Reperfusion repercussions: A review of the metabolic derangements following resuscitative endovascular balloon occlusion of the aorta

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BACKGROUND: Current resuscitative endovascular balloon occlusion of the aorta (REBOA) literature focuses on improving outcomes through careful patient selection, diligent catheter placement, and expeditious definitive hemorrhage control. However, the detection and treatment of post-REBOA ischemia-reperfusion injury (IRI) remains an area for potential improvement. Herein, we provide a review of the metabolic derangements that we have encountered while managing post-REBOA IRI in past swine experiments. We also provide data-driven clinical recommendations to facilitate resuscitation post-REBOA deflation that may be translatable to humans.

METHODS: We retrospectively reviewed the laboratory data from 25 swine across three varying hemorrhagic shock models that were subjected to complete REBOA of either 45 minutes, 60 minutes, or 90 minutes. In each model the balloon was deflated gradually following definitive hemorrhage control. Animals were then subjected to whole blood transfusion and critical care with frequent electrolyte monitoring and treatment of derangements as necessary.

RESULTS: Plasma lactate peaked and pH nadired long after balloon deflation in all swine in the 45-minute, 60-minute, and 90-minute occlusion models (onset of peak lactate, 32.9 ± 6.35 minutes, 38.8 ± 10.55 minutes, and 49.5 ± 6.5 minutes; pH nadir, 4.3 ± 0.72 minutes, 26.9 ± 12.32 minutes, and 42 ± 7.45 minutes after balloon deflation in the 45-, 60-, and 90-minute occlusion models, respectively). All models displayed persistent hypoglycemia for more than an hour following reperfusion (92.1 ± 105.5 minutes, 125 ± 114.9 minutes, and 96 ± 97.8 minutes after balloon deflation in the 45-, 60-, and 90-minute occlusion groups, respectively). Hypocalcemia and hyperkalemia occurred in all three groups, with some animals requiring treatment more than an hour after reperfusion.

CONCLUSION: Metabolic derangements resulting from REBOA use are common and may worsen long after reperfusion despite resuscitation. Vigilance is required to detect and proactively manage REBOA-associated IRI. Maintaining a readily available "deflation kit" of pharmacological agents needed to treat common post-REBOA electrolyte abnormalities may facilitate management. (*J Trauma Acute Care Surg.* 2020;89: S39–S44. Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.)

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Resuscitative endovascular balloon occlusion of the aorta (REBOA) use has increased over the last five years, now encompassing applications in trauma, cardiac arrest, obstetric hemorrhage, and gastrointestinal bleeding.[1,2] Irrespective of indication, ischemia-reperfusion injury (IRI) associated with prolonged use of REBOA limits the safe duration of REBOA and may have a dose-dependent impact on survival.[3] Concomitant shock or traumatic injury further complicates patient management. Although REBOA literature has largely focused on reducing IRI by reducing distal ischemia through partial and intermittent flow strategies, there have been few publications focused on prescribed methods for managing IRI when it occurs.[4,5]

Existing literature has laid the framework for anesthetic management and resuscitation of REBOA patients.[6–8] However, more granular detail regarding the timing and peak effect of metabolic alterations can facilitate resuscitation in the postdeflation period.[9] The present review represents our collective observations from swine and humans undergoing REBOA. Our swine experiments consisted of hemorrhagic shock (induced by controlled or uncontrolled hemorrhage) followed by complete REBOA for 45 minutes, 60 minutes, and 90 minutes. Swine in the 60 minute occlusion experiment were subjected to traumatic brain injury (TBI) in addition to controlled hemorrhage, while swine in the 90-minute occlusion experiment were subjected to 30% liver amputation and induced dilutional coagulopathy in addition to controlled hemorrhage.[10–12] Definitive hemorrhage control was achieved, the REBOA balloon was gradually

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deflated, and resuscitation ensued, including whole blood transfusion, followed by critical care for up to 24 hours after the initial injury. In over 300 large animal experiments over the last 5 years, we have noted consistent metabolic derangements. While the differences in injury models between the three experiment groups preclude statistical analysis comparing the effects on metabolic derangements of varying durations of aortic occlusion (45, 60, and 90 minutes), our data demonstrate a consistent picture of metabolic derangements across experiment models that generally seem to worsen with increasing durations of occlusion.

To address these derangements, we developed preemptive treatment strategies and reactionary countermeasures that have a foundation in standard critical care practices. Drawing from these experiences and relevant literature, we present this review with the objectives of providing an overview of the etiologies of metabolic derangements that may be encountered in the care of REBOA patients and data on metabolic derangements recorded from 25 animals undergoing REBOA that were part of larger experiments. Finally, we provide data-driven clinical recommendations to facilitate resuscitation post-REBOA deflation. These findings may significantly impact anesthesia care in the operating room and subsequent management in the ICU. Potential etiologies and treatment recommendations are outlined below.

ELECTROLYTE DERANGEMENTS

Applied research models in swine and clinical report of patients undergoing aortic occlusion suggest that lactic acidosis, hyperkalemia, hypoglycemia, and hypocalcemia are severe enough to warrant intervention regardless of the level, degree, or duration of aortic occlusion.[3,6] Our own experience with swine models of zone 1 aortic occlusion at different durations, described below and in Table 1, indicates the same. While these metabolic and electrolyte abnormalities are multifactorial in origin, our findings support the conventional wisdom that increasing ischemia (more proximal occlusion, decreased volumes of distal blood flow, and longer occlusion times) is associated with more severe abnormalities and the need for more aggressive pharmacologic countermeasures. These are outlined with dosages specific to porcine large animal models in Table 2.

ACIDOSIS

The vascular surgery literature has long documented the relationship between increasing durations of aortic occlusion and worsening acidosis manifesting after reperfusion.[3,6] In our translational models, the magnitude of lactic acidosis was proportional to the initial ischemic burden imposed prior to resuscitation; however, we found lactic acid peaked within an hour following reperfusion and eventually normalized with adequate resuscitation. The three different experiments of induced hemorrhagic shock with 45 minutes, 60 minutes, and 90 minutes of aortic occlusion, demonstrated times to pH nadir of 4.3 ± 1.9, 26.9 ± 32.6, and 42 ± 19.7 minutes, respectively, with lowest pH values of 7.16 ± 0.1, 7.08 ± 0.04, and 7.05 ± 0.07, respectively (Table 1). Average times to peak lactate concentrations of 10.38 ± 4.16 mmol/L, 11.3 ± 1.81 mmol/L, and 12.73 ± 1.16 mmol/L were reached at 32.9 ± 16.8 minutes, 38.8 ± 27.9 minutes, and 49.5 ± 6.58 minutes following reperfusion in the 45-minute, 60-minute, and 90-minute occlusion groups, respectively (Table 1).

Other groups using swine models have also found lactic acidosis increased in a dose-dependent fashion with longer periods of REBOA, manifesting a delayed nadir pH and peak lactate after reperfusion that eventually normalized.[9,13–15] This acidosis was present during both complete and intermittent aortic occlusion and markedly worsened following subsequent reperfusion, persisting even after the immediate reperfusion period.[5,12,16,17] Clinically, reports of prolonged durations of acidosis and multisystem organ failure have been observed in multiply injured patients requiring REBOA.[18]

The relationship between ischemia and acidosis is of critical importance in the care of trauma patients. Lactic acidosis decreases cardiac performance which in itself can lead to hypothermia that halts the coagulation cascade. Impaired coagulopathy can result in ongoing hemorrhage, worsened hemorrhagic shock and subsequent increasing acidosis in the cycle commonly known as the "trauma triad of death." Tissue hypoxia from hypoperfusion stimulates anaerobic metabolism-producing lactate, the main driver of ischemic metabolic acidosis. Of note, neither elevated lactate nor metabolic acidosis is directly

TABLE 1. Quantified Electrolyte Derangements from Translational Studies

	Williams et al.* (n = 7)		Johnson et al.** (n = 8)		Russo et al.† (n = 10)	
	Mean	SEM	Mean	SEM	Mean	SEM
Lowest pH	7.16	0.04	7.08	0.02	7.05	0.02
Time to low pH, min	4.3	0.72	26.9	12.32	42	7.45
Peak lactate, mmol/L	10.38	1.57	11.3	0.68	12.73	0.44
Time to peak lactate, min	32.9	6.35	38.8	10.55	49.5	6.58
Peak potassium, mEq/L	5.18	0.19	7.58	0.21	6.99	0.28
Time to peak Potassium, min	71.4	30.92	5	0	13.5	1.78
Lowest calcium, mmol/L	1.05	0.02	0.7	0.09	0.96	0.06
Time to low calcium, min	51.4	15.57	8.1	3.33	24	8.96
Lowest glucose, mg/dL	64.29	6.51	45.5	11.15	28.7	6.68
Time to low glucose, min	92.1	39.87	125	43.43	96	36.96

* Complete REBOA duration: 45 min; injury, controlled hemorrhage of 25% estimated blood volume.
** Complete REBOA duration: 60 min; injuries: controlled hemorrhage of 25% estimated blood volume + TBI.
† Complete REBOA duration: 90 min; injuries: controlled hemorrhage of 25% estimated blood volume + 30% liver amputation + induced dilutional coagulopathy.

TABLE 2. Interventions for Metabolic Derangements Following REBOA in Porcine Models

Drug	Timing	Dosage	Comments
Calcium gluconate (10.0%)	• 5 min prior to deflation • Immediately prior to blood transfusion start • After every 2 units of PRBCs • Ca++ <1.0 • K+ >6.0	Prior to Balloon Deflation • 1.5–3 g over 5 min Prior to blood transfusion • 50 mg/kg During blood transfusion • 7 mL per unit of PRBC, infusion rate 1 mL/min Ca++ **<1.0** • 1.0 g over 15 minutes by central line K+ **>6.0** • 50 mg/kg over 15 minutes on syringe pump (60 mL/h)	Used to stabilize cardiac membranes, treat hypocalcemia, countereffects of chelation of unionized calcium by citrate preservatives in transfused blood.
D50	• Prior to deflation • Glucose <60 mg/dL • With insulin administration	Glucose **50–60** mg/dL • D50 1 mL/kg by central line • Start D50 infusion at ½ rate* OR double existing infusion Glucose 40–49 mg/dL • D50 2 mL/kg by central line • Start D50 infusion at ½ rate* OR double existing infusion Glucose <40 • D50 3 mL/kg by central line • Start D50 infusion at ½ rate* OR double existing infusion Insulin Administration • 1 mL/kg D50 slowly by central line • Start D50 infusion*	Used to treat standalone hypoglycemia which may persist for up to 60 min after balloon deflation, counteract additional hypoglycemic effects of exogenous insulin administration required for the treatment of hyperkalemia
Insulin** (regular)	• K+ >6.0	• 10 U IV (clinical recommendation) • 0.25–0.5 units/kg insulin by central line (study dosing)	Increase intracellular potassium uptake to treat hyperkalemia which can persist for up to 60 min after balloon deflation
Albuterol sulfate inhalation solution (0.083%) Albuterol sulfate inhalation aerosol (90 μg/puff)	• K+ >6.0	• 10–20 mg	Counteract hyperkalemia which can persist for up to 60 min after balloon deflation

* Rate: (5 mL/kg × 50) / 1,000 = mL/h.

** Dextrose should always be given when insulin is administered to prevent iatrogenic hypoglycemia. Compared with clinical dosing recommendations, the study dosing of insulin was lowered and the dosing of coadministered D50 was increased due to the frequent occurrence of hypoglycemia in swine.

damaging to tissue under normal physiologic conditions. At low levels, both may be protective against reperfusion-associated free radicals that are known to cause cellular damage.[19] Furthermore, lactate is a secondary source of fuel for the body when it is used by the liver in gluconeogenesis, and the kidneys are also able to normally excrete excess lactate to maintain a normal physiologic level.[20] However, when the ischemia from aortic occlusion damages the liver and kidneys lactate utilization is impaired, and lactate clearance is impeded.[21] The result is further worsening of acidosis. In parallel, the impaired hepatic function can cause profound hypoglycemia. A phenomenon that will be discussed below.

Severe acidosis (pH < 7.2) can also result in transmembrane electrolyte shifts and malfunction of intracellular proteins. These effects are particularly manifest in the myocardium.[22] The resultant alterations in intracellular calcium concentration then produce decreased cardiac output and refractory hypotension. We have observed evidence of myocardial strain following prolonged aortic occlusion in animal models, which may be in part attributed to the metabolic derangements observed. Additionally, we observed increased $etCO_2$ routinely upon balloon deflation, indicative of rising serum CO_2 levels.[11] Increases in ventilation rate were used in these instances to ameliorate hypercarbia.[23] A detailed discussion of these modalities for management of IRI-related acidosis is beyond the scope of this review. Interventions aimed at restoring lost intravascular volume and stabilizing the myocardium are needed to mitigate metabolic acidosis and halt the trauma triad of death.

In our animal models, our practice is to achieve definitive hemorrhage control prior to reperfusion. We then restore blood volume with a massive transfusion of fresh whole blood while concurrently deflating the REBOA balloon in a slow, graded fashion. As described later in this text, we pretreat with calcium bolus followed by a calcium infusion to mitigate the effects of citrate in the transfusate and to prophylax against hyperkalemia from impending IRI. Persistent acidosis may further warrant continuous renal replacement therapy and sodium bicarbonate administration.

HYPERKALEMIA

Retrospective review of our data has demonstrated 100% of animals with zone 1 occlusion exceeding 30 minutes in duration required at least one therapeutic intervention for a potassium ≥5.0 mEq/L. Several other large animal studies employing complete or intermittent aortic occlusion have demonstrated hyperkalemia

requiring treatment as well.[12,13] Clinically, hyperkalemia is a common finding in trauma patients independent of REBOA use. As many as 30% of noncrush trauma victims exhibit at least one episode of hyperkalemia (K ≥ 5.50 mEq/L) within the first 12 hours after injury.[24] Ischemia-reperfusion injury following REBOA may compound hyperkalemia by inducing ischemic cellular lysis, acidosis-driven electrolyte shifts between the intracellular and extracellular spaces, and reduced potassium clearance from subsequent ischemic renal dysfunction.[3,25]

From these reports, it is clear that close monitoring of potassium levels is required during and after REBOA to trend and treat hyperkalemia. Furthermore, following REBOA deflation, there may be a lag in peak hyperkalemia due to gradual distal tissue beds wash out and ongoing cellular breakdown from reperfusion injury. This phenomenon is thought to be the cause of later spikes in potassium. As demonstrated in our own data, practitioners should be prepared for the return of a large bolus of potassium into circulation upon balloon deflation as well as late increases that may require repeated interventions for hyperkalemia.

In our animal models, we routinely administer at least 2 g of calcium gluconate prophylactically prior to balloon deflation when transitioning from complete to partial occlusion and administer additional calcium if needed when completing balloon deflation. Calcium has been hypothesized to stabilize the myocardium in the setting of hyperkalemia but its early use during resuscitation will also counteract the chelating effects that are associated with blood transfusions. We also administer 0.5 μ/kg insulin with 1 mL/kg of Dextrose-50-Water (D50) to reduce the impact of hyperkalemia on cardiac instability by shifting potassium intracellularly. Additional adjuncts for severe hyperkalemia can include sodium bicarbonate as well as albuterol. In all cases, it is recommended to obtain an EKG to assess for a prolonged QRS complex which is an early indicator that hyperkalemia is negatively impacting the heart.

HYPOGLYCEMIA

The presence of *hyper*glycemia in critically ill patients, including trauma patients, has been well demonstrated in both the human and porcine literature.[26] However, we observed refractory *hypo*glycemia in our data. Eighty-eight percent of animals in our experiments became hypoglycemic either during aortic occlusion or following balloon deflation. Although all animals received dextrose in combination with insulin for the treatment of hyperkalemia, almost all required additional dextrose boluses for refractory hypoglycemia. While some microdialysis studies of induced intestinal ischemia have demonstrated local intraperitoneal hypoglycemia following SMA ligation, reports are mixed.[27] Another study of supraceliac balloon occlusion found both a rise in arterial blood glucose and intraperitoneal glucose on reperfusion, again indicating a hyperglycemic response.[28] Literature describing hypoglycemia following aortic occlusion is scant.

While swine are generally more prone to hypoglycemia than humans, refractory hypoglycemia has also been observed clinically. In one case, a patient who underwent prolonged zone 1 partial occlusion developed profound, refractory hypoglycemia requiring a glucose drip for several days after systemic circulation had been restored (unpublished data). Clinicians attributed this profound hypoglycemia to a combination of REBOA-induced adrenal ischemia and liver dysfunction with decreased gluconeogenesis.[29] Other translational researchers studying polytrauma and hemorrhagic shock in swine models have noted severe hypoglycemia even without REBOA, including delayed, refractory cases leading to mortality in a model of prolonged hypotension.[30] In the setting of shock (without aortic occlusion or IRI), where glucose may play either a metabolic or nonmetabolic role in fluid homeostasis, hypoglycemia follows the depletion of glycogen stores and the failure of the gluconeogenesis occurring during the hypermetabolism of shock.[31] Pancreatic responses to hyperkalemia or transient ischemia may further modify metabolic function. However, the fasting state of our swine prior to experimentation also potentially increased the frequency and severity of hypoglycemia.[32] The occurrence of post-REBOA hypoglycemia in our animal work and clinical experience underscores the importance of vigilant glucose monitoring. In our animal models, we treat glucose <60 with 1 mL/kg, 40–60 with 2 mL/kg, and <40 with 3 mL/kg of D50.

HYPOCALCEMIA

While acute acidosis is typically associated with increased ionized calcium as a result of decreased binding of calcium to albumin, we frequently observed hypocalcemia in swine subjected to liver injury with hemorrhagic shock.[33] While hypocalcemia was evident even in the absence of blood transfusion, it was most pronounced in those animals that received transfusion of blood stored in citrated bags. All animals received intravenous calcium gluconate prior to reperfusion with additional doses administered with blood transfusion. Nonetheless, refractory hypocalcemia requiring supplemental calcium boluses occurred in REBOA-treated animals in all our experimental models.

The finding of hypocalcemia associated with lactic acidosis has been echoed by other clinical critical care providers and may be the result of increased calcium binding to free lactate ions, altered parathyroid hormone responsiveness, intracellular calcium shifts, and phosphate chelation of calcium.[34] Previous work revealed that over half of admitted trauma patients are hypocalcemic preresuscitation, and over 70% of patients became hypocalcemic during their resuscitation.[34] The importance of maintaining adequate intracellular and plasma calcium in the REBOA patient must be stressed. In addition to combating cardiac instability and hypotension induced by acidosis and hyperkalemia, ample supplemental calcium is also necessary to counteract the chelating effects of citrate in transfused blood, which is critical for normal clot formation.[35,36]

In our animal models, prior to balloon deflation, concurrent with the initiation of whole blood transfusion, we empirically administer 50 mg/kg of calcium gluconate. We repeat an additional 50 mg/kg of calcium gluconate with every two bags of citrated blood products administered. If ionized calcium is <1.0 or potassium is >6.0, we increase the dose of calcium gluconate administered to 100 mg/kg.

TREATMENT RECOMMENDATIONS

While the specific dosing of treatments utilized in our large animal laboratory is specific to porcine models, the monitoring

and treatment recommendations themselves are applicable to human patients. Given the variable time course for the metabolic derangements to fully manifest, frequent laboratory monitoring is required to facilitate early detection and treatment. Prior to reperfusion, blood drawn from proximal arteries may underestimate abnormalities, as potassium and lactic acid accumulate in distal tissues (particularly within the portal venous system). To detect potentially sudden electrolyte shifts, we draw arterial blood gases with electrolytes every 15 minutes prior to, and immediately following balloon deflation, then every 30 minutes for several hours, thereafter, until electrolytes have stabilized.

Continuous cardiac and hemodynamic monitoring are essential during occlusion and throughout the reperfusion period. Vasoplegic syndromes, most commonly reported after cardiac surgery and liver transplantation, may occur after long periods of REBOA with a high degree of IRI-associated ischemic metabolites. Medications selected for hemodynamic and cardiac support should be short acting as large fluctuations in blood pressure, arrhythmias, and rapid changes in cardiac function can occur with balloon deflation. Restoration of systemic circulation often requires concurrent restoration of blood volume, so practitioners should be prepared with warmed fluids and/or blood products for immediate administration.

During this high-risk period, early detection and proactive treatment of metabolic derangements are paramount. Having pharmacologic countermeasures readily available in appropriate doses expedites the correction of these potentially fatal electrolyte abnormalities. Because REBOA deflation and reperfusion may occur in the OR, IR suite, or ICU, we maintain these countermeasures in a portable kit containing calcium gluconate, insulin, D50, sodium bicarbonate, and albuterol. Administration instructions for porcine experiment models follow the dosing and administration recommendations outlined in Table 2. Similar kits may be beneficial for teams performing REBOA on human patients in other facilities and can be adapted to suit a variety of different practice types and environments. Efficient team dynamics, closed-loop communication, and continuous coordination between providers during REBOA resuscitation are paramount.[7]

CONCLUSION

The management of REBOA patients continues to evolve from a combination of clinical and translational research, experience, and new technological developments. Metabolic derangements associated with REBOA use are common and worsen despite resuscitation for up to an hour following reperfusion. For the clinician at the bedside, vigilance is required in the perideflation period to detect and proactively manage REBOA-associated IRI. Special attention should be paid to the delayed upward trajectories of these abnormalities and the risk of persistent hypoglycemia. A "deflation cocktail" of preprepared resuscitation components stored with REBOA kits may facilitate management.

AUTHORSHIP

M.A.A., R.M.R., G.L.H., J.K.G., T.K.W., L.P.N., and M.A.J. contributed to the literature search and study design. T.K.W., L.P.N., M.A.J., R.M.R., J.K.G., and G.L.H. collected data. J.J.D., R.A.L., T.K.W., L.P.N., and M.A.J. performed data analysis and interpretation. M.A.A., R.M.R., J.J.D., R.A.L., T.K.W., L.P.N., and M.A.J. wrote the article, which all authors critically revised.

DISCLOSURE

T.K.W., M.A.J., and L.P.N. are founders and stockholders of Certus Critical Care, Inc. There are no other conflicts of interest.
The views expressed in this material are those of the authors and do not reflect the official policy of the US Government, the Department of Defense, the Department of the Air Force, the University of Utah, the University of Michigan, the NHS, or Wake Forest University.

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