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Increased risk of atrial fibrillation among patients undergoing coronary artery bypass graft surgery while receiving nitrates and antiplatelet agents

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Abstract

Background: Postoperative atrial fibrillation (POAF) is a frequent complication of coronary artery bypass graft (CABG) surgery. This arrhythmia occurs more frequently among patients who receive perioperative inotropic therapy (PINOT). Administration of nitrates with antiplatelet agents reduces the conversion rate of cyclic guanosine monophosphate to guanosine monophosphate. This process is associated with increased concentrations of free radicals, catecholamines, and blood plasma volume. We hypothesized that patients undergoing CABG surgery who receive PINOT may be more susceptible to POAF when nitrates are administered with antiplatelet agents.

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Methods: Clinical records were examined from a prospectively maintained cohort of 4,124 patients undergoing primary isolated CABG surgery to identify POAF-associated factors.
Results: POAF risk was increased among patients receiving PINOT, and the greatest effect was observed when nitrates were administered with antiplatelet therapy. Adjustment for comorbidities did not substantively change the study results.
Conclusions: Administration of nitrates with certain antiplatelet agents was associated with an increased POAF risk among patients undergoing CABG surgery. Additional studies are needed to determine whether preventive strategies such as administration of antioxidants will reduce this risk.

Keywords
Antiplatelet agents, coronary artery bypass graft, inotropes, nitric oxide, nitrate tolerance, postoperative atrial fibrillation

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Introduction

Postoperative atrial fibrillation (POAF) is a significant predictor of stroke, future arrhythmias, heart failure, and mortality among patients undergoing coronary artery bypass graft (CABG) surgery.[1,2] Nitrates and inotropes are important drugs commonly used to manage cardiorenal function. Both have potent effects on the heart by increasing cyclic purine nucleoside production.[3,4] Inotropes improve cardiac output by their inotropic action (i.e., increasing intracellular calcium), while nitrates/nitroglycerin reduce oxygen demand in the myocardium through a reduction in preload and a weak negative inotropic effect.[4,5] In contrast to inotropic therapy, which increases the risk of POAF, the administration of nitrates have been shown to be protective against POAF.[6–8] Furthermore, the combined use of nitrates with antiplatelet agents is known to reduce the conversion rate of cyclic guanosine monophosphate (cGMP) to guanosine monophosphate (GMP), which may lead to increased concentrations of free radicals and catecholamines, an increased blood plasma volume, and a higher POAF risk.[9,10] The present study was performed to test the following hypothesis: that patients undergoing CABG surgery who receive perioperative inotropic therapy (PINOT) may be at increased risk for POAF when nitrates are administered with antiplatelet agents.

Methods

Setting and data collection

This study was conducted at the East Carolina Heart Institute (ECHI), which provides comprehensive cardiovascular care to patients predominantly from the eastern region of North Carolina, a rural area covering 29 counties. Most patients receiving care live and remain within a 150-mile radius of the Institute.

Clinical information was prospectively entered into the Society of Thoracic Surgeons Adult Cardiac Surgery Database at the ECHI as previously described and summarized below.[11] Patients aged

<60 years and undergoing primary isolated CABG surgery from 1992 to 2007 were included in this analysis. Perioperative inotrope information, which was collected as part of a quality assurance initiative, was not available in our database after 2007.

Comorbidities, demographic data, preoperative medications, and surgical details were obtained at the time of surgery. Patients with a history of preoperative paroxysmal, persistent, or permanent AF/atrial flutter and the use of preoperative inotropic agents were excluded from the study (approximately 2% of patients). The study and a waiver of participant consent were approved by the Institutional Review Board at the Brody School of Medicine, East Carolina University (UMCIRB 12-002107).

Definitions

POAF and comorbidities, such as diabetes mellitus, hypertension, left main coronary artery disease, peripheral artery disease, prior myocardial infarction, three-vessel coronary disease, and unstable heart failure, were defined according to the standard Society of Thoracic Surgeons criteria. We evaluated hospital notes, medication reports, outpatient medical records, physicians' documentation, and radiology readings to document the presence of these comorbidities. The cardiac rhythm was continuously monitored by electrocardiography until the patients were discharged from the hospital.

PINOT included the administration of sympathomimetics (dobutamine, dopamine, epinephrine, isoprenaline, and norepinephrine) and phosphodiesterase-3 inhibitors (amrinone and milrinone). Each class boosts cardiac output and renal perfusion by increasing myocardial contractility, vasodilation, or both. Sympathomimetics increase cardiac contractility by facilitating calcium influx into cardiac myocytes through cyclic adenosine monophosphate-mediated mechanisms.[12] Similarly, phosphodiesterase-3 inhibitors increase intracellular cyclic adenosine monophosphate (by decreasing cyclic adenosine monophosphate degradation) and calcium influx, while additionally increasing cGMP in the vasculature. They also selectively lower the left ventricular end-diastolic pressure and the B-type natriuretic peptide concentration.[13–15]

Antiplatelet agents were defined as inhibitors of adenosine diphosphate (e.g., clopidogrel), glycoprotein IIb/IIIa (e.g., abciximab, eptifibatide, and tirofiban), or phosphodiesterase (e.g., dipyridamole). Except for combination antiplatelet formularies such as extended-release Aggrenox®, aspirin was placed into a separate category because of its different mechanism of antiplatelet activity through the cyclooxygenase pathway.[16]

Organic nitrates, in the form of nitroglycerine, were administered by intravenous injection within 24 hours preceding surgery, mainly to patients with prior routine use of nitrates.

Statistical analysis

Categorical variables are reported as frequencies and percentages, whereas continuous variables are reported as medians and interquartile ranges. Statistical significance for categorical variables was determined using Fisher's exact test and the Deuchler–Wilcoxon procedure for continuous variables. An iterative expectation–maximization algorithm was used to account for missing values.

Log-binomial regression was used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) for POAF.[17] Goodness-of-fit was assessed using Akaike's information criterion and leverage/casewise diagnostic statistics, generalized to log-binomial regression. All models

satisfied convergence and admissibility criteria (i.e., linear predictor constrained to be negative). The nitrates/inotrope category (+/−), believed to represent the lowest risk for POAF, was designated as the reference group for this variable in our log-binomial models.

Multivariable models included variables that have been associated with POAF in prior reports, regardless of their statistical significance in the current analysis.[18,19] These included patient age, diabetes mellitus, hypertension, peripheral arterial disease, race, sex, three-vessel coronary disease, and unstable heart failure. Other demographic variables, prior medical history, and preoperative medicines were entered into the model in a post hoc pairwise manner. Cardiac function variables were not included in the multivariable analyses because of their potential to be a factor in the causal pathway from exposure to outcome (or a descending proxy for such a factor).[20] *P*-values for point estimates were computed assuming asymptotic normality. A likelihood ratio test for risk differences between strata was used to identify statistically significant interaction effects.

The method established by Holly et al.[21] was used for rounding. Analyses were performed using SAS Version 9.4. (SAS Institute, Cary, NC, USA).

Results

In total, 4,124 patients were included in this study (median age, 53 years; interquartile range, 8 years; 70% male) (Table 1). Hypertension (66%) was the most common comorbidity, followed by diabetes mellitus (31%). Approximately 61% of patients had three-vessel coronary revascularization with a median postoperative length of stay of 5 days. Three-vessel coronary disease was present in 65% of patients with POAF, compared with 6% and 29% for one- and two-vessel coronary disease, respectively (P=0.0048).

Preoperative nitrates were used by 17% of patients. Catecholamines were the predominant drug class used for PINOT, with 34% of patients receiving these compounds (Table 2). Only 3% of patients received phosphodiesterase-3 inhibitors. The use of PINOT was associated with a 56% increased RR for POAF (P<0.0001).

In the presence of antiplatelet agents, the use of preoperative nitrates increased the POAF RR difference associated with PINOT (+/+: RR=2.9, 95%CI=1.6–5.1 vs. −/+: RR=2.0, 95%CI=1.2–3.4), in contrast to the absence of antiplatelet agents (+/+: RR=0.90, 95%CI=0.46–1.8 vs. −/+: RR=1.6, 95%CI=0.98–2.5). This opposite effect is illustrated by the vertical arrows in Table 3 ($P_{\text{interaction}}$=0.0069). Multivariable adjustment for age, diabetes mellitus, hypertension, peripheral arterial disease, race, sex, three-vessel coronary disease, and unstable heart failure did not substantively change the results ($P_{\text{interaction}}$=0.011). Similarly, the post hoc pairwise inclusion of other demographic variables, prior medical history, and preoperative medicines from Table 1 into the multivariable models did not affect the findings. The exclusion of phosphodiesterase-3 inhibitors and the adjustment for the time period of surgery (before the year 2000 vs. 2000 and later) also had little effect on the analyses.

Discussion

AF is a common postoperative complication following CABG surgery and is associated with increased mortality, morbidity, hospital costs, and readmission rates.[2,22] The use of PINOT is an established risk factor for POAF.[23] Identifying preoperative factors associated with this risk is an important area of concern.

Table 1. Patient characteristics (N=4124)*.

Patient characteristics†	Inotrope‡			No inotrope‡		
	Nitrate n (%) or Q_2 [IQR]	No nitrate n (%) or Q_2 [IQR]	*P*§	Nitrate n (%) or Q_2 [IQR]	No nitrate n (%) or Q_2 [IQR]	*P*§
Overall	300 (21)	1122 (79)	—	391 (14)	2311 (86)	—
Demographics						
Age	54 [8]	54 [8]	0.57	52 [9]	53 [8]	0.072
Black	63 (21)	260 (23)	0.44	59 (50)	399 (17)	0.31
Male	196 (65)	799 (71)	0.055	300 (77)	1828 (79)	0.29
Obesity (BMI $\geq$ 30 kg/m^2)	156 (52)	591 (53)	0.85	155 (40)	1058 (46)	0.024
Prior Medical History						
Diabetes	112 (37)	453 (40)	0.35	95 (24)	629 (27)	0.24
Dialysis	14 (5)	28 (3)	0.55	0 (0)	36 (2)	0.0068
Elective CABG surgery	23 (8)	487 (44)	<0.0001	38 (10)	1201 (52)	<0.0001
Hypertension	10 (70)	798 (71)	0.72	239 (61)	1476 (64)	0.31
LMCA disease	72 (24)	225 (20)	0.15	68 (17)	382 (17)	0.66
LVEF (%)	45 [23]	50 [25]	0.011	50 [15]	55 [15]	<0.0001
Peripheral artery disease	30 (10)	129 (12)	0.54	23 (6)	152 (7)	0.66
Prior myocardial infarction	173 (58)	471 (42)	<0.0001	200 (51)	720 (31)	<0.0001
Recent smoker	109 (36)	373 (33)	0.34	191 (49)	850 (37)	<0.0001
Three-vessel coronary disease	217 (72)	799 (71)	0.72	209 (53)	1287 (56)	0.41
Unstable heart failure	38 (13)	191 (17)	0.077	21 (5)	147 (6)	0.50
Preoperative medications						
ACEIs/ARBs	79 (26)	375 (33)	0.021	93 (24)	529 (23)	0.70
Anticoagulants	215 (72)	252 (22)	<0.0001	302 (77)	479 (21)	<0.0001
Antiplatelet agents	188 (63)	603 (54)	0.0060	231 (59)	1312 (57)	0.41
Aspirin	193 (64)	755 (67)	0.34	261 (67)	1603 (69)	0.32
Beta blockers	182 (61)	633 (56)	0.19	223 (57)	1228 (53)	0.15
Calcium channel blockers	69 (23)	340 (30)	0.015	78 (20)	737 (32)	<0.0001
Digoxin	14 (5)	65 (6)	0.57	7 (2)	57 (2)	0.59
Diuretics	50 (17)	265 (24)	0.0098	42 (11)	281 (12)	0.45
Lipid-lowering agents	94 (31)	461 (41)	0.0022	108 (28)	840 (36)	0.0009
Perioperative variables						
Cardiopulmonary bypass	292 (97)	1090 (97)	1.0	366 (94)	217 (87)	0.0002
Colloid cardioplegia	219 (73)	918 (82)	0.0011	322 (82)	2020 (87)	0.0079
Crystalloid cardioplegia	236 (79)	857 (76)	0.44	287 (73)	1705 (74)	0.90
Crystalloid+O_2 cardioplegia	143 (78)	495 (44)	0.30	197 (50)	1200 (52)	0.58
Cross-clamp time (min)‖	61 [29]	63 [30]	0.76	57 [29]	56 [26]	0.45
Hospital LOS (days)	5 [3]	5 [2]	0.25	4 [1]	4 [1]	0.27
Intra-aortic balloon pump#	194 (65)	1023 (91)	<0.0001	327 (84)	2246 (97)	<0.0001
Perfusion time (min)	100 [41]	101 [47]	0.91	100 [41]	101 [47]	0.55
Total ICU time (hours)	28 [28]	25 [26]	0.13	22 [7]	22 [8]	0.23

*Isolated primary CABG, 1992–2007. †Comparison group was the complement. ‡Perioperative inotropes. §*P*-values were computed using Fisher's exact or Deuchler–Wilcoxon tests. ‖Excludes patients with poor condition of the aorta, left ventricular weakness, and other contraindicated conditions (<0.5%). #Pre-/intraoperative balloon pump placement only. ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin receptor blockers; BMI=body mass index; CABG=coronary artery bypass graft; ICU=intensive care unit; IQR=interquartile range; LMCA=left main coronary artery; LOS=length of stay; LVEF=left ventricular ejection fraction; O_2=oxygen; Q_2=median

Table 2. Inotropic support and nitrate use by postoperative cardiac rhythm (N=4124)*

	Sinus rhythm†			POAF†		
Inotropic agent	Nitrate n (%)	No Nitrate n (%)	P‡	Nitrate n (%)	No nitrate n (%)	P‡
Overall	81 (16)	412 (84)	—	610 (17)	3021 (83)	—
Sympathomimetics						
Dobutamine	4 (5)	19 (5)	0.78	14 (2)	37 (1)	0.056
Dopamine	43 (53)	150 (36)	0.0061	231 (38)	865 (29)	<0.0001
Epinephrine	8 (10)	31 (8)	0.50	44 (7)	113 (4)	0.0003
Isoprenaline	0 (0)	1 (<1)	1.0	1 (<1)	10 (<1)	0.70
Norepinephrine	10 (12)	18 (4)	0.014	24 (4)	66 (2)	0.015
Total	46 (57)	173 (42)	0.020	250 (41)	927 (31)	<0.0001
Phosphodiesterase-3 inhibitors						
Amrinone	4 (5)	6 (1)	0.065	13 (2)	25 (1)	0.0077
Milrinone	5 (6)	10 (2)	0.082	13 (2)	36 (1)	0.081
Total	9 (11)	14 (3)	0.0065	26 (4)	61 (2)	0.0020

*Isolated primary coronary artery bypass graft procedures from 1992–2007. †Column percentages may add up to more than 100% because some patients received more than one inotrope. ‡*P*-value computed using Fisher's exact test. PDE=phosphodiesterase enzyme; POAF=postoperative atrial fibrillation

Table 3. Relative risk for postoperative atrial fibrillation by preoperative medications (N=4124)*

	Antiplatelet agents (n=2334)			No antiplatelet agents (n=1790)		
Nitrates/ inotropes	n (%)	Univariable RR (95%CI)†	Multivariable‡ RR (95%CI)†	n (%)	Univariable RR (95%CI)†	Multivariable‡ RR (95%CI)†
+/−	231 (10)	1.0 (Ref)	1.0 (Ref)	160 (9)	1.0 (Ref)	1.0 (Ref)
+/+	188 (8)	↑ 2.9 (1.6–5.1)	↑ 2.6 (1.5–4.7)	112 (6)	↓ 0.90 (0.46–1.8)	↓ 0.88 (0.44–1.7)
−/+	603 (26)	↑ 2.0 (1.2–3.4)	↑ 1.8 (1.1–3.1)	519 (29)	↓ 1.6 (0.98–2.5)	↓ 1.4 (0.86–2.1)
−/−	1312 (56)	1.5 (0.92–2.6)	1.5 (0.87–2.4)	999 (56)	0.89 (0.56–1.4)	0.88 (0.56–1.4)

*Isolated primary coronary artery bypass graft procedures from 1992–2007. †RR and 95% CI were computed using maximum likelihood log-binomial regression. ‡Adjusted for age, diabetes, hypertension, peripheral arterial disease, race, sex, three-vessel coronary disease, and unstable heart failure. Arrows indicate direction of the interaction effect. Likelihood ratio test for interaction, $P_{univariable}$=0.0069, and $P_{multivariable}$=0.011. CI=confidence interval; RR=relative risk; Ref=reference.

Interaction of nitrates with antiplatelet drugs

Since the late 19th century, when it was first observed that amyl nitrate alleviated chest pain, organic nitrates have been routinely prescribed as cardioprotective, anti-ischemic agents to treat angina, acute myocardial infarction, heart failure, pulmonary edema, and severe arterial hypertension.[24] These compounds, by releasing nitric oxide (NO), facilitate left ventricular function, vasodilation by venous pooling, and preload reduction. In hypoxic conditions, nitrate therapy results in a redistribution of blood from the central circulation into larger-capacitance veins, thus reducing the ventricular filling pressure and wall tension and decreasing myocardial oxygen consumption.[25] By reducing the mismatch

between oxygen demand and supply in ischemic regions of the heart and vasculature, nitrates further help to reduce the magnitude, frequency, and velocity of reflected waves in the arterial circulation.[26]

Nitrates are an exogenous source of NO, which is a gaseous free radical and cellular messenger that facilitates myocardial relaxation and dilation of the coronary arteries, systemic veins, and arterioles.[27] Conversely, reduced bioavailability of NO is associated with endothelial dysfunction, arterial stiffness, and hypertension. Even in the presence of endothelial dysfunction, organic nitrates are able to produce an endothelial-dependent relaxation factor (i.e., NO).[28]

By way of their conversion to NO, nitrates are believed to play an important role in stabilizing cardiac output, preventing post-infarction ventricular remodeling, and reducing myocardial infarction-related mortality.[25,29,30] Other properties include enhanced antioxidant effects, production of cytoprotective prostanoids, and stimulation of sacrolemmal and mitochondrial K_{ATP} channels.[31] In contrast, they inhibit proapoptotic proteins, beta-adrenergic stimulation, and influx through L-type calcium channels. Although NO has a relatively short half-life, the above-mentioned processes may represent upstream factors that underlie longer-time ischemic postconditioning, including the delayed cardioprotective actions of phosphodiesterase-5 inhibitors, stabilization of tissue pH, decreased generation of reactive oxygen species, cardiac tissue remodeling, and prevention of hypercontraction.[31,32]

Therapeutic doses of antiplatelet agents together with NO are believed to increase cGMP levels, desensitize NO/cGMP-mediated vasodilation, and supersensitize calcium-mediated vasoconstriction.[9] Additionally, nitrates are believed to have nonselective antiplatelet activity making them capable of inhibiting platelet aggregation in response to inotropes.[27,33] NO increases soluble guanylate cyclase and cGMP, which inversely affects platelet aggregation.[34] This is accompanied by the inhibition of agonist-mediated calcium flux and the reduction of fibrinogen binding to the glycoprotein IIb/IIIa receptor. The disruption of fibrinogen binding represents an important mechanism by which platelets are impaired, with nitrates believed to play a mediating role in this process. However, the synergistic effect between nitrates and antiplatelet agents is complicated, both causing and preventing thrombolytic events in patients.[35]

Interpretation of findings

We observed no interaction between nitrates and other preoperative medications in the dataset, suggesting that nitrates and antiplatelet agents may uniquely affect the risk of POAF. Several potential mechanisms may underlie this result, including oxidative stress (free radicals), catecholamines, neurohormonal activation, sulfhydryl group donation, and plasma volume expansion[36] (Figure 1).[10,37–40] Additionally, various metabolic and genetic factors regulating the production, degradation, and conversion of these compounds in cardiovascular tissue may have contributed to this effect.[36] However, explaining the exact mechanism for this interaction, if biologic in nature, was beyond the scope of the present research.

Strengths and limitations

The current analysis was strengthened by its large sample size, few missing values, and systematic collection of exposure and outcome data using standard Society of Thoracic Surgeons definitions. Additionally, our institution implemented special database fields to record information on PINOT use, which is not available

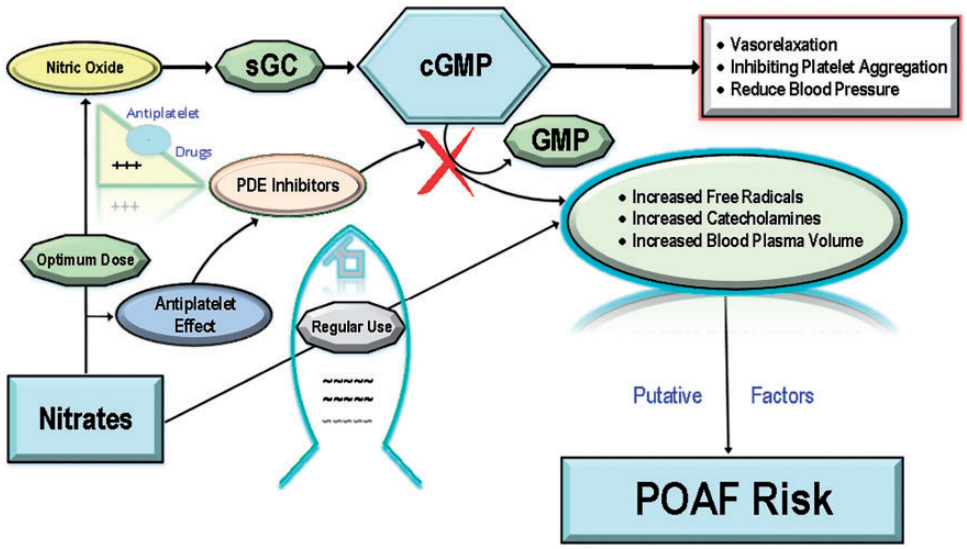

Figure 1. Potential pathways underlying the interaction of nitrates and antiplatelet agents and the risk of POAF

Nitrates are an exogenous source of NO that, under normal conditions, are cardioprotective (by increasing the concentration of cGMP). The use of nitrates in combination with antiplatelet drugs may increase the concentrations of free radicals and catecholamines and the blood plasma volume, which are potential factors contributing to the development of POAF. cGMP=cyclic guanosine monophosphate; GMP=guanosine monophosphate; NO=nitric oxide; PDE=phosphodiesterase; POAF=postoperative atrial fibrillation; sGC=soluble guanylate cyclase.

in the national version of the Society of Thoracic Surgeons database.

However, a few limitations should be noted when considering our results. NO bioavailability is well known to be affected by polymorphisms (rs2070744 and rs1799983) in the endothelial NO synthase gene, including variable numbers of tandem repeats in intron 4.[41–43] Similarly, genetic variants in the cytochrome P450 2C19 gene play an important role in determining if the antiplatelet drug clopidogrel is converted to an active metabolite with antiplatelet activity.[44] These reduced-function polymorphisms, which vary among individuals and populations, may have confounded our findings.[45,46] However, the patients in this study were not genotyped; therefore, we were unable to include these factors in the analyses. Additionally, no information was collected on the dose and duration of inotrope/nitrate use, antiplatelet use, and other factors potentially affecting the risk of POAF (e.g., diet, inflammation, oxidative stress, and atrial size/dimension).[8,47]

Heart failure is both a frequent indication for PINOT and a significant risk factor for POAF, and the possibility remains that preoperative nitrate and antiplatelet use may simply reflect treatment of underlying symptoms rather than directly affect the risk of POAF. To minimize this effect (and other potential sources of intermediate causal confounding by indication), we restricted our analysis to patients aged <60 years, and various outcome-related covariates were included in the multivariable models.[48] Heart failure is an indication for nitrate and inotrope use.[49,50] While we could have excluded patients with heart

failure instead of limiting our analyses by age, this would have prevented examination of the interaction of nitrates/inotropes with antiplatelet agents. Residual selection bias remains a possible explanation of our results; however, this would be an unlikely chance event given the opposite linear RR effects for antiplatelets (yes vs. no) observed in Table 3.

Biological samples were not collected in this study. Consequently, we were unable to directly access the uptake of nitrates into vascular smooth muscles and other factors indicative of pharmacologic tolerance (e.g., decreases in intracellular sulfhydryl groups and cGMP formation, inhibition of guanylate cyclase, stimulation of specific phosphodiesterases, and reduced vasodilation).[51,52] Furthermore, we did not use electron paramagnetic resonance spectroscopy to directly detect NO or perform a proteomic analysis to measure endogenous *S*-nitrosylation. These techniques may prove to be useful in future studies.[53,54]

Future directions

Vitamin C, which has been shown to decrease the incidence of POAF and peroxynitrite formation following atrial pacing, offers one approach toward disrupting the putative interaction between nitrates and antiplatelet agents.[55–60] Another approach is the intermittent use of nitrates (i.e., "nitrate holiday"). However, this strategy has been viewed with caution because of the potential rebound risk and consequent outcomes (e.g., myocardial infraction and death).[61,62] The use of sulfhydryl donor therapy (e.g., acetylcholine, methionine, and captopril) has similarly been associated with undesirable adverse events.

Summary

We observed a hitherto unreported increased risk of POAF associated with the interaction between nitrates and antiplatelet agents among patients undergoing CABG surgery who received PINOT. While the mechanisms underlying this effect are complex, our findings may have practical clinical implications. For example, if the outcomes observed in the current study are indicative of a true pharmacologic interaction, then targeted interventions involving anti-inflammatory agents may potentially be a safe and low-cost option for reducing the risk of POAF. Conversely, the reported interaction between nitrates and antiplatelet therapy may merely reflect a patient's clinical status or the underlying acuity of CABG surgery. Nonetheless, we have identified a set of patients, based on their nitrate and antiplatelet status, who may be at higher risk of POAF. The careful postoperative monitoring of this risk group remains a prudent strategy.

Authors' contributions

J.T.E. and C.J. conceived the manuscript and wrote the first draft. A.C.K., S.A.A., P.B.C., A.P.K., A.S., S.W.D., L.C.K., and E.J.A. provided critical feedback and contributed to the final draft of the manuscript. J.T.E. analyzed the data. L.C.K. supervised the data management and validation of the final dataset. All authors approved the final version of the manuscript.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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