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Acute Kidney Injury Following Resuscitative Endovascular Balloon Occlusion of the Aorta: A Systematic Review

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Background: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is an emergent technology for the treatment of non-compressible torso hemorrhage (NCTH). While aortic occlusion (AO) above the site of hemorrhage provides hemostasis and time for surgical intervention, ischemia-reperfusion injury to the kidneys is a known complication.
We aimed to report the incidence and factors associated with acute kidney injury (AKI) following AO in patients with NCTH or in similar porcine models.
Methods: We searched Pubmed (MEDLINE), Embase, Scopus, and ProQuest Dissertations & Theses from inception to July 2017. We included original studies of trauma patients with NCTH treated with REBOA, or similar porcine studies that included renal parameters, excluding case reports and case series. After duplicate removal, full texts of studies retrieved via the search strategy were evaluated by two authors. Renal parameters (e.g., creatinine concentration, urine output, histopathology) were extracted. Quality of the evidence and risk of bias were assessed.
Results: Twelve out of 2,100 records were included (three trauma patients, nine porcine studies). While one out of three human reports described AO in Zone 1, all swine publications reported Zone 1. All human studies reported renal damage. There were nonetheless inconsistencies in definitions used. Evidence of AKI was reported in three out of nine swine studies.
Conclusions: Consistent reporting of AKI incidence is lacking from human clinical studies of AO in NCTH trauma patients. While comorbidities in trauma patients may contribute to AKI, animal models support the association between AO and AKI. As REBOA is growing in popularity as a therapy for NCTH, further studies determining factors associated with the AKI are needed.

Keywords: *Intra-Aortic Balloon; Trauma; Hemorrhagic Shock; Non-Compressible Torso Hemorrhage; Resuscitation*

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INTRODUCTION

Hemorrhage is the leading cause of preventable deaths in combat theaters [1,2] and is responsible for 33–56% of prehospital deaths and over 80% of deaths that occur in the operating room [3]. Resuscitative endovascular balloon occlusion of the aorta (REBOA) has gained in popularity for the treatment of non-compressible torso hemorrhage (NCTH) owing to its potential benefits over resuscitative thoracotomy (RT) [4–7]. Complete aortic occlusion, with either REBOA or RT, results in profound distal ischemia, which in addition to the original insult further increases the risk of acute kidney injury (AKI) in trauma patients. To minimize ischemia-reperfusion injury, the concept of REBOA has evolved from complete to partial REBOA (pREBOA) to permit a small amount of distal flow to mitigate ischemia while maintaining adequate proximal blood pressure. Little is known about the renal consequences of aortic flow control in trauma patients with NCTH. Specifically, the effects of REBOA and pREBOA on AKI incidence or severity remains unknown.

AKI is a serious sequela in trauma patients. The incidence of AKI range from <0.1% up to 34% and post-traumatic AKI is associated with longer ICU and hospital stays [8–10]. Additionally, after adjusted analysis, both civilian and military studies demonstrate increased mortality in trauma patients who develop AKI with mortality rates ranging from 25 to 34% and acute mortality rates ranging from 18 to 22% [9,10].

The main objective of this systematic review was to report the incidence of AKI in trauma patients with NCTH treated with REBOA or pREBOA. Additionally, we aimed to analyze data from included studies to correlate localization and duration of aortic occlusion with AKI incidence. Our secondary objective was to report details of REBOA- or pREBOA-associated AKI in porcine trauma studies as a significant fraction of the REBOA literature has been based on this species.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations to conduct the search, select the articles, grade the evidence, and report the results [11]. PRISMA recommendations also satisfied guidelines for the reporting of the systematic review of animal data [12]. A health and life sciences librarian was consulted for process validation.

Protocol and Registration

We selected studies using human subjects or pigs. The trauma patients search was registered with the Prospero database (CRD42017067755).

Eligibility Criteria

The patient–exposure–outcome (PEO) question was: P – in trauma patients, E – treated with REBOA or pREBOA, O – what is the incidence of AKI? We had a similar PEO question for porcine studies of traumatic hemorrhagic shock.

Information Sources

We searched Pubmed (MEDLINE), Embase, and Scopus from inception to July 2017. We also screened the ProQuest Dissertations & Theses Database and proceedings from the American Association for the Surgery of Trauma meetings (2004–2016). Reference lists were evaluated for additional articles. Authors of relevant reports were contacted to determine if pertinent unreported data had been gathered.

Search Strategy

The Pubmed (MEDLINE) search strategy was developed and adapted for the other databases with a librarian (Figure 1).

Study Selection Process

Title and abstracts were reviewed. Studies of non-target species (e.g., dogs, or mice) or in a language other than English, Spanish, or French were excluded. We excluded publications non-related to trauma patients (e.g., aortic aneurysm, obstetric patients), case reports, case-series (with ≤5 patients enrolled), reviews, and letters to the editor (Reference lists of those publications were still screened). When available, full-text was then assessed for renal function information: serum creatinine and potassium concentrations, urine output, renal replacement therapy requirement, histopathologic evaluation of renal tissue, and other biomarkers (e.g., neutrophil-gelatinase associated lipocalin, NGAL).

Data Collection Process

Quality of the evidence and risk of bias were evaluated by two authors (GLH, PAC). In case of disagreement, a third author (AMJ) was consulted.

Data Items

Whenever available for human subjects, we recorded population age (adult versus pediatric), introducer sheath size, balloon catheter size, study type (e.g., retrospective study, randomized control trial), comparisons with other resuscitative procedures (i.e., RT), occlusion Zone (Zone 1, proximal to the coeliac artery; Zone 2, between the coeliac and the renal artery; Zone 3, below the renal artery), complete and partial aortic occlusion time.

((((((((((failure[All Fields]) OR injury[All Fields])) AND ((kidney[All Fields]) OR renal[All Fields]))) OR (("acute kidney injury"[MeSH Terms] OR "acute kidney injury"[All Fields] OR "acute renal failure"[All Fields]))))) AND ((((((((((resuscitative[All Fields] OR "resuscitation"[MeSH Terms] OR resuscitation[All Fields])))) OR ((haemorrhage[All Fields] OR "hemorrhage"[MeSH Terms] OR hemorrhage[All Fields])))) OR (("Non-compressible torso hemorrhage"[All Fields] OR "Noncompressible torso hemorrhage"[All Fields] OR "Noncompressible truncal hemorrhage"[All Fields])))) OR trauma[All Fields])) AND ((endovascular[All Fields]) OR (occlusion[All Fields] OR "balloon occlusion"[MeSH Terms]))) AND ("aorta"[MeSH Terms] OR aorta[All Fields] OR aortic[All Fields])))) OR ((REBOA) OR "resuscitative endovascular balloon occlusion of the aorta")

Figure 1 Pubmed (Medline) search strategy.

Table 1 Kidney Disease Improving Global Outcomes (KDIGO) criteria based for the diagnosis of acute kidney injury [16].

Stage	*Serum Creatinine*	*Urine Output*
1	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 µmol/L) increase	<0.5 mL/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5 mL/kg/hour for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m^2	<0.3 mL/kg/hour for ≥24 hours OR Anuria for ≥12 hours

For porcine studies, we also recorded whether tissue trauma (beyond surgical preparation, e.g., liver or spleen laceration) was induced in addition to hemorrhagic shock.

Outcomes and Prioritization

The main outcome was AKI incidence based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 1) [13].

Risk of Bias in Individual Studies

For trauma patient and porcine studies, the risk of bias was rated with the Modified Cochrane Risk of Bias Tool for randomized controlled trials [14] and the SYRCLE's risk of bias tool, respectively [15].

Metabias

Most reports originate from centers with extensive research and clinical experience with the procedure, which may alter publication bias.

Confidence in Cumulative Evidence

For trauma patients, the quality of the evidence was graded with the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [16]. Composite forms were used for porcine experiments.

Summary Measures and Synthesis of Results

Preliminary literature searches retrieved a limited number of studies. We did not aim to report statistical inference (meta-analysis); rather, we reported descriptive statistics.

RESULTS

Study Selection

The search strategy identified 2017 records; 83 additional records were found from non-database resources (Figure 2). Three full-text manuscripts were included for final evaluation of trauma patients (Table 2) and nine were analyzed from porcine experiments (Table 3). Additionally, three abstracts were evaluated; one in trauma patients and two in porcine models.

All three reports of trauma patients were retrospective studies. One of the three reports described Zone 1 REBOA [17]. Occlusion in another study was reported in Zones 1, 2, and 3 in 79%, 2%, and 19% of patients, respectively [7]. The last study did not specifically report the occlusion site [18]. While there were inconsistencies in the definitions used, all three studies in humans reported some degree of AKI. The use of dialysis was reported in 4.3% of patients treated with REBOA and 2.9% of patients treated with open aortic occlusion, a difference that was not statistically significant and there was no data reporting the duration of occlusion resulting

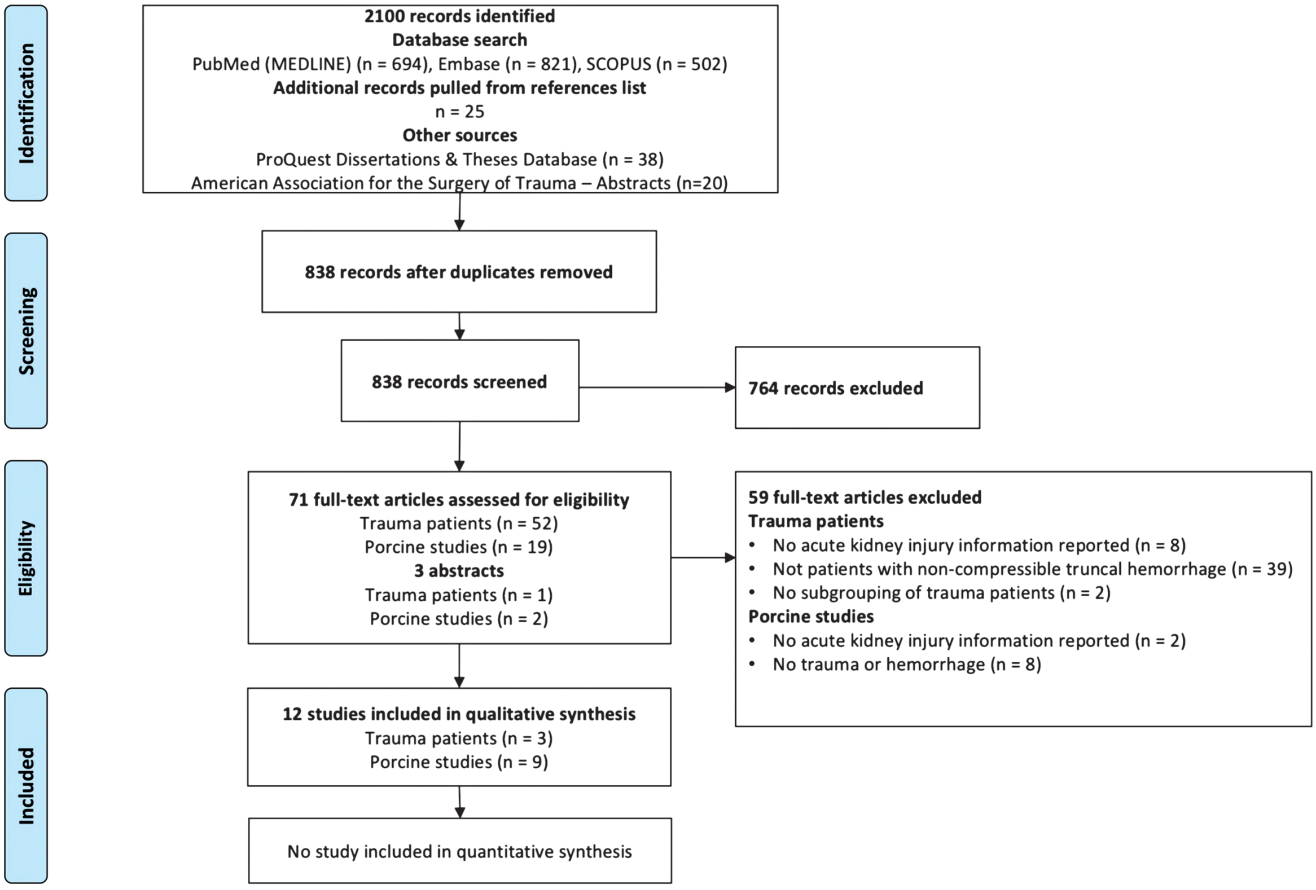

Figure 2 Systematic review process.

in dialysis dependence [7]. In another report [17], 9/24 patients had evidence of AKI according to the Risk Injury Failure Loss End-stage (RIFLE) criteria; 5/9 of those patients were classified in the failure category, but again there was no correlation between duration of occlusion and incidence of AKI. In the third study [18], evidence of AKI was reported in one patient based on an elevation in serum potassium and creatinine concentrations following 37 minutes of partial occlusion, which resolved following fluid therapy. No baseline serum creatinine concentration was reported for this patient. Quality of the evidence was poor in 2/3 reports [17,18] and fair in 1/3 report [7]. The risk of bias was rated as high in all three reports.

One report in abstract form was identified in trauma patients [19]. In this cohort, 26/43 patients were successfully resuscitated with either intermittent REBOA or pREBOA (11/26 patients). There was no difference in the incidence of hyperkalemia, which could be used as a partial proxy for renal injury, between the two groups [4/15 (27%) versus 4/11 (36%), respectively].

Reporting of AKI was more consistent in swine studies with nine studies meeting our inclusion criteria. All publications in swine reported Zone 1 REBOA. Definitive evidence of AKI was reported in 3/9 studies [6,20,21]. Park et al. as well as Russo et al. reported AKI from histopathological data. Morrison et al. reported AKI based on an increase in serum creatinine concentration. In the remaining six studies, two studies reported elevation in serum potassium concentrations [4,5]. One study reported no change in serum creatinine concentration [22]. One study did not report creatinine or potassium concentrations [23]. One study reported a urine output of 0.5 mL/kg/hour in an extracorporeal model of pREBOA [24]. Another study reported improved urine output in pigs undergoing a model of pREBOA compared to REBOA [25]. Histopathologic evaluation of renal tissue was reported in 5/9 studies. Park et al. demonstrated worse renal injury with 60 minutes of occlusion when compared to 30 minutes of occlusion [20]. Russo et al. reported a higher incidence of acute tubular necrosis in pigs treated with pREBOA when compared to animals treated with REBOA [21]. The minimum aortic occlusion time associated with AKI was 30 minutes [20], although similar occlusion times were not associated with renal damage in a separate study [22]. Quality of the evidence was graded as good, fair, and poor in 6/9, 2/9, and 1/9 reports. The risk of bias was low in all porcine studies.

Two reports in abstract form were identified in swine studies [26,27]. One report demonstrated lower renal thiobarbituric acid reactive substances, a by-product of lipid peroxidation, levels in pigs treated with REBOA

Table 2 Data summary for trauma patients with non-compressible truncal hemorrhage.

Authors Year	*Population*	*Number of Patients*	*Introducer Sheath Size (Fr)*	*Aortic Occlusion Catheter Size (Fr)*	*Study Type*	*REBOA compared with*	*Aortic Zone Occluded*	*Complete Occlusion Time (minutes)*	*Partial Occlusion Time (minutes)*	*AKI Information*	*QOE*	*ROB*
Saito 2015	Adults	24	10	NR	Retrospective	NA	1 initially	S: 21 NS: 35	NA	S: 9/14 patients (RIFLE criteria) R (KDIGO stage 1): 3 I (KDIGO stage 2): 1 F (KDIGO stage 3): 5	Poor	High
Irahara 2015	Adults	14	10	NR	Retrospective	NA	NR	S: 46 NS: 224	NR	Rise in [K^+] and [Creatinine] in 1 patient	Poor	High
Dubose 2016	Adults	114	NR	4-18	Retrospective	Open AO	1 (79%) 2 (2%) 3 (19%)	EAO: 20 AO: 25	NA	Dialysis requirement (KDIGO stage 3) EAO: 4.3% AO: 2.9%	Fair	High

AKI, acute kidney injury; AO, aortic occlusion; EAO, endovascular aortic occlusion; NA, not applicable; NR, not reported; NS, non-survivors; QOE, quality of the evidence; REBOA, resuscitative endovascular balloon occlusion of the aorta; RIFLE, risk, injury, failure, loss, end-stage renal failure; ROB, risk of bias; S, survivors.

after 90 minutes of hemorrhagic shock when compared to control (no intervention) [26]. In the other report, following hemorrhagic shock, animals treated with REBOA for 60 minutes had lower renal glutathione concentrations and higher manganese superoxide dismutase activity than pigs immediately transfused with shed blood [27]. The occlusion zone was not specified for either report.

DISCUSSION

REBOA is a promising therapy for the care of trauma patients. Currently, Zone 1 REBOA is limited by a relatively short therapeutic window that has been estimated to be 30 minutes due to the profound distal ischemia that occurs with complete aortic occlusion. We undertook this systematic review of the literature to better understand the effect of duration of occlusion on renal function. We have demonstrated that consistent reporting of AKI incidence is lacking from human clinical studies of REBOA in trauma patients with NCTH. No REBOA-associated risk factors for AKI (such as occlusion Zone or duration) were identified in trauma patients treated with REBOA. Our results also highlight the lack of long-term follow-up of renal function assessment. While confounding factors such as hemorrhagic shock and direct tissue damage contribute to the development of AKI [28], animal models support the strong association between REBOA and AKI but fail to determine maximal occlusion times prior to the onset of measurable AKI.

There is a paucity of studies comparing the effects of occlusion Zone on renal function. Zone 1 occlusion for REBOA, or aortic cross-clamping during surgical interventions, carries the highest ischemia burden. Importantly, the development of renal injury in these patient populations is not solely the result of ischemia from the intervention. Prior to any aortic occlusion, trauma patients are at a high risk of AKI, with an incidence ranging from <0.1% up to 34% [8–10]. The development of AKI is of critical importance as post-traumatic renal failure is associated with longer ICU and hospital stays [8]. Additionally, after adjusted analysis, both civilian and military studies demonstrated an increased risk of mortality in trauma patients who develop AKI with absolute mortality rates ranging from 25 to 34% and acute mortality rates ranging from 18 to 22% [9,10]. In those patients, post-traumatic renal failure has been attributed to direct renal damage, the need for emergent surgical intervention, and renal ischemia overall [8]. Studies evaluating the incidence of AKI in trauma patients treated with REBOA should adjust for the predisposition of this patient population to AKI.

In addition to blood loss and direct tissue damage, trauma-associated decreased oxygen delivery to the kidney can be potentiated by aortic occlusion. As the use of REBOA is still at early stages in clinical use, most the literature regarding the mechanisms behind AKI induced by aortic occlusion stems from studies of open surgical

Table 3 Data summary for porcine studies.

Authors	*Introducer Sheath Size (Fr)*	*Aortic Occlusion Catheter Size (Fr)*	*Hemorrhage*	*Trauma**	*Aortic Zone Occluded*	*Complete Occlusion Time (minutes)*	*Partial occlusion Time (minutes)*	*AKI Information*	*QOE*	*ROB*
Avaro 2011	NR	7	Yes	Yes	1	40 versus 60	NA	Rise in [K^+] No change on renal histopathology	Fair	Low
Markov 2013	15	NR	Yes	No	1	30 versus 90	NA	No change in serum [Creatinine] No change on histopathology	Good	Low
Scott 2013	8 and 14	NR	Yes	No	1	60	NA	No baseline [Creatinine] reported Rise in [K^+]	Good	Low
Morrison 2014	NR	14	Yes	Yes	1	60	1 minute at 20 and 40 minutes	Rise in [K^+] and [Creatinine]	Good	Low
Park 2015	7	7	Yes	No	1	30 versus 60	NA	Damage on renal histopathology	Good	Low
Russo 2016	12	NR	Yes	Yes	1	90	10 minutes of complete then 80 minutes of partial occlusion	No change on renal histopathology	Good	Low
Russo 2016	12	NR	Yes	No	1	90	90	Acute tubular necrosis in 80% of pigs with C-REBOA No change in P-REBOA or control	Fair	Low
Williams** 2016	12	NR	Yes	Yes	1	NA	20 complete then 70 of partial	Mean UOP 0.5mL/kg/hour No control group	Poor	Low
Williams** 2017	NA	NA	Yes	Yes	1	20	70	UOP higher with permissive regional hypotension than complete aortic occlusion	Good	Low

*AKI, acute kidney injury; C-REBOA, complete resuscitative endovascular balloon occlusion of the aorta; NA, not applicable; NR, not reported; P-REBOA, partial resuscitative endovascular balloon occlusion of the aorta; QOE, quality of the evidence; ROB, risk of bias; UOP, urine output. *: beyond surgical preparation. **: studies in which extracorporeal circulation was utilized.*

repair of abdominal aortic aneurysms and open heart surgery. In both settings, aortic cross-clamp time is a predictor for the development of AKI [29,30]. With as little as 40 minutes of total clamp time, a significant decrease in glomerular filtration rate, renal blood flow, and urine output are seen when compared to infrarenal occlusion. Surprisingly, these hemodynamic changes persist even after clamp removal for up to 60 minutes [31]. Additionally, animal studies have demonstrated that following a 45-minute period of aortic occlusion, renal oxygen delivery and cortical tissue oxygen tension remain decreased although other visceral organs demonstrate normal perfusion [32]. These findings suggest that ongoing renal damage may occur despite appropriate systemic oxygen delivery (DO_2) after perfusion is reinstated. There are several potential trauma-related processes that may worsen renal function. Activation of the sympathetic nervous system is associated with worsening of renal function following renal vein and artery occlusion in rats [33], and renin release following aortic occlusion contributes to AKI in dogs following transient suprarenal aortic occlusion [34,35], both of which occur in the setting of significant trauma. Oxidative stress is another important pathologic process in the reperfusion phase. In a non-traumatic porcine model of aortic cross-clamping, 30 minutes of complete supra-coeliac aortic occlusion followed by reperfusion led to a significant increase in serum creatinine and NGAL concentrations in parallel with an increase in serum malondialdehyde (a biomarker of lipid peroxidation) concentration [36]. Our study identified two reports [26,27] demonstrating oxidative imbalances following REBOA therapy in porcine models of traumatic exsanguination however only the abstracts were available. Future studies should, therefore, investigate the effects of REBOA on oxidative stress.

Although considered to be protective of renal function during REBOA, studies of infrarenal aortic cross-clamping have demonstrated conflicting effects on renal function. There is opposing information regarding the association between occlusion in Zone 3 of the aorta and renal damage [37]. While the exact mechanisms remain unclear, alteration in blood flow distribution within the renal parenchyma and inflammatory responses have been proposed as possible causes of renal damages induced by infrarenal aortic clamping [37]. It has also been questioned whether microvascular shunting may be a contributor to AKI following reperfusion during Zone 1 as well as Zone 3 occlusion [38,39]. Additionally, since renal oxygen consumption (VO_2) is driven by sodium reabsorption, the potential increase in renal blood flow and glomerular filtration rate associated with Zone 3 occlusion could increase renal VO_2, which can be detrimental if DO_2 remains constant [40]. Earlier studies have also established the potential for shunting of blood within the renal parenchyma possibly leading to an imbalance between DO_2 and VO_2 [38]. Further studies are needed to elucidate these mechanisms.

To date, there is still a paucity of data comparing the effects of REBOA to aortic cross-clamping. Although animal studies have compared REBOA to RT in trauma models, there have been no renal function comparisons within these studies. Furthermore, although a single study in trauma patients demonstrated no difference in the need for renal replacement, this observational work has limitations secondary to inclusion bias and lack of randomization [7].

The recognition of the profound distal ischemia to the kidneys and other visceral organs that occurs during even brief periods of complete REBOA has driven the development of strategies to mitigate these potential complications. Although intermittent REBOA, in which the balloon is intermittently deflated and then re-inflated to allow a period of distal perfusion, has been suggested as a strategy to mitigate distal ischemia, there are no animal or human studies that assess the impact of this therapy on AKI. Partial REBOA is a technique whereby a small amount of distal flow is allowed past the point of occlusion [41]. Although only minimally studied in animals and not supported by clinical data at this time, a single study has reported reduced AKI risk based upon creatinine with pREBOA when compared to complete REBOA [25]. Histopathologic analysis of renal injury in porcine models of hemorrhagic shock have been less definitive with studies demonstrating both no difference as well as an increase in acute tubular necrosis with pREBOA when compared to complete occlusion [21,23]. Differences between animal studies of pREBOA may be the result of differences in how the therapy is applied, as pREBOA has undergone significant development and improvements in distal flow control since the publication of these manuscripts.

Consistent reporting has long been a source of debate when describing AKI with a multitude of grading systems. Inconsistency in renal function reporting made it often impossible to use commonly accepted guidelines such as Kidney Disease: Improving Global Outcomes (KDIGO) or the Acute Kidney Injury Network (AKIN). One study included in this review, Saito et al., [17] used the RIFLE criteria and reported an AKI incidence of 64%. In another report, Irahara et al., one patient had an elevated creatinine level after 37 minutes of partial occlusion but no baseline serum creatinine concentration was reported [18]. It was therefore impossible to determine whether it was the consequence of AKI, chronic renal failure, or chronic kidney disease with an acute injury. Finally, in the study by Dubose et al., 3.5% of patients undergoing aortic occlusion (open or endovascular) required renal replacement therapy, which would place those patients at stage 3 of the KDIGO guidelines [7]. Moving forward, it is imperative for a common grading system to be used so that the effects of REBOA on renal function can be understood.

The present study carries several limitations. First, similar to other systematic reviews of REBOA use, we

excluded a large number of reports from final inclusion [42,43]. A recent systematic review of the literature [43] identified 15 reports of patients with traumatic abdominopelvic hemorrhage, which included nine case reports or case series (with ≤5 patients). Of the remaining nine studies, only two were eligible for enrollment in our report [17,18]. Similarly, only one [7] in three studies included in a recent meta-analysis [44] were included in the present study. Additionally, systematic reviews and meta-analyses of the use of REBOA in trauma patients with NCTH are limited by the paucity of large reports [44]. Our findings also outline the inconsistent reporting of renal function information. In two of the porcine studies [4,5], serum potassium concentration was used as a surrogate for AKI. While hyperkalemia in trauma patients is multifactorial, sustained hyperkalemia in such patients occurs due to some degree of renal dysfunction. In those two studies, aortic occlusion lasted 45 to 60 minutes, yet hyperkalemia was sustained. Serum creatinine was not reported in one [4] and baseline serum creatinine concentration was not reported in the other [5], making AKI confirmation difficult. Systematic reporting guidelines have been proposed to improve consistency and evidence quality in the future [45].

CONCLUSIONS

In conclusion, consistent reporting of AKI incidence, severity, and outcomes is lacking from human clinical studies of REBOA in trauma patients with NCTH. While comorbidities in trauma patients may contribute to AKI, animal models support the association between REBOA and AKI. As REBOA is growing in popularity, future studies determining risk factors for AKI, as well as its effect on short- and long-term patient outcomes, are needed.

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