ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΜΣ: «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

Τίτλος: Ο ρόλος της υποτασικής αιμόστασης στη διαχείριση ασθενών με ραγέν ανεύρυσμα κοιλιακής αορτής

Title: The role of permissive hypotension in the management of patients with ruptured abdominal aortic aneurysm

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Περίληψη

Στόχος: Διεξήγαμε μία συστηματική ανασκόπηση για να διερευνήσουμε το ρόλο της υποτασικής αιμόστασης στη διαχείριση ασθενών με ραγέν ανεύρυσμα κοιλιακής αορτής (ΡΑΚΑ).

Μέθοδοι: Διενεργήσαμε βιβλιογραφική έρευνα για μελέτες σχετικές με την υποτασική αιμόσταση. Αυτές οι μελέτες ταξινομήθηκαν σε 3 κατηγορίες: α) πειραματικά ζωικά μοντέλα, β) τραυματίες ασθενείς και γ) ασθενείς με ΡΑΚΑ.

Αποτελέσματα: Οι περισσότερες μελέτες σε πειραματόζωα (29) υποστήριξαν την εφαρμογή ελεγχόμενης υπότασης. Από τις 29 μελέτες σε τραυματίες ασθενείς (7 τυχαιοποιημένες κλινικές μελέτες, 22 μελέτες παρατήρησης), οι 19 ανέφεραν θετική συσχέτιση μεταξύ υποτασικής αιμόστασης και κλινικής έκβασης. Δεν υπάρχουν μελέτες που να συγκρίνουν άμεσα την υποτασική με τη νορμοτασική αναζωογόνηση σε ασθενείς με ΡΑΚΑ. Τα περισσότερα στοιχεία, που υποστηρίζουν την εφαρμογή ελεγχόμενης υπότασης, προκύπτουν έμμεσα από λίγες μελέτες παρατήρησης.

Συμπεράσματα: Παρά την έλλειψη αδιάσειστων αποδείξεων, η υποτασική αιμόσταση εφαρμόζεται σήμερα στην καθημερινή κλινική πρακτική. Οι πρόσφατες Αμερικάνικες και Ευρωπαϊκές κατευθυντήριες οδηγίες συστήνουν την εφαρμογή ελεγχόμενης υπότασης ως τμήμα του αλγορίθμου σύγχρονης αντιμετώπισης ασθενών με ΡΑΚΑ.

Λέξεις-κλειδιά: υποτασική αιμόσταση, ελεγχόμενη υπόταση, υποτασική αναζωογόνηση, ζωικά μοντέλα, τραυματίες ασθενείς, ραγέν ανεύρυσμα κοιλιακής αορτής

Abstract

Objective: We conducted a systematic review to document the role of permissive hypotension in the management of patients with ruptured abdominal aortic aneurysm (RAAA).

Methods: Literature search for studies on permission hypotension. These were divided into (i) experimental animal models; (ii) human trauma series; and (iii) RAAA series.

Results: Most animal studies (n=29) supported the use of permissive hypotension. Of the 29 human trauma series (7 randomized controlled trials, 22 observational studies), 19 studies reported positive associations between permissive hypotension and clinical outcome. There are no studies directly comparing hypotensive with normotensive resuscitation in RAAA patients. Most data, in support of permissive hypotension, come indirectly from few observational series.

Conclusions: Despite the lack of high-quality evidence, permissive hypotension is now routine clinical practice. Current American and European guidelines recommend a permissive hypotension policy as part of the modern treatment algorithm of RAAA patients.

Key words: permissive hypotension; hypotensive resuscitation; animal models; trauma; ruptured abdominal aortic aneurysm

Introduction

Hemorrhagic shock in the setting of trauma or ruptured abdominal aortic aneurysm (RAAA) is a leading cause of death.[1-3] Loss of large circulating blood volume due to hemorrhage leads to significant hemodynamic and metabolic changes. The management of hemorrhagic shock is crucial for patient outcome and aims to restore organ perfusion. Replacement of blood volume and plasma and restoration of arterial pressure is important for the viability of tissues and organs.[3]

A rapid and large-volume fluid replacement, known as "normotensive" resuscitation, has the advantage that relatively immediately restores the normal blood pressure. However, evidence suggests that infusing large volumes of fluid leads to hemodilution with reduction of red cell and platelet counts, as well as a decrease in the concentration of clotting factors.[4-6] As a result, a rapid fluid replacement can lead to severe compromise of coagulation mechanisms with rebreeding and persistence of hemorrhagic shock.[2,4-6] An alternative to the normotensive resuscitation strategy is "permissive hypotension", which refers to restricting aggressive fluid resuscitation as long as the patient remains conscious.[7,8] Several synonyms for permissive hypotension can be found in the literature, including "hypotensive hemostasis", or "hypotensive", "controlled", "delayed", "late" or "restrictive" resuscitation, as opposed to the "normotensive", "conventional", "standard", "immediate", "early", or "liberal" resuscitation. Ideally, permissive hypotension should maintain a careful balance between adequate organ perfusion and the risk of rebleeding until definitive hemorrhage control is achieved.[7-9]

Although there are several published animal and human studies on the beneficial role of permissive hypotension in trauma, there is limited data with regards

to the permissive hypotension in the management of hemorrhagic shock in RAAA patients. The aim of this comprehensive review was to summarize in a systematic fashion the available literature data on experimental animal and human studies concerning the role of permissive hypotension in trauma and to present the available evidence on the role of permissive hypotension in the management of patients with RAAA.

Methods

An English-language literature review was undertaken through to August 2021 to define the role of permissive hypotension in the management of hemorrhagic shock in (i) experimental animal trauma series, (ii) human trauma series, and (iii) RAAA patients. This article was prepared according to previously published guidelines for reporting meta-analyses of observational studies. Two authors performed the literature search, study selection and data abstracting. Disagreements between the reviewers were resolved by consensus. Both the Medline and EMBASE databases were searched using a combination of the terms: “hypotensive resuscitation” or “hypotensive hemostasis” or “permissive hypotension” or “controlled resuscitation” or “delayed resuscitation” combined with the search terms “experimental study”, “animal model”, “trauma”, “hemorrhagic shock” (separately or in combination), and “ruptured abdominal aortic aneurysm”. The “advanced” tool (PubMed Advanced Search Builder) was used to combine the above terms using the options “OR” or “AND”. The electronic search was supplemented by a manual search of the reference lists of relevant articles.

Results

The search results (number of articles) per query are presented in table 1. After excluding non-relevant articles, eligible studies were divided into three groups: (i) experimental animal studies investigating a hemorrhagic shock resuscitation protocol; (ii) human trauma series; and (iii) RAAA studies.

Experimental animal studies

A total of 29 experimental animal studies were identified which had investigated the role of permissive hypotension in the management of hemorrhagic shock.[10-39] The basic data extracted from these 29 studies are presented in table 2. The median animal number was 31 (range 12-226) per study. The experimental animals used were rabbits in 4 studies, pigs in 13, rats in 11, and sheep in one. According to the experimental protocol, hemorrhagic shock was induced by penetrating-type injury to the abdominal aorta in 14 studies,[10-15,20,22,25,27,30,31,32,35,36] tail amputation in 5[16,17,19,23,24], liver laceration in one,[26] splenic injury in one,[34] transection of both lumbar veins in one,[21] thoracotomy and laceration to a pulmonary vein branch in one,[18] transection of distal ileocolic artery and vein in one,[13] and, finally, withdrawing blood through an arterial or an inferior vena cava catheter in 5 studies.[28,29,33,37,38] In 4 studies, the experimental protocol also included a combined traumatic brain injury, which was induced by either the weight-dropping method[24,34] or a fluid percussion model.[14,36] Most studies supported the use of permissive hypotension over “standard”, “conventional” or “normotensive” resuscitation. Furthermore, a meta-analysis of randomized controlled trials (RCTs) investigating fluid resuscitation strategies (timing, volume, or resuscitation targets) in animal models of uncontrolled hemorrhage, identified 9 trials that compared hypotensive versus normotensive resuscitation.[39] The relative risk of

death with hypotensive resuscitation was 0.37 (95% CI, 0.27-0.50). Hypotensive resuscitation reduced the risk of death in all the trials investigating it.[39]

Human trauma series

Several human studies exist in the literature investigating the role of permissive hypotension in trauma. Permissive hypotension aims to target lower-than-normal SBP (typically 80 to 90 mmHg) during the fluid resuscitation of patients with hypovolemia. Overall, there are three strategies to deliver permissive hypotension in a trauma patient with hemorrhagic shock: 1) late (vs early) fluid resuscitation, 2) restrictive (vs liberal) volume resuscitation, 3) hypotensive (vs normotensive) resuscitation. A total of 29 eligible series were identified and basic information are presented in table 3.[1,7,8,40-64] There were 7 RCTs and 22 observational series (including 5 registries). Overall, 19 studies reported positive associations between permissive hypotension and clinical outcome. Briefly, of the seven RCTs[7,40,42,43,48,59,60], four reported statistically significant differences in favor of permissive hypotension[7,40,48,59], whereas three failed to show any significant differences.[42,43,60] Of the 22 observational studies, 15 reported positive associations between permissive hypotension and clinical outcome.[8,41,45-47,50,53-55,61,62-64] In detail, it has been shown that aggressive volume administration increased mortality,[8,41,53,61,50,54,47] coagulopathy,[45] multiple organ failure,[54] nosocomial infections,[54] blood transfusion,[54] the incidence of secondary abdominal compartment syndrome (ACS),[46] damage-control laparotomy,[62] and intensive care unit and hospital length of stay.[54] On the other hand, the remaining 7 observational studies[1,6,44,52,56,57,63] failed to document any significant associations between permissive hypotension and outcome. Furthermore, five systematic reviews and meta-analyses have been published on the topic and are presented in table 4.[4,5,65-67] Even when considering

these, the effectiveness of permissive hypotension/hypotensive resuscitation and restricted/controlled resuscitation in trauma patients is still inconclusive.

Interesting information on permissive hypotension can also be extracted from professional society guidelines on the management of trauma. The most recent, 10th edition of the ATLS guidelines advocate "balanced", i.e. hypotensive, resuscitation prior to definitive surgical control of bleeding.[68] Permissive hypotension and restricted fluid resuscitation strategies are also included as recommendations in the 5th edition of the European guideline on management of major bleeding and coagulopathy following trauma.[69] Recommendation 12 states that "We recommend permissive hypotension with a target SBP of 80-90 mmHg (mean arterial pressure 50–60 mmHg) until major bleeding has been stopped in the initial phase following trauma without brain injury. (Grade 1C) In patients with severe brain injury (GCS≤8), we recommend that a mean arterial pressure ≥80 mmHg be maintained. (Grade 1C)". Recommendation 13 also states that "We recommend use of a restricted volume replacement strategy to achieve target blood pressure until bleeding can be controlled. (Grade 1B)." NICE guidelines (2016) also recommend a restrictive approach to volume resuscitation until definitive early control of bleeding has been achieved.[70,71] Finally, the Trauma Hemostasis and Oxygenation Research (THOR) Network has recently published a position paper on the role of hypotensive resuscitation as part of remote damage control resuscitation (DCR), i.e. the prehospital application of DCR. The authors argue that there is emerging evidence suggesting that mortality is worse if the SBP is <110 mmHg on admission, therefore, it is reasonable to aim for higher blood pressure target than the current level of 80-90 mmHg for prehospital providers.[72]

RAAA patients

Very limited literature data exist regarding the role of permissive hypotension in the management of RAAA patients and most of these come indirectly from observational series. Table 5 summarizes the basic facts from the few studies found on the topic. There are no studies directly comparing permissive hypotension with normotensive resuscitation strategies in the management of hemorrhagic shock in RAAA patients, either in an RCT setting or in comparison with a historical control group.

In the earlier era of RAAA literature, Lawer[73] and Crawford[74] were among the first to hypothesize that aggressive fluid resuscitation may, in fact, be harmful, as it may lead to increased blood pressure and subsequent exsanguination that exacerbates hypotension despite increased fluid resuscitation. On the other hand, withholding fluids to allow clot formation and to avoid iatrogenic coagulopathy may prove beneficial in this fragile group of patients.[74] These findings were supported by Hardman et al. who concluded that infusion of more than 3.5L of fluid prior to surgery increased the risk of death by a factor of 3.54.[75]

The concept of hypotensive resuscitation in the RAAA patient management received renewed interest following the successful introduction of endovascular therapy as a treatment option for RAAAs. Veith and colleagues were the first to incorporate the principle of hypotensive hemostasis in the endovascular management of RAAAs.[76,77] However, the introduction of permissive hypotension as part of the modern protocol of “endovascular-if possible” approach for the management of RAAAs was popularized by Lachat and his colleagues in Zurich.[80] Apart from permissive hypotension, the very low 30-day mortality of 13%, could also be attributed to other, equally important components of the Zurich protocol, including adequate imaging, selective aortic balloon occlusion, predominantly local anesthesia, detection and treatment of ACS, team approach and attention to logistics. The Zurich

group also adopted active pharmacologic lowering of blood pressure (phentolamine, esmolol, nitroglycerine), targeting a SBP between 70-90mmHg.[80]

To date, there is only one published study which was designed specifically to investigate a permissive hypotension protocol for RAAA patients.[78] This prospective Dutch study evaluated the feasibility of a protocol of hypotensive hemostasis using intravenous nitrates. The aim was to limit prehospital intravenous fluid administration to 500 mL and to maintain SBP between 50 and 100 mmHg. The desired SBP range was reached in 46% of cases, whereas in 54%, a SBP>100 mmHg was recorded for >60 min. Interestingly, another Dutch study investigated the feasibility of initiating such a protocol for all patients suspected of a RAAA by the ambulance staff in the prehospital setting.[79] This real-world study suggested that, although feasible and low risk, the protocol achieved true controlled hypotension in only 17% of RAAA patients.

Permissive hypotension is a key aspect of the modern resuscitation management of RAAA patients undergoing not only EVAR, but OSR, too. This is supported by another recent Swiss series of predominantly OSR. The impressively very low for OSR mortality of 15.3% is due to a policy of delaying volume resuscitation until surgical control of bleeding is achieved.[9]

In the post-IMPROVE trial era, there is debate about what is the optimal threshold for permissive hypotension in RAAA patients. In the IMPROVE trial, the lowest SBP was strongly and independently associated with 30-day mortality, and it was suggested that a minimum SBP of 70 mmHg is too low a threshold for permissive hypotension in RAAA patients.[82] Finally, the current SVS and ESVS guidelines both recommend implementing hypotensive hemostasis with restriction of fluid

resuscitation in the conscious patient. The level (or class) of recommendation was 1 (strong) and the quality (or level) of evidence was B (moderate).[83,84] Similarly, the NICE (UK) guidelines recommend permissive hypotension during transfer of people with RAAA to regional vascular services.[85]

Discussion

This study clearly demonstrates the lack of quality literature data on permissive hypotension in the management of RAAA patients. Such a policy has not been investigated as a primary end point in a dedicated randomized-controlled or non-randomized clinical study. On the other hand, there are several experimental animal and human trauma studies investigating the role of hypotensive vs normotensive resuscitation strategies for the management of hemorrhagic shock. These studies were summarized here in a systematic fashion and some of the evidence may be extrapolated in the RAAA patient population. With regards to the experimental animal studies, most demonstrate the superiority of hypotensive resuscitation over aggressive resuscitation. Similarly, the human trauma literature suggests that permissive hypotension may offer a survival benefit over conventional resuscitation for patients with hemorrhagic injury. However, one should take into account that these are studies on young, healthy animals, or younger trauma victims with no or few comorbidities, groups dissimilar to the RAAA patients who are elderly and frequently have significant comorbidities.

Despite the lack of evidence, nowadays permissive hypotension is considered a safe, well documented, and widespread practice in the management of RAAA patients.[83-85] It is appropriate both during the transfer to a higher facility and, in-

hospital, until the aneurysm is excluded. Given the above, it is unlikely that there will ever be a RCT comparing permissive hypotension with aggressive resuscitation, since such a study would be unethical to conduct. There are also some unresolved issues. What is the safe minimum SBP threshold for permissive hypotension in RAAA patients? Should this process of lowering the blood pressure be a passive one or should we be more aggressive and promote active lowering of the blood pressure using pharmacological agents?

With regards to the first question, the ideal trigger to fluid resuscitation in RAAA seems to be higher than Crawford's target, which was a SBP of 50–70 mmHg,[74] or Veith's target of SBP of 50mmHg.[76,77] This is particularly true for the older RAAA patient with other cardiovascular diseases and high cardiovascular resistance. In the IMPROVE trial, the 30-day mortality was 51% among patients with a lowest recorded SBP of less than 70mmHg and 34.1% in those with a SBP>70 mmHg.[82] SBP was directly related to outcome in a linear fashion, with each 10-mmHg increase translating to a 13% relative improvement in odds of survival. As a result, most vascular specialists would now opt for permissive hypotension that aims to maintain a mental status and a target systolic pressure between 70-90 mmHg.[83,84]

Whether a policy of actively lowering the blood pressure using pharmacological agents is beneficial remains unclear. Some authors specifically use the term "hypotensive hemostasis" to describe this active management and distinguish it from "permissive hypotension", the latter being more of a passive process of not responding to hypotension, as long as the patent remains conscious and stable albeit hypotensive.[84] The recent SVS guidelines,[83] and series from experienced centers,[80] recommend a policy of limited fluid resuscitation supplemented by intravenous

nitroglycerin, esmolol, sodium nitroprusside, and pain medication, as needed, to avoid hypertension and to minimize the risk of uncontained rupture.

Given that the current American and European guidelines recommend EVAR as the preferred option for RAAA repair, it is important to appreciate that permissive hypotension is only one of the several key elements of the modern treatment algorithm of RAAA.[83,84] With the introduction of "EVAR-if-feasible" approach, permissive hypotension seems to work well with other important components of this algorithm, particularly, performing the endovascular procedure under local anesthesia, balloon endoclamping for proximal aortic control, and expeditiously detecting and managing post-operative ACS. Local anesthesia has been advocated to prevent circulatory collapse caused by the induction of general anesthesia and to promote peritoneal tamponade. As a result, combining permissive hypotension with local anesthesia may contribute to some of the improvement in outcome associated with the endovascular approach. For those patients who, despite permissive hypotension, become decompensated and hemodynamically unstable, aortic balloon occlusion for early proximal control may prove lifesaving. Finally, permissive hypotension may also improve outcome by minimizing the post-operative ACS rate. The latter is a significant cause of post-operative mortality and morbidity in RAAA patients, and aggressive fluid resuscitation has been shown to be a risk factor for ACS after both EVAR and OSR.

Conclusion

This systematic review investigated the role of permissive hypotension in the management of RAAA patients. Most experimental studies demonstrate the superiority of hypotensive resuscitation over aggressive resuscitation in animal models of hemorrhagic shock. Human trauma series suggest that permissive hypotension may offer a survival benefit over conventional resuscitation for patients with hemorrhagic injury, but further research is needed. No studies exist in the literature directly comparing hypotensive with normotensive resuscitation in RAAA patients and most data, in support of permissive hypotension, come indirectly from few observational series. Nevertheless, despite the lack of high-quality evidence, permissive hypotension is now part of routine clinical practice and current American and European guidelines recommend this policy as part of the modern treatment algorithm of managing RAAA patients.

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Table 1. PubMed search strategies using the "advanced" search option and combing different search terms. Results column identifies numbers of eligible articles per search query.

Table 2. Experimental animal studies. Key: SR: Standard (conventional or normotensive) Resuscitation; HR: Hypotensive Resuscitation (or Permissive Hypotension); PH: Permissive Hypotension; LR: Lactated Ringer's solution; MAP: Mean Arterial Pressure; C: Control group; Hb: Hemoglobin; HS: Hetastarch; CI: Cardiac Index; NR: No Resuscitation; CO: Cardiac Output; BD: Base Deficit; StO2: Tissue Oxygen Saturation; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; BE: Base Excess; Ht: Hematocrit; SBP: Systolic Blood Pressure; DDVAP: Desmopressin; FXIII: Factor XIII; PFC: Prolonged Field Care

Table 3. Human trauma studies investigating hypotensive resuscitation. Key: n: number; RCT: randomized control trial; Pts: patients; RIS: rapid infusion system; iv: intravenous; OR: operating room; NS: not significant; ARDS: acute Respiratory Distress Syndrome; AKI: acute kidney injury; SBP: systolic blood pressure; ED: Emergency Department; LOS: length of stay; ICU: intensive care unit; intraop: intra-operative; postop: post-operative; preop: pre-operative; HR: hypotensive resuscitation; SR: standard (or conventional or normotensive or aggressive) resuscitation; DCR: damage control resuscitation; DCL: damage control laparotomy

Table 4. Main findings of the 5 systematic reviews/meta-analyses of human trauma series investigating the role of different fluid resuscitation strategies. Pts: patients; iv: intravenous; HR: hypotensive resuscitation; ARDS: Adult Respiratory Distress Syndrome

Table 5. Literature data on hypotensive resuscitation in RAAA patients. N: number; OSR: open surgical repair; pts: patients; preop: preoperative; BP: blood pressure; HR: hypotensive resuscitation; SBP: systolic blood pressure; RR: risk ratio; AOB: aortic occlusion balloon; EVAR: endovascular aneurysm repair; AUI: aortouniiliac; Fem-fem: femoro-femoral; PH: permissive hypotension; iv: intravenous; US: ultrasound; CTA: computed tomography angiography; ACS: abdominal compartment syndrome; RCT: randomized controlled trial.

Table 1

Search	Query	Results
#1	Search: (((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (experimental study)	1387
#2	Search: (((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (animal model)	1769
#3	Search: (((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (trauma)	4552
#4	Search: (((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (hemorrhagic shock)	1451
#5	Search: ((((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (trauma)) AND (experimental study)	301
#6	Search: ((((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (hemorrhagic shock)) AND (experimental study)	161
#7	Search: ((((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (trauma)) AND (animal model)	656
#8	Search: ((((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (hemorrhagic shock)) AND (animal model)	515
#9	Search: (((((hypotensive resuscitation) OR (hypotensive hemostasis)) OR (permissive hypotension)) OR (controlled resuscitation)) OR (delayed resuscitation)) AND (ruptured abdominal aortic aneurysm)	68

Table 2

	Author, year, animal model	Methods	Results & Conclusions
1	Bickell, 1991, pig	Splenectomy and stainless steel wire placement in infrarenal aorta. Aortotomy. Fluid resuscitation following hemorrhage: SR (80 ml/kg LR) or HR (no fluid)	100% mortality (SR), no deaths (HR)
2	Kowalenko, 1992, pig	Placement of surgical steel aortotomy wire. Preliminary bleed via a femoral artery catheter. Aortotomy, bled to MAP 5 mmHg. 3 groups of fluid resuscitation: SR to achieve MAP 80 mmHg; HR: MAP 40 mmHg; C: nil	1-h mortality 62.5% (SR), 12.5% (HR), 87.5% (C); blood loss 39. 9 ml/kg (SR), 8.2 ml/kg (HR), 6.7 ml/kg (C)
3	Stern, 1993, pig	Placement of surgical steel aortotomy wire. Preliminary bleed via a femoral artery catheter. Aortotomy, bled to MAP 5 mmHg. 3 groups of fluid resuscitation: SR MAP 80 mmHg; HR1 MAP 60 mmHg; and HR2 MAP 40 mmHg	Mortality 78% (SR), 16% (HR1), 11% (HR2); reduced blood loss, Hb, oxygen carriage (SR vs. HR1, HR2); increased oxygen delivery (HR1 vs. HR2); reduced metabolic acidosis (HR1 vs. HR2, SR)
4	Craig, 1994, rat	Laparotomy, transection of distal ileocolic artery and vein and closure. 5 groups were compared: no resuscitation; small volume LR; large volume LR; small volume hetastarch (HS); or large volume HS.	LR or HS animals had greater blood loss and coagulopathy than the no resuscitation group. Survival was highest in non-resuscitated animals
5	Stern, 1995, pig	Placement of surgical steel aortotomy wire. Preliminary bleed via a femoral artery catheter. Aortotomy, bled to MAP 5 mmHg. Resuscitated with blood followed by normal saline to maintain MAPs of 40, 60, and 80 mmHg (groups I, II, and III). Groups IV, V, and VI received the same fluids in reverse order	HR produced comparable improvements in 1-h survival and reductions in hemorrhage regardless of whether blood or saline was administered first. Although HR resulted in improved outcome, it was associated with significant acidosis. This was minimized with moderate rather than severe underresuscitation and early blood administration
6	Owens, 1995, pig	Aortotomy. 3 groups of resuscitation: SR to restore CI to 100% of baseline; HR CI to 60%; and C: no fluid	Increased blood loss and fluid requirement (SR); one death (SR and C), no deaths (HR)
7	Capone, 1995, rat	Uncontrolled hemorrhagic shock; preliminary bleed and 75% tail amputation. Prehospital phase resuscitation followed by hemostasis. Four groups: C (untreated); no prehospital fluid; LR to maintain MAP 40mmHg; LR to maintain MAP 80mmHg	Death within 3 days: no fluid 9/10; MAP 40 4/10; MAP 80 10/10
8	Capone, 1995, rat	Uncontrolled hemorrhagic shock; preliminary bleed and 75% tail amputation. Resuscitation for 90 min followed by surgery. C: no fluid/surgery, NR: no prelim fluid, HR: MAP 40 mmHg, SR: MAP 80 mmHg	C: all dead within hours, NR: 5 survive to surgery, HR: all survive to surgery, SR: 2 survive to surgery
9	Sakles, 1997, sheep	Thoracotomy, a pulmonary vein branch was lacerated, and a chest tube was inserted to monitor hemorrhage. Immediate fluid resuscitation with LR vs no fluid	Immediate fluid resuscitation significantly increased the rate, volume, and duration of hemorrhage
10	Marshall, 1997, rat	Uncontrolled hemorrhagic shock; preliminary bleed and 75% tail amputation; resuscitation to target MAP 40 or 80 mmHg followed by control of bleeding. 4 groups: MAP 40mmHg with LR; MAP 40mmHg with LR and blood; MAP 80mmHg with LR; MAP 80mmHg with LR and blood	Mortality: MAP 40 with LR, 2/8; MAP 40 with LR & blood, 1/8; MAP 80 with LR, 8/8; MAP 80 with LR & blood, 0/8
11	Riddez, 1998, pig	Aortotomy. Fluid resuscitation at ratio to blood loss HR1 1:1, HR2 2:1, SR 3:1, C 0:1	50% mortality (SR and C), 25% mortality (HR1 and HR2); rebleeding is cause of death in HR2; hypovolemic shock is cause of death in HR1
12	Smail, 1998, rat	Laparotomy, both lumbar veins were severed, bled to MAP to 40mmHg. This was maintained for 45min and the abdomen was closed. Resuscitation with 0, 10, or 30mL LR. CO and regional blood flow were determined	10 or 30mL RL increased MAP and CO compared with NR animals. The 10 mL regimen increased total hepatic blood flow. Increasing to 30 mL did not improve hemodynamic parameters or regional perfusion. Moderate instead of NR or larger volume of resuscitation is recommended
13	Burris, 1999, rat	Aortotomy; resuscitation 5 min after injury for 2 h with LR, 7.3% hypertonic saline in 6% hetastarch (HH), or no fluid (NF). Fluids infused to maintain MAP of 40, 80, or 100 mm Hg in 6 groups: NF, LR 40, LR 80, LR 100, HH 40, and HH 80.	Survival was improved with fluids. NF rats did not survive 4h. At 72h, LR 80 rats (80%) and HH 40 rats (67%) showed improved survival over NF rats (0%). Rebleeding increased with MAP. Attempts to restore normal MAP (LR 100) led to increased blood loss and mortality.
14	Soucy, 1999, rat	Tail resection hemorrhage model. 5 groups were compared: NR; resuscitated with moderate or high volume at slower or faster rate (4 groups)	A trend toward improved survival was noted with faster rate of infusion (60 vs. 33.3% with moderate volume and 28.6 vs. 12.5% with high volume, compared with 16.7% in the NR animals)
15	Talmor, 1999, rat	Closed head injury & uncontrolled hemorrhagic shock (25% tail resection). Animals assigned to head injury or no head injury and further subdivided into fluid with saline 3ml/ml blood lost (FR) or no fluid (NR) or resuscitation MAP targets 70, 80, 90mmHg (RE70, RE80, RE90).	Mortality in closed head injury group: NR 3/11; FR 2/10; RE70 10/18; RE80 26/34; RE90 10/10; No head injury: 0/8; FR 1/9; RE70 1/9; RE80 6/14; RE90 10/10. Treatments to support BP increased bleeding and/or decreased survival
16	Stern, 2000, pig	Swine model of combined fluid percussion brain injury and uncontrolled hemorrhage to MAP 30mmHg (induced by 4-mm aortic tear). Three groups: NR; HR: MAP 60mmHg; SR: MAP 80mmHg	Death within 150 min: NR, 6/6; MAP 60, 1/9; MAP 80, 4/9

17	Varela, 2003, pig	Liver laceration. Resuscitation followed by surgery. C: no fluid, HR: MAP 60mmHg, SR: MAP 75mmHg	No deaths; increased blood loss & fluid requirement in SR; increased splanchnic perfusion and oxygen delivery in HR
18	Sondeen, 2003, pig	Laparotomy, splenectomy, aortotomy. At either 5, 15, or 30 min after the end of the initial hemorrhage, resuscitation with LR was begun at either 100 or 300 mL/min. The rebleeding MAP was determined	Rebleeding MAP=64±2, Systolic=94±3, and Diastolic=45±2 mmHg. The rebleeding pressure was not affected by the time or rate of resuscitation. The optimal endpoint of resuscitation in animals without definitive hemorrhage control would be below this rebleeding pressure.
19	Skarda, 2008, pig	Controlled hemorrhagic shock in 24 splenectomized pigs; randomized to SR (SBP=90mmHg), mild HR (SBP=80mmHg), severe HR (SBP=65mmHg), or NR. After the initial 8h of randomized pressure-targeted resuscitation, all animals were resuscitated to a SBP of 90mmHg for 16h	Animals with severe HR were less likely to survive compared with SR. However, mild HR did not lead to a persistent BD or to decreased StO2, suggesting less metabolic stress and less tissue hypoxia
20	Yu, 2009, rabbit	Rabbit model of uncontrolled hemorrhagic shock in pregnancy. Laparotomy; bleeding by transecting a small artery in the mesometrium and blood withdrawal via the carotid artery (to MAP 40-45mmHg). Animals received HR with LR to maintain MAP 50, 60, or 70mmHg (RE50, RE60, RE70); or SR with LR to maintain MAP 80mmHg (RE80)	HR groups significantly decreased blood loss and subsequent volume infusion, leading to higher hematocrit, lower lactate, and shorter PT and APTT. Median survival time in group RE60 was significantly longer than that in groups RE50, RE70, and RE80
21	Rezende-Neto, 2010, rabbit	Aortotomy model, 42 rabbits randomized to: sham; SR; HR (60% baseline MAP); SR plus DDAVP 1 h before (DDAVP SR) or 15 min after beginning of shock (DDAVP T1 SR); and HR plus DDAVP 1 h before (DDAVP HR) or 15 min after beginning of shock (DDAVP T1 HR)	HR reduced bleeding and improved hemostasis compared with SR. DDAVP given preshock exerted similar effects with SR
22	Rezende-Neto, 2010, rabbit	Uncontrolled hemorrhagic shock and hypotensive resuscitation model in 30 male rabbits. Laparotomy & aortotomy. Animals received SR (to achieve baseline MAP; or HR (60% of baseline MAP)	Intraabdominal blood loss was significantly greater in SR. Antithrombin levels decreased significantly in SR animals compared to baseline, sham, and HR animals. Evidence of re-bleeding was also noted in SR group.
23	Schmidt, 2012, rat	Abdominal aortic injury model; 24 male rats randomized to: sham, NR, HR (60% of baseline MAP), or SR	HR caused less intra-abdominal bleeding and maintained equivalent organ perfusion. NR reduced intra-abdominal bleeding but also significantly reduced organ perfusion
24	Ponschab, 2015, pig	Hemorrhagic shock model in pigs. Bleeding was simulated by withdrawing blood through an arterial catheter over 30min. Two resuscitation groups: HR (low volume crystalloid) vs SR (high volume crystalloid) solution	HR increased MAP significantly less; no difference in lactate and BE. Ht after fluid replacement was 0.20 vs. 0.16 (HR vs. SR, $p<0.001$), suggesting a grade of blood dilution of 32 vs. 42% ($p<0.001$). Fibrinogen and ROTEM parameters were less impaired with HR
25	Hu, 2015, rat	Combined traumatic brain injury and uncontrolled hemorrhagic shock model. Laparotomy, bleeding induced by transection of splenic parenchyma plus one branch of the splenic artery. Animals with target resuscitation MAP 50-90mmHg were compared	Rats with MAP of 50, 60 and 70mmHg had less hemorrhage and volume requirements, better cerebral blood flow and longer survival compared to rats with MAP of 80 and 90mmHg. The 70mmHg group had the best brain perfusion.
26	Carreiro, 2015, rabbit	Abdominal aortic injury model; 54 rabbits were randomized in 9 groups: Sham; FXIII and SR; FXIII and HR (MAP 60% baseline); FXIII/DDAVP/SR; FXIII/DDAVP/HR; SR only; FXIII no hemorrhage; FXIII/DDAVP no hemorrhage; HR only	SR provokes more bleeding and worsens coagulation, that is partially reversed by factor XIII and desmopressin. FXIII and DDAVP can synergistically improve coagulation. HR reduces bleeding regardless of those agents
27	Vrettos, 2016, pig	Combined traumatic brain injury and uncontrolled hemorrhagic shock model. Laparotomy & aortotomy. SR group with goal SBP>80mmHg vs HR group	All SR animals died before surgical hemostasis, whereas 50% of the HR animals survived
28	Morgan, 2019, pigs	Animals (n=15) were randomized to non-shock (NS)/normotensive (anesthesia only); NS/PH (bleeding to SBP=85±5mmHg for 6h with SBP maintained via crystalloid, then recovered; and experimental group with controlled hemorrhage to MAP=30mmHg until decompensation (Decomp/PH), followed by 6 hours of PFC. Hemorrhaged animals were then resuscitated with whole blood and observed for 24h	Study of military trauma relevance to determine safety of prolonged PH. After 6h, a prolonged PH strategy showed no detrimental effect on survival or neurologic outcome despite the increased ischemic burden of hemorrhage. Significant fluid volume was required to maintain SBP-a potential logistic burden for prehospital care
29	Chipman, 2020, rat	Prolonged PH model of military relevance. Mice underwent laparotomy and hemorrhagic shock (MAP=35±5mmHg x 90min) followed by PH with either FFP or Hextend® to maintain MAP=55-60mmHg for 6h	FFP maintains its pulmonary protective effects using a PH strategy (compared to Hextend®), which supports the need for further development and implementation of plasma-based resuscitation in the forward environment

Table 3

	First author	Year	Type of Study	n	Methods	Results/Conclusions
1	Kaweski	1990	Retrospective	6,855	Pts with prehospital iv fluids vs pts with no fluids	No influence of fluid administration on survival
2	Dunham	1991	RCT	36	Hypovolemic trauma pts were resuscitated either with the RIS, which can deliver fluids/blood products rapidly at precise rates and normothermic conditions, or with conventional fluid administration	RIS pts needed fewer fluid/blood products and had less coagulopathy; more rapid resolution of hypoperfusion acidosis; better temperature preservation; and fewer hospital complications
3	Bickell[8]	1994	RCT, penetrating torso injuries	598	Pts with a pre-hospital SBP<90mmHg were assigned either to SR or delayed resuscitation (iv cannulation but no fluid resuscitation until they reached the OR)	Survival was significantly better in the delayed-resuscitation group (70% vs 62%, p=0.04)
4	Humbly	1996	Retrospective	527	Trauma pts who received rapid volume resuscitation (via the RIS) vs matched controls	Pts who received rapid fluid infusion had a 4.8 times greater chance of dying (95% CI 2.4-7.1)
5	Sampalis	1997	Retrospective	217	Pts who had on-site iv fluid replacement (IV group) were compared with a matched group without iv fluids (no-IV group)	Pts in the IV group were 2.3 (95% CI, 1.02–5.3) times more likely to die
6	Turner	2000	RCT	1309	Prehospital iv fluid replacement vs no iv fluids in serious trauma pts	No significant differences in outcome were found between the two groups
7	Dutton	2002	RCT	110	Hemorrhagic shock pts were randomized into SR (target SBP>100mmHg) or HR (target SBP 70mmHg)	When compared to SR, HR of hemorrhagic shock did not affect mortality in this study
8	Dula	2002	Retrospective	150	blunt trauma; matched-pairs case-control study; pts who received >500mL prehospital fluids vs no fluids	No significant difference in survival
9	Talving	2005	Retrospective cohort	102	Hypotensive trauma pts (SBP≤90mmHg); the effects of fluid therapy on outcome was investigated	Fluid therapy was initiated at the scene in 73%. NS association was found with outcome
10	Maegele	2007	Retrospective, German Trauma Registry	8724	To determine whether coagulopathy in multiple injury upon ER admission was associated with the amount of iv fluids administered pre-clinically and with impaired outcome	Coagulopathy (34.2%) was associated with the amount of iv fluids administered pre-clinically and impaired outcome
11	Madigan	2008	Retrospective	96	Pts with extremity injuries and secondary ACS were compared to those with no ACS	Early, large volume crystalloid administration was the greatest predictor of secondary ACS
12	Cotton	2011	Retrospective	390	Pts undergoing DCL between 2004-2010 were divided into pre-DCR implementation and DCR groups	DCR reduced crystalloid and blood product administration and was associated with improved 30-day survival
13	Morrison	2011	RCT	90	Trauma pts were randomized to HR (target MAP 50mmHg) or SR (target MAP 65mmHg). Outcome included intraop fluid requirements, mortality, postop complications	HR significantly reduced blood product and iv fluid administration; postop coagulopathy; and early postop death and coagulopathy
14	Ley	2011	Retrospective	3,137	Elderly (≥70 years) vs nonelderly (<70 years) trauma pts who received crystalloid fluid in the ED	Fluid volumes ≥1.5 were significantly associated with mortality in both elderly and nonelderly pts
15	Haut	2011	Retrospective, National Trauma Data Bank	776,734	The study compared trauma pts with vs without prehospital IV fluid administration	Multivariable analysis demonstrated that pts receiving prehospital IV fluids were significantly more likely to die (OR 1.11, 95% CI 1.05–1.17)
16	Duke	2012	Retrospective	307	Pts with penetrating torso trauma received either restrictive (<150mls) or standard (>150mls) crystalloid fluid before arrival at hospital	The restrictive fluid group demonstrated lower odds of death OR 0.69 (95% CI 0.37-0.91)
17	Hampton	2013	Prospective, 10 Level 1 trauma centers	1245	Pts with vs without prehospital iv fluids were compared	Prehospital iv fluid volumes did not result in increased SBP but were associated with decreased in-hospital mortality
18	Hussmann	2013	Registry, German Society for Trauma Surgery	948	Two matched groups were compared according to prehospital fluid replacement, low-volume (0-1500 ml) vs high-volume (≥ 1501ml)	Excessive prehospital fluid replacement led to increased mortality (27.6% vs 22.7%; p<0.01)
19	Kasotakis	2013	Prospective multicenter	1754	Interrogation of the Glue Grant database assessed whether aggressive early crystalloid resuscitation adversely affects outcomes in blunt trauma pts	Crystalloid resuscitation was associated with increased morbidity, ICU and hospital LOS
20	Brown	2013	Prospective multicenter	1216	Blunt trauma pts were divided into high volume (HV) (>500 mL) (68%) or low volume (LV) (≤500 mL) prehospital crystalloid resuscitation. 51% had prehospital hypotension	In pts without hypotension, HV resuscitation was associated with increased mortality and acute coagulopathy, but not in pts with hypotension
21	Leenen	2014	Retrospective; German Trauma Society Registry	908	Elderly pts only; prehospital volume resuscitation: low volume (≤1000 ml) vs high volume (>1000 ml)	No difference in mortality. Low volume resuscitation has a positive effect on the initial coagulation status in elderly pts
22	Geeraedts	2015	Retrospective, level 1 trauma center	941	Hypotensive trauma pts; to investigate associations between prehospital fluid volumes and shock index and blood transfusion, respectively, in the ED and mortality at 24h	Mortality at 24h was not associated with prehospital iv fluids
23	Bridges	2015	Retrospective	2009	National Trauma Data Bank report; HR in pts ≥55y vs HR in pts 18-54y	No synergistic effect of age and admission SBP on mortality. HR is safe in the elderly

24	Schreiber[12]	2015	Multicenter pilot RCT	192	Hypotensive trauma pts (with SBP ≤ 90 mmHg) were randomized in the out-of-hospital setting into those receiving HR or those receiving SR	HR may offer an early survival advantage in blunt trauma (but not in penetrating trauma)
25	Carrick[13]	2016	RCT	168	Pts undergoing laparotomy or thoracotomy for penetrating trauma were randomized to HR (target MAP 50mmHg) or SR (target MAP 65mmHg)	The trial was unable to demonstrate that HR could significantly improve mortality and was terminated early
26	Harada	2017	Retrospective, level 1 trauma center	1571	Pts who were resuscitated with <2 L of crystalloid (low volume) vs those who received ≥2 L (high volume)	Adjusted mortality was higher in high-volume resuscitation group
27	Joseph	2017	Retrospective	1030	Pts undergoing trauma laparotomy. 3 groups: pre-DCR era (2006-2007), transient (2008-2009), and post-DCR (2010-2013)	Post-DCR era was associated with a decrease in the use of DCL; decrease in the use of crystalloid; increase in the use of blood products; and with improved outcome
28	Bores	2018	Retrospective, trauma registry	1966	Prehospital iv fluids in penetrating trauma pts vs no iv fluids	No difference in mortality between groups (23.4 vs 21.3%)
29	Lou	2018	Retrospective, elderly trauma pts	219	3 groups: SR (20-30 mL/min, target MAP 65-75mmHg); HR (4-5 mL/min, target MAP 50-65mmHg); personalized resuscitation (PR) with appropriate iv fluid volume and speed (target MAP 75-85mmHg)	Lower preop infusion volume in HR (vs PR/SR; and PR vs SR). PR group achieved a higher preop MAP (vs HR/SR) and required less prepared time for surgery (vs HR; and vs SR). Lower mortality in PR (vs HR/SR)

Table 4

Author (year)	Studies (pts)	Main findings
Wang (2014)	3 RCTs, 7 observational (15794 pts)	Liberal fluid resuscitation strategies might be associated with higher mortality than restricted fluid strategies (both in RCTs & observational studies). When only adjusted odds ratios were pooled for observational studies, odds for mortality with liberal fluid resuscitation strategies increased. Results should be interpreted with caution due to selection bias and clinical heterogeneity.
Kwan (2014) (Cochrane Library)	6 RCTs (2128 pts)	Examined the effect of fluid management on mortality and coagulation times in hemorrhagic hypovolemia, comparing both early vs delayed resuscitation and larger vs smaller volumes of fluid. The authors did not combine the results quantitatively and a formal meta-analysis was not performed, because the interventions and pt populations were so diverse. They found no evidence from RCTs for or against early or larger volume of iv fluid administration in uncontrolled hemorrhage.
Tran (2018)	5 RCTs (1158 pts)	4 trials suggested a survival benefit for 30-day or in-hospital mortality with HR (although 3 studies were insufficiently powered to find statistical significance). The pooled odds ratio was 0.70 (95% c.i. 0.53-0.92), suggesting a survival benefit for HR. Those pts received fewer blood products and had lesser estimated blood loss.
Albreiki (2018)	5 RCTs, 5 observational (4677 pts)	The mortality rates among pts resuscitated with low volume and large volume in the selected RCTs were 21.5% and 28.6%, respectively, whilst the total mortality rate of HR in 3 of the noncomparative studies was 9.97%.
Owattanapanich (2018)	24 series (2955 pts)	HR was significantly associated with decreased mortality, reduced need for blood transfusion, and lower incidence of multiple organ dysfunction and ARDS.

Table 5

	First author	Year	Type of study	N[a]	Methods	Results & Conclusions
1.	Lawler	1984	Retrospective	43	10-year experience with OSR of RAAA; 77% of pts presented in shock	61% survival rate. Lawler first speculated that preop fluid resuscitation may lead to increased BP and subsequent exsanguination
2.	Crawford	1991	Retrospective	87	Comparison of 87 RAAA pts treated by Crawford with a historical series of 180 pts treated at a level 1 emergency center (comparable numbers of hemodynamically unstable pts). Crawford favored HR (target SBP 50–70 mmHg); level 1 emergency center advocated aggressive fluid management (preop infusion of >2 L of colloid)	90-day survival in Crawford's experience was 77% vs 30-day survival rate of 30% at level 1 emergency center. The 30-day survival rate amongst Crawford's hemodynamically unstable pts was 58%.
3.	Hardman	1996	Retrospective	154	To identify risk factors associated with mortality following OSR of RAAA. The authors correlated hypotension at presentation with mortality	Infusion of >3.5 L of fluid prior to surgery increased RR of death by a factor of 3.54. No data were presented on the association between hypotension, the volume of infused fluid and subsequent mortality. However, as the RR of death associated with BP (per 10 mmHg) was 0.91, it can be inferred that the volume of infused fluid has a more significant impact on the risk of death than SBP
4.	Ohki	2000	Retrospective	25	The Montefiore approach included hypotensive hemostasis (minimizing fluid resuscitation and allowing SBP to fall to 50 mmHg). Other key elements were a transbrachial AOB (if SBP<50mmHg), and EVAR (if anatomically suitable) with AUI stent-graft, contralateral iliac occluder & fem-fem crossover bypass	AOB was required in 9 (of 25) pts. 20 pts were treated with EVAR, 5 with OSR. Two deaths (9%) occurred, both in the EVAR group, in pts with serious comorbidities
5.	Veith	2002	Retrospective	31	As above	25 pts underwent EVAR, 6 OSR. Total operative mortality was 9.7% (3 pts); 10 pts required AOB
6.	Roberts	2006	Review	-	A literature search for articles on HR in RAAA pts	Superiority of HR in animal studies. There are several human trauma studies advocating delayed rather than immediate resuscitation. No direct RAAA data.
7.	van der Vliet	2007	Prospective	95	To investigate whether a PH protocol was feasible for RAAA pts. It was aimed to limit prehospital iv fluids to 500 mL and maintain a target SBP 50-100mmHg, using nitrates when indicated. The diagnosis was confirmed with US, and all unstable pts underwent OSR. In all other cases, CTA determined eligibility for EVAR.	PH with the use of pharmacological agents appeared to be feasible. Protocol violations were sparse (n=5). Uncontrolled hypotension occurred in 36% of pts (who underwent immediate OSR), and the desired SBP range was achieved in 46% of the EVAR pts. 30-day mortality was 30% in EVAR, 49% in OSR.
8.	Mayer	2009	Retrospective	102	RAAA pts treated by EVAR (January 1998-April 2008). The group practiced hypotensive hemostasis with strict limitation of fluid administration and active pharmacologic lowering of BP (phentolamine, esmolol, nitroglycerine). Target SBP 70-90mmHg	EVAR for RAAA resulted in a very low 30-day mortality of 13%. Key components were adequate imaging, hypotensive hemostasis, selective aortic balloon occlusion, predominantly local anesthesia, detection and treatment of ACS, and attention to logistics
9.	Reimerink	2010	Retrospective	266	To evaluate a controlled hypotension protocol (initiated by Amsterdam paramedics in the prehospital setting) for pts suspected of a RAAA and to identify possible harm to pts with a final diagnosis other than RAAA. Protocol was assessed by reviewing SBP (<80 mmHg, 80-100 mmHg or >100 mmHg), administered fluid volume and verbal responsiveness during transport.	Protocol was followed in 83% and violations occurred in 17%. True controlled hypotension was achieved in 10% of all pts and in 17% of RAAA pts. The risk of implementing controlled hypotension for all pts suspected of a RAAA by the ambulance staff was low.
10.	Dick	2013	Retrospective analysis of	248	This study investigated whether preoperatively administered volume correlated inversely with survival after RAAA. Fluid resuscitation was guided clinically by the	Most pts (96%) underwent OSR. 30-day mortality rate was 15.3%. Preop rate of fluid infusion correlated with 30-day mortality after adjustment for confounding

			prospectively gathered data		BP and consciousness level. A strategy of low-volume resuscitation accepting limited periods of SBP 60-70mmHg was generally attempted in all pts as long as they remained conscious.	factors. Each additional L/h increased the odds of death by 1.57-fold. Volume resuscitation should be delayed until surgical control of bleeding is achieved.
11.	Hamilton	2014	Review	-	A literature search using the keywords “PH” and “HR” in RAAA pts	The safety of PH in RAAA pts was documented and found to be widespread, but there were no RCTs directly comparing this practice
12.	IMPROVE	2014	RCT	558	Multicenter RCT in which eligible pts with a clinical diagnosis of RAAA were allocated to a strategy of EVAR or to OSR	Lowest SBP was strongly and independently associated with 30-day mortality (51% among those with SBP<70 mmHg vs 34.1% in pts with SBP>70 mmHg). These findings suggest that a minimum SBP of 70 mmHg is too low for PH
13.	Moreno	2018	Cochrane Systematic Review	-	The Cochrane review included all published and unpublished or ongoing RCTs comparing controlled (permissive) hypotension with normotensive resuscitation protocols in RAAA pts	No relevant RCTS were found