIAL EFFECTS OF PLASMA ON OXYGEN DELIVERY AND TISSUE PERFUSION IN SHOCK: SUMMARIZING SOME CONCEPTS

Several mechanisms of protection may be at play (Figure 4). If plasma decreases endothelial leakage compared to crystalloids, use of plasma will result in improved expansion of the intravascular volume, with improved oxygen delivery and possibly less organ injury, at least in those shock states in which tissue perfusion (and not cellular oxygen consumption) is impaired. Also, if plasma prevents dilutional coagulopathy with ensuing blood loss during bleeding, this will increase intravascular volume. Lastly, plasma may improve an unbalanced coagulation system, relative to the coagulation status of the patient. By correcting an "overshoot" in pro-coagulant activity with a reduction in microthrombi-driven endothelial activation, plasma may contribute to improved microvascular perfusion and less organ injury. Such "overshoot" pro-coagulant activity is apparent in sepsis but also in traumatic patients who survived the initial bleeding, conversion into a hyper-coagulable state is common.[86] Vice versa, in hypo-coagulable patients, plasma may decrease blood loss by restoring coagulation abilities. However, proof for most of these concepts in clinical studies is hitherto sparse. Also, if these concepts hold true, it is not known which mechanism is the most relevant.

6 | DIFFERENCES BETWEEN PLASMA PRODUCTS

In general, three different plasma transfusion products exist: single donor fresh frozen plasma (FFP), multiple donor-pooled solvent detergent plasma (SDP), and dried plasma that can be derived from either single donor or pooled pathogen-inactivated plasma. Traditionally, FFP has been the only product available. Recently, in an effort to mitigate adverse events of plasma transfusion, various countries have switched to SDP. SDP is a pooled plasma product (usually more than 100 donors) that is exposed to multiple washing and filtration steps. As noted, pooling of plasma dilutes any potentially harmful antibodies (anti-HNA and HLA) that could induce TRALI. The washing process eliminates lipid-enveloped viruses, cells, and cell-derived debris from the

FIGURE 3 (A) Proposed effects of crystalloids on shock-induced microthrombi formation. (B) Proposed effects of crystalloids on shock-induced microthrombi formation. The proposed effects of crystalloids (A) and plasma (B) on the formation of shock microthrombi formation are shown. Infusion of crystalloids leads to dilution of ADAMTS-13 and AT, which promotes platelet aggregation and microthrombi formation aggravating endothelial permeability and organ injury. Furthermore, crystalloid infusion directly leads to glycocalyx breakdown which may be caused by a protein poor environment. Plasma transfusion is thought to replenish proteins such as ADAMTS-13 and AT. By replenishing ADAMTS-13, ULVWF multimer formation is hampered resulting in reduced platelet aggregation. By replenishing AT, thrombin-mediated platelet aggregation is inhibited. Both processes lead to less microthrombi formation and thus less obstruction of the microcirculation and associated organ damage. Furthermore, plasma is thought to be directly beneficial to the glycocalyx by providing a protein-rich environment. ADAMTS-13, a desintegrin, and metalloproteinase with thrombospondin type 1 motifs, member 13; AT, antithrombin; ULVWF, ultra-large von Willebrand factor multimers; VWF, von Willebrand factor

product, including cytokines.[87] In addition, the amount of residual cells and cell-derived micro particles is lower in SDP when compared to FFP.[88,89] Reduction of all these mediators may theoretically reduce immunologic effects of plasma transfusion.

In vitro, incubation with SDP reduced LPS-induced cytokine production when compared to incubation with FFP, although endothelial permeability did not differ.[90,91]

Trials that have compared FFP to SDP have mostly focused on coagulation outcomes. With regards to endothelial protection, in a pilot trial in cardiothoracic surgery patients, SDP compared to FFP was associated with less syndencan-1 release,[92] and reduction in time on the ventilator. In terms of adverse events, a retrospective study in critically ill children showed that SDP, but not FFP, was independently associated with reduced mortality.[93] Observational studies also showed a reduction in TRALI in institutions that switched from use of FFP to use of SDP,[94,95] although other factors in clinical practice may also have played a role.[96–98] In a prospective observational study in critically ill children, SDP reduced 30-day mortality compared to the use of FFP.[93]

The availability of freeze-dried plasma to be immediately available for patients who need resuscitation urgently for hypotension secondary to severe sepsis has improved the feasibility of using plasma for this purpose.[99] Data from both in vitro and in vivo animal models indicate that the endothelial protective effects of dried plasma are similar to that of standard FFP, indicating that dried plasma may be just as effective clinically at improving intravascular volume, oxygen delivery, and perfusion as well as achieving hemostatic balance.[88,91,100]

7 | ROADBLOCKS IN THE USE OF PLASMA FOR SHOCK

7.1 | Transfusion-related acute lung injury

Plasma can result in transfusion-related acute lung injury (TRALI). We have previously argued that TRALI is a relevant syndrome in the critically ill, contributing to mortality.[101] Thereby, the hypothesis that plasma may be a beneficial resuscitation fluid may seem in strong contrast to our previous scientific work. However, it is in fact our previous finding that plasma stabilizes the endothelium that has led us to this hypothesis.[38] Concerning the risk of TRALI, following implementation of use of males-only for plasma donation, the association between plasma and TRALI has consistently reduced by around two thirds of cases,[102] due to reduction in antibodies. In addition, the use of pooled plasma also has reduced TRALI incidence due to dilution of residual antibodies. Residual TRALI cases are now thought to be caused by blood products other than plasma.

7.2 | Transfusion-associated cardiac overload

Like TRALI, transfusion-associated cardiac overload (TACO) appears more common in the critically ill and typically presents with bilateral pulmonary infiltrates with hypoxemia. In contrast to TRALI, the pathophysiology underlying the lung edema of TACO is hydrostatic in nature. Risk factors are patient conditions associated with an impaired ability to handle fluid loading of a blood product, including cardiac or renal disease.[103] Thereby, TACO can occur following volume loading due to any blood product, and does not pertain to plasma in particular. Also, in resuscitation of shock, expanding the circulating volume is a wanted intervention. Nevertheless, when patients with shock and concurrent renal or cardiac failure are treated, volume overload can occur. Straightforward interventions that have been shown to decrease the risk of TACO are reduction of infusion speed and the administration of diuretics.[104]

7.3 | Shortage of donors

Plasma is a blood product, derived from blood donors. As such, plasma supply is limited, in particular as females are banned from plasma donation. Engaging the society that shock is a major health care problem and that plasma is beneficial, would be paramount to ensure adequate donor supply. Furthermore, identification of which plasma components are beneficial in shock is a logical and necessary step. Supplementing the necessary component may lead the way to targeted treatment, in which patients may differ from which component is needed, based on a specific condition or based on specific patient factors. Thereby, increased understanding of the mechanisms of action of plasma is warranted.

8 | THE WAY FORWARD

We have argued that there is support to investigate the efficacy of plasma for the treatment of volume-depleted shock, with the aim to preserve endothelial and epithelial barrier integrity, improve intravascular volume, and ultimately oxygen delivery to reduce cellular and organ injury. Despite a worldwide use, knowledge on the effects of plasma on organ failure is highly limited. We

suggest specific mechanisms of action are possible that await exploration. As shock is a major health care problem, we call for the need for research aimed at an improved understanding of which plasma components mediate beneficial effects, with the ultimate aim to move toward component therapy for the treatment of shock states.

CONFLICT OF INTEREST

The author has disclosed no conflicts of interest.

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