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Prevalence and risk factors of atrial fibrillation during lung and esophageal surgery

A Prospective observational study

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Abstract

The aim of this prospective observational study was to screen for risk factors of intraoperative atrial fibrillation (AF) during noncardiac thoracic surgery. The study was conducted as a single-institution study in Zhejiang Cancer Hospital, Hangzhou, China. All the participants were patients with cancer scheduled for thoracotomy.

This study was conducted from July 2013 to August 2016 and included 144 patients scheduled for thoracotomy under general anesthesia. We collected the patients' demographic and perioperative medical data in our hospital. AF was diagnosed using electrocardiography (ECG), on the basis of the presence of characteristic ECG features of AF by one or more ECG leads for at least 30 seconds.

Of the participants, 144 completed the study and 18 developed intraoperative AF. Higher percentages of subjects in the AF group than in the non-AF group had histories of chemotherapy ($P = .014$) and alcohol consumption ($P = .034$) before surgery. The AF group had a lower mean body mass index ($P = .019$), significantly higher mean heart rate ($P < .001$), and lower tidal volume ($P = .01$) than the non-AF group. After the logistic regression analysis, only alcohol consumption (odds ratio [OR] = 5.279; 95% confidence interval [CI]: 1.432–19.467), history of chemotherapy (OR = 4.019; 95% CI: 1.504–15.334), and high heart rate (OR = 1.093; 95% CI: 1.033–1.156) during 1-lung ventilation were identified as the risk factors of AF during lung and esophageal surgeries.

The incidence of intraoperative AF during noncardiac thoracic surgery was 12.5%. Alcohol consumption, history of chemotherapy, and high heart rate during 1-lung ventilation were the risk factors related to intraoperative AF.

Abbreviations: AF = atrial fibrillation, ASA = American Society of Anesthesiologists, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CVP = central venous pressure, ECG = electrocardiography, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HR = heart rate, MAP = mean arterial pressure, POAF = postoperative atrial fibrillation, RR = respiratory rate, VATS = video thoracoscopy-assisted thoracic surgery, V_T = tidal volume.

Keywords: atrial fibrillation, chemotherapy, intraoperative, risk factor

1. Introduction

Perioperative cardiac arrhythmia, especially atrial fibrillation (AF), is much more common in noncardiac thoracic surgery than in general surgery. As reported, the incidence of AF varies widely from 9.9% to 19% in general thoracic surgery.[1–6] Even though it is a transient complication, it is related to longer hospital stays, greater clinical cost, increased stroke risk, and higher mortality rate.[1,3,4,7,8] Therefore, defining the risk factors for AF during general thoracic surgery and preventing the development of AF as much as possible are critical.

In previous studies, many risk factors were reported to be associated with the development of postoperative AF (POAF) such as older age, male sex, hypertension, obesity, smoking, alcohol consumption, and history of chronic obstructive pulmonary disease (COPD).[9–12] Furthermore, some surgical procedures are reported to be related to the occurrence of POAF.[13–16] Muranishi et al reported that mediastinal lymph dissection for patients with early-stage lung cancer is associated with a high risk for the development of POAF.[17] Lee et al reported that open thoracotomy was a more significant risk factor of POAF than video thoracoscopy-assisted thoracic surgery (VATS).[9] AF is a potentially preventable complication, as some risk factors such as smoking or surgical procedures are modifiable. We can evaluate the risk of surgical AF accurately and take actions to prevent the development of AF by defining more risk factors especially in surgical procedures.

A considerable proportion of patients received anti-tumor chemotherapy agents before thoracic surgery. However, whether patients who undergo chemotherapy are more prone to the development of AF than other patient populations during noncardiac thoracic surgery is still unknown. Several chemotherapy agents were reported to be related to cardiotoxicity,[18–22]

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KX and WZ contributed equally to this work.

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such as trastuzumab, 5-fluorouracil, and cisplatin. Neoadjuvant chemotherapy was reported to increase the risk of POAF after esophagectomy.[23] Whether chemotherapy poses a risk factor for AF in general thoracic surgery needs further elucidation.

In addition, most patients developed AF during the first 3 days after surgery.[2,24] Anesthesiologists are present in the operating and recovery rooms and are involved in the postoperative diagnosis and prophylaxis of this complication. However, almost all studies focused on the risk factors of POAF, not just intraoperative AF. The risk factors of intraoperative AF need to be further studied.

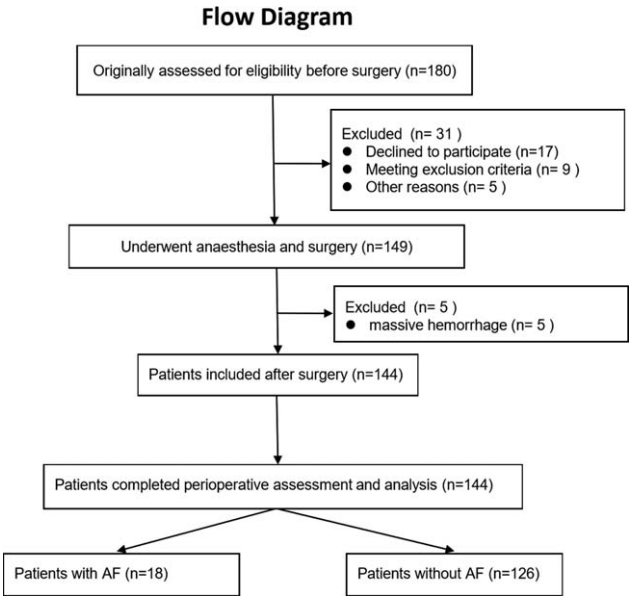
Therefore, we conducted this prospective study to identify more risk factors, including chemotherapy history in patients who underwent lung and esophageal surgeries, and further examine more risk-reducing measures.

2. Subjects and methods

2.1. Subjects

This prospective study was performed between July 2013 to August 2016 after receiving approval from the Human Research Ethics Board of Zhejiang Cancer Hospital (Ref: [2013]-06-98). The registered clinical trial number was ChiCTR-OCS-13003282. A written informed consent document was issued by each patient prior to participation.

The inclusion criteria were as follows: history of general thoracic surgeries for lung tumor, esophageal cancer, or mediastinal neoplasm; age ≥18 years; and normal liver and renal functions, acid and alkali balance, and electrolyte levels. The exclusion criteria included massive hemorrhage; histories of coronary heart disease, AF, ventricular arrhythmia, or other heart diseases; and previous lung or heart surgery before operation. In addition, patients with absolute and relative contraindications for surgery were excluded. Of the 180 patients recruited, only 144 completed the study. A flowchart of the study is presented in Flow Diagram.



2.2. Methods

On day 1, demographic data, including age, sex, body mass index (BMI), American Society of Anesthesiologists, smoking history, alcohol consumption, and chemotherapeutic agents, were collected. Medical history (hypertension, COPD, surgical, and medication history) was also recorded. Spirometry was administered preoperatively in accordance with the American Thoracic Society/European Respiratory Society guidelines.[25] Results of the routine laboratory and arterial blood gas analysis were gathered. Then, each patient was requested to fast for solids and liquids at least 8 hours before surgery. No preoperative prophylaxis for AF was applied. Alcohol consumption was defined as consuming eight alcohol drinks or more per week for women and 15 or more per week for men.[9]

On day 2, standard monitoring (electrocardiography [ECG], pulse oximetry, and invasive radial artery blood pressure) was established in the operating room. In almost all the patients, open thoracotomy was performed with general anesthesia combined with epidural anesthesia, except in those with a contraindication of epidural anesthesia. An epidural catheter was inserted between the T7-to-T8 or T8-to-T9 interspace before induction, and the placement of the catheter was confirmed by the administration of a 3-mL test dose of 1% lidocaine. The epidural catheter was left in situ for an average of about 3 days. In addition, the patients who underwent VATS simply received general anesthesia induced with midazolam (0.04 mg/kg), fentanyl (4 μg/kg), target-controlled infusion of propofol with plasma concentration (2.5–3.5 μg/mL), and rocuronium bromide (0.9 mg/kg). Then, orotracheal intubation was performed with a double-lumen endobronchial tube (Medtronic, Dublin, Ireland) or endobronchial blocker tube (COOPDECH, Daiken Medical Co. Ltd, Osaka-shi, Japan) after induction. The double-lumen tube or blocker position was confirmed using fiberoptic bronchoscopy. Anesthesia was maintained with a continuous infusion of remifentanil and target-controlled infusion of propofol to maintain the value of the bispectral index from 40 to 55, with or without sevoflurane. The intraoperative fluid (including lactated Ringer solution and hydroxyethyl starch) volume loading was performed at the discretion of the attending anesthesiologist. Data on heart rate, invasive blood pressure, arterial oxygen saturation, and ECG were recorded throughout the operation. Mechanical ventilation parameters were set by the attending anesthesiologist to maintain the $PaCO_2$ between 35 and 45 mm Hg and were recorded.

After surgery, all the patients were transferred to the postanesthesia care unit and then transferred back to the ward after complete recovery. All the patients received continuous ECG and oxygen saturation monitoring for at least 72 hours after surgery. Data on 30-day mortality rates and length of hospital stay were also collected.

The AF was diagnosed using ECG on the basis of the presence of the characteristic ECG features of AF by one or more ECG leads for at least 30 seconds.[15] Intraoperative AF was defined as new-onset AF during general thoracic surgery in patients with a normal ECG finding. Then, AF was managed and treated at the discretion of the attending anesthesiologist or surgeon in accordance with the latest guidelines.[15]

2.3. Statistical analysis

The sample size was obtained using PASS (version 11, NCSS). As reported, the incidence of AF is approximately 19% in general thoracic surgery. A sample size of 124 was determined to be required for a power of 0.8 and an α value of 0.1. The SPSS version 22.0 software (SPSS Inc., New York) was used for statistical analysis. Normally distributed continuous data are expressed as mean ± standard deviation, while non-normally distributed data are presented as median (interquartile range

Table 1

Demographic characteristics of the subjects.

	AF group, n = 18 (%)	Non-AF group, n = 126 (%)	P
Age, y	62.83 ± 9.59	59.42 ± 8.59	.123
>70	4 (22.2)	10 (7.9)	.137
>60	8 (44.4)	58 (46.0)	.899
Male/female	16 (88.9)/2 (11.1)	95 (75.4)/31 (24.6)	.330
BMI, kg/m^2	20.60 ± 2.17	22.20 ± 2.74	.019*
Baseline heart rate	79.94 ± 3.06	77.35 ± 1.18	.438
Comorbidity			
Hypertension	3 (16.7)	17 (13.5)	1.00
Diabetes mellitus	1 (5.6)	2 (1.6)	.825
COPD	1 (5.6)	5 (4.0)	1.00
History of any surgery	4 (22.2)	34 (27.0)	.886
History of chemotherapy	7 (38.9)	19 (15.1)	.014*
Median smoking years (IQR)	30.0 (40)	10.5 (40)	.446
Alcohol consumption	12 (66.7)	51 (40.5)	.036*
ASA status			
I	8 (44.4)	66 (52.4)	.529
II	10 (55.6)	56 (44.4)	.376
III	0	4 (3.2)	1.00
Pulmonary function			
FEV_1, L	2.26 ± 0.29	2.35 ± 0.64	.353
FEV_1, %pred	88.13 ± 16.45	85.14 ± 17.54	.535
FVC, L	2.79 ± 0.37	2.77 ± 0.68	.890
FEV_1/FVC, %	82.03 ± 11.28	84.77 ± 9.81	.321

Normally distributed continuous data were expressed as the mean ± standard deviation; non-normally distributed data were expressed as median (IQR). The numbers in the brackets stand for percentage (%) or interquartile range (IQR).

AF = atrial fibrillation, ASA = American Society of Anesthesiologists status, BMI = body mass index, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, IQR = interquartile range.

* $P < .05$.

[IQR]). Categorical data were assessed using the Chi-squared test. Normally distributed variables were analyzed with a 2-tailed *t* test. Non-normally distributed data were further analyzed using of the Mann–Whitney test. To identify the risk factors of intraoperative AF, all the variables with a *P*-value of <.05 between the AF and non-AF group were included in a binary logistic regression model. *P*-values of <.05 were considered statistically significant.

3. Results

3.1. Demographic characteristics of the subjects

Among the 144 patients, 18 developed AF during surgery while 126 did not. The commonly used chemotherapeutic agents by the patients included paclitaxel, fluorouracil, cisplatin, pemetrexed, gemcitabine, taxotere, and endostar (Table 1).

The AF group had higher percentages of subjects with histories of chemotherapy ($P = .014$) and alcohol consumption ($P = .036$) before surgery than the non-AF group. In addition, the AF group had a lower mean BMI than the non-AF group ($P = .019$).

3.2. Surgical and anesthetic differences between the AF and non-AF groups

As shown in Table 2, no significant differences in surgical method (thoracotomy vs VATS), surgical approach (right vs left), type of operation, and skill of the chief surgeon were found between the 2 groups. No significant differences in anesthetic method (general vs combined general-epidural anesthesia) and endotracheal intubation (double-lumen endobronchial tube vs bronchial occludes) were demonstrated. Furthermore, no significant differences in surgical duration, crystal rehydration fluid volume, colloid rehydration fluid volume, and blood loss were found.

3.3. Differences in vital signs during surgery

Table 3 shows the vital signs during surgery. The average heart rate was significantly higher ($P < .001$) and tidal volume ($P < .05$) was significantly lower in the AF group than the non-AF group, but no significant difference in tidal volume per kilogram was observed.

Table 2

Surgical and anesthetic differences between the AF and non-AF groups.

	AF group, n = 18 (%)	Non-AF group, n = 126 (%)	P
Surgical method			
Thoracotomy	16 (88.9)	89 (70.6)	.178
VATS	2 (11.1)	37 (29.4)	
Surgical approach			
Right	12 (66.7)	91 (72.2)	.625
Left	6 (33.3)	35 (27.8)	
Chief surgeon			
Skilled (can perform complex thoracic surgery excellently)	4 (22.2)	52 (41.3)	.196
Unskilled (only can perform complex thoracic surgery independently)	14 (77.8)	74 (58.7)	
Anesthetic way			
General anesthesia	5 (27.8)	47 (37.3)	.431
Combined general-epidural	13 (72.2)	79 (62.7)	
Endotracheal intubation			
Double lumen endobronchial tube	3 (16.7)	17 (13.5)	1.00
Bronchial occluder	15 (83.3)	109 (86.5)	
Operation duration, h	4.1 ± 1.4	3.5 ± 1.4	.138
Median crystal rehydration fluids, mL (IQR)	2000 (500)	1700 (1000)	.169
Median colloid rehydration fluids, mL (IQR)	750 (500)	1000 (500)	.190
Median blood loss, mL (IQR)	200 (200)	200 (200)	.603

Normally distributed continuous data were expressed as the mean ± standard deviation; non-normally distributed data were expressed as median (IQR).

AF = atrial fibrillation, IQR = interquartile range, VATS = video thoracoscopy-assisted thoracic surgery.

Table 3

Differences in vital signs during surgery.

	AF group (n = 18)	Non-AF group (n = 126)	P
Preoperation			
Heart rate, beats/min	79.94 ± 12.99	77.35 ± 13.26	.438
MAP, mm Hg	104.50 ± 12.00	103.91 ± 12.94	.855
Median respiratory rate, breaths/min (IQR)	16.00 (2.00)	16.00 (2.00)	.235
Median temperature, °C (IQR)	36.60 (0.55)	36.60 (0.50)	.528
Median CVP, mm Hg (IQR)	8.00 (4.50)	8.00 (4.50)	.909
During operation (1-lung ventilation)			
Heart rate, beats/min	81.44 ± 15.33	70.30 ± 10.12	<.001*
MAP, mm Hg	81.83 ± 13.11	84.08 ± 10.61	.417
Median respiratory rate, breaths/min (IQR)	13.50 (3.00)	13.00 (2.00)	.299
Median temperature, °C (IQR)	36.10 (0.93)	36.40 (0.65)	.220
Median CVP, mm Hg (IQR)	9.00 (4.25)	10.00 (5.00)	.924
Peak pressure of airway, cm H_2O (IQR)	24.00 (5.50)	25.00 (4.00)	.607
Median V_T, mL (IQR)	450.00 (56.25)	475.00 (50.00)	.010†
V_T/weight, mL/kg	8.22 ± 0.75	7.91 ± 1.17	.287
Blood gas analysis			
Median pH (IQR)	7.38 (0.06)	7.37 (0.09)	.807
Median pO_2, mm Hg (IQR)	219.50 (129.00)	209.00 (170.00)	.838
Median pCO_2, mm Hg (IQR)	42.00 (7.50)	43.00 (10.00)	.339
Median BE (IQR)	−1.60 (4.00)	−0.70 (2.65)	.216
Median lactic acid, mmol/L (IQR)	1.10 (0.80)	0.90 (0.68)	.191
Postoperation			
Heart rate, beats/min	83.61 ± 13.85	76.25 ± 10.94	.012†
MAP, mm Hg	89.19 ± 14.36	91.28 ± 12.91	.527
Median respiratory rate, breaths/min (IQR)	16.00 (1.50)	16.00 (2.00)	.462
Median CVP, mm Hg (IQR)	10.00 (3.00)	8.00 (5.00)	.296

Normally distributed continuous data were expressed as the mean ± standard deviation; non-normally distributed data were expressed as median (IQR).
CVP = central venous pressure, IQR = interquartile range, MAP = mean arterial pressure, V_T = tidal volume.
* $P < .01$.
† $P < .05$

3.4. Binary logistic regression analysis

In the logistic regression analysis, alcohol consumption, history of chemotherapy, high heart rate, and tidal volume during one-lung ventilation were identified as risk factors of AF during surgery (Table 4).

3.5. Length of hospitalization

The length of hospitalization showed no significant difference between the AF and non-AF groups. Moreover, none of the patients died within 1 month after surgery.

4. Discussion

Studies published predominantly focused on perioperative AF, especially POAF. The present study focused on intraoperative AF. The major finding in the present study shows that the incidence of intraoperative AF was 12.5%. Five of 18 patients with POAF needed treatment in this study. AF was predominantly transient, did not affect hemodynamics or require clinical treatment. Furthermore, 41 patients had AF during the whole perioperative period, and the incidence was 28.5%, which is higher than those in previous studies.[2,9]

Table 4

Binary logistic regression analysis.

Variable	Odds ratio (95% CI)	P
Heart rate during operation, beats/min	1.093 (1.033–1.156)	.002*
Median V_T during operation, mL (IQR)	0.977 (0.961–0.993)	.004*
Alcohol consumption, n	5.279 (1.432–19.467)	.012†
History of chemotherapy, n	4.019 (1.504–15.334)	.042†

BMI = body mass index, CI = confidence interval, V_T = tidal volume.
* $P < .01$.
† $P < .05$

The present study also shows that alcohol consumption, history of chemotherapy, and high heart rate during 1-lung ventilation are risk factors of AF during surgery. Alcohol consumption was associated with AF, which was consistent with the finding of a prior study,[9] with the following possible reasons: alcohol consumption contributed to the exacerbation of systemic inflammatory response and cardiac insufficiency, which led to the increased susceptibility to AF,[26] and alcohol consumption might have caused autonomic dysfunction, which is a possible trigger for AF.[27]

We found that patients who underwent chemotherapy before surgery were more prone to develop intraoperative AF than other patient populations. The chemotherapy agents used included 5-fluorouracil, cisplatin, gemcitabine, and docetaxel, which were reported to be related to cardiotoxicity.[18–22] Cancer treatment may be associated with several cardiac events such as severe treatment-induced hypertension, vasospastic and thromboembolic ischemia, and rhythm disturbances, including QTc prolongation.[28,29] Chemotherapy might lead to structural and electrical remodeling of myocardial tissue. As reported, preexisting myocardial structural and electrical remodeling was associated with POAF.[30] Thus, we deduced that preoperative chemotherapy might cause intraoperative AF in patients who undergo noncardiac thoracic surgery.

In addition, we found that the average heart rate during 1-lung ventilation was much higher in the AF group than in the non-AF

group in the present study even though no significant difference in heart rate was found before surgery between the 2 groups. Furthermore, the average heart rate during operation was a risk factor of AF after the logistic regression analysis. Increased heart rate was reported to be associated with higher mortality in patients with AF.[31] Several studies reported that preoperative use of oral beta-blockers prior to cardiac surgery may reduce the incidence of POAF[32–34] and was recommended by several guidelines.[35–37] As already known, beta-blockers could help control the heart rate and decrease the oxygen demand of the myocardium. However, our conclusion that increased heart rate during surgery is a risk factor of AF during noncardiac thoracic surgeries needs further study, as the occurrence of AF could lead to rapid ventricular rates, which might be a confounding factor. Thus, comparison of heart rates before the occurrence of AF during operation is required.

Moreover, the tidal volume in the AF group was smaller than that in the non-AF group. Lower tidal volume during 1-lung ventilation was a risk factor of intraoperative AF. As BMI was significantly higher in the non-AF group, the tidal volume was also highest in this group. Whether tidal volume is a risk factor remains to be clarified. Tidal volume was chosen on the basis of the absolute body weight. As no significant change in tidal volume was observed when normalized by weight, tidal volume is not a risk factor.

In the clinical work, we observed that unskilled (only can perform complex thoracic surgery independently) chief thoracic surgeons cause more intraoperative AF than skilled (perform complex thoracic surgery excellently), as show in my study, the incidence of AF raised 2 folds (14 in 88 [16%] vs 4 in 56 [7%]). But there are no statistical differences after statistical analysis ($P = .196$). We did not find any statistical difference in the skill of the chief surgeon between the 2 groups. Even though no significant differences were found, by enlarging the sample size, unskilled chief thoracic surgeons might be a risk factor of intraoperative AF.

As previously reported, perioperative AF is related to longer hospital stays, higher clinical cost, increased stroke risk, and higher mortality rate. However, whether intraoperative AF is related to the above-mentioned issues needs to be further studied. In the present study, no significant difference in the length of hospital stay was observed between the AF and non-AF groups. More patients developed AF in the AF group on the first day after surgery, but no significant difference was observed on the second and third days. The economic cost was not analyzed because of the many contributing factors. Even though numerous studies showed an increase in mortality in patients with POAF, we did not find such an effect at 30 days after surgery, which was consistent with another study.[38] Mortality may show some differences with increasing duration of follow-up.

4.1. Limitations

A major limitation of the present study is that no long-term follow-up data were collected after surgery, so whether intraoperative AF is related to increased mortality is unknown. Furthermore, the small sample size might cover up the differences between the variables. In addition, no blood samples were collected, so it was quite difficult for us to examine the pathophysiologic mechanism of AF. Recent studies reported that N-terminal pro-B-type natriuretic peptide and microRNA 483-5p levels are useful for identifying patients at risk.[2,39,40] Further studies are urgently needed to obtain more information and prevent the occurrence of AF.

5. Conclusion

The incidence of intraoperative AF during noncardiac thoracic surgery was 12.5%. Alcohol consumption, history of chemotherapy, and high heart rate during 1-lung ventilation were risk factors of intraoperative AF.

Author contributions

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