Low albumin levels and high impedance ratio as risk factors for worsening kidney function during hospitalization of decompensated heart failure patients

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BACKGROUND: Patients hospitalized for decompensated heart failure (DHF) frequently experience worsening of renal function (WRF), leading to volume overload and resistance to diuretics.

OBJECTIVE: To investigate whether albumin levels and whole-body impedance ratio, as an indicator of water distribution, were associated with WRF in patients with DHF.

Methods: A total of 80 patients hospitalized for DHF were consecutively included in the present longitudinal study. WRF during hospitalization was defined as an increase of ≥0.3 mg/dL (≥26.52 µmol/L) or 25% of baseline serum creatinine. Clinical and echocardiographic characteristics were assessed at baseline. Whole-body bioelectrical impedance was measured using tetrapolar and multiple-frequency equipment to obtain the ratio of impedance at 200 kHz to that at 5 kHz. Serum albumin levels were also evaluated. Baseline characteristics were compared between patients with and without deteriorating renal function using a *t* test or χ^2 test. Subsequently, a logistic regression analysis was performed to obtain the independent variables associated with WRF.

RESULTS: The incidence of WRF during hospitalization was 26%. Independent risk factors associated with WRF were low serum albumin (RR=0.11; P=0.04); impedance ratio >0.85 (RR=5.3; P=0.05), systolic blood pressure >160 mmHg (RR=12; P=0.02) and maximum dose of continuous intravenous furosemide required >80 mg/day during hospitalization (RR=5.7, P=0.015).

CONCLUSIONS: WRF is frequent in patients with DHF. It results from the inability to effectively regulate volume status because hypoalbuminemia induces water loss from the vascular space (high impedance ratio), and high diuretic doses lower circulatory volumes and reduce renal blood flow, leading to a decline in renal filtration function.

Key Words: *Albumin concentration; Heart failure; Impedance index; Worsening renal function*

Impaired renal function during decompensated heart failure (DHF) has been referred to as the cardiorenal syndrome (1). This entity has been associated with elevated morbidity (2) reflected in prolonged hospital stay and higher costs, as well as short-term and long-term mortality. It is estimated that up to 50% to 70% of DHF patients will experience some impairment of renal function during hospitalization (3,4). A 15% increase in mortality for every 0.5 mg/dL (44.2 µmol/L) increase in serum creatinine above 1 mg/dL (88.4 µmol/L), as well as for every 10 mL/min/1.73m^2 decrease in glomerular filtration rate (GFR) below 90 mL/min/1.73m^2, has been reported (4). Conversely, improvement in renal function has been associated with a better prognosis (5).

Cardiorenal syndrome has been explained as an intricate balance between hemodynamic changes, decreases in cardiac output and stroke volume, endothelial damage and changes in the intravascular space (6). These changes alter the renin-angiotensin-aldosterone system and sympathetic vasomotor control, as well as the regulation of endothelin and antidiuretic hormone (7,8). The consequences are increased intravascular volume and cardiac and renal damage manifested as tissue hypoxia, inflammation and oxidative stress (9-11). Resistance to diuretic therapy has been described as decreased thiazide tubular effects, diminished loop diuretic intestinal absorption due to bowel edema and decreased bioavailability of loop diuretics due to low serum albumin levels (12-14).

Among the risk factors already associated with cardiorenal syndrome are advanced age, hypertension, diabetes and atherosclerosis, as well as pre-existing chronic renal failure, diuretic therapy and chronic heart failure (15-20). In 2004, Forman et al (21) developed a clinical scale predicting the development of this entity; their results showed that 35% of their sample had ≥3 factors, which translated to a 43% increased incidence of worsening of renal function (WRF) during the next year.

Fluid overload, especially in the form of pulmonary congestion, is observed in the majority of patients with heart failure. Based on the assumption that fluid overload is the result of fluid accumulation, administration of diuretics is recommended, although it is possible that the main pathophysiological mechanism of fluid overload in acute heart failure is related to fluid redistribution rather than accumulation (22). The value of multiple frequency bioimpedance analysis in the evaluation of water distribution in critical illness and in DHF patients has been demonstrated (23,24).

The objective of the present study was to assess whether albumin serum levels and whole-body impedance ratio, as an indicator of water distribution, are associated with WRF in DHF.

METHODS

Study population

Hospitalized patients at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran (INCMNSZ), Mexico City, Mexico, with a primary diagnosis of acute DHF were prospectively enrolled from February 2009 to January 2010. Subjects were consecutively included if they were older than 18 years of age, with a confirmed diagnosis of DHF as defined by the European Society of Cardiology guidelines (25). Written informed consent was obtained from each patient before

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TABLE 1
Baseline clinical variables and comorbidities according to outcome

Variables	Total patients	With WRF (n=20)	Without WRF (n=57)	P
Male/female ratio, n (%)/n (%)	35 (43.8)/ 45 (56.3)	6 (30)/ 14 (70)	28 (49)/ 29 (51)	0.14
Age, years	65.83±16.82	64.1±18	66.6±16.3	0.60
Body mass index, kg/m^2	27.98±7.61	27.2±10	28.2±6.9	0.60
Heart rate, beats/min	85.77±22.04	87.1±29.6	85.7±18.9	0.80
Systolic BP, mmHg	122.1±26.86	126±31.7	120.5±25.3	0.40
Systolic BP >160 mmHg, n (%)	10 (13.24)	5 (25)	5 (8.9)	0.07
Diastolic BP, mmHg	71.8±15.2	70.5±17.6	72.2±14.5	0.70
Central venous pressure, cmH_2O	15.6±5.4	16.3±4.1	14.5±4.9	0.30
Diabetes mellitus, n (%)	30 (37.5)	8 (40)	22 (38.6)	0.90
Systemic hypertension, n (%)	48 (60)	13 (65)	35 (61.4)	0.80
Dyslipidemia, n (%)	34 (42.5)	8 (40)	26 (47.3)	0.60
Atrial fibrillation, n (%)	14 (17.5)	3 (15.8)	11 (19.6)	0.70
Ischemic heart disease, n (%)	44 (55.1)	13 (65)	31 (54.4)	0.41
AMI, n (%)	31 (38.8)	7 (35)	24 (42.1)	0.60
SLE, n (%)	6 (7.5)	1 (5)	5 (8.8)	0.60
Hypothyroidism, n (%)	23 (28.75)	3 (15)	20 (35)	0.09

Data presented as mean ± SD unless otherwise indicated. AMI Acute myocardial infarction; BP Blood pressure; SLE Systemic lupus erythematosus; WRF Worsening of renal function.

inclusion in the study. The protocol was approved by the Committee of Biomedical Investigation in Humans at the INCMNSZ. Patients were excluded due to pregnancy, enrollment in other clinical trials, cerebral vascular event or transient ischemic attack during the three months before enrollment, malfunctioning cardiac valve, obstructive hypertrophic cardiomyopathy, noncorrected congenital heart disease, acute myocarditis, chronic dialysis or kidney transplant, diseases directly related to renal or heart failure (systemic lupus erythematosus, Wegener's disease, Behçet's disease, Goodpasture syndrome, polycystic renal disease, etc), chemotherapy or renal injury secondary to severe sepsis, postrenal obstruction or contrast media infusion.

Clinical and body composition evaluation

Comorbidities, medical treatment, New York Heart Association (NYHA) functional class assessment, heart rate, systemic pressure, and signs and symptoms related to chronic heart failure were recorded.

Weight and height were measured in accordance with the manual reference of anthropometric standardization (26); all subjects wore light clothing and were barefoot. Body mass index was calculated by dividing the total body weight (kg) by the height squared (m). Whole-body bioelectrical impedance was measured in the morning using tetrapolar and multiple-frequency equipment (BodyStat QuadScan 4000, Bodystat Ltd, United Kingdom). All measurements were made according to the tetrapolar method reported in the existing literature (27).

The impedance values were obtained at frequencies of 5 kHz, 50 kHz, 100 kHz and 200 kHz. Using 50 kHz frequency resistance, reactance and phase angle were obtained using the Bodystat phase angle software program (version 1.0) (BodyStat Ltd, United Kingdom). This frequency was selected because it is the standard frequency used for bioelectrical impedance vector analysis. The whole-body impedance ratio at 200 kHz to that at 5 kHz was also obtained; this served as an indicator of water distribution.

Biochemical variables

Blood samples were collected for determination of serum levels of glucose, creatinine, blood urea nitrogen, serum electrolytes, and hemoglobin and hematocrit. Venous blood samples were drawn from patients after an overnight fast. All laboratory values were determined using routine automated analyzers at the Central Laboratory of the INCMNSZ.

Serum albumin levels were measured by the bromocresol green albumin method. Estimated GFR was calculated according to the four-variable Modification of Diet in Renal Disease (MDRD) equation (28):

$$\text{Estimated GFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if black)}$$

WRF was defined as a rise ≥0.3 mg/dL (≥26.52 μmol/L) or 25% of baseline serum creatinine.

All patients underwent complete clinical and laboratory evaluations at the time of hospitalization, as well as serial laboratory measurements at one- to two-day intervals and at hospital discharge. At least one Doppler echocardiography study was performed using Hewlett-Packard Sonos 5500 equipment (Hewlett-Packard, USA) with M-mode, two-dimensional and Doppler images in parasternal long- and short-axis and two- and four-chamber apical views.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables are presented as absolute and relative frequency. Comparisons of baseline variables between groups were made using Pearson's χ^2 test for categorical variables and unpaired *t* test for continuous variables.

Independent risk factors for WRF were identified using Cox regression analysis. Variables were entered at an entry level of significance of P<0.1 in the bivariate analysis using the enter method to establish the independent contribution of each covariable (adjusted relative risk [RR]) on WRF. In addition, 95% CIs were calculated for adjusted RRs. Analyses were performed using SPSS version 10.0 (IBM Corporation, USA) for Windows (Microsoft Corporation, USA).

RESULTS

A total of 120 patients entered the study, of whom 80 were selected according to the inclusion and exclusion criteria. Three patients were lost during follow-up. A total of 29 (37.7%) patients were in renal failure on arrival to the emergency department (ED). During hospitalization, the incidence of WRF was 26% (20 patients). Baseline characteristics of both groups (with and without WRF) are summarized in Table 1. In the WRF group, there was a higher proportion of women (mean age 65 years), the mean body mass index was in the overweight category and the mean systolic blood pressure was 122 mmHg. Comparing the groups, there was a trend toward statistical significance in the number of patients with mean systolic blood pressure >160 mmHg. Hypothyroidism was more prevalent in the group without WRF. There were no other differences between the groups.

No significant differences between the groups were found with respect to heart failure type, pulmonary hypertension or NYHA functional class (Table 2).

Increased renal damage was observed in patients with previous chronic renal disease, compared with patients without previous chronic renal disease. The mean maximum continuous intravenous furosemide dose was 67 mg/day overall; however, patients with deteriorating renal function during hospitalization had a mean dose of 100 mg/day, a statistically significant difference. A threshold dose (80 mg/day) was established, at which there was an increased probability of developing WRF. The maximum continuous intravenous furosemide doses were also found to be temporally related to the maximum creatinine level and, thus, could be considered to be a direct cause.

The mean whole-body impedance ratio was 0.84 overall, although an increased index was observed in patients with WRF (P<0.05). The rest of the bioimpedance measures were nonsignificant.

TABLE 2
Clinical variables and medical treatment before hospital admission according to outcome

Variables	All patients	With WRF	Without WRF	P
Whole-body impedance ratio, mean ± SD	0.84±0.06	0.86±0.03	0.84±0.06	0.05
Total body water, %, mean ± SD	57.9±10.9	55.6±9.4	59.3±10.9	0.3
Total body water, L, mean ± SD	38.2±8.4	37.7±8.8	38.5±8.5	0.8
Extracellular water, %, mean ± SD	26.4±4.6	25.4±4.5	26.9±4.5	0.3
Extracellular water, L, mean ± SD	17.6±3.6	17.3±3.3	17.7±3.8	0.7
Chronic kidney disease stage (KDOQI)				
1	10 (12.5)	2 (12)	8 (18)	0.09
2	21 (26.25)	4 (25)	17 (38)	
3	28 (35)	8 (50)	20 (44)	
4	2 (2.5)	2 (13)	0	
Angina	20 (25)	8 (40)	12 (21.1)	0.10
Hepatomegaly	11 (13.75)	4 (20)	7 (12.3)	0.40
Ascites	6 (7.5)	1 (5)	5 (8.9)	0.60
Jugular venous distension	39 (48.75)	10 (50)	29 (50.9)	0.9
Rales	51 (63.75)	17 (85)	34 (59.6)	0.04
ACEIs	29 (36.25)	7 (35)	22 (39)	0.77
ARAs	20 (25)	5 (25)	15 (26)	0.91
Beta-blockers	29 (36.25)	7 (35)	22 (39)	0.77
Aldosterone blockers	25 (31.25)	5 (25)	20 (35.1)	0.41
Thiazide diuretics	11 (13.75)	2 (10)	9 (16)	0.52
Loop diuretics on ED admission	39 (48.75)	7 (35)	32 (56)	0.10
Maximum loop diuretic dosage before serum creatinine climax	34 (42.5)	15 (75)	19 (33)	0.001
Maximum dosage of furosemide, mean ± SD	67±51	98.9±55.6	54.4±42.7	0.004
Digitalis	19 (23.75)	7 (35)	12 (21)	0.21
Nitrates	15 (18.75)	3 (15)	12 (21)	0.56
Calcium antagonists	14 (17.5)	4 (20)	10 (17)	0.81
Antiarrhythmics	7 (8.75)	3 (15)	4 (7)	0.30
DM medical treatment	18 (22.5)	3 (15)	15 (26)	0.30
Insulin	3 (3.75)	0	3 (5.3)	0.30

Data presented as n (%) unless otherwise indicated. KDOQI Kidney Disease Outcome Quality Initiative; ACEI Angiotensin-converting enzyme inhibitor; ARA Angiotensin receptor antagonist; DM Diabetes mellitus; ED Emergency department; WRF Worsening of renal function

The group without WRF remained in Kidney Disease Outcome Quality Initiative stages I-II, while patients with WRF reached stages III-IV, with a trend toward statistical significance. Patients with WRF had significantly more rales (Table 2), and patients who developed WRF also had increased shortening fractions as well as thicker interventricular septal (Table 3).

Patients with WRF had high previous creatinine levels, lower hematocrit and lower serum albumin levels. There was a trend toward a difference between increased blood urea nitrogen and lower GFR (Table 4).

Under a Cox regression model, serum albumin was showed to be a protective factor. Conversely, it was observed that an increased whole-body impedance ratio >0.85, systolic blood pressure >160 mmHg and continuous intravenous furosemide doses over 80 mg/day were risk factors (Table 5).

DISCUSSION

The incidence of WRF in our sample is similar to that described in the literature (20% to 30%). Despite the comorbidities associated with WRF that have already been described (21,29,30), such as previous heart failure, diabetes mellitus, previous renal failure and atrial fibrillation, no differences were observed between the two groups in any of these parameters in our study. This may be explained by the size of our sample.

TABLE 3
Echocardiographic variables according to outcome

Variables	All patients	With WRF	Without WRF	P
Ejection fraction, %	44.6±17.7	46.9±17.5	43.7±17.9	0.5
Shortening fraction, %	27.3±10.4	34.8±11	24.9±9.2	0.04
LVDD, mm	48.7±10.8	47.2±8.9	49.2±11.5	0.5
LVSD, mm	36.1±12.1	34.3±9.3	36.6±12.9	0.5
IV septum thickness, mm	11.4±2.2	12.4±2.2	11±2.1	0.02
Left ventricle posterior wall, mm	10.2±2.3	10.8±1.9	9.9±2.4	0.20
Ao diameter, mm	30.1±5.1	34.8±11	24.9±9.2	0.30
LA diameter, mm	43.3±8	43.9±7.6	43.1±8.3	0.71
LA/Ao ratio	1.4±0.32	1.49±0.4	1.43±0.3	0.60
RVDD, mm	42.3±9.9	43.1±9.5	42±10	0.71
Right atrium, mm	46.5±10.9	48.9±9.6	45.7±11.3	0.37
SPAP, mmHg	63.2±20.3	57.7±15.3	60.5±17.4	0.60
E/E'	12.9±0.84	15.3±8.1	12.1±5.6	0.3
Filling pattern, n (%)				
Slow	33 (41.25)	9 (60)	24 (65)	0.66
Pseudonormal	9 (11.25)	2 (13)	7 (19)	
Restrictive	10 (12.5)	4 (27)	6 (16)	

Data presented as mean ± SD unless otherwise indicated. Ao Aortic root; E Early transmitral filling velocity; E' Early diastolic mitral annular velocity; IV Intraventricular; LA Left atrial; LVDD Left ventricular diastolic diameter; LVSD Left ventricular systolic diameter; RVDD Right ventricular diastolic diameter; SPAP Systolic pulmonary arterial pressure; WRF Worsening of renal function

TABLE 4
Biochemical results of study groups

Variable	Total	With WRF	Without WRF	P
Serum sodium, mmol/L	135.8±5.3	136.7±3.9	135.3±5.6	0.3
Serum potassium, mmol/L	4.48±0.81	4.4±0.5	4.4±0.7	0.9
Glucose, mmol/L	7.87±4.0	8.0±4.27	7.8±3.9	0.9
BUN, mmol/L	9.96±6.50	11.2±5.93	8.89±4.71	0.09
Previous serum creatinine, µmol/L	99.9±38.0	114.9±58.34	97.2±26.5	0.03
Admission serum creatinine, µmol/L	129.9±76.9	150.3±106.1	126.8±61.9	0.14
Previous $eGFR_{MDRD}$	67±27.2	56.7±27.5	70.6±26.4	0.08
Admission $eGFR_{MDRD}$	57.9±29.9	49.3±32	60.4±27.5	0.19
Hemoglobin, g/L	132±39	124±32	135±24	0.11
Hematocrit, %	39±8.6	35.1±11.3	40.4±7.1	0.02
Serum albumin, g/L	2.97±0.7	2.7±0.43	3.1±0.8	0.02
Microalbuminuria, mg/24 h	712.2±1642.7	553±957.3	775±1866	0.70
Total cholesterol, mmol/L	4.35±1.48	3.83±1.44	4.52±1.46	0.10

Data presented as mean ± SD unless otherwise indicated. BUN Blood urea nitrogen; $eGFR_{MDRD}$ Estimated glomerular filtration rate calculated using the four-variable Modification of Diet in Renal Disease equation; WRF Worsening of renal function

Patients whose renal function decreased during hospitalization had the following relevant characteristics on hospital admission: higher NYHA functional class and higher systolic blood pressure (≥160 mmHg), which represented a 12-fold increased risk for WRF. Another significant variable found was a higher prevalence of pulmonary rales, which was not associated with the type of heart failure or the prevalence of pulmonary hypertension.

Judging from their previous creatinine measurements, our patients were also at risk for WRF because the kidneys were already damaged. In

TABLE 5
Cox regression model predicting worsening renal function

Variable	RR	95% CI	P
Serum albumin <35 g/L	0.11	0.03–0.5	0.04
Whole-body impedance ratio >0.85	5.3	0.81–34	0.08
Furosemide >80 mg/day	5.7	1.4–23.3	0.015
Systolic blood pressure >160 mmHg	12	1.5–93	0.02

addition, they had a higher prevalence of hypoalbuminemia, lower hematocrit and higher fluid retention, detected by electric bioimpedance index and body composition analysis.

It is interesting that the group with WRF had greater intraventricular septum thickness, as well as a higher prevalence of pulmonary rales, which, in the absence of fluid overload revealed by physical examination or body composition measurements, may simply indicate an abnormal distribution of intravascular volume. This may explain why these patients received lower doses of loop diuretic before admission, because they were not significantly overloaded. However, once hospitalized, clinical findings such as rales were misinterpreted as fluid congestion, indicating higher doses of diuretics. As we observed in the present study, the increased diuretic doses led to renal stress and a 5.7-fold risk of WRF during hospitalization.

Loop diuretics possess a great affinity for serum proteins, especially albumin, which limits their volume of distribution and their effect on the proximal tubule (1). Hypoalbuminemia in patients with WRF affects bioavailability, leading to greater resistance to diuretic treatment. In addition, a lower oncotic pressure could favour a leak of effective intravascular volume into the interstitial space, lowering renal input and decreasing renal function (1).

The role of ventricular diastolic dysfunction and altered fluid distribution, as well as elevated systolic blood pressure, may explain this misinterpretation of fluid status. This resulted in more intense diuretic therapy, with decreased intravascular volume and, consequently, worsening of already damaged renal function.

On the basis of our findings, we are obligated to reconsider the clinical and hemodynamic information we obtain from our patients. As a consequence, we should be more cautious about the therapy implemented. Rather than administering higher doses of loop diuretics, cardiac afterload may be lowered with arterial vasodilators, especially in cases of uncontrolled arterial hypertension or lower left ventricular ejection fraction.

In patients with DHF, issues such as hypoalbuminemia with fluid overload (detected by body composition analysis with an impedance index >0.85) may be corrected with intravenous human albumin administration, which could theoretically increase oncotic pressure and lead to a higher response to lower doses of loop diuretics. In accordance with the results of the present study, we recommend the impedance ratio to be a part of routine examination of the patients with DHF.

It is important to emphasize that WRF impacts in-hospital mortality, as documented in the present study. Moreover, there is the finding that renal damage persisted in up to 20% of our patients studied after hospitalization. Patients with compromised renal function have a greater risk of persistently decreased function over time.

CONCLUSIONS

Patients with DHF have an estimated incidence of WRF of 26%. Independent risk factors associated with WRF included a bioimpedance index >0.85, doses of a continuous intravenous loop diuretic >80 mg/day, systolic blood pressure >160 mmHg and hypoalbuminemia.

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