Editorial

Cerebral infarction after lung resection: is it predictable or just a stroke of bad luck?

Jennifer Williams[1], **Marcus Taylor**[2,3]

[1]Department of Thoracic Surgery, University Hospital of Wales, Cardiff, UK; [2]Department of Thoracic Surgery, Manchester University Hospital NHS Foundation Trust, Wythenshawe Hospital, Manchester, UK; [3]Division of Cardiovascular Sciences, University of Manchester, ERC, Manchester University Hospitals NHS Foundation Trust, Manchester, UK

Correspondence to: Marcus Taylor, MBChB. Department of Thoracic Surgery, Manchester University Hospital NHS Foundation Trust, Wythenshawe Hospital, Southmoor Road, Manchester M23 9LT, UK; Division of Cardiovascular Sciences, University of Manchester, ERC, Manchester University Hospitals NHS Foundation Trust, Manchester, UK. Email: marcus.taylor1@nhs.net.

Comment on: Gao S, Zhou Y, Yang R, *et al.* Risk factors for postoperative cerebral infarction in patients after lung resection: a single-center case-control study. J Thorac Dis 2023;15:376-85.

Keywords: Lung resection; segmentectomy; cerebral infarction; risk prediction

Submitted Sep 19, 2023. Accepted for publication Oct 20, 2023. Published online Nov 06, 2023.
doi: 10.21037/jtd-23-1467
View this article at: https://dx.doi.org/10.21037/jtd-23-1467

Post-operative cerebral infarction (POCI) following lung resection is an important outcome to both measure and predict. Despite its generally low reported incidence in contemporary studies (1), it has the potential to be a devastating outcome for patients and their families. The term refers to both cerebrovascular accident (CVA) and transient ischemic attack (TIA). Hence, the range of symptoms, the extent of disability and the duration of deficit can all vary considerably. For those patients afflicted most severely, POCI can be a truly devastating complication. Indeed, it has previously been reported by Hanger *et al.* that 69% of patients with residual paraplegia post-stroke would prefer a painless death over a severe disability (2).

However, measuring and predicting POCI is not straightforward. As previously mentioned, as an umbrella term its wide definition means that diagnosing POCI remains relatively subjective, as is the case with many post-operative complications (3). It is also recognized that not all cerebral infarcts are identifiable on computed tomography (CT) imaging. Thus, with limited availability of magnetic resonance imaging (MRI) in the early post-surgical period, there may be an element of under-reporting of POCI. Additionally, its low incidence means that large patient databases are required for a sufficient number of events to ensure statistical analyses are appropriately powered and robust in nature (4). Indeed, existing evidence suggests a minimum requirement of at least ten events for every candidate predictor parameter included in a multivariable analysis.

The recent paper from Gao *et al.* is a welcome addition to the small body of evidence on this important topic and addresses many of the principal issues (5). The authors rightly highlight the importance of evaluating POCI in lung resection patients and present a case-control study of 338 patients undergoing lung resection in a single Chinese unit between 2015 and 2021. Interestingly, the POCI rate quoted in their study is 6.5% (n=22), which is markedly higher than rates seen in previous studies, which tend to range from 0.6–1.1% (6-8). Whilst it is possible to draw some conclusions as to which subgroups of patients in the Gao *et al.* paper contributed to this increased incidence, the authors do not comprehensively examine why the overall rate of POCI in their study was so high.

The authors reported that peri-operative thromboprophylaxis was provided in the form of anti-embolic stockings (AES) for all patients, with no documented exclusion criteria. It is however recognized that patients with peripheral vascular disease (PVD) should not wear AES and ultimately prescribing these for claudicants is counter-productive (9). Unfortunately, PVD was not included in the dataset as a variable and consequently it is impossible to examine whether an unavoidable alteration to the thromboprophylaxis strategy in those patients affected the incidence of POCI. Gao *et al.* also state that low molecular weight heparin (LMWH) was administered from the second post-operative day to patients who were clinically prone to thrombosis. The manuscript does not provide any information as to whether this was a therapeutic or prophylactic dose of LMWH and also does not provide any criteria for defining which patients were 'clinically prone to thrombosis'. There was also no documented management plan for those not deemed high risk and so it therefore must be assumed that they simply received AES to protect against thrombosis. Finally, none of the 22 patients experiencing POCI had a prior history of atrial fibrillation or were taking oral anticoagulants.

UK practice is that all patients have a venous thromboembolism (VTE) assessment on admission to hospital and again at 24 hours after admission (10). The national standard since 2005 is that a minimum of 95% of all surgical patients should undergo a VTE risk assessment and be prescribed appropriate prophylaxis (10). This followed on from a UK Department of Health report which stated that 25,000 deaths were occurring annually due to hospital-acquired VTE (10). Furthermore, guidelines published in 2019 by the National Institute for Clinical Excellence (NICE) state that patients undergoing thoracic surgery should all have AES prescribed. Peri-operative intermittent pneumatic compression is recommended if patients have contraindications for AES. They further state that clinicians should consider prophylactic LMWH as first line for all thoracic surgical patients for a minimum of 7 days (11). Thus, the VTE strategy outlined by Gao *et al.* would be considered insufficient when compared to UK national standards. The role of appropriate VTE prophylaxis is of even greater significance when considered in the context of the Gao *et al.* study, whereby all patients suffering POCI experienced the complication during the first 2 post-operative days.

Furthermore, extended VTE prophylaxis is recommended by both the European Society of Thoracic Surgeons and the American Association for Thoracic Surgery in their 2022 joint guidelines for the prevention of cancer-associated VTE in thoracic surgery (12). The guidelines support extended VTE prophylaxis post-hospital admission for 28 to 35 days for moderate to high-risk thoracic resection patients (12). This is also recommended in the guidelines for enhanced recovery after surgery (ERAS) (13), where patients deemed to be at high risk of VTE development should be considered for 4 weeks of extended prophylaxis (13).

Over 95% of patients in the Gao *et al.* study underwent video-assisted thoracoscopic surgery (VATS). Consequently, the number of patients undergoing open surgery was too few for surgical approach to be included in the multivariable analysis. However, larger studies comparing VATS to thoracotomy have not identified open surgery as a significant risk factor for POCI (14). Similarly, 87.9% of patients in the study had surgery for malignant disease. Thus, whilst the majority of patients included underwent surgery via VATS for malignant disease, it remains unclear if the malignant disease was mainly primary lung cancer or secondary disease. It is widely postulated that malignancy increases the risk of thromboembolism. Therefore, the Gao *et al.* results whereby 86.4% of patients experiencing POCI underwent resection for malignancy are not surprising (15).

Types of resection performed included lobectomy, segmentectomy, and non-anatomical wedge resection. Whilst the overall incidence of POCI was 6.5%, alarmingly the rate of POCI was 17.6% (n=6/34) after segmentectomy and 8.3% (n=12/145) after sublobar wedge resection, compared to just 1.5% (n=2/134) after lobectomy. Thus, the dramatically higher rates of POCI after sublobar resections (anatomical segmentectomy and non-anatomical wedge resection) demand further investigation. Previous studies have examined a potential link between stump thrombosis and POCI, although many of those studies have reviewed this potential association solely in the context of left upper lobectomy (LUL). Yet although it is logical that increased manipulation of the lung and subsegmental vessels take place during sublobar resections, this has not translated into increased POCI rates in other, equally robust studies (16).

Patients in the Gao *et al.* study with signs and symptoms clinically suspicious for POCI underwent CT imaging of the brain but it remains unclear as to whether they also underwent echocardiography or pulmonary angiography and hence there is no available data from that study as to whether stump thrombosis was identified in any patient experiencing POCI. The authors did however postulate that the pulmonary vein stump is perhaps longer after segmentectomy compared to lobectomy. They also suggested that sublobar resection may be associated with increased damage to the vascular endothelium. Both are reasonable suppositions but require further large-scale studies in addition to histological examination of tissues in order to explore these hypotheses further.

There is limited literature that supports these postulations, but a single case report of POCI following segmentectomy also hypothesized this was due to a long venous stump, something previously identified as a risk factor in LULs (1,17,18). Potential surgical solutions for preventing segmentectomy venous stump thrombus include isolating the proximal veins prior to segmental division and the use of silk ties over surgical staples (17). The use of three-dimensional CT (3D-CT) reconstruction prior to performing a segmentectomy is also recommended to reduce tissue handling and improve anatomical clarity (19).

Interestingly, there was no significant association between POCI and longer operative duration on univariable analysis, although operative duration was not included in the multivariable analysis. It could be suggested that on the whole segmentectomy may take longer than lobectomy, and this may also represent a partial explanation as to why POCI was higher in patients undergoing segmentectomy. We note that the Gao *et al.* case-control study ran from 2015 to 2021: it would be interesting to note if the incidence of POCI in the segmentectomy patients was higher in the earlier period of the study, potentially during the segmentectomy learning curve. However, sublobar wedge resection is frequently a much quicker operation and so the emergence of higher rates of POCI in patients undergoing wedge resection compared to lobectomy would not support this theory. One partial explanation would be if the sublobar resection was unplanned, and only performed after a particularly complex and protracted operation which culminated in an inability to perform an anatomical resection. Such are the difficulties of conducting studies using retrospective data where these granular considerations are frequently absent from datasets.

It was also noted that the incidence of POCI was significantly higher in lower lobectomies. This is a novel finding, as previous studies have identified patients undergoing LUL as being at the highest risk of experiencing POCI, likely due to a longer venous stump (7,18). Conversely, the LUL subgroup had the lowest incidence of POCI in this study. There are a number of potential reasons for a higher incidence of POCI in lower lobectomies. These include more technically challenging basal segmentectomies and the associated increased handling of vessels in the lower lobes compared to a left lingulectomy or left upper lobe trisegmentectomy. Nevertheless, it is also recognized that the most common segmentectomy of the lower lobes is an S6 segmentectomy, which cannot be considered technically challenging in the same way as a basal segmentectomy. Finally, the incidence of unplanned lobectomy after being technically unable to complete a segmentectomy must also not be overlooked.

One of the primary aims of the study from Gao *et al.* was to conduct a multivariable analysis to identify variables independently associated with POCI in their patient cohort. Six variables including previous cerebral infarction, measures of coagulation, body mass index (BMI), type of resection, and location of resection were offered to the model. Previous cerebral infarction, lower activated partial thromboplastin time (aPTT) (<26.5 seconds), and higher BMI (>24.0 kg/m^2) were all independently associated with POCI. Additionally, undergoing lower lobectomy was significantly associated with POCI, as was undergoing sublobar resection. Segmentectomy also emerged as significantly associated with POCI compared to wedge resection. Unfortunately, a number of variables (including age, hypertension, and smoking) which have previously been associated with POCI were not included in this multivariable analysis. Whilst the limited number of events meant that variables offered to the model did indeed need to be rationalized, selecting variables based solely on univariable P values and not based on clinical relevance is no longer considered statistically appropriate and can lead to a significant association between a variable and the outcome being overlooked (20).

It has previously been reported that a shortened aPTT is an independent risk factor for developing ischemic stroke as well as influencing the severity of the stroke (21). These findings confirm the need for adequate pre-operative VTE assessment and appropriate prescription of thromboprophylaxis. The UK ERAS guidelines also deem those individuals with a shortened aPTT to be high risk and therefore should also be prescribed an extended course of LMWH for 28 days (13). Moreover, ERAS guidelines recommend early mobilization to counteract the adverse physiological complications of surgical stress (13). Hence, it would be pertinent to understand the peri-operative mobilization protocol in the study from Gao *et al.* Interestingly, the emergence of higher BMI in this study as an independent risk factor for POCI is at odds with other published evidence which supports the obesity paradox, whereby increased BMI is a protective factor against short-term morbidity and mortality after lung resection (22).

POCI is a clinically significant post-operative complication despite its limited incidence. Gao *et al.* have published an important study examining this topic and identified a number of factors independently associated with POCI. The incidence of POCI in their series was particularly high, especially for patients undergoing sublobar resection, and a number of possible theories for this phenomenon have been considered. Key factors to minimize the risk of POCI include 3D-CT planning to reduce handling of segmental vessels and the more widespread adoption of extended VTE protocols. The association between segmentectomy and POCI, as seen in this study, remains uncertain and hence we welcome additional large-scale studies on this important area of thoracic surgery practice to further examine potential causes and identify preventative measures.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1467/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Taylor M, Abah U, Hayes T, et al. Preoperative Anemia is Associated With Worse Long-Term Survival After Lung Cancer Resection: A Multicenter Cohort Study of 5,029 Patients. J Cardiothorac Vasc Anesth 2022;36:1373-9.
2. Hanger HC, Fogarty B, Wilkinson TJ, et al. Stroke patients' views on stroke outcomes: death versus disability. Clin Rehabil 2000;14:417-24.
3. Seely AJE, Ivanovic J, Threader J, et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg 2010;90:936-42.
4. Riley RD, Snell KI, Ensor J, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med 2019;38:1276-96. Erratum in: Stat Med 2019;38:5672.
5. Gao S, Zhou Y, Yang R, et al. Risk factors for postoperative cerebral infarction in patients after lung resection: a single-center case-control study. J Thorac Dis 2023;15:376-85.
6. Amemiya T, Shono T, Yamagami K, et al. Usefulness of Oral Xa Inhibitor for Management of Ischemic Stroke Associated with Thrombosis in the Pulmonary Vein Stump after Lung Resection. J Stroke Cerebrovasc Dis 2019;28:104321.
7. Xie N, Meng X, Wu C, et al. Both left upper lobectomy and left pneumonectomy are risk factors for postoperative stroke. Sci Rep 2019;9:10432.
8. Hsieh JK, Dalton JE, Yang D, et al. The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients. Anesth Analg 2016;123:933-9.
9. Bradley A. Unseen but present danger: improving the safe prescribing of anti-embolism stockings (AES). BMJ Qual Improv Rep 2014;3:u201797.w1992.
10. Department of Health. Venous thromboembolism prevention. Accessed September 8, 2023. Available at: http://apptg.org.uk/wp-content/uploads/2016/12/VTE-Prevention-A-Patient-Safety-Priority.pdf
11. National Institute for Health and Care Excellence (NICE). Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. 2018. Accessed September 10, 2023. Available online: https://www.nice.org.uk/guidance/ng89
12. Shargall Y, Wiercioch W, Brunelli A, et al. Joint 2022 European Society of Thoracic Surgeons and The American Association for Thoracic Surgery guidelines for the prevention of cancer-associated venous thromboembolism in thoracic surgery. J Thorac Cardiovasc Surg 2023;165:794-824.e6.
13. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg 2019;55:91-115.
14. Al-Ameri M, Bergman P, Franco-Cereceda A, et al. Video-assisted thoracoscopic versus open thoracotomy

lobectomy: a Swedish nationwide cohort study. J Thorac Dis 2018;10:3499-506.
15. Abdol Razak NB, Jones G, Bhandari M, et al. Cancer-Associated Thrombosis: An Overview of Mechanisms, Risk Factors, and Treatment. Cancers (Basel) 2018;10:380.
16. Kneuertz PJ, Zhao J, D'Souza DM, et al. National Trends and Outcomes of Segmentectomy in the Society of Thoracic Surgeons Database. Ann Thorac Surg 2022;113:1361-9.
17. Chen P, Qing Q, Diao M, et al. Surgical procedure of segmentectomy as a possible cause of postoperative cerebral embolism: a case report. J Cardiothorac Surg 2020;15:334.
18. Hattori A, Takamochi K, Kitamura Y, et al. Risk factor analysis of cerebral infarction and clinicopathological characteristics of left upper pulmonary vein stump thrombus after lobectomy. Gen Thorac Cardiovasc Surg 2019;67:247-53.
19. Nagashima T, Shimizu K, Ohtaki Y, et al. An analysis of variations in the bronchovascular pattern of the right upper lobe using three-dimensional CT angiography and bronchography. Gen Thorac Cardiovasc Surg 2015;63:354-60.
20. Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. BMJ 2009;338:b604.
21. Lin CH, Kuo YW, Kuo CY, et al. Shortened Activated Partial Thromboplastin Time Is Associated With Acute Ischemic Stroke, Stroke Severity, and Neurological Worsening. J Stroke Cerebrovasc Dis 2015;24:2270-6.
22. Ahmed-Issap A, Jain S, Habib A, et al. Impact of Extremes of BMI on Outcomes Following Lung Resection. Thorac Cardiovasc Surg 2023. [Epub ahead of print]. doi: 10.1055/a-2072-9869.

Cite this article as: Williams J, Taylor M. Cerebral infarction after lung resection: is it predictable or just a stroke of bad luck? J Thorac Dis 2023;15(12):6390-6394. doi: 10.21037/jtd-23-1467

