Rev Esp Cardiol. 2021;74(4):293–295

Editorial

Significance of potassium alterations. Beyond heart failure

Importancia de las alteraciones del potasio. Más allá de la insuficiencia cardiaca

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Article history:
Available online 16 January 2021

In recent decades, there has been a radical change in the approach to heart failure (HF). This change has been driven by recognition of the neurohormonal response as a key factor in the physiopathology of HF with reduced ejection fraction, as well as its blockade by 2 pharmacological groups: beta-blockers and renin-angiotensin-aldosterone system inhibitors (RAASi). These insights have led to steady improvements in patient survival and quality of life. There is solid scientific evidence in support of neurohormonal pharmacological blockade and its indication is included in clinical practice guidelines.[1] The RAASi group includes angiotensin-conversion-enzyme inhibitors (ACEi), angiotensin II receptor antagonists (ARA-II), mineralocorticoid receptor antagonists (MRA), and the combination medication sacubitril-valsartan, which is an angiotensin receptor-neprilysin inhibitor.[1]

There is evidence that adherence to the therapeutic recommendations of clinical practice guidelines provides significant clinical benefits in patients with HF and reduced ejection fraction. The QUALIFY international registry found improved prognosis in patients with HF with drug prescriptions that adhered to the recommendations.[2] However, in clinical practice, difficulties can arise in implementing guideline-recommended therapeutic measures in relation to prescribing indicated drugs, avoiding contraindicated drugs, and adjusting doses to the objectives specified in clinical trials. The BIOSTAT-CHF study analyzed the frequency and adverse effects of insufficient treatment doses of ACEi and ARA-II in the European population.[3] It concluded that patients who were treated with less than 50% of the recommended target dose tended to have a higher risk of death and more HF admissions than patients who reached the target dose. The American CHAMP-HF registry found that less than 1% of the included patients were simultaneously receiving the target doses of an ACEi, ARB-II, beta-blocker, or MRA as recommended in the clinical practice guidelines.[4] The ESC Heart Failure Long-Term Registry found that there was insufficient adherence to the therapeutic recommendations of the clinical practice guidelines on the target doses of the main pharmacological groups for HF.[5] This finding was also confirmed in the subanalysis of the Spanish cohort.[6] Although therapeutic inertia may play a role in this situation, in many cases the prescription of insufficient doses of RAASi is due to poor clinical tolerance and the appearance of adverse effects, such as hyperkalemia, renal dysfunction, and hypotension.

Potassium is the most abundant cation in humans and is essential to cell function. On average, 98% of the body's potassium content is intracellular and 2% is extracellular; however, its distribution in the different compartments of the body depends on several factors, including renal and gastrointestinal function, diet, drugs, dietary supplements, neurohormonal activation, and acid-base balance. Although previous studies have used different cutoff points to define hyperkalemia and hypokalemia, both are known to be associated with an increased incidence of severe adverse events. This relationship follows a U-shaped curve. In patients with values outside the normal range, life-threatening cardiac arrhythmias pose a special risk.[7]

A Spanish study found a significant association between a higher risk of mortality and abnormalities in serum potassium homeostasis, both in hypokalemia (< 3.5 mmol/L) and hyperkalemia (> 5 mmol/L).[8] Another study found an increased risk of mortality even in patients with plasma potassium concentrations at the lower limit (3.5-4.1 mmol/L) and upper limit (4.8-5 mmol/L) of normality.[9]

Hyperkalemia is an increasing problem in HF patients and is associated not only with the drug treatment received, especially RAASi, but also with comorbidities such as renal dysfunction or diabetes mellitus. A recent subanalysis of the Spanish cohort of the ESC Heart Failure Long-Term Registry found that hyperkalemia (defined as $K > 5.4$ mEq/L) was present in 4.3% of outpatients with chronic HF and in 8.2% of inpatients with acute decompensated HF.[10] That study identified a history of hyperkalemia episodes as an independent predictor of a lower risk of hyperkalemia at 1 year of follow-up. This finding would likely be explained by the use of lower RAASi doses in these patients. A recent analysis of the total cohort of the ESC Heart Failure Long-Term Registry[11] found that the observed association between hyperkalemia and mortality lost statistical significance after adjustment for the effect of RAASi discontinuation. This finding suggests that hyperkalemia could be indicative of treatment discontinuation, which itself entails adverse prognostic effects, rather than an adverse prognostic factor per se.

Revista Española de Cardiología recently published a population-based longitudinal study by Jiménez-Marrero et al.[12] The study

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https://doi.org/10.1016/j.rec.2020.06.013

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https://doi.org/10.1016/j.rec.2020.11.007

assessed the impact of hypokalemia and hyperkalemia on clinical outcomes, resource use, and health care costs in patients with chronic cardiovascular, metabolic, and renal disease, who may be suitable for RAASi treatment.

The authors deserve to be congratulated on their study, which, in our opinion, has 2 outstanding characteristics. First, the authors addressed the repercussions of hyperkalemia in a population of patients who, due to their underlying condition or treatment regime, were at greater risk of this complication; and second, the research design allowed the inclusion of all the patients in a health area, instead of limiting the study only to persons who received care in specialized clinical units.

Over the period 2015 to 2017, their study included 36 269 patients aged at least 55 years from a health area in Catalonia who showed no less than 1 of the following conditions: chronic HF, chronic kidney disease, diabetes mellitus, hypertension, or ischemic heart disease. All participants had at least 1 potassium measurement during the study period. The sources of administrative, primary care and specialty data were the databases of 2 health care centers in the Spanish public health system.

Four statistical analysis models were used to determine the association between serum potassium abnormalities and clinical outcomes. Subpopulations of patients were defined as prevalent cases, incident cases, prevalent cases-prevalent consumers, and incident cases-incident consumers, depending on the time of diagnosing the clinical condition required for their inclusion in the study and the time of initiating treatment with RAASi, if applicable. Hyperkalemia was defined as a serum K^+ level of at least 5 mEq/L, hypokalemia as a serum K^+ level of less than 3.5 mEq/L, and normokalemia as a serum K^+ level between 3.5 and 5 mEq/L. The main outcome variable selected by the researchers was all-cause death. Secondary variables were also assessed, such as emergency hospitalizations and visits to emergency services and the day hospital.

In the subpopulations analyzed, the estimated frequency of hyperkalemia was 2.7% to 4.4% and that of hypokalemia was 1.3% to 2.3%. Hyperkalemia was more frequent in men, older individuals, and patients with chronic kidney disease, whereas hypokalemia was more frequent in women and in HF patients. Patients with hyperkalemia had fewer all-cause deaths, hospitalizations, and visits to emergency services or day hospitals. Multivariable-adjusted analysis showed that hyperkalemia was significantly associated with an increased risk of all-cause death (between 31% and 68% depending on the subpopulation analyzed), and with an increased odds of a yearly health care expenditure higher than the 85th percentile (between 21% and 29% depending on the subpopulation analyzed). These associations were even stronger in patients with hypokalemia.

The results of their study confirmed previous findings on the negative impact of serum potassium abnormalities on clinical outcomes in patients with chronic cardiovascular, metabolic, and renal disease.[7] Potassium abnormalities (especially hyperkalemia) are particularly frequent in patients being treated with RAASi. Recently, this research group conducted a study over the same time period and with the same population as those in their study published in *Revista Española de Cardiología*.[12] They found that 12% of hypertensive patients treated with RAASi had potassium abnormalities.[13]

However, their study design was limited in that it could not address an aspect that is relevant to daily clinical practice: the repercussions of being unable to maintain treatment with RAASi, depending on the reason for their prescription, because of potassium abnormalities or other adverse effects. As mentioned, RAASi are frequently used not only in patients with HF, but also in those with hypertension (its main indication), diabetes mellitus, coronary disease, and certain renal diseases. Novel chelating agents that correct hyperkalemia and have good clinical toleration and few adverse effects have opened a window of opportunity to facilitate the maintenance and adjustment of RAASi doses in such cases. A highly interesting line of future research would be to identify the patient subgroups that can derive the most benefit from these new treatments.

Finally, we would like to emphasize that the study by Jiménez-Marrero et al.[12] provides an excellent example of the potential usefulness of health care administrative databases as information sources for "real life" clinical research studies. Currently, this methodology still has significant limitations due to the uneven recruitment of patients, designs that do fulfill the requirements of clinical trials, and the heterogeneous quality of the information collected. Moreover, very often this type of information cannot be exploited as it is subject to legal restrictions to protect patient confidentiality and privacy. Despite these difficulties, we believe that all initiatives that attempt to make progress in this appealing area of clinical research are worthy of recognition, which is the case concerning the study discussed in this editorial.

FUNDING

The authors are researchers from the Biomedical Research Network Center on Cardiovascular Diseases (HFBERCV) of the Carlos III Health Institute, which receives funding from FEDER.

CONFLICTS OF INTEREST

M.G. Crespo-Leiro has received fees for consulting, training and research activities, or travel expenses from AstraZeneca, Vifor, Boehringer, Rovi, and Novartis. E. Barge-Caballero has received fees for consulting, training activities, or travel expenses from AstraZeneca, Vifor, Boehringer, Rovi, Novartis, and Lilly. J. Muñiz is funded by AstraZeneca as a researcher in a project that is unrelated to this article.

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