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ORIGINAL ARTICLE

Comparison of Serum Cardiac Specific Biomarker Release after Non-Cardiac Thoracic Surgery

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SUMMARY

Background: **The detection of postoperative myocardial infarction can be difficult in patients after lung surgery. The aim of this study was to verify the clinical significance of elevated Troponin I (cTnI), N-terminal pro-natriuretic peptide (NT–pro-BNP), lactate dehydrogenase (LDH), creatine kinase (CK), and CK-MB in the perioperative course.**

Methods: **Between 2007 and 2010, 64 patients (36 men, 28 women) were includeded in this prospective study and underwent thoracotomy and wedge lung resection (n = 20, group I), lobectomy/bilobectomy (n = 24, group II), and pneumonectomy (n = 20, group III). Peri-operative measurements were done for the serum markers: cTnI, NT-pro-BNP, LDH, CK, and CK-MB preoperatively and at 4 hours, 8 hours, and 24 hours postoperatively. Patients were followed over a 90-day period to evaluate postoperative cardiac mortality.**

Results: **No basal troponin I elevation (or CK-MB) was found prior to surgery. Elevation in concentrations of troponin I (>0.32 ng/mL) occurring after the procedure were seen in 9 patients. However, there was neither association with 90-day survival, postoperative ECG changes, nor with elevated levels of the other cardiac serum markers. cTnI correlated significantly with intrapericardial procedures in 7 out of 20 patients (Spearman's rank correlation coefficient: 0.406; p <0.0001). Additionally, of the 20 patients within the pneumonectomy group, 8 patients had postoperative elevated serum cTnI. The grouping of patients into groups I through III was significantly associated with cTnI elevation (Spearman's rank correlation coefficient: 0.455; p <0.0001).**

Conclusions: **Despite the excellent sensitivity of troponin I for detection of acute myocardial infarction the fact remains that troponin I elevations were common after intrapericardial procedures and pneumonectomies. Thus, to differentiate between cardiac ischemia provoked chest pain and wound pain related to thoracotomy remains most difficult. Patients with only marginally elevated cTnI concentrations after intrapericardial resections or pneumonectomy should remain in the intensive care unit and should be followed-up carefully by cardiologists.**

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KEY WORDS

Thoracotomy; pulmonary surgical procedure; myocardial infarction; troponin

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INTRODUCTION

The accurate diagnosis of perioperative myocardial ischemia and infarction in patients undergoing lung resection can be particularly difficult in procedures that involve resection of centrally located structures e.g. pericardium and atrial myocardium. Measuring the levels of serum-troponin I (cTnI) and the activities of creatine kinase and the more cardiospecific isoenzyme CK-MB is

part of the diagnostic and prognostic strategy for detection of myocardial injury.

Elevated troponins were identified as prognostic factors for early postoperative mortality in patients undergoing non-cardiac surgery. In these settings, it is well documented that elevated circulating levels of troponins are associated with poor prognosis, regardless of underlying disease [1,2]. Major operations can lead to a significant increase in serum creatine kinase and in the even more cardiospecific isoenzyme CK-MB from skeletal muscles. Thus postoperative diagnosis of myocardial ischemia relies mostly on chest pain, electro-cardiographic (ECG) changes, and elevated serum troponin level [3]. There is growing interest in new cardiac biomarkers such as N-terminal pro-BNP (NT-pro-BNP).

NT-proBNP plasma levels reflect the extent of myocardial stretch as seen in heart failure exacerbations and cardiac ischemia [4].

Serum lactat dehydrogenase (LDH) activities are used in the diagnosis of late myocardial ischemia [5].

The aim of this study was to determine whether elevated serum troponin I level can be expected after non-cardiac thoracic surgery. We performed a prospective study in which three groups of patients allocated to wedge lung resection, lobectomy/bilobectomy, and pneumonectomy were examined for perioperative ECG changes, serum biomarker levels of troponin I, CK/CK-MB, NT-proBNP, and LDH.

MATERIALS AND METHODS

This prospective observational study recruited 64 patients from the Department of Thoracic Surgery of the Thoraxklinik, Heidelberg University, from 2007 through 2010. Ethics approval was given by the Medical University of Heidelberg Institutional Review Board (S-397/2007). Patients who either underwent thoracotomy and wedge lung resection (n = 20), thoracotomy and lobectomy/bilobectomy (n = 24), and patients with intra- and extrapericardially pneumonectomy (n = 20) were included. Table 1 is a summary of pertinent patient demographics.

Patients' data were obtained for age, gender, previous history of cardiovascular disease and smoking, ASA status, type of surgery, intraoperative blood loss, operation time, and length of stay in the ICU. To obtain information on the 90-day survival rate all available files from the various departments were reviewed and the physicians in charge of the patients were contacted. Additionally, each patient's medical record was manually searched for information on comorbid conditions. In 63 of 64 patients 90-day follow-up data were obtained. One patient was lost from follow-up after being discharged from the hospital at day 13 postoperatively. Serum cardiac troponin I, CK, CK-MB, NT-proBNP, and LDH were measured at given time points. The first analysis was done within 24 hours prior to surgery with the following measurements being performed at 4 hours, 8 hours, and 24 hours postoperatively. Standardized 12 lead electrocardiography were recorded prior to and within 24 hours after surgery.

The cTnI assay used by the hospital laboratory was a chemiluminiscence immunoassay (Immulite 2500, Siemens Healthcare Diagnostics, Eschborn, Germany) with an imprecision level ≤10 % at a cut-off of 0.32 ng/mL [6], the serum creatinine kinase assay was done with Konelab 60i (Thermo Fisher Scientific, Dreieich, Germany), normal range up to 171 U/L in males and 145 U/L in females and detection limit 7 U/L. LDH analysis was also performed on Konelab 60i (Thermo Fisher Scientific, Dreieich, Germany), range 135 - 225 U/L, detection limit 5 U/L. The NT-pro BNP analysis was done with a chemiluminiscence immunoassay (Immulite 2500, Siemens Healthcare Diagnostics, Eschborn, Germany), upper reference value 125 pg/mL and detection limit 10 pg/mL.

cTnI was considered elevated at levels greater than 0.32 ng/mL which is the cut-off criterium recommended by the Committee on Standardization of Markers of Cardiac Damage of the IFCC [6]. The detection limit for cTnI was <0.1ng/mL.

Statistical analyses were performed using SPSS 18.0. Differences in parameter expression between patient groups were tested using the non-parametric Mann-Whitney U-test and the Kruskal-Wallis H-test. Distribution of categorical data was analysed by two-sided Fisher`s exact test or chi² test according to Pearson. Correlation between parameters was analysed with the non-parametric Spearman rank correlation test.

RESULTS

The mean age of patients included in the study was 58 years (standard deviation: 11 years), 36 were male and 28 were female. Elevated cTnI was found in 9 patients (14.1 %).

Coexisting cardiovascular conditions were common, 14 patients (21.8 %) had a diagnosis of arterial hypertension, one patient (1.6 %) had a history of previous MI, and 7 patients (10.9 %) had a history of diabetes mellitus (Table 1). Pericardial resection was performed in 20 patients of group II and group III, 5 and 15 patients, respectively. Blood loss and operating time were significantly different between the surgical groups according to the procedure performed. Procedural data are summarized in Table 2.

No basal troponin elevation (or CK-MB) was found prior to surgery. Elevated concentrations of cTnI (>0.32 ng/mL) after the procedure were seen in one patient in group II and 8 patients in group III. However no association with the 3-month actuarial overall survival could be detected.

In one patient in group II, postoperative elevation of troponin I and elevated serum CK-MB/CK ratio was found, but no postoperative ECG ST-T wave changes were seen. Although two patients of group III (pneumo-

Table 1. Patients` characteristics.

	Group I	Group II	Group III
Age (mean ± SD)	**55 ± 11 years**	**60 ± 12 years**	**58 ± 9 years**
Gender (n)			
Male	**5**	**17**	**14**
Female	**15**	**7**	**6**
Medical history (n)			
Coronary artery disease	**0**	**2**	**0**
Peripheral vascular disease	**0**	**2**	**3**
Hypertension	**1**	**9**	**4**
Stroke	**1**	**3**	**0**
Cardiac arrhythmia	**1**	**0**	**1**
ASA classification (n)			
1	**1**	**2**	**0**
2	**15**	**12**	**12**
3	**4**	**12**	**6**
Histology (n)			
Malignant	**15**	**24**	**18**
Benign	**1**	**0**	**2**

Table 2. Peri- and postoperative characteristics.

	Group I	Group II	Group III
Duration of surgery (mean ± SD)	**79 ± 24 min**	**136 ± 39 min**	**147 ± 42 min**
Intrapericardial resection (n)	**0**	**5**	**15**
Blood loss (mean ± SD)	**110 ± 60 mL**	**320 ± 150 mL**	**700 ± 400 mL**
ICU Stay (mean ± SD)	**1 day**	**1 day**	**3 ± 2 days**
Postoperative ECG			
ST-wave changes (n)	**0**	**0**	**2**
Axis deviation (n)	**0**	**2**	**2**
90-day mortality (n)	**0**	**0**	**3**

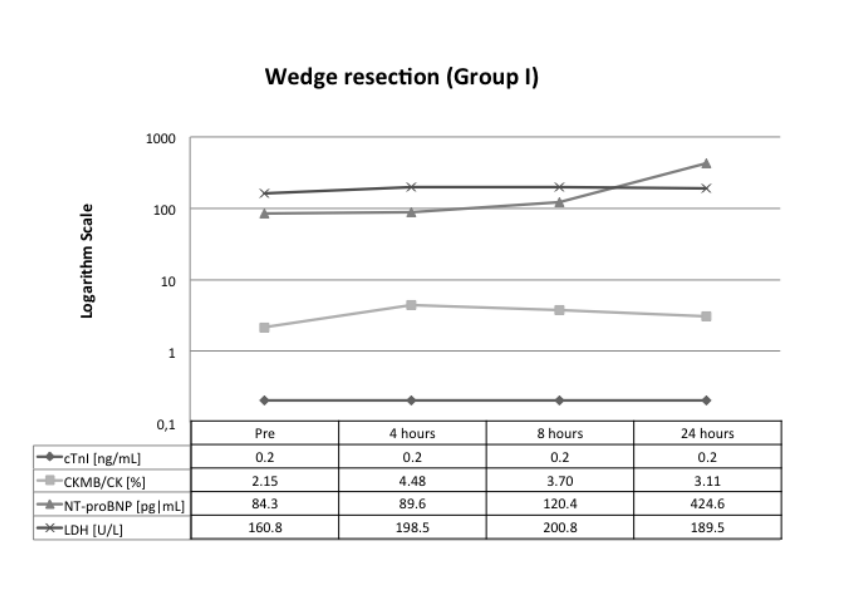
nectomy and intrapericardial pneumonectomy) had a combination of elevated serum troponin I and CK-MB/CK-level (>6 %) together with signs of myocardial ischemia (early ST-segment changes), the further postoperative course was uneventful.

One patient in group III developed classical symptoms of myocardial ischemia in the latter postoperative course and, consequently, had coronary artery stenting. However, within our study period no abnormal laboratory or ECG results were identified. Another patient in group III had severe chest pain 33 hours postoperatively, nevertheless, no pathologic ECG or laboratory findings during the 24 hour postoperative study period were detected. In spite of normal troponin I level and CK-MB and CK activities, cardiac catheterization with stenting was done for two RCA stenoses. However, acute myocardial infarction had been excluded.

Table 3. Cardiac biomarkers before and at 4 hours, 8 hours, 24 hours after lung surgery.

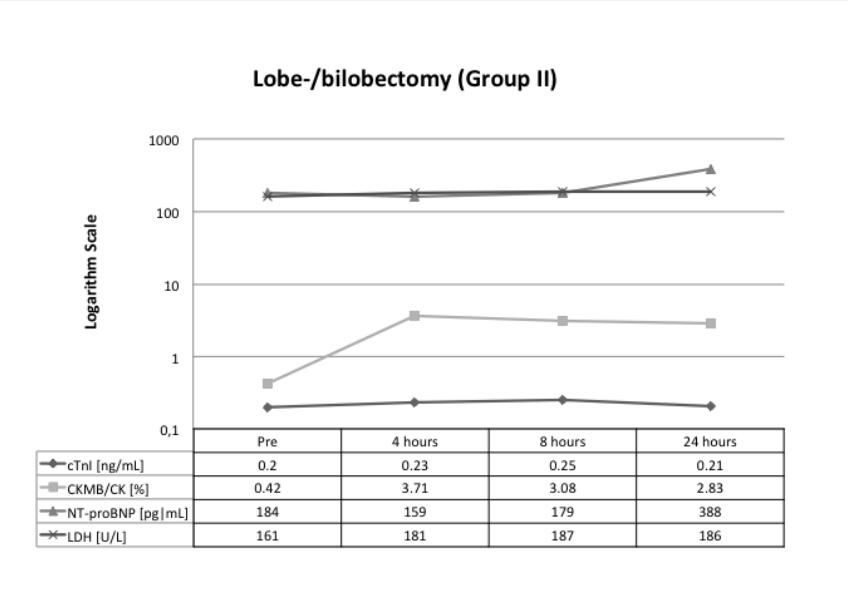
	Group I	Group II	Group III
Troponin I (ng/mL; mean ± SD)			
Pre surgery	**0.2 ± 0.0**	**0.2 ± 0.0**	**0.2 ± 0.0**
4 hours	**0.2 ± 0.0**	**0.23 ± 0.14**	**0.33 ± 0.31**
8 hours	**0.2 ± 0.0**	**0.33 ± 0.22**	**0.53 ± 0.69**
24 hours	**0.2 ± 0.0**	**0.21± 0.07**	**0.42 ± 0.70**
CK/CKMB (%; mean ± SD)			
Pre surgery	**2.2 ± 7.9**	**0.4 ± 2.0**	**2.8 ± 10.0**
4 hours	**4.5 ± 2.8**	**3.7 ± 1.6**	**5.1 ± 2.9**
8 hours	**3.7 ± 2.4**	**3.1 ± 1.3**	**3.6 ± 2.4**
24 hours	**3.1 ± 2.0**	**2.8 ± 1.2**	**3.9 ± 3.3**
NT-pro BNP (pg/mL; mean ± SD)			
Pre surgery	**84.3 ± 54.7**	**184.4 ± 175.1**	**146.6 ± 139.1**
4 hours	**89.6 ± 54.5**	**159.1 ± 143.3**	**141.2 ± 135.3**
8 hours	**120.4 ± 68.3**	**179.4 ± 147.5**	**229.6 ± 201.1**
24 hours	**424.7 ± 549.7**	**387.8 ± 289.3**	**628.3 ± 556.5**
LDH (U/L; mean ± SD)			
Pre surgery	**160.9 ± 30.5**	**161.1 ± 28.8**	**158.0 ± 29.6**
4 hours	**198.6 ± 33.7**	**181.9 ± 39.4**	**193.4 ± 49.8**
8 hours	**200.9 ± 31.2**	**186.9 ± 37.6**	**191.6 ± 38.5**
24 hours	**189.5 ± 29.6**	**186.1 ± 35.9**	**184.3 ± 38.6**

After surgery, serum LDH and NT-proBNP increased and peaked, but mostly remained at that level until the 24 hr sample (Table 3, Figure 1-3). All patients with postoperatively increased serum cTnI (>0.32ng/mL) were found to experience postoperative serum NT-proBNP level elevation. None of the remaining parameters including age >65 years, gender, postoperative blood loss, operation time, early postoperative pathologic ECG, elevated serum CK-MB/CK ratio, elevated serum LDH, and 90-day mortality were significantly associated with cTnI elevation. Nine out of 20 patients who had intrapericardial atrial resections or pericardial resections revealed elevated concentrations of serum cTnI. Furthermore, cTnI correlated significantly with intrapericardial procedures (Spearman's rank correlation coefficient: 0.497; p <0.0001). In one patient, after intrapericardial pneumonectomy, postoperative ECG ST-elevation, serum troponin, and CK/CK-MB ratio elevation were detected, but the further clinical course was uneventful. Of the 20 patients within the pneumonectomy group, 8 patients had postoperative elevated serum cTnI. However, of the 15 patients who underwent intrapericardial pneumonectomy, 6 patients revealed elevated serum troponin I levels postoperatively. The grouping of patients within surgical procedures in group I through III was significantly associated with cTnI elevation (Spearman's rank correlation coefficient: 0.455; p <0.0001.



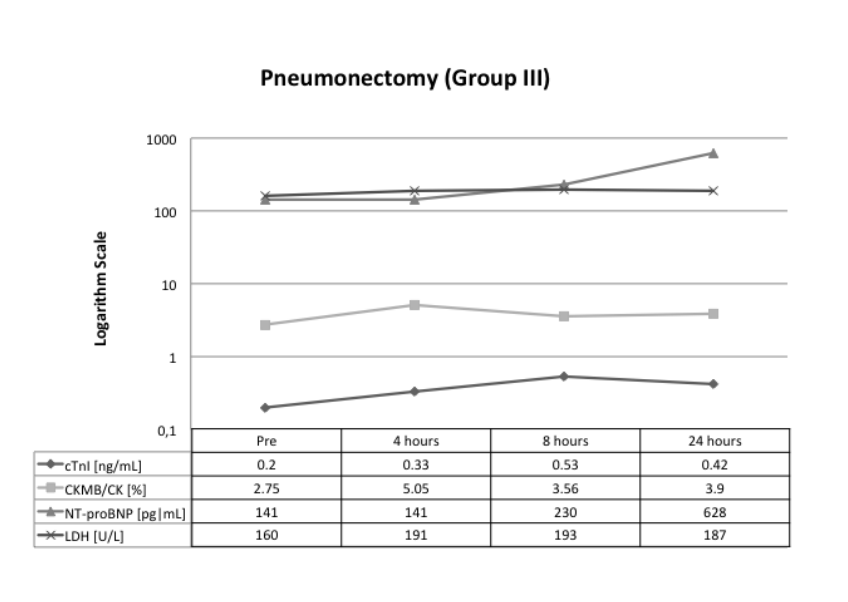
	Pre	4 hours	8 hours	24 hours
cTnI [ng/mL]	0.2	0.2	0.2	0.2
CKMB/CK [%]	2.15	4.48	3.70	3.11
NT-proBNP [pg|mL]	84.3	89.6	120.4	424.6
LDH [U/L]	160.8	198.5	200.8	189.5

Figure 1. Variation in time of cardiac biomarkers (mean) in group I (logarithm scale graph).



	Pre	4 hours	8 hours	24 hours
cTnI [ng/mL]	0.2	0.23	0.25	0.21
CKMB/CK [%]	0.42	3.71	3.08	2.83
NT-proBNP [pg|mL]	184	159	179	388
LDH [U/L]	161	181	187	186

Figure 2. Variation in time of cardiac biomarkers (mean) in group II (logarithm scale graph).



	Pre	4 hours	8 hours	24 hours
cTnI [ng/mL]	0.2	0.33	0.53	0.42
CKMB/CK [%]	2.75	5.05	3.56	3.9
NT-proBNP [pg|mL]	141	141	230	628
LDH [U/L]	160	191	193	187

Figure 3. Variation in time of cardiac biomarkers (mean) in group III (logarithm scale graph).

DISCUSSION

The detection of postoperative myocardial infarction can be difficult in patients after lung surgery especially when intrapericardial procedures are performed. The clinical requirements of early diagnosis, risk stratification, and effective treatment for myocardial infarction have stimulated the development of numerous new and cardiac specific biomarkers (e.g. cardiac troponins). Cardiac troponins are now integral to the diagnosis of myocardial infarction (MI) and have led to the reclassification of MI into either ST elevated MI (STEMI) or non-ST elevated MI (NSTEMI). The recent document of the ESC/ACC Committee for the redefinition of myocardial infarction (MI) has introduced the measurement of cardiac troponin as the biochemical standard for the diagnosis of MI [3]. In this prospective study cardiac troponins were within the reference limit (<0.32 ng/mL) before and after thoracotomy in group I. Among patients of group II one patient had elevated troponin, CK-MB/CK ratio, and NT-proBNP during the early postoperative course after intrapericardial sleeve-resection of the lower lobe. However, no postoperative ECG changes and normal LDH activities were observed within 24 hours after surgery making a differential diagnosis of non-ST elevated myocardial ischemia or surgical damage of the myocardium likely. The value of LDH as a specific cardiac marker after lung surgery is debatable, while Turna et al. [7] found elevated LDH activities to be a significant prognosticator of postoperative pulmonary complication. Within this study no association between elevated LDH activities and serum level of the other tested biomarkers or early postoperative outcome was detected (Table 3).

After intrapericardial procedures or pericardial resection 2 out of 7 do not have CK-MB/CK ratio elevation. After intrapericardial pneumonectomy one patient had symptoms suggestive of myocardial ischemia with troponin and CK-MB/CK ratio elevation along with postoperative ECG changes. However, no cardiac catheterization was performed due to the early postoperative onset of myocardial ischemia along with no further cardiac complications.

Patients with detected serum troponin elevation had no elevated risk of early mortality within the 90-day follow-up period. In all patients preoperative values were measured and no patient had signs of myocardial ischemia.

The development of the cardiac markers showed a typical rise and fall of the CK-MB/CK ratio with a peak value at 4h postoperatively. Katus et al. and Vikenes et al. found serum CK-MB elevations after sternotomies and lateral thoracotomies due to the presence of CK-MB in skeletal muscle [8,9]. However troponin was not detectable in the serum after lung surgery. The role of the biomarkers cTn-I, CK and CK-MB to differentiate between solely muscular lesions and myocardial infarction after cardioversion have been emphasised by Bon-

nefoy et al. [10]. Nevertheless the superiority of serum troponin versus CK-MB/CK ratio in the diagnosis of myocardial infarction is established [11]. In patients after pneumonectomy, troponin I peaked above reference limits at 8h postoperatively.

Due to the limited clinical evaluation by cardiac catheterization postoperatively, it is difficult to assess whether cTnI elevations represent an acute MI or not. The relationship to myocardial ischemia and NSTEMI is more difficult to define, as patients in the early postoperative period did not have chest pain due to the routine use of epidural analgesia with non-opioid analgesics. Thus, the differentiation between cardiac ischemia provoked chest pain and thoracotomy related wound pain remains most difficult. In addition, pathologic ECG ST-elevation was seen in only two patients, underlining the difficulties in differential diagnosis.

Despite the excellent sensitivity of troponin I for the detection of acute myocardial infarction troponin I elevations were common after intrapericardial procedures and pneumonectomies. Only one patient who had troponin I elevation had major cardiac complications before discharge and deceased in the intensive care unit. In a retrospective study by Lim E, et al. [12] postoperative elevated troponin I levels were found to increase the risk of early mortality after resection of lung cancer in 207 patients by multivariate analysis. However, there was no disease specific mortality analyzed and troponin I levels were only available if a troponin sample was requested individually depending on the clinical problem. Nevertheless, five out of 50 patients after pneumonectomy and eight of 143 patients after lobectomy were detected with elevated troponin I levels within 30 days postoperatively.

As in our study the relationship to myocardial infarction was more difficult to delineate. They found that 36 % (5/14) of patients with elevated serum troponin levels did not have chest pain or ECG evidence of ischemia and only 36 % of patients presented classical ST-elevation on ECG [12].

Postoperative echocardiographic data were not available for this population to help assess whether troponin I elevation was related to the surgical myocardial injury done by intrapericardial resection or coronary artery disease with myocardial infarction. No correlation was found between CK-MB/CK ratio and troponin I level. We can all speculate whether early postoperative elevation of the CK-MB/CK ratio is related to skeletal muscle injury during thoracotomy and not from myocardial damage as verified by the normal troponin I level.

Preoperative elevated serum NT-proBNP level in patients with non-cardiac surgery were identified to be associated with increased risk of cardiac mortality and all-cause mortality in a meta-analysis by Ryding [13]. It is noteworthy that within our study perioperative NT-proBNP levels were significantly higher after pneumonectomy in comparison to group I and group II, but no correlation to troponin I or early death within 90 days postoperative was detected.

Despite further evaluation of clinical signs for myocardial infarction, ECG changes, and CK and CK-MB activities cardiac catheterization remains the most needed option.

However cardiac catheterization is not always available and early thrombolysis after thoracic surgery is contraindicated and even the use of anti-platelet agents and heparin may be prohibited.

To date no algorithm has been established in the management of elevated troponin I level after pneumonictomy or intrapericardial lung resections. Vikenes et al. [9] analyzed 24 patients after posterolateral thoracotomy and lung surgery, but there was no information disclosed whether patients after pneumonectomies or intrapericardial procedures were included. Nevertheless, no postoperative pathologic elevation of cTnI and cTnT serum levels were found within the study group, supporting the diagnostic value of serum troponin for differential diagnosis in the early postoperative period. Recommending a strategy might represent a future direction for patient care in the early postoperative period after lung surgery. The positive association to cTnI elevation is compatible with the concept that intrapericardial resections and pneumonectomies may predispose for myocardial injury. Thus we suggest that patients with only marginally elevated cTnI concentrations after intrapericardial resections or pneumonectomy should remain in the intensive care unit and should be followed-up carefully. Further clinical signs for myocardial ischemia should lead to immediate review by an experienced cardiologist.

Declaration of Interest:
There are no conflicts of interest.

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