Cardiopulmonary exercise testing for cardiovascular risk assessment in patients undergoing gastric and oesophageal cancer surgery: results from a prospective interventional cohort study

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ABSTRACT

Background Cardiopulmonary exercise testing (CPET) has shown to be useful for preoperative risk stratification in various types of intra-abdominal and thoracic surgery. However, data about the predictive value of CPET for cardiovascular outcome after gastric or oesophageal cancer surgery are inconclusive. The aim of this study was to evaluate the prognostic value of CPET parameters for the prediction of cardiovascular complications in patients with this type of surgery.

Methods This is a prospective single-centre interventional cohort study including 200 consecutive patients who underwent elective surgery for oesophageal and/or gastric cancer. Symptom-limited CPET was performed preoperatively to evaluate the potential of various test-derived parameters including anaerobic threshold (AT) to predict cardiovascular complications within 30 days after surgery.

Results 200 patients (mean age 68±14.2 years) met inclusion and exclusion criteria: oesophageal surgery 54 pts, gastric surgery 132 pts and combined oesophageal/gastric surgery 14 pts. 41/200 pts (20.5%) experienced cardiovascular complications during and within 30 days after surgery including cardiac events (17.5%), non-cardiac complications (15%) and less serious complications in 30 patients (15%).

Conclusion CPET is a useful tool for preoperative risk assessment for patients undergoing surgery for oesophageal and gastric cancer, which carries a particularly high risk for cardiovascular complications. An AT <9.5 mL/kg/min turned out to be the most reliable predictor for major cardiovascular complications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiopulmonary exercise testing (CPET) has shown to be useful for preoperative risk stratification in various types of intra-abdominal and thoracic surgery. However, data about the predictive value of CPET for cardiovascular outcome after gastric or oesophageal cancer surgery are inconclusive.

WHAT THIS STUDY ADDS

⇒ CPET is a useful tool for perioperative risk assessment for patients undergoing surgery for oesophageal and gastric cancer. An anaerobic threshold <9.5 mL/kg/min turned out to be the most reliable predictor for major cardiovascular complications.

INTRODUCTION

Previous studies indicate that cardiopulmonary exercise testing (CPET) is a useful tool for preoperative risk assessment for patients undergoing major non-cardiopulmonary surgery. Preoperative risk assessment is of particular importance in view of the increasing number of elderly and frail patients with comorbidities. Cardiovascular complications have been reported in up to 3.5% and fatal complications in up to 1.8% of patients undergoing various types of non-cardiac surgery. Cardiorespiratory complications in non-cardiac surgery have been investigated in recent studies. The incidence of perioperative myocardial infarction with various abdominal interventions is up to 5%. The risk of surgery for cancer of stomach, oesophagus or oesophagus with transition to the cardiac part of the stomach
is particularly high—up to 8% for perioperative MI or death, and therefore, the availability of a reliable tool to predict perioperative risk is of particular importance.\(^3\)\(^6\)

CPET provides a whole range of physiological parameters and much of this is underused clinically. CPET allows to assess causes of reduced oxygen consumption, differentiating and determining the degree of respiratory and heart failure, and evaluation of exercise tolerance and metabolism dysfunction in muscle tissue. Among CPET parameters which are used in clinical practice, the anaerobic threshold (AT) turned out to be of particular importance: The AT is reached at the moment when the capacity of aerobic metabolism in muscle tissue becomes insufficient and the anaerobic pathway of oxidative phosphorylation is activated. The level of AT depends on the initial metabolic situation including the glycogen concentration in muscle cells, the number and density of mitochondria, and—to a lesser extent—the arterial blood flow. The prognostic value of the AT index is well known in patients with chronic heart failure and coronary heart disease.\(^7\)\(^9\) CPET allows to determine maximum oxygen consumption which reflects the function of the respiratory and cardiac system, the state of peripheral blood flow and of tissue metabolism. In addition, the method allows to determine the AT—the parameter of the readiness of metabolism for a sharp load or lack of oxygen. During major surgery, episodes of hypoxia or anaemia with increased oxygen demand combined with stress from tissue traumaisation may occur, which may lead to cardiac complications.\(^10\) CPET can be useful to predict the development of complications associated with these problems. In a study including 843 patients who underwent mixed intra-abdominal surgical procedures, an AT <11mL/kg/min was associated with increased hospital mortality with a sensitivity of 88% and a specificity of 47%. At the same time, VE/VCO2>34 was an independent predictor of hospital mortality with a sensitivity 88% and a specificity 47%.\(^11\) Furthermore, it has been shown that patients with postoperative cardiopulmonary complications had a significantly lower _VO2 peak. (19.265.1mL/kg/min) than those without complications (21.46 4.8mL/kg/min) (p=0.04)

At the same time, a leading cause for cardiovascular complications in the perioperative period including the development of myocardial infarction is metabolic failure.\(^3\)\(^12\) Therefore, the aim of our study was to identify the prognostic value of the AT level calculated during CPET in high-risk gastric and oesophageal cancer surgery.

**MATERIAL AND METHODS**

This is a single-centre prospective cohort study with sequential inclusion of patients. The study was conducted at the University Clinical Hospital No. 1 of the First Schenov Moscow State Medical University.

**Study patients**

The aim of the study was to include 200 consecutive patients who underwent elective surgery for oesophageal and/or gastric cancer.

Inclusion criteria were being over 18 years of age and being planned for elective surgery for oesophageal and/or gastric cancer. Exclusion criteria were contraindications to perform an elective surgical intervention\(^6\); contraindications to CPET\(^8\) and refusal of the patient to participate in the study.

The preoperative cardiovascular examination included (1) consultation with a cardiologist, (2) 12-lead resting electrocardiography (ECG); (3) transthoracic echocardiography and (4) cardiopulmonary symptom-limited exercise test (CPET).

Based on the results of the preoperative cardiovascular examination, contraindications and the need for therapeutic interventions prior to the surgery were defined. In case of a significant change of medical treatment in this preoperative period, a re-examination, including repeated CPET, was performed. The analysis included data from the last tests, done just before surgery.

**Cardiopulmonary exercise testing**

We used the SCHRILLER CS-200 CPET system and a treadmill for exercise testing. A modified BRUCE protocol was chosen for all patients. Symptom-limited tests have been performed according to actual guidelines.\(^5\) The following parameters were measured: ventilation (VE); oxygen consumption (VO2); carbon dioxide production (VCO2); Oxygen pulse (O2-pulse). The AT level was determined by the V-slope velocity ratio method by the occurrence of a sharp increase in the ratio of carbon dioxide release to oxygen consumption.\(^8\)

**Definition of cardiovascular outcome**

1. The primary endpoint was defined as
   - Death from cardiovascular causes (defined based on pathoanatomical findings).
   - Myocardial infarction (defined as increased troponin T or troponin I levels in combination with typical ECG dynamics, or based on autopsy data) either/or
   - Stroke (diagnosis confirmed by brain tomography or at autopsy).
2. The secondary endpoints included:
   - Angina pectoris attacks (typical chest pain with ECG changes).
   - Ventricular arrhythmias requiring antiarrhythmic therapy.
   - Persistent or paroxysmal supraventricular tachycardia.
   - Persistent or paroxysmal atrial fibrillation/flutter.
3. The combined endpoint included all complications which are listed above.

Cardiac complications has been registered at the following time points: during surgery, within 30 days after
Cardiac surgery

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surgery or until the end of the hospitalisation period if longer than 30 days.

Statistical analysis
Processing of information for statistical analysis was carried out using Microsoft Excel and a package of statistical programmes including Statistica and SPSS version 17.0. Data are presented as median, IQR (the values 25 and 75 percentiles). Characteristics of the groups were compared using the $\chi^2$ OR was calculated as $(\text{Events treatment} / \text{Non-events treatment}) / (\text{Events control} / \text{Non-events control})$. Fisher test was used for ordinal variables, and the Mann-Whitney U-test for continuous variables. An additional analysis was carried out using receiver operating characteristic (ROC) curves with the SPSS program. Threshold values of indicators were determined by ROC curves according to the optimal ratio of sensitivity and specificity.

RESULTS
A total of 228 consecutive patients have been screened and 200 patients have been included in the study population. The study flow chart is shown in figure 1.

Basic characteristics of the study patients are presented in table 1. Mean age of the patients was 68±14.2 years.

Surgical intervention
Surgery for oesophageal cancer was performed in 54 patients, surgery for gastric cancer in 132 patients and 14 patients underwent combined surgery for oesophageal and gastric cancer. In 28 cases, the surgical intervention was performed both from thoracic and abdominal access. Transhiatal extirpation of the oesophagus with gastric tube plastic surgery and neck anastomosis was performed in early oesophageal cancers stages (1 and 2). In cases of cancers of the body and the cardiac part of the stomach, gastrectomy was performed with extended D2 lymph node dissection and resection of the abdominal oesophagus with Roux-en-Y reconstruction. All operations were performed under a combination of general and regional (epidural) anaesthesia. General anaesthesia was induced and maintained using either intravenous or inhaled agents. The trachea was intubated and all patients were mechanically ventilated. Epidural anaesthesia was used in 112 patients to block pain sensitivity in a particular area and to reduce the need for narcotic analgesics.

Study endpoints
The distribution of study end points depending on the type of operation is presented in table 2.
On the day of surgery, the following complications were registered: one nonfatal myocardial infarction, two episodes of atrial fibrillation and two episodes of sustained ventricular tachycardia which required antitachyarrhythmic treatment. The majority of endpoints (75.6%) were registered within 2–5 days after surgery whereas 12.2% of all endpoints occurred 6–30 days after surgery.

All-cause mortality was 5.5% (11 patients): 3 patients died from sepsis 1–2 weeks after surgery, 2 patients died 1 day after surgery due to internal bleeding. Death from cardiovascular causes occurred in 3.0% (six patients). Combined endpoints were found in 41 patients (20.5%).

We analysed the difference in main characteristics between patient with and without EP. Patients >75 years of age experienced a primary EP significantly more often compared with patients<75 years (36.0% vs 18.7%, p=0.023, OR 2.45, 95% CI 1.21 to 4.98). The highest risk to reach the primary EP was found in patients with previous MI, compared with patients with no previous MI (42.0% vs 20.7%, p=0.034, OR 3.0, 95% CI 1.52 to 5.98).

Echocardiography parameters did not predict the risk for primary and secondary endpoints. It has to be mentioned, that left ventricular ejection fraction did not differ between patients with EP and without them (54.5% vs 54.8%, p=0.43).

Among the various CPET indicators obtained, only a few were significantly associated with EP development (tables 3 and 4).

Parameters of CPET associated with combined endpoint were just similar for those for secondary endpoints: AT (p=0.02), maximal load (p=0.02).

ROC analysis of AT was performed to determine the sensitivity and specificity in PEP prognosis in the perioperative period (figure 2).

AT level <9.5 mL/kg/min had the best sensitivity (93%) and specificity (68%). Positive predictive value was—75.0%, negative predictive value—98.9%.

An AT level <11 had the highest diagnostic accuracy for the occurrence of a primary EP: sensitivity was 88% and specificity 79%. The positive predicative value was 66.7%, the negative predicative value—97.4%.

AT did not prove to be an independent predictor for the occurrence of a secondary EP or for combined EP.

### Table 1 Basic characteristics of patients included in the study (n=200)

| Parameter | N  | (%) of N |
|-----------|----|---------|
| Male      | 55 | 27.5    |
| Over 65 years old | 72 | 36.0 |
| Over 75 years old | 33 | 16.5 |
| Body mass index >30 kg/m² | 12 | 6.0 |
| Body mass index >35 kg/m² | 6 | 3.0 |
| Body mass index <18.5 kg/m² | 3 | 1.5 |
| Arterial hypertension | 60 | 30.0 |
| Ischaemic heart disease | 41 | 20.5 |
| Angina pectoris | 25 | 12.5 |
| Myocardial infarction | 16 | 8.0 |
| Chronic HF with reduced EF | 10 | 5.0 |
| Chronic HF with preserved EF | 5 | 2.5 |
| Atrial fibrillation—permanent | 10 | 5.0 |
| History of stroke | 6 | 3.0 |
| Diabetes mellitus (type 2) | 13 | 6.5 |
| Chronic obstructive pulmonary disease | 12 | 6.0 |

EF, ejection fraction; HF, heart failure.

### Table 2 Endpoints reached in different types of surgery

| Endpoints | For all patients n=200 (%) of n | Oesophagus cancer n=54 (%) of n | Gastric cancer n=132 (%) of n | Combined† surgery n=14 (%) of n |
|-----------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Primary endpoint | 11 (5.5%) | 3 (5.5%) | 6 (4.5%) | 2 (14.3)* |
| Secondary endpoint | 30 (15.0%) | 8 (14.8%) | 18 (13.6%) | 4 (28.6%)* |

Mann-Whitney U-test.

*Combined surgery versus oesophagus cancer as well as gastric cancer (p=0.0124).
†Combined surgery versus gastric cancer (p=0.05).
prospective single centre study with a homogenous team of surgeons, anaesthesiologists, medical staff and the same treatment plans to acquire risk factors and risk rates under controlled conditions.

CPET allows to assess the functional reserve of the body and the presence and degree of cardiac, respiratory and metabolic insufficiency. Decreased metabolic activity in cells, decreased efficiency of oxygen consumption, and decreased functionality of muscle tissue with hypoxia are the major underlying causes for an increased risk of perioperative cardiovascular complications. Therefore, it is most important to determine the functional state of the patient before surgery. Several systematic reviews have been performed over the past few years to evaluate the role of CPET as a risk-assessment method in patients undergoing intra-abdominal or other non-cardiopulmonary surgery. Results confirm that functional capacity evaluated as AT and peak oxygen uptake (VO2peak) have a high predictive value for postoperative morbidity and mortality in the majority of surgical cohort studies. However, it is not unexpected that results differ according to the type of surgery and to cohort

### Table 3  CPET parameters associated with the primary endpoint

| Parameters | Primary EP, n=11 | No primary EP, n=189 | P value |
|------------|------------------|----------------------|---------|
| Mean±SD    | 25%–75%          | Mean±SD              | 25%–75% |         |
| Load duration (s) | 422±112          | 377–612              | 449±121 | 368–625 | >0.05   |
| Max heart rate (beat per min) | 109.2±26.8       | 101–129              | 112±38  | 106–141 | >0.05   |
| Max systolic BP (mm Hg)       | 176.5±32.5       | 144–201              | 166±36.6 | 151–188 | >0.05   |
| RER                         | 0.98±0.08        | 0.88–1.12            | 1.02±0.11 | 0.89–1.15 | >0.05   |
| VE/VO2                      | 27.2±5.9         | 22.8–34.9            | 25.5±6.8 | 19.8–33.8 | >0.05   |
| Maximum load (METS)         | 5.6±3.1          | 3.9–8.2              | 6.8±4.3  | 4.4–10.6 | 0.01     |
| Peak O2 consumption (mL/kg/min) | 15.8±5.0        | 12.8–20.1            | 18.5±4.9 | 13.3–22.8 | 0.01     |
| O2 consumption (% of predicted value) | 79.2±11.1 | 59.28–88.1         | 82.4±9.8 | 67.2–91.5 | >0.05   |
| AT (mL/kg/min)              | 8.8±3.1          | 7.2–12.8             | 11.5±4.4 | 8.6–14.8 | 0.01     |

### Qualitative data

| Parameters | Primary EP, n (%) | No EP, n (%) | OR (95% CI) | P value |
|------------|------------------|--------------|-------------|---------|
| AT<11.0 (mL/kg/min) | 5              | 22           | 6.33 (1.78–22.47) | 0.02    |
| METS<4     | 3                | 13           | 5.11 (1.21–21.58) | 0.015   |

AT, anaerobic threshold; CPET, cardiopulmonary exercise test; EP, end point; METS, metabolic equivalents; RER, respiratory exchange ration; VE/VO2, ventilatory equivalent for carbon dioxide.

### Table 4  CPET parameters associated with the secondary endpoints

| Parameters | Secondary EP, n=30 | No secondary EP, n=170 | P value |
|------------|--------------------|------------------------|---------|
| Mean±SD    | 25%–75%            | Mean±SD                | 25%–75% |         |
| Load duration (s) | 431±119           | 369–622                | 441±118 | 358–628 | >0.05   |
| Max heart rate (beat per min) | 111.3±27.8       | 103–134                | 117±39  | 105–143 | >0.05   |
| Max systolic BP (mm Hg)       | 173.3±34.5       | 143–198                | 165±34.4 | 150–186 | >0.05   |
| RER                         | 0.99±0.05        | 0.87–1.12              | 1.02±0.13 | 0.89–1.16 | >0.05   |
| VE/VO2                      | 27.3±5.6         | 22.3–34.8              | 25.2±6.7 | 19.8–34.4 | >0.05   |
| Maximum load (METS)         | 5.7±3.2          | 3.9–8.9                | 6.9±4.6  | 4.3–10.7 | 0.01     |
| Peak O2 consumption (mL/kg/min) | 16.8±4.9       | 12.4–21.2              | 18.9±4.5 | 13.7–23.2 | 0.05     |
| O2 consumption (% of predicted value) | 79.8±11.5 | 58.3–89.9          | 83.4±9.9 | 64.8–92.2 | >0.05   |
| AT (mL/kg/min)              | 9.1±3.6          | 7.5–13.1               | 11.6±4.1 | 8.8–14.8 | 0.02     |

### Qualitative data

| Parameters | Primary EP, n (%) | No EP, n (%) | OR (95% CI) | P value |
|------------|------------------|--------------|-------------|---------|
| AT<11.0    | 3                | 12           | –           | 0.537   |

AT, anaerobic threshold; CPET, cardiopulmonary exercise test; EP, end point; METS, metabolic equivalents; RER, respiratory exchange ration; VE/VO2, ventilatory equivalent for carbon dioxide.
severe perioperative complications in our study. According to our data, a decrease in the AT below 11 mL/kg/min predicts the development of major cardiac complications with an OR=6.3 (p=0.001). Thus, the obtained data allows us to identify patients with an increased risk of surgery. Our findings can be used for clinical decision-making and for planning of perioperative care. It is of special note that most of the complications did not develop during the operation, but rather on the first postoperative day and then for another 3–5 days. This finding has important implications for the postoperative monitoring patients with higher cardiovascular risk which may be planned for up to 5 days from the date of surgery to allow timely intervention in case of deterioration during this critical period.

The major strength of the study is the relatively large number of consecutive cancer patients with the same type of surgery in the setting of a single surgery department with a stable team of surgeons and well defined operational and treatment procedures. Another strength is the relatively large number of CPET which have been performed using the same procedures and the same protocol by a single team. Furthermore, there was no lost to follow-up.

A limitation of the study is the fact that the numbers of events are rather low to make more deep statistical analysis for some subgroups of patients. This does not allow to make meaningful adjustments of the results for factors such as age (although patients aged >75 years met primary EP more frequently (OR=2.45)), gender, tumour stage or comorbidities.

CONCLUSION

CPET is a useful perioperative risk assessment tool for patients undergoing surgery for oesophageal and gastric cancer, which carries a particularly high risk for cardiovascular complications. An AT <11 mL/kg/min turned out to be the most reliable predictor for minor and AT <9 mL/kg/min for major cardiovascular complications.

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