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REVIEW

Complications following oesophagectomy, a review with future perspectives

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Abstract

Oesophagectomy with gastric tube reconstruction is a complex, high-risk surgical procedure. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated. The two most frequent and important complications following oesophagectomy are anastomotic failure and pulmonary morbidity.

Along with surgical methods, microvascular blood flow is an important factor in the development of anastomotic failure. Location of the anastomosis, tissue supportive techniques and early detection of anastomotic leakage may contribute to a decrease in morbidity.

The pathogenesis of pulmonary complications is multifactorial. Prolonged systemic inflammatory response syndrome responses are associated with pulmonary complications. The cholinergic anti-inflammatory pathway may play a role in this inflammatory response and future research in this direction is necessary in the search for better care.

In our opinion, only clinical pathways that include early extubation, fluid management, pain management and early mobilization and nutrition, are providing opportunities for fewer postoperative pulmonary complications. However, clinical pathways succeed only if surgeons, anaesthetists and intensivists feel they are part of the treatment process and take responsibility as a team for all complications.

Introduction

Oesophagectomy with gastric tube reconstruction is a complex and high-risk surgical procedure. Despite improvements in surgical techniques and perioperative care, the postoperative course is often complicated.[1,2] Complications following oesophagectomy can be divided into two categories, firstly surgical and secondly medical. Unlike any other oncological or gastro-intestinal operation, oesophagectomy is associated with numerous non-surgical complications. It is unclear why patients are more vulnerable following oesophagectomy than patients following, for example, a pneumonectomy or pancreatic surgery.

The complexity, morbidity and in-hospital mortality rates have led to national and international discussion for the need for centralization of oesophageal surgery. Although complication rates are similar in lower and higher volume hospitals, it is more likely that high volume centres treat complications more successfully.[3,4] An increase in volume of this procedure has led to a better understanding and regulation of the infrastructure of the management of patients. The introduction of clinical pathways may help improve the infrastructure surrounding patients following oesophagectomy and also improve complications.[5-7]

In the following section we discuss the two most frequent and important complications following an oesophagectomy: anastomotic failure and pulmonary morbidity.

Gastroesophageal anastomotic failure

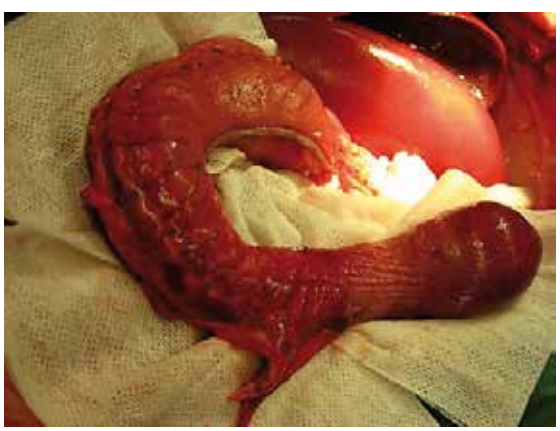
For an acceptable quality of life for patients after radical curative oesophageal resection, continuity of the gastrointestinal tract is necessary. Of all the conduits (colon, jejunum and stomach) gastric tube reconstruction is the one used most often internationally. The gastric tube is constructed by ligating the left and right gastric arteries, the short gastric arteries and the left gastroepiploic artery. These are then fashioned along the greater curvature of the stomach. The fundus side of the gastric tube depends on the right gastroepiploic arterial arcade for arterial supply.[8] In the literature, leakage of the gastroesophageal anastomosis occurs in 0% to 35% patients. The wide range is partly due to the various definitions used for anastomotic leakage. In a recent review of 80 articles on complications following gastric tube reconstruction, 25 different definitions were used for anastomotic leakage.[9]

Compromised microvascular blood flow of the gastric tube, as a result of ligation of the main arteries, is thought to be an important factor in the pathogenesis of anastomotic failure. By vascular conditioning due to endovascular coiling or

laparoscopic clipping of the depending arteries prior to gastric tube reconstruction, stimulation of collateral perfusion of the gastric tissue might be achieved. These techniques are currently being evaluated in research protocols. Large series, and therefore results on outcome, have not yet been published.[10] Other studies have tried to improve arterial circulation by creating vascular anastomosis of the short gastric vessels with vessels in the neck. A remarkable observation was made in the improvement of microcirculation after creating only the venous anastomosis, suggesting that venous congestion plays an important role.[11] This corresponds with our observation, where at the end of gastric tube reconstruction, the fundus of the stomach often has a bluish colour instead of a pale colour. As an impaired arterial blood supply would lead to a pale appearance of the tissue, whereas venous congestion gives a darker colour of the tissue, we underscribed the hypothesis of venous congestion (*figure 1*).

By using a combination of laser Doppler flow and reflection spectrophotometry to measure microvascular blood flow and microvascular oxygenation, we studied the microvascular blood flow during gastric tube reconstruction. We measured an increase in microvascular haemoglobin concentration and gradual decrease in microvascular haemoglobin saturation. According to our hypothesis this would be expected to occur in the presence of venous congestion. Another argument for a role for venous congestion was that after application of topical nitro-glycerine on the gastric fundus, the gastric microvascular blood flow increased.[12] These results roused our curiosity on the relation between tissue perfusion pressure and venous congestion of the gastric tube. We created a gastric tube reconstruction in a pig model and we used nor-epinephrine to increase mean arterial pressures from 50 to 110 mmHg. In a second group, nor-epinephrine was combined with intravenous nitro-glycerine, in a dosage to keep the central venous pressure below 10 mmHg (*figure 2*). We observed that the combination of nor-epinephrine and nitro-glycerine provides a more improved microvascular perfusion of the gastric conduit than nor-epinephrine alone.[13] This observation supports our hypothesis of a role for venous congestion in impaired gastric blood flow following gastric tube reconstruction.

Figure 1. A gastric tube in a pig model, just after the construction of the tube.



The position of the gastroesophageal anastomosis in relation to microcirculation and the limits of the right gastroepiploic arterial arcade seem to be important. In 1946, Ivor -Lewis introduced a technique with an intrathoracic anastomosis of a gastric conduit and the rest of the oesophagus.[14] Unfortunately, leakage of the intrathoracic anastomosis, led to infection of the mediastinum with fatal consequences. Therefore, a technique with a cervical anastomosis was developed.[15] In case of leakage of the cervical anastomosis, drainage to the outside of the neck is often a proper and manageable solution with no great clinical consequences. However, to create a cervical anastomosis a longer and more poorly circulated conduit is necessary. This in return will lead to a greater risk for anastomotic failure. Although most cervical anastomosis leakages are drained to the outside, some may leak into the chest and create infections of the mediastinum as well. Due to the availability of better diagnostic tools, minimal invasive techniques for the management of leakage, and the lower expected incidence of anastomotic failure, the intrathoracic anastomosis has become a procedure of renewed interest in the Netherlands. However, an intrathoracic anastomosis is only suitable for tumours in the lower oesophagus and not for carcinoma in the higher oesophagus and recent analysis failed to provide evidence as to which type of anastomosis is of more benefit to patients.[16]

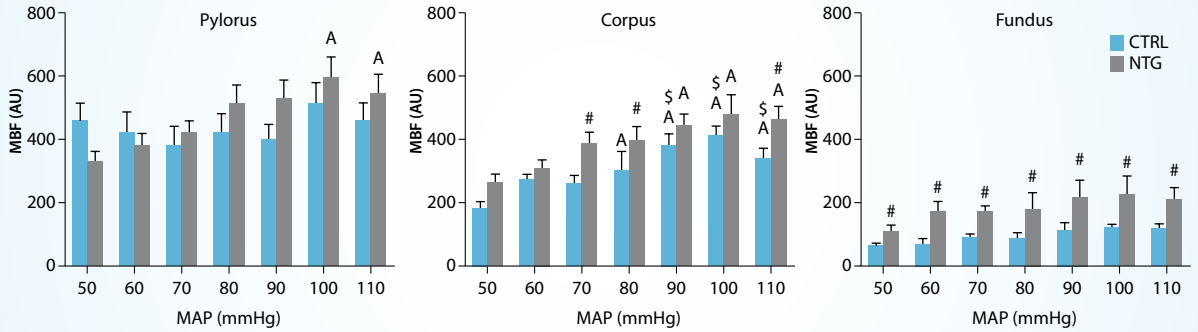
In the treatment of anastomotic leakage, aggressive surgical re-exploration with additional drainage, total parenteral nutrition, nasogastric decompression and broad-spectrum antibiotics are effective, but lead to a prolonged ICU and hospital stay.[17] Occasionally anastomotic repair and reinforcement of the anastomosis with muscle flaps is necessary; the results, however, are poor. To seal anastomotic leakage, recently self-expanding metal or plastic stents in combination with effective drainage seem to be a viable option. However, dislocation of these stents remains a problem.[18]

Pulmonary morbidity

Oesophagectomy is highly associated with pulmonary complications. In a recent review postoperative pneumonia was reported in 57% of the studies. Similar to anastomotic leakage, there are many different definitions of pneumonia.[10] Almost all definitions of post-oesophagectomy pneumonia use a combination of radiologic infiltrates, positive culture of sputum, fever, increased white blood count and clinical suspicion for which antibiotics were started.

The incidence of pulmonary complications is associated with age, operation duration, proximal tumour location and

Figure 2. Microvascular blood flow (MBF) measurements on gastric pylorus, corpus and fundus at increasing MAP levels. Data represent mean ± SEM; # P<0,05 vs CTRL, b P<0,05 vs baseline, ^ P<0,05 vs MAP 50, $ P<0,05 vs MAP 60.



surgical techniques.[19] During a transthoracic oesophagectomy procedure, one lung is collapsed to allow surgical exposure to the oesophagus. This leads to atelectasis and local contusion of the lung. Prolonged duration of procedure predisposes patients undergoing one lung anaesthesia, to increased atelectasis and respiratory complications. Systemic inflammatory response due to surgical trauma of the other lung, can lead to bilateral lung oedema and acute lung injury.[20] Several inflammatory markers including interleukins, tumour necrosis factor and neutrophil endothelial markers are likely to cause persistent injury to the alveolar-capillary barrier function which leads to a shift and accumulation of fluids in the extra vascular space and this induces pulmonary oedema.[21,22] Minimal invasive oesophagectomy, may reduce the pulmonary complications, leading to a reduced length of ICU and hospital stay.[23,24]

There is emerging evidence that next to the influence of surgical techniques, anaesthetic management also directly influences the incidence of pulmonary complications.[25] Early extubation has been shown to reduce pulmonary complications.[26] However, to achieve successful early extubation, effective postoperative analgesia is required.[27] Although subject for debate, thoracic epidural analgesia is recommended to intravenous opiates to achieve effective analgesia during oesophagectomy.[28] Epidural analgesia provides pain relief, reduces respiratory complications, reduces ICU stay and possibly the mortality rate following oesophagectomy.[29,30] There is also a beneficial effect of epidural analgesia on the surgical stress response and associated immune function in oesophagectomy.[31] Effective thoracic epidural analgesia increases tissue oxygenation during abdominal surgery and might improve gastric blood flow following oesophagectomy.[32] Regarding all these arguments we still encourage epidural analgesia for oesophagectomy.

The relation between perioperative fluid management on pulmonary complications following major surgery is well documented. In order not to compromise gastric tube perfusion, perioperative hypotension usually was treated with administration of fluid, thereby avoiding the use of vasoactive medication. As a result, the net fluid balance at times increased in the first 24 hours. In some cases net fluid balance reached up to 10 L. Clinical trials investigating the effect of restrictive fluid management found a reduction in postoperative complications.[33] However, studies using a goal directed fluid management also claim better results. Unfortunately, local differences have led to diverse standards of fluid management; the restrictive treatment in one study is called liberal in the next study.[34] Looking specifically at oesophagectomy patients, several studies favour fluid restriction.[35,36] We have shown in a clinical study that a reduction in administered fluids can reduce pulmonary complications following oesophagectomy without an increased incidence of anastomotic leakage.[37]

It is surprising that only a few studies have been performed that look at perioperative ventilation strategies aimed at reducing pulmonary morbidity. The use of protective mechanical ventilation using low tidal volume during the one lung ventilation reduces the interleukin-6 levels. High levels of Iinterleukin-6 are associated with adverse outcome following surgery and protective ventilation improves postoperative lung function and results in earlier extubation.[38,39]

Prolonged perioperative hypoxemia and haemodynamic instability are associated with higher occurrences of pulmonary complications, e.g. acute lung injury and adult respiratory distress syndrome.[40] Incorrectly positioned double lumen tubes during oesophagectomy have also been noted as a serious contributor to perioperative morbidity.[41] To avoid double lumen tubes or bronchus blockers, we studied the feasibility of two-lung high frequency ventilation. We concluded that two-lung high frequency ventilation is a usable ventilation strategy, although there is no effect on postoperative pulmonary complications.[42]

Inflammatory pathways

In the previous paragraphs we described the two most important complications following oesophagectomy. In both complications there is a role for the systemic inflammatory response syndrome (SIRS). However, what are the effects of SIRS on morbidity following oesophagectomy?

Increased surgical stress parameters (blood loss/body weight and operation time) correlates with the duration of SIRS, or the number of positive criteria for SIRS post-surgery.[43] Morita described the mechanism of an increased inflammatory response post-oesophagectomy in a two hit model. The first hit is the result of great surgical stress, the necrosis and infection around the poorly circulated gastric oesophageal anastomosis, which in return results in the second hit, acute lung injury.[44] The influence of preoperative neoadjuvant chemoradiotherapy is associated with prolonged or severe SIRS parameters.[45] However, neoadjuvant chemoradiation does not appear to increase postoperative morbidity or mortality post-oesophagectomy.[46] There is growing evidence for several agents to reduce SIRS. For example, steroids are recommended in Japanese guidelines.[47] More recently a neutrophil elastase inhibitor was demonstrated to reduce postoperative pneumonia following oesophagectomy.[48] Increased plasmatic cytokine levels are characteristic for post-oesophagectomy patients and especially for post-oesophagectomy patients with postoperative infection including pulmonary infection.[49] Detection during the first 48 h of SIRS criteria, high plasma pro-inflammatory cytokine levels (interleukin 6, tumour necrosis factor alpha) and impairment of PaO_2/FiO_2 predicts the onset of pulmonary complications.[50] Additionally, increased C-reactive protein concentration (CRP) levels in the early postoperative period, are associated with the occurrence of postoperative complications and increased one year mortality.[51] The production CRP in the liver is stimulated by pro-inflammatory cytokines.

It has been shown that the vagus nerve plays a prominent role in inflammation through the cholinergic anti-inflammatory pathway.[52] The vagus nerve down-regulates inflammation by decreasing the release of tumour necrosis factor (TNF)-α by macrophages. Activation of the vagus nerve releases acetylcholine in the vicinity of macrophages within the reticulo-endothelial system, leading to the inhibition of cytokine release. Stimulation of the vagus nerve results in decreased cytokine release, whereas vagotomy results in an increase in cytokine release.[53] In a recent study, trauma patients who underwent vagotomy developed septicaemia eight times more often than the matched control patients.[54]

Therefore, the presence of an intact vagus nerve and gut innervation will decrease the post-injury inflammatory response. In both trans hiatal and or transthoracic oesophagectomy, acute vagotomy is performed thus deactivating the cholinergic anti-inflammatory pathway. In oesophagectomy, where a cervical anastomosis is applied, both the vagus nerves are dissected in the upper mediastinum. However, in oesophagectomy with an intrathoracic anastomosis, the higher branches of the vagus nerve are preserved.

In this context, vagal sparing oesophagectomy might play a role in the prevention of post-operative complications. Vagal sparing oesophagectomy is a well-known technique, first described by Akiyama in 1994.[55] The goal of vagal sparing oesophagectomy is to increase quality of life by preserving postoperative gastric emptying and prevent patients from developing the dumping syndrome and diarrhoea. In later studies, this technique was found to be clinically associated with lower mortality and morbidity.[56] In vagal sparing oesophagectomy the oesophagus is stripped (inverted) out of the mediastinum. Only a highly selective vagotomy is performed on the gastric-oesophageal junction and the colon is used as an oesophageal substitute.[57] However, vagal sparing oesophagectomy is only possible in a limited group of patients. These include patients with: end-stage benign oesophageal disease, Barrett's oesophagus with high-grade dysplasia, or multifocal oesophageal cancer limited to the lamina propria.

There is growing evidence that the cholinergic anti-inflammatory response can be stimulated by nutrition. Nutrition should specifically include dietary lipids, these activate the autonomic nervous system through the afferent vagal nerve and lead to the release of neuro-endocrine hormones.[58]. Thus, nutrition may be used as therapy to prevent excessive inflammation.[59] However, randomized controlled trials are necessary to collect evidence for this interesting hypothesis in the clinical setting from thousands of different individuals, our patients.

Conclusion

Although mortality following oesophagectomy has decreased during the last few decades because of improvements in surgical and perioperative care, the procedure is still associated with high morbidity. Anastomotic failure and pulmonary complications are the most frequent complications. Tissue supportive strategies may reduce the incidence of anastomotic leakage by stimulating the microvascular blood flow of the gastric conduit. Clinical pathways and minimally invasive surgical techniques may influence the rate and severity of pulmonary complications.

The role of SIRS and the cholinergic anti-inflammatory pathway in the pathogenesis of pulmonary complications post-oesophagectomy is a challenging subject for future research. The concentration of highly complex care leads to more experience in the treatment of complications and the development of new multi modal pathways. However, clinical pathways succeed only if surgeons, anaesthetists and intensivists feel that they are part of the process and take responsibility as a team for all complications that occur.

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