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A systematic review of the incidence and risk factors for post-operative atrial fibrillation following general surgery.

Systematic review of postoperative atrial fibrillation.

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Summary

Atrial fibrillation is a common cardiac arrhythmia and can occur *de novo* following a surgical procedure. It is associated with an increased inpatient and long-term mortality. There is limited evidence reporting new-onset atrial fibrillation following abdominal surgery. This study aimed to identify the prevalence of and risk factors for post-operative atrial fibrillation in the general surgical population.

A systematic search of the EMBASE, MEDLINE and Cochrane (CENTRAL) databases was conducted, and the study was reported in line with PRISMA guidelines. Studies included if they reported cases of new-onset atrial fibrillation within 30 days of the index operation. Results were evaluated qualitatively due to substantial clinical heterogeneity. Incidence rates were pooled using a weighted random-effects meta-analysis model.

A total of 835 records were initially identified, from which 32 full texts were retrieved. Following review, 13 studies were included involving 52 959 patients, of whom 10.94% (95% confidence interval 7.22 to 15.33%) developed atrial fibrillation. Five studies of patients undergoing oesophagectomies (n = 376/1 923) had a weighted average rate of 17.66% (95% confidence interval 12.16 to 21.47%), compared to 7.63% (95% confidence interval 4.39 to 11.98%) from eight studies of non-oesophageal surgery (n = 2 927/ 51 036). Identified risk factors included increasing age, history of cardiac disease, and post-operative complications, particularly sepsis, pneumonia and pleural effusions.

New-onset post-operative atrial fibrillation is common, and is more frequent in surgery involving the thorax. Future work should focus on stratifying risk to allow targeted prophylaxis of atrial fibrillation and other peri-operative complications.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the UK with a prevalence of 2.47% in men and 1.56% in women, and an estimated 1.1 million people living with the disease [1]. In the general population, it is associated with increased mortality and secondary thromboembolic events, increasing the risk of cerebrovascular accidents (CVA) by two to five times in periods up to 20 years [2,3].

Post-operative AF is a well-documented complication following cardiac surgery, affecting 16-30% of patients [4–7]. The pathophysiology of post-operative AF is poorly understood, however it is thought an inflammatory post-operative response triggers disorganised electrical activity within atrial myocytes. Patients may also have a predisposition to atrial fibrillation, increasing their risk [8–10]. Post-operative AF after cardiac surgery is independently associated with in-hospital mortality (absolute risk increase: 3%) [6,7], future recurrence of AF episodes [4,11], and long-term mortality (absolute risk increase: 5%)[6,7]. The literature is largely focussed on post-operative AF following cardiac surgery with many cohort, prognostic and preventative studies in this field [4,5,11,12]. Comparatively, there are few studies reporting post-operative AF in the general surgical population, particularly in relation to surgery within the abdomen or along the gastrointestinal tract.

The prevalence of AF has increased over the last decade, in part as a result of ageing populations [13]. Furthermore, the surgical population is ageing with an associated increase in morbidity and mortality [14,15]. Consequently, post-operative AF is likely to become an increasing problem for those involved in peri-operative care in the future. It is therefore important to characterise those at risk of post-operative AF to prevent subsequent complications and understand the risks associated with post-operative AF. This would also underpin future work including randomised trials and other interventional research aimed at preventing post-operative AF.

The primary aim of this study was to identify the incidence of new-onset AF following general surgery. The secondary aim of this study was to ascertain the risk factors for the development of new-onset post-operative AF and the associated outcomes (mortality and thromboembolic disease).

Methods

This review was conducted to a protocol *a-priori* and was registered on the PROSPERO database (CRD 42016040170). Both the Meta-Analysis of Observational Studies in Epidemiology (MOOSE), and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report the findings of this study [16,17].

Included studies reported cases of new-onset post-operative AF after abdominal surgery. Cases with a history of AF were excluded. Post-operative AF was defined as occurring within 30 days post-operatively, and diagnosed on an electrocardiogram (one-off or 24-hour recording). Post-operative AF could be paroxysmal or persistent. If a randomised controlled trial was performed for the prevention of post-operative AF, only the incidence of AF in the control arm was included. Studies without explicit reporting of post-operative AF, for example group reporting of cardiac dysrhythmias, were excluded. All studies where the data could not be used to contribute to the primary outcome were excluded, as well as studies in a cardiac surgery setting or in treatment groups where an intervention had been used for the prevention of post-operative AF. Case reports, case series and any other studies reporting non-consecutive patient populations were excluded. Publications that were abstracts or conference proceedings only were excluded as they were not deemed to have undergone peer review worthy of data quality assurance. Non-English language studies were excluded due to resource limitations.

We searched the EMBASE, MEDLINE, CENTRAL and Cochrane (CENTRAL) databases according to a pre-defined systematic search strategy. The following text word search terms, medical subject headings and operators were used: 'atrial fibrillation' OR 'AF' OR 'atrial flutter' OR 'atrial arrhythmia' OR 'supraventricular arrhythmia' OR exp atrial fibrillation/ AND 'postoperative care' OR 'postoperative complication' OR 'complication' OR 'postoperative' OR exp postoperative complications/ OR 'surgical procedure' OR 'surgery' OR 'operation' OR 'operative' OR 'interventional' OR 'non-cardiac surgery' OR 'general surgery' OR exp surgery/. The search was run on 11th May 2016. There were no limits applied. The search was duplicated by two authors to ensure identical results.

Using an online systematic review tool (www.covidence.org), five authors screened the abstracts of the studies included in the initial search. Following this, the full texts for the included studies were retrieved and screened by authors for potential inclusion within the study. Each abstract and full paper was independently assessed by two reviewers. Conflicts between reviewers were resolved through discussion with authors JW and ML.

The bibliographies of included studies were hand-searched for additional relevant studies.

A data collection proforma was designed *a priori* with desired data fields. Data was extracted from included studies independently by authors RC and EH, and any conflicts in the data were resolved by authors RC, EH and ML.

Data were collected on the following: study details, pre-operative, operative and post-operative factors. Study details included: author, year of publication, study design, eligibility criteria and number of patients. Pre-operative data included: age, gender and drug, cardiovascular, general medical and surgical histories. History of AF, cerebrovascular events, myocardial infarction, hypertension and cardiac failure were also recorded. Operative data included: anaesthetic type, blood loss, operation duration and intra-operative drugs and electrocardiogram (ECG) recording used, as well as intra-operative complications and post-operative care location. Post-operative data included: inpatient stay, reoperation rate, post-operative complications, mortality and quality of life. Specific post-operative complications recorded were infections and thromboembolic, cerebrovascular and cardiovascular events. The definition, ECG findings, timing, type and presence of symptoms with regards to AF were recorded.

The primary outcome was to identify the rate of post-operative AF following general surgical operations. Post-operative AF was defined as AF identified on electrocardiogram (one-off or 24-hour recording) within 30 days post-operatively, without previous history of AF. There was no fixed ECG definition, and AF could be paroxysmal or persistent, symptomatic or asymptomatic.

Secondary outcomes were the: proportion of symptomatic post-operative AF, risk factors for post-operative AF and re-operation rate, mortality rate and quality of life of those diagnosed with post-operative AF. Risk factors were defined using odds ratios (OR) or hazard ratios with confidence intervals.

Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool [18]. This is a risk of bias tool specifically designed for assessing bias in studies reporting prognostic factors. Authors RC and EH independently evaluated the risk of bias in each included study using the tool, and conflicts were resolved by ML.

Where studies were suitably clinically homogeneous, it was intended that estimates of post-operative AF incidence would be pooled to calculate an overall incidence rate presented per 100 patients undergoing a procedure (per cent), alongside a corresponding 95% confidence interval. Where enough adequately sized studies were performed, incidence data were pooled using random effects models to account for inter-study variation across study populations and provide an estimate of incidence. If studies were not judged to be adequately homogeneous a literature synthesis would be performed, calculating an overall incidence rate using a pooled model would not take into consideration differences across study populations, but would serve to provide a descriptive statistic of incidence.

Results

A total of 835 records were identified, of which 32 full text articles were screened and 13 studies were eligible for inclusion. Reasons for study exclusion can be seen in the PRISMA flow diagram (figure 1). Ten retrospective cohort studies, two prospective observational studies, and one randomised controlled trial were included. Studies were mostly conducted in the USA, and five studies reported data exclusively from oesophagectomy cohorts. A summary of the characteristics of the included studies can be seen in table 1.

Risk of bias was assessed for each study by two authors (table 2). Included studies had a low risk of bias for study participation and attrition where they were continuous cohort studies with complete follow-up. There was a moderate risk of bias in prognostic factor measurement and moderate to high risk of bias in confounding factor measurement as these factors were often poorly defined and measured. There was a moderate to high risk of bias in outcome measurement as post-operative AF was usually identified by symptomatic assessment only, and post-operative screening of all patients was rarely performed. There was a low to moderate risk of bias in statistical analysis where multivariate analyses were conducted. Bias was not assessed in studies where statistical analysis of prognostic factors was not performed.

In total 52 959 patients were included, of whom 3 303 patients developed post-operative AF. Using an epidemiological random effects model, pooled incidence of post-operative

AF was calculated as 10.94% (95% confidence interval 7.22 to 15.33%). Individual studies rarely differentiated between symptomatic and asymptomatic post-operative AF.

The POAF rate of each study is displayed in table 1 and figure 2. For studies exclusively reporting data from oesophagectomy cohorts, the pooled incidence was also calculated separately due to their high representation in the included studies and likely thoracic component to the operation. Five studies of patients undergoing oesophagectomies (n with AF = 376/1 923) had a weighted average rate of 17.66% (95% confidence interval 12.16 to 21.47%), compared to 7.63% (95% confidence interval 4.39 to 11.98%) from eight studies of non-oesophageal surgery (n with AF = 2 927/ 51 036).

The estimated pooled incidence of post-operative AF was also compared between studies with a high risk of bias and those without. Six studies (n with AF = 2 859/ 50 223) with a high risk of bias reported a weighted average post-operative AF rate of 6.93% (95% confidence interval 3.69 to 11.36%), compared to 15.09% (95% confidence interval 9.58 to 20.19%) of seven studies (n = 444/ 2 736) without a high risk of bias.
Many studies reported that patient age significantly increased the risk of developing POAF [19–22]. Using logistic regression, Kazaure *et al* found that the odds of post-operative AF increased with age by OR 2.08 (95% confidence interval 1.84 to 2.35) at ages 65-74 years to OR 3.56 (95% confidence interval 3.08 to 4.12) at ages ≥85 years [20]. History of cardiac disease was often associated with a significant risk of post-operative AF, specifically congestive cardiac failure (OR 1.64, 95% confidence interval 1.49 to 1.86) [20] and hypertension (OR 3.66) [23,24], although not all studies reported

a significant relationship [19,22,23,25]. One study reported that a history of thyroid disease was associated with post-operative AF (OR 6.29, 95% confidence interval 1.54 to 25.65) [19]. On multivariate analysis, Kazaure *et al* found that non-white race and female sex were associated with a lower risk of post-operative AF (OR 0.68, 95% confidence interval 0.62 to 0.75; OR 0.79, 95% confidence interval 0.73 to 0.86) [20]. Where assessed, smoking was not associated with an increased risk of post-operative AF [19,21].

The incidence of post-operative AF may be associated with different surgical approaches, especially operations which involve the thoracic cavity as well as the abdominal cavity [19]. Sui *et al* found that an open abdominal approach increased the risk of post-operative AF versus laparoscopic techniques (OR 3.30, 95% confidence interval 1.30 to 8.00) [25], however this was not always corroborated [19]. Ojima *et al* reported that an operation lasting longer than 600 minutes increased the risk of post-operative AF (OR 1.38, 95% confidence interval 0.30 to 6.48) [23].

The development of post-operative complications had a consistent positive association with post-operative AF [19–21,24,26]. Kazaure *et al* reported that developing greater than one post-operative complication increased the risk of developing post-operative AF (OR 4.12, 95% confidence interval 4.12 to 4.93) [20]. Pulmonary complications, such as pneumonia (OR 5.92) and pleural effusions (OR 3.03, 95% confidence interval 1.77 to 5.17) were most frequently associated with post-operative AF [21,26]. Sepsis was associated with POAF in all cases in one study [27]. Electrolyte abnormalities, such as hypokalaemia, were also found to be significantly associated with an increased rate of post-operative AF (OR 1.41, 95% confidence interval 1.26 to 1.57) [20] However, after multivariate analysis, Walsh *et al* found that there was no increase in the rate of post-operative AF with the development of all post-operative complications [24].

The all-cause mortality and thromboembolic rates varied between studies, and could not be quantitatively analysed. In their large coding study Kazaure et al. found statistically significant higher rates of thromboembolic events (2.40% vs 0.50%) and stroke (0.30% vs 0.10%) for those with post-operative AF. Furthermore, they found those with post-operative AF independently had doubled odds of mortality (OR 2.00, 95% confidence interval 1.70 to 2.40) [20].

Some studies also found statistically significant higher rates (n mortality = 17/209 vs 38/788) [22] and odds (OR 1.46, 95% confidence interval 1.04 to 1.05) [28] of mortality up to 6 months postoperatively for those with post-operative AF. Conversely, other studies found no significant difference in thromboembolic event (n event = 12/209 vs 16/788; 1/96 vs 2/377) [21,22] and mortality (n mortality = 2/25 vs 17/538; 2/96 vs 7/377) [21,25] rates for those with and without post-operative AF. Re-operation rate and quality of life were poorly reported. Not reporting important outcomes may be considered as a form of reporting bias.

Discussion

We have presented a systematic review of the rate of diagnosis and risk factors for new onset post-operative AF in general surgery, and found that 10.94% of patients are diagnosed with post-operative AF. This figure is lower than the incidence of 16-30% reported in cardiothoracic surgery, a field in which the aetiology, incidence, prevention and management of post-operative AF are well characterised [4,5,11,12].

The incidence of post-operative AF was the primary outcome in eleven studies and the secondary outcome in two other studies. Definitions for the diagnosis of post-operative AF were poorly defined throughout the studies, with little concordance across studies. In the studies which did define post-operative AF, the most commonly used definition was a new onset irregularly irregular rhythm without discernible P waves on any ECG tracing, occurring in a patient with no prior diagnosis of AF [26]. However, there was substantial heterogeneity in the frequency and type of ECG monitoring used. A summary of these definitions can be found in table 3.

The study populations also varied, with five studies reporting results following oesophageal surgery [19,21–23,26]. We note that those patients undergoing oesophagectomies are more likely to receive a diagnosis of post-operative AF. We hypothesised the increased rate of post-operative AF in these studies may be due to a thoracic component of the surgery leading to inflammation and mechanical disturbance of the pulmonary vasculature. Systemic factors such as activation of the sympathetic system, hypoxia leading to pulmonary vein vasoconstriction and electrolyte imbalance have been implicated in the pathophysiology of post-operative AF [29].

The operative approach for oesophagectomy varied between and within studies, particularly whether there was a thoracic component. All five studies reported no statistically significant difference between operative approach and post-operative AF rates. Only two studies directly studied the effect of a thoracic operative component on the post-operative AF rate. Comparing thoracic and non-thoracic oesophagectomies, one study found a similar rate of post-operative AF (n with AF = 150/743 (20.20%) vs 59/254 (23.20%)) [22], whilst another found a higher non-significantly different rate of POAF (n with AF = 37/134 (27.60%) vs 8/58 (13.80%)) [19].

Other confounding factors were rarely measured or considered, leading to a high risk of bias assessment. The definition and measurement of pre-operative AF was variable, with most studies not actively measuring for pre-operative AF beyond conducting a one-off ECG. Multivariate analyses were sparse, limiting inferential interpretation of the data. The level of evidence of the included studies was generally low, with few prospective studies, and only one randomised controlled trial.

Whilst we found the overall rate of diagnosis of post-operative AF to be 10.94%, this should be considered a conservative estimate, as we suspect that the incidence of post-operative AF is higher than this due to its paroxysmal course and the high risk of detection bias. Performance of intra-operative cardiac monitoring was reported in only one study (crude post-operative AF rate: 7.40%), although it is assumed that this is one situation where all patients have continuous monitoring [28]. In the post-operative setting, two studies used continuous cardiac monitoring for at least 72 hours post-operatively [22,23], and three studies reported conducting 'regular' ECGs [30–32], reporting a range of crude post-operative AF rates (8.80 to 21.00%). No studies followed up patients post-discharge with continuous ECG monitoring. Ambulatory monitoring is commonly used to screen for paroxysmal AF following a stroke or TIA. In this setting it has been shown that 7-day ambulatory monitoring, 24-hour ambulatory monitoring and a single ECG identify rates of paroxysmal AF of 5.70%, 5.00% and 2.70% respectively [33]. Therefore, it is likely that the studies included in this review mostly identified patients with symptomatic or clinical AF, but have not identified all patients with POAF, especially where it is asymptomatic.

Although all studies excluded patients with known pre-operative AF, not all studies screened patients pre-operatively for arrhythmias. Where pre-operative screening was performed it was with single ECGs, not extended periods of monitoring. Therefore, patients with pre-operative paroxysmal AF may have been included and been identified as those developing post-operative AF. The lack of definition, monitoring and precision in identifying both pre-operative and post-operative AF is a strong contributor to bias in most of the included studies. These studies report the incidence of post-operative AF as a discrete event. It is conceivable that some of these episodes were paroxysmal in nature, relating to underlying sepsis or electrolyte imbalance. Long term follow-up data with retesting is not available for patients from these studies, so it is not possible to describe the course or impact of post-operative AF.

None of the studies included in this review were designed for the reporting of prognostic factors and in two of our thirteen studies, the incidence of post-operative AF was not the primary outcome. As with many areas of surgical research, the majority of our included studies were observational. In this review, these are associated with a moderate to high level of intrinsic bias and have led to a high degree of heterogeneity in our results. Furthermore, the relationship between post-operative AF and other post-operative complications is difficult delineate. Surgical site infections and other post-operative infections are common following general surgery [34]. These can be sufficient to trigger an inflammatory response which can in turn herald the onset of AF in those susceptible [35].

To establish the true rate of post-operative AF it would be necessary to screen patients without a diagnosis of AF pre-operatively using ambulatory monitoring. Post-operatively it would be necessary to use extended periods of cardiac monitoring, preferably throughout the patients' inpatient stay. Advances in peri-operative monitoring, including recent interest in the use of wearable technologies that can track a patient's biometrics wirelessly, may also allow for monitoring for post-operative AF following discharge [36]. This would not only establish the true rate or post-operative AF, but would also allow prognostic factors to be reliably identified. Furthermore, there is a paucity of long-term data on the development of AF and its sequelae following surgery. A well-designed multicentre cohort study should be undertaken to clarify prognostic factors and facilitate risk stratification for developing post-operative AF.

Conclusion

Atrial fibrillation after abdominal surgery affects at least 1 in 10 patients in the early post-operative period, although it is not clear whether this arrhythmia is persistent or paroxysmal. The current evidence base has not robustly identified those at risk of this complication.

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Fig. 1 PRISMA flow diagram.

Fig.2 Bar chart displaying the rate of post-operative atrial fibrillation by operative type and study, and the overall weighted average calculated from all the studies.

Table 1 Characteristics of each study, including the rate of post-operative atrial fibrillation (POAF) identified.

First author	Year	Design	Type of surgery	Setting	Number of patients	Number of POAF cases	Raw POAF rate (%)
Batra	2001	Retrospective cohort, single centre	Colorectal	University Hospital, Salford, UK	226	20	8.8
Bender	1995	Retrospective cohort, single centre	General abdominal	University Hospital, Baltimore, USA	206	9	4.4
Kazaure	2015	Retrospective cohort, multicentre	General abdominal	California Inpatient Database, USA	46 716	2 679	5.7
Larson	2015	Retrospective cohort, multicentre	Partial nephrectomy	Multicentre database, USA	1 532	17	1.1
Lohani	2015	Retrospective cohort, single centre	Oesophagectomy	University Hospital, Creighton, USA	195	45	23.1
McCormack	2014	Prospective observational, single centre	Oesophagectomy	University Hospital, Dublin, Ireland	473	96	20.3
Ojima	2014	Retrospective cohort, single centre	Oesophagectomy	University Hospital, Wakayama, Japan	207	19	9.2
Rao	2012	Retrospective cohort, single centre	Oesophagectomy	University Hospital, Nottingham, UK	997	209	21.0
Siu	2005	Retrospective cohort, single centre	Colectomy	University Hospital, Hong Kong, China	563	25	4.4
Stawicki	2011	Retrospective cohort, single centre	Oesophagectomy	University Hospital, Ohio, USA	156	32	20.5
Walsh	2005	Prospective cohort, single centre	Colectomy	University Hospital, Upton, UK	51	7	13.7
Xia VW	2015	Retrospective cohort, single centre	Liver and renal transplant	University Hospital, Los Angeles, USA	1 387	102	7.4
Xia J	2014	Randomised controlled trial, single centre	General abdominal	University Hospital, Beijing, China	250	43	17.2

Table 2 Bias assessment results for each study and each domain using the Quality in Prognostic Studies (QUIPS) tool.

First author	Year	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Batra	2001	Low	Low	Mod	High	High	N/A
Bender	1995	Low	Low	Mod	High	High	N/A
Kazaure	2014	Low	Low	Mod	High	High	Low
Larson	2015	Low	Low	Low	High	High	N/A
Lohani	2015	Low	Low	Mod	Mod	Mod	Mod
McCormack	2014	Low	Low	Mod	Mod	Mod	Low
Ojima	2014	Mod	Low	Mod	Low	Low	Low
Rao	2012	Low	Low	Mod	Low	Mod	Low
Siu	2005	Low	Low	Mod	Mod	Mod	Mod
Stawicki	2011	Low	Low	Mod	Mod	Mod	Low
Walsh	2005	Mod	Low	Mod	Mod	High	N/A
Xia VW	2015	Low	Low	Mod	Mod	High	Mod
Xia J	2014	Low	Low	Low	Low	Low	Low

Each study was adjudged to be have a low (Low), moderate (Mod), high (High) or non-applicable (N/A) risk of bias from each domain of the QUIPS tool.

Table 3 The outcome type and definition of post-operative atrial fibrillation in each included study.

First Author	Year	Post-operative atrial fibrillation outcome type	Definition
Batra	2001	Primary	Not defined
Bender	1995	Primary	Not defined
Kazaure	2015	Primary	Clinical coding
Larson	2015	Secondary	Not defined
Lohani	2015	Primary	Electrocardiographical and clinical presence
McCormack	2014	Primary	Confirmed on 12-lead electrocardiogram
Ojima	2014	Primary	Sustained or repetitive arrhythmia documented by electrocardiogram that required antiarrhythmic therapy
Rao	2012	Primary	Confirmed on 12-lead electrocardiogram
Siu	2005	Primary	Sustained episodes documented by electrocardiogram which lasted >10mins during inpatient stay
Stawicki	2011	Primary	Irregularly irregular atrial rhythm without discernible P waves on any electrocardiogram tracing
Walsh	2005	Primary	Rhythm other than sinus on electrocardiogram
Xia VW	2015	Primary	Confirmed on electrocardiographic tracings, reports, and notes of anaesthetist, cardiologist and the intensive care team
Xia J	2014	Secondary	Episodes of atrial fibrillation that lasted >5min registered by the monitoring system on a rhythm strip or 12-lead electrocardiogram

Competing interests

No authors have conflicts of interest to declare. This work was unfunded.