# Effects of lung resection on heart structure and function: A tissue Doppler ultrasound survey of 43 cases

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Abstract. Changes in heart structure and function after lung resection in patients with lung cancer are challenging to manage. Therefore, a non-invasive and reliable measurement tool to gauge such changes is critical. The purpose of the present study was to compare cardiological changes before and after lung resection using tissue Doppler imaging (TDI). A total of 43 patients (19 men and 24 women) with primary non-small cell lung cancer (n=37) and metastatic cancer in the lungs (n=6) were enrolled in the study.nTDI was used to determine the thickness of the ascending aorta, the open size of the ascending valve, the anterior-oposterior diameters of the left atrium and left ventricle, and the thickness of the ventricular septum and right ventricle before and after lung resection. Left ventricular (LV) ejection fraction (EF), pulmonary valve flow rate, tricuspid annular or mitral leaflet tip early (E) peak/late (A) diastolic blood flow velocities, tricuspid regurgitation flow, the lateral mitral annulus early (e') diastolic velocity and mitral E/e' ratio were used to determine LV filling pressure. Results revealed no significant differences between male and female patients in terms of the open size of the ascending valve, the anterior-posterior diameter of the left ventricle and the mitral E/e' ratio. Significant differences were found in the width of the ascending aorta, anterior-posterior diameter of the left atrium, width of the LV septum and right ventricular (RV) diameter before and after lung resection. Finally, there were

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significantchanges in EF and tricuspid pressure. The results indicated that TDI was useful as a non-invasive method for assessing left and right heart function following lung resection. The LV and RV dimensions were affected, but LV filling pressure was preserved after lobectomy.

## Introduction

Globally, lung cancer is the most lethal cancer type among men and women (1), with up to 1.8 million associated deaths, accounting for 18% of all cancer-associated deaths in 2020 (2). Treatment for the disease includes surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, depending on the patient Tumor-Node-Metastasis (TNM) stage and differentiation grade (3,4). If a patient's TNM stage is localized, surgery is the best choice (5). However, patients frequently experience perioperative complications, such as cardiopulmonary dysfunction and limited exercise capacity during lung resection (6,7). These changes occur particularly in the right ventricle, causing dysfunction, and affect left ventricular (LV) systolic function due to pulmonary vascular bed loss (8). Few reports have described right ventricular (RV) dysfunction and increased mortality rates after lung resection (9-11). This type of surgery also alters cardiopulmonary interactions. Eventually, this can lead to changes in blood oxygen levels, which can directly and indirectly affect heart function. A previous cardiovascular magnetic resonance (CMR) study reported that RV ejection fraction (EF) decreased by ~10% compared with that before surgery (10). However, the CMR method frequently requires the patient to breath-hold and requires isolation of the patient in a small chamber, and as such, this tool has limited extensive application. Therefore, a more convenient method, such as bedside echocardiography, may be alternative.

Transthoracic echocardiography (TTE) is a non-invasive, convenient and reliable tool for assessing heart function (12). Multiple parameters can easily measure RV and LV function (11). Other common echocardiographic modalities are M-mode (13) and two-dimensional or pulse-wave Doppler (14) due to the ventricular volume status and rate of myocardial relaxation. In addition, these methods are preload-dependent and have low accuracy (15). Cardiac magnetic resonance imaging and computed tomography angiography have been

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Abbreviations: EF, ejection fraction; LV, left ventricular; PA, pulmonary artery; RA, right atrium; RV, right ventricular; TDI, tissue Doppler imaging

used to visualize the coronary arteries and detect blockages or narrowing (16,17). The technique can also provide information regarding structure and other cardiovascular conditions. However, these modalities only provide approximate, not detailed, information regarding cardiac functions. Recent studies have demonstrated that tissue Doppler imaging (TDI) has greater capacity than two-dimensional Doppler echocardiography for recording systolic and diastolic velocities in the myocardium, as well as at the corner of the annulus (18-21). TDI can record peak velocities for early (E) and late (A) diastolic filling, deceleration time and isovolumic relaxation time, which reflect mitral valve inflow and aortic valve outflow (22). For the lateral mitral annulus, TDI can be used to record peak early (e') velocity of diastole. Therefore, TDI is a better tool for assessing function of the myocardium and mitral annulus after lung resection due to its less preload-dependent (23).

In the present study, TDI was used to measure the diameter of the ascending aorta, ascending aorta size, anterior-posterior diameters of the left atrium and ventricle, and widths of the ventricular septum and right ventricle. Heart function indices, such as LVEF, pulmonary valve flow rate, tricuspid annular or mitral valve E peak/A peak, tricuspid regurgitation flow, lateral mitral annulus e' and E/e' ratio, were also determined. The study assessed parameters of heart function and recommends the more routine clinical application of a method to measure heart function before and after lung resection

## Materials and methods

Patients. The present study retrospectively analyzed data from an observational cohort that underwent TDI to assess left and right heart function after lung resection. In total, 43 patients with non-small cell lung cancer (NSCLC) (n=37) and metastatic cancer in the lungs (n=6) were enrolled. Patients diagnosed and admitted to Peking University Cancer Hospital (Beijing, China) between October 2015 and January 2020, who fulfilled predefined enrolment and exclusion criteria, were included. Inclusion criteria were as follows: i) An age >18 years; ii) primary lung cancer and metastatic lung cancer confirmed by a combination of clinical features, imaging data and pathological diagnosis of tumour issue or biopsy; and iii) all patients underwent selective lung resection with lobectomy. Exclusion criteria were as follows: i) Non-malignant tumour or other benign diseases in the lungs; and ii) aberrant heart, liver and kidney functions before lobectomy. Surgery mainly included a single lobar lung resection of the left or right lung. The surgical method and anesthetic techniques were standardized. To precisely address structural and functional changes after lobectomy, all patients were selected from among those with lung cancer and no history of chronic cardiopulmonary disease. This study was reviewed and approved by the Ethics Committee of Peking University Cancer Hospital and Institute (Beijing, China; approval number, 20210915). Written informed consent was obtained from all participants.

*TDI*. Compared with traditional Doppler echocardiography, TDI is less affected by afterload alterations, valvular regurgitations and changes in heart rate. Therefore, TDI is a powerful device to detect diastolic ventricular function. TDI data were collected preoperatively and at 3 months postoperatively using

Table I. Clinical characteristics, demographics and surgery styles of 43 patients.

Demographics	Value
Mean age (range), years	59 (41-75)
Sex, n (%)	
Male	19 (44.2)
Female	24 (55.8)
TNM stage, n (%)	
T1N0M0	26 (60.5)
T1N1M0	4 (9.3)
T2N0M0	5 (11.6)
T2N2M0	1 (2.3)
T3N2M0	2 (4.7)
Metastatic	5 (11.6)
Pathological type, n (%)	
Lung adenocarcinoma	31 (72.1)
Lung squamous cell carcinoma	5 (11.6)
Carcinoid	1 (2.3)
Other metastatic cancer types	6 (14.0)
Lung resections, n (%)	
Left upper lobe	12 (27.9)
Left lower lobe	6 (14.0)
Right upper lobe	16 (37.2)
Right middle lobe	2 (4.7)
Right lower lobe	7 (16.3)

TNM, Tumor-Node-Metastasis.

an ultrasound device (EPIQ CVx5.0; Philips Healthcare). Images were acquired according to a standardized protocol that incorporated all aspects required for a comprehensive standard echocardiogram. First, a standard four-chamber section was captured in the apical view (Fig. 1A). Pulmonary arterial blood flow was measured in sections along the parasternal short axis (Fig. 1B).

To assess left and right heart function, TDI was used to capture changes in the mitral annulus (Fig. 2A) and blood flow through the tricuspid valve (Fig. 2B). As shown in Fig. 2A, the probe of the TDI device was placed at the apex to record a bimodal narrowband waveform. The first peak is the E peak of the mitral valve, which is generated in the early diastolic phase of the left ventricle, and the second peak is the A peak, which is generated by left atrial contraction in the late diastolic phase of the left ventricle. The E/A rate, which reflects LV relaxation capacity of the entity, was then calculated. In addition, the lateral mitral annulus e' peak was measured using a four-chamber section from the apical view. The probe of the TDI device was placed at the mitral annulus and images were captured during the diastolic and systolic phases. In addition, a capture window was placed on the intraventricular side of the mitral annulus to measure Doppler images of the lateral mitral annulus to obtain the e' peak (Fig. 3), which reflects the movement of the myocardium. The E/e' ratio, which reflects the movement capacity of the myocardium, was also calculated.

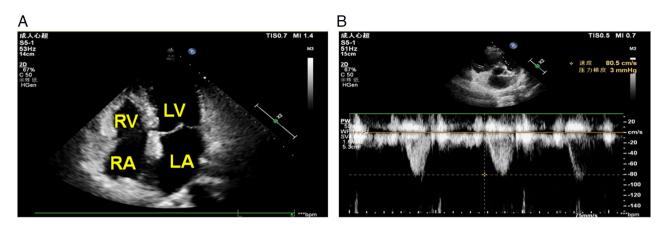


Figure 1. Four-chamber view by TDI. (A) Standard four-chamber section from the apical view. (B) Measurement of pulmonary artery blood flow in sectionsalong the parasternal short axis. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; TDI, tissue Doppler image.

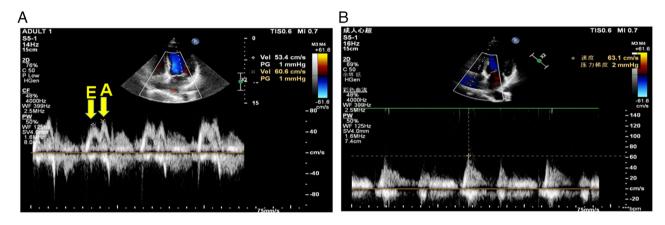


Figure 2. Measurement of the mitral E/A and tricuspid valve blood flow. (A) Capture of the mitral annulus and measurement of E/A from the apical view in a four-chamber section. Arrows point to the E and A peaks. E represents the mitral peak velocities of early diastolic filling. A represents the mitral peak velocities of late diastolic filling. (B) Measurement of tricuspid valve blood flow from the apical view in a five-chamber section.

To measure tricuspid valve blood flow, a capture window was placed in the right atrium (RA) from the apical four-chamber section (Fig. 4A). Aortic valve blood flow was also measured from the apical view of the five-chamber section (Fig. 4B).

To determine the clinical significance of these measurements, the normal range of flow rate (m/sec) of the pulmonary artery (PA) was defined as <1.0 m/sec. If the pulmonary valve flow rate was >1.0 m/sec, PA stenosis was suspected, with 3, 3-4 and >4 m/sec representing mild, moderate and severe stenosis, respectively. By contrast, the normal blood flow rate of the aortic artery is 0.7-1.7 m/sec. Flow rates of 2.6-2.9, 3.0-4.0 and >4 m/sec represented mild, middle, severe aortic valve stenosis, respectively. In normal situations, the E/A ratio for the mitral annulus is >1, indicating that the E peak is higher than the A peak. An E/A value of <1 reflected low LV relaxation capacity. In addition, the lateral mitral annulus e' peak was calculated using TDI. This metric reflects the movement of heart muscles. When the mitral e' peak was <8.5 cm/sec (side) or <8 cm/sec (intraventricular), it indicated damage to the heart muscle. When the E/e' value was calculated, <8 reflected normal LV filling pressure. If the E/e' value was >15, the left ventricle relaxation was damaged and indicated a poor prognosis. Another measurement included the tricuspid valve E/A value, which is similar to the mitral E/A and reflects the blood flow rate at the relaxation phase of the RA. The normal tricuspid valve E/A value is 0.8-2.1. Tricuspid regurgitation indicates incomplete tricuspid valve closure. The degree of damage was categorized as mild (<20), medium (20-40%) and severe (>40%). Pulmonary hypertension was determined based on blood flow rate during tricuspid regurgitation.

Statistical analysis. Comparison of cardiac structure and function parameters preoperatively and postoperatively was performed using paired Student's t-test. Data are presented as the mean  $\pm$  standard deviation and was analyzed using GraphPad Prism version 9 (GraphPad; Dotmatics). P<0.05 was considered to indicate a statistically significant difference.

# Results

*Clinical characteristics of patients with lung cancer.* To analyze the specific effects of different types of lobectomy on heart structure and function, 43 patients who had undergone lobectomy only were selected for the study. The clinical characteristics of the 43 patients [mean age, 59 years; age range, 41-75 years; 19 men (44.2%) and 24 women (55.8%)] included in this study are summarized in Table I. A total of 37 patients were diagnosed with NSCLC at stages T1-2, N0-2

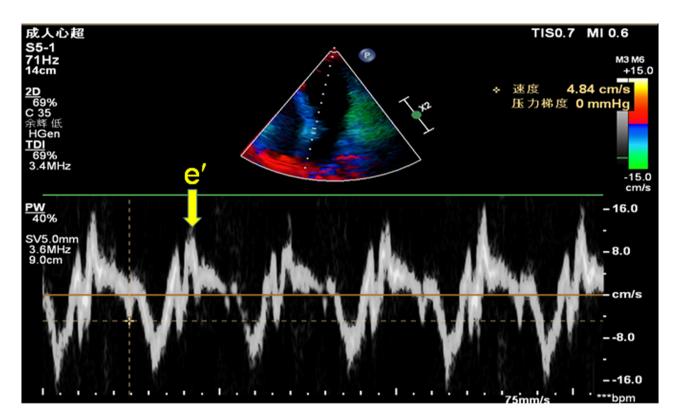


Figure 3. Measurement of the mitral e' peak. Images of the lateral mitral annulus were captured and measured by TDI to obtain the e' peak (arrow). e', early; TDI, tissue Doppler image.

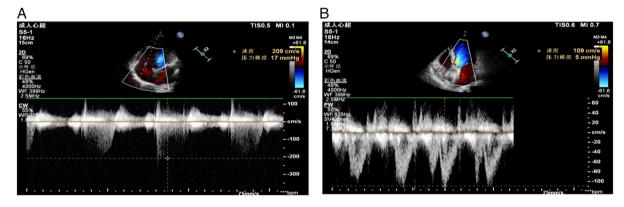


Figure 4. Measurement of tricuspid valve regurgitation and aortic valve blood flow. (A) Images of the right atrium from the apical view in the four-chamber section were captured and tricuspid valve regurgitation was measured. (B) Aortic valve blood flow was measured from the apical view in the five-chamber section.

and M0, whereas the other 6 patients had other tumor tissues that had metastasized to the lungs. Among the 37 patients with NSCLC, 31 (72.1%) exhibited lung adenocarcinoma, lung squamous cell carcinoma, or mixed lung cancer(s); the other 6 with metastatic lung cancers comprised 5 (11.6%) and 1 (2.3%) cases, respectively. These patients underwent resection of the following lobes: Left upper lobe (n=12; 27.9%), left lower lobe (n=6; 14.0%), right upper lobe (n=16; 37.2%), right middle lobe (n=2; 4.7%) and right lower lobe (n=7; 16.3%). To further evaluate the effects of lobectomy on structure and function, end-diastolic diameter (mm), posterior wall thickness, interventricular thickness (mm), ejection fraction (EF), E/A ratio and E/e' ratio of the left ventricle at pre- and post-lobectomy were compared. The results showed that left upper lobectomy was associated with a significantly decreased posterior wall thickness, interventricular septum thickness and LVEF of the left ventricle (Table II). The right upper and right middle lobectomies were also associated with a decreased interventricular septum thickness and LVEF of the left ventricle respectively.

Changes in cardiac structure after lung resection. After lung resection, cardiac structure exhibited significant hemodynamic changes. The results are summarized in Table III. Ascending aorta diameters before and after surgery were  $28.7\pm4.04$  vs.  $30.88\pm2.81$  (P<0.001). There was a significant increase in width after lung resection. The left atrial anterior-posterior meridian was  $30.88\pm5.77$  vs.  $33.10\pm4.24$  (P<0.001), which was also longer after lung resection. Intraventricular septum

Table II. Comparison of left ventricle structure and function parameters (mean $\pm$ SD) pre- and post-lobectom	Table II. C	Comparison o	of left ventricle	e structure and	l function	parameters	$(\text{mean} \pm \text{SD})$	pre- and	post-lobectomy
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Variable	Pre-lobectomy	Post-lobectomy	P-value	
End-diastolic diameter, mm				
Left upper	45.78±5.70	47.00±3.89	0.50	
Left lower	46.00±4.34	48.00±4.34	0.23	
Right upper	$43.00 \pm 5.57$	45.44±5.33	0.07	
Right middle	44.50±3.54	44.50±3.53	0.50	
Right lower	$42.43 \pm 1.70$	45.29±3.04	0.11	
Posterior wall thickness, mm				
Left upper	9.24±1.36	8.08±0.90	0.01ª	
Left lower	9.17±2.79	9.50±1.26	0.76	
Right upper	9.69±2.33	8.31±1.45	0.02ª	
Right meddle	9.00±2.83	7.50±0.71	0.66	
Right lower	8.86±1.35	8.00±1.16	0.27	
Interventricular septum thickness, mm				
Left upper	9.33±1.38	8.42±1.17	0.03ª	
Left lower	$9.50 \pm 2.88$	$9.50 \pm 1.05$	0.93	
Right upper	$10.06 \pm 1.95$	8.31±1.40	0.002ª	
Right middle	9.00±2.83	7.50±0.71	0.71	
Right lower	9.00±1.56	8.14±1.46	0.29	
LVEF, %				
Left upper	66.58±4.12	61.17±6.33	0.04ª	
Left lower	66.67±4.93	63.83±2.56	0.34	
Right upper	67.00±4.87	65.19±5.54	0.31	
Right middle	71.00±5.66	60.50±4.95	0.03ª	
Right lower	67.00±2.02	64.29±6.08	0.44	
LV E/A ratio				
Left upper	0.87±0.26	0.83±0.24	0.57	
Left lower	0.76±0.22	$0.76 \pm 0.18$	0.98	
Right upper	0.93±0.28	0.92±0.32	0.94	
Right middle	0.81±0.09	0.83±0.01	0.89	
Right lower	1.20±0.33	1.03±0.23	0.39	
LV E/e' ratio				
Left upper	$10.11 \pm 2.84$	$13.00 \pm 4.06$	0.06	
Left lower	11.10±1.41	$10.93 \pm 4.85$	0.93	
Right upper	10.16±2.30	$10.33 \pm 2.52$	0.86	
Right middle	$9.60 \pm 1.41$	10.75±0.35	0.53	
Right lower	12.21±4.33	8.23±1.42	0.08	

<sup>a</sup>P<0.05. LVEF, left ventricular ejection fraction; LV E/A ratio, mitral valve inflow velocities (cm/sec) at early (E) diastolic phase/late (A) diastolic phase of the left ventricle. LV E/e' ratio, inflow velocities (cm/sec) at early (E) diastolic phase of mitral valve/early (e') diastolic phase of mitral valve.

thickness was  $9.56\pm1.84$  vs.  $8.40\pm1.29$  (P<0.001). Posterior wall thickness of the left ventricle was  $9.32\pm1.97$  vs.  $8.28\pm1.2$  (P=0.001). Right ventricle diameter was  $20.33\pm3.03$  vs. 19.74±1.90 (P=0.043). By contrast, there were no significant differences in the ascending aortic valve opening or LV anterior-posterior meridian.

*Functional changes after lung resection*. In addition to structural changes, changes in cardiac function were also assessed, with results summarized in Table IV. Changes in LVEF, flow rate (m/sec) in the PA and aortic valve, tricuspid regurgitation (m/sec) and tricuspid pressure (mmHg) were compared before and after surgery. LVEF was  $67.02\pm4.62$  vs.  $64.91\pm4.80$ (P=0.04), showing a significant decrease after lung resection. Tricuspid pressure was  $20.58\pm5.85$  vs.  $24.31\pm24.1\pm5.93$  mmHg (P=0.02), which was significantly elevated. By contrast, there were no significant differences in the pulmonary value flow rate ( $0.87\pm0.17$  vs.  $0.92\pm0.15$  m/sec, respectively; P=0.07) and tricuspid regurgitation ( $2.32\pm0.13$  vs.  $2.44\pm0.29$ , respectively; P=0.16) before and after surgery. These results indicate that

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Table III. C	omparison	of care	liac structure	before and	after	lung resection.

Structure name	Before surgery	After surgery	P-value
Ascending aorta diameter, mm	28.70±4.04	30.88±2.81	<0.01
Ascending aorta valve open, mm	$18.00 \pm 2.01$	18.19±1.71	0.55
Left atrium anterior-posterior meridian, mm	30.88±5.77	33.10±4.24	< 0.01
Intraventricle septum thickness, mm	9.56±1.84	8.40±1.29	< 0.01
Left ventricle anterior-posterior meridian, mm	44.18±5.35	46.02±4.41	0.09
Posterior wall thickness of the left ventricle, mm	9.32±1.97	8.28±1.20	< 0.01
Right ventricle diameter, mm	20.33±3.03	19.74±1.90	0.04

Table IV. Comparison of cardiac function parameters before and after lung resection.

Variables	Before surgery	After surgery	P-value
LVEF, %	67.02±4.62	64.91±4.80	0.04
Pulmonary valve flow rate, m/sec	0.87±0.17	0.92±0.15	0.07
Tricuspid regurgitation, m/sec	2.32±0.13	2.44±0.29	0.16
Tricuspid pressure, mmHg	20.58±5.85	24.31±5.93	0.02

lung resection damaged the EF functions of the heart and that tricuspid pressure compensated for the elevation.

*E/A and E/e' ratio of the lateral mitral annulus preoperatively and postoperatively.* To further evaluate the entity LV relaxation and movement capacity of the myocardium, the E/A and E/e' ratios of the lateral mitral annulus were also measured. The results are summarized in Table V. Preoperative and postoperative mitral E/A ratios were  $1.12\pm0.50$  vs.  $0.89\pm0.27$ (P=0.28), respectively. Mitral E/e' ratio was 12 vs. 9 (P=0.32), 19 vs. 19 (P=0.88) and 12 vs. 15 (P=0.41) in the <8, 8-12 and >12 groups, respectively. These results revealed no effects of lung ventricle relaxation or the movement capacity of the myocardium.

# Discussion

With early detection and increased accuracy due to technological advances, patients with NSCLC can be diagnosed at an earlier stage and treated with the appropriate surgery. However, cardiopulmonary function undergoes significant changes after lung resection. The main findings of the present study revealed that the widths of the ascending aorta and left atrium anterior-posterior meridian after surgery were significantly wider and longer than those before resection. By contrast, the intraventricular diameter, posterior wall of the LV and RV diameter decreased after lung resection. In addition, LVEF was significantly decreased, but tricuspid pressure was significantly increased compared with preoperative values.

Compared with traditional transthoracic echocardiography, which is preferred to assess right-side functions (12), TDI has many advantages, as it can more accurately measure the functions of the left ventricle as well as the right ventricle (24-26). Table V. Comparison of mitral E/A and E/e' before and after lung resection.

Variables	Before surgery	After surgery	P-value
Mitral E/A ratio	1.12±0.5	0.89±0.27	0.28
Mitral E/e'			
<8	12	9	0.32
8-12	19	19	0.88
>12	12	15	0.41

Mitral E/A, early (E) peak/late (A) diastolic blood flow velocities of the mitral leaflet tips; mitral e', the early (e') diastolic velocity of the lateral mitral annulus; mitral E/e', ratio used to determine left ventricular filling pressure.

TDI can be also used to detect systolic and diastolic dysfunction in both ventricles, as well as LV filling pressure (27). The present study exhibits clear images for different functions. A total of 43 patients with primitive and metastatic lung cancer, who underwent lung resection, exhibited significant changes. The results revealed that the ascending aortic diameter significantly widened after surgery. It was also observed that the postoperative left atrial anterior-posterior meridian was markedly longer than the preoperative meridian. This indicates that the left atrium and left ventricle have compensatory capacity due to the loss of oxygen exchange after lung resection. These results show some differences from a previous report (18), which revealed that there were no significant differences in the left atrial dimensions pre- and post-lung resection. This difference may be caused by different genetic backgrounds. The intraventricular diameter, posterior wall of the LV, and RV diameter were significantly decreased post-resection. This may have resulted in insufficient blood circulation after lung resection.

The study also measured LVEF, pulmonary valve flow rate, tricuspid regurgitation and tricuspid pressure, and found that LVEF significantly declined after lung resection. By contrast, tricuspid pressure exhibited robust elevation. This further confirmed the compensatory capacity in both ventricles in response to reduced postoperative oxygen exchange.

Previous studies have revealed that lung resection affects LV expansion (28,29). If this is true, then the left atrium, PA and pulmonary capillary pressures should increase. In fact, the present study showed that the ascending aorta exhibited a significantly increased width and confirmed this concept. In addition, mitral E/A and E/e' are sensitive indicators for left ventricle relaxation capacity and myocardial movement. Lung resection results in pulmonary vascular reduction, which decreases LV expansion. The present results revealed that in the mitral E/e' <8 normal, 8-12 and >12 groups, there were no significant differences before and after surgery. This may have been due to the small sample size. If the E/e' value is >15, the left ventricle relaxes and the patient has a poor prognosis (30). Another measurement taken was the tricuspid valve E/A value, which is similar to the mitral E/A value and reflects the blood flow rate in the relaxation phase of the RA. The E/A value for a normal tricuspid value is within the range of 0.8-2.1 (31). Tricuspid regurgitation indicates incomplete tricuspid valve closure. In the present study, the degree of damage was categorized as mild (<20), medium (20-40%) and severe (>40%). The results confirmed that the mitral E/e' is an excellent indictor for evaluation of LV diastolic function. Pulmonary hypertension was determined based on blood flow rate during tricuspid regurgitation. However, the present results demonstrated no significant differences for preoperative vs. postoperative comparisons.

The present study had a few limitations. First, the data demonstrated that lobectomy in patients with lung cancer can affect cardiac structure and functions based on a limited number of cases (i.e., n=43), which may be the result of sampling bias. Larger-scale studies including more patients are required to confirm these findings. Second, data from this investigation were obtained from a single center, which may have generated selection bias. Multicenter studies may eliminate this bias. Third, this study did not include a healthy control group. The TDI reference parameters used in this study were obtained from the literature, which may have resulted in procedural bias. As such, include healthy controls should be included in future studies. In addition, parameters in this study were only from TDI measurements, and other traditional echocardiographic data such as two-dimensional Doppler echocardiography were not compared. Therefore, to confirm TDI is superior to other echocardiography techniques, data comparison between TDI and other machines will be required in later studies.

In conclusion, in the present study, lung resection significantly affected LVEF, ascending aorta width, tricuspid pressure, left atrial anterior meridian and intraventricular diameter, but did not affect the mitral E/e' ratios, indicating that the LV and RV dimensions were affected, but that the LV filling pressure was preserved after lobectomy. These results highlight the need to devote more attention to postoperative changes.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

JC conceived and designed the study. DS, ZS, and YZ performed the experiments and analyzed the data. JC and LZ performed the statistical analysis. JC, DS and ZS drafted the manuscript, and all authors read and approved the final manuscript. JC and DS confirm the authenticity of all the raw data.

## Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Study approval was granted by the Ethics Committee of Peking University Cancer Hospital and Institute (Beijing, China; approval number, 20210915). Written informed consent was obtained from all participants before surgery.

# Patient consent for publication

Written informed consent was obtained from the patients for publication of anonymized case details and associated images.

#### **Competing interests**

The authors declare that they have no competing interests.

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