

Experimental Study of Cardiorespiratory and Stress Factors in Esophageal Surgery Using Robot-Assisted Thoracoscopic or Open Thoracic Approach

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Background: Our aim was to compare cardiovascular and stress response to robotic technology during thoracoscopic mobilization and anastomosis of the esophagus vs the conventional open approach.

Design: Randomized experimental study.

Setting: Department of Experimental Surgery, University of Heidelberg.

Subjects: Twelve pigs randomized to undergo robotic or conventional surgery (6 animals each).

Interventions: Fundus rotation gastropasty followed by esophageal mobilization and intrathoracic anastomosis by conventional or robotic surgery.

Main Outcome Measures: Mean arterial pressure, central venous pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac output, pulmonary vascular resistance, partial oxygen pressure, al-

veolar-arterial difference in partial pressure of oxygen, and arteriovenous oxygen content difference measured preoperatively, during esophageal manipulation, and 30 minutes after operation. Operative stress was assessed by plasma levels of cortisol and substance P.

Results: Hemodynamic measures showed higher intraoperative central venous pressure and pulmonary vascular resistance in the open surgery group, whereas cardiac output was significantly decreased compared with the robotic group. Blood gas values showed significant deterioration during esophageal manipulation with open surgery in contrast to the robotic group. Substance P and cortisol levels were significantly higher with the open approach.

Conclusions: The robot-assisted approach is associated with improved intraoperative cardiopulmonary function and seems to be a less stressful technique.

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TRADITIONALLY, ESOPHAGEAL resection has been performed by thoracotomy to access the intrathoracic esophagus. With the aim of avoiding the potential morbidity of the open thoracic approach, thoracoscopic mobilization of the esophagus has been described in recent years.¹ Most studies concluded that thoracoscopic mobilization can be performed safely with satisfactory outcomes in a specialized center having advanced endoscopic surgery skills.^{2,3} However, endoscopic surgery is laden with limitations such as fixed axis points at the trocar insertion sites, 2-dimensional video monitors, limited dexterity at the instrument tips, lack of haptic sensation, and, in some cases, poor ergonomics. The creation of a surgical robot system with 3-dimensional visual capacity would seem to deal with most of these limitations. Several case reports have indicated that many abdominal operations, such as gastrectomy,⁴

choledochotomy,⁵ choledochojejunostomy,⁶ pancreatectomy,⁷ splenectomy,⁸ adrenalectomy,⁹ inguinal hernia repair,¹⁰ and rectopexy,¹¹ can be performed successfully with robotic assistance.

However, the optimal approach to esophagectomy remains controversial. The strategy to reduce surgical invasiveness and to avoid the potential morbidity of open thoracotomy has been debated, and further assessment of new techniques such as the robotic technology for thoracoscopic surgery is needed.^{12,13} It appears possible that computer-enhanced robotic surgery will decrease the morbidity associated with open esophagectomy, including substantial blood loss, postoperative pain, pulmonary complications, wound complications, and anastomotic leaks. The role of computer-enhanced devices in the operating room will continue to expand, providing significant benefits to the next generation of patients.¹⁴⁻¹⁶ The purpose of this study was to examine the effects of tho-

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racoscopic esophageal mobilization and intrathoracic anastomosis, using a robotic manipulation system (da Vinci Surgical System; Intuitive Surgical, Sunnyvale, California), on cardiorespiratory functions and stress responses of the body and comparing them with the traditional open procedure in an experimental porcine setting.

METHODS

EXPERIMENTAL DESIGN

The experimental procedures were approved by the German Committee for Animal Care, Karlsruhe, Germany. During the experiments, all animals received humane care in compliance with the National Institutes of Health and institutional guidelines established for the Animal Care Facility at the University of Heidelberg. Twelve animals (German Landrace pigs; mean [SD] weight, 45 [4.6] kg; range, 38-54 kg) were randomized in 2 experimental groups (n=6 each): robot-assisted thoracoscopic approach and conventional open thoracotomy approach. All experiments were performed with the animals under general anesthesia and undergoing continuous cardiopulmonary monitoring. Animals were killed immediately after the experiments by intravenous high-dose potassium chloride infusion under anesthesia.

ANESTHESIA

After premedication with azaperone (1-2 mg/kg intramuscularly) and midazolam hydrochloride (0.5-0.7 mg/kg intravenously), anesthesia was induced with ketamine hydrochloride (10 mg/kg intravenously) and midazolam hydrochloride (1.0-1.4 mg/kg intravenously). After endotracheal intubation, animals were ventilated with a mixture of oxygen, 1.5 to 2.0 L/min; air, 0.5 to 1.0 L/min; nitrous oxide, 1.5 to 2.0 L/min; and isoflurane, 0.75% to 1.5% (half-open ventilation system). For analgesia, piritramide (11 mg/h intravenously) was administered. During the procedures, the temperature was continuously monitored and maintained above 36°C with heated blankets in both groups.

HEMODYNAMIC MEASURES AND BLOOD GAS VALUES

A percutaneous electrocardiogram recording was used for detection of heart rate. A Swan-Ganz catheter was inserted from the left external jugular vein and an arterial catheter was placed in the carotid artery for the evaluation of systemic hemodynamics and blood gas analyses. Mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and mean pulmonary arterial pressure (MPAP) were recorded, and cardiac output (CO) was measured with the thermodilution technique. Blood samples were withdrawn from carotid artery and central venous catheters for subsequent determination of arterial and mixed venous oxygen contents (PaO₂, mixed venous partial pressure of oxygen, PaCO₂, mixed venous partial pressure of carbon dioxide, arterial oxygen saturation, and venous oxygen saturation). The other measures were calculated by standard formulas:

$$PVR = [(MPAP - PCWP) \times (80/CO)],$$

in which PVR indicates pulmonary vascular resistance;

$$PAO_2 - PaO_2 = [FIO_2 \times (\text{Barometric Pressure} - \text{Water Vapor Pressure}) - (PaCO_2 / \text{Respiratory Quotient})] - PaO_2,$$

in which PAO₂ - PaO₂ indicates alveolar-arterial difference in partial pressure of oxygen, FIO₂ indicates the fraction of inspired oxygen, the barometric pressure equals 760 mm Hg, the water vapor pressure equals 47 mm Hg, the respiratory quotient equals 0.8, and PaO₂ is given in millimeters of mercury; and

$$C(a-v)O_2 = \{1.34 \times \text{Hemoglobin} \times (\text{CaO}_2 - \text{Mixed Venous Oxygen Saturation}) + [0.003 \times (\text{PaO}_2 - \text{Partial Venous Pressure of Oxygen})\},$$

in which C(a-v)O₂ indicates the arteriovenous oxygen content difference, hemoglobin is given in grams per deciliter, CaO₂ indicates the arterial oxygen saturation, the mixed venous oxygen saturation is given as a percentage, and the partial venous pressure of oxygen is given in millimeters of mercury.

OPERATIVE PROCEDURE

All operations were performed by the same team of surgeons, who were experienced with both the conventional and the robot-assisted surgical procedures. The technique of gastroplasty was identical in both groups. Animals in both groups were placed in a left lateral position. After open laparotomy and complete mobilization of the stomach, fundus rotation gastroplasty was performed by stapling (TLC 55; Ethicon GmbH, Norderstedt, Germany) as previously described.¹⁷ The abdomen was then closed, the right side of the chest was prepared and draped, and the chest was entered via conventional open thoracotomy or robot-assisted thoracoscopic approach.

CONVENTIONAL OPEN THORACOTOMY APPROACH

Thoracotomy was performed through the right fifth intercostal space on the right side. A part of the fifth rib was removed to widen the operating field. After a gentle retraction of the right lung under 2-lung ventilation, the whole mediastinum appeared. The esophagus was easily mobilized after it was separated from the paraesophageal structures such as the aorta and the vagus nerve; small esophageal arteries were coagulated. The stomach was then pulled into the chest. The back row of the anastomosis was performed initially with interrupted 5-0 polydioxanone sutures (PDS; Ethicon, Somerville, New Jersey). After the esophagus and stomach were sharply opened, the inner layer was completed with simple sutures (5-0 polydioxanone sutures). The outer row was then finished with interrupted sutures as was done for the back row. Finally, the chest wall was closed, approximating the ribs and muscles with continuous polyglyconate suture (Maxon; Davis and Geck Inc, Danbury, Connecticut), and the skin was clamped.

ROBOT-ASSISTED THORACOSCOPIC APPROACH

The first trocar (the 12-mm camera trocar) was inserted into the chest through a minithoracotomy (15 mm) at the seventh intercostal space on the midaxillary line. The next two 8-mm trocars for the instrument arms were introduced under direct vision at the fifth and ninth intercostal spaces, respectively. The trocar for the lung retractor was inserted ventrally through the seventh intercostal space, so that it did not hinder the movement of the robot arms. The robot was positioned posterior to the animal, 90° to its body axis, and the robot arms were connected with the trocars.

One assistant stood at the table to change the instruments and to insert suture materials. The operative steps were similar to those for the open thoracotomy procedure. After minimal retraction of the right lung and exploration of the chest,

Table 1. Changes in Hemodynamic Measures

Measure	Mean (SD)					
	Open Surgery			Robotic Surgery		
	T1	T2	T3	T1	T2	T3
MAP, mm Hg	73.5 (18.3)	37.3 (9.9) ^a	73.7 (12.3) ^a	71.2 (15.3)	47.5 (14.7)	72.3 (5.1)
CO, L/min	4.2 (0.3)	3.9 (0.2)	4.1 (0.3)	4.2 (0.3)	4.9 (0.3) ^b	4.6 (0.6)
CVP, mm Hg	14.2 (1.3)	15.8 (0.8)	14.5 (1.8)	13.3 (1.0)	12.3 (1.0) ^b	12.2 (1.0)
PCWP, mm Hg	14.2 (2.0)	16.7 (2.6)	15.5 (1.8)	13.3 (1.0)	14.3 (0.5)	13.8 (1.2)
MPAP, mm Hg	21.5 (1.0)	24.5 (2.1)	23.7 (1.9)	22.7 (2.0)	23.5 (2.1)	23.0 (0.9)
PVR, dynes/s per cm ²	172 (24)	247 (27) ^a	199 (26)	169 (21)	197 (23) ^{c,d}	178 (22) ^c

Abbreviations: CO, cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; MPAP, mean pulmonary-arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; T1, immediately after insertion of catheter and before laparotomy; T2, during intrathoracic anastomosis; T3, 30 minutes after surgery.

^aSignificant difference from T1 to T2 or from T2 to T3, $P < .01$.

^bSignificant difference at T2 between the 2 groups, $P < .001$.

^cSignificant difference from T1 to T2 or from T2 to T3, $P < .001$.

^dSignificant difference at T2 between the 2 groups, $P < .01$.

Table 2. Duration of Operative Procedures

Operative Procedure	Time, Mean (SD), min		P Value
	Open Surgery	Robotic Surgery	
Abdominal part	80 (16)	85 (13)	.80
Thoracic part	110 (11)	128 (21)	.10
Total	188 (17)	233 (12) ^a	<.001

^aSetup time for the robotic manipulator system is included.

the esophagus was prepared and mobilized by means of the coagulation hook. The stomach was pulled into the chest and 2 corner stitches fixed it to the esophagus. The back row of the anastomosis was then constructed with interrupted 5-0 polydioxanone sutures. Esophagus and stomach were opened by means of a coagulation hook, and the inner layer of the anastomosis was completed with continuous 5-0 polydioxanone sutures. The outer row was then finished with interrupted sutures as described for the back row.

LABORATORY ANALYSIS

Chemical mediator levels were determined from venous blood samples. Serum was separated by centrifugation at 3000 rpm for 10 minutes and immediately frozen and stored at -70°C until analysis. Serum levels of interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), substance P, and cortisol were measured by immunoassays (R&D Systems Inc, Minneapolis, Minnesota). The enzyme-linked immunosorbent assay was performed in the standard fashion according to the manufacturer's protocol. The absorbance of the samples was measured with a bichromatic enzyme-linked immunosorbent assay reader at 405 and 690 nm.

MEASUREMENT PROTOCOL

Time points were set immediately after insertion of the Swan-Ganz and arterial catheters and before the laparotomy (T1), during the intrathoracic manipulation (T2), and 30 minutes after the end of the thoracic surgery (T3). Blood samples for the determination of stress measures and cytokine levels were obtained from all animals at T1 and T3, and for the blood gas analy-

sis at T1, T2, and T3. Hemodynamic measures were also documented at T1, T2, and T3.

STATISTICAL ANALYSIS

We used SAS statistical software (release 9.1; SAS Institute Inc, Cary, North Carolina) for statistical analysis. Descriptive statistics of the quantitative hemodynamic measures, blood gas values, cytokine levels, and stress measures are presented as means with standard deviations. The paired t test was applied to compare the robot-assisted thoracoscopic group and the conventional open thoracotomy group at each time point according to the hemodynamic measures, blood gas values, cytokine levels, and stress measures. Changes in the quantitative measures between the 3 time points were compared within each group by the t test for paired values. Two-sided P values were always computed, and an effect was considered statistically significant at $P < .01$.

RESULTS

CHANGES IN HEMODYNAMIC MEASURES

Mean values of all perioperative measurements for animals treated with either the conventional open approach or the robot-assisted approach are summarized in **Table 1**. The mean duration of the operation for the abdominal and thoracic portions and the total duration in both groups are shown in **Table 2**. The hemodynamic measures between the 2 groups at T1 did not differ significantly.

Changes in MAP were similar between the 2 groups. Intraoperatively, in animals treated with the conventional open approach, the mean MAP decreased significantly ($P = .005$) and returned nearly to the preoperative level after the operation, whereas the intraoperative reduction in MAP in the robotic surgery group was not statistically significant. Comparison between the 2 groups showed no significant differences.

The CO was slightly decreased intraoperatively and returned to the baseline in the open surgery group, whereas the CO increased during the operative procedure in the ro-

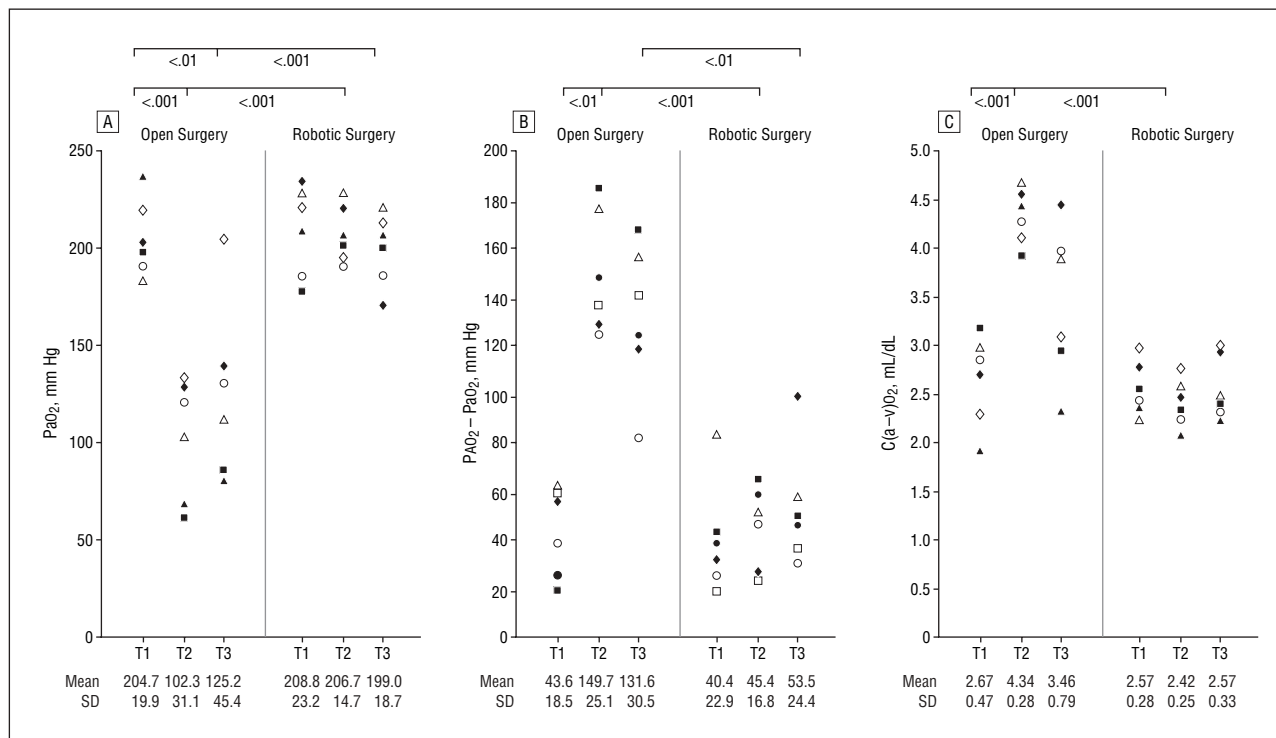


Figure 1. Changes in blood gas values. A, Oxygen partial pressure (PaO₂); B, alveolar-arterial difference in partial pressure of oxygen (PAO₂-PaO₂); and C, arteriovenous oxygen content difference [C(a-v)O₂]. Single values for each animal are presented in dot plots, each animal being represented by a different symbol. P values are given at the top of each panel. T1 was immediately after insertion of catheter and before laparotomy; T2, during intrathoracic anastomosis; and T3, 30 minutes after surgery.

botic group. The difference between groups was significant ($P < .001$). Intraoperatively, the CVP in the open surgery group showed an elevation, whereas in the robotic surgery group the CVP was decreased. Comparison of the groups showed a significant difference in the intraoperative CVP ($P < .001$). In both groups, PCWP increased intraoperatively, and a more notable elevation was observed in the open surgery group. However, the difference between groups was not statistically significant.

The changes in MPAP were similar to those in PCWP. Although the intraoperative MPAP increase was higher in the open surgery group than in the robotic surgery group, there was no significant difference between the groups. In both groups, PVR increased significantly during the operative procedure, but the increase was significantly higher in the open surgery group than in the robotic surgery group ($P = .006$).

CHANGES IN BLOOD GAS VALUES

The values of all blood gas measures for the 2 groups are shown in **Figure 1**. The PaO₂ showed a constant intraoperative level with no significant alteration in the robotic surgery group as opposed to the open surgery group, where it fell during the intrathoracic manipulation to 50% of the initial values ($P < .001$) and remained significantly decreased after surgery ($P = .006$) (Figure 1A). The differences in PaO₂ levels between the 2 groups intraoperatively and postoperatively were significant (both $P < .001$).

The PAO₂-PaO₂ in the open surgery group showed significantly higher levels intraoperatively and postopera-

tively compared with the preoperative baseline level ($P = .009$) (Figure 1B). In the robotic surgery group, PAO₂-PaO₂ showed an almost constant level with a slight, nonsignificant increase during intrathoracic manipulation and after surgery. The PAO₂-PaO₂ levels between the 2 groups were significantly different during intrathoracic manipulation ($P < .001$) and after the operative procedure ($P = .007$).

The changes in C(a-v)O₂ were similar to those in PAO₂-PaO₂. In detail, in the open surgery group the values for all animals increased by up to 60% during the intrathoracic anastomosis ($P < .001$) compared with the baseline (Figure 1C). After the chest was closed, in 3 of the animals, C(a-v)O₂ returned to initial levels, whereas in the others, C(a-v)O₂ remained at high levels. In the robotic surgery group, C(a-v)O₂ remained almost constant during the whole operation. The C(a-v)O₂ values of the 2 groups during the intrathoracic procedure were significantly different ($P < .001$).

CHANGES IN CYTOKINE LEVELS AND STRESS MEASURES

The data for each animal are presented in **Figure 2**. The plasma samples preoperatively showed nondetectable amounts of IL-6. After surgery, IL-6 was detected in both groups at levels between 20 and 60 pg/mL (Figure 2A). In 2 pigs in the robotic surgery group, IL-6 level was elevated above 50 pg/mL, but the difference was not significant between the 2 groups.

Starting with a baseline level of around 100 pg/mL, 4 of 6 pigs in each group showed a significantly decreased

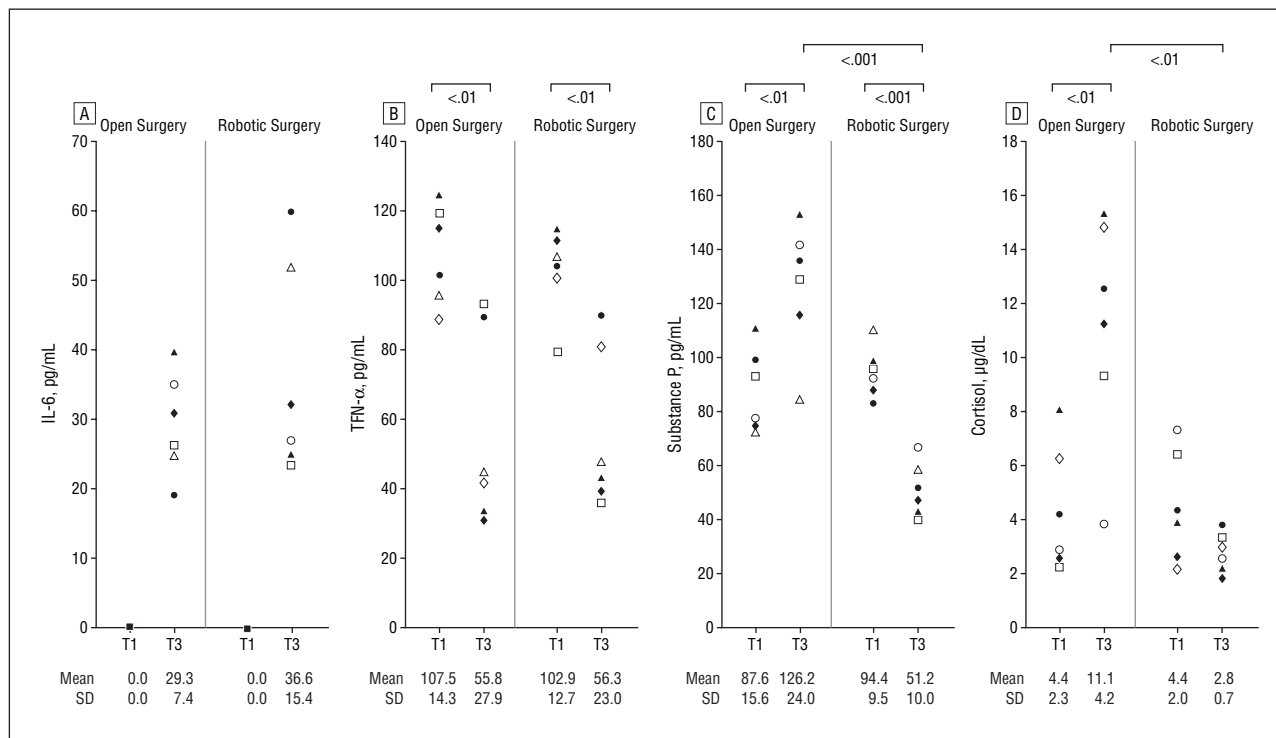


Figure 2. Changes in plasma concentration of different mediators by enzyme-linked immunosorbent assay. A, Interleukin 6 (IL-6); B, tumor necrosis factor α (TNF- α); C, substance P; and D, cortisol. Single values for each animal are presented in dot plots, each animal being represented by a different symbol. *P* values are given at the top of each panel. T1 was immediately after insertion of catheter and before laparotomy; T2, during intrathoracic anastomosis; and T3, 30 minutes after surgery. To convert substance P to picomoles per liter, multiply by 0.742; cortisol to nanomoles per liter, multiply by 27.588.

TNF- α value of about 50 pg/mL after surgery ($P = .009$) (Figure 2B). In the other 2 animals in each group, TNF- α values remained at the initial level. There was no significant difference between groups. In pigs undergoing open thoracotomy, the substance P level increased postoperatively up to 44% above the baseline ($P = .007$) (Figure 2C). In contrast, in the robotic surgery group, substance P values intraoperatively showed a reduction of 45% from the baseline ($P < .001$). Postoperative values between the 2 groups differed significantly ($P < .001$). In the open surgery group, 5 of 6 pigs showed a significant increase in postoperative cortisol values compared with the initial preoperative levels ($P = .006$) (Figure 2D). In contrast, in the robotic surgery group, cortisol levels remained almost constant during the whole procedure. The postoperative cortisol levels between the 2 groups differed significantly ($P = .006$).

COMMENT

In the past decade, advances in laparoscopic and endoscopic procedures have revolutionized minimally invasive surgery. However, a number of inherent drawbacks hinder surgeons in performing difficult thoracoscopic and laparoscopic procedures, such as esophagus or pancreas resections. Robotic surgery was developed to overcome those pitfalls and to reduce the incidence of morbidity and mortality. Recent efforts have been made to improve the prognosis of patients with advanced esophageal cancer through aggressive resections and lymph node dissection, but this surgical procedure is associ-

ated with a high incidence of postoperative complications. Until recently, anastomotic leakage, pulmonary complications, and cardiovascular insufficiency have been the major complications of surgery for esophageal cancer.¹⁸ Mortality due to anastomotic leakage and cardiovascular insufficiency has been markedly reduced by improvements in perioperative care, whereas pulmonary complications still remain a major problem.¹⁹ Reducing the pulmonary complications has therefore become one of the greatest challenges in the contemporary surgical treatment for thoracic esophageal cancer. One strategy is to perform esophagectomy via thoracoscopy rather than the open procedure. In addition, it is hypothesized that minimally invasive surgery results in less pain, which in turn means less stress and less stimulation of the immune system. Whether this hypothesis is indeed true for robot-assisted esophageal surgery is still unproved. These facts prompted us to evaluate the perioperative effects of robot-assisted thoracoscopic esophageal approach on cardiorespiratory functions and stress measures in an experimental setting.

In our experiments, we observed that the hemodynamic functions and intraoperative pulmonary measures were significantly better in the robotic group. The surgical approach in esophagus resection affects cardiac function, as mentioned in several studies.^{1,2,20} Like others,²¹ we observed a transient intraoperative increase in CVP, PCWP, MPAP, and PVR and a decrease in MAP in animals with the open surgery, and less pronounced intraoperative changes in hemodynamic function in the robotic group. Notably, during the operation, CVP and PVR

significantly increased in animals with the open thoracotomy approach. The minimal retraction of the right lung and the precise preparation of the esophagus owing to the image enlargement by the camera in the robotic group, in contrast to the more extensive compression of lung and heart during the open process, may influence the direction and amplitude of the deterioration. Consistent with these findings, the reduction in CO in animals undergoing the open approach could be the result of marked intrathoracic manipulation leading to mechanical compression of the heart's atria and an impediment to ventricular ejection by cardiac displacement. The decrease in CO also produced the widening of the $C(a-v)O_2$ difference, which could be shown with open thoracotomy.

In contrast to the transient effects on cardiovascular responses, the surgical approach affected pulmonary measures significantly differently in both groups. We observed a prominent decrease in PaO_2 in animals undergoing an open thoracotomy compared with unchanged intraoperative and postoperative PaO_2 values in the robotic group. This significantly sustained lower PaO_2 for a minimum of 30 minutes postoperatively, despite continuous respiratory ventilation, is clearly a sign of prolonged reduction of pulmonary function due to compression, traumatic injury, and partial atelectasis of the lung. In contrast to the PaO_2 , the significantly increase in $PAO_2 - PaO_2$ in pigs undergoing thoracotomy reflects first the reduced oxygenation of the right lung and second the subsequent rise of the right-to-left shunting despite vasoconstriction in nonventilated areas. In contrast, pulmonary function in animals operated on with robot-assisted thoracoscopy remained almost in a steady state as a result of the minimal manipulation and compression of the right lung. Similar to our results, Duda et al,²² in a comparison among endoscopic esophagectomy, blunt esophagectomy, and thoracoabdominal esophagectomy in sheep, showed significant pathological decreases in MAP, PaO_2 , and CO and increased $PAO_2 - PaO_2$ and PVR in the thoracoabdominal esophagectomy group, whereas these measures in the endoscopic group were unchanged.

Some authors^{23,24} have stated that pneumonia resulting from traumatic injury and atelectasis is the most important complication after conventional esophagectomy. Atkins et al,²⁵ in a large retrospective study of 379 patients who underwent esophagectomy, showed that more than 28% had respiratory complications. These complications, especially pneumonia, were associated with an increased risk of mortality. In a similar review of 386 patients, Mariette et al²⁰ demonstrated a pulmonary complication rate of 20.7%. Altogether, the authors postulated that pulmonary complications could be important predictors of postoperative mortality. It is noteworthy that the purpose of 2-lung instead of 1-lung ventilation in our procedure was the technical difficulty of performing 1-lung ventilation in the porcine model. Generally, with 1-lung ventilation, the nonventilated lung is exposed to less stress and injury during surgery, but because 2-lung ventilation was performed in both of our groups, it can be postulated that the obtained data would be comparable.

Another purpose of this study was to compare the stress responses in both groups. Substantial tissue injury ini-

tiates an elaborate cascade of events that result in inflammation and regeneration. There are several studies comparing minimally invasive procedures with open surgery with regard to the stress response of the animal or patient.²⁶⁻²⁸ Interleukin 6 is one of the most-studied stress and inflammatory measures, being used not only in research but also for clinical examination of patients. We found an increase in IL-6 levels in both groups after surgery, suggesting that either the abdominal step of the operation or the esophagus manipulation may influence the intensity of trauma more than the type of the operation. The value of measuring IL-6 levels in thoracic surgery has been controversial. Takemura et al²⁹ demonstrated a higher IL-6 level after thoracoscopic esophagectomy compared with conventional thoracotomy and postulated that the longer duration of the intrathoracic procedure of thoracoscopic esophagectomy could be more stressful than the thoracotomy. In contrast, Fukunaga et al³⁰ in a similar study found a significantly smaller increase in IL-6 level after the thoracoscopic procedure than after transthoracic esophagectomy. Narumiya et al³¹ mentioned lower IL-6 levels in patients who underwent esophagectomy through minithoracotomy in comparison with conventional thoracotomy.

Analogous to IL-6, we could not detect a significant difference of TNF- α levels between the 2 groups. In our series we observed a postoperative decrease in TNF- α levels in most of the animals. We assume that TNF- α is involved in complex metabolic and immune pathways; therefore, it may be a nonspecific marker of the stress response. In addition, the measurement 30 minutes after the operation is probably not optimal, and possible changes may be detectable later in the postoperative course. In a controlled trial on children who underwent open or laparoscopic Nissen fundoplication, McHoney et al³² reported no significant response in TNF- α levels in the postoperative period in either group. However, in an experimental study on pigs, Collet et al³³ showed increased serum TNF- α activity in open fundoplication compared with the laparoscopic group.

Cortisol is the main hormone in the pathway of the "neuroendocrine stress response." The degree of serum hormone elevation is generally proportional to the severity of injury. Our data confirm these observations, and we found a significant increase in cortisol level in the open group and a steady-state mode in the robotic group postoperatively. Tashiro et al³⁴ mentioned a marked cortisol increase in patients who underwent open esophagectomy and concluded that cell-mediated immunosuppression preceded by a hyperinflammatory response was an observable reaction in patients after esophageal surgery. Our study suggests that robot-assisted thoracoscopy is less stressful than thoracotomy in the operative and postoperative period. These results are in contrast to the published data on minimally invasive abdominal surgery, where corticotropin and cortisol levels seemed to be elevated in comparison with the open approach.³⁵ A possible explanation for this difference is that acute stretching of the peritoneum by insufflation of carbon dioxide, as a trigger of corticotropin and cortisol release, does not play an important role in the thoracoscopic approach. Another aspect that contributes to the "opera-

tive stress” is the subjective postoperative pain of the patient. It is well known that less postoperative pain is accompanied by a lower rate of pulmonary complications because of better lung function.

In our series, we measured substance P as a pain marker. Substance P is a neuropeptide involved in pain modulation. There are clinical and experimental studies using substance P in the monitoring of operative stress and postoperative pain or analgesia.^{36,37} In our experiment, we observed a marked contrast between the increased levels in the open group and the decreased levels in the robotic group. This difference could be explained by the thoracotomy, which caused additional pleural trauma, and the resection of the rib, which caused additional pain due to the periosteal injury. On the other hand, substance P is widely distributed in the central nervous system and periphery, localized in the primary sensory neurons and the intrinsic neurons of the gastrointestinal tract, so that the observed difference could be a result of many unknown pathways, such as the difference of the oxygenation in the peripheral tissue between the 2 groups or the reduced clearance activity of the lung during the open thoracotomy.

In conclusion, in recent years there have been many reports of video-assisted dissection of the esophagus³⁸⁻⁴¹ or even esophagogastric reconstruction⁴² in combination with a standard open laparotomy to complete the esophagectomy,^{43,44} as well as the transhiatal dissection technique⁴⁵ in experimental settings. These initial and other current series, which also combined thoracoscopic and laparoscopic procedures,^{46,47} confirmed that total laparoscopic and thoracoscopic esophagectomy could be safely executed and have provided an extensive array of experience in both minimally invasive and open esophageal surgery. The goal of all these activities was to decrease the traditionally high morbidity associated with esophagectomy. With the introduction of robotic surgery and further technologic advances, as well as the development of training modules for the robotic surgery system in visceral surgery, there is an opportunity to provide significant benefits to patients.^{48,49} Our experimental data undoubtedly support ongoing development of computer-enhanced devices, but further clinical experience and validation are needed to determine the role of “robots” in the operating theater.

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