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High serum osmolarity at admission determines a worse outcome in patients with heart failure: Is a new target emerging?

José Carlos Arévalo-Lorido [a,*], Juana Carretero Gómez [a], Francesc Formiga [b], Alicia Conde-Martel [c], Margarita Carrera-Izquierdo [d], Alberto Muela-Molinero [e], Melitón Francisco Dávila-Ramos [f], Ana Serrado-Iglesias [g], Luis Manzano-Espinosa [h], Manuel Montero-Pérez-Barquero [i]

[a] Internal Medicine Service, Zafra County Hospital, Ctra Badajoz-Granada s/n. 06300, Zafra, Spain
[b] Internal Medicine Service, University Hospital of Bellvitge, Feixa Llarga, s/n, 08907 L'Hospitalet de Llobregat, Barcelona, Spain
[c] Internal Medicine Sevice, University Hospital of Gran Canaria Dr. Negrin, Barranco de la Ballena, s/n, 35010 Las Palmas de Gran Canaria, Las Palmas, Spain
[d] Internal Medicine Service, Hospital of Soria Santa Bárbara, P° de Santa Bárbara, s/n, 42005, Soria, Spain
[e] Internal Medicine Service, Hospital of León, Altos de Nava s/n. 24071, León, Spain
[f] Internal Medicine Service, University Hospital Nuestra Señora de la Candelaria, Ctra. Gral. del Rosario, 145, 38010 Santa Cruz de Tenerife, Spain
[g] Internal Medicine Service, Hospital Municipal de Badalona, Via Augusta, 9–13, Badalona, Barcelona, Spain
[h] Internal Medicine Service, University Hospital "Ramón y Cajal", Ctra. de Colmenar Viejo, Km. 9,100, 28034 Madrid, Spain
[i] Internal Medicine Service, University Hospital Reina Sofia, Av. Menéndez Pidal, s/n, 14004 Córdoba, Spain

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ABSTRACT

Aims: The osmolarity of human serum is restricted to a tightly regulated range, and any deviation has clinical implications. Our aim in this study was to establish whether differences in serum osmolarity in heart failure (HF) patients are related with a worse outcome.
Methods: We evaluated the prognostic value of serum osmolarity in patients with HF from the Spanish National Registry on Heart Failure (RICA), a multicenter, prospective registry that enrolls patients admitted for decompensated HF and follows them for 1 year. Patients were divided into quartiles according to osmolarity levels. Primary endpoint was the combination of all-cause mortality and hospital readmissions for HF.
Results: A total of 2568 patients (47.46% men) were included. Patients with higher osmolarity were older, presented more comorbidities (especially diabetes mellitus and chronic kidney disease), and consequently had higher levels of glucose, urea, creatinine and potassium. During the 1-year follow-up, mortality among the quartiles was 18% (Q1), 18% (Q2), 23% (Q3) and 28% (Q4), $p < 0.001$. After adjusting for baseline characteristics, high serum osmolarity was significantly associated with all-cause mortality (RR 1.02, 95% CI 1.01–1.03, $p < 0.001$). We also found a significant increase in the combined endpoint of mortality and readmission among quartiles with higher osmolarity ($p < 0.001$). Diabetes, eGFR, Barthel index, systolic blood pressure, body mass index, hemoglobin, NYHA class and beta-blocking agents were also independently associated with the primary endpoint.
Conclusions: In patients admitted for decompensated HF, high serum osmolarity predicts a worse outcome, and is associated with a higher comorbidity burden, supporting its use as a candidate prognostic target in HF.

1. Introduction

Hyponatremia has been identified in several studies as a risk factor for increased morbidity and mortality in patients with congestive heart failure (CHF) [1]. It can be broadly classified into two types, dilutional or depletional, depending on the underlying pathophysiology. Dilutional hyponatremia, caused by excess water retention, is the most common form. Hyponatremia can be further categorized as either hypervolemic or euvolemic, depending on the patient's volume status, which can be measured by serum osmolarity [2].

Serum osmolarity is normally maintained within a narrow range of 275–295 mOsm/L. Stability is achieved by the rapid raising or lowering of total body water to compensate for changes in sodium intake and obligatory insensible and urinary water loss. These adjustments in body water content are made by overlapping hypothalamic osmostats that regulate thirst and secretion of the antidiuretic hormone arginine vasopressin (AVP) [2].

However, serum osmolarity is not only determined by serum sodium. Glucose and urea, which are often abnormal in CHF patients with other common comorbidities, such as diabetes mellitus or chronic

* Corresponding author.
E-mail address: joscarlor@gmail.com (J.C. Arévalo-Lorido).

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kidney disease, are also involved. Moreover, a number of disorders are associated with systemic elevations in extracellular fluid osmolarity, including diabetes or inflammatory bowel disease [3], and recent studies have shown how higher osmolarity may contribute to acute and chronic inflammation [4].

In CHF, hypervolemic hyponatremia develops as a compensatory response to decreasing cardiac output and effective circulating blood volumes [5] that activate the release of AVP [6]. In patients with HF, the administration of vaptans, a class of competitive AVP-receptor antagonists, have been shown to increase overall plasma sodium levels, but they fail to improve long-term mortality or readmission rates. This effect could be related with a worse outcome in patients with higher serum osmolarities [7].

The aim of the present study was to identify differences in serum osmolarity among hospitalized CHF patients and to evaluate if high osmolarity is related with a worse outcome, irrespective of serum sodium levels.

2. Methods

Patients were recruited through the National Registry of Heart Failure (RICA), supported by the Heart Failure Working Group of the Spanish Society of Internal Medicine (SEMI-IC). The RICA Registry is an ongoing multicenter, prospective cohort study. Previous reports from RICA have recently been published [8]. This registry included consecutive unique patients with CHF, defined according to the criteria of the European Society of Cardiology [9], admitted to internal medicine wards of public and private hospitals in Spain between March 2008 and March 2013. They were enrolled at discharge after

Table 1
Baseline characteristics of patients according to serum osmolarity quartiles.

	Q1 (243.10–299.80 mOsm/kg)	Q2 (299.80–306.39 mOsm/kg)	Q3 (306.39–313.23 mOsm/kg)	Q4 (313.23–362.50 mOsm/kg)	p
N	642	641	643	642	
Age (years)	79.4 (72.9–84.5)	79.7 (73,6–84.5)	81.2 (75.5–85.3)	81.2 (75.6–85.7)	<0.001
Male (%)	302 (47%)	295 (46%)	321 (50%)	301 (47%)	0.527
Hypertension	524 (82%)	532 (83%)	564 (88%)	574 (89%)	<0.001
Diabetes mellitus	251 (39%)	248 (39%)	323 (50%)	384 (60%)	<0.001
Smoke	249 (39%)	232 (36%)	257 (40%)	243 (38%)	0.558
Alcohol	154 (24%)	139 (22%)	138 (21%)	121 (19%)	0.169
Dyslipidemia	301 (47%)	298 (46%)	322 (50%)	326 (51%)	0.298
Atrial fibrillation/flutter	361 (56%)	359 (56%)	362 (56%)	332 (52%)	0.273
Liver disease	69 (11%)	24 (3.7%)	33 (5.1%)	43 (6.7%)	<0.001
CKD					
• No	0	0	0	0	–
• eGFR >60 ml/min	374 (58%)	339 (53%)	246 (38%)	110 (17%)	<0.001
• eGFR 30–59 ml/min	235 (37%)	270 (42%)	334 (52%)	344 (54%)	<0.001
• eGFR < 30 ml/min	33 (5.1%)	32 (5.0%)	63 (9.8%)	188 (29%)	<0.001
Charlson index (points)	2 (1–4)	2 (1–4)	3 (1–5)	3 (2–5)	<0.001
Barthel index (points)	95 (70–100)	95 (75–100)	90 (70–100)	90 (65–100)	<0.001
Pfeiffer index (points)	1 (0–3)	1 (0–2)	1 (0–3)	1 (0–3)	0.214
BMI (Kg/m2)	27.7 (24.9–31.6)	28.3 (25.2–32.0)	28.3 (25.0–32.5)	28.5 (24.5–32.0)	0.304
SBP (mm Hg)	131 (119–151)	136 (120–154)	140 (120–160)	137 (120–156)	0.001
DBP (mm Hg)	71 (64–83)	75 (64–90)	75 (65–89)	72 (62–82)	<0.001
Hemoglobin (g/dl)	12.2 (10.8–13.5)	12.4 (10.9–13.7)	12.0 (10.7–13.4)	11.5 (10.2–13.0)	<0.001
Creatinine(mg/dl)	1.00 (0.80–1.30)	1.07 (0.89–1.32)	1.21 (0.95–1.60)	1.55 (1.20–2.06)	<0.001
Urea (mg/dl)	45 (34–60)	52 (41–67)	63 (49–81)	92 (68–128)	<0.001
Sodium (mEq/l)	135 (132–137)	139 (138–141)	141 (139–143)	142 (140–145)	<0.001
Potassium (mEq/l)	4.2 (3.9–4.6)	4.2 (3.9–4.6)	4.3 (4.0–4.7)	4.4 (4.0–4.9)	<0.001
Glucose(mg/dl)	110 (92–134)	111 (94–138)	121 (97–164)	131 (101–194)	<0.001
Uric acid (mg/dl)	7.1 (5.7–9.0)	7.3 (5.9–9.2)	7.6 (6.3–9.3)	8.6 (7.0–10.1)	<0.001
BNP (pgr/ml)	622 (324–1.535)	653 (320–1.320)	685 (351–1.167)	821 (494–1.802)	0.304
LVEF (%)	54 (40–62)	53 (39–62)	55 (40–62)	55 (40–64)	0.426
LVEF > 45	438 (68%)	424 (66%)	443 (69%)	445 (69%)	0.625
Atrial diameter (mm)	48 (43–53)	48 (43–52)	47 (42–52)	47 (42–52)	0.179
Estimated PASP (mm Hg)	47 (35–55)	45 (36–55)	45 (35–55)	47 (40–58)	0.046
Osmolarity (mOsm/Kg)	294 (290–298)	303 (302–305)	309 (308–311)	319 (316–323)	<0.001
NYHA					
• I	60 (9.5%)	81 (13%)	62 (9.8%)	42 (6.7%)	0.004
• II	346 (55%)	342 (54%)	339 (54%)	301 (48%)	0.062
• III	206 (33%)	197 (31%)	213 (34%)	251 (40%)	0.005
• IV	19 (3.0%)	14 (2.2%)	17 (2.7%)	33 (5.3%)	0.012
Etiology of HF					
• Ischemic	175 (27%)	153 (24%)	171 (27%)	181 (28%)	0.368
• Hypertensive	121 (19%)	134 (21%)	85 (13%)	123 (19%)	0.002
• Valvular	219 (34%)	225 (35%)	290 (45%)	246 (38%)	<0.001
• Other	127 (20%)	125 (20%)	94 (15%)	92 (14%)	0.007
Medications at discharge					
• ACE inhibitors	338 (53%)	342 (53%)	317 (49%)	271 (42%)	<0.001
• ARBs	194 (30%)	197 (31%)	223 (35%)	225 (35%)	0.128
• Beta-blocking agents	421 (66%)	414 (65%)	437 (68%)	418 (65%)	0.592
• Loop diuretics	599 (93%)	595 (93%)	607 (94%)	601 (94%)	0.706
• Thiazides	97 (15%)	88 (14%)	74 (12%)	126 (20%)	<0.001
• Aldosterone antagonists	292 (45%)	247 (39%)	229 (36%)	211 (33%)	<0.001

Qualitative data are shown as number (percentage) and quantitative data as median (interquartile range). ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; BMI: body mass index; BNP: brain natriuretic peptide; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PASP: pulmonary arterial systolic pressure; and SBP: systolic blood pressure.