BNP AND NGAL AS EARLY BIOMARKERS IN CARDIO-RENAL SYNDROME IN THE CRITICAL PATIENT

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ABSTRACT

Introduction*: Cardio-renal syndrome (CRS) is a combined disorder in which acute or chronic dysfunction of one of the organs causes acute or chronic dysfunction in the other. CRS affects 20-40% of patients in intensive care.*

Materials and methods*: The study enrolled 27 patients hospitalized in the ICU of Catania's Gaspare Rodolico Polyclinic Hospital between April 2014 and May 2015. The patients were 18 to 85 years old, 15 females and 12 males, who were admitted to ICU with worsening of a chronic cardiovascular pathology, potentially classifiable as Type 1 or 2 CRS.*

Results*: The study found that neutrophil gelatinase-associated lipocalin (NGAL) was able to predict acute renal damage and provided a risk stratification, and when B-type natriuretic peptide (BNP) was also used they increased the capacity to predict a clinical exacerbation.*

Conclusion*: The findings confirmed that NGAL and BNP values are helpful biomarkers in the diagnosis and treatment of CRS.*

Key words*: Cardio-renal syndrome, cardiac insufficiency, renal insufficiency, biochemical markers, intraglomerular perfusion.*
DOI:10.19193/0393-6384_2016_1_07

Received *January 30, 2015;* ***Accepted*** *March 30, 2015*

Introduction

The National Heart, Lung and Blood Institute define CRS as a combined heart and renal pathology in which acute or chronic dysfunction of one organ causes acute or chronic dysfunction in the other[1]. There are five types of CRS: Type I (acute), in which acute cardiac injury causes renal damage, and affects 19-45% of ICU patients[2]; Type II (chronic), in which progressive renal damage is secondary to chronic cardiac insufficiency, and affects 45-63% of patients hospitalized for congestive heart failure[2]; Type III, acute cardiac-renal syndrome, in which acute renal damage causes subsequent acute cardiac damage; Type IV is the chronic condition of Type III; Type V CRS is a condition secondary to diabetes, amyloidosis, and sepsis. CRS is characterized by a decrease in cardiac output and perfusion pressure on the intraglomerular level, with worsening of renal damage caused by a condition of acute renal insufficiency[3,4].

Materials and methods

The study enrolled 27 patients (15 females and 12 males) hospitalized in the ICU of Catania's Gaspare Rodolico Polyclinic Hospital between April 2014 and May 2015. The inclusion criteria were: age between 18 and 85 years old, cardiogenic shock, and acute or chronic cardiac insufficiency. The exclusion criteria were: age under 18 or over 85, acute renal insufficiency, sepsis, and amyloidosis.

On admission to the department the patients presented with a worsening of chronic cardiovascular pathology, potentially classifiable as CRS Type I or II. The demographic characteristics of the enrolled patients are summarized in Table 1.

Demographic Characteristics	Number	Percentage
Male sex	12	44.4
Female sex	15	55.6
Average age	78	73
No recent surgery	15	55.6
Recent surgery	12	44.4
Deceased	18	66.7
Survivors	9	33.3

Tab. 1: Demographic characteristics of the enrolled patients.

Monitoring of the patients included BNP, NGAL, and creatinine, performed at three times:

1. T0: within 24h of admission
2. T1: on the second day of hospitalization
3. T2: on the fifth day of hospitalization

In addition at time T0 we evaluated the SOFA score: Sequential Organ Failure Assessment, as an extra negative prognostic indicator. At T1 and T2 we evaluated the possibility of acute renal insufficiency (ARI) by using the RIFLEN criteria for renal damage. Then BNP and NGAL were evaluated together to determine their predictive power, using the Triage test meter, in which a technology of rapid fluorescence immunoassay at point-of-care doesn't require sending samples to a laboratory. This method is fast, which is important in an emergency setting. The NGAL upper reference limit is 153ng/ml, while the upper reference limit of BNP is 100pg/ml. Statistical significance was considered $p<0.05$. The Chi-square test was used to evaluate the difference between the variables and groups. The median and range interquartile was used to describe the continuous demographic variables and clinical outcomes; the category variables were described using absolute numbers and percentages. The odds ratio was used to measure frequency of death. The Spearman test was used to evaluate the correlation between levels of creatinine, NGAL, and renal damage.

Results

The aim of our study was to evaluate NGAL as a predictive marker of renal damage relative to creatinine, so the data of interest was extrapolated from the database acquired during the study: NGAL (Tab. 2), and serum creatinine (Tab. 3).

Patient	NGAL T0	NGAL T1	NGAL T2
1	259	241	166
2	1300		
3	356	768	
4	356	130	309
5	113	115	96
6	788	830	810
7	212	195	401
8	779		
9	310	395	426
10	259	241	166
11	1300		
12	356	768	
13	356	130	309
14	113	115	96
15	788	830	810
16	212	195	401
17	779		
18	310	395	426
19	259	241	166
20	1300		
21	356	768	
22	356	130	309
23	113	115	96
24	788	830	810
25	212	195	401
26	779		
27	310	395	426

Tab. 2: NGAL values in ng/ml of the enrolled patients at T0, T1 and T2.

The first correlation analysis found that NGAL values at T0 had a direct correlation with creatinine, in that they both increased over time, and the correlation continued increasing from T0, T1, and T2. A second analysis compared NGAL using the RIFLEN criteria for diagnosis of acute renal damage. Following the measurement of NGAL at T0 we found that the 9 patients with creatinine in the normal range did not increase enough to classify them as having acute kidney injury (AKI). In the 12 patients with creatinine values from 1.1 to 2 at T0,

only 3 patients had values compatible with AKI at T2; in such patients there was an increase in NGAL at T1. In the 6 patients with creatinine values over 2mg/dl at T0, 3 patients died on the fifth day after a diagnosis of AKI at T2 combined with chronic renal insufficiency (CRI). Such patients had a larger increase in NGAL at T1 (figure 1).

Patient	sCr T0	sCr T1	sCr T2
1	0.71	0.67	0.7
2	2.1		
3	0.89	1.1	
4	1.32	1.21	1.4
5	0.98	1.02	0.65
6	2.45	3.55	4.9
7	1.2	0.8	1.2
8	1.9		
9	1.7	1.8	2.1
10	0.71	0.67	0.7
11	2.1		
12	0.89	1.1	
13	1.32	1.21	1.4
14	0.98	1.02	0.65
15	2.45	3.55	4.9
16	1.2	0.8	1.2
17	1.9		
18	1.7	1.8	2.1
19	0.71	0.67	0.7
20	2.1		
21	0.89	1.1	
22	1.32	1.21	1.4
23	0.98	1.02	0.65
24	2.45	3.55	4.9
25	1.2	0.8	1.2
26	1.9		
27	1.7	1.8	2.1

Tab. 3: Creatinine Values in mg/dl of the enrolled patients at T0, T1 and T2.

The patients were divided into two groups, survivors and deceased, to establish prognostic staging on the worsening of their clinical condition. The rate of death during hospitalization was 66.7%. Observing the changes in NGAL and creatinine over time in both groups, (fig. 1 and 2) we found:

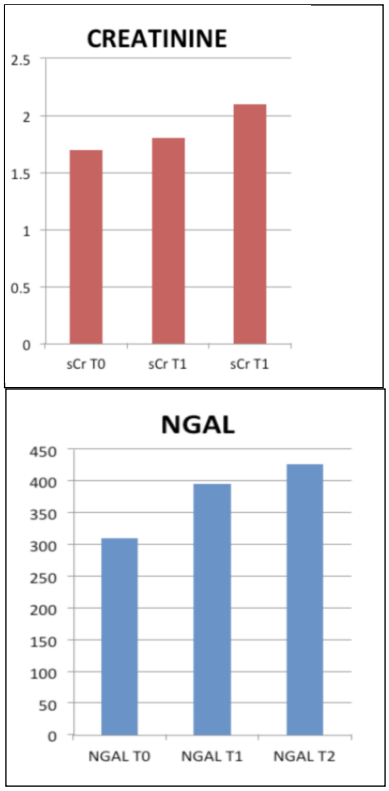

Figure 1: Comparison between NGAL and creatinine in the second group of patients, with creatinine values at T0 from 1.1 to 2mg.

• NGAL increased 8% at T1 compared to T0, and 14.9% at T2 compared to T1, for a total increase of 22.9% in the deceased;

• NGAL decreased 10.9% at T1 compared to T0, and 7.8% at T2 compared to T1, for a total decrease of 18.7% in the survivors;

• Creatinine increased 5.9% at T1 compared to T0, and 16.7% at T2 compared to T1, for a total increase of 22.6% in the deceased;

• Creatinine decreased 18.4% at T1 compared to T0, and 12.%% at T2 compared to T1, for a total decrease of 30% in the survivors.

In the fourth analysis we calculated the intra-variable difference in the manifestation of the death event at T0 and T1. This analysis found that:

• patients with NGAL values within the reference range at T0 and T1 all survived;

• patients with NGAL values above the upper limit at T1 had an OR of 1.5 compared to patients in the normal range but without statistical significance ($p>0.05$);

• patients with NGAL at T1 greater than at T0 were more frequently deceased, and with statistical significance ($p<0.05$); patients with NGAL values above the upper limit at T0 had a clear trend to die compared to survivors.

We then attempted to determine if BNP has predictive value of a worsening of clinical condition. The BNP data are reported in Table 4.

PATIENT	BNP T0	BNP T1	BNP T2
1	216	171	123
2	2700	NE	NE
3	472	500	NE
4	158	124	784
5	14.6	9.7	31.6
6	1200	1490	1680
7	726	734	711
8	880	NE	NE
9	1720	1170	426
10	216	171	123
11	2700	NE	NE
12	472	500	NE
13	158	124	784
14	14.6	9.7	31.6
15	1200	1490	1680
16	726	734	711
17	880	NE	NE
18	1720	1170	426
19	216	171	123
20	2700	NE	NE
21	472	500	NE
22	158	124	784
23	14.6	9.7	31.6
24	1200	1490	1680
25	726	734	711
26	880	NE	NE
27	1720	1170	426

Tab. 4: BNP values at three sampling times (pg/ml).

Evaluation of the change in BNP values over time in the two groups (fig. 3) is shown in figure 3.

• BNP increased 23.5% at T1 compared to T0, and decreased 6.1% at T2 compared to T1, for total increase of 17.4% in the deceased patients;

• BNP decreased 20.8% at T1 compared to T0, and 28.1% at T2 compared to T1, for a total decrease of 48.9% in the survivors.

The sixth intra-variable analysis revealed that:

• patients with BNP values higher at T1 compared to T0 were more frequently deceased, and this finding was statistically significant ($p<0.05$).

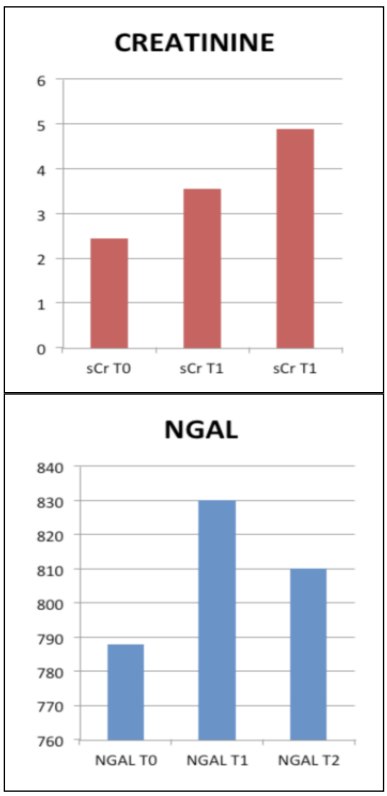

Figure 2: Comparison between NGAL and creatinine in the third group of patients, with creatinine values at T0 over 2mg.

• patients with BNP values within the reference range at T0 and T1, and no higher than T0 at T2, all survived.

Finally, we attempted to determine if NGAL and BNP values together might increase the power to predict clinical worsening. First we evaluated the changes over time in combination in the deceased (Fig. 4), and survivors (Fig. 5).

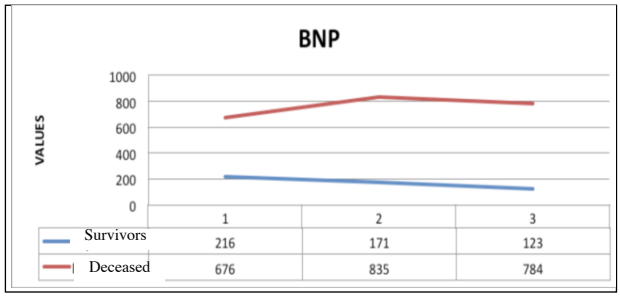

Figure 3: Changes in BNP values over time: Survivors (in blue) and Deceased (in red).

These figures show that:

• BNP increased 23.5% at T1 compared to T0, and decreased 6.1% at T2 compared to T1, for a total increase of 17.4% in deceased patients;

• NGAL increased 8% at T1 compared to T0, and 14.9% at T2 compared to T1, for a total increase of 22.9% in deceased patients;

• BNP decreased 20.8% at T1 compared to T0,

and 28.1% at T2 compared to T1, for a total decrease of 48.9% in surviving patients.

• NGAL decreased 10.9% at T1 compared to T0, and 7.8% at T2 compared to T1, for a total decrease of of 18.7% in survivors.

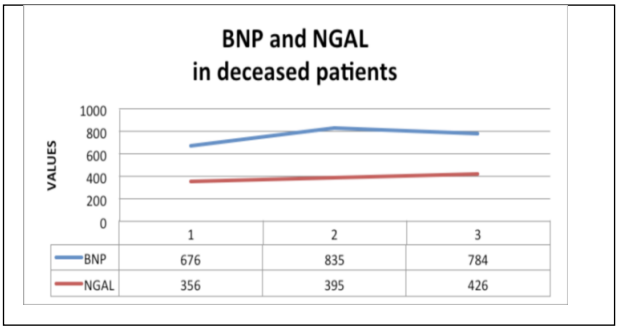

Figure 4: Changes in BNP and NGAL over time in the deceased.

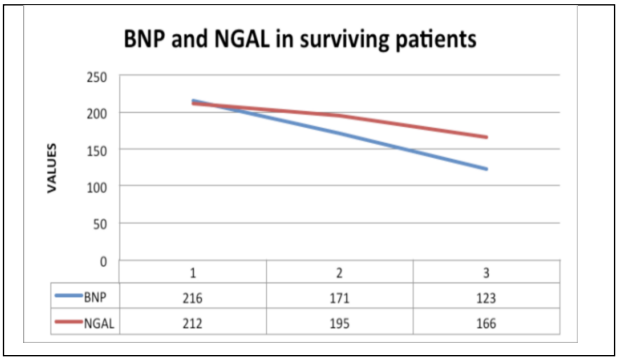

Figure 5: Changes in BNP and NGAL over time in survivors.

The combination of BNP and NGAL values indicates no deaths in patients with NGAL under 300ng/ml, regardless of BNP values. The deaths were observed only in patients with NGAL values over 300ng/ml, and that was statistically significant. In patients with NGAl over 300ng/ml and BNP over 300pg/ml, more deaths were observed ($p<0.01$).

Discussion

In the analysis of the correlation between NGAL and creatinine values, it seems that NGAL is more predictive of renal damage, since the correlation between the two parameters is stronger at T2. That means at T0 the NGAL level is already altered compared to creatinine values, which in contrast are altered at T1 and even more at T2. Comparing NGAL with the RIFLEN criteria, the increase at T1 has a more significant role than creatinine, whose increase is found only at T2. Observing the change of NGAL and creatinine over time in the two subgroups we examined (deceased and survivors), it seems that NGAL has better negative predictive power at T1 than creatinine. The intra-variable analysis seems to confirm that the increase of NGAL at T1 compared to T0 is a negative prognostic indicator of mortality. In contrast, evaluating the prognostic value of BNP and its change over time, the value at T1 seems fundamentally important, since only patients with an increase at T1 compared to T0 died. The intra-variable analysis confirms the hypothesis that BNP value at T1 is fundamentally important since patients who had a lower BNP value at T0 all survived, while a higher BNP value at T1 higher than T0 statistically correlated with death. Comparing the prognostic value of the two principle markers shows that BNP is a negative prognostic index when evaluating its change over time, but its change is less stable and progressive compared to NGAL. The latter seems to be a good positive prognostic index since its decline is greater in surviving patients than the decrease in NGAL. Analyzing their prognostic value when used together it seems that BNP presents a negative prognostic power when associated with NGAL, but that isn't true for NGAL.

Conclusion

By now it is established that careful evaluation of the interaction between heart and kidney has some important practical implications from a clinical point of view, above all in critical patients where the time factor is fundamental[6]. In this context it's useful to grant a role for hemo-chemical parameters in clinical diagnostics and practice through emerging cardiac and renal biomarkers[7]. In the light of that consideration, the authors confirmed that NGAL seems more predictive of renal damage than creatinine both at T0 and T1, while at T2 creatinine is more predictive, at least in our limited sample of chronic cardiac patients worsening in intensive care. NGAL has been confirmed as an excellent index of renal damage in our study and in the international literature[9,10]. In addition, it seems that NGAL may be used as a measure of risk level, and when associated with BNP increases its power to predict clinical deterioration, in our study as well as in the international literature[11,12].

Despite the limited number of patients enrolled and possible enrollment bias, as well as being a single center study, we believe these biomarkers have a useful role in the fast-paced setting of cardio-renal syndrome and its early treatment. Hence, consider-

ing its ease of use as well, it's wise to use these biomarkers more and more in the early diagnosis of this pathology.

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