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ABOUT COVER

AIMS AND SCOPE

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ORIGINAL ARTICLE

Retrospective Study

Impact of gout on in-hospital outcomes of acute coronary syndrome-related hospitalizations and revascularizations: Insights from the national inpatient sample

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Abstract

BACKGROUND

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations

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and post-revascularization is inadequate.

AIM
To evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

METHODS
We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

RESULTS
We identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ($P < 0.001$). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44, CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ($P < 0.001$). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ($P < 0.001$). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

CONCLUSION
Although gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS, it did increase post-revascularization complications.

Key words: Gout; Serum uric acid; Acute coronary syndrome; Unstable angina; Myocardial infarction; Revascularization; Percutaneous coronary intervention; Coronary artery bypass grafting; In-hospital outcomes

Core tip: Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate. In this largest nationwide cohort, we identified 3144744 ACS-related hospitalizations, of which 105198 (3.35%) also had gout. Coronary artery bypass grafting was required more often in the ACS-gout cohort. Post-revascularization (percutaneous coronary intervention/coronary artery bypass grafting) complications including cardiovascular (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher and raised the mortality odds whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort. Mean length of stay, transfers and hospital charges were higher in the ACS-gout cohort.

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INTRODUCTION

Acute coronary syndrome (ACS) comprises a range of diseases including unstable angina (UA), non-ST segment elevation myocardial infarction, and acute ST-elevation myocardial infarction (STEMI)[1]. It is one of the major causes of mortality around the world. Several independent predictors including advanced age, gender, history of diabetes or hypertension, obesity, and socioeconomic status have been determined for the unfavorable outcomes and rise in the overall mortality in ACS patients[2,3]. Gout is a common inflammatory disease associated with hyperuricemia and has shown to be associated with almost 410% increase in the hospitalizations in the last two decades in the United States[4]. The clinical evidence has shown that uric acid (UA) may have a pro-inflammatory effect on the vascular cells contributing to the negative effects of hyperuricemia in cardiovascular diseases (CVD) including ACS[5,6]. Previous studies have also suggested that gout patients have two to five-fold higher mortality risk in patients with CVD[7,8]. Recent studies have also established the crucial role of high UA levels in predicting the higher odds of MI and subsequent in-hospital mortality in ACS and STEMI hospitalizations[9,10]. Furthermore, microvasculature is becoming a key prognostic factor in patients undergoing percutaneous coronary intervention (PCI) since UA has been found to induce microvascular lesions, accounting for vascular dementia and allograft vasculopathy post-cardiac transplantation[11]. While quick restoration of blood flow through an infarct-related artery is important, the presence of distal microvascular disease can result in impaired myocardial flow leading to an increased risk of major adverse cardiac events after acute MI[12,13]. Nevertheless, the relationship between gout and healthcare resource utilization and post-revascularization outcomes in ACS hospitalizations has not been previously studied on a large scale in the United States. Therefore, in this retrospective population-based study, we aim to evaluate the impact of gout on the in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality using the largest nationwide cohort from January 2010 through December 2014.

MATERIALS AND METHODS

Source of data

The study cohort was derived from the national inpatient sample (NIS) database from January 2010 through December 2014, which is a part of the Healthcare Cost and Utilization Project held by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest publicly accessible all-payer inpatient database in the United States and incorporates diverse identifiers for the hospitalization and clinical data for each visit including up to 25 discharge diagnoses and 15 procedures[14]. It includes discharge statistics from 20% inpatient discharges of all non-federal United States hospital facilities (not including rehabilitation and long-term acute care hospitals), disclosing up to 95% of hospital releases across the country. Nationwide assessments were generated utilizing discharge weights provided by AHRQ.

Study population

All ACS-related adult hospitalizations were recognized by applying International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) codes 410.1x and 411.1 for the primary discharge diagnosis. These codes have been successfully utilized in earlier studies[15]. We then divided ACS population into the two cohorts: one who had baseline gout and another without gout by using ICD-9 CM codes 274.x or 274.xx in any of the secondary discharge diagnoses.

Study variables

Patient and hospital-level variables including age, gender, race, median household income, primary payer, hospital location/teaching status, bed size, and regions were studied and compared between ACS hospitalizations with *vs* without gout. Underlying comorbid illnesses were also compared between the ACS population with *vs* without gout. Revascularization comprised of thrombolysis (ICD-9 CM diagnosis code V45.88 or procedure code 99.10), PCI (ICD-9 CM procedure codes 00.66, 36.01, 36.02, 36.05, 36.06, and 36.07, 17.55) OR CABG (ICD-9 CM procedure codes 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.3, 36.31, 36.32, 36.33, 36.34, 36.39). Since the NIS is an openly available database with de-identified data, our study was exempt from an Institutional Review Board authorization.

Study outcomes

The primary outcomes of interest were all-cause in-hospital mortality, revascula-

rization (thrombolysis, PCI or CABG) rates, discharge disposition, length of hospital stay (LOS), and total hospital charges (denotes the total amount payable for service rather than the actual payment received). The secondary outcomes were post-revascularization complications in ACS-hospitalizations including all-cause in-hospital mortality, hemorrhage, blood transfusion, hypotension/shock, cardiac complications, postoperative myocardial infarction, stroke, respiratory complications, gastrointestinal complications including gastrointestinal hemorrhage, acute kidney injury (AKI) requiring dialysis, urinary complications, postoperative infections, and predictors of in-hospital mortality. Comorbidities and postoperative complications were identifying from the secondary discharge diagnoses. The codes used in the study to identify comorbidities and post-revascularization complications are mentioned in Supplementary Table 1.

Statistical analyses

We integrated the discharge weights to unweighted records, to generate the national estimates. The missing data (< 10% for any variable) were omitted from the analysis. The baseline characteristics were compared amongst ACS patients with gout and without gout by applying Pearson's Chi-square test for categorical and Student's t-test for the continuous variable where appropriate. We developed a two-step hierarchical multivariate logistic regression model to evaluate for the patient and hospital level components, and in-hospital outcomes such as in-hospital mortality and procedural complications related to the ACS. This model permitted us to represent the possible relationship of insights into each hospital visit. Both patient and hospital level components along with all relevant comorbidities were incorporated into the multivariable model to control confounders. In addition to unadjusted analysis, post-revascularization outcomes were also analyzed using a propensity score-matched analysis with a caliper width of 0.01 without replacement and adjusting for demographics and all relevant comorbid conditions (Supplementary Tables 2 and 3). A two-tailed *P*-value of < 0.5 was considered statistically significant. All statistical analyses were completed utilizing SPSS Statistics 24 (IBM Corp., Armonk, NY).

RESULTS

Population demographics and comorbidities

We identified 3144744 ACS-related hospitalizations during the study period, of whom 3.34% (n = 105198) also had gout as comorbidity (Table 1). Patients with gout were older with more than two-thirds being > 65 years old (mean age 71.3 years), white (71.8%), mostly males (74%), and Medicare enrollees (69.1%). Interestingly, the ACS-gout cohort consisted of comparatively higher median household income population (76-100th percentile: 21.9% *vs* 19.1%, P < 0.001), and were more likely to be admitted to urban-teaching (54.3% *vs* 50.5%, P < 0.001) and Southern region hospitals (20.6% *vs* 17.7%, P < 0.001) as compared to those without gout. The majority (94.1%) of admissions was non-elective, and 74.4% of admissions occurred on the weekdays. As compared to ACS patients without gout, those with gout had a higher prevalence of baseline comorbidities, except CHF and previous history of cardiac arrest (Table 2). The ACS-gout patients had higher frequency of traditional comorbid risk factors such as: hypertension (83.3% *vs* 71.4%, P < 0.001), dyslipidemia (71.0% *vs* 61.8%, P < 0.001), diabetes (46.7% *vs* 36.6%, P < 0.001), and obesity (21.9% *vs* 14.6%, P < 0.001). They also had the higher prevalence of chronic kidney disease (45.5% *vs* 19.0%, P < 0.001), AKI (45% *vs* 18.7%, P < 0.001), and deficiency anemias (26.7% *vs* 16.0%, P < 0.001).

Revascularization rates and in-hospital outcomes in ACS-related hospitalizations with vs. without gout

As shown in Table 2, the ACS patients with gout had a higher rate of undergoing CABG (9.2% *vs* 8.1%, P < 0.001) as compared to those without gout. All-cause in-hospital mortality associated with revascularization was lower in the ACS patients with gout compared to those without gout (4.3% *vs* 5.0%, P < 0.001). Gout patients were more likely to be discharged to skilled nursing facilities, intermediate care facility or similar facilities (14.8% *vs* 12.1%, P < 0.001) and were less likely to be discharged routinely (56.7% *vs* 61.8%, P < 0.001). The average LOS was higher (5.1 d *vs* 4.5 d, P < 0.001) and mean total hospital charges were higher ($72328 *vs* $71312, P < 0.001) for ACS patients with gout compared to those without gout (Table 3).

Post-revascularization outcomes in ACS hospitalizations with gout

The ACS-gout cohort undergoing PCI or CABG demonstrated a higher number of postoperative complications including cardiovascular, respiratory, stroke,

Table 1 Baseline characteristics of acute coronary syndrome hospitalizations without *vs* with gout (*n* = 3144744)

Variables	Without gout(*n* = 3039546)	With gout(*n* = 105198)	*P* value
Age (yr) at hospitalization			**< 0.001**[a]
mean (± SD)	66.9 (± 14.2)	71.3 (± 12.5)	
18-44	171857 (5.7)	2337 (2.2)	
45-64	1178621 (38.8)	28567 (27.2)	
65-84	1288783 (42.4)	57054 (54.2)	
≥ 85	400285 (13.2)	17240 (16.4)	
Sex			**< 0.001**[a]
Male	1830228 (60.2)	77834 (74.0)	
Female	1209120 (39.8)	27355 (26.0)	
Race			**< 0.001**[a]
White	2102509 (75.4)	69431 (71.8)	
African American	302121 (10.8)	14798 (15.3)	
Hispanic	218605 (7.8)	4833 (5.0)	
Asian and Pacific Islander	61156 (2.2)	4799 (5.0)	
Native American	16624 (0.6)	394 (0.4)	
Others	88091 (3.2)	2477 (2.6)	
Admission type			**< 0.001**
Non-elective	2847182 (93.9)	98886 (94.1)	
Elective	185903 (6.1)	6149 (5.9)	
Median household income percentile for patient's zip code[1]			**< 0.001**[a]
0-25th	894564 (30.1)	29758 (28.8)	
26-50th	807784 (27.2)	26606 (25.8)	
51-75th	701363 (23.6)	24152 (23.4)	
76-100th	566069 (19.1)	22637 (21.9)	
Primary expected payer			**< 0.001**[a]
Medicare	1709250 (56.4)	72559 (69.1)	
Medicaid	218428 (7.20)	4232 (4.0)	
Private including HMO	803459 (26.5)	22757 (21.7)	
Self-pay/no charge/others	301827 (10.0)	5433 (5.2)	
Control/ownership of hospital			**< 0.001**[a]
Government, nonfederal	305519 (10.1)	9697 (9.3)	
Private, non-profit	2258936 (74.7)	81175 (77.4)	
Private, invest-own	459942 (15.2)	13962 (13.3)	
Bed size of hospital			0.157
Small	351544 (11.6)	12101 (11.5)	
Medium	767625 (25.4)	26387 (25.2)	
Large	1905229 (63.0)	66346 (63.3)	
Location/teaching status			**< 0.001**[a]
Rural	312292 (10.3)	10030 (9.6)	
Urban non-teaching	1183544 (39.1)	37858 (36.1)	
Urban teaching	1528562 (50.5)	56946 (54.3)	
Region of hospital			**< 0.001**[a]
Northeast	575864 (18.9)	19077 (18.1)	
Midwest	705042 (23.2)	24946 (23.7)	
South	1219352 (40.1)	39502 (37.5)	
West	539288 (17.7)	21672 (20.6)	

[a]*P* < 0.05 indicates clinical significance. The bed size cutoff points are derived from https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nisnote.jsp. [1]Represents a quartile classification of the estimated median household income of residents in the patient's ZIP Code, derived from https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp. HMO: Health maintenance organization; SNF: Skilled nursing facility; ICF: Intermediate care facility.

hemorrhage, hypotension/shock, need of blood transfusion, AKI requiring dialysis,

Table 2 Comorbidities in acute coronary syndrome without *vs* with gout

Comorbidities	ACS + no gout	ACS + gout	*P* value
Alcohol abuse	95449 (3.1)	3768 (3.6)	**< 0.001**[a]
Deficiency anemias	487126 (16.0)	28065 (26.7)	**< 0.001**[a]
Rheumatoid arthritis/collagen vascular diseases	72214 (2.4)	3343 (3.2)	**< 0.001**[a]
Congestive heart failure	24213 (0.8)	811 (0.8)	0.357
Chronic pulmonary disease	634046 (20.9)	22789 (21.7)	**< 0.001**[a]
Coagulopathy	152932 (5.0)	7283 (6.9)	**< 0.001**[a]
Diabetes, uncomplicated	911629 (30.0)	36556 (34.7)	**< 0.001**[a]
Diabetes with chronic complications	200881 (6.6)	12597 (12.0)	**< 0.001**[a]
Drug abuse	95449 (3.1)	1519 (1.4)	**< 0.001**[a]
Hypertension	75189 (2.5)	87598 (83.3)	**< 0.001**[a]
Hypothyroidism	2170519 (71.4)	15366 (14.6)	**< 0.001**[a]
Liver disease	334044 (11.0)	2013 (1.9)	**< 0.001**[a]
Fluid and electrolyte disorders	43749 (1.4)	26081 (24.8)	**< 0.001**[a]
Other neurological disorders	636496 (20.9)	6138 (5.8)	**< 0.001**[a]
Obesity	186097 (6.1)	23082 (21.9)	**< 0.001**[a]
Peripheral vascular disorders	443723 (14.6)	16964 (16.1)	**< 0.001**[a]
Renal failure	355484 (11.7)	47359 (45.0)	**< 0.001**[a]
Valvular disease	568903 (18.7)	327 (0.3)	**< 0.001**[a]
Dyslipidemia	7101 (0.2)	74674 (71.0)	**< 0.001**[a]
Coronary atherosclerosis	1879620 (61.8)	89777 (85.3)	**< 0.001**[a]
Previous history of MI	2500606 (82.3)	16972 (16.1)	**< 0.001**[a]
Family history of CAD	359298 (11.8)	8442 (8.0)	**< 0.001**[a]
Previous PCI	298852 (9.8)	18591 (17.7)	**< 0.001**[a]
Previous CABG	439722 (14.5)	13165 (12.5)	**< 0.001**[a]
Previous history of cardiac arrest	247161 (8.1)	405 (0.4)	0.786
Smoking	11543 (0.4)	34019 (32.3)	**< 0.001**[a]
History of venous thromboembolism	1210142 (39.8)	3146 (3.0)	**< 0.001**[a]
Chronic kidney disease	66017 (2.2)	47909 (45.5)	**< 0.001**[a]
Dialysis status	576268 (19.0)	4388 (4.2)	**< 0.001**[a]

[a]$P < 0.05$ (bold value) indicates clinical significance. ACS: Acute coronary syndrome; MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting.

and gastrointestinal and urinary complications as compared to those without gout (Table 3). However, overall in-hospital mortality was lower (2.2% *vs* 3.0%, $P < 0.001$) in patients with gout and there were no significant differences in the post-revascularization myocardial infarction and infection rates between both the cohorts. We also confirmed the comparable results with a comprehensive propensity-score matched analysis (Supplementary Tables 2 and 3).

Predictors of in-hospital mortality

On multivariable analysis, advanced age (> 85 years *vs* 18-44 years: OR 15.63, 95%CI: 5.51-44.39; $P < 0.001$), non-elective admissions (OR 2.00, 95%CI: 1.44-2.79; $P < 0.001$), and lower household income (OR 1.44; 95%CI: 1.17-1.78; $P < 0.001$) had significantly higher odds of in-hospital mortality in ACS patients with gout undergoing PCI or CABG (Table 4). Among ACS-gout cohort, Hispanics (OR 0.45, CI: 0.31-0.67; $P < 0.001$) and Asians (OR 0.65, CI: 0.45-0.94; $P < 0.001$) undergoing PCI or CABG demonstrated significantly lower odds of in-hospital mortality as compared to whites (Table 5). Rheumatoid arthritis/collagen vascular diseases, valvular heart diseases, CHF, fluid and electrolyte disorders, coagulopathy, drug abuse, neurological disorders, peripheral vascular disorders, and renal failure independently predicted a greater risk of in-hospital mortality. Additionally, ACS-gout cohort undergoing PCI or CABG revealed highest odds of in-hospital mortality due to postoperative infections followed by hypotension/shock, postoperative myocardial infarction, and postoperative stroke, respiratory, AKI, and cardiac complications.

Table 3 Revascularization rates and outcomes in acute coronary syndrome with *vs* without gout

Outcomes	ACS + no gout(*n* = 3039546)	ACS + gout(*n* = 105198)	*P* value
Revascularization			
Thrombolysis	56694 (1.9)	1408 (1.3)	**< 0.001**[a]
PCI	1369759 (45.1)	38301 (36.4)	**< 0.001**[a]
CABG	245983 (8.1)	9657 (9.2)	**< 0.001**[a]
All-cause in-hospital mortality	151213 (5.0)	4539 (4.3)	**< 0.001**[a]
Disposition			**< 0.001**[a]
Routine	1878724 (61.8)	59605 (56.7)	
Transfer to short-term hospital	290145 (9.6)	10506 (10.0)	
Other transfers (SNF, ICF, other)	367183 (12.1)	15586 (14.8)	
Home Health Care	318501 (10.5)	14208 (13.5)	
Against Medical Advice	30531 (1.0)	681 (0.6)	
Length of stay (d) mean (± SD)	4.5 (± 5.2)	5.1 (± 5.0)	**< 0.001**[a]
Hospital charges ($) mean (± SD)	71312.73 (± 85186.10)	72328.21 (± 86223.92)	**< 0.001**[a]

[a]$P < 0.05$ indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; SNF: Skilled nursing facility; ICF: Intermediate care facility.

DISCUSSION

This is the first large scale study that evaluates the impact of gout on in-patient mortality in ACS patients and post-revascularization outcomes, predictors of in-hospital mortality during the post-revascularization period and healthcare resource utilization using the largest nationally representative cohort of ACS hospitalizations.

We found that ACS hospitalizations with gout comprised of older white men with a higher median household income, mostly Medicare beneficiaries, and were likely to be admitted to urban-teaching and Southern region hospitals more frequently. These patients also had a higher prevalence of comorbidities. Furthermore, the average LOS and total hospitalization charges were significantly higher. ACS patients with gout underwent CABG more often whereas the PCI revascularizations were comparable between both the cohorts. Those who underwent revascularizations (PCI or CABG) had shown higher overall complications; however lower all-cause in-hospital mortality compared to those without gout. A multivariate analysis demonstrated that older age, Hispanic and Asian race, lower household income, non-elective admissions, a previous history of CHF, valvular diseases, septicemia, shock, and cardiovascular complications were independent predictors of in-hospital mortality in ACS hospitalizations with gout post-revascularization.

In the study, the prevalence of gout among ACS patients was about 3.35% similar to the prevalence of gout among healthy United States population to be 3%-5%, with the age-standardized prevalence of hyperuricemia being 12%-15%[16]. In this study, gout has been prevalent in ACS patients with lower all-cause mortality compared to without gout. More recently, Latif *et al*[17] indicated that higher UA levels are associated with lower all-cause and cardiovascular mortality, however, they included only hemodialysis patients. Similarly, another study using the NIS suggested that co-occurring gout is associated with reduced in-hospital mortality among postmenopausal women admitted for AMI[18]. The paradoxical association with mortality could be due to focus on the short-term post-revascularization in-hospital outcomes, residual confounding factors in administrative data, or missed diagnosis in patients without gout. As shown with previous studies, our findings also showed that ACS hospitalizations with gout consisted of older white men, with higher co-existing comorbid conditions, mostly Medicare enrollees, and a lower median income quartile[19-21]. Surprisingly, Harrold *et al*[22] found that older women with gout more often had coronary heart disease. The results of our study suggest that ACS patients with gout had prolonged hospital stays post-revascularizations and management costs. A few other studies have also confirmed similar findings[23,24]. These studies have given a possible explanation for a prolonged stay and increased hospital cost due to increased risk of recurrent events and complications; however, the results were limited to the economic impact of ACS in general. This would be one of the few studies to describe the impact of gout on outcomes of ACS hospitalizations in terms of healthcare resource utilization including revascularization, the ensuing economic impact and the predictors of post-revascularization inpatient mortality.

Table 4 Post-revascularization (percutaneous coronary intervention or coronary artery bypass grafting) complications in acute coronary syndrome patients with *vs* without gout

Complications	No gout(*n* = 1592156)	Gout(*n* = 47307)	*P* value
All-cause in-hospital mortality	47466 (3.0)	1038 (2.2)	**< 0.001**[a]
Hemorrhage	43541 (2.7)	1470 (3.1)	**< 0.001**[a]
Blood transfusion	12272 (0.8)	524 (1.1)	**< 0.001**[a]
Hypotension/shock	7319 (0.5)	261 (0.6)	**0.004**[a]
Cardiac complications	46511 (2.9)	1523 (3.2)	**< 0.001**[a]
Postoperative myocardial infarction	27176 (1.7)	798 (1.7)	0.74
Stroke	3926 (0.2)	140 (0.3)	**0.033**[a]
Respiratory complications	46531 (2.9)	1642 (3.5)	**< 0.001**[a]
Gastrointestinal complications	25573 (1.6)	980 (2.1)	**< 0.001**[a]
AKI requiring dialysis	7843 (0.5)	628 (1.3)	**< 0.001**[a]
Urinary complications	4641 (0.3)	307 (0.6)	**< 0.001**[a]
Post procedural infections	24473 (1.5)	687 (1.5)	0.139

[a]$P < 0.05$ indicates clinical significance. ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; AKI: Acute kidney injury.

We found that age, race, median income, relevant comorbidities, and post-revascularization outcomes/postoperative complications in ACS patients undergoing PCI or CABG were independently predictive of in-hospital mortality in ACS patients with gout. Conversely, no association was observed in gender, which is consistent with a previous meta-analysis[25]. The gender-specific relative risk for congestive heart diseases (CHD) in that metanalysis for each increase of 1 mg/dL in serum UA was similar, but not statistically significant. However, subgroup analysis showed a significant association between hyperuricemia and CHD incidence in men, but increased risk of CHD mortality in women. The result differs from the previous studies that showed both men and women with gout have increased the risk of cardiovascular mortality compared with those without gout[26-28]. A retrospective study of STEMI patients who underwent PCI reported that one in every five patients had higher UA levels and it was independently associated with increased risk of in-hospital mortality[10]. Ndrepepa *et al*[29] reported that every 1 mg/dL rise in UA increased by 12% in the adjusted risk for 1-year mortality in an unselected cohort. Alcohol consumption and dyslipidemia have been associated with significantly increase the risk of hyperuricemia[30,31], which could further precipitate or increase the severity of gout. Interestingly, we observed the lower odds of in-hospital mortality with alcohol abuse, dyslipidemia, and obesity in ACS patients with gout undergoing revascularization. The implication of our findings is important for targeted preventive intervention in a certain population at the risk of gout and ACS.

Several potential mechanisms including causal role of UA in hypertension and atherosclerosis development, vasoconstriction, role of UA as pro-oxidant or gout per se promoting atherosclerosis, explain the increased risk of cardiovascular mortality in patients with gout[32,33]. However, whether gout is an independent factor with a pathogenic role in ACS or only attributing for associated risk factors of ACS, such as obesity, renal diseases, and diabetes, remains debatable[26,34]. In several large sample studies, gout was linked to increased all-cause and CV mortality rates[28,35,36], nonetheless, data on the impact of gout on post-revascularization remains limited in the literature.

Our study extends on the impact of gout on ACS patients with other comorbid conditions and revascularization complications. The study showed that cardiac, renal, pulmonary and vascular comorbidities are the risk factors for post-revascularization complications as well. Previous studies have shown an association of gout and hyperuricemia with many comorbid conditions. Demir *et al*[37] showed increased serum UA levels in calcific aortic valve stenosis (AS), with a positive correlation in the severity of the disease. Raised serum UA level may initiate calcification in the aortic valve and accelerate the progression by causing endothelial dysfunction[32]. Similarly, a prospective longitudinal study with a large cohort of 11681 men also concluded that CHF decompensation is independently associated with increased risk of hyperuricemia and likely gout, by increased urate production and decreased renal urate excretion[38]. Our study also shows an increased risk of in-hospital mortality in ACS patients with gout who are drug abusers that have never been evaluated in the

Table 5 Predictors of in-hospital mortality in acute coronary syndrome patients with gout undergoing revascularization

Predictor	Adjusted odds ratio	95%CI (LL-UL)	*P* value
Age in years at admission			**< 0.001**[a]
45-64 *vs* 18-44	2.99	1.08-8.30	**0.036**[a]
65-84 *vs* 18-44	5.72	2.04-16.01	**0.001**[a]
≥ 85 *vs* 18-44	15.63	5.51-44.39	**< 0.001**[a]
Male *vs* female	0.89	0.75-1.05	0.155
Race			**< 0.001**[a]
African American *vs* white	1.09	0.88-1.35	0.413
Hispanic *vs* white	0.45	0.31-0.67	**< 0.001**[a]
Asian *vs* white	0.65	0.45-0.94	**0.022**[a]
Non-elective *vs* elective admission	2.00	1.44-2.79	**< 0.001**[a]
Median household income quartile 0-25th *vs* 76-100$^{th\#}$	1.44	1.17-1.78	**0.001**[a]
Comorbidities			
Alcohol abuse	0.49	0.31-0.79	**0.003**[a]
Rheumatoid arthritis/collagen vascular diseases	1.57	1.09-2.25	**0.016**[a]
Congestive heart failure	5.91	3.54-9.86	**0.000**[a]
Coagulopathy	1.29	1.05-1.58	**0.014**[a]
Drug abuse	2.33	1.34-4.05	**0.003**[a]
Fluid and electrolyte disorders	2.88	2.49-3.35	**< 0.001**[a]
Other neurological disorders	1.72	1.33-2.23	**< 0.001**[a]
Obesity	0.79	0.66-0.95	**0.012**[a]
Peripheral vascular disorders	1.60	1.36-1.88	**< 0.001**[a]
Renal failure	2.04	1.13-3.70	**0.019**[a]
Valvular disease	8.15	3.87-17.15	**< 0.001**[a]
Dyslipidemia	0.63	0.54-0.72	**< 0.001**[a]
Outcomes/postoperative complications			
Hypotension/shock	2.97	1.93-4.56	**< 0.001**[a]
Cardiac complications	1.59	1.19-2.11	**0.002**[a]
Postoperative myocardial infarction	2.53	1.74-3.68	**< 0.001**[a]
Perioperative stroke	2.48	1.20-5.10	**0.014**[a]
Respiratory complications	1.80	1.41-2.30	**< 0.001**[a]
Postoperative acute kidney injury	1.48	1.26-1.74	**< 0.001**[a]
Infections/septicemia	3.94	3.01-5.16	**< 0.001**[a]

[a]$P < 0.05$ indicates clinical significance. CI: Confidence interval; LL: Lower level; UL: Upper level, Multivariate regression model was adjusted for age, gender, race, admission type, median household income, payer status, hospital characteristics and all relevant comorbidities and prior medical history.

past.

Systemic (kidney, respiratory and vascular) complications of revascularization in ACS patients with gout were likely to increase in-hospital mortality compared to patients without gout. This could also be the reason for prolonged hospitalization and increased treatment cost. Ejaz *et al*[39] showed that the UA is associated with a five to eight-fold increase in the post-cardiac surgery AKI. A study from the United Kingdom found 1.71 times higher risk of stroke in patients with gout than in the general population[40]. A nationwide population-based cohort study showed that gout was associated with an increased risk of pulmonary embolism by almost 53%[41]. Several studies have shown an association between gout and collagen vascular diseases, such as systemic sclerosis and rheumatoid arthritis[42,43]. Our findings would be prospective to initiate the discussion of screening and appropriate treatment of gout in ACS patients, and other dynamics responsible for gout should be considered when targeting new therapeutic strategies to prevent postoperative complications. In addition, appropriate screening for CVD in patients with gout is suggested as these patients have worse cardiovascular outcomes.

Our retrospective database study has few limitations which need to be mentioned. Due to the administrative nature of this database, some baseline patient's data might be missing, and follow up data was not available. There is a possibility of a misclassification bias from the use of diagnostic codes to define gout based on the clinical

findings by physicians or to diagnose ACS, with a possible change in terminology and use of generalized diagnostic codes by the clinicians. The NIS database does not contain information on serum uric acid level in gout patients so the severity and the extent of worse outcomes in ACS and post-revascularization outcomes with a unit increase in uric acid levels are not possible to be evaluated. In addition, each hospitalization is considered separately in the NIS, which could result in overestimation of the number of admissions for the same patient. Furthermore, the study emphasizes the short-term in-hospital impact of gout, lacking long-term follow-up outcomes. Nevertheless, the current study showed several important strengths, including nationwide large sample size, standardized methods, and absence of selection bias.

In conclusion, although gout did not increase the in-hospital mortality in ACS-related hospitalizations, the findings from this nationwide cohort highlight the significant impact of gout on in-hospital outcomes in ACS patients in terms of higher cardiovascular comorbidities, CABG frequency, post-revascularization complications, hospital stay, and total hospital charges.

ARTICLE HIGHLIGHTS

Research background

Previous studies have established a role of gout in predicting risk and prognosis of cardiovascular diseases. However, large-scale data on the impact of gout on inpatient outcomes of acute coronary syndrome (ACS)-related hospitalizations and post-revascularization is inadequate.

Research motivation

Limited data exist on impact of gout on in-hospital outcome of ACS in terms of healthcare utilization and post-revascularization outcomes.

Research objective

The study aimed to evaluate the impact of gout on in-hospital outcomes of ACS hospitalizations, subsequent healthcare burden and predictors of post-revascularization inpatient mortality.

Research methods

We used the national inpatient sample (2010-2014) to identify the ACS and gout-related hospitalizations, relevant comorbidities, revascularization and post-revascularization outcomes using the ICD-9 CM codes. A multivariable analysis was performed to evaluate the predictors of post-revascularization in-hospital mortality.

Research results

Out of 3144744 ACS-related hospitalizations, 105198 (3.35%) patients had gout. The ACS-gout cohort were more often older white males with a higher prevalence of comorbidities. ACS-gout cohort showed comparativly higher prevalence of Coronary artery bypass grafting. Post-revascularization complications including cardiac (3.2% *vs* 2.9%), respiratory (3.5% *vs* 2.9%), and hemorrhage (3.1% *vs* 2.7%) were higher whereas all-cause mortality was lower (2.2% *vs* 3.0%) in the ACS-gout cohort ($P < 0.001$). An older age (OR 15.63, CI: 5.51-44.39), non-elective admissions (OR 2.00, CI: 1.44-2.79), lower household income (OR 1.44; CI: 1.17-1.78), and comorbid conditions predicted higher mortality in ACS-gout cohort undergoing revascularization ($P < 0.001$). Odds of post-revascularization in-hospital mortality were lower in Hispanics (OR 0.45, CI: 0.31-0.67) and Asians (OR 0.65, CI: 0.45-0.94) as compared to white ($P < 0.001$). However, post-operative complications significantly raised mortality odds. Mean length of stay, transfer to other facilities, and hospital charges were higher in the ACS-gout cohort.

Research conclusions

Gout was not independently associated with an increased risk of post-revascularization in-hospital mortality in ACS. However, gout did increase post-revascularization complications.

Research perspectives

This study may help clinicians making evidence-based decision in patients with history of gout who are admitted with primary diagnosis of ACS and have undergone re-vascularization.

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ORIGINAL ARTICLE

Observational Study

Feasibility and safety of cryoballoon ablation for atrial fibrillation in patients with congenital heart disease

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Abstract

BACKGROUND

The prevalence of atrial fibrillation (AF) is on the rise in the aging population with congenital heart disease (CHD). A few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF centered on electrically isolating pulmonary veins (PV) in patients with CHD. In contrast, cryoballoon ablation has not previously been studied in this patient population despite its theoretical advantages, which include a favorable safety profile and shorter procedural time.

AIM

To assess the safety and feasibility of cryoballoon ablation for AF in an initial cohort of patients with CHD.

METHODS

The study population consisted of consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Procedural complications, acute success, and 1-year freedom from recurrent AF after a single procedure with or without antiarrhythmic drugs were assessed. Procedures were performed under conscious sedation. Left atrial access was obtained via a single transseptal puncture or through an existing atrial septal defect (ASD). Cryoballoon occlusion was assessed by distal injection of 50% diluted contrast into the pulmonary vein. At least one 240-second cryothermal application was performed upon obtaining complete pulmonary vein occlusion. Following ablation, patients were routinely followed at outpatient visits at 1, 3, 6, and 12 mo, and then annually.

RESULTS

Ten patients, median age 57.9 (interquartile range 48.2-61.7) years, 60% female, met inclusion criteria and were followed for 2.8 (interquartile range 1.4-4.5) years.

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Two had moderately complex CHD (sinus venosus ASD with partial anomalous pulmonary venous return; aortic coarctation with a persistent left superior vena cava), with the remainder having simple defects. AF was paroxysmal in 8 (80.0%) and persistent in 2 (20.0%) patients. The pulmonary vein anatomy was normal in 6 (60.0%) patients. Four had left common PV (n = 3) and/or 3 right PV (n = 2). Electrical pulmonary vein isolation (PVI) was acutely successful in all. One patient had transient phrenic nerve palsy that recovered during the intervention. No major complication occurred. One year after a single ablation procedure, 6 (60%) patients remained free from AF. One patient with recurrent AF had recovered pulmonary vein conduction and underwent a second PVI procedure. A second patient had ablation of an extra-pulmonary vein trigger for AF.

CONCLUSION
Cryoballoon ablation for AF is feasible and safe in patients with simple and moderate forms of CHD, with an excellent acute success rate and modest 1-year freedom from recurrent AF.

Key words: Congenital heart disease; Atrial fibrillation; Cryoballoon ablation; Pulmonary vein isolation; Catheter ablation

Core tip: Whereas, a few studies have described radiofrequency ablation for atrial fibrillation (AF) in patients with congenital heart disease (CHD), herein we report the first case series of cryoballoon ablation. Ten patients with CHD, median age 57.9 years, underwent cryoballoon ablation and were followed for a median of 2.8 years. Pulmonary vein isolation was acutely successful in all. No major complication occurred. One year after a single procedure, 6 (60%) patients remained free from AF. In conclusion, cryoballoon ablation is feasible and appears to be safe, with an excellent acute success rate and modest 1-year freedom from recurrent AF.

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INTRODUCTION

As patients with congenital heart disease (CHD) live longer, they are subject to numerous late complications of which arrhythmias figure prominently[1]. Atrial arrhythmias are the leading cause of morbidity and hospitalizations, with an estimated prevalence of 50% by the age of 65 years[2,3]. Whereas intra-atrial reentrant tachycardia (IART) is the most pervasive arrhythmia in patients with CHD, the prevalence of atrial fibrillation (AF) is on the rise in the aging population. Indeed, AF has already surpassed IART as the most common presenting arrhythmia in patients with CHD over 50 years of age[4].

A few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF centered on electrically isolating pulmonary veins (PV) in patients with CHD. In the largest series of 57 patients, single procedure arrhythmia-free survival rates on or off antiarrhythmic drugs were 63% at 1 year and 22% at 5 years[5]. Cryoballoon ablation for paroxysmal AF is generally considered non-inferior to radiofrequency ablation in patients with normal hearts or acquired heart disease[6]. However, cryoballoon ablation has not previously been assessed in patients with CHD. Theoretical advantages include the favorable safety profile and shorter procedural time, which could be of value when targeting multiple substrates, as is often the case in patients with CHD[6,7]. We, therefore, assessed our early experience with cryoballoon ablation in patients with CHD.

MATERIALS AND METHODS

Study population

The study population consisted of all consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Eligible patients were identified through the institutional adult CHD catheter ablation database and the tailored informatics system, CONGENERATE, which contains comprehensive diagnostic and procedural codes for patients followed at the Montreal Heart Institute Adult Congenital Center. All patients had symptomatic and drug refractory paroxysmal or early persistent AF (< 1 year in duration), documented by a surface electrocardiogram (ECG). Written informed consent for procedures was obtained in all patients. The study was approved by the local institutional review board.

Pulmonary vein isolation procedure

Patients were anticoagulated a minimum of 4 wk prior to the intervention. For those on vitamin K antagonists, the anticoagulant was continued throughout with a targeted international normalized ratio of 2 to 3. Direct oral anticoagulants were interrupted 24 h prior to the procedure. All patients underwent pre-procedural transesophageal echocardiography to rule-out thrombus, in addition to an imaging study by cardiac computed tomography (CT) or magnetic resonance imaging (MRI) to assess PV anatomy and exclude PV stenosis.

Procedures were performed under conscious sedation, with boluses of remifentanil for analgesia and a continuous infusion of propofol. A diagnostic 6-French deflectable decapolar catheter was positioned in the coronary sinus and a 9-French 9-MHz intracardiac echocardiography (ICE) catheter placed in the right atrium. Left atrial access was obtained via a single transseptal puncture or through an existing atrial septal defect (ASD) under ICE and fluoroscopic guidance. In the setting of an ASD closure device, ICE was used to identify areas of the native septum considered suitable for the transseptal puncture. Intravenous heparin was administered as a combination of boluses and an infusion to achieve and maintain an activated clotting time (ACT) > 300 s after transseptal access. The standard transseptal sheath was exchanged for a 15-French FlexCath (Medtronic CryoCath LP, Montreal, Canada) steerable sheath, through which a first- or second-generation 23- or 28-mm cryoballoon was advanced to the left atrium.

The size of the cryoballoon was selected according to PV diameters determined by CT, MRI, or PV angiography, with a preference for the larger 28-mm size (Figure 1A). PV potentials were recorded by a circular mapping catheter (Achieve, Medtronic, Minneapolis, MN) introduced in the central lumen of the cryoballoon catheter. The Achieve catheter was advanced distally into the PV to optimize support during cryoballoon positioning. The cryoballoon was inflated within the left atrium under fluoroscopic guidance and advanced to the PV ostium. The Achieve catheter was then withdrawn proximally to record PV potentials. Cryoballoon occlusion was assessed by distal injection of 50% diluted contrast into the PV. At least one standard 240-scryothermal application was delivered upon obtaining complete PV occlusion. Additional lesions were not systematically applied in the absence of a clinical reason to do so, such as delayed pulmonary vein isolation (PVI) or relatively warm ablation temperatures[8,9].

During cryoballoon ablation of right-sided PVs, diaphragmatic excursion was monitored by abdominal palpation while pacing the right phrenic nerve by the decapolar catheter positioned at the superior vena cava cranial to the right superior PV. In addition, diaphragmatic electromyographic monitoring of the compound motor action potential was systematically performed using a technique we previously described[10,11]. The procedural endpoint was PVI, as assessed by entrance and exit block. No extra-PV substrate was systematically targeted, although additional arrhythmias were also treated.

Post-ablation management and follow-up

Oral anticoagulation was restarted the evening following the intervention, typically 6 h post-procedure, and continued for a minimum of 6 mo. Patients were discharged home within 24 h. All patients were treated with proton-pump inhibitors for 4 wk. The decision to pursue antiarrhythmic therapy post procedure was at the physician's discretion based on clinical elements. Patients were routinely followed at outpatient visits with ECG recordings at 1, 3, 6, and 12 mo, and then annually. Regular telephone interviews were also performed and medical consultations were promptly scheduled in the event of symptoms suggestive of arrhythmia. For patients with recurrent symptoms not captured by ECGs, 24-h Holter and/or event recorder monitoring was performed. Recurrence was defined as any episode of AF lasting more than 30 s after

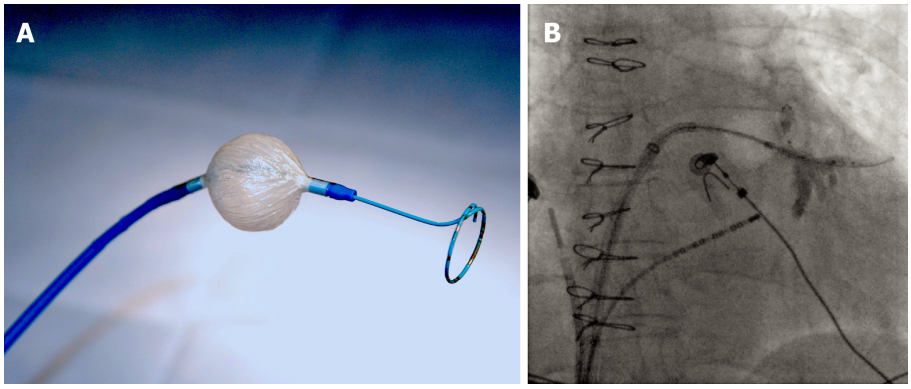

Figure 1 Cryoballoon ablation for atrial fibrillation in a patient with a sinus venosus atrial septal defect and partial anomalous pulmonary venous return. A: A 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN) along with a circular mapping catheter (Achieve, Medtronic, Minneapolis, MN) introduced in its central lumen; B: The cryoballon is positioned at the ostium of the left inferior pulmonary vein (LIPV) in a patient with a sinus venous atrial septal defect and partial anomalous pulmonary venous return. The circular mapping catheter is placed inside the proximal LIPV. Contrast injection reveals complete cryoballoon occlusion of the LIPV.

a 3-mo blanking period. The primary endpoint was 1-year freedom from recurrent AF after a single procedure, with or without antiarrhythmic drugs.

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR; 25th-75th percentile) and categorical variables as frequencies and percentages. Recurrence-free survival was plotted using the Kaplan-Meier product limit method. Complete data were available in all patients. Considering the descriptive nature of the study, inferential statistics were not performed. Statistical analysis was conducted using R software, version 3.3.2 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics

Ten patients, median age 57.9 (IQR 48.2-61.7) years, 60% female, met inclusion criteria and underwent cryoballoon ablation for AF. Baseline clinical characteristics are summarized in Table 1. Eight patients had simple forms of CHD [*i.e.*, ASD (n = 6), ASD associated with ventricular septal defect (VSD; n = 1), and quadricuspid aortic valve with aortic stenosis (n = 1)]. Two had moderately complex CHD [*i.e.*, sinus venosus ASD with partial anomalous pulmonary venous return (n = 1; Figure 1B), and aortic coarctation with a persistent left superior vena cava (n = 1)]. Three patients with ASDs had percutaneous device closure 3 to 6 months following the AF ablation procedure. In the remaining 7 patients, cryoballoon ablation was performed a median of 15.5 (IQR 8.2-30.3) years after repair of CHD (Table 2).

All patients experienced palpitations during AF episodes. In addition, 8 (80.0%) reported dyspnea, with 2 (20.0%) having associated congestive heart failure. Seven (70.0%) had unplanned hospitalizations for AF, and 6 (60.0%) had electrical cardioversions. The AF pattern was paroxysmal in 8 (80.0%) and early persistent in 2 (20.0%). Patients were referred for AF ablation a median of 4.6 (IQR 0.9-10.3) years after the initial diagnosis of AF and had received a median of 2 (IQR 2-3) antiarrhythmic drugs. All patients had preserved left ventricular ejection fractions (when in sinus rhythm), with a median indexed left atrial volume of 34.5 (IQR 27.3-44.0) mL/m^2 by echocardiography. IART and/or focal atrial tachycardia (FAT) were also documented in 5 (50.0%) patients, with one having had a prior catheter ablation procedure (for a cavotricuspid isthmus-dependent IART, lateral right atrial IART, and inferoseptal non-automatic FAT).

Pulmonary vein anatomy and procedural characteristics

The PV anatomy was normal in 6 (60.0%) patients. Two had a left common PV (LCPV), 1 had a LCPV with 3 right PVs, and 1 had 3 right PVs. In all patients, left atrial access was obtained through a portion of the native or surgically repaired atrial septum. A single 28-mm cryoballoon was used in 6 (60.0%) and a single 23-mm cryoballoon in 3 (30.0%) patients. In one patient, both 28- and 23-mm cryoballoons were used. Main procedural characteristics are summarized in Table 3. PVI was

Table 1 Baseline characteristics

	n = 10
Age, yr	57.9 (48.2-61.7)
Female gender, *n* (%)	6 (60.0)
Type of congenital heart disease, *n* (%)	
Simple	8 (80.0)
Atrial septal defect	6 (60.0)
Atrial and ventricular septal defects	1 (10.0)
Quadricuspid aortic valve with aortic stenosis	1 (10.0)
Moderate	2 (20.0)
Sinus venosus atrial septal defect with PAPVR	1 (10.0)
Aortic coarctation with persistent left superior vena cava	1 (10.0)
Age at repair, yr	44.3 (12.9-54.7)
Hypertension, *n* (%)	5 (50.0)
Dyslipidemia, *n* (%)	3 (30.0)
Diabetes mellitus, *n* (%)	1 (10.0)
Body mass index > 30 kg/m^2, *n* (%)	2 (20.0)
Current smoker, *n* (%)	1 (10.0)
Coronary artery disease, *n* (%)	3 (30.0)
Symptoms/signs associated with atrial fibrillation, *n* (%)	
Palpitations	10 (100.0)
Dyspnea	8 (80.0)
Congestive heart failure	2 (20.0)
Prior hospitalization for atrial fibrillation, *n* (%)	7 (70.0)
Left ventricular ejection fraction, %	60 (55-60)
Left atrial volume, mL/m^2	34.5 (27.3-44.0)
Pattern of atrial fibrillation, *n* (%)	
Paroxysmal	8 (80.0)
Persistent	2 (20.0)
Time from diagnosis of atrial fibrillation to procedure, years	4.6 (0.9-10.3)
Number of antiarrhythmic drugs tried	2 (2-3)
Pharmacological therapy, *n* (%)	
Antiarrhythmic drug	10 (100.0)
Beta-blockers	7 (70.0)
Amiodarone	3 (30.0)
Sotalol	2 (20.0)
Flecainide	2 (20.0)
Propafenone	1 (10.0)
Dofetilide	1 (10.0)
Dronedarone	1 (10.0)
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	4 (40.0)
Anticoagulant	8 (80.0)
Diuretic	2 (20.0)

Continuous variables are expressed as median and interquartile range (25th-75th percentile). PAPVR: Partial anomalous pulmonary venous return.

achieved in all patients. Transient phrenic nerve palsy occurred in one patient, requiring prompt termination of the cryoballoon application. Diaphragmatic excursion fully recovered during the intervention. No major complication occurred.

Recurrence of AF during follow-up

Patients were followed for a median of 2.8 (IQR 1.4 to 4.5) years after ablation. One year after a single procedure, 6 (60%) patients remained free from AF, including 4 (66.7%) without antiarrhythmic agents. Propafenone was continued in 2 patients. Freedom from AF is plotted in Figure 2. Two of the four patients with recurrent AF

Table 2 Individual patient characteristics

Patient #	Age(yr)	Sex	CHD	Type of repair	Age at repair(yr)	Age at first AF(yr)	AF pattern	Number AADs	LA volume (mL/m²)
1	46.4	F	ASD + VSD	Surgical patch	1.5	38.5	Paroxysmal	5	27
2	55.8	F	ASD	Percutaneous device	55.7	55.3	Paroxysmal	5	52
3	60.0	F	SVASD + PAPVR	Surgical patch	44.3	46.3	Paroxysmal	2	26
4	69.2	F	ASD	Percutaneous device	53.7	67.8	Paroxysmal	2	45
5	69.5	F	ASD	Surgical patch	24.3	68.6	Paroxysmal	2	39
6	62.3	F	ASD	None	N/A	61.4	Paroxysmal	2	23
7	15.4	M	AoCo + LSVC	Surgical AoCo repair	0.0	14.4	Paroxysmal	3	30
8	59.9	M	Quadricuspid AS	Aortic valvuloplasty	59.0	37.9	Persistent	3	45
9	38.8	M	ASD	None	N/A	28.5	Paroxysmal	2	28
10	53.4	M	ASD	None	N/A	53.0	Persistent	2	41

CHD: Congenital heart disease; AF: Atrial fibrillation; AAD: Antiarrhythmic drug; LA: Left atrial; F: Female; M: Male; ASD: Atrial septal defect; SVASD: Sinus venosus ASD; PAPVR: Partial anomalous pulmonary venous return; AoCo: Aortic coarctation; LSVC: Left superior vena cava; AS: Aortic stenosis; N/A: Not applicable

had a subsequent catheter ablation procedure. One had recovered PV conduction and underwent antral PVI with radiofrequency energy. In the other patient, AF was triggered by a scar-based IART circuit that was ablated with radiofrequency energy, along with the cavotricuspid isthmus.

DISCUSSION

This study is the first to report on the feasibility and safety of cryoballoon ablation for AF in patients with CHD. Main findings were as follows: The procedures were acutely successful in all, no major complication occurred, and the 1-year single-procedure success rate was modest and within the range reported for radiofrequency catheter ablation.

With AF poised to become the next arrhythmic epidemic after IART in patients with CHD, a better understanding of mechanisms and management are key challenges for the coming years. Atrial arrhythmias are notoriously difficult to control with antiarrhythmic drugs in patients with CHD. Moreover, in those with fragile physiologies, these arrhythmias can result in rapid hemodynamic deterioration, heart failure, and sudden death. The disappointing experience with long-term medical therapy has contributed to the growing preference for non-pharmacological options[12,13]. Yet, while numerous studies have focused on IART or FAT in CHD, few have reported acute and long-term outcomes for AF ablation and none have used the cryoballoon.

The largest report on radiofrequency catheter ablation of AF included 57 patients of whom 35 (61.4%) had mild, 10 (17.5%) moderate, and 12 (21.1%) severe forms of CHD[5]. If PVI failed to restore sinus rhythm, additional linear lesions were performed and complex fractionated atrial electrograms were targeted. Consistent with our results, the one-year arrhythmia-free survival rate after a single procedure was 63%. It then declined to 22% at 5 years. In another series of 36 patients with CHD and AF, the majority of whom had atrial (61%) or ventricular (17%) septal defects, antral PVI was performed[14]. Additional ablation sites in some patients included the superior vena cava junction, left atrial septum and posterior wall, coronary sinus ostium, and crista terminalis. After a single procedure, freedom from recurrent AF in the absence of antiarrhythmic drugs was 42% at 300 d and 27% at 4 years. These rates were not significantly different from age-matched controls without CHD. Two series of 39 and 45 patients with AF and ASD closure devices reported successful transseptal access in 90%-98%, with 76-77% freedom from recurrent arrhythmias with or without antiarrhythmic drugs at 12 to 14 mo[15]. For more complex forms of CHD, the literature is largely limited to case reports of AF ablation[16,17].

The small sample size in our early case series precludes definitive conclusions as to

Table 3 Procedural characteristics

	n = 10
Access to the left atrium, *n* (%)	
Across an atrial septal defect	3 (30.0)
Trans-septal puncture across the native septum	5 (50.0)
Trans-septal puncture across a surgical patch	2 (20.0)
Trans-septal puncture across a percutaneous closure device	0 (0.0)
Cryoballoon size, *n* (%)	
23 mm	4 (40.0)
28 mm	7 (70.0)
Total cryoablation time, seconds	
Left superior pulmonary vein	374 (252-475)
Left inferior pulmonary vein	480 (240-480)
Left common pulmonary vein	480 (480-700)
Right superior pulmonary vein	360 (261-453)
Right inferior pulmonary vein	315 (247-450)
Number of applications	
Left superior pulmonary vein	2 (1.5-2.0)
Left inferior pulmonary vein	1 (1.0-2.0)
Left common pulmonary vein	2 (2.0-3.5)
Right superior pulmonary vein	2 (1.25-2.75)
Right inferior pulmonary vein	2 (1.0-2.0)
Minimal temperature reached, °C	
Left superior pulmonary vein	-49 (-49, -51)
Left inferior pulmonary vein	-45 (-41, -52)
Left common pulmonary vein	-48 (-46, -54)
Right superior pulmonary vein	-45 (-40, -51)
Right inferior pulmonary vein	-45 (-39, -54)
Total procedural time, min	183.0 (152.5, 224.0)
Total fluoroscopy time, min	33.5 (27.5-43.0)

Continuous variables are expressed as median and interquartile range (25^{th}-75^{th} percentile).

whether the observed 1-year arrhythmia free survival rate of 60% is significantly lower than the 75%-80% rate reported with cryoballoon ablation in patients without CHD[6,18-20]. However, anatomical, mechanistic, and technical aspects can potentially contribute to lower success rates in patients with CHD. First, access to the left atrium can lead to an unusual course of the ablation catheter by virtue of abnormal septal anatomy, traversing an existing ASD, or puncturing at an unconventional site. The resulting lack of support can render it more difficult to achieve complete cryoballoon PV occlusion. The high number of applications in each PV and relatively lengthy fluoroscopy times reflect these technical challenges. Second, although it is well documented that most triggers for paroxysmal AF arise from PVs in patients with structurally normal hearts, this is not necessarily the case for those with CHD[21]. Anatomical differences, surgical scarring, hemodynamic sequelae, and/or hypoxic stress can contribute to a higher prevalence of extra-PV triggers, as observed in one of our patients[22]. Focal non-PV drivers for AF have been described in a few patients with CHD[23]. These drivers were characterized by circumscribed areas exhibiting continuous electrical activity coexisting with parts of the atrium activated in a regular manner. Application of radiofrequency energy at these sites terminated AF. These extra-PV substrates cannot be targeted by the cryoballoon. Third, AF ablation outcomes are more favorable in patients with a short-lasting history of AF and no extensive atrial remodeling[24]. In contrast, considering the challenges discussed, CHD patients are typically referred later in their disease course, often after failing several antiarrhythmic drugs[14]. A higher perceived level of difficulty combined with uncertain outcomes may discourage operators from considering AF ablation at an earlier stage. Delayed referral can theoretically impact results owing to a higher degree of atrial structural and electrical remodeling changes. Lastly, chronic volume and pressure loads in patients with CHD result in thickening of atrial walls that can

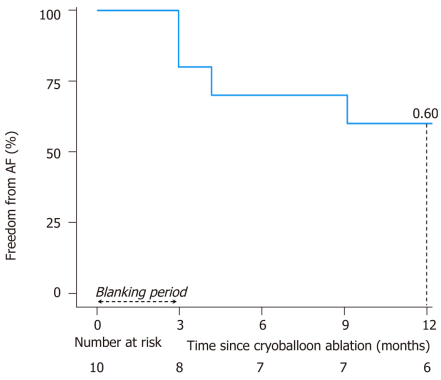

Figure 2 Kaplan–Meier survival curve for freedom from atrial fibrillation after a single cryoballoon ablation procedure.

hinder the creation of durable circumferential PV ablation lesions[25].

In our study, a substantial proportion of patients had factors classically associated with AF in the general population. Hypertension, dyslipidemia, smoking, higher body mass index, and coronary artery disease have also recently been associated with AF in a multicenter study of patients with heterogeneous forms of CHDs[4]. This observation paves the way for future studies as to whether education and preventive risk factor management can significantly impact the AF burden in patients with CHD. Furthermore, it highlights the epidemiological changes associated with the aging CHD population and the potential interplay between CHD and acquired comorbidities.

In addition to AF, half the patients in our study had coexisting atrial arrhythmias, mainly IART, and benefitted from catheter ablation of these other substrates. The co-occurrence of AF and other atrial arrhythmias is well described in patients with CHD[4]. Considering the propensity to develop various forms of arrhythmias, catheter ablation procedures in adults with CHD should generally be considered palliative[12]. Some evidence suggests that even if arrhythmias are not entirely eliminated, clinical outcomes improve[26].

Limitations

This single-center retrospective study represents the first foray into cryoballoon ablation for AF in CHD and demonstrates feasibility and safety. The study is underpowered to explore factors associated with recurrent arrhythmias. Although ECGs were systematically performed at regular follow-up intervals, continuous monitoring was symptom-based such that asymptomatic self-terminating episodes of AF may have escaped detection. The population is limited to patients with simple or moderate forms of CHD such that results should not be extrapolated to those with complex CHD. No direct comparisons were made to AF ablation using radiofrequency energy in patients with CHD, or to cryoballoon ablation in controls without CHD.

In conclusion, cryoballoon ablation for AF is feasible and appears to have an acceptable safety profile in patients with simple and moderate forms of CHD. In this initial experience, the acute success rate for PVI was high, with a modest 1-year event-free survival rate after a single procedure. Recurrences may be due to non-PV triggers. Further studies are required to provide mechanistic insights regarding triggers and substrates for AF in the various forms of CHD, and to compare cryoballoon to radiofrequency catheter ablation.

ARTICLE HIGHLIGHTS

Research background

The prevalence of atrial fibrillation (AF) is on the rise in the growing and aging population with congenital heart disease (CHD). Whereas a few case series have described the feasibility and early outcomes associated with radiofrequency catheter ablation of AF, cryoballoon ablation has not previously been studied in this patient population.

Research motivation

Theoretical advantages of cryoballoon ablation include its favorable safety profile and shorter procedural time, which could be valuable when targeting multiple arrhythmias during a single

intervention, as is often the case in patients with CHD.

Research objectives
We sought to assess feasibility, safety, and recurrence-free survival in our initial experience with cryoballoon ablation for AF in patients with CHD.

Research methods
A single-center cohort study was conducted on consecutive patients with CHD and cryoballoon ablation for AF at the Montreal Heart Institute between December 2012 and June 2017. Procedural complications, acute success, and 1-year freedom from recurrent AF after a single procedure with or without antiarrhythmic drugs were assessed.

Research results
Ten patients with CHD, median age 57.9 years, underwent cryoballoon ablation and were followed for a median of 2.8 years. Pulmonary vein isolation was acutely successful in all. No major complication occurred. One year after a single procedure, 6 (60%) patients remained free from AF.

Research conclusions
Cryoballoon ablation for AF is feasible and appears to have an acceptable safety profile in patients with CHD. In our initial experience, the acute success rate for PVI was high, with a modest 1-year event-free survival rate after a single procedure.

Research perspectives
Further studies are required to provide mechanistic insights regarding triggers and substrates for AF in the various forms of CHD, and to compare cryoballoon to radio-frequency catheter ablation.

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