Atrial Fibrillation and Adverse Outcomes in Patients Undergoing Simultaneous Pancreas-Kidney Transplantation

Tapio Hellman[a*], Kaisa Ahopelto[b], Juulia Räihä[c], Mikko J. Järvisalo[d,e], Marko Lempinen[b], and Ilkka Helanterä[b]

[a]Kidney Center, University of Turku and Turku University Hospital, Finland; [b]Department of Transplantation and Liver Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [c]Department of Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [d]Department of Anaesthesiology and Intensive Care, University of Turku and Turku University Hospital, Turku, Finland; and [e]Perioperative Services, Intensive Care and Pain Medicine, University of Turku and Turku University Hospital, Turku, Finland

ABSTRACT

Background. There are no published data on atrial fibrillation (AF) in patients receiving simultaneous pancreas-kidney transplantation (SPKT). We explored the epidemiology and adverse outcomes of AF in SPKT recipients in this retrospective observational cohort study.

Materials and Methods. All 200 SPKT recipients in Finland to date between March 2010 and April 2021 were included in the present study. Demographics, comorbidities, medications, and transplantation data were collected from the electronic patient records. Outcome measures included new-onset AF (NOAF), ischemic stroke, and death.

Results. Median age was 42 years (interquartile range [IQR] 35-49), 69 (35%) were female, and median dialysis vintage was 13 months (IQR 9-19). Altogether 7 patients (4%) had a previous diagnosis of AF at baseline, and heart failure was independently associated with prior AF in the age-adjusted multivariable logistic regression analysis. After a median follow-up of 3 years (IQR 1-5), 2 patients (1%) were observed with incident NOAF, 4 (2%) with ischemic stroke, and 7 patients (4%) died. Prior AF or NOAF were not associated with cardiovascular adverse outcomes, mortality or graft outcomes.

Conclusions. We demonstrate a low prevalence and incidence of AF for the first time in this large observational study comprising all SPKT recipients in Finland to date.

ATRIAL fibrillation (AF) is a common condition in patients with type 1 diabetes mellitus (DM1) and chronic kidney disease (CKD) and increases the risk of morbidity and mortality in those affected [1−3]. In patients with DM1 the risk of AF is increased in individuals with concomitant CKD compared with those with normal kidney function, and the risk increases further along with a deteriorating kidney function [1,2,4]. The burden of AF is especially high in patients with end-stage kidney disease on maintenance dialysis but nevertheless remains increased after successful kidney transplantation (KT) [5,6]. In fact, the incidence of new-onset atrial fibrillation (NOAF) appears to be higher during the first year after transplantation compared with patients on the transplant waiting list decreasing thereafter to a lower level [7]. Moreover, AF is associated with attenuated patient and graft survival in KT recipients [6,7].

Simultaneous pancreas-kidney transplantation (SPKT) is the treatment of choice in DM1 patients with end-stage kidney disease and improves patient outcomes compared with KT alone [8]. SPKT recipients, by definition, have several comorbidities associated with AF, and thus, are expected to be at increased risk for AF. However, as of yet no previous data have been published on AF in patients undergoing SPKT.

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*Address correspondence to Tapio Hellman, MD, PhD, Kidney Center, Turku University Hospital, PO Box 52, 20521, Turku, Finland, Tel: +358-2-3139287. E-mail: tapio.hellman@tyks.fi

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We sought to explore the epidemiology of AF and associated risk factors and adverse outcomes in a retrospective cohort comprised of every SPKT performed in Finland to date.

MATERIALS AND METHODS

The present study is a retrospective observational cohort study performed at the Helsinki University Hospital department of transplantation and liver surgery—the sole institution to perform transplantation surgery in Finland. Pancreas transplantations were started in Finland in 2010, and the study cohort comprises all consecutive recipients of SPKT to date between 2010 and April 2021. Pancreas after kidney transplants or single pancreas transplants were excluded (Fig 1). Thus, the final study cohort included 200 patients. No power calculations were performed owing to the retrospective nature of the study.

Data Collection, Definitions, and Outcomes

The patients were identified and data on demographics, comorbidities, medications, and transplantation were manually collected from the national Finnish Transplant Registry and electronic medical records of the research hospital. Previous diagnoses of AF were gathered from the electronic patient archives and confirmed by ICD-10 code for AF (I48). As transthoracic echocardiography (TTE) is part of the pretransplantation evaluation protocol in Finland, TTEs were performed in every patient before transplantation according to clinical standards at the referring hospitals. For the purposes of the present study, available data on left ventricular ejection fraction (EF), left ventricular end-diastolic diameter, left atrial diameter, and left ventricular hypertrophy were collected. Left ventricular hypertrophy was defined as diastolic septal or posterior wall thickness in the left ventricle >9mm in women and >10mm in men.

All incident cases of NOAF were collected from the patient records of the research hospital. All SPKT patients in Finland are regularly followed-up at least every 4 months by the nephrology outpatient clinics of the patients' regional hospitals and at each visit screened for signs of cardiovascular disease including arrhythmic symptoms, and all symptomatic patients are referred to further studies including an electrocardiography. The clinical records of each follow-up visit at the regional hospital are periodically collected by the transplantation unit of the research hospital and entered into the transplant registry, which is a follow-up registry obliged by law. Furthermore, all SPKT recipients visit the research hospital annually for control examinations and are similarly screened for cardiovascular disease and arrhythmias. Moreover, mortality data were collected from the national Digital and Population Data Services Agency directly linked to the electronic medical records to include all deaths occurring outside the health care district of the research hospital.

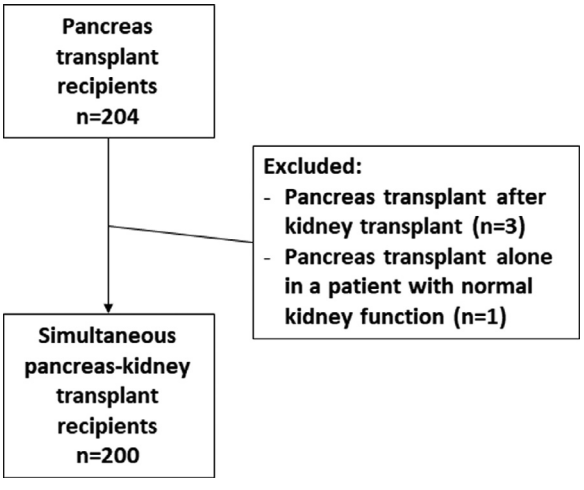

Fig 1. Flowchart of the study patients.

During manual data collection heart failure was defined as a hospitalization for a symptomatic event of congestive heart failure owing to systolic left ventricular dysfunction and confirmed with the ICD-10 code for heart failure (I50), excluding cases of fluid retention owing to terminal CKD at the time of dialysis initiation. All cases of coronary artery disease were confirmed with coronary angiography. The CHA_2DS_2-VASc score was defined as congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), prior stroke or systemic thromboembolism (2 points), prior acute myocardial infarction or coronary artery disease or peripheral artery disease (1 point), age 65 to 74 years (1 point), and female sex (1 point).

The primary outcome of the study was an incident NOAF observed during follow-up. AF or atrial flutter were not segregated in this study. Secondary outcomes included incident ischemic nonhemorrhagic stroke and all-cause mortality. Data on coronary interventions, acute myocardial infarctions, amputations, and graft survival also were collected.

SPKT Surgery Protocol

All SPKTs were cytotoxic cross-match-negative and ABO compatible. All patients were initiated on standard maintenance immunosuppression (tacrolimus, mycophenolate, and oral corticosteroids) preceded by a single induction dose of antithymocyte globulin at transplantation. The post-transplantation trough level target for tacrolimus was set at 12 to 15 μg/mL for days 1 to 14 and 10 to 12 μg/mL for days 15 to 90 after transplantation. Exocrine drainage was performed using enteric proximal jejunal anastomosis in all SPKTs, and in patients on peritoneal dialysis before transplantation, peritoneal catheters always were removed during surgery. All patients received dalteparin or tinzaparin 2500 IU bid or enoxaparin 20 mg bid according to the choice of anticoagulation during hemodialysis for days 1 to 14 and 2500 IU qd for days 15 to 28 for postoperative thrombosis prophylaxis. Patients undergoing pre-emptive SPKT and those who received peritoneal dialysis before transplantation received dalteparin. In the patients with prior oral anticoagulation medication, oral anticoagulation was resumed 4 weeks after transplantation.

Ethics

This study was approved by the Institutional Review Board of Helsinki University Hospital (HUS/155/2021) and conforms to the Declaration of Helsinki and the Declaration of Istanbul. Because of the retrospective, observational design of the study the regulatory review board waived the need for informed consent.

Statistics

The categorical variables were reported with absolute and relative (percentage) frequencies. The continuous variables were reported as mean ± standard deviation (SD) and median (interquartile range) for normally distributed and skewed variables, respectively. Normality in continuous variables was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests.

The groupwise comparisons (prior diagnosis of AF vs no prior AF, Table 1 and Table 2) were performed using the Pearson χ^2 test,

Table 1. Baseline Characteristics of Patients With and Without History of Atrial Fibrillation

Characteristics	History of AF(n = 7)	No Prior AF(n = 193)	*P*
Age mean (median), y	46 (46)	42 (42)	.25
Female	2 (29)	67 (35)	1.0
BMI	22.6 (20.6-24.7)	24.1 (21.7-27.2)	.17
Duration of diabetes, y	34 (± 5)	32 (± 8)	.41
Dialysis vintage, mo	17 (13-21)	13 (9-19)	.11
Tx waiting time, d	159 (9-288)	70 (31-134)	.26
Pre-emptive transplantation	0 (0)	9 (4.7)	1.0
PRA >20%	1 (14)	27 (14)	1.0
HLA mm	4 (3-6)	4 (3-5)	.89
History of smoking	2 (29)	104 (54)	.26
Hypertension	7 (100)	192 (99)	1.0
History of heart failure	4 (57)	13 (7)	.01
Coronary artery disease	2 (29)	45 (23)	.67
Prior myocardial infarction	1 (14)	5 (3)	.20
Prior stroke	1 (14)	10 (5)	.33
Peripheral artery disease	1 (14)	15 (8)	.45
Prior amputation	1 (14)	12 (6)	.38
CHA_2DS_2-VASc score	3 (3-4)	3 (2-3)	.06
History of malignancy	0 (0)	5 (3)	1.0
Medications			
Beta-blocker	6 (86)	151 (78)	1.0
ACEi/ARB	4 (57)	107 (55)	1.0
Calcium channel blocker	5 (71)	135 (70)	1.0
Warfarin	2 (29)	0 (0)	.01
Echocardiography			
Ejection fraction* %	60 (55-63)	64 (60-70)	.05
LVEDD mm†	50 (± 6)	49 (± 5)	.91
LAD mm‡	38 (33-41)	41 (38-48)	.08
LVH§	5 (71)	75 (54)	.46

Categorical values in parentheses are % unless stated otherwise. Continuous variables are expressed as mean (± standard deviation) or median (IQR) for normally distributed and skewed covariates, respectively. The presence of coronary artery disease was confirmed with coronary angiography. The reported PRA was assessed immediately prior to transplant operation.

ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes, prior stroke or thromboembolism (doubled), vascular disease, age 65 to 74 years and female sex; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVH, left ventricular hypertrophy; HLA mm, HLA mismatch; PRA, panel-reactive antibodies.

* Data missing in 12 (6%) patients.

† Data missing in 77 (39%) patients.

‡ Data missing in 89 (45%) patients.

§ Data missing in 55 (28%) patients.

Student's *t* test and Mann-Whitney *U*-test for categorical variables, normally distributed continuous variables, and skewed continuous variables, respectively. The univariate associations between tested covariates and prior diagnosis of AF or incident NOAF were separately analyzed using logistic regression models or Cox proportional hazards models, respectively. The covariates correlating at $P < .05$ significance level with the dependent variable were entered in the multivariable logistic regression model or cox proportional hazards model, as appropriate. The multivariable models were first adjusted with age and then further with dialysis vintage or sex, separately to avoid overfitting.

The univariate associations between adverse outcomes during follow-up (eg, ischemic stroke or death) and prior diagnosis of AF or incident NOAF were explored using univariate cox proportional hazards models. The associations were then further analyzed with a multivariable cox proportional hazards model adjusted with age. Further adjustments of the multivariable model with dialysis vintage and sex were separately tested.

All analyses were two-sided and $P < .05$ was considered statistically significant. IBM SPSS Statistics software version 26.0 was used to perform all analyses.

RESULTS

Altogether 200 patients undergoing SPKT were included in the present study. Median age was 42 (35-49) years, 69 (35%) were female, 17 (9%) had been diagnosed with heart failure before listing, median EF measured in TTE was 64% (60%-70%), and only 1 patient had EF <50%. Median time on the transplantation waiting list was 71 days (30-136). Before transplantation 191 (96%) patients received maintenance dialysis and median dialysis vintage was 13 months (9-19), whereas 9 patients (4%) received a pre-emptive transplantation. Out of the previously dialyzed 191 patients, 74 patients (39%) received hemodialysis, 84 patients (44%) received peritoneal dialysis, and 33 (17%) had received both before transplantation. Moreover, 4 patients (2%) had previously received a KT, and one of these patients a simultaneous islet cell and kidney transplantation. The median functional transplant vintage of the prior KTs was 176 months (115-254), and the patient with previous islet cell transplantation never achieved freedom from insulin.

Table 2. Adverse Outcomes During Follow-up According to Atrial Fibrillation Status

Outcome	No prior AF (n = 193)	History of AF (n = 7)	*P*	Incident NOAF (n = 2)	*P*
Death	7 (4)	0 (0)	-	1 (50)	.07
Graft failure death censored	7 (4)	0 (0)	-	0 (0)	-
Delayed graft function	21 (11)	0 (0)	-	1 (5)	.20
Post-Tx coronary PCI or CABG	2 (1)	0 (0)	-	0 (0)	-
Post-Tx AMI	3 (2)	0 (0)	-	0 (0)	-
Post-Tx amputation	6 (3)	1 (14)	0.22	1 (50)	.07
Post-Tx stroke	3 (2)	1 (14)	0.13	0 (0)	-

Categorical values in parentheses are %.
AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; NOAF, new-onset atrial fibrillation; PCI, percutaneous coronary intervention; Tx, transplantation.

Altogether 7 patients (4%) had a prior diagnosis of AF—one categorized as permanent AF and the other 6 as paroxysmal AF. Out of the 7 patients with a history of AF, 2 patients received warfarin and the other patients with prior AF did not receive oral anticoagulation before or after SPKT. All AF patients were on maintenance dialysis at the time of transplantation and none of the patients received antiarrhythmic medication. The baseline characteristics of the study patients according to prior diagnosis of AF are summarized in Table 1. In the univariate logistic regression model, history of heart failure and left atrial diameter measured by echocardiography were associated with the prior diagnosis of AF. In the age-adjusted, multivariable, logistic regression model history of heart failure was independently associated with prior diagnosis of AF (odds ratio 20.59, 95% confidence interval [CI] 3.94-107.62, $P < .01$). The results did not change when the multivariable model was further adjusted with dialysis vintage or sex (data not shown).

The median follow-up time was 3 years (1-5) after transplantation. Out of the 193 patients without prior diagnosis of AF, 2 patients (1%) were observed with NOAF corresponding an incidence rate of 3.1 cases per 1000 person-years. NOAF was observed in one patient on the first postoperative day and in the other patient 427 days after transplantation. Neither of the patients observed with NOAF during follow-up received oral anticoagulation. None of the tested baseline covariates were associated with NOAF in univariate cox proportional hazards models.

During follow-up, 4 (2%) patients were observed with an ischemic stroke, and one of these patients had a prior diagnosis of AF (Table 2); no strokes were observed in patients with NOAF. None of the stroke patients with or without AF were on oral anticoagulation. Furthermore, 7 patients (4%) died within follow-up (4 owing to cardiovascular causes, 2 owing to infection, and one owing to malignancy) and in the deceased median time to death was 292 days [137-492]. The distribution of observed adverse outcomes according to AF status is shown in Table 2. None of the patients with prior diagnosis of AF died, and one of the patients observed with NOAF perished during follow-up. In the univariate cox proportional hazards model NOAF was associated with mortality (hazard ratio [HR] 14.32, 95% CI 1.72-119.03, $P = .01$). However, the association did not remain significant in the age-adjusted multivariable cox proportional hazards analysis (HR 7.52, 95% CI 0.87-65.26, $P = .07$). Moreover, prior diagnosis of AF was not associated with incident stroke (HR 8.22, 95% CI 0.84-80.13, $P = .07$). Prior AF was not associated with incident amputation during follow-up in univariate cox proportional hazards analysis (HR 4.60, 95% CI 0.55-38.67, $P = .16$). In contrast, incident NOAF was associated with incident amputation during follow-up in univariate cox proportional hazards analysis (HR 11.48, 95% CI 1.35-97.45, $P = .03$) but the association was not significant in the age-adjusted multivariable cox proportional hazards analysis (HR 7.23, 95% CI 0.75-69.34, $P = .09$).

DISCUSSION

This is the first study to explore AF and associated outcomes in SPKT recipients. The prevalence of AF and NOAF rates was surprisingly low in this observational cohort study. Prior diagnosis of AF was independently associated with heart failure, and NOAF was not associated with the tested baseline covariates. Neither prior diagnosis of AF nor incident of NOAF was associated with adverse cardiovascular outcomes, mortality, or graft survival.

The prevalence of pre-existing AF (4%) was lower in SPKT recipients in this study than in KT recipients (5%-8%) and higher than in a similarly aged cohort of unselected diabetic patients without CKD (1%) in previous studies [6,7,9,10]. Strikingly, the incidence of NOAF was only 3.1 cases per 1000 person-years during follow-up—a two-to-nine-fold lower rate compared with previous studies on NOAF incidence in KT recipients [7,11] and comparable to the NOAF rate (2.4 cases per 1000 person-years) reported in a recent large study on DM1 patients with normal kidney function and mean age similar to our cohort [1]. This is somewhat unexpected as all SPKT recipients intrinsically have several risk factors associated with AF; a combination of long duration of diabetes with poor glycemic control, CKD, and maintenance dialysis precedes most transplantations [1,3,5,12]. Furthermore, virtually all patients in our study were hypertensive and a third had coronary artery disease, both of which are known risk factors for AF [13]. However, the patients in our study were significantly younger and had shorter dialysis vintage and lower body-mass index (BMI) compared with the reference studies on KT recipients [7,9]. It is plausible that younger age partly explains the lower prevalence and incidence of AF in our study cohort compared with KT recipients in prior studies, as AF burden has been demonstrated to rise substantially with age in the general population as well as in those who underwent KT [7,14]. Moreover, better cardiovascular fitness is required from SPKT

candidates compared with KT recipients, as cardiovascular adverse events are the leading cause of death after SPKT, and thus more comorbid patients with a higher risk for AF may be deferred from SPKT [15,16]. Furthermore, elevated BMI, an established risk factor for AF, is associated with poor pancreas graft outcomes and BMI >30 kg/m^2 is generally considered a relative contraindication for SPKT in many centers [17,18]. Ultimately, the reason for the low AF rate in the present study cannot be determined from these observational data, and further research on AF in SPKT recipients is required. However, as the pretransplantation prevalence of AF was markedly higher in our SPKT patients compared with the prevalence in unselected diabetic patients of similar age and normal kidney function, but the incidence of AF following SPKT was similar to that in diabetic patients without CKD, it may be hypothesized that SPKT may lower the risk for incident AF [1,10]. Our findings raise the question whether the simultaneous amelioration of insulin production, glycemic control, and kidney function with SPKT may lead to a markedly lower AF risk after transplantation. However, these hypotheses need to be addressed in future studies. In line with this hypothesis, it has been shown that diabetes and glycemic control are associated with atrial structural remodeling, including atrial enlargement and fibrosis [19]. Furthermore, higher glycated hemoglobin at the time of catheter ablation for AF has been shown to be associated with higher AF recurrence, whereas, improvement in HbA1c by >10% in the 12 months before ablation is strongly associated with reduced AF recurrence [20]. In patients undergoing sole KT the incidence of NOAF has been shown to fall below the incidence in patients remaining on the transplant waiting list 18 months after transplantation [7].

Heart failure was independently associated with a previous diagnosis of AF in this study. This is the first time such an association has been described in SPKT patients, although the link between heart failure and AF is intuitive and has been demonstrated in prior studies in healthier patients as well as KT recipients [9,13]. However, causality between heart failure and AF cannot be discerned from these data owing to the temporal relationship between the 2 conditions [21]. Nevertheless, the finding is interesting as data on heart failure has not been described in SPKT patients before and this is the largest study to date reporting TTE data in these patients. Prevalence of heart failure has ranged between 6% and 23% in previous studies on KT recipients [7,9]. The moderate prevalence of heart failure (9%), good EF (median 64%), and the fact that only 1 patient had EF <50% in the study might explain the lower AF prevalence and incidence in this study. This is possibly owing to patient selection, as better cardiovascular reserve is required of SPKT recipients compared with KT patients [16]. The measurements of left ventricular systolic function assessed by TTE in our cohort were largely in line with a previous small study [22].

Neither prior diagnosis of AF nor incident NOAF was associated with adverse cardiovascular events, mortality, or graft outcomes. However, NOAF tended to be associated with mortality in the age-adjusted multivariable model (P = .07). Furthermore, 1 out of the 4 strokes observed in this study occurred in a patient with prior AF even though the association was not statistically significant (P = .07). The connection between AF and ischemic stroke as well as mortality has been firmly established in previous studies in the general population as well as in KT recipients [23−25]. The stroke rate (3%) in our study was in line with a large study on 1699 SPKT recipients investigating the incidence of cardiovascular adverse outcomes during 5 years of follow-up [26]. However, a pooled cardiovascular outcome variable was used and incident stroke was not singled out for separate outcome analyses. Furthermore, data on AF was not reported in the study [26]. It is notable that the use of oral anticoagulation was poor in the present study as only 2 out of 9 patients affected with AF received oral anticoagulation at the end of follow-up despite the fact that virtually all SPKT recipients are intrinsically at high risk for stroke according to the CHA_2DS_2-VASc-score [27]. Importantly, 1 out of the 7 AF patients not on anticoagulation was observed with an incident of stroke during follow-up. The current European Society of Cardiology guidelines on the management of AF recommend the use of oral anticoagulants in KT recipients [28].

This study has several limitations and most of which pertain to the retrospective design. The sample size and event rate were limited for definite conclusions on the associations between prior or NOAF and incident adverse events. However, the present study included all SPKT recipients in Finland to date diminishing the selection bias of the study. Moreover, the baseline characteristics and echocardiography data were largely in line with reports from other centers reinforcing the generalizability of our findings [8,15,22,26]. All patients were followed-up annually by visits to the research hospital and at least every 4 months at the regional hospitals. Furthermore, all patients were evaluated and operated on by the same facility securing a firm standard of care. Incident AF episodes are often asymptomatic and some cases of NOAF may have been missed. However, the research hospital collects periodically patient data from the regional hospitals, reinforcing a good supply of outcome data concerning symptomatic AF episodes. The follow-up time varied substantially in the study patients. Nevertheless, median follow-up was 3 years with an interquartile range of 1 to 5 years leading to decent time-exposure on average. Despite these limitations we believe these data can shed light on AF in an unexplored clinical setting of SPKT recipients and guide future research.

CONCLUSIONS

In conclusion the prevalence and incidence of AF was low and similar to the incidence in DM1 patients without CKD in this large, observational, real-world cohort study comprising all SPKT recipients in Finland to date.

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