Does moderate hyperkalemia influence survival in HF? Insights from the MECKI score data base[☆]

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A B S T R A C T

Background: The prognostic role of moderate hyperkalemia in reduced ejection fraction (HFrEF) patients is still controversial. Despite this, it affects the use of renin–angiotensin–aldosterone system inhibitors (RAASi) with therapy down-titration or discontinuation.

Objectives: Aim of the study was to assess the prognostic impact of moderate hyperkalemia in chronic HFrEF optimally treated patients.

Methods and results: We retrospectively analyzed MECKI (Metabolic Exercise test data combined with Cardiac and Kidney Indexes) database, with median follow-up of 4.2 [IQR 1.9–7.5] years. Data on K^+ levels were available in 7087 cases. Patients with K^+ plasma level $\geq$ 5.6 mEq/L and < 4 mEq/L were excluded. Remaining patients were categorized into normal >4 and < 5 mEq/L (n = 4826, 68%) and moderately high $\geq$5.0 and $\leq$ 5.5 mEq/L (n = 496, 7%) K^+. Then patients were matched by propensity score in 484 couplets of patients. MECKI score value was 7% [IQR 3.1–14.1%] and 7.3% [IQR 3.4–15%] (p = 0.678) in patients with normal and moderately high K^+ values while cardiovascular mortality events at two years follow-up were 41 (4.2%) and 33 (3.4%) (p = 0.333) in each group respectively.

Conclusions: Moderate hyperkalemia does not influence patients' outcome in a large cohort of ambulatory HFrEF patients.

1. Introduction

In reduced ejection fraction (HFrEF) heart failure patients, hyperkalemia has been reported up to 18% of cases with a higher incidence in patients with more severe HF [1].

Several mechanisms have been advocated as causes of hyperkalemia including both pathophysiological alterations and iatrogenic factors [2]. Moreover, some frequently observed HF comorbidities, such as diabetes and renal failure, by reducing K^+ elimination in the kidney, are reported as hyperkalemia causes [3,4]. Finally, renin angiotensin aldosterone system inhibitor (RAASi) therapy, which is recommended as a disease modifier HF therapy [5], may further increase the risk of hyperkalemia in HFrEF [1,6,7]. Consequently, in case of hyperkalemia RAASi therapy is usually down-titrated or discontinued [5,8].

However, the effect of moderate hyperkalemia in determining HFrEF prognosis is still controversial albeit a few studies suggest that hyperkalemia is associated with poor prognosis, arrhythmias, intensive care admission and death [9–11]. Specifically, the prognostic role of moderate hyperkalemia in well characterized HFrEF patients is basically unknown.

The aim of our study is to assess the prognostic role of moderate hyperkalemia in a large cohort of ambulatory optimally treated chronic HFrEF patients. We performed a post-hoc analysis of MECKI (Metabolic Exercise test data combined with Cardiac and Kidney Indexes) score database to investigate whether moderately elevated potassium levels, between 5.0 and 5.5 meq/L, independently affected long-term survival.

2. Methods

We retrospectively analyzed data from MECKI score database, which includes a cohort of patients with a history of HFrEF recruited between 1993 and 2020 and prospectively followed [12]. MECKI score inclusion/ exclusion criteria and follow up modalities were previously reported in details [12]. In brief, MECKI score inclusion/exclusion criteria were: history of HFrEF [left ventricle (LV) EF < 40%], clinical stability and optimized HF treatment and ability to perform a cardiopulmonary exercise testing (CPET). Exclusion criteria were: history of pulmonary embolism, moderate to-severe aortic and mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina, significant ECG alterations or presence of any clinical comorbidity interfering with exercise performance and scheduled changes in therapy. For the present analysis recording of plasma K^+ was needed.

Follow-up was carried out according to the local HF program. MECKI score primary endpoint was the combination of cardiovascular death, urgent heart transplantation (HT) or left ventricular assist device (LVAD) implantation. Of the 7803 patients actually enrolled in the MECKI score database, data on K^+ levels were available in 7087 cases. Patients with K^+ plasma level $\geq$ 5.6 mEq/L (n = 70, 1% of cases) and < 4 mEq/L (n = 1695, 24% of cases) were excluded. Remaining patients were categorized into normal ($\geq$4 and < 5 mEq/L) (n = 5012, 71%) and high ($\geq$5.1 and $\leq$ 5.5 mEq/L) (n = 496, 7%) K^+ groups. Patients were matched for the following variables: gender, age, hemoglobin, peak VO_2, reported as a percentage of predicted, left ventricular ejection fraction (LVEF) and kidney function by means of MDRD [13]. We obtained by propensity score matching 484 couplets of patients with moderately high and normal serum K^+ levels. MECKI score was calculated in all patients.

Data are reported as mean $\pm$ SD or median and IQR, as appropriate. We used Kaplan–Meier plots to evaluate associations of moderate hyperkalemia with the primary MECKI score endpoint (combination of cardiovascular death, urgent HT or LVAD implantation).

3. Results

The studied population included 484 couplets of stable and optimally treated chronic HFrEF patients (Table 1). In normal K^+ patients ($K^+ \geq$ 4.0 and < 5.0 mEq/L) average daily diuretic dose was 50 [25.0–75.0] mg and carvedilol equivalent β-blockers dosage was 18.75 [12.5–25.0] mg while in high K^+ patients ($K^+ \geq$ 5and $\leq$5.5 mEq/L) diuretic dose was 50 [25.0–100.0] mg (p = 0.748) and equivalent β-blockers dosage was 12.5 [12.5–25.0] mg (p = 0.162). HF etiology was ischemic in around 50% of cases and idiopathic in little <40% of cases. No differences as regards etiology were observed between groups. MECKI score value was 7% [IQR 3.1–14.1%] and 7.3% [IQR 3.4–15%] in patients with normal and moderately high K^+ values. The median follow-up time of the total population was 4.2 [IQR 1.9–7.5]] years; however, as in the MECKI score, a follow up to 2 years was considered for the survival analysis of matched population. Cardiovascular mortality events were 41 (4.2%) in normal K^+ and 33 (3.4%) in high K^+(p = 0.333). Fig. 1 report the Kaplan Meier curves in the two study groups according to the combined end point of cardiovascular mortality, urgent HT or LVAD. Moderate hyperkalemia is not associated with more negative outcomes in a large cohort of ambulatory patients with chronic HF.

Table 1
Study population grouped as normal K^+ (4 to 5 meq/L) and moderately hyperkaliemic (5 to 5.5 meq/L).

	$K^+ > 4$ and < 5 mEq/L	$K^+ \geq 5.0$ and ≤ 5.5 mEq/L	P
Variables	$n = 484$	n = 484	
Age (years)	63.4 ± 11.4	63.6 ± 11.9	0.820
BMI (kg/m2)	26.4 ± 4.1	26.3 ± 4.4	0.592
LVEF (%)	31.7 ± 10.3	32.1 ± 10.4	0.560
MDRD (mL/min/1.73 m^2)	64.2 ± 24.6	64.5 ± 23.2	0.725
Peak VO_2 (ml/min)	1082 ± 386	1061 ± 387	0.399
Peak VO_2 (ml/min/kg)	14.1 ± 4.6	14.0 ± 4.5	0.671
Peak VO_2% pred	52 ± 16	52 ± 16	0.806
VE/VCO_2 Slope	34.3 ± 7.8	33.6 ± 7.9	0.205
VO_2/WORKLOAD slope	9.34 ± 2.02	9.59 ± 2.12	0.131
Peak RER	1.11 ± 0.13	1.11 ± 0.12	0.813
VO_2 AT (ml/min)	767 ± 277	762 ± 284	0.784
VO_2 AT (ml/min/kg)	9.7 ± 3.7	9.7 ± 3.7	0.943
Na + (mEq/L)	139 ± 3	139 ± 4	0.777
K^+(mEq/L)	4.39 ± 0.27	5.16 ± 0.16	<0.0001
Hb (g/dl)	13.3 ± 1.6	13.3 ± 1.8	0.908
Creatinine (mg/dl)	1.15(0.99;1.47)	1.20(1.00;1.51)	0.171
MECKI score (%)	11.1 ± 0.12	11.5 ± 0.12	0.678
NYHA 1 (n, %)	56(11.6%)	52(10.7%)	0.954
NYHA 2 (n, %)	279(57.6%)	276(57%)	
NYHA 3 (n, %)	142(29.3%)	149(30.8%)	
NYHA 4 (n, %)	7(1.4%)	7(1.4%)	
Idiopathic etiology (n, %)	148 (30%)	150(31%)	0.4782
Ischemic etiology (n, %)	229(47%)	256(53%)	
Valvular etiology (n, %)	21 (4.3%)	17 (3.5%)	
Diabetes (n, %)*	85 (26%)	65 (23%)	0.464
Therapy			
ACE Inhibitors (n, %)	352(72.7%)	364(75.4%)	0.350
AT1 inhibitors (n, %)	85(18.4%)	88(18.9%)	0.862
Beta-blockers (n, %)	423(87.4%)	416(86%)	0.508
Diuretics (n, %)	403(83.3%)	412(85.1%)	0.428
Statins (n, %)	241(49.8%)	254(52.6%)	0.385
Mineralcorticoid antagonists (n, %)	267(27.6%)	267 (27.6%)	0.7689
Antiplatelets (n, %)	270(55.8%)	309(64%)	0.009
Anticoagulants (n, %)	160(33.1%)	157(32.5%)	0.855
Amiodarone (n, %)	132(29.3%)	122(26.5%)	0.345

Patients were matched for gender, age, hemoglobin, peakVO2, reported as a percentage of predicted, LVEF and kidney function by means of MDRD formula. BMI = body mass index; LVEF = left ventricular ejection fraction; Peak VO_2 = Peak oxygen uptake; VE/VCO_2 slope = minute ventilation/carbon dioxide production; RER = respiratory exchange ratio; Na^+ = Sodium, K^+ = potassium; Hb = Hemoglobin; NYHA = New York Heart Association class; ACE = angiotensin converting enzyme; AT1 = angiotensin receptors blockers.
• This datum was available in 325 and 274 cases respectively

4. Discussion

Results of the present study spread some light on the field of moderate hyperkalemia in HF showing that *per se* moderate hyperkalemia is not associated to a worst outcome provided that patients have been properly matched for clinical characteristics, HF severity and treatment. Accordingly, our findings are similar to those of Beusekamp et al. [14] who, differently from several other reports [9–11] showed that hyperkalemia was not associated with adverse outcomes but associated to a greater probability of RAASi suspension which may lead to faster HF worsening [15]. Moreover, the present study findings confirm the strong prognostic power of the MECKI score even in specific HF population as those studied in the present report. Indeed, MECKI score was similar in the two K^+ groups in parallel to survival analysis.

The clinical meaning of the present report most be considered within the frame of a few relevant limitations. First, the study is retrospective. Second, MECKI score data set provides a single point analysis and we do not know whether major therapeutic changes have been done in the two years follow up. Regardless, we believe that this is an unlikely event since patients were in stable a clinical and therapeutic setting and a study inclusion criterion was that no therapeutic changes were scheduled. Third, albeit daily doses of diuretic and β-blockers were known and not different between the two matched groups we have no information as regards doses of RAASi therapy. The latter is a major study limitation albeit relevant RAASi dosages differences between groups seems to us unlikely since presence of diabetes and renal failure as well as severity of renal failure was similar between patients with normal and moderately elevated plasma K^+ levels. Fourth, our observation is valid only within the present study inclusion/exclusion criteria, *i.e.* only for patients with moderate hyperkalemia, moderate HF and should not be extended to patients with more severe hyperkalemia. As a matter of facts in our study population average plasma K^+ was 5.16 meq/L.

In conclusion the present findings argue against RAASi down-titration or discontinuation in case of moderate hyperkalemia. Of note, RAASi down-titration or discontinuation has been associated to worsening HF clinical outcomes [16].
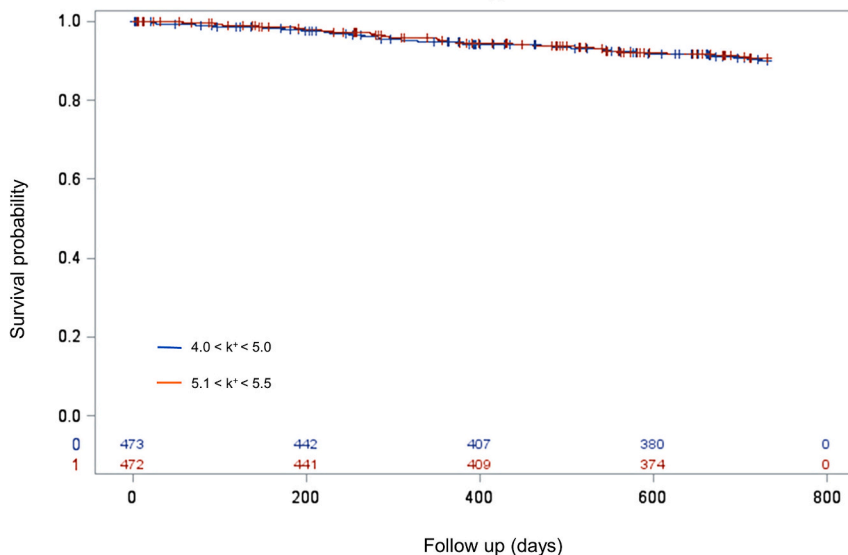
Fig. 1. Population survival according to Kaplan–Meier analysis.

Appendix A. Appendix

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