Short-term Serial Measurement of Galectin-3 in Hospitalized Patients With Acute Heart Failure

Valores seriados de galectina-3 a corto plazo en pacientes hospitalizados por insuficiencia cardiaca aguda

To the Editor,

In recent years, high blood concentrations of galectin-3 (Gal-3) have been associated with a worse clinical outcome in patients with heart failure (HF).[1] In patients hospitalized due to acute HF, high concentrations are associated with an increased risk of death and rehospitalization.[2] However, it has not been established whether this phenotype is modifiable in the short-term; therefore, the aim of this study was to evaluate the kinetics of Gal-3 in the first 30 days following an episode of acute HF.

The study included 109 patients admitted due to acute HF (60% were male; mean age, 71 ± 11 years; left ventricular ejection fraction, 41 ± 15%). Serial blood samples were taken at 3 distinct time points: *a)* on arrival at the emergency department (first sample; n = 109); *b)* on the day of discharge (median stay, 7 days; n = 109), and *c)* 30 days after discharge (n = 98). The Gal-3 concentrations were measured with the automated immunoassay system VIDAS (mini-Vidas, bioMérieux). A cutoff value of 17.8 ng/mL, the 90th percentile of normal, was taken to be a high concentration, as per the data sheet and the approved use for risk stratification.[3]

The median Gal-3 concentration on arrival at the emergency department was 17.2 ng/mL [interquartile range, 13.9-22.9 ng/mL]. When we used the cutoff value of 17.8 ng/mL, those patients with a higher concentration (n = 50) were older (76 [68-81] vs 71 [60-78] years; $P = .027$), a higher proportion had previously been admitted for HF (58% vs 34%; $P = .013$), and more of them required intravenous dopamine (20% vs 5%; $P = .020$). Gal-3 concentration correlated significantly with worse renal function parameters: urea ($r_s = 0.50$; $P < .001$), creatinine ($r_s = 0.423$; $P < .001$), estimated glomerular filtration rate ($r_s = -0.53$; $P < .001$), and cystatin C ($r_s = 0.55$; $P < .001$); and with higher concentrations of N-terminal probrain natriuretic peptide ($r_s = 0.36$; $P < .001$) and high-sensitivity troponin T ($r_s = 0.23$; $P = .020$). The other clinical variables, including ejection fraction, showed no significant associations. On multiple linear regression analysis, the only independent predictor was cystatin C concentration ($P < .001$; $\beta = 0.479$; $R = 0.547$) (Figure 1).

The median concentrations at discharge and at 30 days were 16.8 [14.01-22.1] and 17.6 [13.9-21.4] ng/mL and, as shown in Figure 2, the serial measurements analysis–on arrival at the emergency department, at discharge, and at 30 days–showed no differences ($P = .660$). Equally, there were no differences when we analyzed the percentage of patients with Gal-3 > 17.8 ng/mL: 46% at admission, 45% at discharge, and 46% at 30 days.

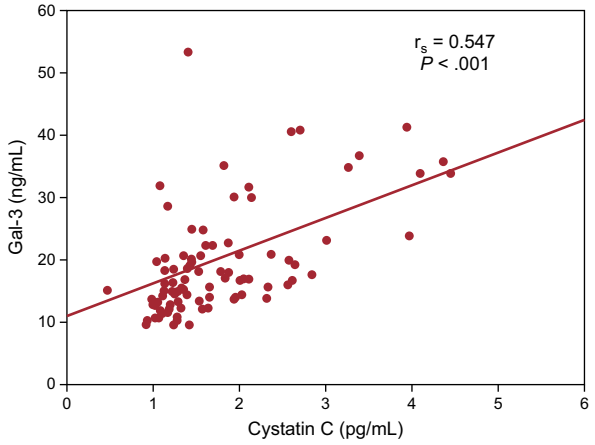

Figure 1. Correlation between blood concentrations of Gal-3 and cystatin C. Gal-3, galectin-3.

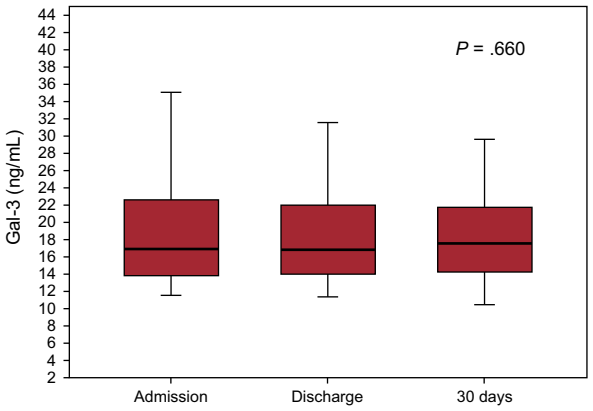

Figure 2. Box plot of Gal-3 concentrations at different time points: at admission, at discharge, and at 30 days. Gal-3, galectin-3.

As an exploratory analysis, we evaluated the relationship between Gal-3 and prognosis. Over a median follow-up of 453 [156-1076] days, a total of 53 patients (48%) had an adverse event (25 died and 28 were readmitted). On univariable Cox regression analysis, Gal-3 at admission as a quantitative variable (per ng/mL, hazard ratio [HR], 1.70; 95% confidence interval [95%CI], 1.02-2.84; $P = .042$) or dichotomous variable (> 17.8 ng/mL, HR, 2.17; 95%CI, 1.25-3.77, $P = .006$) was associated with a higher risk of adverse events; however, after adjustment for renal function, this significance disappeared ($P > .1$).

In patients with chronic HF, an increased Gal-3 at 3 to 12 months has been found to confer increased mortality and hospitalization.[3–5] In patients with acute HF, the only data available are those from the COACH study, in which patients with an increase > 17.8 ng/mL in Gal-3 at 6 months after discharge or a 15% relative increase from baseline had a higher risk of death and/or hospitalization due to HF.[4] Our investigation is the first to study the behavior of Gal-3 in the short-term (the first 30 days) after an episode of acute HF. Admission concentrations were similar to those at discharge (median stay, 7 days) and at 30 days. Therefore, in patients hospitalized due to acute HF, Gal-3 concentrations show no dynamic changes from admission, and monitoring these values provides no additional information in the first month after discharge. This indicates that the underlying pathophysiological process is unmodifiable in the short-term. Gal-3 concentrations distinguish a phenotype of more severely ill patients, who are more likely to have a greater deterioration of renal function and a worse clinical outcome in the long-term, with more readmissions and higher mortality. The prognostic analysis was limited by the single-center nature and the small population of this study, but the findings confirm the high dependence of Gal-3 on renal function, as has previously been noted.[6] Further studies are needed to ascertain the clinical usefulness of Gal-3 and its relationship to renal function.

FUNDING

The reagents for this study were supplied by bioMérieux without charge.

CONFLICTS OF INTEREST

D.A. Pascual-Figal has received fees for lectures from Biomerieux, Roche, and Novartis.

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Available online 1 May 2017

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http://dx.doi.org/10.1016/j.rec.2017.03.013
1885-5857/

Aspergillus fumigatus Empyema in Heart Transplant Recipients

Empiema por Aspergillus fumigatus *en pacientes con trasplante cardiaco*

To the Editor,

Infections were the main cause of death between the first month and the first year after transplant in the 250 patients who underwent heart transplantation in 2014 in Spain (36.6% of deaths).[1] The incidence of fungal infections has increased due to the more widespread use of immunosuppressants. These infections account for a high proportion of the morbidity and mortality in heart transplant recipients, despite the effectiveness of new treatments.[2]

Fungal pleural empyema is a rare condition that, despite an associated mortality greater than 70%, is not included in the classification of *Aspergillus*-related pulmonary diseases. The most common mechanism by which the fungus reaches the pleural cavity is rupture of an aspergilloma cavity or complication of preexisting chronic empyema. We present 2 cases of fungal pleural empyema in heart transplant recipients between October and December 2015 in our hospital.

The first case is a 65-year-old man who was placed on the heart transplant waiting list because of dilated idiopathic cardiomyopathy with advanced heart failure. After 3 months on the waiting list, he was admitted in a state of cardiogenic shock requiring implantation of percutaneous ventricular assist device (Impella CP) and emergency heart transplant. Serology (cytomegalovirus, syphilis, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, herpes zoster virus, and *Toxoplasma*) and the Mantoux test were negative before transplant. Myocardial biopsy during follow-up did not reveal any findings indicative of acute cellular rejection. On day 34 after transplant, asymptomatic right pleural effusion was detected. Chest drainage was performed, with 850 mL of purulent and malodorous liquid collected. Broad-spectrum antibiotic treatment (meropenem and linezolid) was started and urokinase was administered intrapleurally. Prophylactic treatment was maintained (trimethoprim/sulfamethoxazole, valganciclovir), along with immunosuppression with mycophenolate mofetil, prednisone, and tacrolimus. Culture of pleural empyema detected growth of more than 10^3 colony-forming units of *Aspergillus fumigatus*, and voriconazole monotherapy was started on post-transplant day 39. *Aspergillus, Pneumocystis, Mycobacterium tuberculosis* and galactomannan were not detected by polymerase chain reaction of bronchioloalveolar lavage. The patient completed 2 months of treatment with voriconazole (with measurement of tacrolimus concentrations every 2 weeks) and prophylaxis continued with inhaled amphotericin B, with good clinical and radiological outcomes.

The second patient was a 63-year-old man with a diagnosis of hypertrophic cardiomyopathy in dilated phase and advanced heart failure who was admitted in a state of cardiogenic shock requiring inotropic drugs and intra-aortic balloon counterpulsation. After requesting an emergency transplant, he underwent heart transplant. Serology and the Mantoux test before transplant were negative. A month and a half after heart transplant (day 50), he showed symptomatic cytomegalovirus infection (the first infection with this virus), requiring intravenous ganciclovir treatment. He developed severe pancytopenia that required discontinuation of mycophenolate mofetil and tacrolimus dose reduction. After 3 months, his clinical status deteriorated, and severe ventricular dysfunction was detected. An endomyocardial biopsy showed acute humoral rejection. He received treatment with methylprednisolone, plasmapheresis, gammaglobulins, and rituximab, and immunosuppressive therapy was adjusted. A follow-up chest X-ray performed on post-transplant day 123 revealed right pleural effusion. He had low-grade fever. Empirical antibiotic therapy was initiated. In view of his deteriorating condition and suspected opportunistic infection (Figure), the intensity of the antibiotic therapy was increased in the following 48 hours (piperacillin-tazobactam and linezolid). Flexible fiberoptic bronchoscopy was performed; no endobronchial abnormalities were detected but polymerase chain reaction was positive for *Aspergillus*. Biochemical analysis of the pleural effusion was consistent with empyema, and a growth of *Aspergillus fumigatus* was isolated. Treatment was initiated with intravenous voriconazole on day 137 after transplant. Despite these pharmacological measures, the patient died after 12 days of treatment.

Treatment of fungal empyema is not often required and there is no standard approach due to the variable penetrance of systemic antifungals in the pleura; combinations of 1, 2 or 3 drugs are used (voriconazole, amphotericin B, and echinocandin).[4,5] Current recommendations indicate immediate antifungal monotherapy after isolation of *Aspergillus fumigatus* in immunosuppressed patients.