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Review

The recipe for TACO: A narrative review on the pathophysiology and potential mitigation strategies of transfusion-associated circulatory overload

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ABSTRACT

Transfusion associated circulatory overload (TACO) is one of the leading causes of transfusion related morbidity and mortality. TACO is the result of hydrostatic pulmonary edema following transfusion. However, up to 50% of all TACO cases appear after transfusion of a single unit, suggesting other factors, aside from volume, play a role in its pathophysiology. TACO follows a two-hit model, in which the first hit is an existing disease or comorbidity that renders patients volume incompliant, and the second hit is the transfusion. First hit factors include, amongst others, cardiac and renal failure. Blood product factors, setting TACO apart from crystalloid overload, include colloid osmotic pressure effects, viscosity, pro-inflammatory mediators and storage lesion byproducts. Differing hemodynamic changes, glycocalyx injury, endothelial damage and inflammatory reactions can all contribute to developing TACO. This narrative review explores pathophysiological mechanisms for TACO, discusses related therapeutic and preventative measures, and identifies areas of interest for future research.

1. Introduction

Transfusion-associated circulatory overload (TACO) is a transfusion complication typically characterized by respiratory distress and pulmonary edema. The incidence of TACO varies between different patient populations, ranging from 1% for admitted patients to 5.5% of patients transfused intra-operatively and up to 11% in critically ill patients. TACO can lead to major morbidity including intensive care admission, intubation and mechanical ventilation and ultimately to mortality in up to 6.5% [1–3].

TACO is hypothesized to be the result of hydrostatic pulmonary edema, which differentiates it from transfusion-related acute lung injury (TRALI). Whereas in TRALI an inflammatory trigger increases capillary permeability, causing exudative pulmonary edema, in TACO a transfusion results in an increased pulmonary capillary pressure. Starling's forces result in increased net filtration pressure and fluid is driven into the lungs [4]. When the lymphatic fluid drainage mechanism is overwhelmed, fluid will accumulate in the alveoli. TACO is characteristically viewed as a side-effect of the absolute volume transfused, in essence not dissimilar to circulatory overload from intravenous fluids. Increasing transfused volumes can lead to an increased risk of developing TACO, however in another cohort 50% TACO reports were after a single transfused unit (±300 mL) [5,6]. This indicates that other factors are potentially at play in the pathophysiology of TACO.

The aim of this review is to summarize the current evidence on the pathophysiology of TACO, explore possible therapeutic and preventative approaches to TACO based on these mechanisms, and identify areas of interest for future research, both in pre-clinical and clinical studies.

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2. Methods

A systematic review of the literature was performed. A broad search strategy was employed to identify all articles containing: "transfusion-associated circulatory overload" or "transfusion associated cardiac overload" within PubMed, EMBASE, TRIP Pro and the Cochrane library (Supplementary Appendix A). Databases were searched from inception till the 31st of October 2019. The search was updated and extended until the 3rd of June 2021. A snowball approach was performed to find additional relevant studies. Screening was performed by two independent reviewers (E.B & R.K). Articles were first screened based on title and abstract for relevance. Subsequently articles about TACO were screened for inclusion based on full text. Finally, articles that elaborated on the pathophysiology of TACO were included in the review (Fig. S1). Articles not in English and in abstract form only were excluded from this review.

3. Development of TACO

3.1. Pulmonary edema by increased hydrostatic pulmonary capillary pressure

TACO is diagnosed by a set of clinical criteria, manifesting as respiratory distress caused by pulmonary edema occurring within 12 h following transfusion [7]. Pulmonary edema in TACO is by definition the result of an increased hydrostatic pressure. The exact mechanism by which blood products increase intravascular pressure is still unclear although there are several pathophysiological mechanisms through which this might occur. In this review we summarized all studies, both with original data and reviews, reporting on the pathophysiology of TACO (Tables 1 and 2).

Important hemodynamic measures, which most closely reflect capillary pressure in TACO, include left-atrial pressure and left-ventricular end-diastolic pressure, which is equal to the P_{max} in the left-atrium under normal conditions. Measurement of these hemodynamic indices is invasive and requires specialized equipment, personnel, and training. The gold-standard for measuring these indices in humans is through use of a Swan-Ganz catheter (or pulmonary artery catheter),

Table 1
Included studies with original data on the pathophysiology of TACO.

Author	Year of publication	Study design	Population	TACO definition	Transfusion product	Pathophysiological mechanism	Outcome
Blumberg [61]	2010	Retrospective observational	Hospital wide	Study criteria[a]	Mixed	Inflammatory process	TACO incidence decreased by 49% after leukoreduction
Maslanka [65]	2015	Retrospective observational	Pulmonary transfusion reaction	ISBT criteria 2011	Mixed	Storage lesion/ inflammatory process	No significant associations of any mediator with TACO
Roubinian [64]	2015	Case control	Pulmonary transfusion reaction, ARDS	NHSN criteria 2011	Mixed	Inflammatory process	Elevated IL-10 pre and post-transfusion, elevated IL-6 posttransfusion
Parmar [63]	2017	Retrospective observational	Transfusion reaction	Study criteria[b]	Mixed	Inflammatory process	31,7% of patients with TACO had a concurrent fever
Saadah [27]	2017	Retrospective observational	Transfusion reaction	IHN definition 2011	Plasma	Inflammatory process	Significant reduction in TACO(OR 0.46) with pathogen reduced plasma
Masuda [18]	2018	Interventional animal study	Swine	NA	RBC	Two-hit model	P/F ratio < 300 only in RBC transfusion after hemorhagic shock
Andrzejweski [24]	2012	Retrospective observational	Transfusion reaction	Study criteria[c]	RBC	Inflammatory process	Temperature, heart rate and blood pressure all significantly increased in TACO patients
Roubinian [87]	2020	Case control	Pulmonary transfusion reaction, ARDS	NHSN criteria	Mixed	Cardiac stress/ overload	Elevetad NT-proBNP levels in cases of TACO compared to TRALI or controls
Warner [96]	2017	Randomized controlled trial (protocol)	Cardiac surgery	NA	RBC	Inflammatory process	Aim to reduce biological modifiers by washing transfusion products
Klanderman [19]	2019	Interventional animal study	Rats	NA	RBC	Two-hit model	The combination of volume incompliance and transfusion is essential for the development of TACO
van Hout [74]	2019	Retrospective observational	Transfusion reaction	TRIP guidelines 2008	Platelets	Storage lesion	No differences in TACO incidence with different storage times of transfusion products
Klanderman [40]	2018	Interventional animal study	Rats	NA	RBC	Hydrostatic pressure	Circulatory overload increases with transfusion volume, non-significant increasing trend with faster administration
Klanderman [48]	2020	Observational	Healthy blood donors	NA	Mixed	Colloid osmotic pressure	Traditional transfusion products have COP levels below physiological levels, storage lesion does not increase COP

Legend: ARDS = acute respiratory distress syndrome, RBC = red blood cells, TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury, IL = interleukin, COP = colloid osmotic pressure, BNP = brain natriuretic peptide, NT-proBNP = N-terminal prohormone brain natriuretic peptide.

[a] New or worsening cardiogenic pulmonary edema (not attributable to other causes) and responding to diuretics.

[b] following criteria ≤6 h after transfusion, new or worsening dyspnea or hypoxia or pulmonary edema and evidence of fluid overload (cardiovascular symptoms and/or elevated BNP).

[c] ≥ 2 of the following criteria (not attributable to other causes then transfusion); respiratory distress, pulmonary edema, hypertension, tachycardia, positive fluid balance or elevated (NT-pro)BNP levels.

Table 2
Included reviews with statements on the pathophysiology of TACO.

Author	Year of publication	Population	Transfusion product	Pathophysiological mechanisms	Conclusion
Bosboom [38]	2019	TACO	Mixed	1. Inflammatory process 2. Endothelial barrier disruption 3. Storage lesion	TACO is the result of hydrostatic pressure, possibly combined with inflammation, glycocalyx disruption or vasoconstriction caused by NO scavenging from storage lesion
Semple [8]	2019	TACO	Mixed	1. Two-hit model 2. Inflammatory process	A two-hit model is suggested where the first hit is a preexisting clinical condition of the patient, resulting in poor fluid adaptability and the second hit is conveyed by the transfusion, which could induce inflammation seen the elevated IL-6 levels and fever present in many TACO patients
Roubinian [9]	2018	TACO	Mixed	1. Hydrostatic/oncotic pressure 2. Inflammatory process 3. Storage lesion	Transfusion results in elevated hydrostatic and oncotic pressure compared to crystalloid infusion and can possibly induce inflammation, also products of storage lesion(cfHb, NO scavengers) can increase systemic vascular resistance by vasoconstriction
Andrzejweski [39]	2013	TACO	Mixed	1. Inflammatory process 2. Mechanical stress/ barotrauma	Volume overload may damage the endothelium by inducing barotrauma, also inflammatory pathways cannot be dismissed in the pathophysiology of TACO
Graham [10]	2021	Transfusion complications in oncology	Mixed	Two-hit model	TACO is a two hit model, the first hit is patient specific and leads to impaired ability to adapt to volume changes, the second hit contains transfusion related factors, such as transfused volume and infusion speed
van den Akker [60]	2021	TACO	Mixed	Inflammatory process	Hydrostatic pressure causes pulmonary edema, however a new-onset fever in 1/3 of TACO patients argues against a purely volume-overloaded pathogenesis

Legend: TACO = transfusion-associated circulatory overload, NO = nitric oxide, IL = interleukin, cfHb = cell-free hemoglobin.

which is infrequently pursued due to its invasive nature.

3.2. TACO as a two-hit disease

Numerous groups have postulated that TACO follows a two-hit disease model [8–10]. The first hit includes inherent risk factors and comorbidities that lower the patient's ability to compensate for an increased intravascular volume, rendering the patient volume intolerant. The patient-related risk-factors for TACO include cardiac dysfunction, renal disease and need for renal replacement therapy; the extremes of age; and, a positive fluid balance [11–17]. Volume intolerance as a first hit lowers the threshold for a subsequent blood transfusion (the second hit) to increase hydrostatic pulmonary pressure, and therefore less transfused volume is required to develop TACO (Fig. 1).

The two-hit hypothesis is supported by animal studies of TACO. A study in healthy adult swine compared a massive infusion (100% of estimated circulating volume) of whole blood to crystalloid and colloid fluid infusion. Interestingly massive transfusion in healthy swine did not result in TACO, defined as reaching a P/F-ratio (PaO_2/FiO_2) <300 (the definition of significantly impaired oxygenation). Only in the transfusion group with preceding hemorrhagic shock, as first hit, did the pulmonary pressures increase and the P/F-ratio decrease to <300 [18]. An animal experiment in rats confirmed this hypothesis, showing that TACO only developed when a RBC transfusion was combined with a preceding first hit of either heart or renal failure [19].

While neither current animal models develop a classic TACO phenotype, they demonstrate that a first hit is essential in developing TACO. Furthermore, they demonstrate that pulmonary pressures increase in transfusion and not after fluid infusion.

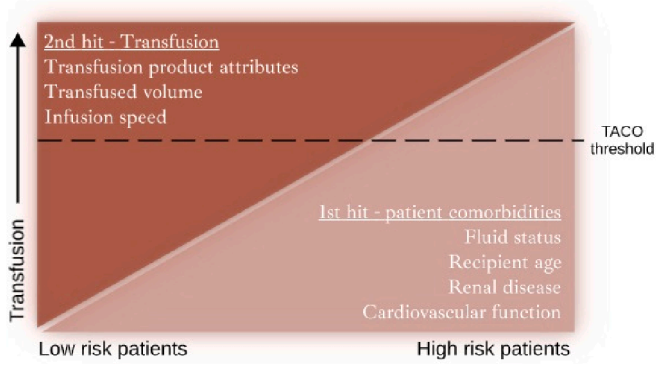

Fig. 1. TACO as a two-hit model.
The first hit consists of patient-specific characteristics or comorbidities resulting in volume incompliance. The second hit is a blood transfusion leading to circulatory overload and is determined by different aspects of the transfusion process and the transfusion product.

4. First hit

4.1. Recipient age

Patients 60 years of age or older appear to be at higher risk of TACO and cohort studies seem to support this claim [20–22]. In a review of 626 reported TACO cases the great majority (64%) were in patients 70 years of age or older, and only 2.4% were in patients younger than 18 years-of-age [23]. In 4070 adult patients transfused during non-cardiac surgery, the incidence of TACO increased steadily with age, from 2.1% in patients younger than 50, to 7.4% in those 80 years or older [2]. A cohort study of 339 adult patients with suspected transfusion reactions showed patients with TACO were statistically more likely to be older than those with other types of transfusion reactions (68 vs 58, respectively, $p > 0.05$) [24]. Conversely, two studies in critically ill patients did not show a significant age based difference [25,26]. An important limitation of these cohort studies is that enrolled patients may not have all faced the same risk exposure. Older patients may be more prone to develop TACO because they are transfused more often, receive larger volumes [24,27]. Alternatively, clinicians may adopt a more cautious transfusion practices (ie., slower infusion rates) with their older patients or be more alert in reporting complications in these at risk patients. In studies that attempt to correct for different exposures, the significance of increasing age as a risk factor for TACO becomes less clear. For example in a case-control study attempting to correct for transfusion intensity.

While the age of TACO patients was slightly higher, age ceased to be a significant predictor after correcting for covariates [13]. Similar limitations apply to studies that suggest an increased risk of TACO in young children, specifically those <3 years of age. In the UK's 2019 Serious Hazards of Transfusion report only 4 of 133 (3%) reported cases occurred in patients younger than 18. However, all cases were in children 3 years of age or less, suggesting that TACO occurs more often in the very young. Whether this reflects a pathophysiologic susceptibility to this type of transfusion reaction, or simply a greater risk exposure to transfusion is unclear.

4.2. Cardiac dysfunction

Cardiac dysfunction plays a major role in the pathophysiology of TACO. While cardiac dysfunction often serves as the first hit, this risk-factor contributes to TACO in two ways. First the heart is unable to deal with acute increases in volume, overwhelming the left-ventricle (LV) and resulting in increased left ventricular end-diastolic pressure and pulmonary congestion. Second, heart failure is associated with decreased renal perfusion and fluid retention, predisposing patients to hypervolemia [28]. Clinical manifestations include dyspnea, pitting edema, orthopnea and nocturia.

Previous studies describe cardiac risk factors of TACO to include coronary artery disease, LV-dysfunction as well as a history of heart failure. All conditions are associated with, but not necessarily the result of, a decreased systolic LV-function. In patients with an already compromised LV-function, acute volume loading results in stretching of the cardiomyocytes past the peak of the Frank-Starling curve [29]. Overdistention of the LV beyond this point will further decrease LV-function, and while the preload to the LV remains increased, the volume leaving the LV does not rise proportionally. Blood backs up and pools in the left-atrium resulting in left-atrial hypertension and the pressure is conferred to the pulmonary capillary bed, increasing hydrostatic pulmonary capillary pressure.

Heart failure with preserved ejection fraction, also known as diastolic dysfunction, can also result in increased filling pressures and thereby predispose to TACO. In a study of 100 TACO cases, diastolic dysfunction was in fact twice as prevalent as a decreased LVEF [1]. Diastolic dysfunction is characterized by increased LV-stiffness, which can be due to acute myocardial ischemia, fibrosis, chronic hypertension, and aging. During transfusion, when there is an acute increase in preload, the ventricle in these patients has a low compliance and will not expand. The increased preload results in left atrial hypertension and increased hydrostatic pulmonary capillary pressure.

There are numerous other cardiac pathologies that will predispose to TACO including valvular heart disease, but these fall beyond the scope of this review. In summary, both LVEF as well as diastolic function are important in assessing a patient's tolerance to acute changes in volume.

4.3. Myocardial performance following transfusion

Transfusion of RBCs may result in a decreased myocardial function. One explanation for this could be changes in blood viscosity following transfusion. Increased blood viscosity is one reason why specifically RBC transfusion does not directly increase cardiac output. Even more so, in patients with a decreased LVEF transfusion and thereby an increase in blood viscosity can reduce cardiac function further, possibly contributing to TACO [30]. The REALITY randomized trial supports this hypothesis, showing a possible harm from liberal transfusion, as compared to restrictive transfusion, in patients with a myocardial infarct [31]. Apart from blood viscosity, transfusion can also affect oxygen delivery to the tissues, which can impair myocardial performance. While the goal of transfusion is to increase the delivery of oxygen (DO_2), transfusion of stored RBC's can limit oxygen delivery capacity. Storage of RBCs results in decreased levels of 2,3-DPG thereby left-shifting the oxygen-hemoglobin dissociation curve; this increases oxygen affinity of hemoglobin and reduces off-loading in the tissues [32]. In a systematic review there was no increase in oxygen consumption in tissues (VO_2) in the majority of studies, even though DO_2 increased [33]. This potentially indicates that even though transfused RBCs carry oxygen and increase DO_2, they are unable to off-load oxygen in the tissues. In the case of myocardium, where oxygen utilization is already the highest in the body during rest (O_2-extraction ratio: 70%) a transfusion effectively dilutes functional RBCs, limiting its oxygen supply. To date one model in rats shows that fresh blood significantly reduces the size of an induced myocardial infarction [34].

4.4. Renal disease

Renal dysfunction is another major risk factor for developing TACO [1,26,35], verified in a TACO animal model where acute kidney injury was the first hit in the development of TACO [19]. Risk factors for TACO identified in clinical studies include a history of chronic kidney disease, acute kidney injury and patients requiring kidney replacement therapy. Odds ratios from a case-control study showed that the risk of development of TACO was even higher in patients with chronic renal failure, in whom the odds ratio was 27 (CI 5.4–143), than in patients with a history of congestive heart failure with an odds ratio of 6.6 (CI 2.1–21) [15]. Renal disease leads to a combination of renin-angiotensin-aldosterone-system activation and an impaired diuresis, impeding hemodynamic compensatory mechanisms to compensate for acute changes in circulating volume. Moreover, the impaired diuresis makes patients prone to develop hypervolemia prior to transfusion. However, another explanation for this phenomenon in observational studies could be that renal disease is strongly associated with decreased levels of erythropoietin (EPO) and anemia, therefore patients are more prone to receive RBC transfusions and develop TACO.

4.5. Fluid balance

A pre-transfusion positive fluid balance is an often-cited risk-factor for TACO [13,25,37]. A positive fluid balance is part of the diagnostic criteria for TACO, however it is further undefined and an indirect measure that speaks to the pathophysiology. A positive fluid balance in hospital is likely used as a surrogate marker for the patient's pre-transfusion state of volume overload. Logically patients that have sufficient or surplus intravascular volume will be predisposed to increased hydrostatic pressure from a volume challenge and therefore will be more susceptible to develop TACO.

5. Second hit – pathophysiological mechanisms potentially leading in TACO

There are several hypothesized pathways in which transfusion, as opposed to conventional fluids, can result in circulatory overload (Fig. 2). These include transfusion product-specific factors including biochemical and inflammatory mechanisms as well as endothelial and vascular interaction with transfusion products [38,39].

5.1. Transfusion volume and speed

Correlations between transfused volume and pulmonary vascular pressures have been seen in previous studies. An animal study showed an association between the amount of volume transfused and left ventricular end-diastolic pressure [40]. This effect was also seen in human studies in participants with chronic severe anemia. There was a linear relation between transfused volume and pulmonary arterial wedge pressure [41]. The effects were mainly caused by the amount of volume transfused and less by the infusion speed [40,42]. There have been numerous studies investigating a restrictive versus liberal transfusion strategy, Restrictive transfusion strategies decrease the transfused volume in patients and have shown to reduce mortality and in some studies

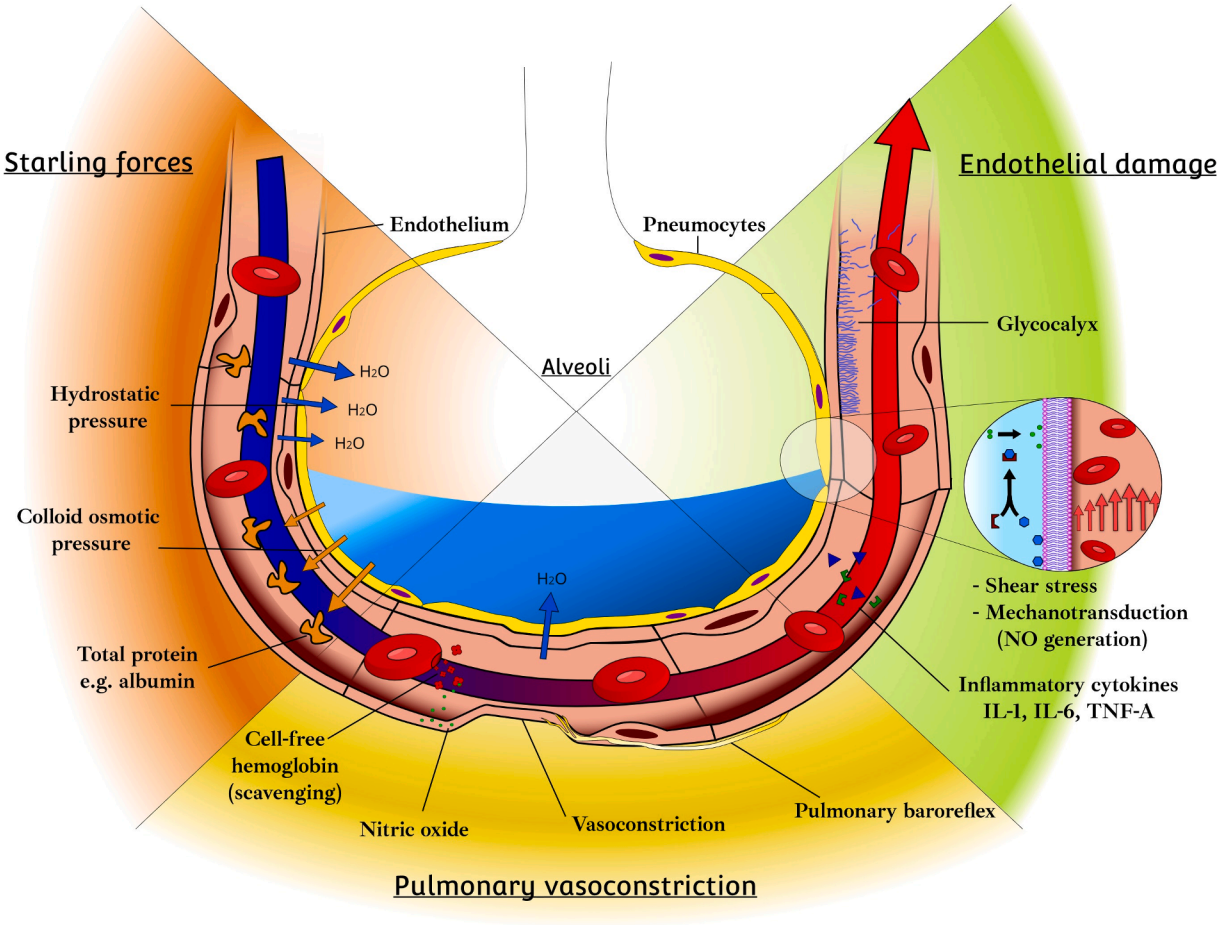

Fig. 2. Pathophysiologic pathways potentially involved in TACO.
There are multiple potential mechanisms involved in TACO and they can be divided into three groups, based on their mechanism of pulmonary edema formation. Starling forces including hydrostatic and colloid osmotic pressure force fluid either into or out of the vessel, an imbalance in these forces leads to edema formation. Pulmonary vasoconstriction can be caused by nitric oxide scavenging or the pulmonary baroreflex, it increases intravascular pressure and thereby forces fluid into the extravascular and intra-alveolar space. Endothelial damage is a result of inflammatory processes, shear stress, mechanotransduction and glycocalyx shedding, it facilitates fluid flux and hence promotes pulmonary edema.

TACO [43]. The REALITY trial did not show a significant benefit from a restrictive transfusion strategy on a composite outcome of cardiovascular events. This study did not look specifically at TACO as one of their outcomes [31]. In children results are conflicting, where some studies show no difference in mortality or adverse events with liberal and restrictive transfusion strategies and other studies show a beneficial effect of transfusion restriction on mortality and acute lung injury [45,46]. Another study showed a decrease in pulmonary edema in a pediatric intensive care population, there was no difference in mortality in this non-inferiority study [47]. Concluding a reduction of transfused volume prevents TACO in some cases. However TACO was also reported after transfusion of a small volume through a single unit transfusion, implying other mechanisms apart from volume overload are at play in TACO's pathophysiology [6].

5.2. Colloid osmotic pressure

Following the Frank-Starling principle, fluid flux is the net effect of intra versus extravascular differences in hydrostatic pressure and colloid osmotic pressure (COP). This implies that COP of transfusion products could also be (partly) responsible for the development of TACO as it could cause fluid from the tissue interstitium to be recruited to the intravascular space, contributing to a state of circulatory overload. However when COP of different blood products was measured in vitro, all of the conventional blood products appeared to be hypo-oncotic compared to human plasma and therefore cannot increase the COP of intravascular circulating volume [48].

5.3. Endothelial damage

5.3.1. Glycocalyx

Forces behind fluid flux are actually more complicated than the classical Frank-Starling principle and the model was revised to account for the role of the endothelial glycocalyx (EG) [49]. The EG is a layer of glycoproteins and glycosaminoglycans lining the luminal side of the endothelium, which form a barrier and regulate fluid and solute exchange across vessel walls [49,50]. The revised Frank-Starling model sets a “no absorption rule”, which means that intravascular COP does somewhat prevent the efflux of fluid driven by hydrostatic pressure, but it does not reverse fluid flux [4].

A disrupted endothelial barrier integrity can contribute to the formation of pulmonary edema [49]. Mechanisms directly damaging the EG include amongst others rapid intravenous infusion, as well as inflammation during sepsis or severe inflammatory response syndrome and cardiac surgery (including cardiopulmonary bypass) [51–53]. Allogenic blood products contain inflammatory components, which can interact with the EG. A small study in septic patients showed that transfusion of non-leukodepleted compared to leukodepleted RBC's resulted in higher levels of syndecan-1, a breakdown protein of the EG [54].

5.3.2. Mechanotransduction

Transfusion could indirectly affect the EG and endothelium by mechanotransduction. Non-linear increases in endothelial permeability following a rise in hydrostatic pressure can be attributed to this phenomenon [50,55]. As blood flow increases in the pulmonary capillary vessels following transfusion, shear stress on the endothelium increases. Shear stress is transferred by the EG to endothelial cells by mechanotransduction [50]. While shear stress in a physiological amount can aid the integrity of the endothelial cell layer by enhancing cell-matrix attachment, high shear forces can increase endothelial permeability through activation of cell signaling pathways [56,57].

Mechanotransduction through the EG is an essential component in this cascade. Experiments show that pressure-induced pulmonary vascular leakage decreases if the EG in the pulmonary vasculature is disabled [55]. Additionally, mechanotransduction activates endothelial nitric oxide synthase (eNOS) and release of nitric oxide (NO) leading to vasodilation. However, eNOS and NO also enhance local vascular permeability and inflammation, promoting leukocyte transmigration and more inflammation [50,58,59]. To date however there is no research concerning the role of the endothelial glycocalyx and mechanotransduction in the pathophysiology of TACO.

5.3.3. Inflammatory processes

Whether inflammatory processes play a role in the TACO pathophysiology is a topic of much debate. Originally TACO was thought to be a purely hydrostatic phenomenon, whereas TRALI at the other end of the spectrum is an inflammatory process resulting in permeability edema. Whether these two transfusion complications are entirely distinct from one another, however, is questionable and differentiation of TRALI and TACO in clinical practice can be challenging. Evidence is accumulating that inflammatory processes do in fact contribute to TACO [60]. Firstly a decrease in TACO incidence of 49% was seen in an observational cohort after implementation of universal leukoreduction of blood products [61]. A similar trend in TACO incidence was seen in an international hemovigilance cohort comparing pathogen inactivated plasma with untreated plasma products [27]. One could argue that the before-after design of these studies confounded the results, however, as transfusion practices have improved over time, including more restrictive transfusion indications and implementation of single-unit transfusion policies [62].

Fever is also a frequent occurrence in TACO, being present in up to one third of patients, which is a significantly higher rate than what is seen in patients with an uncomplicated transfusion or an allergic transfusion reaction [24,63]. While fever is associated with TACO, there is little knowledge of which inflammatory pathways are responsible. In a study examining cytokine levels in patients with different pulmonary transfusion reactions, elevated post-transfusion levels of the proinflammatory cytokine interleukin (IL)-6, but not IL-8 was seen in TACO patients compared to a control group [64]. In TRALI patients IL-6 and IL-8 were elevated both pre- and post-transfusion. Furthermore, there was an elevation in pre- and post-transfusion levels of the anti-inflammatory cytokine IL-10 in TACO patients, compared to TRALI and control patients. A possible explanation could be that IL-10 levels increase because of chronic inflammatory diseases like heart or renal disease, which are often associated with TACO [64]. Conversely another study showed no difference in cytokine profiles of transfusion products received by TACO patients and transfused controls [65]. Further studies will be necessary to clarify if and which inflammatory mechanisms could contribute to TACO pathophysiology.

5.4. Storage lesion

Another factor that could contribute to developing TACO is the storage lesion. When cellular blood products are stored, cells start to degrade over time, due to continuing metabolism. Nutrients are used, the pH decreases, platelets and RBCs degrade releasing microparticles and, in the case of RBCs, hemolysis increases cell-free hemoglobin. Hemolysis is further aggravated by irradiating blood products for immunocompromised patients, a common recipient population. Hemolysis rates are also modified by donor characteristics for unclear biological reasons [66,67], which may result in some products carrying an intrinsically higher risk of TACO.

Effects of the storage lesion in experimental studies appear to be present [68–70]. However, to date large randomized trials have not shown an overall benefit of fresh RBC products over standard transfusion products, which was recently confirmed in a Cochrane review [71–73]. Moreover for TACO in particular there was no association with storage duration of platelet products [74]. Fresh blood was stored for approximately 3–6 days in these studies, while older products were stored for 22–26 days on average in the randomized clinical trials. It is possible the effects of storage lesion are more pronounced when products are transfused nearer to the end of their allowed storage period, which is up to 42 days in many jurisdictions. It is also the case that these large studies have not specifically investigated patients at-risk for TACO.

5.4.1. Cell-free hemoglobin

Cell-free hemoglobin is released when RBCs hemolyze either during storage, or intravascularly following transfusion. Cell-free hemoglobin reacts with NO to form methemoglobin, disrupting NO's potent vasodilating function. Decreased NO-levels can in turn cause vasoconstriction. A study in rats showed supernatants of RBC products stored 39 days resulted in increased blood pressure and increased systemic vascular resistance, compared to rats who received supernatant from a 4 day old RBCs [68]. Autologous transfusion of stored RBCs products in healthy volunteers resulted in decreased blood flow, impaired vasodilatory capacity and increased pulmonary artery pressure when compared with transfusion of fresh RBC products [69,70]. Pulmonary artery pressure decreased when volunteers would simultaneously inhale NO, demonstrating a possible therapeutic to prevent TACO that has not been previously investigated [70].

5.5. Pulmonary vascular system

The pulmonary vasculature is very distinct from its systemic counterpart in how it reacts to stimuli, for example the phenomenon of hypoxic pulmonary vasoconstriction. Potential contributory pathways in developing TACO include the pulmonary baroreceptor reflex, pulmonary blood volume and pulmonary vasoconstriction.

The pulmonary vasculature contains baroreceptors primarily located proximal in the pulmonary artery [70]. The function of these baroreceptors is incompletely understood and what little is known is based on animal studies. A study in dogs has shown that increasing the mean pulmonary artery pressure leads to an increased systolic blood pressure, potentially explaining hypertension often seen in TACO [75].

Whether TACO occurs due to an increase in total pulmonary blood volume is unknown. There is a possibility for blood products to pool in the pulmonary system through numerous mechanisms. Both a decreased left-ventricular ejection fraction as well as the viscosity of blood products (primarily RBC's), both discussed elsewhere, can result in left-sided heart failure and an increase in pulmonary blood volume. Very little is known about pulmonary blood volume following transfusion and quantitative methods including transpulmonary thermodilution are not precise enough to accurately track the effects of a transfusion of 300 mL. Ex-vivo animal lungs studies show that hypoxic capillary vasoconstriction does not decrease pulmonary blood volume, since this is controlled by arterial vasoconstriction [76].

6. Potential mitigation strategies and ongoing research

Despite TACO being the leading cause of death according to hemovigilance programs in the United States, the United Kingdom, and Canada, very few randomized trials have been performed to advance our

understanding of the efficacy of mitigation strategies. The unique rheology and induced endothelial disturbances by specific blood products are yet to be elucidated. We summarized mitigation strategies currently used or researched (Table 3). Evidently more extensive research in TACO pathophysiology and mitigation strategies is necessary.

6.1. Preclinical research

Whereas several animal models for TRALI have existed for decades now [77], the first animal model for TACO using Lewis rats was not described until 2019 [19]. In this model, the necessity of a two-hit process was observed. This model represents an important preliminary system for future experimental questions that are not ethically resolvable in humans, such as factors culminating in fatal TACO, the role of inflammatory processes in susceptibility (Fig. 3), preventative diuretic dose-finding and the reversibility of varying severities of induced TACO.

6.2. Optimizing transfusion practices

Current mitigation strategies primarily focus on improving clinical transfusion practices through encouragement of slower infusion rates, pre-transfusion diuretics, and computerized physician order decision support to detect at risk patients [78]. While a restrictive transfusion strategy that reduces transfused volume by half would logically suggest a major reduction in the incidence of TACO, systematic reviews of liberal and restrictive strategies have been conflicting [79–81]. In addition, a pilot randomized controlled trial in patients with acute myocardial infarction, potentially the population most acutely at-risk for TACO, failed to find a difference in the rates of heart failure when a transfusion threshold of 80 g/L vs. 100 g/L was applied [31].

The pilot double-blinded RCT, Transfusion-Associated Circulatory Overload: Best Eliminated With Lasix? (TACO BEL, NCT02802696), studied the feasibility of furosemide 20 mg IV, as compared to placebo administration, within an hour of RBC administration [82]. In addition, this pilot trial was followed by audits of 10 Canadian partner sites collectively transfusing approximately 12,000 RBC annually to determine recruitment rates required for a multicenter trial [83]. A definitive trial with a sample size of 3000 (to assess for a $\geq$ 50% reduction in the observed 3% incidence of TACO) can be completed within a year in this network if background assumptions remain stable.

Table 3
Possible mitigation strategies.

Process / Mechanism	Product	Administration	Patient
General			• Pre-transfusion risk assessment • Digital system to capture cases
Hydrostatic pressure/ volume overload	• Volume-reduced products	• Restrictive transfusion practices • Single-unit transfusions • Slow infusion rates	• Pre/post-transfusion diuretics • Peri-transfusion fluid management
Endothelial damage/ glycocalyx injury		• Slow infusion rates	
Inflammation	• Leukoreduced products • Washing of products		
Storage lesion	• Washing of products	• Limit storage duration	• Inhaled Nitric oxide

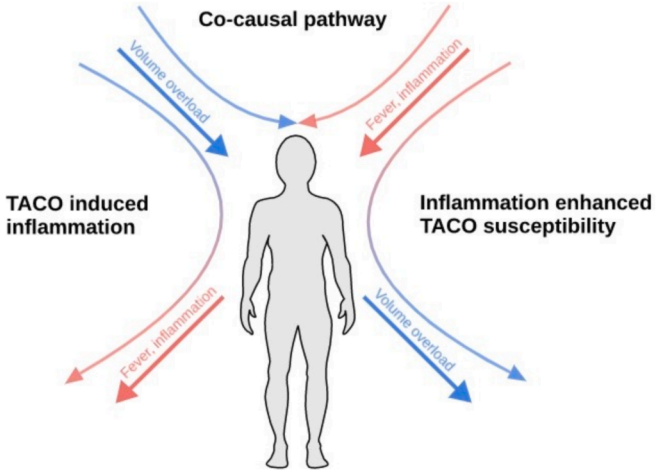

Fig. 3. The relationship between TACO and inflammation.
TACO is defined as hydrostatic pulmonary edema, however up to a third of patients also develops fever. Whether inflammatory processes contribute to TACO or whether they are a result of TACO is unclear.

6.3. Recognition and prediction of cases

Thorough investigation of cases and reporting of TACO to blood banks are rarely performed. A study in children undergoing non-cardiac surgery found a rate of TACO similar to adults (3.4%); notably, none of the cases were reported to the blood transfusion service [17] The use of digital capture of cases may improve reporting and allow deployment of better mitigation strategies in large multicenter studies [2]. The use of physician pre-transfusion checklists to increase adoption of risk mitigation strategies was shown in a single center study to be effective, although was not powered to look for a reduction in TACO [84]. Recognizing and reporting TACO following consistent definitions is essential to be able to mitigate TACO and improve research. A retrospective study shows TACO is accompanied by changes in vital signs. Monitoring these vital signs during and following transfusion could therefore aid early recognition of TACO [24].

The Transfusion Associated Dyspnea: Prospective Observation & Laboratory Assessment (TADPOL) study (NCT04267029) applies an expanded diagnostic clinical and laboratory investigative approach to cardiopulmonary transfusion reactions, with febrile transfusion reactions as a pragmatic comparator. Adults at four academic centers in Toronto, Canada are assessed within 24 h of their disturbance, with the aim of enhancing certainty in event reporting, as cardiopulmonary reactions are typically more challenging to conclude than febrile reactions [85,86]. Secondary goals include correlative biomarker mapping for cases fulfilling the revised definitions of TACO and TRALI [9].

6.4. NT-proBNP as a predictor for TACO

Elevated levels of serum natriuretic peptides are emerging as another option for the pre-transfusion detection of myocardial strain and can also indicate renal dysfunction [26]. The utility of pre-transfusion NT-proBNP to risk stratify for TACO was confirmed in a case-control study of patients experiencing pulmonary transfusion reactions, in which it was observed that patients who developed TACO had higher baseline levels than control patients transfused without pulmonary edema. A particularly high risk for developing TACO was observed if NT-proBNP levels exceeded 1000 pg/mL [87]. It may be concluded that not only is pre-transfusion NT-proBNP a useful predictor of TACO risk, but it may serve as a convenient screen for both cardiac or renal dysfunction.

6.5. Optimizing transfusion products

The use of volume reduction or split products to mitigate TACO in high-risk patients has not been studied for red blood cell transfusions. However in platelet transfusions, a reduction in all transfusion reactions was seen when half-dose units were compared to transfusion of full units [88]. The transition to platelet additive solutions on the other hand has had no impact on the incidence of TACO [74,89]. The transition from plasma to prothrombin complex concentrates was associated with a reduction in the risk of post-infusion congestive heart failure [90,91]. Transfusion of male-only plasma (vs. mixed donor plasma) was also associated with a reduction in pulmonary dysfunction (including TACO) in a small case-control study [92]. No improvement in TACO rates was observed, however, in a systematic review of 48 studies of pathogen reduction technology [93].

Washing red blood cells for patients undergoing cardiac surgery has shown conflicting results in controlled studies in reducing post-transfusion inflammatory markers [94,95]. The randomized controlled trial Washing of Allogeneic Red blood cells for the Prevention of transfusion-related Respiratory Complications (WAR-PRC) (NCT02094118) has completed the enrollment of 171 patients by standard-of-care RBC versus point-of-care washed RBC transfusion, with study results pending [96].

7. Summary and future directions

TACO is seen as a two-hit model in which the first hit is pre-existing volume intolerance of the patient and the second hit is the transfusion itself. Recent studies suggest that, in addition to the hydrostatic forces, pathways involving mechanotransduction, endothelial damage, and inflammatory properties of the transfusion product may also play a role. In the past decade animal models of TACO have been developed which may help to further understand the pathophysiology of this life threatening syndrome and set the first step in designing preventive and therapeutic strategies.

Adequately powered RCTs of mitigants and treatments that draw from existing resources may yield the most practical and immediately deployable options, as the universal implementation of validated product modifications may be a slower, costlier, more complex, and less equitable process in the advance of blood transfusion services around the world.

Practice points

- TACO is a transfusion complication caused by pulmonary edema, presenting with symptoms ranging from dyspnea to respiratory failure.
- TACO follows a two-hit principle. The first hit, patient's comorbidities, cause volume incompliance, followed by the second hit being the transfusion
- Cardiovascular disease, renal impairment and extremes of age are risk factors for TACO
- Current preventative measures include a restrictive transfusion strategy, slower infusion rates and pre-transfusion furosemide

Research agenda

- More knowledge on the pathophysiology of TACO is essential to guide research for more extensive preventative or therapeutic options e.g. the role of the glycocalyx and mechanotransduction or inflammatory pathways involved
- Newly developed animal models should be used to research pathophysiological pathways and new mitigations strategies
- Currently used and investigated mitigation strategies (pre-transfusion diuretics, washing of blood products) should be researched in adequately powered clinical trials, to be able to implement them in general clinical practice

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Declaration of competing interest

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