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Review Article

Impact of pharmacological interventions on intrapulmonary shunt during one-lung ventilation in adult thoracic surgery: a systematic review and component network meta-analysis

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Abstract

Background: Intrapulmonary shunt is a major determinant of oxygenation in thoracic surgery under one-lung ventilation. We reviewed the effects of available treatments on shunt, Pao_2/FiO_2 and haemodynamics through systematic review and network meta-analysis.

Methods: Online databases were searched for RCTs comparing pharmacological interventions and intrapulmonary shunt in thoracic surgery under one-lung ventilation up to March 30, 2022. Random-effects (component) network meta-analysis compared 24 treatments and 19 treatment components. The Confidence in Network Meta-Analysis (CINeMA) framework assessed evidence certainty. The primary outcome was intrapulmonary shunt fraction during one-lung ventilation.

Results: A total of 55 RCTs were eligible for systematic review (2788 participants). The addition of N_2O (mean difference [MD]=−15%; 95% confidence interval [CI], −25 to −5; P=0.003) or almitrine (MD=−13%; 95% CI, −20 to −6; P<0.001) to propofol anaesthesia were efficient at decreasing shunt. Combined epidural anaesthesia (MD=3%; 95% CI, 1–5; P=0.005), sevoflurane (MD=5%; 95% CI, 2–8; P<0.001), isoflurane (MD=6%; 95% CI, 4–9; P<0.001), and desflurane (MD=9%; 95% CI, 4–14; P=0.001) increased shunt *vs* propofol. Almitrine (MD=147 mm Hg; 95% CI, 58–236; P=0.001), dopexamine (MD=88 mm Hg; 95% CI, 4–171; P=0.039), and iloprost (MD=81 mm Hg; 95% CI, 4–158; P=0.038) improved Pao_2/FiO_2. Certainty of evidence ranged from very low to moderate.

Conclusions: Adding N_2O or almitrine to propofol anaesthesia reduced intrapulmonary shunt during one-lung ventilation. Halogenated anaesthetics increased shunt in comparison with propofol. The effects of N_2O, iloprost, and dexmedetomidine should be investigated in future research. N_2O results constitute a research hypothesis currently not backed by any direct evidence. The clinical availability of almitrine is limited.

Systematic review protocol: PROSPERO CRD42022310313.

Keywords: intrapulmonary shunt; meta-analysis; one-lung ventilation; oxygenation; thoracic surgery

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Editor's key points

- Anaesthetic maintenance and adjuvant agents can modify intrapulmonary shunt and oxygenation during one-lung ventilation in thoracic surgery. The extent of those physiological changes and their impact on clinical outcomes remain unclear.
- This systematic review is the first report to describe a hierarchy of the effects of drugs used during anaesthesia on shunt and oxygenation during one-lung ventilation.
- Adding N_2O or almitrine to propofol anaesthesia reduced intrapulmonary shunt during one-lung ventilation, and volatile anaesthetics increased shunt compared with propofol.
- Improved knowledge and novel research hypotheses regarding shunt and oxygenation during one-lung ventilation should guide further clinical trial design focusing on clinical outcomes.

One-lung ventilation (OLV) is a requirement for many surgeries that can result in substantial hypoxaemia through ventilation/perfusion mismatching.[1] Animal studies reported worrying consequences after OLV, such as inflammatory damage and ventilator-induced lung injury.[2] In humans, thoracic surgery under OLV was reported to be associated with up to 20% of postoperative pulmonary complications.[3] Lung isolation through a double-lumen tracheal tube or bronchial blocker results in the shunting of blood through the non-ventilated lung, with partial compensation from hypoxic pulmonary vasoconstriction (HPV).[4] Intrapulmonary shunt fraction (Q_s/Q_t) amounts to 2–5% of cardiac output in daily life. General anaesthesia impacts lung function and raises this fraction to ~10%, and surgery under OLV further increases it to 20–30%. In animal models, volatile anaesthetics result in a dose-dependent inhibition of HPV through induction of NO synthase,[5,6] whereas propofol potentiates HPV through inhibition of K^+-ATP channels.[7] Anaesthetic agents with improved pharmacological profiles regarding the modulation of HPV and inflammation might help prevent complications and improve patient outcomes after surgery.[4,8] The wide choice of available drugs has only been subject to narrative review or focused meta-analysis of select candidates until now, and the clinical impact remains unclear.[9] Significant variations in thoracic anaesthesia practice exist, including choice of maintenance agent, regional analgesia, or administration of adjuvant drugs. The literature pertaining to Q_s/Q_t and oxygenation under OLV naturally reflects this diversity. Hence, the large number of experimental conditions to include in a thorough review of the topic makes traditional meta-analysis unsuitable owing to multiple comparison issues, which would make the analysis complex and results confusing. However, the topic is a perfect fit for network meta-analysis (NMA), which uses networking effects to yield comparatively clearer and more precise results, allowing us to use the diversity of experimental designs to our advantage. In addition, component network meta-analysis (CNMA) is specifically designed for the analysis of combined treatments, accounting for a large part of the trial designs relevant to this paper. In this systematic review with CNMA, we summarise the comparisons between available treatments into a comprehensive qualitative and quantitative assessment and isolate the effects of adjuvant treatments through CNMA.

Our primary endpoint is the Q_s/Q_t difference associated with the various anaesthetic drug regimens at the longest time available under OLV in adult patients undergoing thoracic surgery.

Methods

We conducted a systematic review with NMA and CNMA, with a preregistered protocol available on PROSPERO (CRD42022310313). Ethical approval was waived by the review board owing to the absence of new data collection. Protocol deviations are reported in Supplement 1.5. Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-NMA extension (Supplement 1.6) and the PRISMA 2020 statement (Supplement 1.2).[10,11]

Study eligibility

Eligibility was assessed according to Population, Intervention, Comparison, Outcomes, and Study type(PICOS) criteria. RCTs conducted in adult patients (>18 yr old) undergoing thoracic surgery under general anaesthesia and OLV comparing pharmacological interventions aimed at modifying Q_s/Q_t were considered for inclusion. No merging or clustering was used, and all treatments belonged to distinct network nodes. Non-pharmacological interventions and alternative experimental designs were excluded. Comparators included pharmacological interventions, placebo, or usual care arms. The primary outcome was Q_s/Q_t under OLV. A secondary performance outcome was the Pa_{O_2}/FiO_2 (Horowitz) ratio. Safety outcomes were MAP and HR.

Information sources and search

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched without limitation of year of publication or language. Reference lists of retrieved reports were screened for additional citations. Clinical Trials.gov was searched for published, unpublished, and ongoing studies. Trial authors were queried if outcome data were missing or unclear. Searches were updated until March 30, 2022. Reproducible searches can be found in Supplement 1.14.

Study selection and data collection

Literature screening was independently conducted by two investigators (RS, AP). Disagreements were resolved through consensus or arbitrage (BB). Reports were examined at the title, abstract, and full-text levels. Duplicates were removed manually. Studies satisfying inclusion and exclusion criteria with missing outcome or exposure data were included in the systematic review only. Data extraction (RS, ALD) consisted in the study population, interventions, outcomes, funding, and variables potentially invalidating the transitivity assumption (FiO_2, inclusion of pneumonectomy, OLV<30 min). A stable period of at least 30 min under OLV without surgical manipulation is required to collect accurate Q_s/Q_t measurements, and studies failing to fulfil this requirement were recorded as such (Supplement 1.9). One author verified the extracted data (ALD). Outcome data were collected for the longest time under OLV available.

Geometry of the network

Network geometry was reported according to graph theory criteria.[12] Reported elements included the number of nodes, edges, and studies per edge (edge thickness, with median and inter-quartile range [IQR]), network density, percentage of

common comparators, and the percentage of strong edges (edges with >1 study). A network graph is presented.

Quality assessment

Within-study risk of bias was assessed by two investigators (RS, AP) using the RoB 2 tool.[13] Overall assessment for the primary outcome was classified as 'low', 'some concerns', or 'high' according to recommended criteria. For outcomes considered 'low', all domains were rated as low risk. For those assessed to have 'some concerns', no domains were rated as high risk, and there was at least one 'some concerns' rating. A rating of 'high' means at least one domain was rated as high risk, or multiple domains were rated as concerning in a way that substantially lowered the confidence in the results. The certainty of evidence assessment used the framework of Confidence in Network Meta-Analysis (CINeMA) and covered six areas: within-study bias (using RoB2 input), reporting bias, indirectness, imprecision, heterogeneity, and incoherence.[14] CINeMA extends the grading of recommendations, assessment, development, and evaluations (GRADE) framework in the context of NMA.[15]

Data synthesis

Central tendencies and spread were transformed to mean with standard deviation where possible.[16] A random-effects NMA (full interaction model) was conducted for each outcome. Treatment effects were estimated using the mean difference (MD) with 95% confidence interval (95% CI) and ranked using the *P*-score, a frequentist analogue of surface under the cumulative ranking curve (SUCRA).[17] The transitivity assumption was assessed by comparing potential effect modifiers across treatment comparisons. Inconsistency was evaluated by the side-splitting approach at the comparison level and by a full design-by-treatment model at the global level. Heterogeneity was assessed globally, with its between- and within-design components assessed through decomposition of the Q statistic. Major contributors to heterogeneity were defined as designs presenting a $P<0.05$ on hypothesis

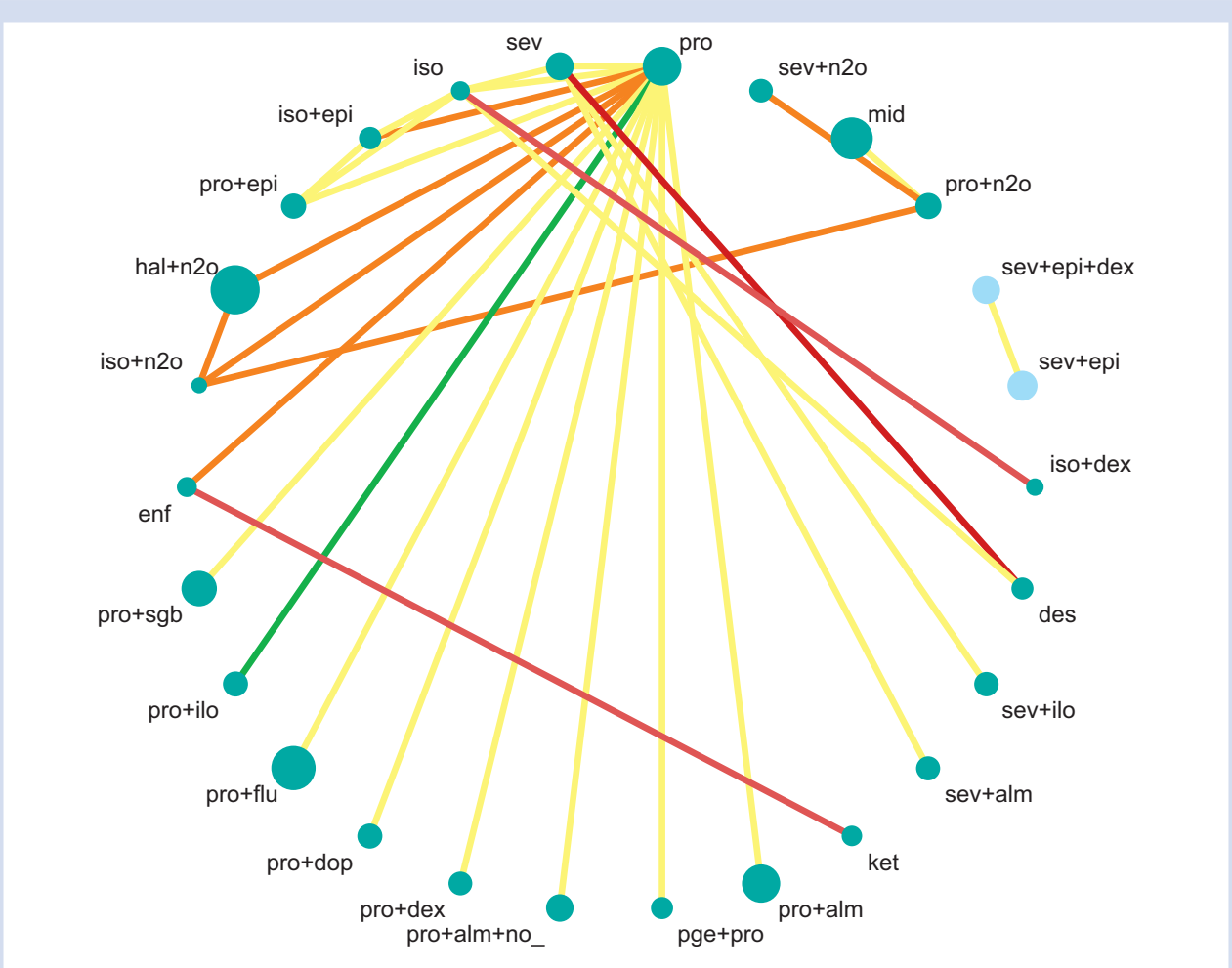

Fig 1. Network plot of treatments for intrapulmonary shunt in thoracic surgery under one-lung ventilation. Dark blue nodes: network meta-analysis model; light blue nodes: additional treatments included in disconnected component network meta-analysis; light green: low risk-of-bias (not represented); yellow: some concerns; red: high risk-of-bias. Dark green, orange, and dark red indicate comparisons for which indirectness was detected. Node size is log sample size. alm, almitrine; des, desflurane; dex, dexmedetomidine; dop, dopexamine; enf, enflurane; epi, epidural; flu, flurbiprofen axetil; hal, halothane; ilo, iloprost; iso, isoflurane; ket, ketamine; mid, midazolam; n2o, N_2O; no, NO; pro, propofol; sev, sevoflurane; sgb, stellate ganglion block.

tests against the Q statistic. Inconsistency was detailed in net heat plots and pairwise forest plots. We used a complete-case analysis. Studies with multiple treatment arms were included on a per-arm basis. Disconnected network CNMA assessed individual treatment components, with model fit assessed through a hypothesis test on the Q statistic against the NMA model. Where appropriate, an interaction (multiplicative) CNMA was fit using major contributors to between-design heterogeneity as covariates. Publication bias was assessed through examination of the funnel plot for the main outcome using newly investigated treatments as main comparators. A sensitivity analysis on the low risk-of-bias subgroup was planned but could not be performed because of the scarcity of data in this subpopulation.

The analysis was performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) with the package netmeta and typeset using the Org-mode literate programming framework according to reproducible research principles.[18–20] Cut-offs for the definition of clinically significant effects were within ±10% for Q_s/Q_t, within ±50 mm Hg for Pao_2/FiO_2, within ±10 mm Hg for MAP, and within ±10 beats min^{-1} of the main comparator treatment for HR. Treatment effects were deemed potentially clinically significant when the mean effect magnitude was equal or larger than the relevant cut-off value. NMA results are expressed as comparisons with propofol TIVA.

Results

We identified 1159 citations, including 810 unique documents of which 110 full-text articles were assessed for eligibility. We included 54 RCTs in the meta-analysis for a total of 2728 participants (55 reports and 2788 participants in the systematic review; see Supplement 1.1). Adequate information, full reports, or both could not be retrieved for four references.[21–24] One study was excluded from meta-analysis owing to missing precision data.[25] Additional studies were excluded from the Pao_2/FiO_2 ratio (three studies[26–28]), MAP (eight studies[27,29–35]), and HR (nine studies[27–35]) analyses for missing outcome data. There were four multi-arm RCTs included in the analysis.[30,36–38] One author had a large number of retracted studies according to retractionwatch.com.[39] The study selection process is displayed using a PRISMA flowchart (Supplement 1.2). There was no evidence against the assumption of transitivity other than N_2O administration being naturally associated to a $FiO_2<1$. Ten out of 55 studies used an OLV stabilisation period <30 min. Five studies did not report the duration of the stabilisation period. Forty studies satisfied the stable period requirement. A summary of eligible RCTs is provided in Supplement 1.3.

Network geometry

The network contained 26 nodes and 68 edges (direct and indirect comparisons). Edge density was 0.21, whereas the percentage of common comparators was 46% and median edge thickness was 1 (IQR, 1–2.75). Edge thickness is detailed in Supplement 10.1. There was a gap in evidence resulting in two disconnected components in the network. A network graph is presented in Fig. 1.

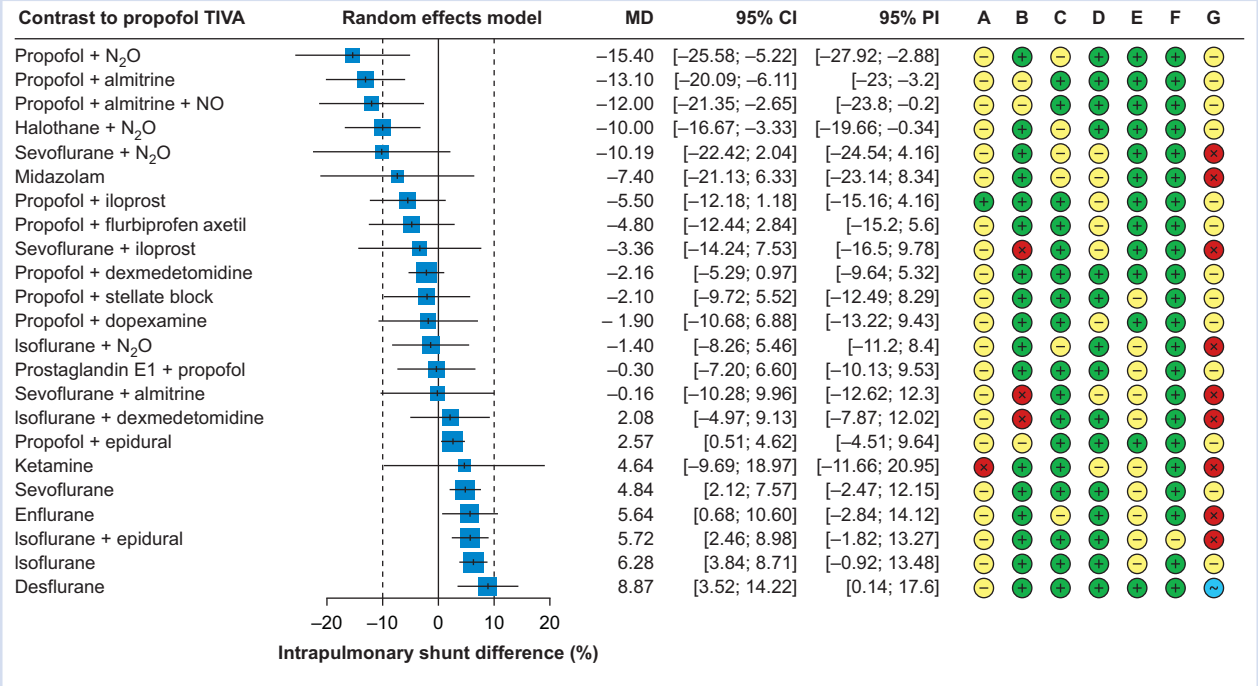

Fig 2. Forest and traffic lights plot of treatments for intrapulmonary shunt in thoracic surgery under one-lung ventilation. Letters are headings for the CINeMA confidence in the evidence assessment. A, within-study bias; B, reporting bias; C, indirectness; D, imprecision; E, heterogeneity; F, incoherence; G, overall rating. Colours and symbols are ratings on the confidence in the evidence. Green (+): high confidence; blue (~) moderate confidence; yellow (−): low confidence; red (×): very low confidence. Dashed lines: clinical significance limits for treatment effect magnitude. 95% CI, confidence interval; 95% PI, prediction interval; CINeMA, Confidence in Network Meta-Analysis; MD, mean difference.

Full interaction model

The primary outcome analysis included 54 RCTs, for a sample size of 2728 participants.[26–79] There were 24 distinct treatments participating in 28 study designs. The overall risk of bias was unclear on average, with respectively 1 (2%), 45 (85%), and 7 (13%) studies at low, unclear, and high risk of bias (Supplement 1.4). Some comparisons were downgraded for indirectness because of an FiO_2 <1. See Supplement 2 for a per-comparison risk-of-bias summary and Supplement 3 for details of this assessment.[26,28–30,37,41,44,70,72,75] Halothane+N_2O and propofol with almitrine, NO, or N_2O reduced Q_s/Q_t by a clinically significant magnitude with a prediction interval excluding zero, whereas combined epidural anaesthesia, halogenated anaesthetics, and especially desflurane were associated with an increase. Major contributors to heterogeneity were sevoflurane *vs* isoflurane,[31,40] isoflurane *vs* isoflurane+epidural[32,37,38,65] (within-design), and propofol *vs* isoflurane+epidural (between-designs).[37,38,72] No significant inconsistency was present (Q=9.283, df=9, P=0.412). Confidence in network estimates was moderate to very low, mostly degraded by the large proportion of studies at unclear risk of within-study bias and the systematic downgrading of comparisons including N_2O for indirectness owing to FiO_2<1 (Fig. 2). Publication bias could not be reliably identified from the funnel plot (Supplement 1.10.4). A ranking of treatments can be found in Fig 3. Details on heterogeneity (Supplement 1.10.2), inconsistency (Supplement 1.10.3), and strength of evidence (Supplement 3) are reported in the Supplementary material.

Component meta-analysis

Inclusion of the isoflurane×epidural interaction into a multiplicative CNMA allowed a substantial improvement in fit *vs* the additive model (Q=285, df=42, P<0.001), although the fit remained inferior to the full-interaction model (Q=268, df=36, P<0.001). Further adjustment did not improve model fit. CNMA estimates were broadly compatible with NMA (Supplement 1.11.6). Among the treatment estimates allowed through CNMA only, sevoflurane+epidural+dexmedetomidine increased Q_s/Q_t. Almitrine, N_2O, and iloprost all decreased Q_s/Q_t, although only almitrine held potential clinical significance (Table 1). Propofol+N_2O was ranked as the most efficient treatment to decrease Q_s/Q_t (Fig. 3).

Secondary outcomes

Pa_{O_2}/FiO_2 was available from 51 RCTs, amounting to 28 experimental designs and 2606 participants.[29-79] NMA supported mildly worse oxygenation under isoflurane, whereas combining propofol with iloprost, dopexamine, or almitrine with or without NO was associated with improvements.

Treatment	Q_s/Q_t	P/F	MAP	HR
Propofol + N_2O	0.9482	NA	NA	NA
Propofol + almitrine	0.9045	0.9472	0.6360	0.4405
Propofol + almitrine + NO	0.8698	0.9511	0.6180	0.3215
Halothane + N_2O	0.8321	0.6200	NA	NA
Sevoflurane + N_2O	0.8040	NA	NA	NA
Midazolam	0.7060	NA	NA	NA
Propofol + iloprost	0.6862	0.8106	0.5400	0.5680
Propofol + flurbiprofen axetil	0.6540	0.6186	0.5386	0.4641
Sevoflurane + iloprost	0.5805	0.5174	0.8417	0.5657
Propolol + dexmedetomidine	0.5555	0.6753	0.5220	0.6653
Propofol + stellate block	0.5372	0.4713	0.6819	0.8296
Propofol + dopexamine	0.5241	0.8262	0.2333	0.0086
Isoflurane + N_2O	0.4992	0.3941	NA	NA
Prostaglandin E1 + propofol	0.4528	0.5366	0.5389	0.6680
Sevoflurane + almitrine	0.4435	0.5132	0.3232	0.2238
Propofol	0.4388	0.4365	0.6772	0.6250
Isoflurane + dexmedetomidine	0.3372	0.3753	0.5112	0.1493
Propofol + epidural	0.3064	0.4134	0.2586	0.8472
Ketamine	0.2629	0.3836	0.4050	0.7012
Sevoflurane	0.1902	0.2597	0.5658	0.4811
Enflurane	0.1585	0.1237	0.6892	0.5426
Isoflurane + epidural	0.1466	0.2941	0.0903	0.5939
Isoflurane	0.1146	0.1052	0.4401	0.3566
Desflurane	0.0474	0.2268	0.3893	0.4482

Fig 3. P-score ranking of treatments for intrapulmonary shunt, Pa_{O_2}/FiO_2, MAP, and HR in thoracic surgery under one-lung ventilation. Blue (large value): high ranking; white: average ranking; red (small value): low ranking. NA, not available; P/F, Pa_{O_2}/FiO_2.

Table 1 Treatment component effect summary for intrapulmonary shunt (Q_s/Q_t), Pa_{O_2}/FiO_2 (P/F), MAP, and HR in thoracic surgery under one-lung ventilation. Significant results under $\alpha<0.05$ are in **bold** font. White rows include the null effect within CI bounds. Colours classify mean effect magnitude according to clinical significance cut-offs. Q_s/Q_t: ■ marked decrease, ■ mild decrease, ■ mild increase, ■ marked increase; Pa_{O_2}/FiO_2: ■ marked increase, ■ mild increase, ■ mild decrease, ■ marked decrease; MAP: ■ marked increase, ■ mild increase, ■ mild decrease, ■ marked decrease; HR: ■ marked decrease, ■ mild decrease, ■ mild increase, ■ marked increase. MD, mean difference; 95% CI, 95% confidence interval.

Treatment	Outcome	MD	CI low	CI high	*P*-value
Almitrine	Q_s/Q_t (%)	**–10.46**	**–15.85**	**–5.08**	**<0.001**
	P/F (mm Hg)	**91.43**	**32.61**	**150.25**	**<0.001**
	MAP (mm Hg)	–3.01	–14.62	8.61	0.61
	HR (beats min^{-1})	7.74	–4.52	20.01	0.22
Desflurane	Q_s/Q_t	**5.7**	**0.77**	**10.64**	**0.02**
	P/F	–5.56	–55.8	44.69	0.83
	MAP	–2.92	–11.22	5.38	0.49
	HR	1.42	–7.91	10.75	0.77
Dexmedetomidine	Q_s/Q_t	**–2.84**	**–5.37**	**–0.32**	**0.03**
	P/F	**42.91**	**9.33**	**76.49**	**0.01**
	MAP	–2.44	–7.63	2.74	0.36
	HR	–2.64	–9.07	3.79	0.42
Dopexamine	Q_s/Q_t	–1.81	–10.4	6.79	0.68
	P/F	**87.69**	**6.49**	**168.88**	**0.03**
	MAP	–4.59	–10.01	0.83	0.1
	HR	**15.73**	**10.21**	**21.24**	**<0.001**
Enflurane	Q_s/Q_t	1.89	–2.3	6.08	0.38
	P/F	–22.15	–71.97	27.67	0.38
	MAP	3.57	–3.73	10.88	0.34
	HR	–0.99	–9.68	7.7	0.82
Epidural	Q_s/Q_t	**2.75**	**0.81**	**4.68**	**0.01**
	P/F	–3	–23.8	17.81	0.78
	MAP	**–7.67**	**–11.1**	**–4.25**	**<0.001**
	HR	**–5.17**	**–8.93**	**–1.41**	**0.01**
Flurbiprofen Axetil	Q_s/Q_t	–4.8	–12.04	2.44	0.19
	P/F	36	–44.46	116.46	0.38
	MAP	–2	–15.06	11.06	0.76
	HR	4	–11.34	19.34	0.61
Halothane	Q_s/Q_t	–5.28	–11.99	1.43	0.12
	P/F	17.73	–56.09	91.56	0.64
Iloprost	Q_s/Q_t	**–6.23**	**–11.55**	**–0.9**	**0.02**
	P/F	**64.07**	**9.49**	**118.65**	**0.02**
	MAP	2.69	–6.52	11.91	0.57
	HR	–0.35	–10.8	10.1	0.95
Isoflurane	Q_s/Q_t	**3.32**	**0.31**	**6.34**	**0.03**
	P/F	–20.27	–53.13	12.6	0.23
	MAP	–1.82	–7.24	3.61	0.51
	HR	3	–3.02	9.02	0.33
Ketamine	Q_s/Q_t	0.89	–11.3	13.09	0.89
	P/F	19.85	–93.65	133.35	0.73
	MAP	–3.43	–22.39	15.53	0.72
	HR	–6.99	–26.52	12.54	0.48

Treatment	Outcome	MD	CI low	CI high	*P*-value
Midazolam	Q_s/Q_t	–4.2	–14.66	6.26	0.43
	P/F	–17.96	–133.18	97.27	0.76
	MAP	1.27	–5.26	7.81	0.7
	HR	5.68	–1.78	13.14	0.14
N_2O	Q_s/Q_t	**–8.46**	**–15.24**	**–1.68**	**0.01**
	P/F	45.15	–30.66	120.97	0.24
	MAP	–1.27	–7.81	5.26	0.7
	HR	–5.68	–13.14	1.78	0.14
NO	Q_s/Q_t	–1.54	–12.05	8.98	0.77
	P/F	60.57	–47.97	169.11	0.27
	MAP	3.01	–14.96	20.97	0.74
	HR	1.26	–20.12	22.63	0.91
Prostaglandin E1	Q_s/Q_t	–0.3	–6.76	6.16	0.93
	P/F	20	–56.56	96.56	0.61
	MAP	–2	–14.88	10.88	0.76
	HR	–2	–17.52	13.52	0.8
Propofol	Q_s/Q_t	**–3.74**	**–6.33**	**–1.15**	**<0.001**
	P/F	**28.89**	**1.24**	**56.54**	**0.04**
	MAP	2.54	–2.3	7.39	0.3
	HR	–2.63	–8.11	2.85	0.35
Sevoflurane	Q_s/Q_t	1.41	–1.74	4.55	0.38
	P/F	–0.54	–36.48	35.39	0.98
	MAP	0.78	–6.07	7.63	0.82
	HR	0.51	–7.67	8.69	0.9
Stellate block	Q_s/Q_t	–2.1	–9.33	5.13	0.57
	P/F	9	–80.41	98.41	0.84
	MAP	2	–13.55	17.55	0.8
	HR	–8	–24.67	8.67	0.35

Propofol+almitrine with or without NO displayed a prediction interval excluding the null effect. Between-design heterogeneity stemmed from the propofol *vs* isoflurane+epidural,[37,38,72] isoflurane *vs* propofol+epidural,[36–38] and propofol *vs* propofol+epidural[33,36–38,41,46,49–51,55,73,75,78] designs. No specific contributor to within-design heterogeneity could be identified, although there was evidence for an overall effect (Q=105, df=25, *P*<0.001). Inconsistency stemmed from isoflurane+epidural *vs* propofol[37,38,72] or isoflurane[32,37,38,65] on side-splitting. Almitrine, dopexamine, and iloprost were associated with better oxygenation (Table 1). Potential clinically significant treatments were propofol+almitrine with or without NO (Fig. 4).

Data on MAP were provided by 46 RCTs, 27 designs, and 2312 participants.[26,28,36-79] NMA revealed a potential clinically significant reduction in MAP for combined epidural anaesthesia with propofol or isoflurane (Supplement 1.12.5). Prediction intervals all included zero. Between-design heterogeneity contributors were propofol *vs* isoflurane+epidural[37,38,72] and isoflurane *vs* isoflurane+epidural[37,38,65] designs. Within-design heterogeneity was present but could not be traced back to a particular culprit (Q=124, df=21, *P*<0.001). No inconsistency could be detected. CNMA *vs* NMA showed a small decrease in MAP for isoflurane with or without dexmedetomidine, and additional potential clinically relevant decreases for sevoflurane+epidural with or without dexmedetomidine. Epidural anaesthesia moderately reduced MAP, with borderline clinical significance (Table 1).

Information on HR was provided by 45 RCTs, 27 designs, and 2272 participants.[26,36-79] NMA indicated a small decrease in HR with combined propofol+epidural anaesthesia. Increases in HR were seen with isoflurane with or without dexmedetomidine and with propofol+dopexamine, which was the only condition presenting a strictly positive prediction interval (Supplement 1.13.5). Global heterogeneity was present, with no clearly identified origin (Q=397, df=29, *P*<0.001). No inconsistency could be detected. CNMA *vs* NMA showed unchanged estimates and did not detect additional influential treatments (Table 1).

Further details on all secondary endpoints results can be found in Supplement 1.11-13.

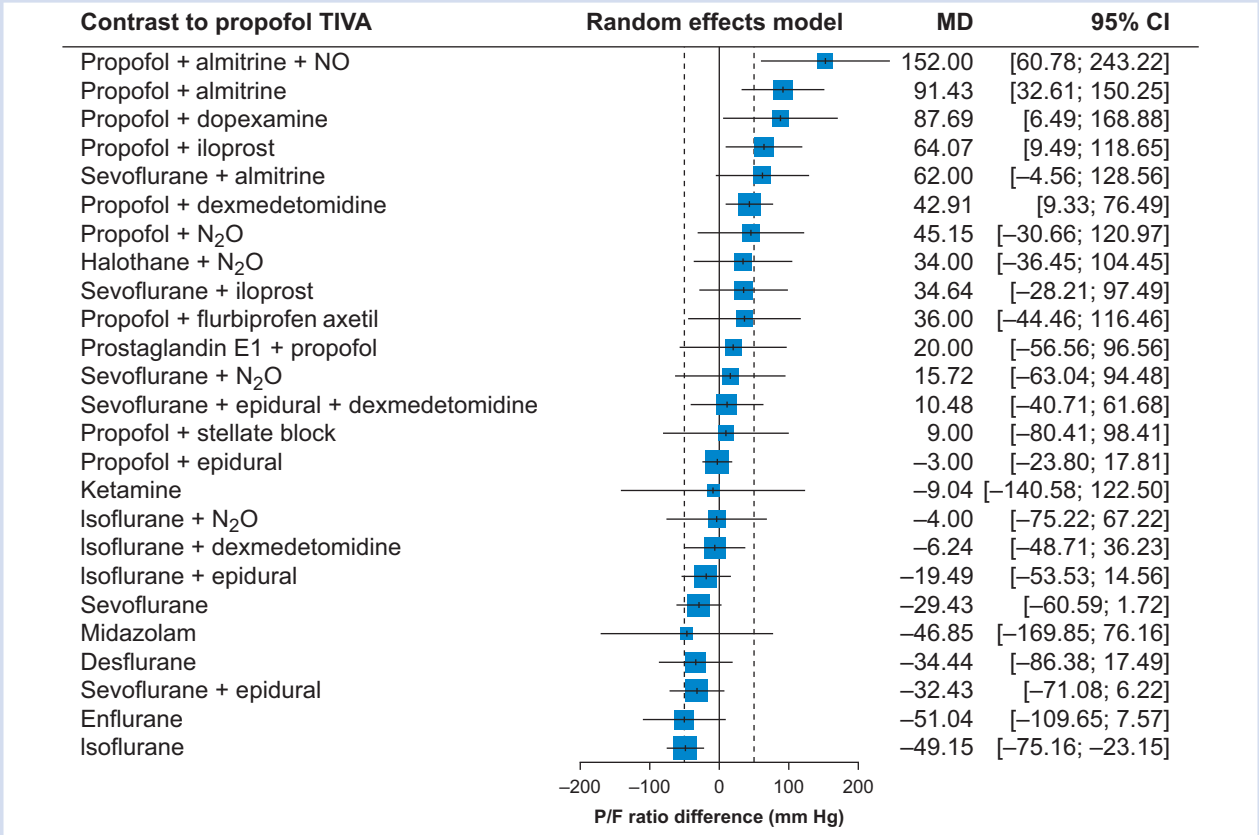

Fig 4. Forest plot of treatments for Pa_{O_2}/FiO_2 in thoracic surgery under one-lung ventilation. Dashed lines are clinical significance cut-offs for treatment effect magnitude. 95% CI, confidence interval; MD, mean difference; P/F, Pa_{O_2}/FiO_2.

Discussion

To our knowledge, this is the first report to synthesise evidence from all adjuvant treatments effects pertaining to Q_s/Q_t and Pa_{O_2}/FiO_2 in thoracic surgery under OLV. Results were broadly compatible with current knowledge, suggesting appropriate model fit. However, the low network density and the percentage of common comparators indicate significant potential for improvement through network densification and updated NMA remains.

Almitrine, a selective pulmonary vasoconstrictor agent (currently unavailable in North America, still available for research purposes only in Europe), held the largest positive influence over Q_s/Q_t and oxygenation. At the other end of the spectrum, halogenated anaesthetics and desflurane in particular showed moderate worsening of Q_s/Q_t and Pa_{O_2}/FiO_2. Isoflurane was ranked last among available treatments because of additional associations with worse haemodynamics. Results for NO and particularly N_2O were unexpected. Indeed, NO is widely used in anaesthesia and critical care as a Q_s/Q_t regulator and oxygenation optimising agent in the context of acute respiratory distress syndrome.[80] Here, the effect of NO was mostly non-significant but remained beneficial when combined with almitrine. N_2O had a larger effect than NO on Q_s/Q_t, and comparable effect on Pa_{O_2}/FiO_2 with potential for clinical significance. Substantial imprecision and confidence in the evidence, ranging from 'moderate' to 'very low' mostly because of within-study bias, do temper our confidence in those results. Persistence of N_2O effects and general coherence between our different models is, however, encouraging.

Haemodynamic safety conformed to expectations. Combined epidural anaesthesia and dopexamine administration were associated to undesirable haemodynamic effects of potential clinically significant magnitude, with low confidence in the evidence. No effect on oxygenation could be detected. There was little support for effects of either almitrine, iloprost, dexmedetomidine, NO, or N_2O on MAP or HR.

Certainty of evidence in reported effects considered within-study risk of bias, imprecision, heterogeneity, and incoherence of (in)direct comparisons. This revealed substantial uncertainty regarding drug-induced modification of Q_s/Q_t in thoracic surgery under OLV. Uncertainty was distributed evenly across comparisons and pointed to a generally low quality of evidence.

Context and reference to prior work

Recent literature regarding Q_s/Q_t and oxygenation on OLV has been focusing on adjuvant treatments. Dexmedetomidine was the object of several meta-analyses yielding encouraging results.[81,82] Other adjuvants under study have been almitrine, iloprost, and NO. Notably, N_2O was never a focus of research regarding Q_s/Q_t, and our findings pertaining to it are incidental.

A heated controversy has been surrounding N_2O as an adjuvant to general anaesthesia in the past decade, after reports of cardiac toxicity thought to result from the inhibition of methionine synthase, including the Evaluation of Nitrous Oxide in the Gas Mixture for Anaesthesia (ENIGMA) trial.[83] In addition, drawbacks such as emesis, myelopathy and hyperhomocysteinaemia discouraged N_2O use.[84–86] In thoracic surgery, N_2O enlarges airspace through diffusion.[87] However, N_2O also presents the advantage of enhancing lung collapse and remains in use for OLV in some centres.[88,89] Recently, reports of safety under N_2O inhalation from the PeriOperative ISchemic Evaluation (POISE) and ENIGMA II trials have rehabilitated N_2O.[90,91] In addition, there is evidence for fewer respiratory complications and reduced mortality with N_2O, possibly driven by lung protection against hyperoxia and promotion of surfactant synthesis through *N*-methyl-D-aspartate (NMDA) receptor inhibition.[92–94] Our results support the use of N_2O in thoracic surgery under OLV, with very low confidence in the evidence owing to it being derived from indirect network effects exclusively, therefore making it fragile and highly subject to potential rebuttal in the future.

Almitrine acts on the pulmonary circulation by enhancing HPV in non-ventilated areas with a dose–response effect.[69,95] Used as a continuous infusion, large improvements in oxygenation can be achieved, especially when combined with NO.[96] Almitrine was, however, reported as inefficient when combined to inhalation anaesthesia.[43] Undesirable effects of almitrine include pulmonary hypertension and peripheral neuropathy, but those do not appear with low-dose short-term administration in combination with NO.[69,97] Our results partially agree with the literature. Indeed, although almitrine with propofol showed superior effectiveness on shunt and oxygenation outcomes, results disallow rejecting an effect of almitrine when combined with sevoflurane. The direct evidence for this particular comparison was based on a single RCT and would deserve further investigation.[43]

Acting mainly through $\alpha 2$ adrenoreceptor agonism, dexmedetomidine also regulates inflammation and oxidative stress. In addition, dexmedetomidine is an attractive adjuvant improving oxygenation, while decreasing Q_s/Q_t and heart rate.[82,98] Preclinical evidence in animals showed that dexmedetomidine reduced ventilator-induced lung injury[99] and regulated inflammation in OLV models.[100] In humans, anti-inflammatory effects have been shown to persist at least until postoperative Day 1. Mode of administration matters, as a preoperative bolus dose does not provide the same benefits as continuous infusion.[81] Although this review covers the intraoperative period only, dexmedetomidine results on Q_s/Q_t and Pa_{O_2}/FiO_2 agree with previously published protective effects. Although dexmedetomidine is well established as a drug lowering blood pressure and heart rate, the effect was small and non-significant in our results.[101]

Iloprost is a synthetic prostacyclin PGI2 analogue gaining interest as a modulator of the pulmonary circulation. In its inhaled form, iloprost selectively dilates pulmonary arteries and affects Q_s/Q_t by preferentially distributing into well-ventilated areas.[102,103] This correlates well with our results, and although the effect size on Q_s/Q_t was small, iloprost was associated with a substantial improvement in oxygenation. Results are therefore promising, and several RCTs are underway or awaiting publication, which could make iloprost a strong choice for thoracic surgery if the preliminary evidence is consolidated.[59,104–106]

Aside from adjuvant agents, the main hypnotic strategy for thoracic surgery under OLV also is of critical importance. The choice between propofol and inhalation anaesthesia is the main clinical and research paradigm, and comparing those strategies has long been a major focus for authors.[107] Sevoflurane has been reported to protect against ischaemia–reperfusion lung injury associated to OLV through preservation of the glycocalyx layer protecting epithelia and reduction of inflammation.[108,109] Those benefits translate to a reduced incidence of postoperative pulmonary complications, even though shunt and oxygenation are moderately worse compared with propofol.[8] This correlates with our data, with improved shunt and oxygenation under propofol, followed by sevoflurane over other halogenated anaesthetics.

Some evidence suggests that thoracic epidural anaesthesia (TEA) has a negative impact on Q_s/Q_t and oxygenation.[110] Previous research on the topic suggests that epidural does not impact Q_s/Q_t as long as cardiac output is maintained.[111] Our results support a minimal increase in Q_s/Q_t with epidural, but the effect magnitude is small enough to be considered clinically insignificant and lies below the reliable measurable threshold of current measurement techniques. In addition, epidural results were present in many of our inconsistency assessments, making unbiased interpretation difficult. TEA may alleviate inflammation in the oncological lung resection context,[112] and remains the most widespread regional anaesthesia procedure for analgesia after thoracic surgery.[113,114] Pain after surgery resulted in a prolonged hospital stay after video-assisted thoracic surgery in 15% of patients in a recent RCT.[115]

Interestingly, our evidence contradicts a purely physiological interpretation of Q_s/Q_t as the main actor of oxygenation performance under OLV. Indeed, dexmedetomidine and sevoflurane both improve Pa_{O_2}/FiO_2 while exerting opposite effects on Q_s/Q_t.

Implications for clinical practice and future research

A large part of the published literature assessed combination treatments for the modification of Q_s/Q_t and oxygenation during thoracic surgery under OLV. Crucially, the variety of those combined treatments made the literature difficult to assess for clinical guidance up to now. A novel research paradigm uncovered in our analysis is that N_2O may prove an attractive adjuvant decreasing Q_s/Q_t and improving Pa_{O_2}/FiO_2, while causing little haemodynamic disruption. N_2O is easy to administer and widely available, especially compared with more involved options such as NO. With high uncertainty, combining N_2O and sevoflurane is supported by the data as a maintenance anaesthetic regimen, in light of the N_2O-driven compensation of sevoflurane drawbacks regarding Q_s/Q_t and Pa_{O_2}/FiO_2. The use of sevoflurane is further supported by the literature arguing in favour of persistent protective effects during and after surgery.[8] Dexmedetomidine+propofol is an alternative to sevoflurane for organ preservation supported by both our data and the published literature, although significantly more expensive and less widespread than N_2O. The use of N_2O of course remains discouraged in the presence of lung pathologies associated to air-filled cavities, such as emphysema.

Our results suggest several avenues for research on gas exchange and haemodynamic outcomes in thoracic surgery. From a structural standpoint, evidence increasing the quality and density of the treatment network is a priority given the

currently very low to moderate confidence in the presented evidence. A study connecting the subnetwork components in this work was in fact conducted, but unfortunately had to be excluded because of the unavailability of the complete report.[21] Secondly, further high-quality RCTs using N_2O and dexmedetomidine adjuvants are necessary to improve the precision of estimates. The current market status of almitrine makes interventional research involving this compound difficult, and authors seeking a more applicable alternative might prefer to focus on other adjuvants, such as iloprost, dexmedetomidine, or N_2O.

Strengths and limitations

NMA allowed best use of the available data and improved the precision of estimates compared with pairwise meta-analysis (median NMA leverage=0.25; IQR, 0.07–1). The main strength of this study is its state-of-the-art methodology, which allowed the coherent synthesis of a large number of trial designs and the first ever meta-analysis including the various anaesthetic regimens affecting Q_s/Q_t and Pao_2/FiO_2 under OLV. A key feature of CNMA was the ability to decompose the effects of combined treatments into their maintenance/adjuvant constituents, including those not represented by direct trial evidence (e.g. N_2O). Traditional meta-analysis or standard NMA would have limited us to the assessment of combined treatments. The newly identified research hypothesis regarding the effect of N_2O, although supported by fragile evidence and requiring validation by direct clinical evidence, would have not been allowed by a traditional methodology. This deserves to be highlighted, as the generation of such new hypotheses is recognised as one of the main goals of meta-analytical techniques.[116]

Several limitations must, however, be acknowledged. First, the influence and potential contamination between study arms of interventions left unreported or not included may have biased effect estimates with unpredictable magnitude and direction. Haemodynamic support, analgesia, or paralysing agents are candidates for such confounders. Unavailable physiological data, such as mixed venous oxygen content, could also qualify as an unmeasured confounder preventing a complete assessment of oxygenation. Second, risk of bias was designated as 'some concerns' or 'high' for most reports. Within-design risk of bias was the major factor that lowered confidence in the evidence. The downgrading of comparisons including N_2O owing to $FiO_2<1$ also played a part. Third, we conducted a complete-case analysis with no imputation of missing data. Missing data occurred in an all-or-nothing pattern across studies and was considered to not be missing at random. Fourth, multiple comparisons using $\alpha=0.05$ were performed. This is an unresolved issue within the NMA framework. Mitigation was attempted by appraising results without unnecessarily highlighting *P*-values or 95% CI cut-offs and using prediction intervals where available. Fifth, substantial heterogeneity was present in some pairwise comparisons. We presented the prediction interval of the pairwise aggregated estimates to better inform the reader in such cases. Sixth, the natural association of N_2O administration with lower FiO_2 weakened transitivity and might have biased estimates. Reasoning based on HPV would expect a decrease in FiO_2 to increase Q_s/Q_t and degrade oxygenation. The converse effect on Pao_2/FiO_2 is anticipated for the N_2O incidental association to reduced hyperoxia. The direction and magnitude of bias associated to N_2O therefore remains unknown. Finally, although physiological outcomes such as Q_s/Q_t, Pao_2/FiO_2, MAP, and HR certainly are an important substrate for clinical reasoning, evidence relating those to adverse clinical outcomes of end-organ injury and lung recovery remains scarce. Overcoming this scarcity appears necessary to judge the relevancy of this line of research. This has already been called out in a 2013 Cochrane review on a closely related topic by Módolo and colleagues.[107]

Conclusions

The addition of N_2O and almitrine to propofol reduced Q_s/Q_t during OLV in thoracic surgery. Halogenated anaesthetics increased Q_s/Q_t in comparison with propofol. Almitrine, dopexamine, and iloprost improved Pao_2/FiO_2. Network structure shows that significant potential for improvement in the strength of evidence remains with the conduct of high-quality RCTs investigating the adjuvant agents supported by this review. Readers should be aware that our appraisal of N_2O results currently constitutes a research hypothesis lacking direct evidence support, and that almitrine is a research drug currently unavailable for clinical purposes.

Authors' contributions

Conceptualisation: RS
Literature search: RS, AP
Hits screened and reviewed: RS, AP
Data curation: RS, ALD, AP
Analysis of data: RS.
Supervision: RS, AP
Access to data: all authors
Interpretation of data: all authors
Manuscript drafting: RS, AH
Manuscript revision, editing, and approval: all authors.

Declarations of interest

AH has received speaker fees from Medtronic International (Sàrl, Tolochenaz, Switzerland) regarding an unrelated topic. The other authors have no direct or indirect conflict of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.08.039.

References

1. Guenoun T, Journois D, Silleran-Chassany J, et al. Prediction of arterial oxygen tension during one-lung ventilation: analysis of preoperative and intraoperative variables. *J Cardiothorac Vasc Anesth* 2002; **16**: 199–203
2. Chiumello D, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999; **160**: 109–16
3. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. *Ann Thorac Surg* 2006; **81**: 1830–7
4. Lumb AB, Slinger P. Hypoxic pulmonary vasoconstriction: physiology and anesthetic implications. *Anesthesiology* 2015; **122**: 932–46

5. Qin G, Luo H, Yin X, et al. Effects of sevoflurane on hemodynamics and inducible nitric oxide synthase/soluble guanylate cyclase signaling pathway in a rat model of pulmonary arterial hypertension. *Anesth Analg* 2017; **125**: 184–9
6. Ishibe Y, Gui X, Uno H, Shiokawa Y, Umeda T, Suekane K. Effect of sevoflurane on hypoxic pulmonary vasoconstriction in the perfused rabbit lung. *Anesthesiology* 1993; **79**: 1348–53
7. Nakayama M, Murray PA. Ketamine preserves and propofol potentiates hypoxic pulmonary vasoconstriction compared with the conscious state in chronically instrumented dogs. *Anesthesiology* 1999; **91**: 760–71
8. Pang Q-Y, An R, Liu H-L. Effects of inhalation and intravenous anesthesia on intraoperative cardiopulmonary function and postoperative complications in patients undergoing thoracic surgery. *Minerva Anestesiol* 2018; **84**: 1287–97
9. Parab S, Gaikwad S, Majeti S. Inhalational versus intravenous anesthetics during one lung ventilation in elective thoracic surgeries: a narrative review. *Saudi J Anaesth* 2021; **15**: 312–23
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71
11. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777–84
12. Tonin FS, Borba HH, Mendes AM, Wiens A, Fernandez-Llimos F, Pontarolo R. Description of network meta-analysis geometry: a metrics design study. *PLoS One* 2019; **14**: e0212650
13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898
14. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020; **17**: e1003082
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336**: 924–6
16. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135
17. Rücker G, Schwarzer G. Resolve conflicting rankings of outcomes in network meta-analysis: partial ordering of treatments. *Res Synth Methods* 2017; **8**: 526–36
18. Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J* 2020; **62**: 808–21
19. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.
20. Schulte E, Davison D, Dye T, Dominik C. A multi-language computing environment for literate programming and reproducible research. *J Stat Softw* 2012; **46**: 1–24
21. Ueda IM, Yamasaki K. Comparison of sevoflurane and propofol combined with thoracic epidural anesthesia on arterial oxygenation during one-lung ventilation for thoracotomy. *Anesth Resusc* 1999; **35**: 139–43
22. Wei W, Wang M. Does small dose adrenaline administration benefit of oxygenation during one-lung ventilation? *Eur J Anaesthesiol* 2011; **28**: 73
23. Kwak S-H, Kim J-S, Choi J-I, et al. The effect of isoflurane and thoracic epidural anesthesia on arterial oxygenation in one lung anesthesia. *Korean J Anesthesiol* 2002; **42**: 747–56
24. Abd El-Hakeem E, Abdel-Aal F. Total intravenous anaesthesia versus thoracic epidural combined with general anaesthesia for thoracic surgery. *Egypt J Anaesth* 2004; **20**: 119–25
25. Abdelrahman RS. Effects of thoracic epidural anesthesia on pulmonary venous admixture and oxygenation with isoflurane or propofol anesthesia during one lung ventilation. *Egypt J Chest Dis Tuberc* 2012; **61**: 477–83
26. Kellow NH, Scott AD, White SA, Feneck RO. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. *Br J Anaesth* 1995; **75**: 578–82
27. Liu W, Gao D, Zhang L. Effects of dexmedetomidine on perioperative intrapulmonary shunt rate, inflammatory factors and Claudin-4 in patients undergoing radical operation of esophageal cancer. *Cancer Res Clin* 2020; **6**: 680–4
28. Xu W-Y, Wang N, Xu H-T, et al. Effects of sevoflurane and propofol on right ventricular function and pulmonary circulation in patients undergone esophagectomy. *Int J Clin Exp Pathol* 2013; **7**: 272–9
29. Abay IG, Aykac Z. The effects of sevoflurane on hypoxic pulmonary vasoconstriction during one-lung ventilation in thoracic surgery. *Br J Anaesth* 2000; **84**: 14
30. Gąsowska J, Brzeziński K, Przesmycki K, Nestorowicz A. Effects of halothane, isoflurane, and propofol on venous admixture during one-lung ventilation in patients undergoing thoracoscopic procedures. *Clin Invest* 1999; **5**: 929–33
31. Goren S, Basagan-Mogol E, Kaya FN, Sahin S, Korfali G. Comparison the effects of isoflurane and sevoflurane on hemodynamics and oxygenation during one lung anesthesia. *Gogus-Kalp-Damar Anestezi Ve Yogun Bakim Dernegi Dergisi* 2005; **11**: 16–22
32. Wang J, Li W, Li Y. The effect of lower thoracic epidural block on intrapulmonary shunt (Qs/Qt) during one-lung ventilation. *Lingnan J Emerg Med* 2004; **9**: 277–9
33. Wang Z, Luo X, Wang D, Ma Z. Influence of general-thoracic epidural anaesthesia on intrapulmonary shunt and blood oxygenation during one-lung ventilation. *Mod Med J* 2007; **35**: 390–2
34. Jin Y, Zhao X, Li H, Wang Z, Wang D. Effects of sevoflurane and propofol on the inflammatory response and pulmonary function of perioperative patients with one-lung ventilation. *Exp Ther Med* 2013; **6**: 781–5
35. Zhiguo Y, Nanxiang Z, Jinyu M. Analysis of comparative anesthetic effects of sevoflurane and propofol on lung and cognitive functions. *Pak J Pharm Sci* 2019; **32**: 2423–6
36. Kwak CSH, Park H. The effects of anesthetic techniques on arterial oxygenation and pulmonary shunt during one lung ventilation. *Chonnam Med J* 2002; **38**: 218–27
37. Özcan PE, Şentürk M, Sungur Ulke Z, et al. Effects of thoracic epidural anaesthesia on pulmonary venous admixture and oxygenation during one-lung ventilation. *Acta Anaesthesiol Scand* 2007; **51**: 1117–22
38. Zheng X, Lv Z, Yin K, Peng M. Effects of epidural anesthesia combined with inhalation anesthesia or

intravenous anesthesia on intrapulmonary shunt and oxygenation in patients undergoing long term single lung ventilation. *Pak J Med Sci* 2018; **34**: 799–803
39. Boldt J, Müller M, Uphus D, Padberg W, Hempelmann G. Cardiorespiratory changes in patients undergoing pulmonary resection using different anesthetic management techniques. *J Cardiothorac Vasc Anesth* 1996; **10**: 854–9
40. Abe K, Mashimo T, Yoshiya I. Arterial oxygenation and shunt fraction during one-lung ventilation: a comparison of isoflurane and sevoflurane. *Anesth Analg* 1998; **86**: 1266–70
41. Aksoy T, Yurtseven N, Aydemir B, et al. The effect of different anesthesia techniques in thoracic surgery effects on hemodynamics, oxygenation and shunt values. *Gogus-Kalp-Damar Anestezi Ve Yogun Bakim Dernegi Dergisi* 2005; **11**: 30–6
42. Beck DH, Doepfmer UR, Sinemus C, Bloch A, Schenk MR, Kox WJ. Effects of sevoflurane and propofol on pulmonary shunt fraction during one-lung ventilation for thoracic surgery. *Br J Anaesth* 2001; **86**: 38–43
43. Bermejo S, Gallart L, Silva-Costa-Gomes T, Vallès J, Aguiló R, Puig MM. Almitrine fails to improve oxygenation during one-lung ventilation with sevoflurane anesthesia. *J Cardiothorac Vas Anesth* 2014; **28**: 919–24
44. ÇeliK HK, Üstün FE, Çelik B, Başoğlu A. Effects of desflurane and sevoflurane on oxygenation and shunt fraction during one-lung ventilation and on recovery time. *Turk Klin J Med Sci* 2009; **29**: 1222–9
45. Chai X-Q, Ma J, Xie Y-H, Wang D, Chen K-Z. Flurbiprofen axetil increases arterial oxygen partial pressure by decreasing intrapulmonary shunt in patients undergoing one-lung ventilation. *J Anesth* 2015; **29**: 881–6
46. Chen S, Fang N, Zhao Q, Zhang J. The effect of thoracic epidural block on atrial oxygenation and intrapulmonary shunt during one-lung ventilation. *J Clin Anesthesiol* 2002; **18**: 432–3
47. Choi H, Jeon J, Huh J, Koo J, Yang S, Hwang W. The effects of iloprost on oxygenation during one-lung ventilation for lung surgery: a randomized controlled trial. *J Clin Med* 2019; **8**: 982
48. El-Hakeem EEA, Mohamed MS, Ali SM, El-Minshawy AM. Haemodynamic and pulmonary shunt fraction changes with sevoflurane or propofol anaesthesia during one-lung ventilation for thoracic surgery. *Egypt J Anaesth* 2004; **19**: 233–41
49. Feng Y, Sun Y, Yang B. The effect of epidural ropivacaine on arterial oxygenation and intrapulmonary shunt during one-lung ventilation. *Chin J Anestesiol* 2002; **22**: 143–7
50. Garutti I, Cruz P, Olmedilla L, et al. Effects of thoracic epidural meperidine on arterial oxygenation during one-lung ventilation in thoracic surgery. *J Cardiothorac Vasc Anesth* 2003; **17**: 302–5
51. Garutti I, Quintana B, Olmedilla L, Cruz A, Barranco M, Garcia de Lucas E. Arterial oxygenation during one-lung ventilation: combined versus general anesthesia. *Anesth Analg* 1999; **88**: 494–9
52. Gu Z, Yang J, Xin L, Xu J, Yang Y, Wang Z. Dose-dependent effects of dexmedetomidine during one-lung ventilation in patients undergoing lobectomy. *Int J Clin Exp Med* 2017; **10**: 5216–21
53. Guo W, Jin X-J, Yu J, et al. Effects of stellate ganglion block on the peri-operative vasomotor cytokine content and intrapulmonary shunt in patients with esophagus cancer. *Asian Pac J Cancer Prev* 2014; **15**: 9505–9
54. He X, Liu L, Chang Y. Comparison of the effects of propofol and isoflurane on the pulmonary shunt fraction during one lung ventilation. *Bull Hunan Med Univ* 2002; **27**: 481–2
55. Jung SM, Cho CK, Kim YJ, et al. The effect of thoracic epidural anesthesia on pulmonary shunt fraction and arterial oxygenation during one-lung ventilation. *J Cardiothorac Vasc Anesth* 2010; **24**: 456–62
56. Kar P, Durga P, Gopinath R. The effect of epidural dexmedetomidine on oxygenation and shunt fraction in patients undergoing thoracotomy and one lung ventilation: a randomized controlled study. *J Anaesthesiol Clin Pharmacol* 2016; **32**: 458–64
57. Kim CHS, Kwak S. A comparison of the effects of isoflurane versus propofol anesthesia on blood gas parameters during one lung ventilation for lung surgery. *Korean J Anesthesiol* 2002; **42**: 737–46
58. Kwak CSH, Yoo K. Effects of desflurane and isoflurane on arterial oxygenation and intrapulmonary shunt in one lung anesthesia. *Korean J Anesthesiol* 2000; **38**: 623–31
59. Lee K, Oh YJ, Kim M, Song SH, Kim N. Effects of iloprost on oxygenation during one-lung ventilation in patients with low diffusing capacity for carbon monoxide: a randomized controlled study. *J Clin Med* 2022; **11**: 1542
60. Li P, Gu L, Bian Q, et al. Effects of prostaglandin E1 nebulization of ventilated lung under 60% O_2 one lung ventilation on patients' oxygenation and oxidative stress: a randomised controlled trial. *Respir Res* 2020; **21**: 113
61. Luo X, Chen S, Huang H. Comparison of the effects of propofol and isoflurane on intrapulmonary shunt during one-lung ventilation. *Xiandai Yixue* 2010; **38**: 380–2
62. Moutafis M, Dalibon N, Liu N, Kuhlman G, Fischler M. The effects of intravenous almitrine on oxygenation and hemodynamics during one-lung ventilation. *Anesth Analg* 2002; **94**: 830–4
63. Müller M, Sticher J, Schindler E, et al. Auswirkungen von Dopexamin. *Anaesthesist* 1997; **46**: 771–5
64. Muller M, Sticher J, Schindler E, Padberg W, Janich S, Hempelmann G. Effects of dopexamine and volume loading on hemodynamics and oxygenation parameters in patients undergoing pulmonary resection. *Acta Anesthesiol Scand* 2000; **44**: 858–63
65. Ozcan P, Senturk M, Camci E, Talu G, Pembeci K, Tugrul M. Tek Akciger ventilasyonunda genel anestezi ve kombine anestezinin intrapulmoner sant ve oksijenasyona etkisi. *GKD Anest Yog Bak Dern Derg* 2003; **9**: 124–8
66. Pagel PS, Fu JL, Damask C, et al. Desflurane and isoflurane produce similar alterations in systemic and pulmonary hemodynamics and arterial oxygenation in patients undergoing one-lung ventilation during thoracotomy. *Anesth Analg* 1998; **87**: 800–7
67. Pan J, Fan J, Xie Y. Effects of propofol and enflurane on intrapulmonary shunt and plasma levels of endothelin and nitric oxide during one-lung ventilation. *Chin J Anesthesiol* 2000; **20**: 649–51
68. Rees DI, Gaines GY. One-lung anesthesia—a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane. *Anesth Analg* 1984; **63**: 521–5
69. Silva-Costa-Gomes T, Gallart L, Vallès J, Trillo L, Minguella J, Puig MM. Low- vs high-dose almitrine combined with nitric oxide to prevent hypoxia during open-chest one-lung ventilation. *Br J Anaesth* 2005; **95**: 410–6

70. Spies C, Zaune U, Pauli MH, Boeden G, Martin E. [A comparison of enflurane and propofol in thoracic surgery]. *Anaesthesist* 1991; **40**: 14–8
71. Sun Y, Feng Y, Yang B. Comparison of the effects of isoflurane and propofol in conjunction with thoracic epidural block on oxygenation and shunt fraction during one-lung anesthesia. *Chin J Anesthesiol* 2002; **22**: 403–7
72. Von Dossow V, Welte M, Zaune U, et al. Thoracic epidural anesthesia combined with general anesthesia: the preferred anesthetic technique for thoracic surgery. *Anesth Analg* 2001; **92**: 848–54
73. Wu L, Zhu H, Zhou Y, Dong L, Xu G. Influence of general anesthesia combined with epidural block on the aged during one-lung ventilation. *Chin J Clin Med* 2009; **16**: 443–5
74. Xia R, Xu J, Yin H, et al. Intravenous infusion of dexmedetomidine combined isoflurane inhalation reduces oxidative stress and potentiates hypoxia pulmonary vasoconstriction during one-lung ventilation in patients. *Mediators Inflamm* 2015; **2015**, 238041
75. Xu Y, Tan Z, Wang S, Shao H, Zhu X. Effect of thoracic epidural anesthesia with different concentrations of ropivacaine on arterial oxygenation during one-lung ventilation. *Anesthesiology* 2010; **112**: 1146–54
76. Xu B, Gao H, Li D, Hu C, Yang J. Nebulized dexmedetomidine improves pulmonary shunt and lung mechanics during one-lung ventilation: a randomized clinical controlled trial. *PeerJ* 2020; **8**: e9247
77. Xue F, Chen Z, Liu C, Wang S. Effects of dexmedetomidine on intrapulmonary shunt and arterial oxygenation during one lung ventilation. *J New Drugs Clin Remedies* 2015; **34**: 861–5
78. Zhang G, Wu L. Clinical observations of influence of general anesthesia combined with epidural block on the aged patient. *Acta Acad Med JiangXi* 2009; **49**: 84–6
79. Zhang L, Zhang Y, Li Y, Weng L, Chen Q, Jiang L. Effects of dexmedetomidine on intrapulmonary shunt and oxygen pressure of the artery during one-lung ventilation. *Acta Univ Med Anhui* 2014; **9**: 1291–4
80. Tatham KC, Ferguson ND, Zhou Q, et al. Evolution of practice patterns in the management of acute respiratory distress syndrome: a secondary analysis of two successive randomized controlled trials. *J Crit Care* 2021; **65**: 274–81
81. Bai Y-X, Zhang J-H, Zhao B-C, Liu K-X, Bai Y-W. Dexmedetomidine attenuates one-lung ventilation associated lung injury by suppressing inflammatory responses: a systematic review and meta-analysis. *Clin Exp Pharmacol Physiol* 2021; **48**: 1203–14
82. Huang S-Q, Zhang J, Zhang X-X, et al. Can dexmedetomidine improve arterial oxygenation and intrapulmonary shunt during one-lung ventilation in adults undergoing thoracic surgery? A meta-analysis of randomized, placebo-controlled trials. *Chin Med J (Engl)* 2017; **130**: 1707–14
83. Leslie K, Myles PS, Chan MTV, et al. Nitrous oxide and long-term morbidity and mortality in the ENIGMA trial. *Anesth Analg* 2011; **112**: 387–93
84. Yuan JL, Wang SK, Jiang T, Hu WL. Nitrous oxide induced subacute combined degeneration with longitudinally extensive myelopathy with inverted V-sign on spinal MRI: a case report and literature review. *BMC Neurol* 2017; **17**: 222
85. Myles PS, Leslie K, Chan MTV, et al. Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 2007; **107**: 221–31
86. Rao LK, Francis AM, Wilcox U, Miller JP, Nagele P. Preoperative B-vitamin infusion and prevention of nitrous oxide-induced homocysteine increase. *Anaesthesia* 2010; **65**: 710–5
87. Seaberg DC, Yealh DM, Ilkhanipour K. Effect of nitrous oxide analgesia on pneumothorax. *Acad Emerg Med* 1995; **2**: 287–92
88. Liang C, Lv Y, Shi Y, Cang J, Miao C. The fraction of nitrous oxide in oxygen for facilitating lung collapse during one-lung ventilation with double lumen tube. *BMC Anesthesiol* 2020; **20**: 180
89. Pfitzner J. Reasons for using nitrous oxide in one-lung ventilation, especially for thoracoscopic surgery. *Anaesth Intensive Care* 2019; **47**: 478–9
90. Leslie K, Myles P, Devereaux PJ, et al. Nitrous oxide and serious morbidity and mortality in the POISE trial. *Anesth Analg* 2013; **116**: 1034–40
91. Leslie K, Myles PS, Kasza J, et al. Nitrous oxide and serious long-term morbidity and mortality in the evaluation of nitrous oxide in the gas mixture for anaesthesia (ENIGMA)-II trial. *Anesthesiology* 2015; **123**: 1267–80
92. Tang F, Yue S, Luo Z, et al. Role of *N*-methyl-d-aspartate receptor in hyperoxia-induced lung injury. *Pediatr Pulmonol* 2005; **40**: 437–44
93. Shen L, Li L, She H, Yue S, Li C, Luo Z. Inhibition of pulmonary surfactants synthesis during *N*-methyl-d-aspartate-induced lung injury. *Basic Clin Pharmacol Toxicol* 2010; **107**: 751–7
94. Turan A, Mascha EJ, You J, et al. The association between nitrous oxide and postoperative mortality and morbidity after noncardiac surgery. *Anesth Analg* 2013; **116**: 1026–33
95. Takasaki M, Oh-Oka T, Saito Y, Kosaka Y. Low dose almitrine bismesylate improves pulmonary gas exchange during canine one-lung hypoxia. *Crit Care Med* 1989; **17**: 661–5
96. Moutafis M, Liu N, Dalibon N, et al. The effects of inhaled nitric oxide and its combination with intravenous almitrine on PaO2 during one-lung ventilation in patients undergoing thoracoscopic procedures. *Anesth Analg* 1997; **85**: 1130–5
97. Bouche P, Lacomblez L, Leger JM, et al. Peripheral neuropathies during treatment with almitrine: report of 46 cases. *J Neurol* 1989; **236**: 29–33
98. Bao N, Tang B. Organ-protective effects and the underlying mechanism of dexmedetomidine. *Mediators Inflamm* 2020; **2020**, 6136105
99. Chen C, Zhang Z, Chen K, Zhang F, Peng M, Wang Y. Dexmedetomidine regulates inflammatory molecules contributing to ventilator-induced lung injury in dogs. *J Surg Res* 2014; **187**: 211–8
100. Wang J, Yi X, Jiang L, et al. Protective effects of dexmedetomidine on lung in rats with one-lung ventilation. *Exp Ther Med* 2019; **17**: 187–92
101. De Cassai A, Sella N, Geraldini F, et al. Preoperative Dexmedetomidine and intraoperative bradycardia in laparoscopic cholecystectomy: meta-analysis with trial sequential analysis. *Korean J Anesthesiol* 2022; **75**: 245–54
102. Dernaika TA, Beavin M, Kinasewitz GT. Iloprost improves gas exchange and exercise tolerance in patients with

pulmonary hypertension and chronic obstructive pulmonary disease. *Respiration* 2010; **79**: 377–82
103. Rimeika D, Sanchez-Crespo A, Nyren S, Lindahl SGE, Wiklund CU. Iloprost inhalation redistributes pulmonary perfusion and decreases arterial oxygenation in healthy volunteers. *Acta Anaesthesiol Scand* 2009; **53**: 1158–66
104. NCT03936140. *The effect of iloprost on oxygenation during one-lung ventilation for lung surgery*. Available from: https://clinicaltrialsgov/show/NCT03936140; 2019
105. NCT04583046. *Effects of iloprost on pulmonary oxygenation in obese patients during one-lung ventilation*. Available from: https://clinicaltrialsgov/show/NCT04583046; 2020
106. NCT04927039. *Effects of iloprost on oxygenation during one-lung ventilation in supine-positioned patients*. Available from: https://clinicaltrials.gov/ct2/show/NCT04927039; 2021
107. Módolo NS, Módolo MP, Marton MA, et al. Intravenous versus inhalation anaesthesia for one-lung ventilation. *Cochrane Database Syst Rev* 2013; **2013**: CD006313
108. Schilling T, Kozian A, Senturk M, et al. Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. *Anesthesiology* 2011; **115**: 65–74
109. Chappell D, Heindl B, Jacob M, et al. Sevoflurane reduces leukocyte and platelet adhesion after ischemia-reperfusion by protecting the endothelial glycocalyx. *Anesthesiology* 2011; **115**: 483–91
110. Li X-Q, Tan W-F, Wang J, Fang B, Ma H. The effects of thoracic epidural analgesia on oxygenation and pulmonary shunt fraction during one-lung ventilation: a meta-analysis. *BMC Anesthesiol* 2015; **15**: 166
111. Ishikawa S, Lohser J. One-lung ventilation and arterial oxygenation. *Curr Opin Anaesthesiol* 2011; **24**: 24–31
112. Okuda J, Suzuki T, Wakaizumi K, Kato J, Yamada T, Morisaki H. Effects of thoracic epidural anesthesia on systemic and local inflammatory responses in patients undergoing lung cancer surgery: a randomized controlled trial. *J Cardiothorac Vasc Anesth* 2022; **36**: 1380–6
113. Defosse J, Schieren M, Loop T, et al. Current practice of thoracic anaesthesia in Europe — a survey by the European Society of Anaesthesiology: Part I — airway management and regional anaesthesia techniques. *BMC Anesthesiol* 2021; **21**: 266
114. Eldawlatly A, Turkistani A, Shelley B, et al. Anesthesia for thoracic surgery: a survey of middle eastern practice. *Saudi J Anaesth* 2012; **6**: 192–6
115. Huang L, Kehlet H, Petersen RH. Reasons for staying in hospital after video-assisted thoracoscopic surgery lobectomy. *BJS Open* 2022; **6**. zrac050
116. Higgins J, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions. Version 6.3* (updated February 2022). 6.3 ed. Cochrane Collaboration; 2022

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