Review Article

Application of standardized hemodynamic protocols within enhanced recovery after surgery programs to improve outcomes associated with anastomotic leak and conduit necrosis in patients undergoing esophagectomy

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Abstract: Esophagectomy for cancer is associated with high risk for postoperative morbidity. The most serious regularly encountered complication is anastomotic leak and the most feared individual complication is conduit necrosis. Both of these complications affect the length of stay, mortality, quality of life, and survival for patients undergoing esophageal resection. The maintenance of conduit viability is of primary importance in the perioperative care of patients following esophageal resection. It has been shown that restrictive fluid management may be associated with improved postoperative outcomes in abdominal and other types of surgery, but many factors can affect the incidence of anastomotic leak and the viability of the gastric conduit. We have performed a comprehensive review with the aim to give an overview of the available evidence for the use of standardized hemodynamic protocols (SHPs) for esophagectomy and review the hemodynamic protocol, which has been applied within a standardized clinical pathway (SCP) at the Department of Thoracic surgery at the Virginia Mason Medical Center between 2004–2018 where the anastomotic leak rate over the period has been 5.2% and the incidence of conduit necrosis requiring surgical management is zero. The literature review demonstrates that there are few high quality studies that provide scientific evidence for the use of a SHP. The evidence indicates that the use of goal-directed hemodynamic monitoring might be associated with a reduced risk for postoperative complications, shortened length of stay, and decreased need for intensive care unit stay. We propose that the routine application of a SHP can provide a uniform infrastructure to optimize conduit perfusion and decrease the incidence of anastomotic leak.

Keywords: Esophageal cancer; goal-directed therapy; hemodynamic protocol; perioperative care; esophagectomy; postoperative complications

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Introduction

Esophagectomy remains an important component of the treatment of localized esophageal and gastroesophageal junctional cancer in physiologically appropriate patients (1). The operation is associated with a high risk for postoperative complications, which affect morbidity, mortality, cost, and negatively impact upon long-term health related quality of life (2-4). Hemodynamic deregulation that occurs commonly in the setting of esophagectomy may predispose patients to morbidity through impaired tissue perfusion.
The introduction of enhanced recovery after surgery (ERAS) pathways and centralization of care to high volume centers has been shown to reduce postoperative morbidity (5-8). The focus of perioperative management should be to optimize the patient's physiology in order to facilitate postoperative recovery. ERAS guidelines provide a framework within which therapeutic goals can be set and clear strategies enacted where there is the potential for unintended deviation from the expected course. Several central components of ERAS pathways including restrictive fluid protocols, epidural analgesia, and early mobilization, while intended to advance recovery may also contribute to perioperative hypotension. A balanced approach to perioperative care should include adherence to ERAS principals (7) whilst maintaining appropriate hemodynamic conditions for perfusion of organs and the gastric conduit.

The Esophageal Complications Consensus Group (ECCG) has reported a 59% overall complication rate, 11.4% anastomotic leak, and 1.3% incidence of conduit necrosis in a large contemporary international multicenter study including only high-volume centers (9). While reported rates of anastomotic leak after esophagectomy vary widely between individual centers (4-25%), it remains the most commonly encountered major postoperative complication (10-15). Likewise, conduit necrosis, which is caused by impaired perfusion and subsequent ischemia of the proximal part of the conduit, is a devastating postoperative complication frequently requiring immediate re-operation, often in the setting of multiple organ failure and high postoperative mortality (4). For those surviving conduit necrosis there still remains the ominous challenge of reconstruction. The tenuous blood supply to the conduit, mainly based on a single feeding vessel, makes this organ particularly vulnerable to ischemia. The administration of neoadjuvant chemoradiotherapy can also affect the microvascular perfusion of the proximal stomach (16-18). Establishing and maintaining good perfusion to the conduit reduces the risk of anastomotic leak and conduit necrosis (19,20).

The aim of this review is to provide a systematic review of the current literature concerning hemodynamic protocols in the perioperative management of esophageal and gastroesophageal junctional cancer and to present a standardized hemodynamic protocol (SHP) for use in the immediate postoperative period after esophagectomy to decrease the incidence of anastomotic leak and conduit necrosis.

Methods

We conducted a literature search to identify relevant studies in PubMed and the Web of Science. Randomized controlled trials (RCTs), high quality meta analyses, and retrospective studies published between 1988 and 2018 were identified using the search terms: “hemodynamic monitoring” or “fluid restriction” or “goal-directed treatment” and “esophagectomy” or “esophagogastrectomy” or “esophageal surgery”. All articles were written in English. Inclusion criteria were studies reporting on esophagectomy patients and hemodynamic protocols in some form. Exclusion criteria were studies including non-esophageal surgery.

An SHP was introduced in 2004 at Virginia Mason Medical Center; it was developed by a multidisciplinary team of surgeons, anesthesiologists, intensivists, nursing staff and physiotherapists. The prospective IRB approved esophagectomy database at Virginia Mason Medical Center was used to identify the incidence of anastomotic leak and conduit necrosis since the initiation of the SHP.

Literature review of hemodynamic protocols for esophagectomy

Literature search resulted in 243 articles. One article was excluded, as it was not written in the English language. After a review of the titles and abstracts, 50 articles were chosen for full text review, of these 23 articles met the inclusion criteria (Figure 1). The included articles are presented in Table 1 (21-43).

Perioperative hemodynamic management in esophageal surgery has been an area of interest for many years but there are few high quality studies and little scientific evidence regarding SHPs (37). A number of retrospective studies have found that a positive cumulative fluid balance after esophagectomy was associated with increased length of stay, increased risk for postoperative pulmonary and cardiac complications (24,29,41).

Methods of assessing hemodynamic status

The hemodynamic status of a patient is multifactorial and difficult to evaluate with high certainty. As such there are different strategies to evaluate the hemodynamic status in the perioperative period (44). Arterial pressure variation guided fluid management is a technique that uses the peripheral arterial catheter to calculate variation in stroke volume and a stroke volume index. The technique can be
used to evaluate fluid responsiveness during surgery and in the postoperative period (26,45). Fluid management that was guided by stroke volume variation after esophagectomy was evaluated in two small studies and was shown to be a reliable predictor for intravascular volume depletion and possible hypotension in the postoperative period (31,32).

One study of ten patients undergoing esophagectomy showed that central venous pressure was not a reliable predictor of intravascular volume in the postoperative period compared to pressure parameters including the diameter of the inferior vena cava and the left ventricle (35). Anesthetic management, the position of the patient, and the surgical technique during esophagectomy also impacts upon hemodynamic status during surgery (33,42,43).

**Restrictive fluid therapy**

A restricted fluid strategy with intraoperative fluid limited to <4 liters and mean arterial blood pressure (MAP) maintained above 65 mmHg with the use of norepinephrine infusion in combination with early postoperative extubation has been shown to significantly reduce pneumonia in a cohort of 83 patients who underwent open esophagectomy (23). Fluid balance above average on the day of surgery, and the first 4 postoperative days was associated with increased risk for postoperative complications in another retrospective study (25). However, two small RCTs did not show any significant difference comparing restrictive vs. liberal postoperative fluid therapy guided by intrathoracic blood volume index (27,28). One concern is that restricted fluid management protocols could lead to harmful effects such as acute kidney injury. A retrospective study in a mixed cohort of 1,442 patients undergoing either esophageal or pulmonary resection showed that fluid restriction did not lead to postoperative acute kidney injury (21). In comparison, another study showed that patients with a stroke volume index <35 mL/m² had decreased renal function on postoperative day 1–3 after surgery and increased risk for acute kidney injury (38).

**Goal-directed fluid therapy**

One Japanese study compared the results of esophagectomy before and after the introduction of a goal-directed fluid
<table>
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<tr>
<th>Author</th>
<th>Country</th>
<th>Year</th>
<th>Study type</th>
<th>Included patients</th>
<th>Exposure/study design</th>
<th>Findings</th>
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<tr>
<td>Glatz et al.</td>
<td>Germany</td>
<td>2017</td>
<td>Retrospective cohort study</td>
<td>335 esophagectomy patients 1996–2014</td>
<td>Intra- and postoperative fluid management and</td>
<td>Intra- and postoperative fluid overload was associated with</td>
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<td>postoperative morbidity</td>
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<td>Haase et al.</td>
<td>Germany</td>
<td>2013</td>
<td>Randomized controlled trial</td>
<td>22 esophagectomy patients randomized after surgery</td>
<td>Restrictive vs. liberal fluid management on</td>
<td>No significant difference</td>
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<td>postoperative pulmonary function</td>
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<tr>
<td>Karaman et al.</td>
<td>Croatia</td>
<td>2015</td>
<td>Randomized controlled trial</td>
<td>16 esophagectomy patients randomized</td>
<td>Liberal vs. restrictive intraoperative fluid</td>
<td>No significant difference</td>
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<td>Ahn et al.</td>
<td>South Korea</td>
<td>2015</td>
<td>Retrospective cohort study</td>
<td>1,442 patients with thoracic surgery, 12% esophagectomy</td>
<td>Risk factors for acute postoperative kidney</td>
<td>Fluid restriction was not a risk factor for kidney injury</td>
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<td>Sugasawa et al.</td>
<td>Japan</td>
<td>2013</td>
<td>Retrospective cohort study</td>
<td>128 esophagectomy patients</td>
<td>Intraoperative stroke volume variation as a</td>
<td>Low stroke volume index at the end of surgery may be a risk factor for</td>
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<td>predictor for acute kidney injury</td>
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<td>Taniguchi et al.</td>
<td>Japan</td>
<td>2018</td>
<td>Retrospective cohort study</td>
<td>92 esophagectomy patients</td>
<td>Two cohorts, before and after the introduction</td>
<td>Enhanced gastrointestinal recovery and mobilization, postoperative</td>
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<td>of a goal-directed therapy, were compared</td>
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<td>or incidence of complications</td>
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<td>Veelo et al.</td>
<td>The Netherlands</td>
<td>2017</td>
<td>Retrospective cohort study</td>
<td>199 patients operated 2012–2014</td>
<td>Goal directed fluid therapy was compared to</td>
<td>No change in overall complications or mortality but reduced ICU stays,</td>
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<td>standard monitoring</td>
<td>pneumonia and conduit necrosis</td>
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<td>Al-Rawi et al.</td>
<td>UK</td>
<td>2007</td>
<td>Prospective cohort study</td>
<td>10 esophagectomy patients</td>
<td>The effect of intraoperative thoracic epidural</td>
<td>An epidural bolus significantly</td>
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<td>bupivacaine and subsequent adrenaline infusion</td>
<td>decreased flux at the anastomotic end of the gastric tube. An</td>
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<td>on hemodynamics in the gastric tube</td>
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<td>Klijn et al.</td>
<td>The Netherlands</td>
<td>2010</td>
<td>Experimental animal study</td>
<td>9 pigs with constructed gastric conduit</td>
<td>Blood flow and temperature was measured in the</td>
<td>Blood flow in the upper part of the gastric tube was decreased compared</td>
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<td>conduit with laser speckle imaging at</td>
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<td>different MAPs</td>
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<td>Low et al.</td>
<td>USA</td>
<td>2007</td>
<td>Retrospective cohort study</td>
<td>340 consecutive esophagectomy patients 1991–2006</td>
<td>The outcomes of patients included in a</td>
<td>Surgical treatment of esophageal cancer can be done with moderate</td>
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<td>Neal et al.</td>
<td>USA</td>
<td>2003</td>
<td>Case series</td>
<td>56 consecutive esophagectomy patients 1999–2000</td>
<td>The results of a consecutive series of patients</td>
<td>Significant reduction in esophagectomy-related morbidity was shown using</td>
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<td>a standardized multimodal approach in routine clinical practice</td>
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therapy protocol using stroke volume variation and stroke volume index to guide fluid therapy. Findings demonstrate earlier gastrointestinal functional recovery and increased serum albumin six months after discharge. There were no significant differences concerning length of stay or complications (39). A similar study from the Netherlands, investigated the results before and after the introduction of a goal-directed fluid management system, based on variation in stroke volume. The patients in the goal-directed therapy group received significantly less fluids but more colloids. There was no difference in overall morbidity or mortality, but there was a decrease in pneumonia, intrathoracic abscesses formation, conduit necrosis, and length of stay in intensive care (40).

Assessment of conduit perfusion

A significant component of the esophagectomy literature has evolved assessing various approaches to improve perioperative conduit health. Indocyanine green angiography and laser Doppler flowmetry are techniques that have been utilized to visualize the circulation in the gastric conduit during surgery (46-49). Preoperative ischemic conditioning of the conduit can be performed by laparoscopic preparation of the conduit 3–7 days before transthoracic esophagectomy, with the aim to improve microcirculation in the proximal conduit and decrease anastomotic leaks (50,51). Theoretically, these techniques can be used to assess and improve the conduit blood flow, optimize the location for the anastomosis, and enhance conduit healing, however none of these techniques have been conclusively demonstrated to improve outcomes in prospective studies, and none have seen widespread clinical application.

Al-Rawi et al. reported a trial in humans that involved suturing Doppler flow probes at the pylorus and the perianastomotic area of the gastric conduit during surgery. Conduit perfusion variation was assessed following an epidural bolus of 0.1 mL/kg of bupivacaine 0.25%. Epidural bolus was shown to significantly decrease conduit perfusion at the proximal (anastomotic) end of the conduit but not in the region of the pylorus. Perfusion to the anastomotic end of the conduit was restored with adrenaline infusion without the need for additional fluid (22). Klijn et al. assessed blood flow in the gastric conduit in a pig model. The application of vasopressors under normovolemic conditions had no detrimental effect on conduit microvascular circulation. The study demonstrates that MAP >70 mmHg was optimal for conduit perfusion but maintaining MAP above 90 mmHg did not lead to any additional improvement in conduit perfusion (30).

Complex invasive and non-invasive methodologies have therefore not been shown to have any substantial beneficial effect on short-term outcomes following esophagectomy. However, there is data to support maintaining a MAP >70 mmHg, and evidence that, when other hemodynamic parameters are stable, vasopressors can be utilized to increase MAP and optimize microvascular perfusion of the anastomosis and conduit.

SHP at the Virginia Mason Medical Center

With the intention to minimize individual variation in patient care during the immediate postoperative period a standardized clinical pathway (SCP) for esophagectomy has been used at the Virginia Mason Medical Center since 1991. Our experience of using this SCP has been presented in two previous publications (34,36). The SCP has evolved over time and the SHP was added in 2004, with its evolution principally influenced by the anesthetic literature.

The SHP at Virginia Mason Medical Center has also evolved over time but has been in its present form since 2010. The SHP provides a framework to set hemodynamic goals, and standardize the immediate post-operative hemodynamic management of patients after esophagectomy. The protocol was embedded within pre-existing SCP and ERAS program and also within the intensive care unit checklists and ordersets. It was based initially, and evolved according, to the best information available at the time documenting the importance of maintaining certain systemic blood pressure levels and then providing a structured framework for response. During the same period that the SHP was introduced patients were subject to fluid restrictive protocols, patient controlled epidural anesthesia (PCEA) and were undergoing attempted mobilization on the day of surgery. One of the most important changes was the elimination of epidural boluses for postoperative pain control, which reduces the risk for immediate postoperative hypotension. Changes in epidural infusion are done through variation of infusion rate and not administration of boluses of narcotic analgesia and local anesthetic.

The SHP established a “best practice” approach to perioperative hypotension and standardized treatment that minimized the potential for variation associated with changing personnel including staff surgeons, nurses and trainees. The protocol was developed with the active
participation of the entire multidisciplinary team including anesthesiology, interventionists and intensive care unit nursing and physical therapy. Designated surgical and nursing staff, in the intensive care unit, and the surgical ward monitors the patients for the first 24–48 postoperative hours. Thoracic epidural catheter is the primary choice for initial pain management, using an infusion of bupivacaine 0.05%, and hydromorphone 10-microgram/cc at 8 mL/h. If there is any uncertainty regarding the position of the epidural catheter then an epidurogram is performed before leaving the operating room. The catheter is repositioned or replaced when indicated, to ensure a functioning pain treatment system. Blood transfusions are not given unless a hematocrit <25% is demonstrated in two consecutive measurements or where the patient has a documented history of coronary artery disease. A staff surgeon typically reviews the patient prior to transfusion. The fluid management is conservative, and perioperative fluid administration is aimed toward avoiding weight gain of >2 kg (7). The volume of intraoperative fluid administered in the 501 esophagectomy patients between 2004 and 2018 was on average 2,895 mL with an average length of the procedure being 6.5 hours. Postoperative fluid is set at 0.5 mL/kg/h to a maximum of 100 mL/h, MAP is maintained >70 mmHg with the use of phenylephrine when indicated. Colloids are not used unless specific indications exist. The order sets require a clinical review when a patient has a MAP <70 mmHg for more than 15 minutes. The “in house” managing clinical team has the SHP available for review within the postoperative order sets (Table 2). Since the introduction of the SHP in 2004, the complication rate is 53.2%, anastomotic leak rate 5.2%, and conduit necrosis rate 0%. These outcomes compare favorably with outcomes published by the ECGC where complication rates were 59%, anastomotic leak rate 11.4% and conduit necrosis 1.3% (9).

**Discussion**

SCPs have been demonstrated to improve outcomes, of which SHPs are an important component (34,36,52). The current surgical literature has considered a number of methods for invasive and non-invasive perioperative monitoring and has assessed various approaches to fluid utilization both intra- and postoperatively (53-58). No consensus can be reached that any of these interventions significantly improve outcomes although restrictive or goal-directed fluid protocols are currently recommended per ERAS guidelines (7). Fluid restriction with the aim to maintain the patients’ preoperative weight in the immediate postoperative period, is included in many enhanced recovery pathways, since it has been shown to decrease the risk for total postoperative complications, cardiopulmonary complications, and tissue healing in colorectal cancer surgery and other abdominal surgeries (7,8,59-67).

Perioperative fluids are administered to treat hypotension during surgery caused by anesthesia and epidural induced vascular dilatation, bleeding and insensible losses. The use of vasopressors has been identified as a potential risk for decreased conduit circulation (68), but studies have shown that intravenous adrenaline, phenylephrine, or ephedrine can increase MAP and maintain conduit perfusion as long as...

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**Table 2 Standardized treatment of perioperative hypotension according to a standardized hemodynamic protocol**

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<td>Give fluid bolus with 500 mL crystalloid</td>
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<tr>
<td>Repeat 500 mL crystalloid bolus</td>
</tr>
<tr>
<td>Lower the epidural rate from 8 to 6 mL/h</td>
</tr>
<tr>
<td>Check if there is a significant change in Hct from postoperative level, initiate phenylephrine and titrate to maximum 30 mcg/kg/min</td>
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<tr>
<td>Staff review of the patient, by a surgeon or surgical chief resident</td>
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<tr>
<td>Bolus 500 mL crystalloid over 30 minutes</td>
</tr>
<tr>
<td>Repeat staff review if required</td>
</tr>
<tr>
<td>Lower the epidural rate from 6 to 4 mL/h</td>
</tr>
<tr>
<td>Titrate phenylephrine dose to 60 mcg/kg/min as required</td>
</tr>
<tr>
<td>Repeat staff review if required</td>
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</table>

Each step is sequential, and progressing through the protocol steps requires the patient to continue to demonstrate MAP <70 mmHg.
the patient is otherwise hemodynamically stable (22,69-71). Fluid overload can threaten anastomotic integrity and confer increased risk for postoperative morbidity and mortality (72-74). Goal-directed therapy is a fluid treatment approach that focuses on physiological output measurements (75-78). Stroke volume variation monitoring has been shown to reduce the number of hypotensive events and lactate levels during major abdominal surgery, and to decrease the risk for postoperative complications (79). A meta-analysis including 4188 patients with major surgery showed significantly decreased risk for postoperative infections and pneumonia with the use of goal-directed therapy or routine hemodynamic protocol practice (52).

Anastomotic leak and conduit necrosis remain the most problematic issues following esophagectomy. Leak rates even in high volume centers remain over 11% and conduit necrosis between 1–2% (9). Both of these complications affect perioperative mortality, length of stay, HRQOL and costs. Although very little (7) has been published on SHP, we have utilized an SHP in our SCP since 2004. During that period the anastomotic leak rate has been 5% and we have not experienced any incidence of clinically significant necrosis in over 500 consecutive resections. An SHP does not remove the requirements for individual assessment and clinical judgment. It does provide specific targeted goals for perioperative monitoring and a structured framework for response. This is increasingly important in situations where staff turnover is a regular feature even in high volume centers. These SHPs need to be imbedded within ordersets and the evolution needs to involve all major stakeholders, including nursing, anesthesia, intensivists and trainees. Applying a SHP will make the conduit less prone to misadventure.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


38. Sugasawa Y, Hayashida M, Yamaguchi K, et al. Usefulness


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