

Cadaveric validation of porcine model suggests noninvasive positive pressure ventilation may be safe following esophagectomy

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Background: We previously used a pig model to demonstrate that noninvasive positive pressure ventilation (NPPV) may be a safe alternative to endotracheal intubation (ET). We sought to validate our model by quantifying the pressure threshold of esophageal anastomoses in human cadavers as a step before a clinical trial.

Methods: We performed stapled side-to-side, functional end-to-end esophageal anastomoses in 10 cadaveric specimens from autopsy. With intraluminal pressure monitoring, we insufflated the anastomosis with air until a leak was observed, and measured the maximum tolerated pressure.

Results: Cadaveric esophageal anastomoses tolerated 101 ± 39 cmH₂O (range, 63-140 cmH₂O) of pressure before leak was observed. The maximum pressure threshold ranged from 59 to 246 cmH₂O. The leak was always at the anastomosis. There was no significant difference in pressure threshold between cadaveric and previously described porcine anastomoses.

Conclusions: We created a human cadaveric model that in conjunction with our porcine data demonstrates that a human esophageal anastomosis can tolerate manifold higher pressures than are delivered to the esophagus by NPPV. This is the final step before a trial of NPPV in patients following esophagectomy.

Keywords: Esophagectomy; laryngeal mask airway (LMA); positive pressure ventilation; esophageal cancer

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Introduction

Respiratory complications occur in about 40% of patients following esophagectomy (1). Noninvasive positive pressure ventilation (NPPV) has been shown to reduce complications, mortality, and cost when compared to endotracheal intubation (ET). However, clinicians have been hesitant to use NPPV following esophagectomy due to the hypothetical risk of barotrauma to the anastomosis. In our previous study, we used an *ex vivo* and *in vivo* porcine model to quantify the pressure tolerance of an esophageal anastomosis and the pressure received in the esophagus

during NPPV (2). We found that a porcine esophageal anastomosis tolerates manifold higher pressures than are delivered to the esophagus during NPPV, suggesting that NPPV may be a safe alternative to ET after esophagectomy. The validity of our porcine model in human beings remains an open question. In this study, we created a substitute model for a clinical trial by quantifying the pressure threshold of cadaveric esophageal anastomoses, and comparing it to our porcine data. This is the critical final step before a trial of NPPV in patients undergoing esophagectomy.

Table 1 Characteristics of esophageal tissue donors

Cause of death	Age (years)/sex
Chronic renal failure	53/M
Pulmonary emboli	49/M
Acute myocardial infarction; occlusive LAD thrombus	68/M
Metastatic ovarian neoplasm	62/F
Subdural hematoma	55/M
Adenocarcinoma	51/F
Respiratory failure, bronchopneumonia, coronary artery disease	72/M
Acute myocardial infarction and dissection	63/F
Ischemic cardiomyopathy and brain infarct	43/M
Thrombotic thrombocytopenic purpura LAD, left anterior descending artery.	52/F

Methods

Sample acquisition

Consent was waived by our Institutional Review Board. Ten human cadaveric esophageal specimens were obtained from autopsied patients at our institution. Esophageal specimens were only obtained from patients whose esophagus was not suspected to contain pathology and consequently was not dissected during autopsy. The entire length of the esophagus from the proximal pharynx to the gastroesophageal junction was harvested by the forensic pathologist. The stomach was not available for harvest as the autopsy protocol in our institution requires complete gastric removal and dissection. Upon receipt of the specimen, the esophagus was frozen at -20°C until experimentation, following the protocol observed in our last study (2).

Measurement of pressure threshold of cadaveric esophageal anastomosis

Since no gastric specimens were obtained, we performed esophagoesophageal anastomoses in all our cadaveric specimens following a protocol identical to that published in our previous work (2). Briefly, we transected a segment of cadaveric esophagus and used a linear cutter (DST GIATM 80 mm; Covidien) to perform a side-to-side, functional end-to-end anastomosis of both esophageal segments. With intraluminal pressure monitoring, we insufflated the anastomosis with air until an anastomotic leak was observed, and measured the pressure threshold of the anastomosis.

A leak was identified by failure of the anastomosis to maintain pressure and by excursion of air bubbles from the anastomosis when immersed in a water bath. All experiments were performed by the same author as in the previous study to minimize inter-operator variability.

Measurement of pressure threshold of porcine gastroesophageal and esophagoesophageal anastomoses

Next, we investigated if there is a difference in pressure tolerance between gastroesophageal and esophagoesophageal anastomoses using our previously established *ex vivo* porcine model. Following the above protocol, we performed 10 gastroesophageal and 10 esophagoesophageal anastomoses in porcine tissue, insufflated the anastomoses until a leak was observed, and measured the maximum tolerated pressure. To minimize variables, the same author performed all experiments, alternating gastroesophageal and esophagoesophageal anastomoses in a single sitting.

Statistical analysis

All data is reported as a mean with 95% confidence interval and error bars representing the standard error of the mean (S.E.M.). The Student's t Test was used to compare continuous data. Statistical analysis was performed with GraphPad Prism version 6.00 (GraphPad Software, La Jolla, California, USA).

Results

Characteristics of patients

The interval between death and autopsy, age, sex, and cause of death of each patient whose esophagus was used are detailed in *Table 1*. No gross esophageal pathology was noted in any specimen.

Pressure threshold of cadaveric anastomoses

Ex vivo cadaveric esophagoesophageal anastomoses tolerated 101 ± 39 cmH₂O (range, 63-140 cmH₂O) before an anastomotic leak was observed (*Figure 1*). The recorded maximum tolerated pressure ranged from 59 to 246 cmH₂O (median 86 cmH₂O). Leaks only occurred at the staple line and not in other parts of the tissue. There was no significant difference in pressure tolerance between cadaveric and previously reported *ex vivo* (P=0.98) and *in vivo* (P=0.46) porcine esophagogastric anastomoses (*Figure 1*).

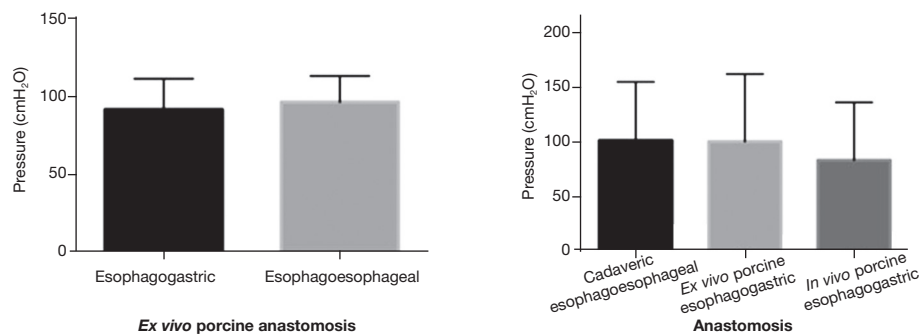


Figure 1 Graph demonstrating the pressure tolerance of cadaveric esophageal anastomoses in comparison to previously published porcine data (2). The grey line represents the maximum pressure sensed by the esophagus with NPPV, 15 cmH₂O, as demonstrated in our previous study (2).

Pressure threshold of porcine gastroesophageal vs. esophagoesophageal anastomoses

Ex vivo porcine gastroesophageal anastomoses tolerated 92±14 cmH₂O (range, 78-106 cmH₂O) before anastomotic leak (Figure S1). Esophagoesophageal anastomoses tolerated 96±12 cmH₂O (range, 85-102 cmH₂O) before leak was observed. There was no significant difference (P=0.42) between porcine gastroesophageal and esophagoesophageal anastomoses.

Discussion

In this study, we found that cadaveric esophageal anastomoses tolerate significant pressure before leak, which corroborates the findings in our recent porcine model (2). In our previous study, we found that the proximal porcine esophagus senses 5 to 15 cmH₂O when 20 to 40 cmH₂O of pressure via a laryngeal mask airway (LMA) were applied (2). Therefore, an esophageal anastomosis can tolerate a much greater pressure than is delivered to the esophagus by NPPV, suggesting that NPPV may pose a minimal threat to an esophageal anastomosis and may be safe following esophagectomy.

Our study has several limitations. The most important limitation in this study was the use of esophagoesophageal rather than esophagogastric anastomoses that are most common clinically. Unfortunately, the stomach is always dissected in autopsy and consequently unavailable for our study. We did demonstrate, however, that the pressure tolerance of esophagoesophageal and esophagogastric anastomoses is similar in porcine specimens, which suggests that the same may be true in human cadaveric tissue (Figure S1). Two, we used cadaveric rather than live human tissue. Live tissue would not suffer necrotic changes and would be expected to have

a higher pressure tolerance, so our study likely erred on the side of caution. Additionally, we found no difference in pressure thresholds between *ex vivo* and *in vivo* esophageal anastomoses in pigs in our previous study, suggesting that cadaveric tissue might have a similar pressure tolerance to that of live human tissue as well. Three, our model only tests the pressure tolerance in the immediate post-operative setting. As inflammation peaks several days post-operatively, the pressure threshold of an anastomosis may change. Four, we discovered in our previous work that NPPV results in significant gastric distension, which may compromise flow and perfusion to the conduit (2). Our cadaveric model was not designed to evaluate this potential risk, which needs further investigation.

Conclusions

We created a cadaveric model as a proxy for a live, human trial and established the pressure threshold of an esophageal anastomosis. Along with our previous work, we suggest that an esophageal anastomosis can tolerate a significantly higher pressure than is sensed by the esophagus during NPPV. NPPV is likely safe following esophagectomy. This is the important final step before a trial of NPPV in patients undergoing esophagectomy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

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Supplementary

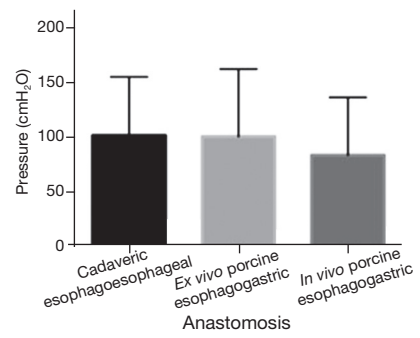


Figure S1 Graph demonstrating the pressure tolerance of porcine *ex vivo* esophagogastric and esophagoesophageal anastomoses.