Far Forward Gaps in Hemorrhagic Shock and Prolonged Field Care

An Update of ALM Fluid Therapy for Field Use

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ABSTRACT

Future expeditionary missions are expected to occur in more remote austere environments where combat medics and casualties may have to wait up to 7 days before resupply or safe evacuation. Currently, there is no effective fluid therapy for hemorrhagic shock (HS) at the point-of-injury and continuum-of-care over this extended period. We have been developing a small-volume IV or IO ALM therapy for noncompressible HS and have shown in preclinical models that it extends survival to 3 days, reduces abdominal bleeding by 60%, blunts inflammation, corrects coagulopathy, preserves platelet function, and prevents immunodeficiency. The ALM-survival phenotype is associated with an upregulation of the master genes of metabolism and mitochrondrial biogenesis in heart and brain and a downregulation in the periphery. Future translational studies will investigate the timing and nature of the "switch" and extend survival to 7 days. We will also discuss some of the controversies of ALM resuscitation in pigs, present our Systems Hypothesis of Trauma (SHOT), and discuss future clinical safety trials before field use.

KEYWORDS: *hemorrhage; trauma; survival; genetics; metabolism; inflammation; military medicine; resuscitation*

> *Today, defense of the homeland focuses on placing military capabilities as far forward as possible.*
> —Joint Operating Environment 2035[1p25]

Background: The New Combat Environment: Challenge of Change

The 2016 Joint Operating Environment document posits that over the next 20 years there will be a wide range of threats and persistent conflicts. Future expeditionary missions are expected to occur in more remote, austere environments, where combat medics and casualties may have to wait up to 5 to 7 days before resupply or evacuation.

Hemorrhagic Shock: A Widening Gap in Far Forward Medicine

In 1984, Col Ronald Bellamy launched a challenge to develop new resuscitation fluid therapies to treat combatants with severe blood loss and reduce preventable deaths in austere environments.[2–5] "For every casualty who dies of wounds in a medical treatment facility (MTF)", he wrote, "as many as 9 have already died."[2] Over 3 decades later, this capability gap remains wide open. A 2012 US Joint Trauma System study reported 87.3% of combat deaths in the Iraq and Afghanistan wars occurred *before* the casualty reached an MTF *(*4,596 deaths), with 24.3% deemed potentially survivable.[4,6] Of those deaths, 91% were from hemorrhage with 67% being truncal (noncompressible), 19% junctional, and 14% peripheral-extremity.[6] Similarly, in the civilian prehospital setting, rapid transport of the wounded to a tertiary trauma care facility to resuscitate and surgically intervene is not always possible.[7] A second capability gap that remains wide open in the far forward combat environment is prolonged field care to stabilize the casualty and reduce secondary injury progression. Secondary injury progression is one of the most critical windows of opportunity to reduce morbidity and mortality. Time is the biggest killer in both these acute and continuum-of-care scenarios.

The First ALM "Idea": Human Translation into Cardiac Surgery

Twenty years ago, GPD asked if it was possible to pharmacologically manipulate the human heart to operate more like the heart of a natural hibernator for improved protection during cardiopulmonary bypass or valvular surgery.[8–10] Within 10 years, we translated a high-dose ALM cardioplegia from an isolated rat heart into human cardiac surgery. We chose adenosine (A) to inhibit the sinoatrial node and reduce the atrial and ventricular action potential (AP) duration (A1 receptor subtype and A1 linked opening of K_{ATP} channels), lidocaine (L) to reduce AP amplitude by arresting Na^+ fast channels, and magnesium (M) to stabilize the membrane and protect against reperfusion arrhythmias.[11] We theorized this strategy will arrest the heart at its resting membrane potential and avoid the use of high potassium, which depolarizes the membrane and promotes "ischemic" injury currents.[12,13] Two prospective, randomized, clinical trials have shown the ALM cardioplegia to be superior to high potassium cardioplegia with less days in hospital.[14,15] After surgery, the heart is reanimated in sinus rhythm with 10 times lower concentrations of ALM, which is facilitated because its resting membrane potential is "ready to fire." This resuscitation strategy led to a second idea; namely, could low-dose ALM resuscitate the heart after major trauma?[10]

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ALM for Trauma: Teaching Old Drugs New Tricks

Our first proof-of-concept ALM trauma experiments were conducted in 2009.[16,17] We have subsequently shown in rat models that boluses and infusions of low-dose ALM protect the heart and whole body against regional myocardial ischemia,[18–20] cardiac arrest,[21,22] pressure- and volume-controlled hemorrhagic shock,[16,17,23] polymicrobial sepsis,[24,25] and surgical trauma.[26] Importantly, the individual actives, A, L, or M do not confer these benefits alone.[10,27] Standout features of ALM protection and pro-survival properties include (1) potent antiarrhythmic, (2) lowering myocardial energy demand, (3) ability to hypotensively resuscitate mean arterial pressure (MAP) from different shock states, (4) correction of coagulopathy, (5) preservation of platelets, 6) endothelial protection, (7) anti-inflammatory, and (8) immunomodulatory[10,28] (Table 1). Studies carried out by US Army Institute of Surgical Research have also shown that ALM protects against endothelial glycocalyx shedding with 97% restoration after hemorrhagic shock.[29] On the basis of our ALM trauma studies, which are summarized next, we hypothesize that if the central nervous system (CNS) control of cardiovascular coupling is maintained following trauma, the endothelium will be protected, mitochondrial energetics will be maintained, and coagulopathy and inflammation will be minimized. This conceptual scheme is termed the Systems Hypothesis of Trauma (SHOT) and helps to explain why certain groups of severely bleeding trauma patients are still dying despite receiving the best medical care.[28]

TABLE 1 *Defining the ALM-Induced Survival Phenotype After Severe Trauma*

• Potent antiarrhythmic
• Cardiac preconditioning mimetic and lowers energy demand
• Correction of trauma-induced coagulopathy
• Preserved platelet aggregation
• Reduced systemic inflammation
• Protection against immunodeficiency and infection
• Improved left ventricular–arterial coupling
• Increased blood flow to brain and gut
• Restoration of endothelial–glycocalyx shedding
• Improved tissue oxygenation
• Hypotensive resuscitation with neuroprotection
• Reduced sympathetic/parasympathetic input to heart
• Maintenance of membrane potential in healthy and injured cells
• Differential expression of master genes of metabolism
• Improved thermoregulatory control
• Improved central nervous system–cardiovascular–endothelial coupling as part of the Systems Hypothesis of Trauma (SHOT)

Noncompressible Hemorrhagic Shock

Shock is: "a momentary pause in the act of death."
—John Collins Warren (1895)

In 2015 our first USSOCOM-funded study showed that 3% NaCl ALM bolus and 0.9% NaCl ALM drip improved survival (100% vs 62% for controls), significantly increased cardiac output (CO) (2.4-fold) and left ventricular fractional shortening, and increased blood flow to gut and kidney.[30] This acute experiment in anesthetized rats involved uncontrolled blood loss from resecting the liver (60% left lateral lobe and 50% medial lobe) with 6-hour monitoring.[30] An unexpected finding was showing that ALM reduced internal blood loss by up to 60% and acted like a pharmacological tourniquet.[30] We argued that this may be related to ALM correction of coagulopathy, which was also consistent with preserved platelet function and reduced endothelial activation and suppressed systemic inflammation[31] (Tables 1 and 2). In addition to traumatic hemorrhage, we also examined the effect of the same 3% NaCl ALM bolus and 0.9% NaCl ALM drip therapy in a rat model of moderate traumatic brain injury (TBI) and showed a survival benefit compared with controls, and a major reduction in secondary injury expression including correction of coagulopathy, blunting of endothelial activation, and reduced systemic inflammation and brain injury markers[32] (Table 2).

The second noncompressible hemorrhage study in rats examined if ALM therapy could increase survival to 72 hours in the conscious animal. We showed the mean survival time for saline controls was 22 hours and ALM group was 72 hours ($P < .001$, experimental endpoint).[33] Survival was associated with higher CO, reduced inflammation, protection from immunosuppression, preserved platelet function, correction of coagulopathy, and differential regulation of the master genes of metabolism. Expression of ampk, sirt-1, and PGC-1α were significantly upregulated 2- to 3-fold, and $mtCO_3$ was upregulated 10-fold in the heart and brain compared with controls. The upregulation of mtCO3 indicates improved structure and stability of cytochrome **c** oxidase, the complex that drives ATP synthesis. More recently, we have shown TFAM (transcription factor A, mitochondrial), a gene involved in mitochondrial biogenesis, was also significantly increased in heart and brain. Mitochondrial biogenesis is the process by which cells increase mass via growth and division of preexisting mitochondrial networks.[34] In direct contrast, ALM downregulated ampk, sirt-1, PGC-1α, and $mtCO_3$ expression in the periphery. For example, mtCo3 expression in liver was downregulated by 90% indicating a *major reduction of hepatic ATP demand*. Our new data appear to show that *ALM switches and reprograms the whole body into a pro-survival phenotype with suppression of secondary injury processes*. Key questions remain: Given that the half-lives of each active in ALM are seconds to a few hours,[10] when does the "switch" occur? How long can the survival phenotype be sustained? Future efforts will examine if survival time can extend to 7 days which has significant military relevance.

Rat-to-Pig Translation

In our first translational study in pigs, we showed that a 20mL bolus of 7.5% NaCl ALM (0.5mL/kg) led to a 40% reduction in fluid volume (IV Ringers acetate) required to increase MAP from 30–35mmHg to a target MAP of 50mmHg after 90 min of 74% controlled blood loss.[35] We also found returning shed blood (1.6 to 2L) after 60 min with a 10mL bolus of 0.9% NaCl AL resulted in a significant 27% drop in whole body O_2 consumption, higher CO, and significantly improved renal function compared with controls[10,35] (Table 3). In our second study using the pressure-controlled hemorrhage model (73% blood loss), a single bolus of 4mL/kg 7.5% NaCl ALM bolus (~7% of shed volume), with no other fluid, raised MAP from 30–35 to 55mmHg accompanying a nearly 2-fold increase in stroke volume (SV) at 60 min compared with saline controls, which began to decompensate (MAP 32 ± 3mmHg) with one death.[36] The 2-fold increase in SV was due to an increase in systolic ejection time (129 ± 10 vs 84 ± 12 ms, $P < .05$) and ~20% decrease in heart rate (HR).[36] After 60 min hypotensive

TABLE 2 *Summary of the Effect of ALM Therapy in Rat Models After Hemorrhagic Shock, Sepsis, Traumatic Brain Injury, and Surgery (2011 to Present)*

Study	Hemorrhagic Shock	Study Duration/ Anesthesia	Bleed Time (min)	Shock Period (min)	Hypotensive Resuscitation (60 min)	IV Drip 0.5mL/kg/hr	Traumatic-induced Coagulopathy	Inflammation	Other Major Outcomes
1, 2	Pressure controlled (40% blood loss)	Acute 3 hours Thiopentone Ventilator	20	60	0.7mL/kg MAP 60 vs 36 (controls)	—	—	—	First report showing 7.5% NaCl ALM as a possible hypotensive resuscitation fluid. ALM is a potent antiarrhythmic. Hextend led to increased mortality.[16,17]
3	Volume controlled (60% blood loss)	Acute 3 hours Thiopentone Ventilator	50	30	0.7mL/kg MAP 40 vs 15 (controls)	—	—	—	No deaths in ALM animals. 75% mortality in saline controls. ALM animals showed 89-96% reduction in arrhythmias.[23]
4–6	Pressure controlled (40% blood loss)	Acute 3 hours Thiopentone Ventilator	20	60	0.7mL/kg MAP 69 vs 43 (controls)	—	ALM therapy Corrected in 5 min (ROTEM) and 60 min (PT, aPTT, ROTEM)	—	Controls failed to clot at 5 and 60 min. 7.5% NaCl ALM correction indicates clotting factors present & pathways operational. ALM possible anti-fibrinolytic.[27,46,47]
7	Noncompressible hemorrhage (30% to 40% blood loss)	Acute 6 hours Thiopentone Ventilator	Free to bleed	15	0.7mL/kg MAP ~60 over 2–6 hours	4 hours	ALM therapy corrected (ROTEM)	IL-4, IL-6, TNF-levels were < baseline or shams	*3% NaCl ALM improved 6 hours survival after liver resection. ALM ↓ internal bleeding by 60%; ↑ CO, ↑ flow to gut, kidney; preserved platelet aggregation. Hextend led to poor outcomes.[31]
8	Noncompressible hemorrhage (30% to 40% blood loss)	Chronic 72 hours Isoflurane Conscious	Free to bleed	15	0.7mL/kg MAP ~100 during "drip"; 120 at 72 hours	4 hours	Corrected coagulopathy (ROTEM)	Inflammation suppressed by 70%	3% NaCl ALM led to 100% 3-day survival with immune protection and platelet preservation. Controls died day 1. ALM provided a metabolic 'boost' to heart and brain and downregulated periphery.[33]
Polymicrobial Sepsis									
9	Cecal ligation puncture	Acute 5 hours Thiopentone Ventilator	—	—	0.7mL/kg MAP 60–80 over 5 hours	4 hours (1mL/kg/hr)	ALM corrected PT, aPTT at 1 and 5 hours	—	0.9% NaCl ALM induced a reversible hypotensive, antiarrhythmic state, and ↓ lung edema compared to controls. [24]
10	Cecal ligation puncture	Chronic 6 days Isoflurane Conscious	—	—	0.7mL/kg MAP 90–107 over 24 hours	4 hours (1mL/kg/hr)	ALM corrected day 4 coagulopathy (ROTEM)	ALM ↓ cytokine storm by >70%	ALM therapy ↑ survival to 6 days (88%) without antibiotics, ↓ necrotic ischemia in cecum and lung injury, and prevented immunosuppression. 75% mortality in controls.[25]
Traumatic Brain Injury/Surgery									
11	Moderate fluid percussion injury	Acute 5 hours Thiopentone Ventilator	—	—	0.7mL/kg MAP 77 (3 hours)	3 hours	Corrected coagulopathy (ROTEM)	~80% ↓ IL-1, RANTES and TNF-α, ↑ IL10	ALM ↑ survival, ↑ brain blood flow 3-fold, ↑ CO, ↑ fractional shortening, 70% ↓ brain injury markers, ↓ syndecan[32]
12	Trauma of surgery (laparotomy)	Acute 7 hours Isoflurane Conscious	—	—	No bolus MAP 122–132 over 6 hours	6 hours	ALM ↓ fibrinolysis	ALM ↓ IL-6, ↑ IL-10	ALM ↓ lactate, ↓ respiratory alkalosis, ↓ stress-induced release of neutrophils and platelets, ↓ acid-base disturbance.[26]

*Hypertonic saline with ALM was decreased from 7.5% to 3.0% since the latter is FDA approved for clinical use.
MAP = mean arterial pressure; ROTEM = rotational thromboelastometry; PT = prothrombin time; aPTT= activated partial thromboplastin time; CO = cardiac output

resuscitation, shed blood was returned with 10mL 0.9% NaCl AL bolus and whole body O_2 consumption fell by ~15%, systemic vascular resistance increased by 30%, and urine output increased 3-fold in the ALM group compared with saline controls.[36] In our third study, we showed that ALM infusion significantly reduced the inflammatory response in the pig model of lipopolysaccharide (LPS)-induced endotoxemia.[37] ALM infusion dropped the MAP to 47mmHg yet maintained CO and SV leading to no change in tissue oxygen perfusion, with a concomitant fall in whole body oxygen consumption[37] (Table 3).

Our most recent USSOCOM-funded pig study was a military-relevant, noncompressible hemorrhage model induced by laparoscopic liver resection.[38] ALM-treated pigs had higher survival (100%) compared with saline controls (80%), lower HRs and a stable permissive hypotensive state (MAP 47–61mmHg). At these hypotensive blood pressures, ALM was neuroprotective with little or no change in brain lactate or glycerol compared with 2-fold higher levels in saline controls ($P < .05$). We also found a significant 40% reduction of hypoxia inducible factor (HIF) expression in ALM-treated brain cortex.[38] These data indicate the ALM therapy resuscitates the animal into a permissive hypotensive range, and reduces secondary brain ischemia at these low MAPs, which is consistent with our previous TBI rat study[32] (Table 2). During infusion of 0.9% NaCl ALM, O_2 delivery was improved from a higher CO and a more compliant vascular system compared with saline controls. In summary, ALM supported a high flow, hypotensive, vasodilatory state with improved O_2 delivery and cerebral protection in a pig model of noncompressible hepatic hemorrhage[38] (Table 3).

Pig ALM Resuscitation Controversy: Superior or Inferior?

Our three pig studies involving pressure-controlled (~74% blood loss) and noncompressible hemorrhage (~30–40% blood loss) models are in contrast to the recent study of How and colleagues from Naval Medical Research Unit San Antonio (NAMRU-SA). The group evaluated three different bolus ALM doses and two drip doses across four treatment groups in a pressure-controlled porcine model of hemorrhagic shock designed to mimic field and Tactical Combat Casualty Care (TCCC) conditions.[39] They reported that ALM was inferior to Hextend in terms of survival but demonstrated a superior coagulation benefit (Table 3).

It is difficult at this time to identify the reasons for the loss of ALM protection although the group did report to us problems with ALM solubility and "cloudy" solutions (not noted in their publication).[28] We consider this a "red flag" as we have never experienced this problem in our rat or pig studies at James Cook University, Australia, nor at Aarhus University Hospital, Denmark. This implies that one or more of the actives in the ALM drip solution has exceeded their solubility limits, known as phase joining or precipitation. It is therefore possible that increased mortality reported by How and colleagues may have been due to incorrect dosing. In addition, the use of the opioid analgesic buprenorphine in their study may also be problematic, as we have shown its combination with ALM leads to less protection and increased mortality.[40] Buprenorphine is known to cause cardiac and respiratory depression including decreases in systolic and diastolic pressures, MAP, and cardiac index.[40,41] Notwithstanding these discrepancies, the results of How and colleagues reinforce the importance of performing dose safety studies of ALM therapy in small and large animals prior to human translation, which are currently under way at our institution.

Experimental Conundrum: Why Do Pigs Require Higher ALM Doses Than Rat Models?

In rats, the resuscitation bolus is 0.7mL/kg and the drip 0.5mL/kg/hr, whereas in pigs the optimal bolus is 4mL/kg and followed by a 3mL/kg/hr infusion. Why is there a species difference? A possible explanation is differences in concentrations of plasma α-acid glycoprotein (AGP), a major drug binding protein, which is >7-fold higher in pigs than rats[42,43] (Table 4). AGP, which is also known as orosomucoid, is one of the most highly glycosylated proteins in plasma and can bind >300 drugs including heparin, steroids, histamine. and lidocaine (70% bound) with higher specificity than albumin (>95%).[44,45] Thus, a higher plasma AGP level will influence the free plasma concentrations of lidocaine, which may explain why higher ALM doses are required in pigs during resuscitation and stabilization (see earlier). This is further complicated during trauma because AGP levels can increase by 2- to 5-fold as part of the acute phase response, which would also reduce the bioavailability of lidocaine during infusions. Interestingly, AGP levels in human plasma are lower than pigs, which suggests that the lower bolus and infusion doses in rats may be suitable for translation (Table 4). In addition to bioavailability, other reasons for rat-to-pig differences may relate to differences in drug metabolism and clearance of the drug actives. Further studies are required to examine this question.

Safety and Translation to Humans

Understanding the mechanisms of ALM or any drug therapy is vitally important for safe field transition and wider adoption into civilian prehospital medical care because "among 222 novel therapeutics approved by the FDA from 2001 through 2010, 71 (32.0%) were affected by a postmarket safety event."[46] This is an extraordinary statement despite the high level of institutional review board scrutiny and FDA oversight on new trials testing new drugs and appropriate pathways for regulatory approvals. Our mission, therefore, is to avoid potential adverse events during translation of ALM therapy through research by further examining the drug's underlying mechanisms and human testing in a "controlled" environment of major surgery before undertaking more complex trauma trials.

Final Remarks

We have presented a brief history of ALM drug development from cardiac surgery to combat casualty care. The potential military benefit of the IV or IO fluid is that it resuscitates after severe hemorrhage or neurotrauma by improving CNS–cardiovascular–endothelium coupling and tissue oxygenation, and reduces complications arising from secondary injury progression such as coagulopathy, inflammation, and infection. This conceptual scheme has been termed SHOT.[28,47] The ALM therapy also has the advantage of having low cube weight and is stable over a wide temperature range tailored for small expeditionary missions in remote austere environments. The ALM fluid IV or IO "drip" may also support and amplify the far

TABLE 3 *Summary of the Effect of ALM Therapy in Pig Models After Hemorrhagic Shock and Endotoxemia (2012 to Present)*

Study	Hemorrhagic Shock	Study Duration[a]/ Anesthesia	Bleed/Shock Time (min)	Hypotensive Resuscitation	IV Drip	Coagulopathy Inflammation	Other Major Outcomes
1	~40-kg female pigs pressure controlled (74% blood loss, nonsplenectomized)	Acute 7 hours ventilator midazolam/ ketamine/fentanyl	90	[b]7.5% NaCl ALM in Ringer's acetate led to 40% less fluid to raise MAP to 50mmHg	No	Model did not induce inflammatory response (no difference in cytokine levels)	Reduced postshock fluid requirements in ALM-treated animals was associated with ↑ cardiac contractility and ↑ SVR. After 30-min hypotension, shed blood was returned with another AL bolus that led to 27% ↓ in whole body O_2 consumption and improved kidney function (↑ GFR, ↓ creatinine).[35]
2	35- to 40-kg female pigs pressure controlled (73% blood loss, nonsplenectomized)	Acute 4 hours ventilator midazolam/ ketamine/fentanyl	90	4mL/kg bolus 7.5% NaCl ALM At 60 min MAP 48mmHg vs 33mmHg (controls)	No	Not measured	After 60-min hypotensive resuscitation, ALM animals had 2-fold ↑ CO and SV, ↑ systolic ejection time, maintained ventriculoarterial coupling, ↓ lactate. After returning shed blood, ALM animals had ↓ whole body O_2 consumption (15%), ↓ lactate, and 3-fold ↑ kidney output. One control died.[36]
3	70- to 90-kg male pigs pressure controlled (44% to 60% blood loss)	Acute 4 hours ventilator 1% to 3% isoflurane Telazol, Buprenex	Variable (40 to 81 min)	Hextend/lactated Ringer's: 500mL bolus at a time, 3% NaCl ALM 2 or 4mL/kg bolus	0.5mL/kg/hr (1–2 hours) *or* 3mL/kg/hr (2 hours)	Hextend led to TIC and ↓ platelet aggregation. ALM corrected coagulopathy (ROTEM, STAGO)	1.43L Hextend (3 × 500mL bolus) was superior to any other treatment to resuscitate. ALM was inferior. Controls and ALM groups showed ↓ systolic pressure and ↓ MAP. Kidney and liver function comparable among groups.[39]
4	59-kg female pigs noncompressible hemorrhage (removed 0.45L blood and laparoscopic liver resection)	Acute 6 hours ventilator midazolam/ ketamine/propofol/ fentanyl	Free to bleed	4mL/kg bolus [c]3% NaCl ALM At 4 hours MAP 47mmHg (ALM) vs 62mmHg (controls)	3mL/kg/hr for 4 hours	ALM IL-6/IL-10 ratio 50% lower than controls. ALM ↑ fibrinogen. After drip control antiplasmin fell 20%.	ALM therapy led to no deaths compared to 20% mortality in saline controls. Compared to controls, ALM animals had ↑ CO, ↑ SV, ↓ dP/dt_{min} (less stiff heart), ↓ cerebral perfusion pressure, ↓ cerebral O_2 consumption (28%), ↓ brain glycerol (60%), ↓ brain lactate (47%), and ↓ cortical expression of hypoxia inducible factor. ALM group had lower creatinine and increased urine output.[38]
Endotoxemia (LPS)							
5	40-kg female pigs LPS infusion (1mg/kg/hr) with and without ALM	Acute 6 hours ventilator midazolam/ ketamine/ fentanyl	—	0.9% NaCl ALM maintained constant 47mmHg MAP. Controls were 80–90mmHg	5 hours (high dose 1 hour, low dose 4 hours)	ALM-LPS–infused animals ↓ TnF-α (90 min) ↓ leukocyte superoxide production	ALM induced a reversible profound hypotensive state with ↓ SVR and maintained CO, SV, and ventriculoarterial coupling, ↓ mean pulmonary arterial pressure, maintained tissue blood flow, ↓ lactate, ↓ whole body O_2 consumption, and ↑ urinary output post-infusion.[37]

[a]Study duration represents monitoring time from start of treatment.
[b]Ringer's acetate with 20mL 7.5% NaCl or Ringer's acetate with 20mL 7.5% NaCl ALM.
[c]Hypertonic saline with ALM was decreased from 7.5% to 3.0% since the latter is FDA approved for clinical use.
SVR = systemic vascular resistance; CO = cardiac output; SV = stroke volume; LPS = lipopolysaccharide; MAP = mean arterial pressure; ROTEM = rotational thromboelastometry; TIC = trauma-induced coagulopathy.

TABLE 4 *Summary of Baseline Plasma Levels of α¹-Acid Glycoprotein (*AGP) (also called Orosomucoid) in Mouse, Rat, Pig and Human.*

Adult Species	µg/mL	Relative to Human	Comment	Reference
Mouse	100	~20%	↑ 20 times during acute phase activation	Smith and Waters (2019)[43]
Sprague-Dawley rat	230–320 (275)	48%	↑ up to 10 times during surgery, stress, injury, and inflammation	Smith and Waters (2019)[43]
Pig	1,000–3,000 (2,000)	3.5-fold higher	Strongly age dependent. Newborn basal levels 2–6 times ↑ than adults. Adult AGP ↓ after infection and opposite to other species.	Heegaard et al. (2013)[42]
Human	390–740 (565)	—	↑ 2–4 times during heart attack, major surgery, burns, and trauma	Smith and Waters (2019)[43]

*AGP, an important constituent of human and animal plasma, is a major positive acute-phase protein (except pigs) with drug-binding, anti-inflammatory, and immunomodulatory properties. AGP can bind >300 drugs.

forward use of blood products (i.e., person-to-person, prehospital blood banking, freeze-dried plasma/ and platelets) and may have a broad-spectrum public purpose for prehospital civilian trauma and aeromedical retrieval. Notwithstanding our progress in ALM development, it is important to emphasize that more ALM translational studies and trials are required before safe field use is possible.

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Author Contributions

G.P.D. and H.L.L. contributed equally to literature search, study design, data interpretation, and writing of the manuscript.

Conflict of Interest Statement

G.P.D. is the sole inventor of the ALM concept for cardiac surgery, trauma, sepsis, and cardioplegia. H.L.L. has no conflicts to declare.

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Availability of Data and Materials

The datasets supporting the conclusions of this manuscript can be made available by emailing the authors.

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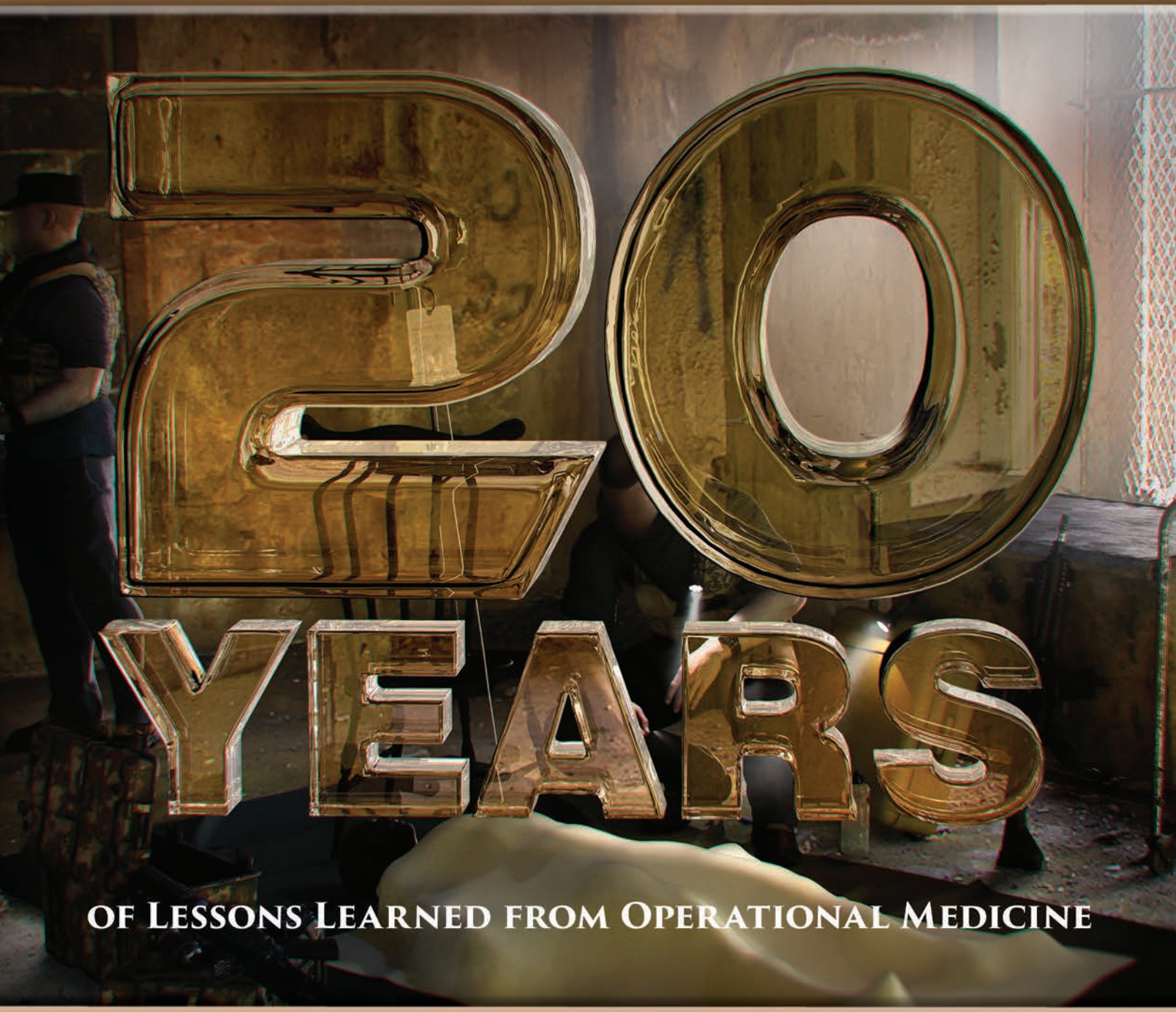

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