Urinary Isoxanthopterin as a Novel Predictor following Catheter Ablation for Atrial Fibrillation

（心房細動に対する経皮的心筋焼灼術後の頻脈性心房性不整脈発症を予測する尿中イソキサントプテリン）

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Abstract

Background:
Oxidative stress is associated with atrial fibrillation recurrence following catheter ablation. Urinary isoxanthopterin (U-IXP) is one of the non-invasive markers which reflect the reactive oxygen species; however, its ability to predict atrial tachyarrhythmias (ATAs) occurrence following catheter ablation remains uncertain.

Methods:
Among the patients who received scheduled catheter ablation for atrial fibrillation, baseline U-IXP levels were measured just before the procedure. The prognostic impact of baseline U-IXP upon ATAs occurrence following catheter ablation was investigated.

Results:
Among 107 patients (71 years old, 68% men), baseline U-IXP level was 0.33 nmol/gCr on the median. During a mean of 603 days of follow-up, 32 patients had ATAs. Baseline higher U-IXP was independently associated with the occurrence of ATAs following catheter ablation with a hazard ratio of 4.69 (95% confidence interval 1.82 – 12.37, $p = 0.001$) adjusted for the left atrial diameter, a persistent type, and hypertension which were potential confounders, accompanying a cut-off of 0.46 nmol/gCr, which stratified cumulative incidence of ATAs occurrence ($p < 0.001$).

Conclusion:
U-IXP can be used as the non-invasive predictive biomarker for ATAs following catheter ablation for atrial fibrillation.

Keywords:
Atrial fibrillation, Atrial tachyarrhythmias, Oxidative stress, Urinary isoxanthopterin.

Abbreviations

AF: atrial fibrillation
ATAs: atrial tachyarrhythmias
U-IXP: urinary isoxanthopterin

Introduction

Pulmonary vein isolation for atrial fibrillation (AF) has become widely accepted as a therapeutic strategy irrespective of the AF duration. However, the success rates of the first procedure are limited to around 50-70% in paroxysmal and 40-50% in persistent AF.[1] Moreover, asymptomatic recurrence rate is approximately 50% following catheter ablation.[2,3] Patients with asymptomatic recurrence are at risk of cardiovascular events due to the lack of physician care. Implantable loop recorders are recommended to monitor the recurrence of AF following catheter ablation. However, given its invasiveness and high cost, it cannot be recommended for all candidates for catheter ablation.[4] Methodologies to identify high-risk cohorts have been desired.

Several biomarkers, including myocardial injury biomarkers, natriuretic peptides, and serum uric acid, as well as left atrial size, are proposed to predict post-procedural AF recurrence, although their predictability remains under satisfactory levels.[5,6,7]

Oxidative stress, which evokes cardiovascular inflammation, has recently been clarified to have a deep association with AF recurrence. However, given its complexity to quantify the degree of oxidative stress, their detailed association remains uncertain. Recently, urinary isoxanthopterin (U-IXP), which is converted from pterin mainly by xanthine oxidase, was proposed as a novel biomarker to predict clinical outcomes in the heart failure cohort.[8] I hypothesized that baseline U-IXP might be an independent marker to predict AF recurrence following catheter ablation.[9]

Methods

Study population

Patients who were hospitalized to receive AF catheter ablation in our institute between November 2019 and August 2021 were screened prospectively. AF was detected on 12-lead surface electrocardiograms within the past 1 year. Patients who met the following criteria were excluded: (1) aged under 20 years old, (2) patients who received cardiac intervention within the past three months, (3) end-stage renal disease on dialysis, (4) patients receiving angiotensin receptor-neprilysin inhibitors, and (5) patients who were lost follow-up within six months following the procedures. The present study was conducted in compliance with the Declaration of Helsinki and was approved by the institutional review board at the University of Toyama. Written informed consents were obtained from all patients.

Patient characteristics

Baseline clinical characteristics on admission including demographics, electrocardiographic, echocardiographic parameters, and laboratory data were retrieved from the electronic medical record. I adopted troponin I as a myocardial injury biomarker and N-terminal pro brain natriuretic peptide (NT-proBNP) as a representative of natriuretic peptides.

Urinary biomarker testing

Urine was prospectively collected in plastic tubes on the day before the procedures. The samples were stored at –80°C after centrifugation at room temperature for 10 minutes at 3,000 rpm until analyses. U-IXP was measured by HPLC (column, YMC-Triart C18; size 100 mm × 4.6 mm (length × diameter); detector, UV at 2,534 nm; YMC, Kyoto, Japan). The U-IXP/urinary-creatinine ratio quotient was calculated as an independent variable.

Pulmonary veins isolation for catheter ablation

Catheter ablation for AF using the EnSite mapping system (Abbott Inc., Chicago, Illinois) or the CARTO mapping system (Biosense Webster Inc., Irvine, California) were performed in the sedated state using noninvasive bispectral electroencephalogram analysis with activated clotting times over 300 seconds. Pulmonary vein isolation was performed with 40W of radiofrequency delivery until reaching the Lesion Size Index of 5.0 in the EnSite or the Ablation Index of 500 in the CARTO. In cases using the cryoballoon system (Medtronic Inc. Minneapolis, Minnesota), each pulmonary vein was frozen until plus 120 seconds from pulmonary vein isolation achieving or until a maximum of 240 seconds. Additional isolations for the left atrial posterior wall were left to the discretion of the operators.

Clinical outcomes

Occurrence of any atrial tachyarrhythmias (ATAs) including AF, atrial flutter, and atrial tachycardia following catheter ablation was defined as the primary endpoint. Twelve-lead surface electrocardiogram, 24-hour or two-week Holter monitors, or portable electrocardiograph (OMRON Corp., Kyoto, Japan) were used for detecting ATAs. Symptoms alone without any evidence of ATAs were not counted as events. The occurrences of ATAs during the 90-day blanking period following the procedures were not counted as events.

Statistical analysis

Data were expressed as the mean and standard deviation for normally distributed variables and as the median with the interquartile range for non-normally distributed data. The Shapiro-Wilk test was performed to assess normality. Categorical data are expressed as numbers and percentages.

Multivariable cox proportional hazard model analyses were performed to evaluate whether the biomarkers were independently associated with the primary endpoints following the procedures, adjusted by the clinical variables with $p < 0.05$ in the univariable analyses. Receiver operating characteristics analyses were performed to calculate cutoffs to best discriminate the primary endpoints during one year following the catheter ablation. Kaplan-Meier survival curves were drawn, and the log-rank test of the curve was conducted to evaluate group differences. Data analysis was performed using JMP ver. 14 (SAS, NC, USA).

Results

Clinical characteristics

Among a total of 125 screened patients, 107 subjects (mean 71 years old, 68% man) were enrolled (Table 1). Of them, 39 subjects (36%) had persistent AF. Sixty-five (61%) patients had hypertension, and about half of the subjects received angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The mean left atrial diameter was 42 mm. The U-IXP exhibited non-normal distribution and the median value was 0.33 [0.16 – 0.67] μmol/gCr (Figure 1).

Cather ablations were performed successfully without any peri-procedural complications in all patients. The posterior wall isolation in addition to pulmonary veins isolation was performed in 29 (27%) patients.

Biomarkers and the primary endpoints

During the follow-up periods (mean 603 [262 – 726] days), ATAs were encountered in 32 subjects. Referencing the findings of univariable analyses (Table 2), U-IXP was demonstrated to be an

independent predictor of the primary endpoints among potential biomarkers and clinical parameters in several models adjusted for statistically derived potential confounders (Table 3).

A cut-off of U-IXP to best discriminate the primary endpoint was calculated as 0.46 μmol/gCr (Figure 2). A higher baseline U-IXP level above the cut-off was associated with a four-fold occurrence of the primary endpoints compared with those with lower baseline U-IXP (59.4% versus 18.5%, p = <0.001; Figure 3-A). The results were the same as in both a paroxysmal type and a persistent type (Figures 3-B and 3-C).

Relationships between U-IXP and the durability of pulmonary veins isolation

Among 32 patients with ATAs occurrence during follow-up, 24 patients underwent the redo procedures. Of them, 11 (46%) patients had pulmonary vein reconnection. U-IXP level in patients without pulmonary veins reconnection demonstrated higher tendency compared with those with (0.81 [0.20 – 1.12] vs. 0.36 [0.19 – 0.68], p = 0.183, Figure 4).

Discussion

I demonstrated that baseline higher U-IXP was independently associated with the future occurrence of ATAs following catheter ablation.

Oxidative stress and ATAs

Although several factors were established as AF recurrence predictors, oxidative stress has been known as one of the most seminal pathogenesis.[10-12] Excessive production of reactive oxygen species is involved in the structural and electrical remodeling of the atrium, leading to pro-

arrhythmogenicity.[13] Among the key factors of oxidative stress production including mitochondria, NAD(P)H oxidase, xanthine oxidase, uncoupled nitric oxide synthase, and cytochrome C oxidase, xanthine oxidase activity contributes to producing U-IXP and fluctuated along with induced type nitric oxide.[14-17] These previous studies suggest that U-IXP levels should reflect not only xanthine oxidase activity but also induced type nitric oxide-mediated oxidative stress, which promotes cardiomyocyte apoptosis in human atrial fibrillation.[18] Xanthine oxidase produces also uric acid; however, uric acid could not be associated with ATAs in the present study.[16] Induced type nitric oxide might affect the difference in the predictive values between U-IXP and uric acid.

Induced inflammatory by oxidative stress is known as the pathogenesis of AF recurrence; however, detailed mechanisms remain unclear.[19,20] In terms of electrophysiological studies, mainly two factors have been established as influencers of ATAs following AF ablation; pulmonary veins reconnection and non-pulmonary veins triggers.[21] In the present study, ATAs patients without pulmonary vein reconnection tended a higher U-IXP level compared with those with pulmonary vein reconnection. Although no statistically significant difference was observed between the two, high U-IXP may reflect non-pulmonary vein triggers influenced by high oxidative stress-induced electrical remodeling.

Clinical impacts of U-IXP

The current guideline recommends the continuation of oral anticoagulants in patients with CHADS2 scores equal to or above 2, considering the potential AF recurrence following the procedures.[22] However, CHADS2 or CHA2DS2-VASc scores are not associated with future AF recurrence.[23] U-IXP might be a useful index to distinguish optimal candidates for long-term

anticoagulation therapy following the procedures.

Regarding the approaches for AF suppression, several observational studies have revealed that the improvement of symptoms and the degree of AF type were related to the degree of weight loss, and the weight loss demonstrated favorable outcomes following AF catheter ablation.[24-26] Adipose tissues mediated oxidative stress in obesity is known as a pathogenesis of cardiovascular diseases.[14] The present cut-off value of U-IXP might be a performance indicator of the weight loss program for retrieving physiological redox balance.

Study Limitations

This study has several limitations. First, this was a single-center study with small sample size. Therefore, although the ATAs mechanisms should be different between the paroxysmal and persistent types, I could not analyze in a multivariate each type. Second, other previously reported biomarkers reflecting oxidative stress were not evaluated. Therefore, I could not conclude that U-IXP has the most robust biomarker among the oxidative stress biomarkers. Third, ATAs detection might lack in some subjects because detecting ATAs following catheter ablation is difficult without continuous monitoring of cardiac rhythm.

Conclusions

U-IXP which was collected before the procedures was a non-invasive predictor of ATAs occurrence in patients with AF catheter ablation.

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Figure Legends

Figure 1. The distribution of urinary isoxanthopterin

Figure 2. The receiver operating characteristics analyses of urinary isoxanthopterin to best discriminate atrial tachyarrhythmias occurrence during one year following catheter ablation

ATAs, atrial tachyarrhythmias.

Figure 3. Kaplan-Meier curves of atrial tachyarrhythmias free rate

A. All subjects

B. Patients with paroxysmal atrial fibrillation

C. Patients with persistent atrial fibrillation

CI, confidence interval; HR, hazard ratio.

Figure 4. Comparison of urinary isoxanthopterin for patients with the redo procedure between those with pulmonary vein reconnection and those without