Clinical investigation

Potassium infusion increases the likelihood of conversion of recent-onset atrial fibrillation – a single-blinded, randomized clinical trial

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Abstract

Background: The optimal antiarrhythmic management of recent-onset atrial fibrillation or atrial flutter (ROAF) is controversial and there is a considerable variability in clinical treatment strategies. It is not known if potassium infusion has the potential to convert ROAF to sinus rhythm (SR). Therefore, we aimed to investigate if patients with ROAF and plasma-potassium levels ≤ 4.0 mmol/L have increased probability to convert to SR if the plasma-potassium level is increased towards the upper reference range (4.1-5.0 mmol/L).

Methods: In a placebo-controlled, single-blinded trial, patients with ROAF and plasma-potassium ≤ 4.0 mmol/L presenting between April 2013 and November 2017 were randomized to receive potassium chloride (KCl) infusion ($n=60$) or placebo ($n=53$). Patients in the KCl group received infusions at one of three different rates: 9.4 mmol/h ($n=11$), 12 mmol/h ($n=19$), or 15 mmol/h ($n=30$).

Results: There was no statistical difference in the number of conversions to SR between the KCl group and placebo [logrank test, $P=0.29$; hazard ratio (HR) 1.20 (CI 0.72-1.98)].

However, KCl-infused patients who achieved an above-median hourly increase in plasma-potassium (>0.047 mmol/h) exhibited a significantly higher conversion rate compared with placebo [logrank $P=0.002$; HR 2.40 (CI 1.36-4.21)] and KCl patients with below-median change in plasma-potassium [logrank $P<0.001$; HR 4.41 (CI 2.07-9.40)]. Due to pain at the infusion site, the infusion was prematurely terminated in 10 patients (17%).

Conclusions: Although increasing plasma-potassium levels did not significantly augment conversion of ROAF to SR in patients with potassium levels in the lower-normal range, our results indicate that this treatment may be effective when a rapid increase in potassium concentration is tolerated and achieved.

Clinical Trial Registration –[URL:https://clinicaltrials.gov](https://clinicaltrials.gov). Unique identifier:

NCT01818583

Key words: atrial fibrillation, potassium, antiarrhythmic drugs, treatment.

1 Introduction

2 Atrial fibrillation (AF) is the most common arrhythmia, with an estimated prevalence of
3 approximately 3% in adults aged 20 years or older. Atrial flutter has lower prevalence, with
4 an incidence <1/10 that of AF ¹. Recent-onset atrial fibrillation or atrial flutter (ROAF),
5 defined as an abrupt onset of symptoms within 48 hours from admission, are highly
6 prevalent in emergency departments ². Current European and American guidelines describe
7 different treatment options and strategies for management of ROAF ¹. This is reflected by a
8 wide variability of treatment approaches employed in clinical practice ². Indeed, common
9 strategies range from a “wait and see” approach to conversion to sinus rhythm (SR) by use of
10 anti-arrhythmic medication or direct-current cardioversion ³.

11 About 50% of patients with ROAF with duration less than 48 hours convert spontaneously to
12 SR ^{4,5}. Several antiarrhythmic drugs have been shown to increase the likelihood of conversion
13 to SR to about 70% within 12 hours ⁶. However, most current antiarrhythmic drugs are not
14 atrial specific, and they all have significant risk of side-effects, including atrial and ventricular
15 proarrhythmia, heart failure exacerbation, lung-, hepatic-, and thyroid toxicity, and death ⁷.

16 Furthermore, antiarrhythmic drugs have several contraindications including bradycardia,
17 sinoatrial node dysfunction, AV conduction disturbances, prolonged QT interval, heart
18 failure, coronary artery disease, and structural heart disease ⁷. By comparison, direct-current
19 cardioversion has been shown to have a success rate of more than 90% in ROAF patients ⁸.

20 However, this approach requires deep sedation and a six hours postprandial period to ensure
21 gastric emptying, associated with additional costs, resources, and risk.

22 Clinical studies have shown that lower serum concentrations of potassium (<3.5 mmol/L) are
23 associated with a higher risk of AF ⁹. This association is independent of age, sex, serum

magnesium, antihypertensives, myocardial infarction, heart failure, and other potential confounders ⁹. It has been suggested that hypokalemia may trigger AF through adverse effects on the sinoatrial node and increased pulmonary vein arrhythmogenesis ¹⁰. Hypokalemia causes resting membrane hyperpolarization, Na⁺-K⁺ ATPase inhibition and suppression of K⁺ channel conductances resulting in action potential duration prolongation, reduced repolarization reserve, early afterdepolarizations, delayed afterdepolarizations, and automaticity. These changes are believed to increase the risk of developing AF ¹¹. Thus, increasing potassium intake with subsequently increased or normalized plasma-potassium levels might be beneficial in AF patients, mirroring previous work showing that this approach reduces both blood pressure and the risk of lethal ventricular arrhythmias in patients with ischemic heart disease, heart failure, and left ventricular hypertrophy ¹². There are several case reports of patients with AF converting to SR during hyperkalemia ¹³⁻¹⁸. However, to our knowledge there are no studies investigating whether potassium infusion has the potential to convert AF to sinus rhythm. We presently hypothesized that patients with ROAF or atrial flutter with plasma-potassium levels ≤ 4.0 mmol/L have increased probability to convert to SR if the plasma-potassium level is increased towards the upper part of the reference range; between 4.1 and 5.0 mmol/L. Thus, our aim was to investigate whether potassium, a cheap treatment with few contraindications, could be an alternative to more expensive drugs with potentially serious side-effects.

Materials & methods

Study design

A single center, placebo-controlled, parallel-group study was conducted with equal randomization (1:1), blinded for patients but not for the healthcare providers, at Diakonhjemmet Hospital, Oslo, Norway, from April 2013 to November 2017. Diakonhjemmet Hospital is a local urban hospital in Oslo, Norway, serving approximately 135 000 inhabitants. The patients are referred to the emergency department from general

practitioners, municipal emergency services, nursing homes, community health services, or directly by ambulance ordered from a dispatch center.

Participants

Eligible participants were patients ≥ 18 years of age visiting the emergency department with AF or atrial flutter with abrupt onset of symptoms within 48 hours from admission and plasma-potassium ≤ 4.0 mmol/L. Patients with or without a documented history of previous AF/atrial flutter were included. A 12-lead ECG was recorded (Mortara ELI 280, Mortara Instruments, Inc., Milwaukee, WI), at rest and interpreted by the treating physician. Exclusion criteria were kidney failure with estimated glomerular filtration rate (eGFR) < 30 mL/min, current usage of antiarrhythmic medication (flecainide, amiodarone, dronedarone, sotalol, dofetilide or propafenone), infection, metabolic acidosis with pH < 7.2 , pregnancy, or lactation. Patients participating in other clinical trials or who had previously been included in our trial were also excluded. Duration of symptoms, age, gender, body mass index (BMI), comorbidities and medications were registered shortly after patient inclusion, based on a review of medical records. After conversion to SR and before discharge, transthoracic echocardiography was performed, registering the following parameters: left ventricular (LV) ejection fraction, left atrial area, LV end-diastolic diameter (LVEDD), LV mass, mitral regurgitation, systolic pulmonary artery pressure (SPAP), and the LV diastolic parameters E/A-ratio (ratio between mitral valve early and late diastolic inflow) and E/e' (ratio between early mitral inflow velocity and mitral annular early diastolic velocity).

The study was approved by the Regional Committee for Medical and Health Research ethics, The Norwegian Medicines Agency, and the hospital's research committee, and was registered at Clinicaltrials.gov (NCT01818583). All study patients provided their informed written consent. KT was funded by The South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF); grant number: 2013011. Helse Sør-Øst RHF had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors are

solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Randomization, study treatment, and monitoring

Patients were assigned to either the potassium chloride (KCl) group or placebo group following blocked randomization by shuffling opaque concealed envelopes. The KCl group was treated with 60 mmol KCl added to 1000 mL of 50 mg/mL dextrose in an infusion bag, which was then inverted ten times to ensure that the solution was well-mixed. KCl was administered through a peripheral venous catheter in a large vein, preferably the antecubital vein, at a rate of 166 mL/h (9.4 mmol KCl/h), 212 mL/h (12 mmol KCl/h), or 265 mL/h (15 mmol KCl/h). An interim analysis was performed to determine whether serum/plasma-potassium increased as hypothesized. Since there was a smaller increase than expected, only the highest infusion rate was continued. Patients in the KCl group exhibiting serum magnesium levels ≤ 0.80 mmol/L also received magnesium sulfate infusion (0.5 mmol/kg added to 1000 mL of 9 mg/mL sodium chloride) over 24 hours at a rate of approximately 42 mL/h.

KCl infusion was stopped if the patients converted to SR, the plasma-potassium level reached ≥ 5.5 mmol/L, severe ventricular arrhythmia or symptomatic bradycardia occurred, eGFR declined to < 30 mL/min, or more than weak pain was experienced at the infusion site. The placebo group received only 50 mg/mL dextrose at the same infusion rate as in the KCl treatment group.

One of the trial investigators (KT) performed a day to day monitoring of potential adverse clinical events. Patients who did not convert to SR during infusion of KCl or placebo were treated by direct-current cardioversion the day after the start of infusion. The minimum infusion time for patients who did not convert to SR during infusion was 12 hours and the maximum infusion time was 24 hours. Patients with tachycardia (heart rate > 100 beats/min) could receive rate-reducing treatment with a beta-blocker, a calcium-antagonist, digoxin or a combination of agents (beta-blocker + digoxin or calcium antagonist + digoxin) after the

treating physician's assessment since these drugs are considered to have little converting properties and not regarded as antiarrhythmic drugs ¹.

Serum levels of potassium, magnesium, and creatinine (venipuncture) and plasma-potassium (arterial blood gas) were measured at inclusion. Serum-potassium, magnesium, and creatinine were further analyzed every 8 hours after the start of infusion and when the infusion was stopped, whereas plasma-potassium were measured 4 hours after start of infusion and thereafter every 8 hours, i.e. in between the serum analyses, and when the infusion was halted. Thus, serum- or plasma-potassium was monitored every 4 hours.

Continuous ECG-monitoring by telemetry was performed on all patients.

At the follow-up consultation performed roughly 3 months after discharge, a 12-lead ECG was recorded at rest, and all patients with SR were equipped with a hand-held "thumb ECG" recorder (Zenicor-EKG®; Zenicor Medical Systems AB, Stockholm, Sweden) for 3 days. Patients were instructed to perform 30 second rhythm recordings once in the morning, once in the evening, and whenever they experienced palpitations or arrhythmia symptoms. The recorded signal corresponded to lead I in a standard 12-lead ECG. AF was defined as irregular ventricular rhythm without visible or regular p-waves for 30 seconds, whereas atrial flutter was defined by regular P waves at a rate of 250-350/min.

End Points

The co-primary endpoints were time to and frequency of conversion to SR. The secondary endpoints were serious adverse (e.g. ventricular arrhythmia, symptomatic bradycardia, death) and adverse events (e.g. pain at the infusion site) during infusion, detection of AF or atrial flutter, hospital visits due to AF or atrial flutter, episodes with tachycardia lasting for at least one hour, and serum- and plasma-potassium during follow up.

Statistics

We assumed that 50% of the patients would convert spontaneously to SR ^{4, 19} and postulated that potassium infusion would increase the rate of conversion to 75%. With a power of 80%

to detect this increase, at least 58 patients were predicted to be required in both the KCl infusion and placebo groups to detect a significant treatment effect.

Continuous variables are presented with median and interquartile range (IQR), and categorical variables are presented as count and percentage. Statistical differences between any two groups were examined with Pearson's Chi-squared test for categorical variables and a 2-sample Wilcoxon rank-sum (Mann-Whitney) test applied for continuous variables. Differences in time to conversion between groups were also assessed with Kaplan-Meier plots, a log-rank test, and Cox proportional hazard regressions. The assumption of proportional hazard was tested using Schoenfeld residuals as well as visual inspection of a log-log plot.

The primary analysis was *intention-to-treat* and involved all randomized patients included. All patients who were randomized into either group were considered to be in the *intention-to-treat* sample (n=113). From these, 5 patients were excluded from the placebo group and 11 patients were excluded from the KCl group (Figure 1). All other patients for whom the protocol was followed (n=97) were included in a prespecified *per-protocol* analysis with the same endpoints as for the intention-to-treat analysis.

Statistical analyses were performed using Stata/SE version 14.2 (Stata Corporation, College Station, TX). A P value ≤ 0.05 was considered statistically significant.

Results

Study Participants

Due to slower inclusion than expected, a total of 113 patients were randomized, of whom 53 were allocated to the placebo group and 60 to the KCl group (Figure 1). The vast majority of included patients presented exclusively with AF (>90%), while 9 patients (8%) had atrial flutter and 2 patients (1.8%) alternated between AF and atrial flutter. Eleven patients received KCl at an infusion rate of 166 mL/h (9.4 mmol KCl/h), 19 patients at a rate of 12 mmol KCl/h, and 30 patients at a rate of 15 mmol KCl/h. Forty-eight patients in the placebo

group and 49 patients in the KCl group completed the protocol. Baseline characteristics (Table 1) were similar between these groups, apart from a higher percentage of men and a higher median LVEDD in the KCl group. However, adjusting for these variables in Cox regression models did not change our result to any significant degree.

Figure 1. Study enrollment and randomization.

KCl, potassium chloride. * Patients who had received fluid corresponding to <10 mmol KCl in the placebo group and <10 (1.25-6) mmol KCl in the KCl group.

Table 1. Baseline characteristics

	Placebo (n=53)	KCl (n=60)
Age, y	63 (54-73)	67 (53-74)
Sex, % male	27 (50.9%)	44 (73.3%)*
BMI, kg/m ²	24.6 (22.5-27.2)	25.8 (22.9-28.1)
Duration of symptoms, hrs	2.75 (1.8-5.0)	4.2 (2.0-12.5)
Heart rate, bpm	128 (116-143)	131 (111-148)
Medical history		
Atrial fibrillation	32 (60.4%)	39 (65.0%)
Kidney function (eGFR)		
- ≥60 mL/min	44 (83.0%)	53 (88.3%)
Hypertension	19 (35.9%)	19 (31.7%)
Stroke/TIA	5 (9.4%)	2 (3.3%)

Coronary heart disease	3 (5.7%)	7 (11.7%)
Previous ablation	3 (5.7%)	5 (8.3%)
Diabetes mellitus	2 (3.8 %)	4 (6.7%)
Hypo-/hyperthyroidism	3 (5.7%)	3 (5%)
Medications		
ASA	8 (15.1%)	12 (20.0%)
Warfarin	5 (9.4%)	6 (10%)
NOAC	12 (22.6%)	10 (16.7%)
Beta-blocker	14 (26.4%)	20 (33.3%)
Digoxin	1 (1.9%)	0
ACE-I or ARB	15 (28.9%)	15 (25%)
Diuretic (loop or thiazide)	9 (17.0%)	13 (21.7%)
Potassium-sparing diuretic	1 (1.9%)	1 (1.7%)
CCB (non-dihydropyridines)	6 (11.3%)	8 (13.3%)
CCB (dihydropyridines)	1 (1.9%)	2 (3.3%)
Statin	12 (22.6%)	13 (21.7%)
Levothyroxine	2 (3.8%)	2 (3.3%)
Echocardiographic characteristics		
LAA, cm ² , n=107	21 (18-27)	22.5 (19-27)
LVEDD, mm, n=108	47 (44-52)	50 (47-54)*
LV mass, g, n=107	60.7 (45.8-83.3)	66.3 (52.8-81.7)
LVEF $\geq$ 50%, n=107	51 (98.1%)	52 (94.6%)
Mitral regurgitation [†] , n=108	4 (7.7%)	7 (12.5%)
E/A-ratio, n=89	1.2 (0.9-1.6)	1.2 (1.1-1.7)
E/e', n=95	7.9 (6.0-10.1)	7.7 (5.8-10.5)
SPAP, mmHg, n=59	30.5 (26.5-36.0)	26.5 (25.0-30.0)
Pre-infusion		
S-potassium, mmol/L	4.1 (3.8-4.2)	4.1 (3.9-4.2)
S-potassium <3,5 mmol/L, n=3	3.3 (3.3-3.3)	3.4 (3.3-3.4)
P-potassium, mmol/L	3.8 (3.6-4.0)	3.8 (3.6-3.9)
P-potassium <3,5 mmol/L, n=11	3.3 (3.3-3.4)	3.4 (3.2-3.4)
Magnesium, mmol/L, n=111	0.81 (0.78-0.85)	0.83 (0.76-0.87)
Creatinine, μ mol/L	79 (66-91)	80 (71-90)
NT-proBNP, ng/L, n=97	262 (80-1023)	304 (127-1023)
Troponin T, ng/L, n=111	11 (10-16)	11 (10-17)
CRP, mg/L	1 (1-2)	1 (1-2)
TSH, mIU/L, n=100	2.2 (1.1-3.1)	2.3 (1.5-3.4)
Free T ₄ , pmol/L, n=100	16 (15-18)	16 (15-17)

1 Values are median and interquartile range or number and percentage.

2 † Moderate to severe. *p value <0.05

3 BMI: body mass index; TIA: transient ischemic attack; ASA: Acetylsalicylic acid; NOAC: Non-vitamin

4 K antagonist oral anticoagulant; ACE-I: angiotensin converting enzyme inhibitor; ARB: Angiotensin

5 receptor II blocker; CCB: calcium channel blocker; LAA: left atrial area; LVEDD: left ventricle end-

6 diastolic diameter; LV: left ventricle; LVEF: left ventricle ejection fraction; E/A: ratio between mitral

7 valve early and late diastolic inflow; E/e': ratio between early mitral inflow velocity and mitral annular

8 early diastolic velocity; SPAP: Systolic pulmonary artery pressure

9 Time to and frequency of conversion to SR

- 1 There was no significant effect of KCl infusion on the co-primary endpoint of time to or
2 frequency of conversion to SR compared with placebo when all KCl patients were grouped
3 independent of infusion rate (Table 2 and 3).

Table 2. Outcomes by *intention-to-treat* analysis

Variables	All participants		265 mL/h	All KCl	
	Placebo (n=53)	KCl (n=60)	KCl (15 mmol/h) (n=30)	Δ P-potassium below median p- potassium/h (n=28)	Δ P-potassium above median p- potassium/h (n=28)
Time to conversion, h	6.8 (1.6-15.5)	5.5 (2.3-12.1)	5.3 (1.8-10.9)	8.1 (3.0-13.2)	5.4 (2.2-11.7)
Number of patients who converted to SR	28 (52.8%)	34 (56.7%)	20 (66.7%)	10 (35.7%)	23** (82.1%)
Infusion time, h	13.0 (4.7-17.2)	9.6 (2.8-16.0)	6.0 (2.2-13.5)	13.8 (9.8-22.7)	5.6* (2.2-10.7)
Total potassium infused, mmol	0	120.1 (34.1-209.4)	90.0 (32.5-202.5)	169.5 (107.8-255)	82 (33.1-143.8)
Pain from the infusion	0	12** (20%)	9*** (30%)	2* (7.1%)	6*** (21.4%)
S-potassium, mmol/L [†]	4.0 (3.8-4.2)	4.7 (4.3-5.1)	4.6 (4.2-5.1)	4.7 (4.4-5.1)	4.6 (4.2-5.1)
P-potassium, mmol/L [†]	3.8 (3.6-3.8)	4.3 (4.1-4.6)	4.4 (4.0-4.7)	4.3 (4.2-4.6)	4.4 (4.0-4.7)

4 Values are median and interquartile range or number and percentage.

5 *P value <0.05; **P value <0.01; ***P value <0.001

6 † After stopping the infusion (post-infusion).

7 All treatment groups were statistically compared with the placebo group.

Table 3. Outcomes by *per-protocol* analysis

Variables	All participants		265 mL/h	All KCl	
	Placebo (n=48)	KCl (n=49)	KCl (15 mmol/h) (n=22)	Δ P-potassium below median p- potassium/h (n=25)	Δ P- potassium above median p- potassium/h (n=24)
Time to conversion, h	7 (2-15.6)	5.7 (2.3-12.4)	5.3 (2.2-12.1)	8.1 (3.0-13.2)	5.4 (2.2-11.7)
Number of patients who converted to SR	25 (52.1%)	32 (65.3%)	18* (81.8%)	10 (40.0%)	22** (91.7)
Infusion-time, h	13.4 (5.8-17.6)	12.1 (3.9-17.9)	6.8 (2.2-14.2)	14 (11.8-23.0)	5.7* (2.2-12.9)
Total potassium infused, mmol	0	141.0 (37.1-222.7)	102.6 (33.7-213.7)	180.0 (119.0-242.0)	80.5 (33.1-192.9)
Pain from the infusion	0	2 (4.1%)	2* (9.1%)	1 (4.0%)	1 (4.2%)
S-potassium, mmol/L [†]	4.0 (3.8-4.2)	4.7 (4.3-5.1)	4.6 (4.2-5.1)	4.7 (4.4-5.1)	4.6 (4.2-5.1)
P-potassium, mmol/L [†]	3.8 (3.6-3.8)	4.3 (4.1-4.6)	4.4 (4.0-4.7)	4.3 (4.2-4.6)	4.4 (4.0-4.7)

Values are median and interquartile range or number and percentage.

*P value <0.05; **P value <0.01; ***P value <0.001

† After stopping the infusion (post-infusion).

All treatment groups were statistically compared with the placebo group.

A Kaplan-Meier plot showed only a trend toward increased number of patients who converted to SR, which was non-significant by logrank test ($P=0.29$, Figure 2a), and Cox regression showed a hazard ratio (HR) of 1.20 (CI 0.72-1.98, $P=0.72$) for KCl infusion compared with placebo. When analyzing the KCl group receiving the fastest infusion KCl rate of 15 mmol/h, there was still no significant difference in conversion rate nor in time to conversion in the *intention-to-treat* analysis compared with placebo. However, when comparison was done in patients without a history of AF, significantly more patients in the KCl group converted to SR compared with the placebo group (85.7 vs 52.4%; $P=0.019$; Supplementary Table 1a) independently of infusion rate of KCl.

Supplementary Table 1a. Outcomes by *intention-to-treat* analysis – AF-naïve patients

Variables	All AF-naïve		265 mL/h	All KCl	
	Placebo (n=21)	KCl (n=21)	KCl (15 mmol/h) (n=8)	ΔP-potassium below median p- potassium/h (n=10)	ΔP-potassium above median p- potassium/h (n=10)
Time to conversion, h	4.0 (1.3-15.6)	8.4 (3.0-12.7)	6.4 (2.3-12.1)	9.8 (4.0-13.2)	8.4 (2.9-12.1)
Number of patients who converted to SR	11 (52.4%)	18* (85.7%)	7 (87.5%)	7 (70%)	10** (100%)
Infusion time, h	12 (4.0-16.4)	9.8 (4.0-15.0)	6.8 (3.7-14.5)	13.0 (6.4-20.2)	8.4 (2.9-12.1)
Total potassium infused, mmol	0	115 (37.1-182)	102.6 (54.8-217.9)	138.9 (91.6-242)	111.9 (34.2-182)
Pain from the infusion	0	3 (14.3%)	3 (37.5%)	1 (10%)	1 (10%)
S-potassium, mmol/L [†]	4.0 (3.9-4.2)	4.7 (3.4-5.0)	4.6 (4.3-5.2)	4.6 (4.4-4.9)	4.7 (4.5-5.2)
P-potassium, mmol/L [†]	3.7 (3.6-3.9)	3.8 (3.6-4.0)	4.4 (4.2-4.9)	4.3 (4.1-4.5)	4.4 (4.1-4.8)

Values are median and interquartile range or number and percentage.

*P value <0.05; **P value <0.01; ***P value <0.001

† After stopping the infusion (post-infusion).

All treatment groups were statistically compared with the placebo group.

Supplementary Table 1b. Outcomes by *intention-to-treat* analysis – patients with history of AF

Variables	All not AF-naïve		265 mL/h	All KCl	
	Placebo (n=32)	KCl (n=39)	KCl (15 mmol/h) (n=22)	ΔP-potassium below median p- potassium/h (n=18)	ΔP-potassium above median p- potassium/h (n=18)
Time to conversion, h	7 (1.7-15.4)	3.7 (1.7-7.7)	5.2 (1.5-9.7)	2.3 (1.0-13.5)	5.2 (1.8-5.8)
Number of patients who converted to SR	17 (53.1%)	16 (41.0%)	13 (59.1%)	3 (16.7%)	13 (72.2%)
Infusion time, h	13.3 (4.7-17.6)	9.5 (2.1-17.1)	5.6 (2.1-13.5)	15.5 (11.8-23.3)	5.5* (1.9-9.5)
Total potassium infused, mmol	0	131.5 (31.3-213.8)	83.6 (31.3-202.5)	203.8 (141-268)	79 (22.8-142.5)
Pain from the infusion	0	9 (23.1%)	6 (27.3%)	1 (5.6%)	5 (27.8%)
S-potassium, mmol/L [†]	4.0 (3.7-4.3)	4.7 (4.3-5.1)	4.5 (4.2-5.1)	4.8 (4.4-5.1)	4.4 (4.2-5.1)
P-potassium, mmol/L [†]	3.8 (3.6-4.0)	3.8 (3.7-3.9)	4.3 (3.9-4.7)	4.3 (4.2-4.6)	4.3 (4.0-4.7)

Values are median and interquartile range or number and percentage.

*P value <0.05; **P value <0.01; ***P value <0.001

[†] After stopping the infusion (post-infusion).

All treatment groups were statistically compared with the placebo group.

Twelve patients in the KCl group experienced pain at the infusion site (20%), and most of these were allocated to receiving KCl at the fastest infusion rate of 15 mmol/h. In 10 of these patients, the KCl infusion had to be prematurely terminated due to the pain (Table 2). After excluding these patients, the *per-protocol* analysis showed that significantly more patients converted to SR in the KCl 15 mmol/h group compared with the placebo group (82% vs 53%, $P=0.018$, Table 3). Significant differences between the KCl 15 mmol/h and placebo groups were also observed when tested with a Kaplan Meier plot (logrank $P=0.02$) and Cox regression (HR 2.26, CI 1.09-3.71, $P=0.024$, Figure 2b). Again, when comparison was done in patients without a history of AF, significantly more patients in the KCl group converted to SR compared with the placebo group (85% vs 47.4%; $P=0.013$; Supplementary Table 2a) independently of infusion rate of KCl.

Supplementary Table 2a. Outcomes by *per protocol* analysis – AF-naïve patients

Variables	All AF-naïve		265 mL/h	All KCl	
	Placebo (n=19)	KCl (n=20)	KCl (15 mmol/h)	ΔP-potassium below median	ΔP-potassium above median

			(n=7)	p- potassium/h (n=10)	p- potassium/h (n=10)
Time to conversion, h	4 (2.2-15.6)	9.6 (4.0-12.7)	6.8 (5.1-12.1)	9.8 (4.0-13.2)	8.4 (2.9-12.1)
Number of patients who converted to SR	9 (47.4%)	17* (85%)	6 (85.7%)	7 (70%)	10** (100%)
Infusion time, h	12 (4.0-17.3)	10.7 (4.5-16.0)	7.3 (5.1-16.9)	13.0 (6.4-20.2)	8.4 (2.9-12.1)
Total potassium infused, mmol	0	117.0 (56.4-202.3)	108.8 (75.8-253.8)	138.9 (91.6-242)	111.9 (34.2-182)
Pain from the infusion	0	2 (10%)	2 (28.6%)	1 (10%)	1 (10%)
S-potassium, mmol/L [†]	4.1 (3.9-4.2)	4.7 (4.4-5.0)	4.6 (4.3-5.2)	4.6 (4.4-4.9)	4.7 (4.5-5.2)
P-potassium, mmol/L [†]	3.8 (3.5-3.9)	4.4 (4.1-4.6)	4.4 (4.2-4.9)	4.3 (4.1-4.5)	4.4 (4.1-4.8)

Values are median and interquartile range or number and percentage.

*P value <0.05; **P value <0.01; ***P value <0.001

† After stopping the infusion (post-infusion).

All treatment groups were statistically compared with the placebo group.

Supplementary Table 2b. Outcomes by *per protocol* analysis – patients with history of AF

Variables	All not AF-naïve 265 mL/h			All KCl	
	Placebo (n=29)	KCl (n=29)	KCl (15 mmol/h) (n=15)	ΔP-potassium below median p- potassium/h (n=18)	ΔP-potassium above median p- potassium/h (n=18)
Time to conversion, h	7.4 (1.8-17.4)	2.3 (1.5-9.7)	3.7 (1.4-11.6)	2.3 (1.0-13.5)	3.4 (1.7-7.7)
Number of patients who converted to SR	16 (55.2%)	15 (51.7%)	12 (80.0%)	3 (20%)	12* (85.7%)
Infusion time, h	14 (7.0-17.9)	13.3 (2.3-21.2)	5.6 (1.5-14.3)	17.1 (12.4-24)	5.4 (1.8-13.6)
Total potassium infused, mmol	0	149 (33.8-225.5)	83.5 (22.5-213.8)	205 (141-268)	65.7 (22.5-203.8)
Pain from the infusion	0	0	0	0	0
S-potassium, mmol/L [†]	4.0 (3.7-4.2)	4.7 (4.2-5.1)	4.5 (4.2-5.1)	4.8 (4.5-5.1)	4.4 (4.2-4.7)
P-potassium, mmol/L [†]	3.8 (3.6-4.0)	4.3 (4.0-4.7)	4.3 (3.9-4.7)	4.3 (4.2-4.6)	4.3 (4.0-4.7)

Values are median and interquartile range or number and percentage.

*P value <0.05; **P value <0.01; ***P value <0.001

† After stopping the infusion (post-infusion).

All treatment groups were statistically compared with the placebo group.

Figure 2. Kaplan – Meier curve for time to conversion and conversion to sinus rhythm (per protocol analysis). All patients who received KCl infusion (n=49) versus placebo (n=48) **(a)**. Patients in the 15 mmol/h group (n=22) versus placebo (n=48) **(b)**. All patients who received KCl with a median plasma potassium change per hour above (n=24) and below (n=25) median (0.047 mmol/h) versus placebo (n=48) **(c)**.

Of note, KCl-infused patients who achieved an above-median hourly increase in plasma-potassium (>0.047 mmol/h) exhibited a significantly higher conversion rate, but no difference in time to conversion compared with placebo (Table 2 and 3 and Supplementary Table 1a and 2a). Kaplan Meier plots also showed a significant difference between this above-median group compared with both the placebo group (logrank $P=0.002$) and KCl patients with below-median change in plasma-potassium (logrank $P<0.001$). There was no difference between the below-median group and placebo (logrank $P=0.09$, Figure 2c). Cox regression showed an HR of 2.40 (CI 1.36-4.21, $P=0.002$) when comparing above median change with placebo, and HR=4.41 (CI 2.07-9.40, $P<0.001$) compared with below median change.

The group which received KCl at a rate of 15 mmol/h exhibited a greater increase in plasma-potassium (0.07 [0.04-0.18] mmol/L/h) than patients who received 9.4 mmol/h (0.04 [0.03-0.05] mmol/L/h; $P=0.015$) and 12 mmol/h (0.04 [0.03-0.06]; $P=0.043$). Patients that converted to SR had a higher change in both serum- and plasma-potassium per hour than those that did not convert to sinus rhythm (0.08 [0.04-0.18] and 0.07 [0.03-0.18] mmol/L vs. 0.05 [0.02-0.06] and 0.04 [0.03-0.05] mmol/L, respectively, $P<0.01$).

When analyzing whether lower baseline plasma-potassium levels yield higher probability for conversion to SR after KCl infusion, we found that in the KCl group receiving the highest infusion rate of 15 mmol/h, all patients with plasma-potassium at baseline <3.8 mmol/L ($n=13$) converted to SR, whereas 70% with plasma-potassium between 3.8-4.0 mmol/L ($n=17$) converted to SR.

Atrial flutter

For the small subgroup of patients with atrial flutter, only 2 of 9 patients (22%) converted to SR, and both of these were in the placebo group. However, these findings should be interpreted cautiously due to the small number of atrial flutter patients included in this trial.

Administration of MgSO₄

A total of 14 (23.3%) patients in the KCl group were also administered MgSO₄; 4 in the 9.4 mmol/h group, 1 in the 12 mmol/h group, and 9 in the 15 mmol/h group. There was no significant difference ($P=0.26$) between this subset of patients and those receiving only KCl regarding conversion to SR during the infusion.

Heart rate-reducing medication

Seventy percent of the patients in the KCl group and 91% of the patients in the placebo group received heart rate-reducing medication. In the KCl group, 62% of the patients were treated with metoprolol, 5% with verapamil, and 3% with digoxin, respectively vs. 79%, 2%, and 9%, respectively, in the placebo group. Among the patients who converted to SR, 68% were

treated with metoprolol, 6% with verapamil, and 6% with digoxin, respectively, in the KCl group vs. 82%, 0%, and 11%, respectively, in the placebo group.

Follow-up

At the follow-up consultation after discharge, most patients in both groups had SR at rest and during the 3 days with ambulatory ECG recording (Table 4). No patients had atrial flutter. Although numerically there was a higher proportion of patients in the placebo group than in the KCl group who exhibited AF at rest or during ambulatory ECG registration, and these patients had a lower number of contacts with the hospital for AF, these differences were not significant.

Table 4. Post-discharge follow-up

	Placebo (n=48)	KCl (n=54)
Time of follow-up after discharge (months), n=102	3.8 (3.3-4.8)	3.9 (3.3-4.5)
Heart rate, bpm	65 (57-75)	65 (57-76)
ECG at rest, n=102*		
- Sinus rhythm	43 (89.6%)	49 (92.6%)
- Atrial fibrillation	4 (8.3%)	3 (5.5%)
- Atrial flutter	0	0
Ambulatory ECG, n=93†		
- Sinus rhythm	37 (86.0%)	48 (96.0%)
- Atrial fibrillation	6 (14.0%)	2 (4.0%)
- Atrial flutter	0	0
Number of contacts with Diakonhjemmet Hospital for atrial fibrillation/atrial flutter after discharge, n=102*		
- No contacts	36 (67.9.0%)	49 (81.7%)
- One or more times	17 (32.1%)	11 (18.3%)
Total number of ECG-documented atrial fibrillation/atrial flutter, n=113	25 (47.2%)	15 (25.0%)
History of palpitations during ≥1 hour, n=102*	17 (35.4%)	12 (22.2%)
Serum-potassium, mmol/L, n=102*	4.4 (4.2-4.6)	4.3 (4.1-4.4)
Plasma-potassium, mmol/L, n=101‡	4.1 (3.9-4.3)	4.0 (3.9-4.2)
Difference between serum- and plasma-potassium, mmol/L, n=101‡	0.3 (0.2-0.3)	0.3 (0.2-0.4)

* Eleven patients did not attend the follow-up consultation.

† Eleven patients did not attend the follow-up consultation, and nine patients did not receive ambulatory ECG monitoring since they exhibited atrial fibrillation in an ECG performed at rest.

‡ Eleven patients did not attend the follow-up consultation. In one patient plasma-potassium was not measured.

Discussion

This is the first study to investigate the effects of KCl infusion in patients with ROAF or atrial flutter. Our results did not demonstrate any significant effect of potassium infusion on the

primary endpoint, time to and frequency of conversion to SR. However, the *per protocol* analysis indicates that an increase in circulating potassium may increase the likelihood of conversion of ROAF to SR if the patient does not experience pain at the infusion site but only if the hourly increase is sufficiently high.

Previous work has shown that roughly 50% of patients with ROAF convert spontaneously to SR within 48 hours ^{4, 19}, well in accordance with the results in the placebo group in our study. However, few patients with atrial flutter converted to SR indicating that this arrhythmia may be less likely to spontaneously convert to SR and be less affected by potassium correction. Of note, the number of patients in our study who converted to SR after KCl infusion was the same as for the placebo-treated patients. However, in a *post-hoc* analysis, we found that an increase in circulating potassium in our patients with potassium levels in the lower normal range may promote conversion to SR if the speed of potassium increase is sufficiently high, independent of the total amount infused. In fact, the median total amount of potassium infused was lowest in the group of patients receiving this rapid infusion, and there was no significant difference in the final plasma-potassium level between this KCl group and the two other KCl groups. Furthermore, no patients developed clinically significant hyperkalemia despite infusion of up to 366 mmol KCl.

Antiarrhythmic drugs have previously been shown to increase the likelihood of conversion of ROAF to SR to approximately 70% within 12 hours ⁶. Interestingly, the patients in our study receiving KCl infusion at a concentration of 15 mmol/h exhibited a similar conversion rate to SR (66.7%) within a median infusion time of just 5.3 hours. Unfortunately, in 17% of the patients receiving KCl infusion at the highest infusion speed, the infusion had to be stopped due to pain at the infusion site. Of the remaining fast-infusion patients that completed the study protocol, the vast majority (82%) converted to SR, and in the group of patients with an increase of plasma-potassium above median levels of increase, as many as 91.7% of these patients and all patients without a history of AF achieved conversion to SR. Furthermore, our results may suggest that KCl infusion is particularly effective in patients with the lowest

1 plasma-potassium levels. Thus, in patients without potassium-induced infusion pain, rapidly
2 applied KCl may be as effective as other antiarrhythmic drugs and does not carry the risk or
3 burden of additional resources inherent with direct-current cardioversion therapy. We
4 therefore suggest that patients with ROAF with plasma-potassium ≤ 4.0 mmol/L are
5 candidates for receiving KCl infusion at 15 mmol/h for up to 12 hours. Indeed, of the patients
6 in our study that experienced a rapid and substantial increase in circulating potassium, 75%
7 converted to SR within this time. However, if a patient experience more than weak pain at the
8 infusion site or if there is only a slight increase in plasma/serum-potassium, the KCl infusion
9 should be terminated and another treatment strategy should be chosen.

10 None of our patients developed clinically significant hyperkalemia despite infusion of up to
11 366 mmol KCl. This can be explained by the fact that the healthy kidney has a robust capacity
12 to excrete potassium. Under normal conditions, most persons can ingest very large quantities
13 of potassium (400 mmol per day or more) without clinically significant hyperkalemia. In the
14 kidneys, potassium ingestion stimulates potassium secretion and inhibits potassium
15 reabsorption ²⁰.

16 It is known that potassium chloride is vesicant and to avoid this, proper catheter position
17 prior to and during infusion, in addition to a well-mixed infusion bag is important. Despite
18 taking these steps, we were surprised that 12 of our patients reported pain at the infusion site,
19 which was alleviated when the infusion was stopped. According to our protocol, staff were
20 instructed to invert the infusion bag ten times after adding potassium chloride to the
21 dextrose, to be sure that the solution was well-mixed. In addition, the protocol dictated that
22 the peripheral vein catheter was to be placed in the antecubital vein and not at a more distal
23 location. In some of the patients who experienced side-effects, the infusion bag may not have
24 been well mixed, and in a few patients the peripheral vein catheter was placed on back of the
25 hand, not following the study instructions. We suggest that in future investigations the
26 solution should be pre-mixed by a pharmacist.

1 It is uncertain whether magnesium infusion can promote conversion of AF to SR, as the
2 findings of two previous meta-analysis studies were contradictory ^{21, 22}. Our patients in the
3 KCl group who exhibited serum magnesium levels ≤ 0.8 mmol/L also received magnesium
4 infusion since magnesium depletion reduces intracellular potassium concentration due to
5 renal potassium wasting ²³. However, few patients fit this criterion and received magnesium
6 infusion, and indeed, median serum magnesium level at the start of the protocol was >0.80
7 mmol/L in all groups. In addition, magnesium infusion was not associated with altered
8 conversion to SR, suggesting that inclusion of magnesium infusion in a subset of patients did
9 not markedly affect the study results.

10 It could be argued that the placebo infusion with 50 mg/mL dextrose may decrease plasma-
11 potassium and in this way augment the likelihood that the active arm of KCl infusion would
12 work. However, the reduction of plasma-potassium in the placebo group was very small, with
13 unchanged median values and only a small change in IQR from 3.6-4.0 mmol/L to 3.6-3.8
14 mmol/L. Thus, we believe this very small reduction in plasma-potassium had little effect on
15 our results.

16 Seventy percent of the patients in the KCl group and 91% of the patients in the placebo group
17 received heart rate-reducing medication after admission. Of these, most received metoprolol
18 while only a few patients received verapamil or digoxin. Among the patients who converted to
19 SR, 68% were treated with metoprolol in the KCl group vs. 82% in the placebo group,
20 indicating that metoprolol did not contribute to the increased conversion rate in the KCl
21 group.

22
23 At the post-discharge follow-up, we did not find any significant difference in the number of
24 patients with AF between the KCL and placebo groups. However, this study had a low
25 statistically power to detect such a difference. Moreover, since patients who did not convert
26 to SR after KCl or placebo infusion were treated by direct-current cardioversion the day after
27 the start of infusion, and since plasma- and serum-potassium levels at post-discharge follow-

up were similar in the KCl and placebo groups, a significant difference in the frequency of AF is not to be expected. Whether potassium supplementation may have long-term effects in preventing AF in patients with circulating potassium in the lower normal range is not known and should be investigated in future studies.

The electrophysiological effects of potassium depend not only on its extracellular concentration but also on the direction (hypokalemia vs. hyperkalemia) and rate of change ²⁴. Gradually increasing plasma-potassium induces a biphasic electrical sequence, with initial augmentation and then depression of excitability, conduction, and automaticity ²⁵. Atrial muscle is more sensitive than ventricular muscle to elevated potassium levels, whereas specialized fibers such as in the sinoatrial node, internodal tracts, and the bundle of His are practically resistant ^{26, 27}. The presently observed conversion of AF to SR upon increasing potassium levels could thus be due to a transient conduction acceleration which could terminate a re-entrant circuit in the atria ^{14, 28}. Alternatively, return to SR may result from reduced triggered activity of atrial cardiomyocytes. Previous work in isolated ventricular myocytes has shown that hypokalemic conditions result in inhibition of the Na⁺-K⁺ ATPase, and subsequent cellular calcium overload associated with generation of both early and delayed afterdepolarizations ^{29, 30}. If similar pro-arrhythmic alterations occur in atrial myocytes, elevating blood potassium levels may favour a return to SR via a direct cellular action.

We measured plasma-potassium levels for the inclusion of patients, since the use of plasma is superior to serum for accurate determination of potassium ³¹. While either plasma or serum can be used to assess potassium using an ion-selective electrode ³², as presently employed, platelet release from platelets during the clotting process results in serum-potassium levels which are 0.36 ± 0.18 mmol/L higher in serum than those measured in plasma ³¹. This difference is in accordance with our findings of serum- and plasma-potassium levels measured at baseline (Table 4).

Limitations

Our study has several limitations. Firstly, due to slower than expected inclusion rate, five fewer patients in the placebo group were recruited than planned based on the pre-study power analysis. Secondly, since our results may indicate that KCl should be given at a speed of 15 mmol/h, more significant results would have been expected if a greater number of patients had been assigned to this patient group. Thirdly, our beneficial findings are results of a *post-hoc* analysis and thus should be regarded as hypothesis-generating. Fourthly, although earlier studies have shown conflicting results regarding the ability of magnesium to convert ROAF to SR, we cannot rule out a confounding effect of magnesium in our study. However, few patients received magnesium infusion and the treatment was not associated with increased rate of conversion. Nevertheless, our study was not powered to address the effect of parallel infusion of magnesium and KCl. Fifthly, due to our exclusion criteria it is possible that our results do not apply to the whole ROAF population.

Conclusion

Overall, our data do not demonstrate any increase in frequency or rate of conversion of ROAF to SR after increasing plasma-potassium levels in patients with levels in the lower normal range. However, in a *post hoc* analysis, we found that a rapid increase in circulating potassium may increase the likelihood of conversion of ROAF to SR. However, pain at the infusion site was relatively frequent and thus, not all patients with ROAF are able to complete such a treatment. Our findings are hypothesis driving and need to ultimately be reexamined in a larger study with higher statistical power. If verified, potassium's low-risk profile, electrophysiological effects and few contraindications could make it an adjunct or alternative to acute short-term conventional therapies used for conversion of ROAF.

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