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Catecholamine Vasopressors and the Risk of Atrial Fibrillation After Noncardiac Surgery: A Prospective Observational Study

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Background: Catecholamine vasopressors are commonly used for intra- or post-operative hypotension for cardiac surgery, which have a side effect of new-onset atrial fibrillation (AF) and myocardial ischemia. However, it is not entirely clear whether catecholamine vasopressors increase the risk of new-onset AF after noncardiac surgery.

Aim: The aim of this study was to analyze the association between the use of catecholamine vasopressors and the risk of developing new-onset AF after noncardiac surgery.

Methods: In this prospective trial, available data from eligible elderly individuals receiving noncardiac surgery at a single center from November 2022 to January 2024 were gathered. Propensity score matching (PSM) was used to balance patient baseline characteristics and to control for confounders. To determine the association between catecholamine vasopressors and the risk of new-onset AF, univariate and multivariate logistic regression analyses were performed.

Results: A total of 6000 subjects were included in this study (mean [SD] age, 70.73 [6.37] years; 910 [50.9%] males). After PSM, the patients were stratified into catecholamine vasopressor (n = 357) and comparator groups (n = 1432). A total of 18/357 patients in the catecholamine vasopressor group developed AF, and 25/1432 patients in the comparator group developed AF (incidence rate, 5.0% vs 1.7%). Compared with the comparator group, the catecholamine vasopressor group had an increased risk of new-onset AF (aOR, 2.77; 95% CI, 1.28–5.89). Some sensitivity analyses also revealed consistent findings of increased new-onset AF risk associated with catecholamine vasopressor treatment.

Conclusion: The findings from this study suggest that catecholamine vasopressor treatment is associated with an increased risk of new-onset AF and may help physicians select a modest medication for patients while also assessing the risk of new-onset AF.

Keywords: catecholamine vasopressors, new-onset atrial fibrillation, risk, prospective trial, noncardiac procedures

Introduction

Atrial fibrillation (AF) after noncardiac procedures is common in acute arrhythmogenesis in adults[1] and has increased associations with the risk of mortality and stroke.[2] Catecholamine vasopressors are very commonly used for hypotension in the perioperative period; however, there are side effects associated with all catecholamines, including rhythm disturbances and myocardial ischemia.[3] Catecholamines are important for the electromechanical function of the heart. They regulate intracellular Ca^{2+} through β-adrenoceptor activation. An increase in the levels of catecholamines is arrhythmogenic and has been suggested to be a central component of the pathogenesis of AF after cardiac surgery.[4,5] Under intra- and postoperative conditions, catecholamine excess, inflammatory cytokines,[6] metabolic dysregulation, impaired metabolic balance and compromised myocardial energy[7] have been proposed to contribute to the development of AF after cardiac surgery.[8,9] Previous randomized controlled trials have shown a lower occurrence of AF in patients receiving vasopressin (63.8% vs 82.1%) than in patients receiving norepinephrine for the treatment of vasoplegic shock

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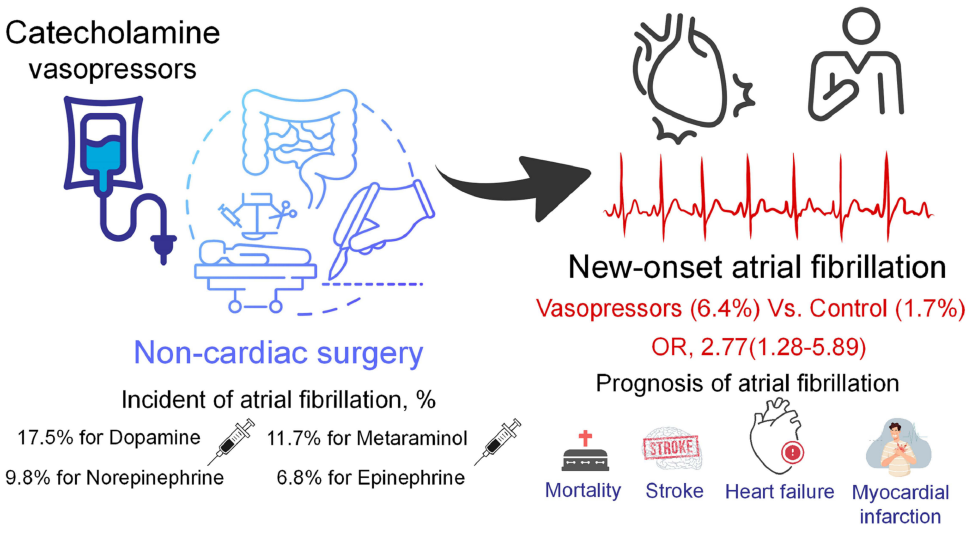
Graphical Abstract



after cardiac surgery.[10] There are more differences in pathophysiology between patients with AF after cardiac surgery and those with AF after noncardiac surgery. No association between catecholamine vasopressors and AF after noncardiac surgery has been found to date. The main objective of this trial was to determine whether catecholamine vasopressors could trigger new-onset AF after noncardiac surgery.

Materials and Methods

Study Cohort

In this prospective trial, data from eligible patients who underwent noncardiac surgery at a single center from November 2022 to January 2024 were collected. ECG and echocardiogram (cardiac echo) data, which are routinely obtained before procedures, were reviewed to identify preexisting arrhythmias and cardiac function deterioration. All noncardiac surgery patients who met the following additional exclusion criteria were excluded in the study: preexisting atrial fibrillation or atrial flutter, supraventricular tachycardia, missing ECG and echocardiogram data at baseline, hospital stay <3 days, age less than 65, and insufficient medical record data. Telephone follow-up was performed within 30 days of surgery by blinded personnel. The ethics Committee of the Sixth Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital) approved this trial (IRB-2022-141; IRB-2023-031), which was registered with the Chinese Clinical Trials Registry (Registration ID: ChiCTR2200065738; ChiCTR2300074253) before the subjects were enrolled. Approving ethics committee approved the written or oral informed consent that was obtained from all subjects. The work was reported in accordance with the STROCSS criteria.[11] The study complies with the Declaration of Helsinki.

Outcome and Exposure

The study's main endpoint was new-onset AF occurring within 30 days of a noncardiac procedure, defined as ECG-documented AF leading to angina pectoris, severe heart failure, or persistent hypotension or requiring treatment with measures such as rate-controlling drugs, antiarrhythmic drugs, or transthoracic electroconversion. We performed no electrocardiogram (ECG) screening for new-onset AF other than routine clinical monitoring, which involves noninvasive blood pressure (NIBP), resting heart rate, pulse rate, and blood oxygen saturation (SpO_2) within 24 h postoperatively. The recorded AF events were diagnosed by 2 independent expert physicians based on previous guidelines.[12]

Catecholamine vasopressors consist of at least any of the following: norepinephrine, epinephrine, dopamine, or metaraminol. Norepinephrine (2mg; GRAND PHARMA, China), or epinephrine (1mg; GRAND PHARMA, China),

were, respectively, mixed in identical 50-mL syringes of 5% dextrose in water, with final concentrations of 40 μg/mL in the norepinephrine, and 20 μg/mL in the epinephrine. Dopamine (20 mg; White Medicine Pharmaceutical, China) was mixed in identical 20-mL syringes of 0.9% sterile saline, with final concentrations of 400 μg/mL. Metaraminol (10 mg; YOOKON, China) was mixed in identical 20-mL syringes of 0.9% sterile saline, with final concentrations of 200 μg/mL. The drug infusion was initial at $5mL.h^{-1}$ and raised by $2.5mL.h^{-1}$ every 10 min during the first hour to obtain an optimal target rate of $30mL.h,^{-1}$ so that norepinephrine doses ranged from 0.05 to 0.4 μg/min/kg, epinephrine doses from 0.05 to 0.4 μg/min/kg, dopamine doses from 4 to 12 μg/min/kg, and metaraminol doses from 6 to 10 μg/min/kg.[13] In addition, the above concentrations can be optimally adjusted according to the actual intraoperative situation.

The catecholamine vasopressor infusion was intravenously pumping to maintain at least an mean arterial pressure (MAP) of 65 mmHg or systolic blood pressure (SBP) of 90 mmHg. When the targeted MAP or SBP was exceeded, any vasopressors were tapered over time. The vasopressor infusion was withdrawn or stopped if any of the following critical adverse outcomes emerged: acute ST-segment enhancement documented by a 12-lead ECG, serious or fatal arrhythmia, acute mesenteric ischaemia, or hyponatraemia.

Clinical Data Collected

The data for this study were collected prospectively. Covariates selected for adjustment were selected based on prior reports[14] (traditional AF risk factors as previously described) and included the following at the baseline examination with noncardiac procedures: age, male, general anaesthesia, ASA III–IV, emergency surgery, hypertension, diabetes, coronary artery disease (CAD), chronic kidney disease (CKD), stroke, sepsis, β-blocks, angiotensin converting enzyme inhibitors (ARB)/angiotensin II receptor blocker (ACEI), calcium channel blockers (CCB), antidiabetic agents, dexmedetomidine, abdominal surgery, thoracic surgery, vascular surgery, and neurointerventional surgery.

Sample Size

A prevalence of AF of approximately 2.5% in previous reports was used to calculate the sample size.[15] We anticipated enrolling approximately 1000 patients and detecting 20 patients with AF. With the C-statistic set at 0.8 and the number of candidate predictor parameters set at 21, the smallest sample size necessary to develop a model would be 5908 subjects, given an allowable difference of 0.05 in the apparent adjusted R2 and a margin of error of 0.05 in estimating the intercept.[16]

Propensity-Matching Analysis (PSM) and Sensitivity Analyses

PSM was performed to adjust for baseline differences and to evaluate potential confounding variables. First, a propensity score was calculated for each individual to assess the odds of being allocated to the catecholamine vasopressor group using multivariable logistic regression models based on all covariates listed in Table 1 and STable 1. A 1:4 propensity score for the catecholamine vasopressor and noncatecholamine vasopressor groups was then calculated.[17] The stability of our results was confirmed by several sensitivity analyses. First, in the sensitivity analysis (1:4 ratio), propensity score matching was used to adjust for confounders. The second propensity score method used to control for confounders was stabilized inverse probability of treatment weighting (IPTW).[18] Third, in the multivariate Cox analysis, we performed a sensitivity analysis, or by adjusting for different competing factors.

Statistical Analyses

Continuous variables are shown as the means (±SD) and were compared using the *t* test or Wilcoxon rank sum test based on the outcome of the Kolmogorov–Smirnov normality test. Skewed data is presented as median (IQR). Categorical variables are presented as frequencies (percentages) and were analyzed with the chi-squared test. To assess the relationship between the administration of catecholamine vasopressors and the risk of AF, univariable and multivariable adjusted logistic regressions were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). A two-tailed p value lower than 0.05 was regarded as indicating statistical power, and all statistical evaluations were carried out using SPSS version 25 (IBM) and R 4.2.1, which are based on the R Foundation.

Table 1 Baseline Characteristics of Catecholamine Vasopressors and Comparison Groups After Propensity Score Matching (1:4 Ratio)

	Overall n=1622	Vasopressor Group n = 323	Comparator Group n =1299	*P* value	SMD
Variable					
Age (mean (SD))	70.75 (6.63)	70.58 (6.53)	70.79 (6.65)	0.615	0.031
Male (%)	815 (50.2)	158 (48.9)	657 (50.6)	0.637	0.033
General anaesthesia (%)	1136 (70.0)	233 (72.1)	903 (69.5)	0.394	0.058
ASA III–IV(%)	626 (38.6)	130 (40.2)	496 (38.2)	0.536	0.042
Emergency surgery (%)	649 (40.0)	128 (39.6)	521 (40.1)	0.925	0.01
Comorbidity					
Hypertension (%)	533 (32.9)	114 (35.3)	419 (32.3)	0.33	0.064
Diabetes (%)	266 (16.4)	54 (16.7)	212 (16.3)	0.929	0.011
CAD (%)	147 (9.1)	27 (8.4)	120 (9.2)	0.701	0.031
CKD (%)	166 (10.2)	41 (12.7)	125 (9.6)	0.127	0.098
VVD (%)	81 (5.0)	13 (4.0)	68 (5.2)	0.453	0.058
Stroke (%)	100 (6.2)	24 (7.4)	76 (5.9)	0.354	0.063
Sepsis (%)	18 (1.1)	8 (2.5)	10 (0.8)	0.02	0.135
Medications					
β-blocks (%)	250 (15.4)	50 (15.5)	200 (15.4)	1	0.002
ARB/ACEI (%)	286 (17.6)	57 (17.6)	229 (17.6)	1	<0.001
CCB (%)	328 (20.2)	80 (24.8)	248 (19.1)	0.028	0.138
Antidiabetic agents (%)	560 (34.5)	116 (35.9)	444 (34.2)	0.602	0.036
Dexmedetomidine (%)	59 (3.6)	13 (4.0)	46 (3.5)	0.803	0.025
Types of surgery					
Abdominal surgery (%)	592 (36.5)	107 (33.1)	485 (37.3)	0.18	0.088
Thoracic surgery (%)	85 (5.2)	15 (4.6)	70 (5.4)	0.691	0.034
Vascular surgery (%)	104 (6.4)	19 (5.9)	85 (6.5)	0.759	0.027
Neurointerventional surgery (%)	44 (2.7)	16 (5.0)	28 (2.2)	0.01	0.152

Abbreviations: AF, atrial fibrillation; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Results

We collected data from November 2022 to January 2024, and a total of 6000 subjects were enrolled in the study. The exclusion criteria were as follows: <65 years (n = 19,035), length of stay <3 days (n = 10,756), missing electrocardiogram at baseline (n = 3315), missing medical records (n = 1025), and disagreement to participate in the study (n = 438) (Figure 1).

Patient Characteristics

A total of 6000 participants who had been exposed to catecholamine vasopressors were eligible for the trial (521 in the catecholamine vasopressor group and 5479 in the comparator group). The median (SD) age was 70.6 (6.4) years, and 61.4% were male. The majority of the baseline characteristics were similar between the two arms (STable 1). STable 2 presented the baseline characteristics in the new-onset AF and non AF groups.

After propensity score matching, 1622 patients (mean [SD] age, 70.7 [6.3] years; 815 [49.8%] females and 807 [50.2%] males) were enrolled 323 from the catecholamine vasopressor group and 1299 from the comparison group. There were standard differences for all covariates < 0.10, and all baseline features were well matched between the two groups (Table 1, STable 1 and SFigure 2). The flowchart of patient selection is presented in Figure 1.

Risk of developing new-onset AF

Twenty-one participants in the catecholamine vasopressor group developed AF, and 25 participants in the comparator group developed AF (incidence rates, 6.4 vs 1.7%). Catecholamine vasopressor treatment was associated with an increased risk of incident new-onset AF (adjusted OR, 2.77; 95% CI, 1.28–5.89; p=0.008) according to multivariate logistic regression models (Table 2).

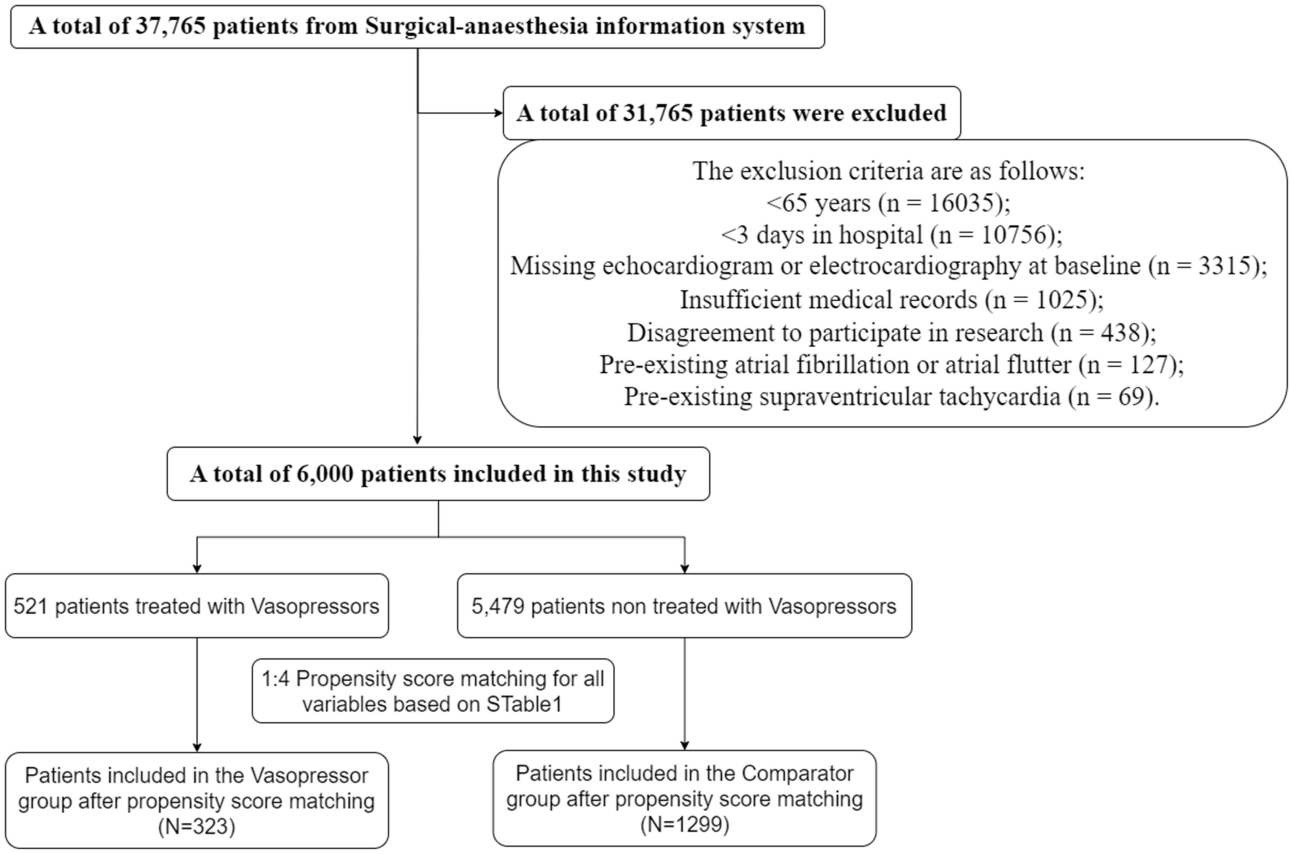


Figure 1 Flowchart of subject selection.

Sensitivity Analyses

The sensitivity analyses comprised multivariable logistic regressions without PSM (adjusted OR, 2.90; 95% CI, 1.68–4.91, $p<0.001$) and IPTW (adjusted OR, 1.37; 95% CI, 1.09–1.64, $p<0.001$) adjusted for various confounders, and the results were robust. The sensitivity analysis adjusted for left or right atrial hypertrophy as a competing risk factor also showed robust results (adjusted OR, 3.36; 95% CI, 1.88–5.89, $p<0.001$) (Table 3).

Subgroup and Interaction Analyses

SFigure 1 shows the Risk of new-onset AF development between Vasopressor and Comparator groups in the subgroup and interaction analyses.

Table 2 Risk of AF Development in the Catecholamine Vasopressors and Comparison Groups After Propensity Matching Score

	Catecholamine Vasopressors Group (n =323)	Comparator Group (n =1299)
AF event, No.	21	23
Incidence rate	6.4%	1.7%
Adjusted OR (95% CI)[a]	2.77(1.28–5.89)	1 [Reference]

Note: [a]Calculated using the multivariable logistic regression model.
Abbreviation: OR, odd ratio.

Table 3 Sensitivity Analyses to Assess the Risk of Af Development in the Catecholamine Vasopressors and Comparison Groups

	Adjusted OR (95% CI)	P value
Multivariable regression models without propensity score methods[b]		
Catecholamine vasopressors group	2.90 (1.68–4.91)	<0.001
Comparator group	1 (Reference)	
Stabilized IPTW[c]		
Catecholamine vasopressors group	1.37 (1.09–1.64)	<0.001
Comparator group	1 (Reference)	
Adjusted competing risks[d]		
Catecholamine vasopressors group	3.36(1.88–5.89)	<0.001
Comparator group	1 (Reference)	

Notes: [b]Calculated using the multivariable logistic regression model without the propensity score-matched population. [c]Using stabilized IPTW instead of propensity score matching to control for potential confounding effects. [d]Adjusted for the left and right atrial hypertrophy.

New-Onset AF and Adverse Outcomes

STable 4 demonstrated Univariate and multivariate logistic analysis between new-onset atrial fibrillation after non-cardiac surgery and postoperative adverse events.

Risk of Developing New-Onset AF and Various Vasopressor Drugs

STable 3 presented an incident of developing new-onset AF in the various vasopressor drugs.

Discussion

Overall, in this prospective cohort study, patients who received treatment with catecholamine vasopressors for noncardiac surgery had a significantly greater risk of developing postoperative AF than patients who did not receive catecholamine vasopressors, suggesting a potential association between catecholamine vasopressors and increased AF risk after noncardiac surgery. The robustness of the results is demonstrated by the fact that these findings were consistent with some sensitivity analyses.

Autonomic effects are crucial in the pathogenesis of both nonsurgical and cardiac surgical AF.[19] Postoperative use of dopamine has also previously been reported to increase the risk of AF after cardiac surgery,[20] and intraoperative renal-dose dopamine is associated with a 1.74 odds ratio of pAF developing after coronary artery bypass grafting (CABG) in the 1731 patients who underwent CABG.[21] In 330 randomized patients, Ludhmila et al suggested that norepinephrine may increase the risk of AF after cardiac surgery. These reports suggested the possible synergistic effects of catecholamine drugs and catecholamine hypersecretion on AF after cardiac surgery. Compared with the unique complex and multifactorial pathophysiology of AF after cardiac surgery, such as inflammation, surgery-related myocardial tissue injury (venous cannulation via right atriotomy or manipulation and suturing of the perivalvular atrial tissue in mitral and tricuspid surgery), myocardial ischemia due to extracorporeal circulation or the disease itself, or gene expression changes,[22] this pathophysiology of AF after noncardiac surgery may be more simple. Emerging evidence suggests that age, preoperative levels of natriuretic peptides, chronic obstructive pulmonary disease (COPD) and thoracic surgery are independent risk factors for this type of atrial fibrillation.[23] In addition, the incidence of AF varies in different contexts. Approximately 30% of cardiac surgery patients progress to postoperative AF, and the occurrence of AF after noncardiac and nonthoracic procedures ranges from 0.4% to 15%. [24,25] Several reports have suggested that intraoperative or postoperative activation of the sympathetic nervous system by nociceptive stimuli,[26] surgical trauma, pain,[27] and baseline comorbidities, including hypertension,[28] heart attack, and diabetes in noncardiac surgeries, are associated with cardiovascular events.[29] To date, the association between sympathetic activation and AF after noncardiac surgery is unclear. We hypothesized that the use of vasoactive drugs in noncardiac surgery might increase the risk of postoperative atrial fibrillation as well as cardiac surgery. Therefore, we conducted this study to determine the relationship between catecholamine vasopressors and AF after noncardiac surgery.

The mechanism of catecholamine vasopressor-induced AF may be related to the following possible causes: vasopressors can enhance adrenergic activation via B1 receptors, leading to enhanced ectopic atrial activity and, consequently, an elevated

incidence of AF.[30] Vasopressor-induced sympathetic activation results in heightened calcium gradients and afterdepolarizations that can induce cardiac arrhythmias, particularly in the context of concomitant parasympathetic irritation.[31] Catecholamine-induced sympathetic overload can drive focused activity via any of the main cellular mechanisms: increased automaticity, early afterdepolarizations or delayed afterdepolarizations (EADs) related to triggered activation. I_{K1} mediates a diastolic outward flow that inhibits spontaneous Phase 4 depolarization to the threshold voltage by the pacemaker "funny" current that drives spontaneous automaticity. Automaticity is increased by decreased I_{K1}, which may occur with α-adrenergic pacing, or enhanced "funny" conduction, which may occur with β-adrenergic activation. Stage 2 EAD-induced premature ectopic activation likely underlies a greater risk of AF in patients,[32]. [[33] Vasopressor stimulation increases practically all the events that regulate Ca^{2+} inflow, accumulation and release in the myocardium. These effects are triggered by PKA and amplified by Ca^{2+}-calmodulin-dependent protein kinase type II (CaMKII).[34] PKA and CaMKII are implicated in phosphorylating many of the same proteins (albeit at different sites): the L-type Ca^{2+} channel (ICaL), the sarcoplasmic reticulum (SR) Ca^{2+} release channel ryanodine receptor (RyR2) and phospholamban. SR Ca^{2+} release events facilitated by increased SR Ca^{2+} load and RYR2 channels may cause delayed afterdepolarizations as a substrate of AF.[35]

New-Onset AF After Non-Cardiac Surgery: Possible Risk Factors and Mechanisms

Increasing age is the most powerful independent predictor of AF, but identifying age-related AF promotion mechanisms is demanding because a number of co-morbidities (coronary heart diseases, diabetics, valvular heart disease, and HF) increase in prevalence and severity with age. However, advanced age-related atrial structural remodelling, which includes atrial enlargement and histological fibrosis, and the associated slowing of electrical conduction speed, is a common observation in both animals (in the absence of any confounding comorbidities) and humans. Ageing is also linked to gap junction remodelling, in part through increased levels of c-Jun N-terminal kinase (JNK) activation, which may provide an additional re-entry-promoting substrate. Sensitisation of the preoperative atrial substrate to postoperative AF triggers has been suggested by surgical ischaemia. A minority of investigations have been able to obtain atrial specimens just before or after cross-clamping of the aorta, making it possible to analyse signs of atrial ischaemia-reperfusion. The functioning of mitochondria is intimately involved in arrhythmogenesis via the production of ROS and the regulation of Ca^{2+} balance. Consistent with this, preoperative versus postoperative changes in inflammatory biomarkers, protein catabolism, and modulators of oxidative status and atrial cycling are more marked in the setting of surgical ischaemia in those with postoperative atrial fibrillation (POAF) than in those without POAF. Fluid overload of the right and left atria is also a predisposition to AF. Atrial stretching causes electrophysiological alterations via mechano-electrical coupling that may facilitate the initiation of AF. Simultaneously, atrial fibrillation encourages atrial dilation, which creates a positive loop that contributes to the perpetuation of AF. The pathophysiological state resulting from long-term atrial dilation is marked by structural alterations in the heart's atrium, whereas transient electrophysiological alterations may occur during short-term atrial dilation. Temporary alterations in atrial conductivity slowing and refractoriness are accompanied by acute stretching. An elevation of atrial strain in the exposed rabbit cardiac muscle produced a reversible induction of atrial fibrillation that was tightly associated with a shorter atrial ERP. Variations in atrial wall density create a nonuniform local stretching response and may affect regional conduction disturbances and atrial refractoriness. In contrast, atrial stretch, through afferents carried mainly by the vagal nerve, has been shown to activate the autonomic nervous system. After four weeks of simulated sleep apnoea, animal experiments show atrial conduction disturbances combined with connexin abnormalities and enhanced atrial fibrotic formation. CaMKII-dependent phosphorylation of $Na_V1.5$ impairs sodium conductivity of the atrial myocyte in hypoxically stressed subjects, with proarrhythmic consequences independent of comorbidities. Long-term chronic hypoxaemia favours remodelling by regulating the production of hypoxia-inducible factors (HIFs) 1 and 2, which are important players in the adaptation to hypoxia and regulate hypoxia-induced endoplasmic reticulum (ER) stress. These factors ultimately drive atrial fibrillation.

Limitations

There are several limitations to this study. First, there is clearly some bias in the study due to the nonrandomized nature of the subject population. Randomized controlled studies are needed in the future. Second, we do not know the type of AF, such as paroxysmal or permanent AF, atrial flutter, or fast or slow rate AF. There was no further information about subsequent treatments for AF. Third, the mechanism underlying the increased risk of AF associated with the use of catecholamine vasopressors is unclear and requires additional clinical or animal studies for confirmation. Fourth, we did not perform a valid stratified analysis due to sample size limitations; a larger sample would be needed in the future to stratify multiple preoperative comorbidities.

Conclusions

The findings of this cohort trial showed that catecholamine vasopressors increase the risk of atrial fibrillation in elderly patients undergoing noncardiac surgery. The findings may help surgeons or anesthetists choose the most appropriate medication for patients while also assessing the risk of AF.

Abbreviation

AF, atrial fibrillation; PSM, Propensity score matching; ECG, electrocardiogram; NIBP, noninvasive blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; ARB, angiotensin converting enzyme inhibitors; ACEI, angiotensin II receptor blocker; CCB, calcium channel blockers; ORs, odds ratios; CIs, confidence intervals; IPTW, inverse probability of treatment weighting; EADs, afterdepolarizations; CaMKII, Ca^{2+}-calmodulin-dependent protein kinase type II; ICaL, L-type Ca^{2+} channel; SR, the sarcoplasmic reticulum.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Data Sharing Statement

All clinical data will be uploaded to the China Clinical Trials Centre (https://www.chictr.org.cn/) after publication, where readers will be able to download them at their convenience.

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Disclosure

All authors declare no competing interests in this work.

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