Heart and Vessels (2019) 34:641–649
https://doi.org/10.1007/s00380-018-1288-0

ORIGINAL ARTICLE

The relationship between serum indoxyl sulfate and the renal function after catheter ablation of atrial fibrillation in patients with mild renal dysfunction

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Received: 24 June 2018 / Accepted: 26 October 2018 / Published online: 8 November 2018

Abstract
Indoxyl sulfate (IS), a protein-bound uremic toxin, induces renal disorders and atrial fibrillation (AF). It is well known that renal dysfunction is a risk factor for AF and radiofrequency catheter ablation (RFCA) improves the renal function. However, the improvement in the renal function after RFCA in patients with early stage chronic kidney disease (CKD) and the serial changes in the IS level have not been fully elucidated. This study aimed to investigate whether IS affects the improvement in the renal function. A total of 91 consecutive patients with mild kidney dysfunction (CKD stage I–II) who underwent RFCA and maintained sinus rhythm were prospectively enrolled. The plasma IS level and estimated glomerular filtration rate (eGFR) were determined before, 3 months, and 1 year after RFCA. The patients were divided according to the IS quartiles (Q1–4; < 0.4, 0.4–0.7, 0.7–1.2, and > 1.2 μg/ml). There was no significant difference in the eGFR among the IS quartiles. A significantly higher eGFR improvement rate was obtained for IS-Q4 than the other quartiles ($p = 0.039$). The IS-Q4 IS level significantly decreased at 1 year after RFCA (1.8 ± 0.8 to 1.2 ± 0.7 μg/ml, $p < 0.01$). The multivariable logistic model revealed that a high-IS level (IS-Q4) was an independent predictor of an eGFR improvement (OR 3.33; 95% CI 1.16–9.59; $p = 0.026$). A high-IS level reduction after RFCA improved the renal function in AF patients with mild kidney dysfunction.

Keywords Indoxyl sulfate · Atrial fibrillation · Renal function · Catheter ablation

Introduction

Recently, there have been many reports regarding renal dysfunction being a risk factor for developing atrial fibrillation (AF) and radiofrequency catheter ablation (RFCA) in patients with AF improves the renal function [1–7]. However, the improvement in the renal function after RFCA in patients with early stage chronic kidney disease (CKD) is controversial.

Indoxyl sulfate (IS) is a highly protein-bound and poorly dialyzable uremic toxin metabolized by dietary tryptophan [8–11]. Furthermore, it has been proposed as a critical factor accelerating the fibrosis in various tissues and facilitates not only the progression of CKD and cardiovascular disease, but also atrial fibrosis and AF [9, 11–15].

After RFCA, the serial changes in the IS level in patients with a normal kidney function or mild kidney dysfunction have not been fully elucidated. The present study aimed to investigate the improvement in the renal function after RFCA in AF patients with mild kidney dysfunction and to evaluate whether IS affects the improvement in the renal function.

Methods

Study population and study design

This study enrolled 121 consecutive patients with CKD stage GI-II (eGFR ≥ 60 ml/min/1.73 m^2) who underwent RFCA of AF at our institute between January 2016 and April 2017.

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The patients were followed up for at least 1 year after the RFCA (19.6 ± 4.4 months). Of those patients, 30 who had recurrent AF during the follow-up period were excluded. Finally, 91 patients who successfully underwent an RFCA and maintained sinus rhythm (SR) for at least 1 year after the RFCA were reviewed in this analysis. The serum IS level and eGFR were determined before, at 3 months, and 1 year after the RFCA. The patients were divided into 4 groups based on the quartiles of the serum IS level measured before the RFCA. The serial changes in the IS and eGFR of the patients who maintained sinus rhythm after the RFCA were investigated. The improvement in the renal function was defined as a ΔeGFR> 5 ml/min/1.73 m^2 at 1 year after RFCA [4, 6, 16]. The types and classification of AF were defined according to the guidelines [17]. The serum IS concentrations were measured using high-performance liquid chromatography (HPLC) (GULLIBER; JASCO Corporation, Tokyo Japan). Each serum sample (10 µl) was analyzed by a reversed-phase HPLC (Capcell Pak MF Ph-1 SG80S5 4.6 mm I.D. × 150 mm; SHISEIDO CO., LTD., Tokyo Japan). The mobile phase, 0.1 M KH_2PO_4/Tetrahydrofuran (95/5, V/V) (pH 6.5), was delivered at a flow rate of 1.0 ml/min at 37 °C. The serum IS levels were determined by fluorescence detection (excitation, 295 nm; emission, 390 nm).

RFCA procedure

All antiarrhythmic drugs (AADs), except for amiodarone, were discontinued for at least 7 half-lives prior to the procedure and all patients were effectively anticoagulated for more than 1 month. We did not perform the routine contrast cardiac CT after RFCA. The electrophysiological study and RFCA were performed under sedation with dexmedetomidine and propofol. A 7Fr 20-pole 3-site mapping catheter (BeeAT, Japan-Life-Line, Tokyo, Japan) was inserted into the coronary sinus via the right jugular vein. The transseptal procedure was performed using fluoroscopic landmarks, and 2 SL0 sheaths (St. Jude Medical) were advanced into the left atrium (LA). After a trans-septal puncture, a 3.5-mm open-irrigated tip ablation catheter was used to circumferentially and extensively perform the pulmonary vein isolation (PVI) with the double-lasso technique. RFCA was guided with the use of a 3D mapping system (CARTO, Biosense-Webster or EnSite NavX, St. Jude Medical). The endpoint of the PVI was the elimination of all PV potentials between the LA and PVs at least 30 min after the successful PVI, and the elimination of any dormant PV conduction revealed by adenosine triphosphate. Further, an incremental isoproterenol infusion was also given before and after the PVI to identify any induction of AF or any non-PV triggers. If frequent atrial premature contractions originating from non-PV sites were present, focal ablation was added to eliminate any non-PV foci. A cavotricuspid isthmus line ablation (CTI ablation) was performed if any common atrial flutter was detected before or during the procedure.

Post-RFCA follow-up

All patients were followed up every 1–3 months in the outpatient clinic within 1 year after the RFCA. A 12-lead electrocardiogram, 24-h-Holter electrocardiogram, and assessment of the symptoms were checked every month within 4–6 months after the RFCA. The blood tests including the serum IS level and eGFR were checked before, at 3 months, and 1 year after RFCA. Freedom from AF was defined as no detectable AF/atrial tachycardias (ATs) on the electrocardiogram modalities performed multiple times after the final procedure. AF recurrence was defined as sustained AF/AT lasting more than 30 s after a 3-month blanking period. AF recurrence within a 3-month period after the procedure was considered transient. The AADs were not resumed in the patients with paroxysmal AF; however, the AADs were resumed for 3 months following the ablation in patients with persistent AF. The patients who experienced AF recurrence were excluded in this study.

Statistical analysis

All continuous data were expressed as the mean ± standard deviation, medians (quartile: 25–75%), or numbers (%). Comparisons between groups were analyzed using a univariate analysis (Unpaired t test, Mann–Whitney *U* test and Fisher's exact test) and a multivariate analysis using a logistic analysis model. A p value < 0.05 was considered statistically significant. The statistical analyzes were performed using EZR software (Jichi Medical University, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [18].

Ethical considerations

The study protocol was approved by the institutional review board of the Toho University Medical Center Omori Hospital. All patients gave their informed consent for the study protocol.

Results

Baseline characteristics

The mean age was 63.5 ± 11.3 years, and 69 (75.8%) were male. Paroxysmal AF was present in 64 patients (70.3%).

In the 86 (94.5%) patients, AF occurred more than every month. The mean eGFR and serum IS levels at baseline were 77.2 ± 13.2 ml/min/1.73 m^2 and 0.9 ± 0.7 μg/ml, respectively. The patients were divided according to the quartiles of the serum IS level (Q1–4; < 0.4, 0.4–0.7, 0.7–1.2, and > 1.2 μg/ml, respectively). Those baseline characteristics are listed in Table 1. There was no significant difference in the eGFR between the IS quartiles. Furthermore, the serum IS had little correlation with the eGFR in those patients ($r = -0.245$, $p = 0.019$).

Regarding the past medical history, there were no significant differences in the patients with diabetes mellitus, dyslipidemia, chronic heart failure, and ischemic cardiac disease between the IS quartiles. However, the number of those with hypertension differed between the 4 groups. The left ventricular diastolic diameter (LVDd) in the

Table 1 Patients characteristics among IS Q1–4

Factor	IS-Q1 $N=23$	IS-Q2 $N=23$	IS-Q3 $N=22$	IS-Q4 $N=23$	p value
Age (years)	64.5 ± 11.5	60.5 ± 9.8	61.5 ± 12.4	67.3 ± 11.0	0.16
Height (cm)	165.3 ± 10.4	167.3 ± 10.3	165.8 ± 7.9	166.5 ± 6.8	0.88
Weight (kg)	63.5 ± 10.5	68.0 ± 16.3	61.8 ± 10.5	65.5 ± 9.8	0.34
BMI (kg/m^2)	23.2 ± 2.6	24.1 ± 4.4	22.4 ± 3.2	23.6 ± 3.0	0.38
Male (%)	17 (73.9)	17 (73.9)	15 (68.2)	20 (87.0)	0.50
PAF (%)	14 (60.9)	17 (73.9)	17 (77.3)	16 (69.6)	0.65
$CHADS_2$ score	1.17 ± 1.11	0.78 ± 0.85	0.82 ± 1.22	1.22 ± 0.67	0.30
HT (%)	13 (56.5)	8 (34.8)	5 (22.7)	17 (73.9)	0.003
CHF (%)	1 (4.3)	2 (8.7)	2 (9.1)	2 (8.7)	0.92
DL (%)	5 (21.7)	9 (39.1)	10 (45.5)	7 (30.4)	0.36
DM (%)	3 (13.0)	4 (17.4)	2 (9.1)	1 (4.3)	0.54
Stroke (%)	3 (13.0)	1 (4.3)	2 (9.1)	1 (4.3)	0.63
Beta blocker (%)	12 (52.2)	8 (34.8)	11 (50.0)	5 (21.7)	0.12
ARB (%)	7 (30.4)	6 (26.1)	2 (9.1)	7 (30.4)	0.29
Diuretics (%)	1 (4.3)	2 (8.7)	2 (9.1)	2 (8.7)	0.92
AADs (%)	18 (78.3)	16 (69.6)	16 (72.7)	17 (73.9)	0.72
UA (mg/dl)	5.65 ± 1.32	5.94 ± 1.50	5.85 ± 1.13	5.67 ± 1.02	0.83
Cr (mg/dl)	0.73 ± 0.09	0.73 ± 0.16	0.76 ± 0.15	0.79 ± 0.12	0.36
eGFR (ml/min/1.73 m^2)	78.0 ± 11.4	81.4 ± 16.7	75.6 ± 11.1	73.9 ± 12.5	0.25
CCR (ml/min)	88.5 ± 23.2	100.8 ± 24.6	85.8 ± 21.4	84.3 ± 25.8	0.09
IS (μg/ml)	0.26 ± 0.10	0.59 ± 0.11	0.96 ± 0.14	1.82 ± 0.77	< 0.001
BNP (pg/dl)	59.6 ± 57.6	38.7 ± 31.9	95.7 ± 114.9	64.0 ± 78.8	0.11
EF (%)	65.4 ± 7.0	68.4 ± 8.8	68.0 ± 7.3	70.5 ± 11.6	0.29
LVDd (mm)	50.7 ± 5.9	49.0 ± 5.9	45.3 ± 4.5	52.0 ± 5.2	0.001
LVDs (mm)	32.2 ± 4.0	30.1 ± 5.5	28.0 ± 3.9	30.8 ± 6.5	0.05
LAD (mm)	37.4 ± 6.1	38.0 ± 7.8	35.4 ± 6.8	38.2 ± 6.6	0.52
Total procedure time (min)	176.5 ± 30.8	168.9 ± 32.6	177.8 ± 37.6	158.4 ± 36.8	0.25
Total RFCA time (min)	38.1 ± 12.4	32.5 ± 11.3	34.4 ± 9.6	37.7 ± 12.3	0.34
Contrast agent (ml)	27.3 ± 5.5	24.4 ± 6.9	26.6 ± 4.8	29.4 ± 10.6	0.18
Extra PV foci (%)	10 (43.5)	7 (31.8)	8 (42.1)	4 (19.0)	0.31
Post-beta blocker (%)	10 (43.5)	9 (39.1)	6 (27.3)	4 (17.4)	0.22
Post-ARB (%)	5 (21.7)	6 (26.1)	1 (4.5)	7 (30.4)	0.16
Post-diuretics (%)	0 (0.0)	1 (4.3)	2 (9.1)	2 (8.7)	0.49
Post-AADs (%)	8 (34.8)	3 (13.0)	5 (22.7)	5 (21.7)	0.38

The patients were divided according to the quartiles of the IS (Q1–4; < 0.4, 0.4–0.7, 0.7–1.2, and > 1.2 μg/ml)

BMI body mass index, *PAF* paroxysmal atrial fibrillation, *HT* hypertension, *CHF* congestive heart failure, *DL* dyslipidemia, *DM* diabetes mellitus, *ARB* angiotensin receptor blocker, *AADs* anti-arrhythmia drugs, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *CCR* creatinine clearance, *IS* indoxyl sulfate, *BNP* B-type natriuretic peptide, *EF* ejection fraction, *LVDd/Ds* left ventricular diameter (diastolic/systolic), *LAD* left atrial diameter, *RFCA* radiofrequency ablation, *PV* pulmonary vein

IS-Q4 patients was significantly larger than that for the other quartile patients.

The transition in the renal function

We investigated the serial change of IS and eGFR in the 91 patients who maintained sinus rhythm after RFCA during the follow-up period (19.6 ± 4.4 months). Figure 1 shows the transition in the eGFR and serum IS levels. The serum IS level in the high IS group (IS-Q4) significantly decreased at 1 year after the RFCA (from 1.8 ± 0.8 to 1.2 ± 0.7 μg/ml, $p < 0.001$). Although the eGFR in all groups did not change between that before and 1 year after the RFCA (from 77.2 ± 13.2 to 75.2 ± 12.7 ml/min/1.73 m^2, $p = 0.066$), the eGFR in the IS-Q4 patients significantly increased after the RFCA as compared to that of the eGFR in the patients in the other quartiles (from 73.9 ± 12.5 to 76.1 ± 15.4 ml/min/1.73 m^2, $p = 0.036$).

On the other hand, Fig. 2 shows the transition in the eGFR and serum IS levels in the AF recurrent groups. The serum IS level in the high IS group (IS-Q4) once decreased at 3 months after the RFCA, however, the serum IS level at 1 year after the RFCA numerically increased as compared to the IS at 3 months (from 1.1 ± 1.2 to 1.4 ± 0.62 μg/ml, $p = 0.49$). Furthermore, the eGFR in the IS-Q4 patients numerically decreased after the RFCA (from 66.0 ± 5.13 to 63.1 ± 10.7 ml/min/1.73 m^2, $p = 0.38$).

The clinical characteristics of the patients with/without an eGFR improvement are listed in Table 2. For the past medical history, echocardiographic parameters, post-RFCA medical therapies and dosage of the contrast agents, there were no significant differences in the patients with/without an improvement in the eGFR. In addition to thebaseline clinical factors, the dosage of the contrast agent during the RFCA procedure in the patients with an eGFR improvement did not different from the dosage in those without an eGFR improvement. Table 3 shows the serial change in the laboratory data in the patients with/without an eGFR improvement before, at 3 months, and 1 year after the RFCA. The patients with an improvement in the eGFR had a significantly higher baseline IS level (1.18 ± 1.06 vs. 0.83 ± 0.56 μg/ml, $p = 0.049$); however, the baseline eGFR and creatinine clearance (CCR) in the patients with an improvement in the eGFR did not differ between the eGFR and CCR in those without an improvement in the eGFR (eGFR; 73.2 ± 12.5 vs. 78.4 ± 13.3 ml/min/1.73 m^2, $p = 0.12$, CCR; 89.7 ± 31.1 vs. 90.0 ± 22.4 ml/min, $p = 0.96$). Furthermore, a significantly higher rate of an eGFR improvement was obtained for the IS-Q4 group than the other quartile groups ($p = 0.039$). At 1 year after the RFCA, the serum IS level and uric acid level significantly

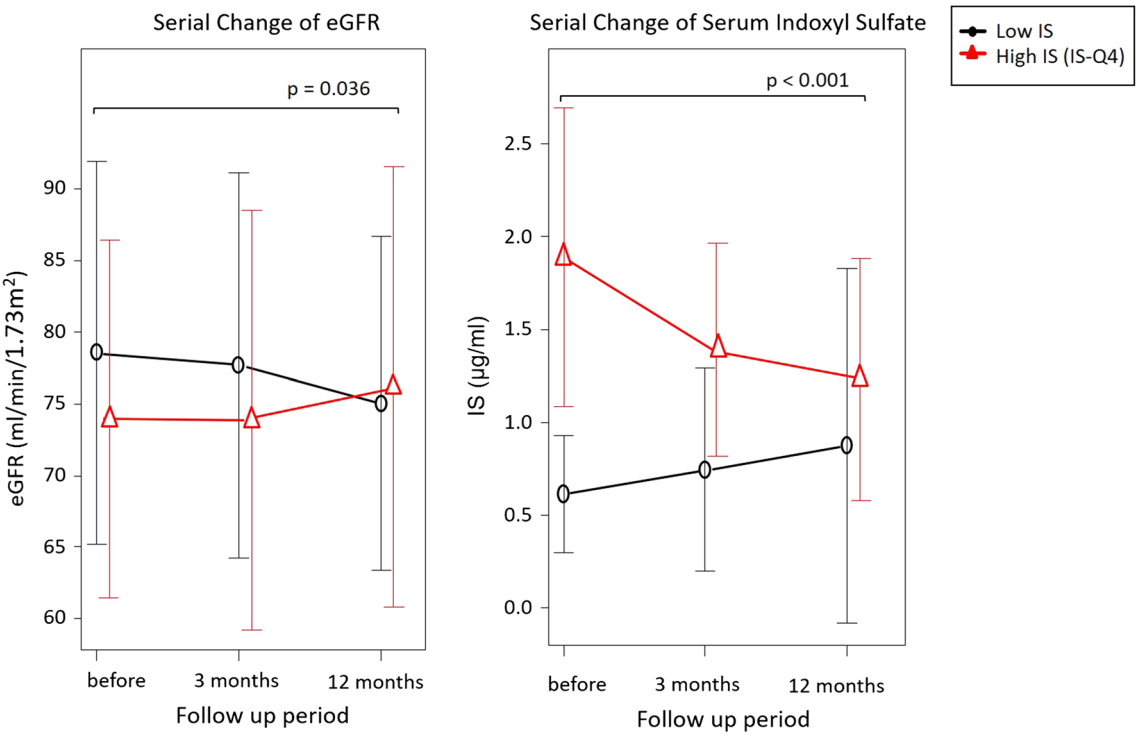

Fig. 1 Serial Change in the eGFR and IS in the SR group. The figure shows the transition of the eGFR and serum IS levels. The red color line represents the high IS group (IS-Q4) and the black line represents the low IS group

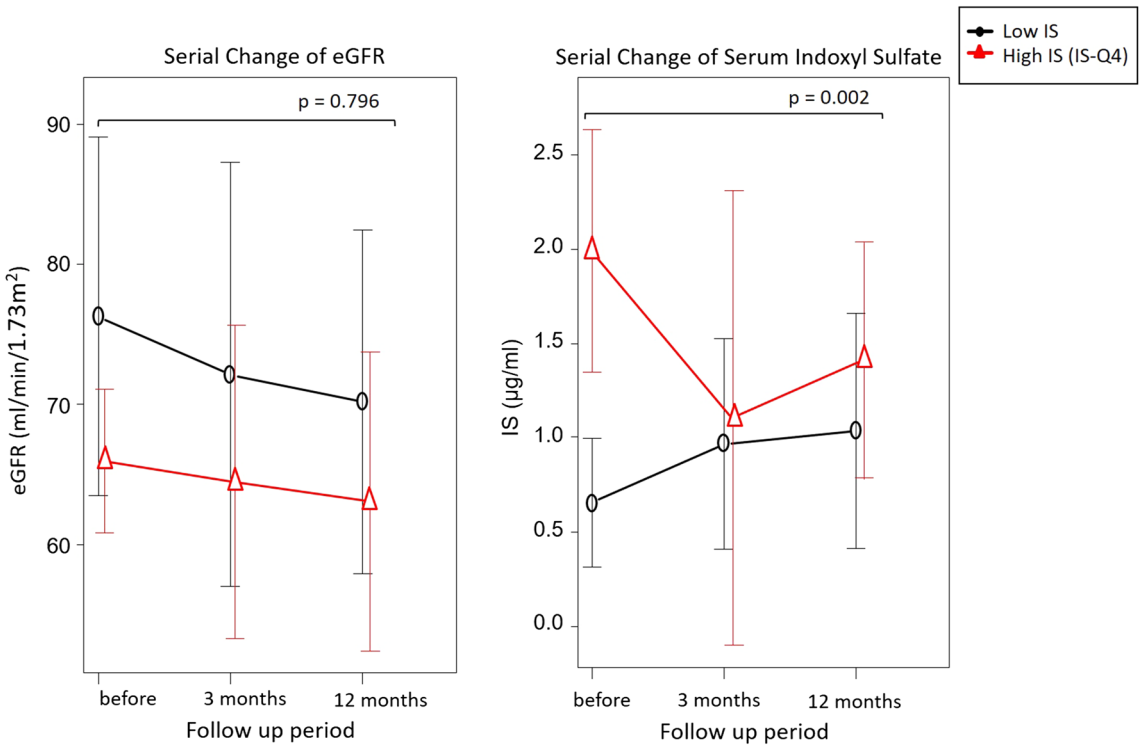

Fig. 2 Serial Change in the eGFR and IS in the AF recurrent group. The figure shows the transition of the eGFR and serum IS levels. The red color line represents the high IS group (IS-Q4) and the black line represents the low IS group

decreased in the patients with an improvement in the eGFR (Table 3).

The multivariable logistic model after adjusting for the $CHADS_2$ score, type of AF, medical drugs after the RFCA, and eGFR revealed that only a high IS (IS-Q4) was an independent predictor of an eGFR improvement (OR, 3.33; 95% CI, 1.16 – 9.59; $p = 0.026$, Table 4).

We also investigated the relationship between the change in the IS and eGFR measured before and at 1 year after the RFCA, ΔIS, and ΔeGFR, respectively. Regarding the correlation between the ΔIS and ΔeGFR, since the ΔIS decreased, the ΔeGFR significantly increased ($r = -0.41$, $p < 0.001$).

Discussion

Main findings

The main findings were as follows. First, a high IS was significantly associated with an improvement in the renal function in AF patients with mild kidney dysfunction. Second, the maintenance of SR after RFCA decreased the serum IS level in the patients with a high IS.

We considered the following factors. There was no significant difference in the baseline eGFR between the IS quartiles. Furthermore, the serum IS had little correlation with the eGFR in those patients. The serum IS level was a significant predictor for an improvement in the renal function, independent of the eGFR. According to these findings, IS decreased after RFCA and a reduction in IS might improve the renal function after 1 year regardless of the eGFR. As a result, a high IS was significantly associated with an improvement in the renal function after RFCA.

Indoxyl sulfate and AF

It is well known that CKD has a higher incidence of AF and the prevalence of AF in patients with CKD causes a decrease in their eGFR [2, 3, 6,7]. The mechanism of this is proposed to be inflammation and oxidant stress [19]. IS is a highly protein-bound uremic toxin and, further, directly increases the oxidative stress and production of reactive oxygen species due to the activation of NADPH oxidases [20, 21]. IS exaggerates cardiac fibrosis and exacerbates the development of AF substrates [11, 22]. Another study showed that IS increases delayed afterdepolarizations (DADs) in pulmonary veins (PVs) and burst firings [23]. Therefore, CKD causes AF to develop due to enhancing the PV arrhythmogenesis and AF substrate through the toxicity of IS. Healthy kidneys excrete IS from the circulation into the urine [24].

Table 2 Characteristics of the patients with/without an eGFR improvement

Factor	eGFR imp (−) $N=71$	eGFR imp (+) $N=20$	p value
Age (years)	63.7 ± 10.6	62.8 ± 13.9	0.77
Height (cm)	164.3 ± 19.7	165.4 ± 10.4	0.81
Weight (kg)	64.3 ± 11.9	66.4 ± 12.9	0.49
Male (%)	54 (76.1)	15 (75.0)	0.99
PAF (%)	50 (70.4)	14 (70.0)	0.99
$CHADS_2$ score	1.03 ± 1.07	0.90 ± 0.64	0.61
HT (%)	33 (46.5)	10 (50.0)	0.81
CHF (%)	5 (7.0)	2 (10.0)	0.65
DL (%)	26 (36.6)	5 (25.0)	0.43
DM (%)	9 (12.7)	1 (5.0)	0.45
Stroke (%)	7 (9.9)	0 (0.0)	0.34
EF (%)	67.3 ± 7.7	70.7 ± 12.2	0.13
LAD (%)	37.3 ± 7.2	37.1 ± 5.4	0.89
Post-beta blocker (%)	22 (31.0)	7 (35.0)	0.79
Post-ARB (%)	17 (23.9)	2 (10.0)	0.23
Post-diuretics (%)	3 (4.2)	2 (10.0)	0.30
Post-AADs (%)	15 (21.1)	6 (30.0)	0.55
Flecainide (%)	6 (8.5)	2 (10.0)	0.99
Amiodarone (%)	2 (2.8)	0 (0.0)	0.99
Bepridil (%)	7 (9.9)	4 (20.0)	0.25
Total procedure time (min)	173.2 ± 35.0	158.9 ± 31.3	0.13
Total RFCA time (min)	36.0 ± 11.8	34.8 ± 11.0	0.72
Contrast agent (ml)	27.0 ± 7.8	26.8 ± 5.7	0.95
Extra PV foci (%)	24 (35.3)	5 (29.4)	0.78

Data are expressed as the mean ± SD or number (%)

PAF paroxysmal atrial fibrillation, *HT* hypertension, *CHF* congestive heart failure, *DL* dyslipidemia, *DM* diabetes mellitus, *EF* ejection fraction, *LAD* left atrial diameter, *ARB* angiotensin receptor blocker, *AADs* anti-arrhythmia drugs, *RFCA* radiofrequency ablation, *PV* pulmonary vein, *eGFR* estimated glomerular filtration rate, *eGFR imp* improvement of eGFR

Table 3 Serial change in the laboratory data in the patients with/without an eGFR improvement

Factor	eGFR imp (−) $N=71$	eGFR imp (+) $N=20$	p value
Pre-RFCA			
Cr (mg/dl)	0.75 ± 0.14	0.79 ± 0.12	0.24
eGFR (ml/min/1.73 m^2)	78.4 ± 13.3	73.2 ± 12.5	0.12
CCR (ml/min)	90.0 ± 22.4	89.7 ± 31.1	0.96
IS (μg/ml)	0.83 ± 0.56	1.18 ± 1.06	0.049
IS-Q4	14 (19.7)	9 (45.0)	0.039
UA (mg/dl)	5.85 ± 1.30	5.51 ± 1.04	0.29
BNP (pg/ml)	60.8 ± 74.7	77.5 ± 91.5	0.42
Post-RFCA 3 months			
Cr (mg/dl)	0.77 ± 0.15	0.73 ± 0.12	0.31
eGFR (ml/min/1.73 m^2)	76.0 ± 13.7	79.2 ± 14.2	0.35
CCR (ml/min)	87.2 ± 21.5	96.7 ± 34.0	0.13
IS (μg/ml)	0.86 ± 0.65	0.99 ± 0.56	0.44
UA (mg/dl)	5.81 ± 1.24	5.26 ± 0.93	0.07
BNP (pg/ml)	32.0 ± 32.5	24.7 ± 17.2	0.35
Post-RFCA 12 months			
Cr (mg/dl)	0.79 ± 0.15	0.69 ± 0.11	0.005
eGFR (ml/min/1.73 m^2)	72.8 ± 11.5	84.1 ± 12.4	< 0.001
CCR (ml/min)	84.4 ± 21.3	101.6 ± 34.9	0.008
IS (μg/ml)	0.97 ± 0.96	0.86 ± 0.57	0.66
UA (mg/dl)	5.77 ± 1.27	5.08 ± 0.97	0.027
BNP (pg/ml)	29.9 ± 41.1	21.0 ± 15.0	0.35

Data are expressed as the mean ±SD or number (%)

RFCA radiofrequency ablation, *eGFR* estimated glomerular filtration rate, *CCR* creatinine clearance, *IS* indoxyl sulfate, *UA* uric acid, *BNP* B-type natriuretic peptide, *eGFR imp* improvement of eGFR

Table 4 Predictors of an eGFR improvement by a multivariable logistic analysis

Factor	Odds ratio (95% CI)	p value
High IS (IS-Q4)	3.33 (1.160–9.590)	0.026
Post diuretics	4.15 (0.387–44.40)	0.240
Post AADs	1.71 (0.518–5.640)	0.378
PAF	1.43 (0.258–7.930)	0.681
eGFR	0.97 (0.927–1.020)	0.204
$CHADS_2$ score	0.76 (0.404–1.430)	0.392

IS indoxyl sulfate, *AADs* anti-arrhythmia drugs, *PAF* paroxysmal atrial fibrillation, *eGFR* estimated glomerular filtration rate, *95% CI* 95% confidence interval

Thus, IS is not accumulated and its level has been reported to be 0.6 μg/ml in normal adults in the previous reports [13].

In this present study, the mean IS level at baseline was 0.9 ± 0.7 μg/ml; however, there were some patients with a high IS level (IS > 1.2 μg/ml). The serum IS level was mildly higher than that in the previous reports, because this study enrolled patients presenting with AF.

Indoxyl sulfate and the renal function

IS accumulates in patients with renal dysfunction, especially with an impaired renal tubular excretory function [24]. Further, patients with advanced renal dysfunction have increased serum IS levels. On the other hand, it is reported that in some patients who have a relatively well-preserved eGFR, the serum IS level is increased [8, 9]. The reason is reported to be that mildly a damaged renal tubular function, high-protein diet, and gut-microflora affect the serum IS level [25, 26]. In those patients with a well-preserved renal function, the IS level may temporary increase and may not be associated with a future risk [8].

In the present study, patients with a preserved renal function (eGFR ≥ 60 ml/min/1.73 m^2) were enrolled to eliminate

the effect of renal dysfunction causing an accumulation of the serum IS. There were no significant differences in the characteristics of the patients such as in the weight, body mass index, dyslipidemia, diabetes mellitus, or eGFR among the IS quartiles. Furthermore, the serum IS level had a week correlation with the eGFR in those patients. In the patients who maintained SR after the RFCA, the serum IS level significantly decreased in the patients with a high IS and the renal function in those patients with a high IS improved. In the low-IS group, the serum IS level did not change, because IS is metabolized by dietary tryptophan and cannot be eliminated completely in the body. Therefore, RFCA did not decrease the serum IS level in the low-IS group, compared to that of the high-IS group. On the other hand, in the AF recurrent group with high-IS level, the IS level temporarily decreased after 3 months; however, the IS was tended to increase at 1 year after RFCA. This may show because these patients restored SR immediately following RFCA, serum IS level once decreased at 3 months after RFCA as the acute effect of RFCA and reduction of AF burden. However, the serum IS level at 1 year after RFCA increased because of the recurrence of AF. Thus, in the AF recurrent group, the eGFR did not change after RFCA.

We suggest that IS may affect renal dysfunction in patients with a preserved renal function or mild renal dysfunction, unlike that in the previous reports. Furthermore, a reduction in the IS in those patients may be useful for improving their renal function.

Mechanism of the improvement in the renal function

Kidney dysfunction increased the risk of new onset AF, and AF increased the risk of the development of kidney disease. The mechanisms of the increase in the prevalence of AF in the CKD patients have been well reported [2, 3, 6, 7]. However, the mechanism of developing renal dysfunction in AF patients has not been fully elucidated, because AF and CKD share risk factors, and common pathophysiologic processes drive both outcomes. It is well known that RFCA of AF improves the renal function in patients with CKD [4, 6]. AF patients with CKD present with a reduction in the left atrial (LA) contractile function, decreased LA appendage velocity, and higher prevalence of a spontaneous contrast echo [27]. After the RFCA, an improvement in the left atrial function is demonstrated [28–30]. Furthermore, the improvement in the renal function can result from the improvement in the LA function and cardiac output [4]. On the other hand, several studies have shown that in patients with an eGFR of > 90 ml/min/1.73 m^2, their eGFR decreases after RFCA regardless of any freedom from AF [4, 6]. This may be attributed to the phenomenon of the regression to the mean [6].

Actually in this present study, the eGFR in the patients with a low IS had a decreased level at 1 year after the RFCA. However, the IS level in those with a high IS level significantly decreased gradually at 3 months and 1 year after the RFCA, and the eGFR improved. This may be able to deny the effect of the regression to the mean in the group. Furthermore, compared to the eGFR and IS level in the AF recurrent group, serum IS and eGFR were significantly improved after RFCA in the patients who maintained SR. The maintenance of SR may increase the renal flow and reduce the serum IS level in patients with a mild renal dysfunction. As a result, a reduction in the IS level prevented the progression of CKD. On the other hand, we could not check the change of LV function in the echocardiographic parameters; however, the BNP level was significantly decreased after RFCA. The reduction of serum BNP level suggested that RFCA improved the LV function and the improvement of LV function might increase the renal flow. We considered that IS may play a significant role in the development of CKD in AF patients with a preserved kidney function. To prevent a progression of CKD in patients with AF, a reduction in the IS level by RFCA is a feasible treatment.

Study limitations

This study had some potential limitations. First, this study was a single-center trial. We did not have very many patients. Second, we also considered the effect of the times of the plasma IS and eGFR examinations. The plasma IS levels were examined at only one point in time, before, at 3 months, and at 1 year, which might have caused a statistical bias.

Third, the precise mechanism of the improvement in the renal function still remains unclear. We could not completely deny other mechanisms that suggested that increasing the renal flow improved the eGFR and, as a result, the IS was just washed out. Further, we did not measure the cardiac output or the renal flow before and after RFCA in this study. However, the baseline characteristics showed that there was no significant difference in the eGFR between the IS quartiles and the serum IS had little correlation with the eGFR. Therefore, it is better to propose that a reduction in the IS level prevented the progression of CKD. Further research is needed with a greater number of patients to confirm this.

Conclusions

In the patients with a high IS level, their serum IS level decreased after a successful RFCA. Further, a high IS level was a significant predictor of an improvement in the renal function in the AF patients with mild kidney dysfunction. A

reduction in the IS level after RFCA prevented the progression of CKD.

Acknowledgments This manuscript was supported in part by Grants-in-Aid (15K09103 and 16K01433 to T.I.) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We thank Mr. John Martin for his help with the preparation of the manuscript and Mr. Osuka for his help in supporting this present study.

Compliance with ethical standards

Conflict of interest This research received no grants from any funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there is no conflict of interest.

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