Original Article

Vol. XX, No. XX; 2021; pp XX–XX
DOI: 10.26676/jevtm.v%i%.219

Morphometric Analysis of the Aorto-Esophageal Relationship in Swine for Trans-Esophageal Aortic Blood Flow Occlusion

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Background: Trans-esophageal aortic blood flow occlusion (TEABO) is an emerging technology undergoing laboratory research that offers a strategy for temporary hemorrhage control. The purpose of this study was to evaluate the anatomical relationship between the esophagus and descending thoracic aorta in two breeds of swine to support a porcine model for future TEABO investigations.

Methods: Thoracoabdominal computed tomography scans were compared in Hanford miniature swine and Yorkshire swine. Measurements were taken at the five vertebral levels proximal to the gastroesophageal junction. Data collected included the distance between the center of the esophagus and the center of the descending aorta, the angle between the vertebral column, descending aorta, and esophagus, and the length the thoracic esophagus travels anteriorly to the descending aorta.

Results: Ten Hanford swine and ten Yorkshire swine were compared. In Hanford swine, the distal thoracic esophagus travels anteriorly to the descending aorta for a mean distance of 11.5 ± 2.3 cm. In Yorkshire swine, the thoracic esophagus travels to the right of the descending aorta. The mean angle between the vertebral body, descending aorta, and esophagus was 79.6 to 97.8 degrees higher in Hanfords compared with Yorkshires ($P < 0.0001$ at all five vertebral levels compared). The mean distance between the esophagus and descending aorta was 0.2 cm to 0.6 cm higher in Hanfords compared with Yorkshires with a significant difference found at only two vertebral levels ($P = 0.01$ and $P = 0.02$).

Conclusions: Hanford miniature swine possess an aorto-esophageal relationship comparable to humans and should be the preferred animal model for TEABO studies.

Keywords: *Hemorrhage; Esophagus; Aorta; Swine; Anatomy; Transesophageal*

Received: 21 September 2021; Accepted: 27 October 2021

INTRODUCTION

Hemorrhage is the leading cause of potentially preventable death in trauma patients, accounting for 30–40% of deaths following traumatic injury [1–5]. Non-compressible torso hemorrhage (NCTH) is particularly fatal and is associated with up to 85% mortality in the military setting and 50% mortality in civilian patients [6,7]. For patients with NCTH, rapid intervention is imperative to control bleeding and prevent exsanguination and death.

The upper gastrointestinal tract serves as a window to several important cardiovascular structures. Trans-esophageal echocardiography takes advantage of this relationship to assess the heart and aorta. In addition, a new technique – gastroesophageal (GE) resuscitative occlusion of the aorta – has been shown to achieve full, temporary aortic occlusion through deployment of a device within the proximal stomach [8]. Trans-esophageal aortic blood flow occlusion (TEABO) is another emerging technology undergoing laboratory research, which offers a strategy for temporary hemorrhage control in the pre-hospital setting prior to definitive surgical control. TEABO operates via deployment of a compressive actuation mechanism within the distal esophagus to

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compress the adjacent segment of the descending aorta. This compression allows for temporary occlusion of the thoracic aorta until definitive hemostasis can be achieved in the operating room. The TEABO delivery system is designed to be deployed in the distal thoracic esophagus where the esophagus crosses anterior to the descending aorta. At this level, the actuator mechanism can compress the aorta posteriorly against the vertebral column and occlude the vessel. Due to TEABO's strict dependence on the anatomical relationship between the esophagus and descending aorta, this intimate association is an essential criterion when selecting an animal model to study such a trans-esophageal strategy.

Domestic swine (*Sus scrofa domestica*) are used extensively in research settings. They have similarities in gross anatomy, size, and vasculature [9–11]. Functionally, their cardiovascular, digestive, dermal, and urinary processes are analogous to humans [12]. Moreover, their physiologic response to hemorrhage and hemorrhagic shock is more comparable to humans than any other non-primate [13–15]. There is significant evidence that swine would be a suitable physiological model to further evaluate TEABO techniques. However, no study thus far has explored the anatomical relationship between the porcine esophagus and descending aorta. This information must be obtained prior to selecting a porcine model for TEABO research.

The aim of this study is to characterize the anatomical relationship between the esophagus and descending aorta in two breeds of domestic swine. By defining this relationship, we hope to establish the porcine anatomy as functionally suitable for future TEABO studies. In addition, the included cross-sectional images will illustrate the anatomical window for deployment of a trans-esophageal aortic occlusion device.

METHODS

Morphometric analysis of the relationship between the porcine esophagus and descending thoracic aorta was conducted by evaluating computed tomography (CT) scans in two breeds of domestic swine. Yorkshire swine (a common domestic farm breed) and Hanford miniature swine (a common miniature breed) were compared. The CT images used in this study were previously collected by a translational research laboratory. All data were acquired from Institutional Animal Care and Use Committee (IACUC) approved protocols (IACUC protocols 1119008, 0221009, and 0920007). As this study analyzed retrospective data, IACUC approval was not required.

The laboratory's picture archiving and communication system was searched for swine with thoracoabdominal CT scans, and images were obtained. All scans in the laboratory were acquired with a 16-slice portable machine (OmniTom, Samsung Neurologica Corporation, Danvers, MA, USA) using a helical acquisition. Pigs were placed in the supine position when thoracoabdominal scans were taken. All swine included in this study were euvolemic and under general anesthesia at the time of imaging. The swine were maintained under general anesthesia with 1.5–3% isoflurane in 40% oxygen. Animals were mechanically ventilated using a volume-controlled mode of 12–15 ml/kg with a respiratory rate of 10–15 breaths/min. The breed, weight, and sex were obtained for all swine included in this study. Images acquired from the archive were analyzed using Horos v3.3.6 (Brooklyn, NY, USA), an open-source medical image viewer. Several data points were collected using tools within Horos. The length between the center of the esophagus and the center of the descending aorta was measured at the five vertebral levels proximal to the GE junction. In addition, the angle between the vertebral body, the center of the aorta, and the center of the esophagus was measured at the same vertebral levels. Angles were measured such that 180 degrees indicated a straight line between the vertebral body, the aorta, and the esophagus. A value less than 180 degrees indicated the esophagus was to the right of the aorta, and a value greater than 180 degrees designated the esophagus was to the left of the aorta. Length and angle measurements were taken in the axial plane. Finally, a curved planar reformation was generated for the course of the esophagus that was anterior to the descending aorta. The length of the three-dimensional Bezier path produced was measured to quantify the length of the esophagus anterior to the aorta.

Numerical data were collected and stored in a Microsoft Excel (Redmond, WA, USA) file and analyzed using GraphPad Prism v9.1.2 (GraphPad Software Inc, La Jolla, CA, USA). All data are presented as mean with standard deviations. Unpaired *t*-tests were used to compare measurements between Hanford and Yorkshire swine at each vertebral level. Vertebral levels were normalized to the level of the GE junction prior to comparison. Linear regression analysis of the relationship between weight and the mean morphometric measures studied was performed to evaluate the impact of weight on the data. An unpaired *t*-test was also used to compare the weights of the Hanford and Yorkshire swine populations. A P value of less than 0.05 was considered significant.

Ethical Approval and Informed Consent

EQ1

Ethical approval was not required. Informed consent was not possible because XXXX and the information has been anonymized or Informed consent was not required.

RESULTS

A total of twenty swine were included in this investigation. Thoracoabdominal CT scans were found for ten Yorkshire swine and ten Hanford miniature swine. The Yorkshire swine population consisted of seven males weighing between 54 kg and 76 kg and

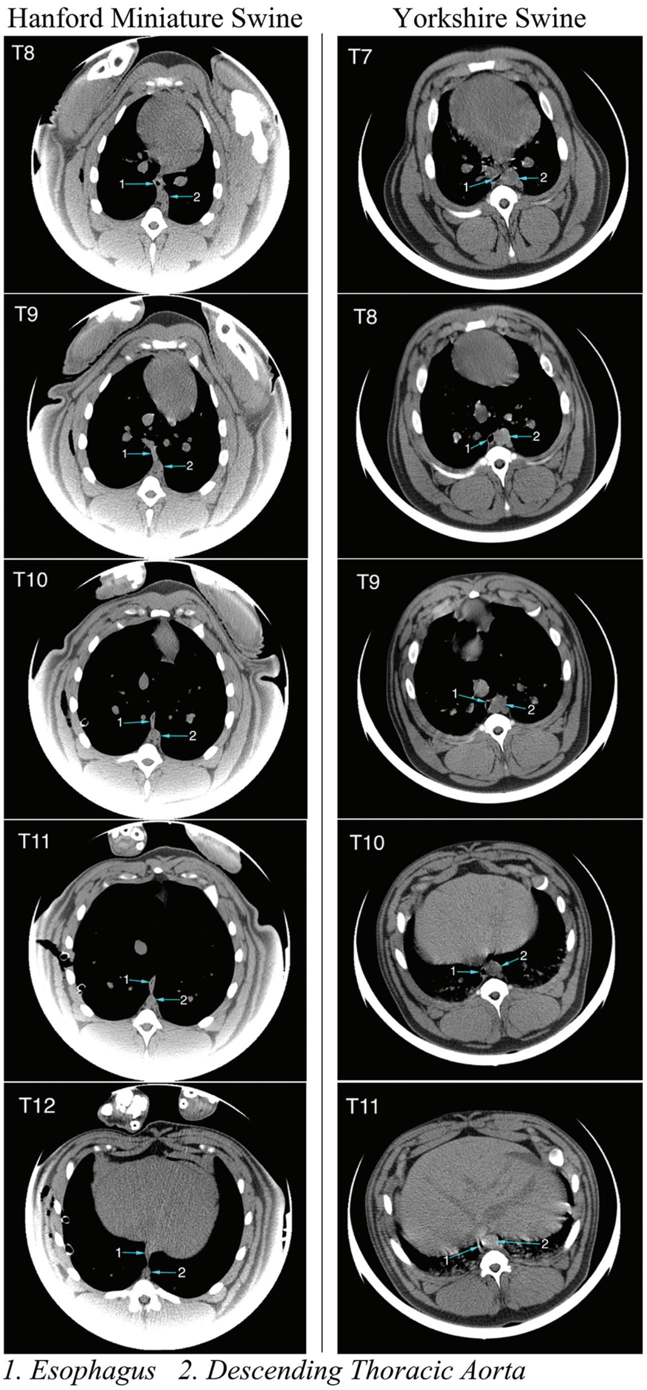

Figure 1 Representative CT images of Hanford miniature swine and Yorkshire swine at the five vertebral levels proximal to the gastroesophageal junction.

three females weighing between 36 kg and 38 kg. The Yorkshire population had a mean weight of 55.2 ± 15.0 kg. The Hanford miniature swine population consisted of ten males weighing between 63 kg and 71 kg with a mean weight of 67.2 ± 2.7 kg. The mean weight of the Hanford swine population was 12.0 kg larger than the mean weight of the Yorkshire population ($P = 0.023$).

The five vertebral levels proximal to the GE junction spanned from T8–T12 in Hanford miniature swine and from T7–T11 in Yorkshire swine. Since data were normalized to the level of the GE junction, measurements taken at T8 in Hanford swine were compared with T7 in Yorkshire swine, T9 in Hanfords with T8 in Yorkshires, and so on. Figure 1 depicts comparative cross-sectional images in both breeds of swine at two vertebral levels proximal to the GE junction (see Figure 1 , for representative cross-sectional images in both breeds of swine of all five vertebral levels analyzed).

EQ2

As seen in Figure 2, the gross relationship between the esophagus and descending aorta differs in Hanford miniature swine and Yorkshire swine. In Hanford swine, the esophagus travels anteriorly and slightly to the right of the descending thoracic aorta. As the thoracic esophagus descends, it moves from slightly right of the aorta to directly anterior and remains anterior to the aorta through the esophageal hiatus. The esophagus travels anteriorly to the descending aorta for a mean distance of 11.5 ± 2.3 cm. The walls of the thoracic esophagus and the descending aorta in Hanford miniature swine are either in direct contact or only slightly separated at all five vertebral levels proximal to the GE junction.

In Yorkshire swine, the thoracic esophagus descends immediately to the right of the aorta. The esophagus remains to the right of the aorta through the esophageal hiatus, and only the GE junction itself passes anterior to the aorta. There was one outlier in the Yorkshire swine population where the thoracic esophagus travels anterior to the aorta, but in all other swine, the esophagus remains to the right of the descending aorta. The walls of the thoracic esophagus and descending aorta in Yorkshire swine are in direct contact with one another at all five vertebral levels proximal to the GE junction.

Measurements of the distance between the center of the esophagus and the center of the descending aorta in both breeds of swine are depicted in Figure 3 and summarized in Table 1. The mean distance between the esophagus and aorta is 0.2 to 0.6 cm higher in Hanford miniature swine compared with Yorkshire swine. No significant difference was found at three out of five vertebral levels.

Measurements of the angle between the vertebral column, descending aorta, and esophagus in both breeds of swine are depicted in Figure 4 and summarized in Table 2. The mean angle was 79.6 to 97.8 degrees higher in Hanford miniature swine compared with Yorkshire swine and was significantly different at all vertebral levels. This difference correlates with the fact that the esophagus travels much more anteriorly to the aorta in Hanford swine.

Linear regression analysis revealed no statistically significant relationship between weight and any of the mean morphometric measures evaluated in the Hanford miniature swine population. In Yorkshire swine, there was no significant relationship between weight and the mean angle between the vertebral column, aorta, and esophagus. However, a statistically significant positive

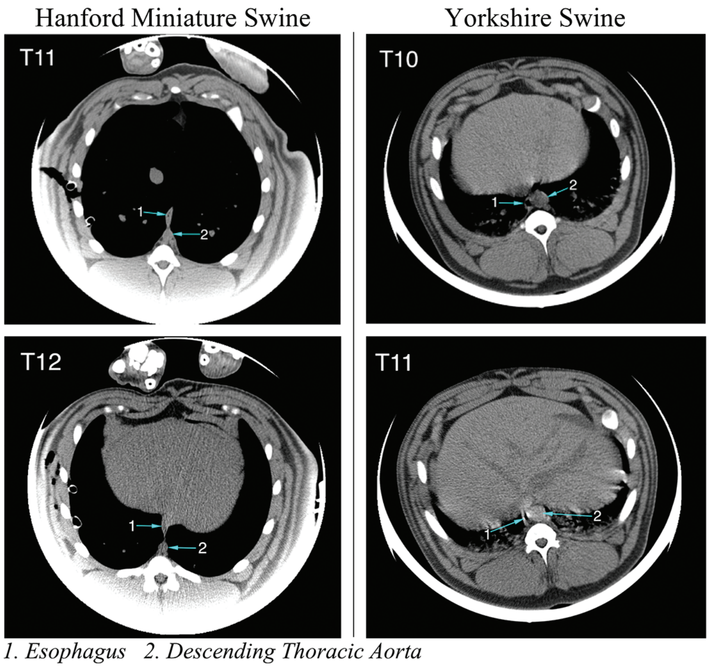

Figure 2 Representative CT images of Hanford miniature swine and Yorkshire swine at the two vertebral levels proximal to the gastroesophageal junction.

relationship was found between weight and the mean distance between the esophagus and aorta. For every 1 kg increase in weight, the mean distance increased by 0.003 cm in Yorkshire swine ($F(1,8) = 24$, $P = 0.0012$, $R^2 = 0.75$).

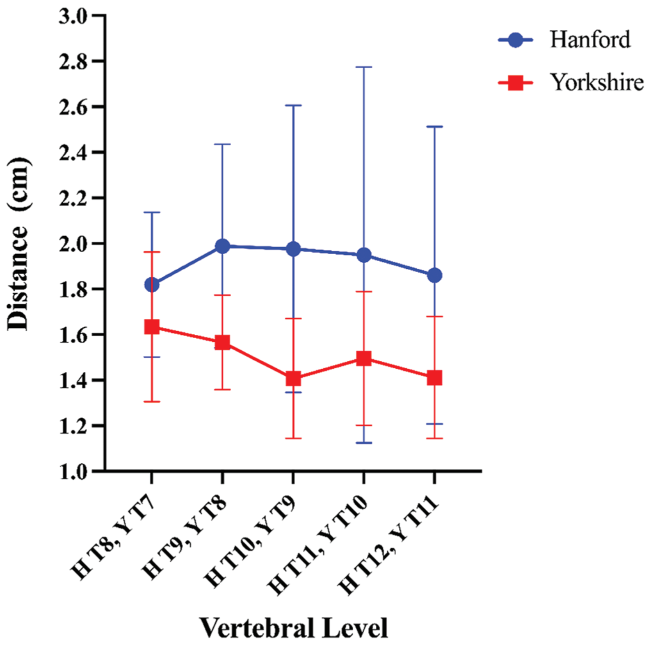

Figure 3 Mean distance between the center of the esophagus and the center of the descending aorta in Hanford miniature swine and Yorkshire swine at the five vertebral levels proximal to the gastroesophageal junction. All values are expressed as mean with standard deviation in centimeters. H: Hanford; Y: Yorkshire.

DISCUSSION

In summary, the gross anatomical relationship of the thoracic esophagus and descending aorta differs in Hanford miniature swine and Yorkshire swine. The distal thoracic esophagus travels anterior to the aorta in Hanford swine, whereas it travels to the right of the aorta in Yorkshire swine. In addition, the center of the esophagus is further from the center of the aorta in Hanford swine compared with Yorkshire swine. These two differences must be considered for selection of an ideal animal model for investigation of anatomically relevant trans-esophageal technologies such as a TEABO device.

Successful trans-esophageal occlusion of the aorta requires the esophagus to be both anterior to the aorta and close enough to the vessel, so an actuator can compress the aorta posteriorly against the vertebral column. The current TEABO device under investigation has a compression mechanism with a diameter expandable to more than 3 cm. The distance between the esophagus and aorta in both Hanford miniature swine and in Yorkshire swine is less than this diameter at all vertebral levels analyzed and thus close enough for the actuator to compress the aorta; however, the thoracic esophagus is only anterior to the descending aorta in Hanford miniature swine. This relationship is not only imperative for a TEABO device to function, but also it parallels the human anatomy. In humans, the thoracic esophagus lies

Table 1 Mean measurements of the distance between the center of the esophagus and the center of the descending aorta.

Vertebral Level	*Hanford Miniature Swine*	*Yorkshire Swine*	*P value*
H T8, Y T7	1.8 ± 0.3	1.6 ± 0.3	0.2163
H T9, Y T8	2.0 ± 0.5	1.6 ± 0.2	0.0144
H T10, Y T9	2.0 ± 0.6	1.4 ± 0.3	0.0168
H T11, Y T10	2.0 ± 0.8	1.5 ± 0.3	0.1187
H T12, Y T11	1.9 ± 0.7	1.4 ± 0.3	0.0597

All values are given as mean ± standard deviation in centimeters. H: Hanford; Y: Yorkshire.

Table 2 Mean measurements of the angle between the vertebral body, descending aorta, and esophagus.

Vertebral Level	*Hanford Miniature Swine*	*Yorkshire Swine*	*P value*
H T8, Y T7	141.3 ± 9.2	61.7 ± 14.7	<0.0001
H T9, Y T8	152.5 ± 10.1	67.6 ± 26.8	<0.0001
H T10, Y T9	163.4 ± 6.7	74.6 ± 27.9	<0.0001
H T11, Y T10	171.2 ± 4.5	75.4 ± 34.1	<0.0001
H T12, Y T11	176.1 ± 3.7	78.3 ± 30.0	<0.0001

All values are given as mean ± standard deviation in degrees. H: Hanford; Y: Yorkshire.

anterior to the descending aorta from T8 to the esophageal hiatus [16]. Therefore, Hanford miniature swine possess an anatomical relationship similar to humans. Conversely, in Yorkshire swine, the thoracic esophagus lies to the right of the aorta. In this case, the deployment of a compressive actuator would likely displace the descending aorta leftward into lung tissue, which is expected to be too compliant to provide sufficient counterforce to compress the aorta.

The results of this study clearly identify Hanford miniature swine as an appropriate animal model for further investigation of TEABO technologies. Swine are used extensively in biomedical research and have already been established as physiologically comparable organisms [9–15]. This study provides additional evidence that the anatomical relationship between the thoracic esophagus and descending aorta in Hanford miniature swine is both comparable to humans and suitable for evaluating anatomically sensitive trans-esophageal strategies such as TEABO. We have found that the thoracic esophagus is anterior to the aorta for a mean distance of 11.5 ± 2.3 cm in Hanford miniature swine. In addition, the center of the esophagus is an average of 1.8–2.0 cm away from the center of the aorta at the five vertebral levels proximal to the GE junction. These values denote an ample anatomical window that the TEABO mechanism can be effectively deployed within. However, one can assume that the closer to 180 degrees the angle between the vertebral column, aorta, and esophagus is, the more successful the TEABO deployment will be. At T11 and T12 in Hanford miniature swine, the mean angle is 171.2 ± 4.5 degrees and 176.1 ± 3.7 degrees, respectively. Thus, the window from T11–T12 is likely the most ideal target to deploy the TEABO device in future investigations.

It should be noted that the region of potential trans-esophageal aortic occlusion in both Hanford miniature swine and in Yorkshire swine is proximal to the celiac trunk. Across all swine analyzed, the celiac trunk arises distally to the level of the GE junction. Thus,

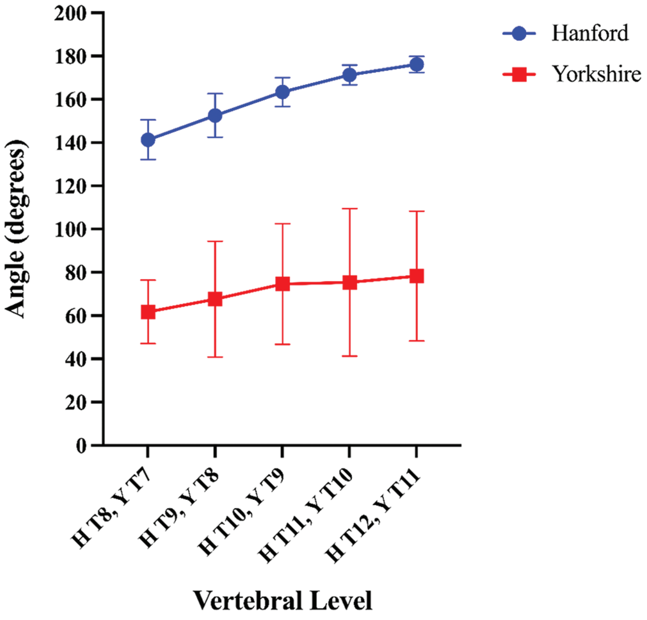

Figure 4 Mean angle between the vertebral body, descending aorta, and esophagus in Hanford miniature swine and Yorkshire swine at the five vertebral levels proximal to the gastroesophageal junction. All values are expressed as mean with standard deviation in degrees. H: Hanford; Y: Yorkshire.

TEABO would produce Zone 1 aortic occlusion in swine at any point within the distal esophagus. In humans, TEABO is also expected to produce Zone 1 aortic occlusion, since once again the level of the GE junction is proximal to the celiac trunk [16].

One limitation of this study is that the Hanford miniature swine analyzed were all males with a weight range of 63–71 kg. In addition, the Hanford swine had a mean weight of 12.0 kg larger than the Yorkshire swine ($P = 0.023$). It is possible that female Hanfords or Hanfords with a significantly lower weight could have a different anatomical relationship between the esophagus and aorta; however, this is unlikely. There was no gross difference observed between the male and female Yorkshire swine included in this investigation. Furthermore, for Hanford miniature swine with much lower weights, the aorta and esophagus would likely be closer without any significant difference in angle, as was observed in the Yorkshire swine population.

The fact that Hanford miniature swine had a higher average weight than Yorkshire swine may partly explain why the mean distance between the aorta and esophagus was higher in Hanfords than in Yorkshires. However, linear regression analysis in Yorkshire swine still predicts that the mean distance between the aorta and esophagus would be 0.4 cm higher in Hanfords compared with Yorkshires at an equivalent mean weight of 67 kg. Nevertheless, this increased distance should not significantly impact the efficacy of TEABO as Hanford miniature swine are still within the expected functional range of the device.

Another limitation of this study is that the swine analyzed were normovolemic at the time of imaging. However, TEABO will be utilized in the setting of hemorrhage. Current research shows that the descending thoracic aorta diameter decreases by an average of 32% after a blood loss of 40% in swine [17]. This decrease in diameter is not expected to significantly impact the aorto-esophageal relationship. Moreover, measurements in this study were taken between the center of the esophagus and the center of the aorta, and a reduction in vessel diameter alone would not impact any of our measured values.

There are several potential complications that could result from a technology such as TEABO. When deploying a trans-esophageal compression device, there is clearly the possibility of esophageal mucosal injury and perforation. This outcome will need to be thoroughly investigated in future TEABO studies. The porcine esophagus is pathologically and physiologically similar to humans and should serve as an appropriate model for identifying mucosal injury. Notably, the porcine and human esophagus have similar size and thickness of the esophageal layers, and both swine and humans possess esophageal submucosal glands, not found in many other animal models, that likely play a role in esophageal repair postinjury [18,19]. In addition, one can expect that the aortic occlusion produced by TEABO will result in similar complications seen with REBOA, including ischemia distal to the site of aortic occlusion, multiple organ dysfunction, and ischemia-reperfusion injury [20–22]. All these risks will need to be further explored in future TEABO investigations.

EQ3

In conclusion, TEABO is an exciting new technology that offers a strategy for temporary hemorrhage control. TEABO has the potential to allow for rapid intervention to stop bleeding and can be deployed with limited medical training. While much research is still required, this study proposes that Hanford miniature swine will be an ideal animal model to further investigate TEABO.

Ethics Statement

(1) All the authors mentioned in the manuscript have agreed to authorship, read and approved the manuscript, and given consent for submission and subsequent publication of the manuscript.
(2) The authors declare that they have read and abided by the JEVTM statement of ethical standards including rules of informed consent and ethical committee approval as stated in the article.

Conflicts of Interest

J.R. has intellectual property associated with the TEABO technology discussed in this study that is assigned to the University of Maryland. All other authors declare no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

S.G.S., J.J.M., and J.R. designed the study. S.G.S., H.A., J.E., N.P., M.J.R., and R.T. completed data collection. S.G.S. completed data analysis. S.G.S. wrote the manuscript. J.J.M., H.A., J.E., and J.R. provided critical revisions.

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