Received: 19 July 2022 | Revised: 9 September 2022 | Accepted: 29 September 2022

DOI: 10.1111/anec.13013

ORIGINAL ARTICLE

WILEY

The influence of sex on early post-operative atrial fibrillation after cardiac surgery

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Abstract

Background: Early post-operative atrial fibrillation (EPOAF) occurs more frequently in male (M) patients. However, most patients included in EPOAF studies were also M. The aim of the present study was to compare, in a matched M and F population, the occurrence of EPOAF episodes and EPOAF characteristics using continuous rhythm monitoring (CRM) during the first five post-operative days.

Methods: Our study population consisted of 30 F patients matched with 30 M patients admitted for elective cardiac surgery. After cardiac surgery, patients were continuously monitored for a maximum of 5 days, and the burden of EPOAF episodes was quantified.

Results: No significant differences in the onset, number, burden, total duration, shortest, median and longest EPOAF episode were detected between M and F patients. However, EPOAF occurred more frequently on the third post-operative day (F: 16 vs. M: 7; $p = .013$).

Conclusions: Except for the occurrence of the EPOAF on the third post-operative day. EPOAF characteristics did not differ between M and F patients.

KEYWORDS
post-operative atrial fibrillation, sex differences, rhythm monitoring

It is commonly known that the occurrence of atrial fibrillation (AF) is higher in males (M) than in females (F) and that early post-operative AF (EPOAF) occurs more frequently in M patients after cardiac surgery (Heeringa et al., 2006; Kavousi, 2020; Schnabel et al., 2015). However, the majority of patients included in EPOAF studies consisted of M patients (65%–88%) (Mathew et al., 2004; Shen et al., 2011; Zacharias et al., 2005; Zaman et al., 2000). In only one study so far, sex differences in EPOAF were reported in an almost equal number M and F patients. In 379 patients (M: 48.8%) who underwent aortic valve surgery, no difference in the EPOAF prevalence was detected between M and F patients. However, cardiac rhythm was continuously monitored only for the first 48 h after surgery (Fragão-Marques et al., 2020). In a recent study, M with F patients who underwent electro-anatomical mapping were compared during the first pulmonary vein isolation procedure. F patients had significantly more advanced left atrial remodeling compared to M patients (Wong et al., 2022). These outcomes suggest a difference in the atrial substrate between M and F patients that may influence the occurrence and characteristics of EPOAF, including the number and duration of EPOAF episodes, which to our knowledge has not been investigated previously.

The aim of the present study was therefore to compare the occurrence of EPOAF episodes and EPOAF characteristics in a matched M

and F population, in whom rhythm was continuously monitored for a maximum period of 5 days after cardiac surgery.

1 | METHODS

1.1 | Study population

Our study population consisted of a total of 60 patients that were admitted for elective cardiac surgery for isolated aortic valve disease (AVD, 26.7%), mitral valve disease (MVD, 13.3%), correction of congenital heart defects (CHD, 6.7%), coronary artery disease (CAD, 23.3%), either isolated or in combination with aortic valve disease (CAD + AVD, 10%) or mitral valve disease (CAD + MVD, 20%). Patients were excluded if they had pre-operative AF, prior ablation of atrial tachyarrhythmia's, severe renal failure, an atrial pacing device or required inotropic support. A total of 30 M and 30 F patients were matched based on common risk factors for AF, including underlying heart disease, left atrial dimension and age. Data on cardiovascular risk profiles were extracted from electronic patient files. Left atrial dimensions were divided into dilated and non-dilated atria, using a cut-off value of 34 ml/m^2/LA >45 mm (Lang et al., 2015).

After cardiac surgery, a beta blocker was administered for a maximum of 3 days and when AF occurred, antiarrhythmic drugs were prescribed (Table 1). Patients were continuously monitored for a maximum of 5 days for the detection of EPOAF episodes by using Draeger Infinity™ monitors. Collected rhythm registrations (CPZ files) were converted into. ECG files and analyzed in MATLAB. Onset and ending of AF episodes were automatically detected. To eliminate false positive AF episodes, all AF episodes were manually checked by two blinded operators.

1.2 | EPOAF characteristics

EPOAF was defined as an atrial rhythm with absent P-waves and irregular RR intervals (Hindricks et al., 2021). EPOAF episodes detected during CRM lasting 15 s or more were included. For every patient, the burden of EPOAF episodes was quantified during the first 5 days after cardiac surgery which was defined as the ratio between the total duration of all AF episodes and the total recording time (AF Burden = total time in AF in minutes/recording time in minutes * 100). AF occurrence is defined as AF episodes starting within 24 h (an AF episode can start in the first window of 24 h, and continue in the next window of 24 h, resulting in an occurrence in both windows of 24 h).

1.3 | Statistical analysis

Using the IBM SPSS Statistics 24 software, statistical analysis was performed. A propensity score matching analysis was performed, using logistic regression, based on age, underlying heart disease and left atrial dimension. The (nearest) neighboring propensity score with a match tolerance of 0.05, determined the randomly assignment of cases to the controls. All data were tested for normality using the Shapiro-Wilk Test. When normally distributed, data is depicted as mean ± standard deviation, whereas skewed data is depicted as median and interquartile range. For related normally distributed variables, a paired *T*-test was used, whereas for related abnormally distributed variables the Wilcoxon Test was used. Dichotomous variables were tested using Mc Nemar test. Ordinal variables were tested using Chi Square test or Fishers Exact test. A two-sided *p*-value of <.05 was considered statistically significant.

2 | RESULTS

2.1 | Study population

The study population consisted of 30 M and 30 F patients without a history of atrial tachyarrhythmias. As demonstrated in Table 1, there were no differences in baseline characteristics between M and F patients, except for a higher prevalence of dyslipidemia in F patients (F: 10 vs. M: 4, $p = .031$).

2.2 | Timing of de novo EPOAF episodes

The majority of both M (82.9%) and F (83.3%) patients had the initial EPOAF episode within the first three post-operative days, and there was no difference in the timing of EPOAF onset ($p > .05$) (Figure 1).

2.3 | Characteristics and occurrence of EPOAF

In the entire study population, a total number of 123 EPOAF episodes were recorded. The number of EPOAF episodes were comparable between M and F patients, respectively 59 (1–14) vs. 64 (1–7) episodes ($p > .05$). Table 2 shows the number of patients who had multiple EPOAF episodes and the number of EPOAF episodes for each day separately. The number of patients who had multiple EPOAF episodes did not differ between M and F patients (8 M vs. 10 F; $p = .05$, Table 2). However, when comparing the occurrence of EPOAF for each post-operative day separately, EPOAF was more often detected on the third day after surgery in F patients (16F vs. 7 M; $p = .013$, Figure 2).

Nonetheless, there was no difference in the total duration (minutes) of all EPOAF episodes between both groups (M: 599 (61–1143) versus F: 375 (58–1050), $p > .05$ (Figure 3)).

The median of all EPOAF episodes durations (minutes) in the entire population was 279 (43–651) and was similar for M and F patients (M: 315 (33–728) versus 180 (48–396), respectively, $p > .05$ (Figure 4)). The overall shortest EPOAF episode lasted 15 s in F patients, whereas the overall shortest EPOAF episode detected in M patients lasted 50 s. However, the median shortest EPOAF episode

TABLE 1 Patient characteristics

	M patients ($N = 30$)	F patients ($N = 30$)	p Value
Age (years)	71 ± 7 (55–84)	71 ± 8.9 (47–85)	.906
Risk factors, *N* (%)			
• Hypertension	10 (33.3)	17 (56.7)	.143
• Diabetes mellitus	15 (50)	9 (30)	.146
• Dyslipidemia	4 (13.3)	10 (33.3)	.031
• BMI	27 (IQR 4.9)	26 (IQR 6.5)	.614
Left ventricular function			.490
• Normal (EF >55%)	23 (76.7)	19 (63.3)	
• Mild impairment (EF 46%–55%)	2 (6.7)	7 (23.3)	
• Moderate impairment (EF 36%–45%)	5 (16.7)	4 (13.3)	
• Severe impairment (EF <35%)	-	-	
AOX time (min.)	1.27 (IQR 1.05)	1.32 (IQR 1.12)	.697
Left atrial dilatation, *N* (%)	16 (53.3)	16 (53.3)	
Monitoring time (h)	87.64 (19.92)	89 (23.28)	.5
Stroke, *N* (%)	1 (0.3)	1 (0.3)	
Surgical procedure, *N* (%)			
• CABG	7 (23.3)	7 (23.3)	
• AVD	8 (26.7)	8 (26.7)	
• MVD	4 (13.3)	4 (13.3)	
• CABG + AVD	3 (10)	3 (10)	
• CABG + MVD	6 (20)	6 (20)	
• CHD	2 (6.7)	2 (6.7)	
Anti-arrhythmic drug usage pre- surgery, *N* (%)			
• None	10 (33.3)	12 (40)	
• Beta blocker	19 (63.3)	18 (60)	
• Amiodarone + beta	1 (3.3)	-	
• Blocker			.366
Anti-arrhythmic drug usage post-surgery, *N* (%)			.966
• None	6 (20)	5 (16.6)	
• Not available	7 (23.3)	5 (16.6)	
• Beta blocker	1 (3.3)	9 (30)	
• Amiodarone	2 (6.6)	1 (3.3)	
• Amiodarone + beta blocker	11 (36.6)	5 (16.6)	
• Digoxine	1 (3.3)	-	
• Beta blocker + digoxine	2 (6.6)	2 (6.6)	
• Amiodarone + beta blocker + digoxine	-	2 (6.6)	
• Sotalol	-	1	

Note: Statistically significant values: $p < .05$.

Abbreviations: AOX, aortic clamping time; AVD, aortic valve disease; BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; F, Female; M, Male; MVD, mitral valve disease.

(minutes) between both groups were comparable (median shortest EPOAF episode in M: 195 (17–673) versus F: 60 (26–368), $p > .05$) (Figure 5).

The overall longest episode in both M and F patients lasted for, respectively, 2547.6 and 5760 min. When comparing these longest episodes between M and F patients, differences were not found (M:

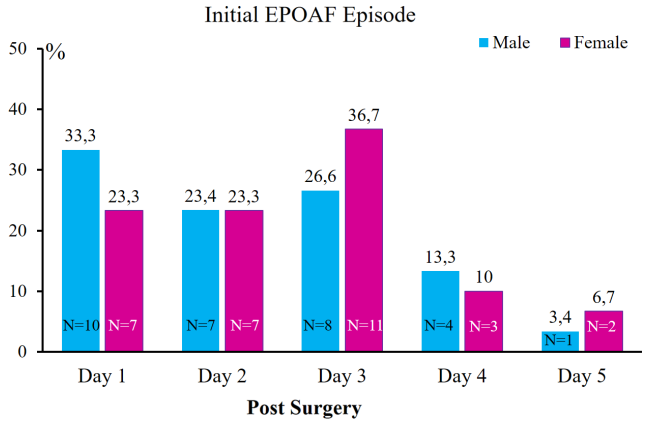

FIGURE 1 Bars demonstrating the timing of the initial EPOAF episode. Most EPOAF episodes occurred within the first 3 days after surgery and they did not differ between M and F patients (M: 82.9% vs. F: 83.3%, $p > .05$) (EPOAF: early post-operative atrial fibrillation, M: male, F: female).

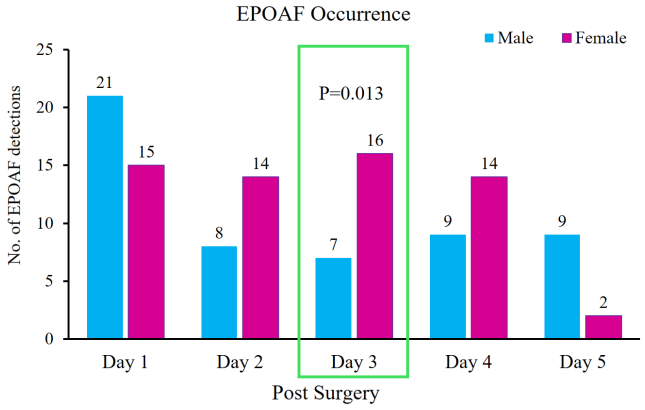

FIGURE 2 Bars demonstrating the daily occurrence of EPOAF for M and F patients separately. On the third day after surgery, EPOAF occurred more frequently in F patients ($p = .013$) (EPOAF: early post-operative atrial fibrillation, M: male, F: female)

TABLE 2 Number of AF episodes for each post-operative day in patients who had multiple AF episodes

Male patients ($N = 8$)					
No. of episodes per day:	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
1	***5***				
2			***1***	***1***	***1***
3		***2***			***1***
4	***2***		***1***	***1***	***1***
5				***1***	***1***
6			***1***	***1***	
7	***5***	***3***	***1***	***2***	***3***
8	***3***				
Female patients ($N = 10$)					
No. of episodes per day:	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
1	***1***	***1***	***1***	***1***	***1***
2		***1***		***1***	***1***
3		***1***	***1***	***1***	
4	***6***				
5	***3***				
6		***1***	***1***		
7			***1***		***2***
8			***1***	***3***	***2***
9	***2***		***2***	***1***	***1***
10		***7***			

The Bold values indicates $p < .05$.

345 (42–912) vs. F: 360 (58–758), $p > .05$; Figure 6). Consequently, the EPOAF burden was also similar in M and F patients; M patients had a 9.8% (1.3–22.7) burden versus 8% (1.4–18.9) in F patients ($p > .05$).

3 | DISCUSSION

In this study, we demonstrated that M and F patients did not differ in the onset, number, burden, median, shortest, longest, and total duration of EPOAF episodes. F patients, however, had a higher occurrence of EPOAF episodes on the third post-operative day. To our knowledge, this is the first study in which EPOAF characteristics during 5 days continuously monitoring were compared between matched between M and F patients.

3.1 | AF episodes in the general population

It is commonly known that, in the general population, there are sex differences in AF symptoms and therapeutic outcomes. F patients, for example, experience more symptoms, have a higher symptom burden, are more anxious, a lower quality of life and a higher mortality compared to M patients. F also differ from M in the underlying arrhythmogenic substrate; F have more extra pulmonary vein foci and differ from M in action membrane potentials (Kavousi, 2020; Linde et al., 2018; Weberndörfer et al., 2019). In addition, reports on sex differences in atrial remodeling (in patients undergoing an index pulmonary vein isolation procedure) showed that F patients had a lower mean global left atrial voltage, a higher proportion of left atrial fractionated signals and a slower mean global conduction velocity compared to M patients (Wong et al., 2022). These results suggest that M and F patients differ from each other in the underlying AF-related arrhythmogenic substrate which in turn may influence the occurrence and characteristics of EPOAF. It is however unknown whether M and F patients differ from each other in EPOAF characteristics after cardiac surgery. In our study, we therefore compared the number, burden, median, shortest, longest and total duration of EPOAF episodes in M and F patients and demonstrated that these EPOAF characteristics were comparable between M and F patients.

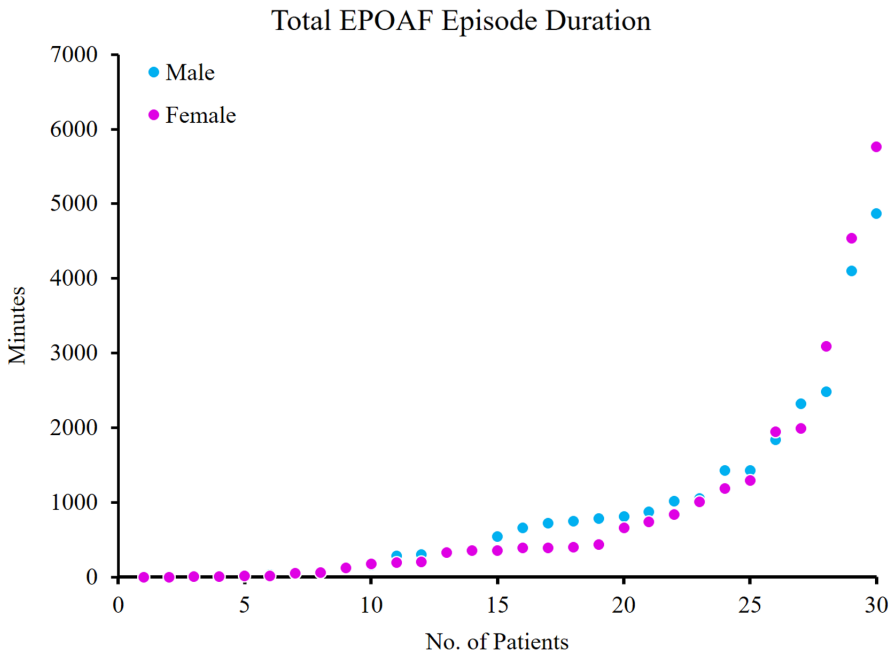

FIGURE 3 Graph demonstrating the total duration of EPOAF episodes for each individual M and F patient; there were no differences between M and F patients (EPOAF: early post-operative atrial fibrillation, M: male, F: female)

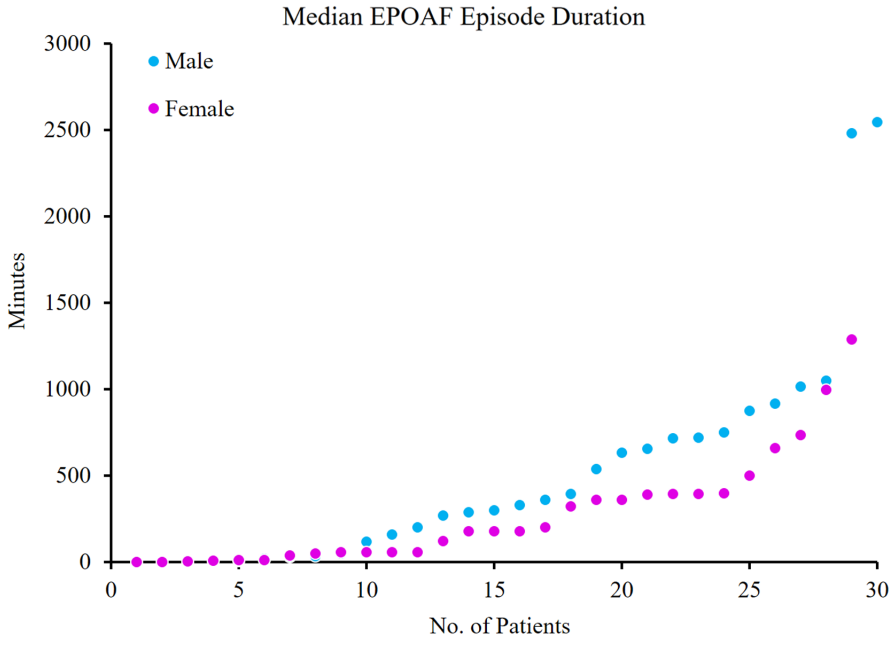

FIGURE 4 Median EPOAF duration is demonstrated for each individual M and F patient and did not differ between both sexes (EPOAF: early post-operative atrial fibrillation, M: male, F: female)

3.2 | EPOAF as a malignant complication

Since the last few decades, EPOAF has increasingly been recognized as a malignant complication after cardiac surgery associated with increased long term cardiovascular morbidity and mortality (Eikelboom et al., 2021).

One of the risk factors for developing EPOAF episodes after cardiac surgery is M sex which has been demonstrated in large cohorts ($N = 326–10,390$). Nonetheless, most patients in these cohorts were also M (65%–88%) (Mathew et al., ; Shen et al., 2011; Zacharias et al., 2005; Zaman et al., 2000). In our study, in which the number of M and F were similar, M and F EPOAF characteristics did not differ between M and F patients.

3.3 | EPOAF episode duration

In previous conducted studies, definitions of EPOAF episodes were not univocal. In one study, EPOAF episodes were included if the duration lasted 30 s on CRM or if they were recorded by 12 lead standard ECGs (if shorter than 30 s) (Fragão-Marques et al., 2020). However, in another study, EPOAF episodes were included if they

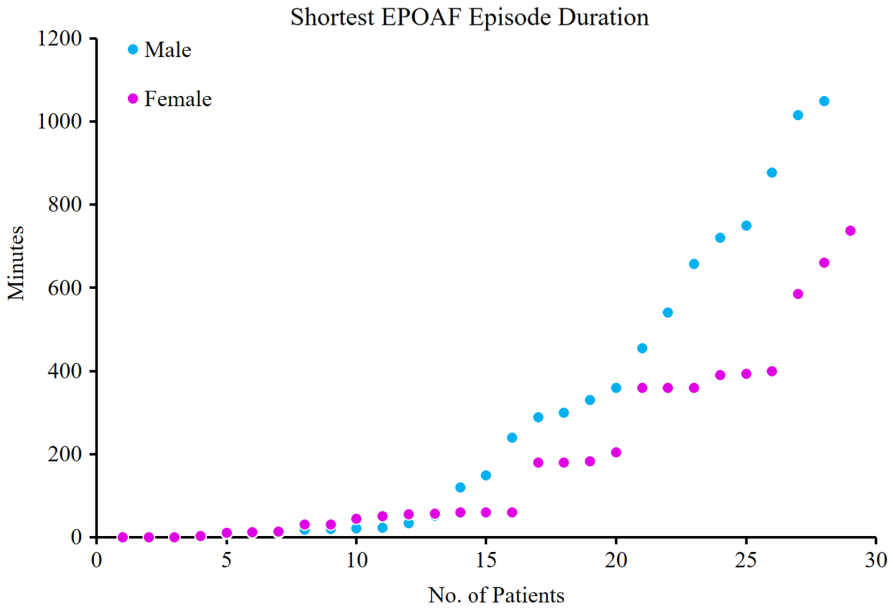

FIGURE 5 The shortest EPOAF episode is plotted for each individual M and F patient; these shortest durations between both groups were comparable (EPOAF: early post-operative atrial fibrillation, M: male, F: female)

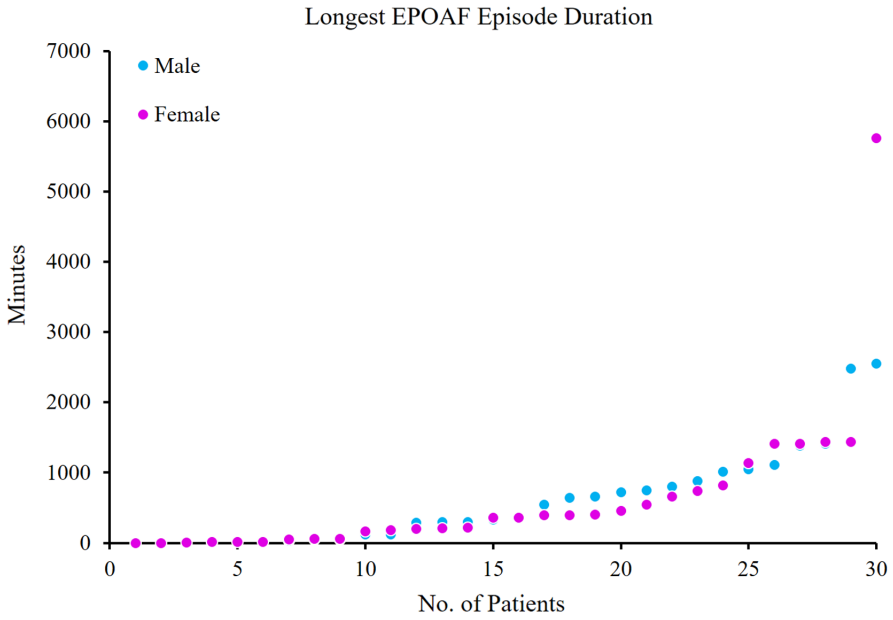

FIGURE 6 Graph demonstrating the longest EPOAF episode for each M and F patient individually which did not differ between both groups (EPOAF: early post-operative atrial fibrillation, M: male, F: female)

lasted >5 min (Auer et al., 2005). In some studies, a definition of EPOAF duration was not provided. (Shen et al., 2011; Zacharias et al., 2005). In our study, the definition for EPOAF episodes was based on the 2007 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation in which AF was defined as an arrhythmia lasting ≥30 s or if present, 10 s on the entire 12-lead standard ECG (Calkins et al., 2012). The shortest EPOAF episodes observed in our study lasted for 15 s in duration, which was also the shortest possible detectable episode.

3.4 | EPOAF occurrence

Early post-operative atrial fibrillation episodes typically occur between the second and fourth day after cardiac surgery, with a peak incidence on the second post-operative day whereas recurrences of EPOAF episodes typically occur on the third day after surgery (Maessen et al., 2012). The timing of the initial EPOAF episodes in our study is in line with these observations. However, when comparing the daily occurrence of EPOAF episodes, F patients had a higher number of EPOAF episodes on the third day after surgery.

4 | LIMITATIONS

Patients included in this study were mainly older patients who underwent cardiac surgery, and our results can therefore not be extrapolated to the general AF population. Another limitation of this study is the relative sample size, and our observations therefore need to be confirmed in a larger study population.

AUTHOR CONTRIBUTIONS

Danny Veen mostly contributed to the data collection, entire data analysis and interpretation of the ECG files, drafting the article, Corina Schram- Serban was involved in the analysis, and Natasja. M.S. de Groot contributed to the critical revision and approval of the article.

CONFLICT OF INTEREST

We state that this manuscript has not been submitted, nor is under consideration for publication elsewhere. All authors have made an important contribution to the manuscript, are familiar with the data, have read, and approved the manuscript. We did not receive financial support for completion of this manuscript, nor are there any conflicts of interest to report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This case control study was performed as part of two prospective observational projects including Quest for Arrhythmogenic Substrate of Atrial fibrillation (QUASAR, MEC 2010–054) and Hsf1 Activators Lower cardiomyocyte damage Towards a novel approach to REVERSE atrial fibrillation (HALT & REVERSE, MEC 2014–393). Approval of both projects was granted by the local ethics committee of the Erasmus Medical Centre and adhere to the Declaration of Helsinki principles; written informed consent was obtained from all participating patients before the surgical intervention.

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How to cite this article: Veen, D., Schram-Serban, C., & de Groot, N. M. S. (2022). The influence of sex on early post-operative atrial fibrillation after cardiac surgery. *Annals of Noninvasive Electrocardiology*, *00*, e13013. https://doi.org/10.1111/anec.13013