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COMMENTARY

Re-conceptualization of the "Chinese Expert Guidelines for the Prevention of Stroke Associated with Patent Foramen Ovale" for the Management of Perioperative Stroke in Patients with Lung Cancer

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Abstract

The Chinese Heart Journal published the "Chinese Expert Guidelines for the Prevention of Stroke Associated with Patent Foramen Ovale" (hereafter referred to as "the Guidelines") in 2021. The Guidelines were initiated by Professor Yushun Zhang of the No.1 Affiliated Hospital of Xi'an Jiaotong University, and 55 domestic experts participated in their discussion and formulation. The Guidelines focus on eight key issues in the prevention of stroke associated with patent foramen ovale (PFO), including definition and epidemiology, anatomical features, ultrasound diagnosis, clinical screening, and prevention and treatment of PFO-associated stroke. The prevention and treatment of PFO-associated stroke include pharmacological prevention, prevention of PFO with transcatheter occlusion and transcatheter occlusion of PFO. Patients with PFO are at elevated risk of perioperative stroke. In China, lung cancer ranks first in incidence among malignant tumors. The number of lung cancer surgeries is increasing each year, and the incidence of PFO in the population is approximately 25%. Although perioperative stroke in patients with lung cancer due to the presence of PFO has rarely been reported, given the high disability rate of stroke, incidence of PFO, and incidence of lung cancer, herein, we consider the Guidelines for the management of perioperative stroke in lung cancer. Our aim is to provide further perspectives in decreasing the risk of perioperative stroke in patients with lung cancer and PFO, to improve their quality of life and increase the safety of surgery.

Keywords: PFO; lung cancer; perioperative stroke

Introduction

China is a large country with a high prevalence of lung cancer. Lung cancer ranks first in mortality among malignant tumors. Moreover, lung cancer is the tumor type with the highest incidence in men and the second highest incidence in women. Perioperative stroke in lung cancer is a rare but serious complication, and long-term neurological disability after perioperative stroke poses a heavy social and economic burden on families and communities. Patients with a preoperative diagnosis of patent foramen ovale

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(PFO) are at elevated risk of perioperative stroke. The "Chinese Expert Guidelines for the Prevention of Stroke Associated with Patent Foramen Ovale," published in The Chinese Heart Journal [1], (hereafter referred to as "the Guidelines") in 2021, focus on eight key issues for the prevention of PFO-associated stroke, including the definition and epidemiology of PFO, anatomical features, ultrasound diagnosis, clinical screening, and prevention and treatment of PFO-associated stroke. Few clinical reports of PFO have been provided in previous studies investigating the perioperative stroke of lung cancer. However, approximately 25% of adults have PFO. Patients with lung cancer require one-lung ventilation during the perioperative period, thus increasing intra-thoracic pressure, circulating blood volume and atrial pressure, and potentially causing the PFO to open. If an embolus is present in the systemic vein, it may enter the left atrium through the foramen ovale, enter the left ventricle, and subsequently travel through the blood flow to the entire body, thus potentially causing a stroke. Preoperative evaluation of systemic venous thrombosis is essential for patients undergoing thoracic surgery, and preoperative PFO occlusion is recommended for patients with PFO. Herein, we present a re-conceptualization of the "Chinese Expert Guidelines for the Prevention of Stroke Associated with PFO" in the context of experience from clinical diagnosis and treatment for the management of perioperative stroke in lung cancer.

Perioperative Stroke in Lung Cancer

Lung cancer's incidence rate and death rates are among the highest for all types of malignant tumors worldwide. According to the most recent epidemiological statistics of cancer in China [2], the number of new cases of lung cancer in China is highest among malignant tumors, at approximately 828,000. The number of deaths from lung cancer also ranks first among malignant tumors, at approximately 657,000. With the popularization of low-dose spiral computer tomography and increasing awareness of the need for physical examination across the country, the early diagnosis rate of lung cancer is increasing. Therefore, surgery is now considered the preferred treatment option for early-stage non-small cell lung cancer. Stroke is a rare but serious complication after surgery.

Perioperative stroke refers to ischemic or hemorrhagic cerebral infarction occurring during or within 30 days after surgery. The incidence of stroke after lung cancer surgery is approximately 0.2%–0.8%. Previous studies have shown that left superior pulmonary vein stump thrombosis after left upper lobectomy is a risk factor for postoperative cerebral infarction in lung cancer [3]. Another retrospective study has reported that 12 of 714 patients with lung cancer who underwent lobectomy had postoperative cerebral infarction; according to the TOAST classification, these cases comprised two cases of large atherosclerotic cerebral infarction; zero cases of cardiogenic cerebral infarction; three cases of small arterial occlusive cerebral infarction; five cases of cerebral infarction of other identified causes; and two cases of cerebral infarction of unknown causes [4]. In the general population, the mortality rate after the first stroke is approximately 15%, whereas the acute mortality rate due to perioperative stroke is approximately 26%. Long-term neurological disability after perioperative stroke poses a heavy social and economic burden on families and communities.

In the past two decades, with the development and promotion of thoracoscopic technology, thoracoscopic surgery has become highly common for patients with lung cancer. Thoracoscopic surgery, compared with traditional thoracotomy, is less traumatic, and is associated with less bleeding, fewer complications and faster postoperative recovery. However, some patients may experience unexplained strokes after surgery; therefore the related etiology and causes must urgently be identified. Patients with lung cancer usually have hypercoagulable blood and are at high risk of thrombotic complications. Patients with a preoperative diagnosis of PFO have a significantly elevated risk of perioperative ischemic stroke within 30 days of surgery [5].

Screening and Prevention of Strokes Associated with PFO

The foramen ovale usually closes spontaneously within 1–2 years after birth, thereby forming a permanent interatrial septum in newborns. Currently, approximately 25% of adults have PFO, which is a residual congenital cardiovascular structure [6]. Normally, the left atrial pressure is higher than that

of the right atrium, and the PFO is closed. When the chronic or transient right atrial pressure elevation exceeds the left atrial pressure, the primary septum of the PFO is pushed open, and a right-left shunt occurs. Currently, PFO is diagnosed through a combination of transthoracic echocardiography, transesophageal echocardiography and transcranial Doppler ultrasound.

Clinically, stroke in adults (younger than 55 years of age), that lacks high-risk factors and occurs suddenly should be considered to be PFO related. The main thrombi in PFO-associated stroke are venous thrombi, such as those from lower limb veins or pelvic veins. A previous history of deep vein thrombosis (DVT) or pulmonary embolism after DVT may be associated with PFO if a stroke occurs. DVT is likely to occur after trauma or prolonged immobilization after surgery, or prolonged car or airplane travel. Blood hypercoagulability, particularly hereditary blood hypercoagulability, is an important factor in the source of thrombosis. Weight-bearing, defecation, pre-stroke Valsalva breathing and sleep apnea increase the probability of paradoxical embolism. In addition, pregnancy, estrogen and thrombosis on the surface of the placed device also increase the risk of paradoxical embolism.

Pharmacological management of PFO-associated stroke includes primarily anticoagulation and antiplatelet therapy. Existing randomized controlled trials of anticoagulation versus antiplatelet therapy have not demonstrated which treatment regimen is better. Surgical treatment of PFO-associated stroke involves the transcatheter closure of the PFO. Surgery is indicated for patients with definite DVT or pulmonary embolism and those without long-term anticoagulant conditions. This method has advantages of high safety and rare complications, such as cardiac tamponade, atrial fibrillation and pulmonary embolism. PFO occlusion is more effective than antithrombotic therapy for cryptogenic stroke in patients with PFO.

Potential Pathophysiological Mechanisms of Perioperative Stroke in Patients with Lung Cancer and PFO

Whether traditional thoracotomy or thoracoscopic surgery is selected, the procedure requires one-lung ventilation, which depresses the side of the lung to be operated upon. Consequently, the original negative pressure in the thoracic cavity disappears and becomes approximately equal to the external atmospheric pressure. The heart is located in the mediastinum; the lungs and pulmonary vessels are located in the thoracic cavity; and the superior vena cava, inferior vena cava and aorta are connected to the heart in the thoracic cavity. The left atrial pressure is higher than the right atrial pressure in the resting state. When thoracic surgery is performed with one-lung ventilation, the patient's intrathoracic pressure changes from negative pressure to atmospheric pressure; the right atrium and right ventricle are influenced by the intrathoracic pressure; the resistance of the superior vein and inferior vena cava reflux increase; and the filling blood volume of the right atrium and right ventricle rapidly decrease. Consequently, a continuous increase in the blood volume of the superior vena cava and inferior vena cava, and an increase in the body's venous pressure occur. The decrease in right heart volume leads to a decrease in the amount of blood pumped into the lungs via pulmonary circulation; a decrease in pulmonary blood volume; and a decrease in the amount of blood returning from the pulmonary veins into the left atrium. The right atrial pressure may then be close to or slightly higher than the left atrial pressure, and a right-to-left shunt may be present in patients with PFO. At the end of the thoracic surgery, the intrathoracic pressure decreases, and the thoracic cavity gradually returns to a negative pressure state. The increased volume of systemic blood during one-lung ventilation flows back into the right atrium via the superior and inferior vena cava, and the right atrial pressure increases with the increase in right atrial blood volume. When the resistance of pulmonary venous return decreases at the end of one-lung ventilation, the blood volume in the superior and inferior vena cava is much greater than that in the lungs. Therefore, the blood flow back to the left atrium is much less than that in the right atrium; the pressure in the left atrium is lower than that in the right atrium; and the PFO is open. If emboli are present in the systemic veins at that time, they can potentially enter the left atrium through the foramen ovale and subsequently enter the left ventricle, which flows to the whole body, thus potentially causing a stroke.

Prevention, Treatment and Management of Perioperative Stroke in Patients with Lung Cancer and PFO

The diagnosis of PFO is currently performed with transthoracic echocardiography, transesophageal echocardiography, transcranial Doppler ultrasound or transthoracic echocardiography contrast-enhanced transcranial Doppler ultrasound (foam test). PFO occlusion is more effective than antithrombotic therapy for cryptogenic stroke in patients with PFO. We therefore believe that preoperative evaluation of systemic venous thrombosis is essential for patients scheduled for thoracic surgery, and we recommend preoperative PFO occlusion for patients with PFO, to decrease the incidence of postoperative cryptogenic stroke and the potential risks associated with surgery, and to improve patient quality of life.

After a perioperative stroke in lung cancer is diagnosed, a multidisciplinary assessment should be performed to determine whether reperfusion therapy for ischemic stroke is required. Close monitoring and timely assessment of fluid intake and output, myocardial enzymes, electrolytes, liver and kidney function, electrocardiography, etc. should be performed. PFO surgery in older patients is controversial [7]. While removing or alleviating causes and triggers, physicians should also provide symptomatic support treatment for the heart, liver, kidney, brain and other important organs [8].

Conclusion

The population with PFO in China is large. The Guidelines standardize the clinical application of PFO occlusion according to current research in China and other countries, considering the specific situation in China. The number of patients undergoing lung cancer surgery in China is increasing each year, and perioperative stroke is an important postoperative complication associated with a high disability rate. Hemodynamic changes, such as increased right-to-left shunt, blood hypercoagulability and venous thromboembolism, all increase the risk of perioperative stroke in patients with PFO. On this basis, we have combined the Guidelines and experience from clinical practice and propose a re-conceptualization of the Guidelines for the management of perioperative stroke in lung cancer. We believe that preoperative evaluation of systemic venous system thrombosis must be improved for patients in whom chest surgery is indicated, and we suggest that patients with PFO undergo PFO occlusion preoperatively to decrease the incidence of postoperative cryptogenic stroke and the potential risks associated with surgery, to ideally decrease the risk of perioperative stroke in patients with lung cancer and PFO. We hope that increasing clinical studies will focus on this aspect in the future, and that multidisciplinary collaborative diagnosis and treatment will better serve patients.

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