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**The role of neutrophil gelatinase-associated lipocalin (NGAL) in the detection of blast lung injury in a military population.**

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## Abstract

### Purpose

To study the relationship between serum neutrophil gelatinase-associated lipocalin (NGAL) and military blast and gunshot wound (GSW) to establish whether potential exists for NGAL as a biomarker for blast lung injury (BLI).

### Method

Patients from the intensive care unit (ICU) of the Role 3 Medical Treatment Facility at Camp Bastion, Helmand Province, Afghanistan were studied over a five month period commencing in 2012. Age, mechanism, trauma injury severity score (TRISS) and serum NGAL were recorded on ICU admission (NGAL1). Serum NGAL (NGAL2) and PaO<sub>2</sub>/FiO<sub>2</sub> ratio (P/F ratio2) were recorded at 24 hours.

### Results

33 patients were injured by blast and 23 by GSW. NGAL1 inversely correlated with TRISS (p=0.020), pH (p=0.002) and P/F ratio 2 (p=0.009) overall. When data was stratified into blast and GSW, NGAL1 also inversely correlated with P/F ratio 2 in the blast injured group (p=0.008) but not GSW group (p=0.27).

## Conclusion

Raised NGAL correlated with increased severity of injury (worse survival probability i.e. TRISS and low pH) in both patient groups. There was an inverse correlation between admission NGAL and a marker of blast lung injury (low P/F ratio) at 24 hours in blast injured group but not GSW group that warrants further investigation.

Abstract word count = 200

**Keywords:** Blast lung injury; military; trauma; biomarker; neutrophil gelatinase-associated lipocalin.

## Introduction

Primary blast injury is caused by the rapid increase in pressure in the immediate vicinity of an explosion. The peak overpressure of the 'shock wave' decreases in magnitude as it travels away from the site of the explosion(1). Lungs are particularly susceptible to the development of a primary blast injury – blast lung injury, BLI – because of the multiple gas/liquid interfaces in this tissue, resulting in rupture of the delicate alveolar-capillary interface causing intrapulmonary haemorrhage and oedema (2). The haemorrhage and oedema contribute to an initial respiratory insult and also to a free radical mediated inflammatory response causing oxidative damage over the following hours and days. Subsequent leucocyte accumulation and epithelial damage leads to endothelial cell damage and further oedema typical of adult respiratory distress syndrome (3).

The extent of lung damage is related to the magnitude of the blast wave exposure with the initial lung injury worsening over the first hours to a peak inflammatory response at 48 hours (4). Hypoxia develops due to ventilation-perfusion mismatch as well as a reduction in the surface area available for gas exchange (5,6) resulting in a low  $\text{PaO}_2/\text{FiO}_2$  ratio (P/F ratio).

Management strategies for treating BLI are mainly supportive, with lung protective ventilation being the mainstay of treatment (7). In severe cases permissive hypercapnia (8), high frequency oscillatory ventilation (5) and inhaled nitric oxide (9) have all been described as potential rescue strategies. BLI

formed the second most common referral for advanced ventilatory support at one European civilian centre due to traumatic lung injury (10).

The management of BLI can be made more challenging by other complex injuries caused by the blast, and the concurrent need for damage control resuscitation and surgery. The lung is susceptible to the effects of fluid loading and transfusion of blood products that may worsen capillary leak and inflammation in the lungs (11). Despite the challenge that these patients present in the immediate phase, long term outcome is good in survivors, with normal lung function regained in patients by one year (12,13).

The prevalence of blast lung injury (BLI) in the deployed military setting is 7-11% (14,15). This prevalence increases in non-survivors with 48% found to have evidence of primary BLI on computed tomography (CT) imaging postmortem, with a higher incidence in mounted fatalities (16). In the civilian setting BLI had a reported prevalence of 8% in all patients injured in the Madrid bombings (17) and up to 70% in one institution treating victims of Israeli mass casualty terrorist events (18). Overall mortality in the initial survivors of blasts from a BLI is around 11% (17,19).

In future conflicts it is possible that evacuation timelines will become more prolonged, in keeping with those seen at the beginning of operations in Afghanistan and Iraq (20,21). This longer evacuation chain may also apply to certain civilian settings where terrorist or civil disaster disrupts infrastructure and response (1). This potential delay in evacuation to centres with the capacity

for advanced ventilatory support makes the creation of a triage tool for early identification of severe BLI attractive. It may allow early repatriation or transfer of survivors with predicted severe BLI for earlier complex ventilatory support.

Serum neutrophil gelatinase-associated lipocalin (NGAL) has previously been studied in blast and gunshot injuries showing it was predictive of poor outcome (22). NGAL is part of a diverse family of proteins that binds to small, hydrophobic ligands and is expressed in a number of tissues including gastrointestinal, respiratory and urinary tracts. It rises in response to inflammation (23) and plays a role in host defence against bacterial infection by chelating iron. Most recently it has been used in the diagnosis and monitoring of acute kidney injury (24) especially in the setting of cardiac surgery and contrast-induced nephropathy (25,26).

Due to its expression in lung tissue, association with inflammation and iron chelating properties we hypothesized that NGAL may be a useful biomarker for outcome in trauma associated with blast, and may give an indication of the degree of undifferentiated blast lung injury sustained. The aim of this study was to investigate the potential relationship between NGAL levels in blast injured and penetrating injured battle casualties.

## Method

The study took place in the intensive care unit (ICU) of the Role 3 Medical Treatment Facility at Camp Bastion, Helmand Province, Afghanistan. A prospective evaluation of patients admitted to the ICU as a result of wounding by



either a blast mechanism (i.e. wounded by improvised or other explosive device e.g. legacy mine) or GSW mechanism (i.e. wounded in penetrating gunshot injury) during the 5 months from December 2012 to April 2013 was undertaken. Royal Centre for Defence Medicine approval was obtained for a service evaluation/audit (Reference RCDM/Res/Audit/1036/12/0298) of the NGAL testing module.

All patients who met the criteria of trauma team activation and admission to ICU were included for data collection. Mechanism of injury for the study period was classified into the four methods of wounding that presented. These included patients injured by a blast mechanism (i.e. wounded by improvised or other explosive device e.g. legacy mine), those injured by GSW (i.e. wounded in penetrating gunshot injury), patient injured with burns and finally patients injured in motor vehicle collisions.

Patient age, mechanism of injury, initial physiological parameters and Trauma Injury Severity Score (TRISS) were collected in the Emergency Department along with arterial blood gas analysis (ABG) using an i-STAT handheld blood gas analyzer (Abbot Point of Care Inc, Princeton, USA).  $\text{PaO}_2/\text{FiO}_2$  ratio (P/F ratio<sup>2</sup>) was collected at 24 hours (P/F ratio 2) after ICU admission.

Serum NGAL was measured as soon as possible on admission to the ICU (NGAL<sup>1</sup>) and after 24 hours (NGAL<sup>2</sup>) using an Alere Triage NGAL test. (Alere Medical, Stockport UK). This point of care test uses a sandwich immunoassay in a single use cartridge. Drops of EDTA blood or plasma are pipetted onto the cartridge

where a filter separates the blood from plasma. The plasma then reconstitutes the fluorescent antibody, which flows into the detection zone by capillary actions. When the cartridge is then inserted into the Triage Meter, a portable fluorescence spectrometer, quantitative measurements of NGAL concentration from 15 to 1600ng/ml are displayed on the meter screen.

Statistical calculations of data were performed using the software package GraphPad Prism (GraphPad Prism version 5.01 for Windows, GraphPad Software, San Diego California USA). Parametric or non-parametric statistical tests were applied after exploring the data for normality using the D'Agostino-Pearson test. For unpaired two-group comparisons of parametric and non-parametric data an unpaired t-test and a Mann-Whitney test were used, respectively. Relationships between NGAL, TRISS, pH and P/F ratio were described using Pearson's (parametric data) and Spearman's (non-parametric data) coefficients.

## Results

Data was collected on 60 patients. 33 patients were injured by blast and 23 by gunshot (GSW). Two patients wounded by burns and two by motor vehicle collision were excluded from data analysis. At 24 hours after ICU admission 22 complete data sets were available for blast injured patients and 16 for the GSW group as some patients had been evacuated by military critical care teams to Kabul, the UK or Germany and two Afghan National Security Forces personnel had died in that time.

The mean patient's age was 25.3 years (range 18-45 years). The mean TRISS was  $80.12 \pm 25.99$  in the blast group and  $85.06 \pm 21.91$  in the GSW group. Initial presenting physiological data is presented in Table 1. On admission to ICU, APACHE score was calculated at  $13 \pm 5$  in the blast group and  $13 \pm 6$  in the GSW group with no statistical difference between groups.

Table 1: physiology at presentation in the Emergency Department.

Mechanism	pH (mean ± SD)	BE mmol/L (mean ± SD)	SpO <sub>2</sub> % (mean ± SD)	Systolic BP mmHg (mean ± SD)	HR (mean ± SD)
Blast	$7.20 \pm 0.12$	$-7.64 \pm 5.00$	$96.8 \pm 3.6$	$114.1 \pm 24.6$	$114 \pm 32$
GSW	$7.24 \pm 0.07$	$-5.55 \pm 4.23$	$94.6 \pm 8.7$	$119.3 \pm 22.6$	$101 \pm 26$

NGAL1 in both groups was measured at a mean time of  $340 \pm 105$  minutes post initial injury. In the blast group mean time to measurement of NGAL1 was  $363 \pm 92$  minutes and in the GSW group was  $306 \pm 120$  minutes post injury with no statistical difference in timing between either group.

Mean NGAL1 was  $123.4 \pm 45.4$  (ng/ml) in the blast group and  $133.7 \pm 73.7$  (ng/ml) in the GSW group. After 24 hours admission in ICU the mean NGAL2 was  $146.3 \pm 78.3$  (ng/ml) in the blast group and  $151.5 \pm 123.6$  (ng/ml) in the GSW group and the mean P/F ratio was  $305.1 \pm 116.4$  in the blast group and  $313.6 \pm 142.6$  in the GSW group. These results are summarised in Table 2.

Table 2: data comparison of NGAL at ICU admission (NGAL1), NGAL at 24 hours (NGAL2) and P/F ratio at 24 hours (P/F ratio2)

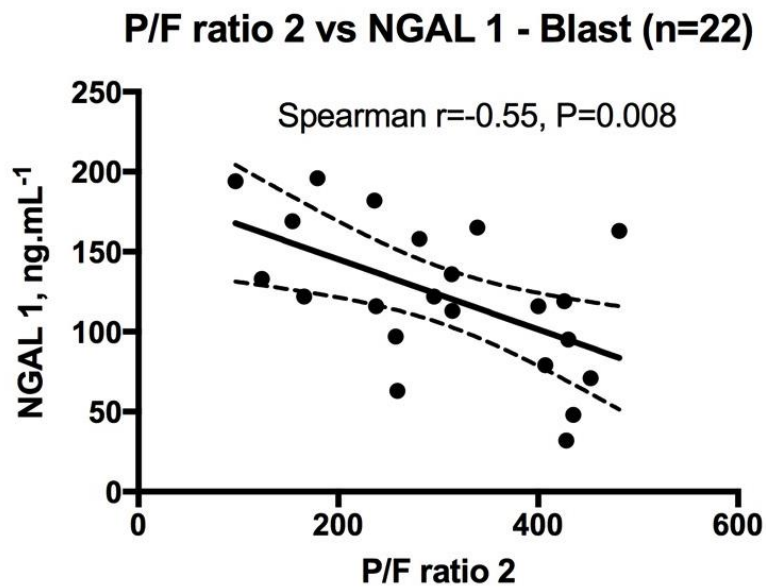
Mechanism	Mean NGAL (ng/ml) on ICU admission (mean $\pm$ SD)	Mean NGAL (ng/ml) at 24 hours (mean $\pm$ SD)	Mean P/F ratio at 24 hours (mean $\pm$ SD)
Blast	123.4 $\pm$ 45.4	146.3 $\pm$ 78.3	305.1 $\pm$ 116.4
GSW	133.7 $\pm$ 73.7	151.5 $\pm$ 123.6	313.6 $\pm$ 142.6

NGAL1 at ICU admission inversely correlated with TRISS (Spearman  $r=-0.322$ ,  $p=0.020$ ) and initial pH (Spearman  $r=-0.401$ ,  $p=0.002$ ). NGAL1 at ICU admission also inversely correlated with P/F ratio (P/F ratio2) at 24hrs (Spearman  $r=-0.420$ ,  $p=0.009$ ) in both groups.

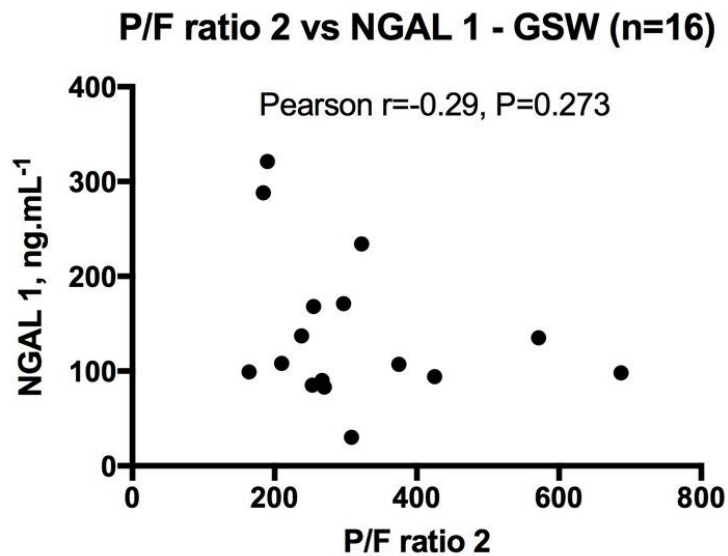
When examining between the blast and GSW groups there was a statistically significant inverse correlation between admission NGAL1 (Spearman  $r=-0.553$ ,  $p=0.008$ ) with P/F at 24 hours (P/F ratio2) in the blast group as shown in Graph 1 not found in the GSW group (Pearson  $r=-0.291$ ,  $p=0.273$ ) as shown in Graph 2.

There was no statistical correlation between NGAL at 24 hours (NGAL2) and P/F ratio 2 in either the blast group (Pearson  $r=-0.371$ ,  $p=0.098$ ) or GSW group (Pearson  $r=-0.020$ ,  $p=0.952$ ).

Graph 1: Graph of P/F ratio at 24 hours (P/F ratio 2) and NGAL at ICU admission (NGAL1) for blast injured patients



Graph 2: Graph of P/F ratio at 24 hours (P/F ratio 2) and NGAL at ICU admission (NGAL1) for GSW injured patients



## Discussion

Our results showed that raised NGAL1 on admission to ICU inversely correlated with TRISS and pH in both blast and GSW groups indicating a relationship between raised NGAL, worse survival probability (i.e. high TRISS) and lower initial pH in line with our previous study (1).

In the blast injury group there was an inverse correlation with high ICU admission NGAL1 and P/F ratio<sup>2</sup> at 24 hours (Graph 1) in the blast injured patients, indicative of a lower P/F ratio, that was not present in the GSW patients (Graph 2). This supports our hypothesis that there may be a potentially predictive relationship between NGAL and subsequent BLI as evidenced by impaired P/F ratio.

The results from this series of trauma patients indicate that a potential link between NGAL and potential BLI that warrants further investigation. In particular to correlate our findings with radiological evidence of BLI that our study did not collect. Our previous study (1) showed no correlation between raised NGAL and type of injury but we only recorded peripheral oxygen saturation, not P/F ratio that is a more sensitive indicator of ARDS and BLI.

There has been considerable previous work on biomarkers in blast injury. It has been established that blast injury induces activation of inflammation and alteration in the levels of cytokines in the blood and tissues. Plasma interleukin 6

(IL-6), a pro-inflammatory cytokine, has been shown to increase following blast exposure to the chest in a murine animal model (27).

Previous work has shown that in human trauma patients, the ratio of IL-6 to interleukin-10 correlates well with severity of injury measured by injury severity score (ISS), and may be used as a predictor of severity of injury (28). However, in another study of blunt chest trauma patients on an intensive care unit, the levels of IL-6 (and procalcitonin) in serum and bronchoalveolar lavage fluid failed to show good correlation with the extent of lung contusion (29), although they were significantly elevated.

Perhaps the most promising marker that has been shown to correlate with the severity of lung injury is the iron-transferrin complex. Transferrin is the iron binding protein carrier that facilitates transport of iron around the body, and is capable of reversibly binding two iron molecules (30).

It has been demonstrated that iron is sequestered into the tissues as a result of trauma (31). This initial study examined 36 patients with traumatic injuries to determine the effect on iron metabolism over the days following injury, and found that significant hypoferraemia was present, and was associated with reduced levels of transferrin. These findings precipitated further studies that sought to identify the effects of blast injury on iron metabolism.

Nikolai Gorbunov and his colleagues at the Walter Reed Institute of Research in Maryland, USA undertook a series of studies to define the role of iron and iron-

transferrin in blast injury, as part of a broader program looking at oxidative stress and free radical damage precipitated by blast injury. It has been demonstrated that iron is sequestered into the tissues as a result of trauma, as mentioned above, and of further relevance this has been demonstrated in blast injury (32). Gorbunov showed that different models of injury, including exposure to blast overpressure in a rat, produced a reduction in the amount of iron-transferrin in the blood, and that this reduction was inversely correlated with the severity of injury (33).

A further report detailed that iron-transferrin was normal at 1 hour following blast exposure, but was significantly reduced compared to sham controls at 3 hours, a reduction that persisted for the 24 hour observation period (33). The group then went on to suggest that the degree of iron sequestration correlated well with the degree of blast lung injury as measured by estimation at post mortem (3).

The link between NGAL and BLI is potentially due to the iron chelating properties of the molecule and raised NGAL representing a response to the higher level of iron sequestered in BLI. If so, this represents a potentially sensitive test for BLI due to the high levels expressed within lung tissue.

As a potentially useful biomarker for blast lung injury, NGAL may represent a useful triage tool. The portable point of care device for measuring NGAL could be of benefit when full laboratory facilities are not available in an austere environment. The device itself is small enough to be transported in suitable



packaging and robust enough that it has been used in adverse climatic conditions at altitude (34).

Limitations of our study include the lack of correlation of low P/F ratio as a marker of BLI with radiological evidence of BLI. It was not possible to collect this data under the RCDM approval for the study. This relatively small study was also hampered by the loss of patients to follow up who were evacuated to different UK or US medical treatment facilities. There was also incomplete long term outcome data owing to Afghan National Security Forces personnel lost to follow up in their own healthcare system. This led to a lack of sufficient patients to draw conclusion on the correlation between raised NGAL and mortality.

## Conclusion

Raised NGAL correlates with more severe injury and worse survival probability in both patients with GSW and blast injury. There is a statistically significant correlation between raised admission NGAL1 and a marker of potential BLI, impaired P/F ratio (P/F ratio 2) that warrants further investigation. Both to further establish the relationship between NGAL and BLI and to correlate this with radiological evidence of BLI.

We propose that the link between NGAL and BLI in this series is due to the iron chelating properties of the molecule and that high expression of NGAL within lung tissue makes it a potentially sensitive predictive test for the degree of undifferentiated BLI. Portability of the point of care testing module also makes it

a potentially useful triage tool for wounded personnel in austere environments aiding the decision to evacuate people for advanced respiratory support earlier in the pathway from wounding.

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