

# Role of Neutrophil Gelatinase-associated Lipocalin in the Detection of Contrast-induced Nephropathy in Patients Undergoing a Coronary Angiography



## Papel de la lipocalina asociada a la gelatinasa neutrófila en la detección precoz de la nefropatía inducida por contraste tras una coronariografía

### To the Editor,

Contrast-induced acute kidney injury (CI-AKI) is an important cause of hospital-acquired acute renal failure and has a poor prognosis. Serum creatinine (sCr) exhibits shortcomings because its elevation is relatively slow and is influenced by extrarenal factors.<sup>1</sup> Recently, neutrophil gelatinase-associated lipocalin (NGAL) has emerged as an early, sensitive, noninvasive biomarker for predicting CI-AKI in different cardiovascular conditions.<sup>2,3</sup> However, the role of early measurements of NGAL for predicting sCr changes in unselected patients with acute coronary syndrome (ACS) and receiving iodixanol, an iso-osmolar nonionic contrast agent, has not been defined. The aim of this study was to evaluate the usefulness of early determinations of NGAL for predicting sCr changes within 48 hours after coronary-angiography ( $\Delta$ Cr-48 h) in ACS patients receiving iodixanol.

We included 105 consecutive patients with ACS undergoing coronary-angiography and receiving iodixanol (Visipaque). Serum creatinine was measured before and 24 and 48 hours after angiography. Serum NGAL was measured before and 4, 8, and 24 hours postprocedure. Per protocol, iodixanol was used in all patients. Additional measures for preventing CI-AKI were individualized according to the attending physician. CI-AKI was defined as an increase in sCr of  $> 25\%$  or  $> 0.5$  mg/dL from baseline within 48 hours postprocedure. NGAL was measured with a fluorescence-immunoassay. Estimated glomerular filtration rate (eGFR) was estimated by applying the 4-variable Modification of Diet in Renal Disease (MDRD) formula. The primary endpoint was to determine the association between NGAL measurements within 24-hours and the maximum absolute  $\Delta$ Cr-48 h. The secondary endpoints were to evaluate: a) whether NGAL measurements were associated with the risk of CI-AKI and, b) the association between volume of contrast and  $\Delta$ Cr-48 h. Continuous variables were expressed as mean  $\pm$  standard deviation (SD) or median [interquartile range (IQR)] when appropriate, and discrete variables as percentages. Linear regression analysis was used to determine the association between NGAL and  $\Delta$ Cr-48 h measurements. The risk of CI-AKI was assessed using a logistic regression model. A 2-sided  $P$ -value of  $< .05$  was considered to be statistically significant.

The baseline characteristics of the sample are summarized in the Table. NGAL values (median [IQR]) increased at each time point: 63 (49, 112), 69 (56, 116), 75 (50, 114), and 77 (64, 174) ng/mL, for baseline and 4, 8, and 24-hours, respectively. The mean sCr on admission and  $\Delta$ Cr-48 h (mg/dL) were  $0.98 \pm 0.35$  and  $0.06 \pm 0.24$ , respectively. Six patients (5.7%) developed CI-AKI at 48 hours. There was a positive linear association between NGAL and  $\Delta$ Cr-48 h in the whole sample irrespective of time point ( $P < .05$  for all comparisons) as shown in the Table of the supplementary material. On multivariate analysis, including age, diabetes mellitus, eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>, type of ACS, and Killip  $> 1$  on admission, NGAL-8 h remained positive, significant and linearly associated with  $\Delta$ Cr-48 h [ $\beta$  coefficient, per 100 ng/mL: 0.63; 95% confidence interval (95%CI), 0.15-1.11;  $P = .011$ ]. The gradient of risk of NGAL-8 h for predicting  $\Delta$ Cr-48 h is shown in the Figure. This model accounted for 33% of the variability in  $\Delta$ Cr-48 h. Ranked in order of importance (drop in R<sup>2</sup>), NGAL-8 h (40%), eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> (21.5%) and diabetes mellitus (17.3%) were the most important covariates predicting  $\Delta$ Cr-48 h. Likewise,

NGAL-24 h was independently related to  $\Delta$ Cr-48 h ( $\beta$  coefficient, per 100 ng/mL: 0.62; 95%CI, 0.08-1.17;  $P = .026$ ), whereas baseline-NGAL and NGAL-4 h remained borderline associated with  $\Delta$ Cr-48 h (Table of the supplementary material). In a univariate analysis, baseline-NGAL, NGAL-4 h, NGAL-8 h and NGAL-24 h, per increase in 10 ng/mL were borderline associated to CI-AKI. The receiving operating curve of NGAL-8 h showed a high discriminative ability for predicting CI-AKI (area under the curve of 0.788). A value  $\geq 92$  ng/mL showed a sensitivity of 100% and a specificity of 60.6%. The volume of contrast administration ( $149.2 \pm 66.4$  mL) was not associated with  $\Delta$ Cr-48 h in the univariate ( $\beta$  coefficient, per 100 mL: 0.02; 95%CI,  $-0.09$ -0.07;  $P = .698$ ) or multivariate analysis ( $\beta$  coefficient, per 100 mL: 0.03; 95%CI,  $-0.05$ -0.10;  $P = .451$ ).

This study shows that NGAL measurements before and early after angiogram predict absolute changes in sCr in ACS patients receiving iodixanol as contrast-agent. Nevertheless, NGAL-8 h postprocedure showed the best diagnostic performance. NGAL has shown, in the absence of diagnostic increases in sCr, to detect patients with subclinical CI-AKI who have an increased risk of

**Table**  
Baseline Characteristics

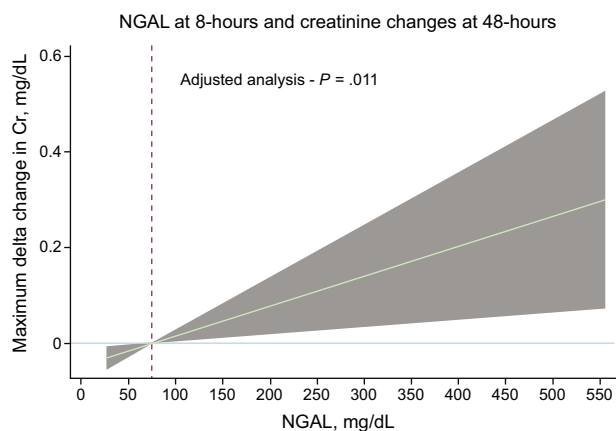
Total sample (n = 105)	
Age, y	65 $\pm$ 11
Male, n (%)	69 (66)
Weight, kg	78.7 $\pm$ 22.5
Height, cm	160.9 $\pm$ 17
Hypertension, n (%)	78 (74)
Diabetes mellitus, n (%)	24 (23)
Insulin-dependent diabetes mellitus, n (%)	6 (6)
Dyslipidemia, n (%)	63 (60)
Current smoker, n (%)	60 (57)
Previous smoker, n (%)	12 (11)
Prior history of MI, n (%)	24 (23)
Prior chronic kidney disease, n (%)	6 (5.7)
Killip class $> 1$ on admission, n (%)	24 (23)
Systolic blood pressure, mmHg	135 $\pm$ 31
Diastolic blood pressure, mmHg	74 $\pm$ 14
Prior history of PCI, n (%)	21 (20)
Indication for PCI at index admission, n (%)	
STEMI	66 (63)
NSTEMI	39 (37)
Number of coronary vessels affected, n (%)	
0	6 (6)
1	60 (57)
2	24 (23)
3	18 (17)
PCI, n (%)	87 (83)
Serum creatinine at admission, mg/dL	0.98 $\pm$ 0.34
eGFR <sup>a</sup> at admission, mL/min/1.73 m <sup>2</sup>	83.6 $\pm$ 28.5
eGFR <sup>a</sup> at admission $< 60$ mL/min/1.73 m <sup>2</sup> , n (%)	21 (20)
Serum NGAL <sup>b</sup> at admission, ng/mL	63 (49, 112)

eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NGAL, neutrophil gelatinase-associated lipocalin; NSTEMI, non-ST-elevation acute myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Data are expressed as no. (%), mean  $\pm$  standard deviation or median [interquartile range].

<sup>a</sup> eGFR was estimated by applying the four-variable Modification of Diet in Renal Disease (MDRD) formula.

<sup>b</sup> Variable expressed as median (interquartile range).



**Figure.** Gradient of risk of NGAL-8 h for predicting maximum absolute  $\Delta\text{Cr}$ -48 h.  $\Delta\text{Cr}$ -48 h, creatinine changes at 48-hours; NGAL-8 h, neutrophil gelatinase-associated lipocalin at 8-hours.

adverse outcomes.<sup>2</sup> Prior studies demonstrate the usefulness of NGAL as an early biomarker of CI-AKI in different scenarios, especially after contrast administration.<sup>3</sup> However, the optimal timing for its determination following coronary angiography has not yet been well elucidated. Herein, a formal comparison among different time points revealed that all of them were predictive of  $\Delta\text{Cr}$ -48 h. Nevertheless, the best performance of NGAL-8 h may help clinicians to identify those patients at higher risk of developing CI-AKI who could benefit from preventive strategies.<sup>4</sup> In this regard, and in agreement with recent findings,<sup>5</sup> we note that the volume of iodixanol was not related to CI-AKI.

Some limitations need to be addressed. This is a small single-center study. The low incidence of CI-AKI precludes obtaining robust estimates of risk regarding this endpoint. A confounding variable such as volume of fluid administration before angiography was not routinely registered, precluding analysis of its influence. Lastly, we did not evaluate CI-AKI beyond 48 hours.

In conclusion, NGAL measurements 8 hours postprocedure predict creatinine changes in ACS patients undergoing coronary-angiography and receiving iodixanol as contrast agent.

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## SUPPLEMENTARY MATERIAL



Supplementary material associated with this article can be found in the online version available at [doi:10.1016/j.rec.2016.01.015](https://doi.org/10.1016/j.rec.2016.01.015).

Ernesto Valero,\* Juan Carlos Rodríguez, Patricia Moyano, Gema Miñana, Juan Sanchis, and Julio Núñez

*Servicio de Cardiología, Hospital Clínico Universitario de Valencia, INCLIVA, Universitat de Valencia, Valencia, Spain*

\* Corresponding author:

E-mail address: [ernestovaleropicher@hotmail.com](mailto:ernestovaleropicher@hotmail.com) (E. Valero).

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## Two Different Sites of Membrane Rupture in the Berlin-Heart EXCOR Ventricular Assist Device



### Dos lugares diferentes de rotura de membrana en la asistencia Berlin-Heart Excor

To the Editor,

The Berlin-Heart EXCOR ventricular assist device (Berlin-Heart AG, Germany) is a paracorporeal pulsed flow device driven by a pneumatic mechanism. Currently, the main application is as a bridge to heart transplant, both in adults and children.<sup>1,2</sup>

The device comprises a pneumatic driving unit, a system of tubes, and a ventricle or pump. This pump is divided into 2 chambers (blood chamber and air chamber) by a 3-layer polyurethane membrane. The negative and positive pressure in diastole and systole, respectively, generated by the drive unit and transmitted to the ventricle, displace the membrane, with the corresponding effect of suction or blood expulsion (Figure 1).

Mechanical problems occur more frequently in pulsed flow devices than in continuous flow ones.<sup>3</sup> Membrane rupture is, however, an uncommon problem and has been reported in a limited number of cases,<sup>4–6</sup> after more than 2000 implants up until 2015. We present 2 cases of membrane rupture in our center.

The first case occurred in a 62-year-old man, with a biventricular Berlin-Heart EXCOR implant after acute myocardial infarction complicated with cardiogenic shock as a bridge to heart transplant. On day 77 of treatment, while the patient was on the ward, a mobile shadow, measuring 3 cm across, was detected in the right pump, with an irregular border and fine bands of adhered fibrin. This image was apparent in systole and disappeared in diastole (Figure 2A and video 1 of the supplementary material). It was only visible in the blood chamber; the membrane appeared normal from the air chamber. The patient was asymptomatic and hemodynamically stable, with no warning alarms showing on the display of the operating panel. Membrane rupture was suspected and an emergency pump change was undertaken. After explanation, a torn area was detected on the internal layer of the membrane (adjacent to the blood chamber).