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*Original Article*

# Renin signals renal hypoperfusion during Parkland fluid resuscitation of severe burns - a prospective longitudinal cohort study

Rosa Vieweg[1], Mikael Järemo[2], Ingrid Steinvall[3], Moustafa Elmasry[3], Islam Abdelrahman[3], Folke Sjöberg[1,3]

*[1]Department of Anaesthesiology and Intensive Care in Linköping, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; [2]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; [3]Department of Hand Surgery, Plastic Surgery and Burns in Linköping, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden*

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**Abstract:** Introduction: Previous investigations have shown that fluid resuscitation of burns using the Parkland formula results in controlled hypovolaemia and that kidney injury is a common complication. Enhancing monitoring of tissue perfusion might reduce complications. Plasma renin has recently been suggested to be a promising marker for tissue hypoperfusion in intensive care patients. The aim of this study was to explore plasma renin levels during the first 48 hours after major burns in patients resuscitated using the Parkland formula. Materials and methods: Patients 18 years or older of age with 10% or more total body surface area (TBSA) burned, admitted to Linköping Burn Intensive Care Unit, and resuscitated using the Parkland formula were included. Samples for plasma renin were drawn at admission and eight-hourly thereafter for 48 hours. Results: Fifteen patients were included. Median TBSA burned was 36% and age 53 years. The fluid volumes provided were in accordance with the Parkland formula. Mean arterial pressure, urinary output, and lactate remained within reference ranges during the first 48 hours. At eight hours after burn median plasma renin was elevated to more than 25 times the upper reference value, decreasing to about four times the upper reference at 48 hours. Renin concentration was associated with lactate levels and TBSA burned. Conclusion: During Parkland fluid resuscitation of severe burns, plasma renin levels were extremely elevated. The fact that the traditionally used endpoints for Parkland fluid resuscitation remained within the reference range raises concerns about whether the increased renin concentrations may signal a relative renal hypoperfusion.

**Keywords:** Burns, fluid resuscitation, renin, lactate, renal perfusion, hypovolaemia

## Introduction

Optimisation of tissue perfusion is central in the early fluid management of patients with severe burns and over the years several protocols for burn shock resuscitation have been suggested [1]. The most commonly used resuscitation strategy world-wide is based on the Parkland resuscitation formula (4 mL/kg body weight/percentage total body surface area (TBSA) burned) [2, 3]. Previous data have shown that this strategy results in controlled hypovolaemia for the first 24 hours after the burn [4-7]. Of specific interest is that kidney injury is a common complication after Parkland fluid resuscitation of severe burns and that it is even more common after suboptimal fluid resuscitation [8-10]. Plasma renin has recently been suggested to be a promising marker for tissue hypoperfusion among patients in general intensive care (ICU) [11-13]. *Critical Care Medicine* published results from Gleeson et al. indicating that plasma renin served as a marker of tissue perfusion and outperformed lactate as a predictor of mortality in ICU [11]. However, this study was conducted on a heterogeneous group of 20 intensive care patients, of whom only 13 fulfilled the criteria of shock (six had septic shock, three haemorrhagic shock, and four cardiogenic shock). In an editorial in the same issue of the journal, Khanna suggested that a larger trial with a more homogenous population would be the best next step after the "hypothesis generating" results of Gleeson et al. [12].

During the late 20$^{th}$ century studies on plasma renin activity in burns have been published

[14-17]. Bozovic et al. studied it in 18 patients with burns in 1971 [14]. They noticed a very large range of plasma renin activity in the entire material, with median values of twice the upper reference value at day 1-4, within reference after day four, and increased to about seven times the upper reference value five days pre-mortem. Dolecek et al. found the highest level of renin-like activity in the first weeks after the burn in 10 patients with major burns [16]. Molteni et al. studied plasma renin activity in 10 patients with burns and found it within normal reference limits at day one, after which it rose progressively up to about six times the upper reference limit at day four [15]. In 1983 Griffiths et al. found the highest levels of plasma renin activity within twelve days of burns and did not find any clear association between the degree of elevation of plasma renin activity and TBSA% burned (n=15, TBSA burned 10-80%) [17]. None of these studies however, directly investigated the specific concentration of renin.

In the light of previous studies showing that resuscitation using the Parkland formula leads to a short period of controlled hypovolaemia, we hypothesised that renin levels may be affected during burn resuscitation [4-7]. Therefore, the aim of this study was to explore the concentration of plasma renin during the first 48 hours after major burns in patients who had been resuscitated using the Parkland formula.

## Materials and methods

### *Sampling design*

Consecutive sample of patients ≥ 18 years of age with TBSA burned ≥ 10%, admitted to Linköping Burn Intensive Care Unit from October 2018 to October 2019.

### *Inclusion criteria*

- Age ≥ 18 years of age.
- TBSA burned ≥ 10%.
- Admitted to Linköping Burn Intensive Care Unit from October 2018 to October 2019.

### *Exclusion criteria*

- Among patients admitted to Linköping Burn Intensive Care Unit, we excluded patients with electrical, chemical, and lightning injuries as well as patients with severe mucocutaneous reactions (i.e. Stevens-Johnson syndrome and toxic epidermal necrolysis).
- Renal or liver failure prior to the burn.

### *Ethics*

The study was approved by the Regional Ethics Review Board in Linköping (2016/273-31, 2018/233-32). All patients gave written informed consent. Those who were unconscious or heavily sedated after injury gave their informed consent after the period of critical care.

### *Treatment of burns and supportive intensive care*

Patients were treated according to a previously well-described protocol [4, 18]. This included resuscitation using the Parkland formula with the following endpoints: urinary output ≥ 0.5 ml/kg per hour, MAP ≥ 65 mm Hg, and plasma lactate within the reference range (0.6-2.4 mmol/L). Fluids were administered through central venous lines, the arterial pressure was monitored by an arterial line, and the use of norepinephrine was decided upon by the intensivist on call. The burns were treated by early excision, grafting, and regular dressing procedures in line with the healing progress of the wounds [19].

### *Laboratory methods*

Samples for plasma renin and lactate were drawn from the arterial line at admission and eight-hourly thereafter for 48 hours. The samples were sent for analysis to the accredited Clinical Chemistry Laboratory at Linköping University Hospital. Plasma renin levels were measured via the direct competitive chemiluminescence immunoassay LIAISON 25-OH Assay CLIA DiaSorin (Stillwater, Minnesota, USA) according to the manufacturer's protocol. This analysis measures the concentration of active renin in plasma. The reference range for plasma renin was 2.8-40 mU/L. Transpulmonary thermodilution was used to determine intrathoracic blood volume index (ITBVI) [4].

### *Data management*

Data were collected and analysed using Microsoft Excel 2016, Statistica 7, and Stata

**Table 1.** Resuscitation fluids and endpoints during the initial 24 hours

| | |
|---|---|
| Ringer-Acetate (mL/kg/TBSA%) | 4.3 (3.9-5.4) |
| Glucose (mL/kg/TBSA%) | 0.21 (0.10-0.46) |
| Albumin (mL/kg/TBSA%) | 0.30 (0.11-0.43) |
| Plasma (mL/kg/TBSA%) | 0.00 (0.00-0.23) |
| Erythrocytes (mL/kg/TBSA%) | 0.00 (0.00-0.00) |
| Total fluids (mL/kg/TBSA%) | 5.7 (4.4-6.6) |
| Urinary output (mL/kg/h) | 1.0 (0.7-1.2) |
| Mean arterial pressure (mm Hg) | 79 (75-80) |
| Plasma lactate (mmol/L) | 2.0 (1.6-2.3) |
| Norepinephrine (μg/kg/minute) | 0.10 (0.05-0.14) |

Data are presented as median (IQR).

v12.0. Data on resuscitation fluids, dose of norepinephrine, mean arterial pressure, and urinary output were collected from the patients' medical records. Aetiology of the injury and TBSA burned (according to Lund and Browder chart) were obtained from the burn centre's data registry [20, 21]. Values for plasma renin and lactate were imported from the laboratory's computer system.

*Missing data*

Data missing at random were managed by mean imputation.

*Statistics*

Data are presented as median and interquartile range (IQR). Multivariable regression for panel data was used with renin as the dependent variable and patient identity as the group variable (STATA v12.0, Stata Corp. LP, TX, USA). Probabilities of less than 0.05 were accepted as significant.

## Results

*Demographics and burn size*

Fifteen patients (12 male and three female) were included, of which there were 14 flame burns and one scald injury. Median age was 53 (IQR 42-73) years. Median TBSA burned was 36% (IQR 26%-42%), full thickness burns 9% (0.4%-16%), deep partial thickness 13% (6%-26%) and superficial partial thickness 2% (0%-9%).

*Adherence to the Parkland formula*

During the initial 24 hours, the fluid volumes provided were in accordance with the Parkland formula, as were the endpoints of urinary output and MAP. Median plasma lactate was within the reference range (**Table 1**). **Figure 1A-D** show urinary output, mean arterial pressure, plasma lactate, and norepinephrine levels at eight-hourly intervals during the first 48 hours after burn. Median ITBVI was 676 (619-686) mL/m$^2$ 18 hours after burn and 696 (692-698) mL/m$^2$ 24 hours after burn (n=3).

*Renin*

Median plasma renin was 1147 (IQR 717-1585) mU/L eight hours after burn, 612 (192-1093) mU/L at 24 hours and 172 (30-425) mU/L at 48 hours. This meant that it was more than 25 times above the upper reference value eight hours after burn, decreasing to about four times above the upper reference at 48 hours (**Figure 2**). Multivariable regression showed an association between plasma lactate and plasma renin levels during the first 48 hours (P=0.002), as well as an association between TBSA burned and renin levels (P=0.02). No associations were found between plasma renin and urinary output, mean arterial pressure, norepinephrine dose, or age (**Table 2**).

## Discussion

The main, new finding in this study was that when patients with severe burns were resuscitated according to the Parkland formula, plasma renin levels increased to more than 25 times the upper reference value, while traditionally used endpoints for fluid resuscitation, such as urinary output, MAP, and lactate, remained within reference. Importantly, it was found that there was an association between plasma renin levels and plasma lactate, and there was also an association between renin levels and the size of the burn (TBSA).

Plasma renin has been suggested a promising marker for tissue perfusion in intensive care patients [11, 12]. In a retrospective pilot study of critically ill medical patients, plasma renin was associated with outcome [13]. Furthermore, it has recently been shown that the systemic renin angiotensin system is activated during resuscitation of severe sepsis and its mediators correlate with measures of microvascular dysregulation, tissue hypoperfusion, and organ failure [22]. To the best of our knowledge, whether all or some of these mechanisms are activated also during the resuscitation period of burns remains to be studied.

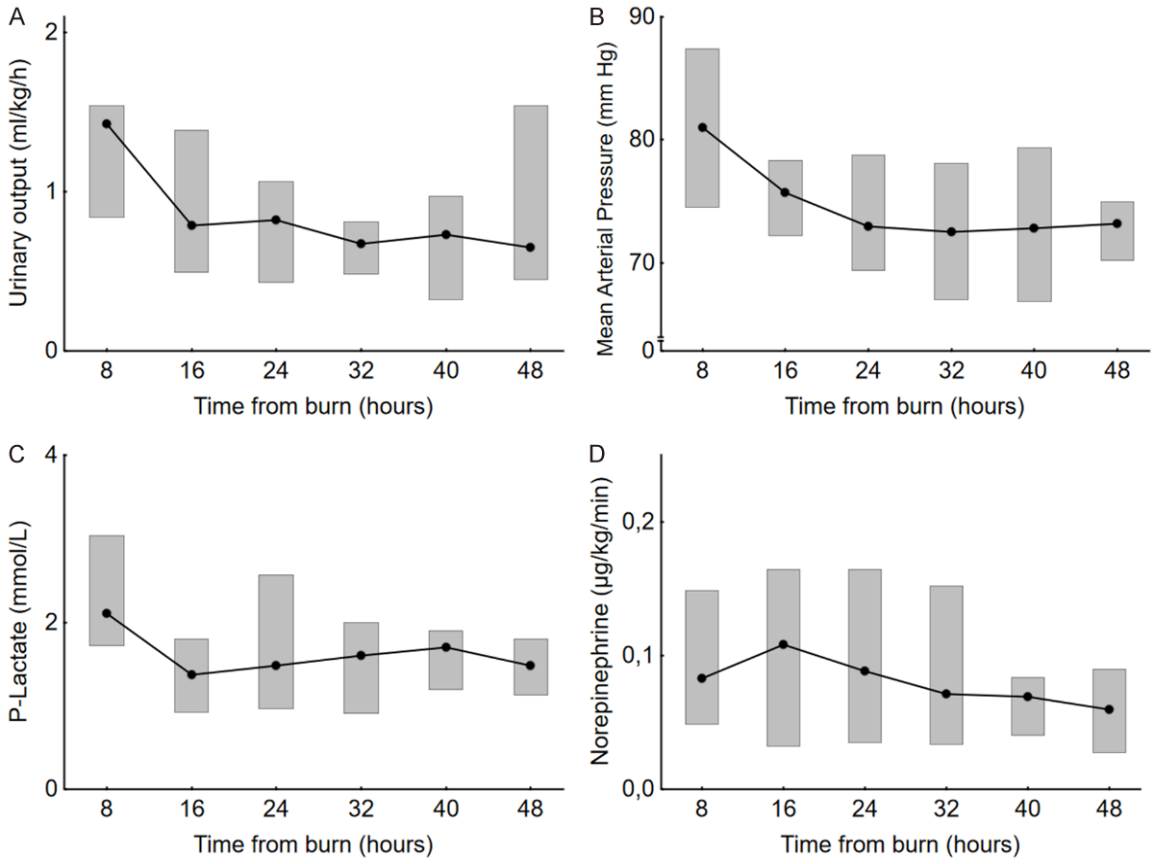


**Figure 1.** (A) Urinary output (ml/kg per hour), (B) mean arterial pressure (mm Hg), (C) plasma lactate (mmol/L) and (D) norepinephrine dose (µg/kg/minute) at eight-hourly intervals during the first 48 hours after burn. Data are presented as median and IQR.

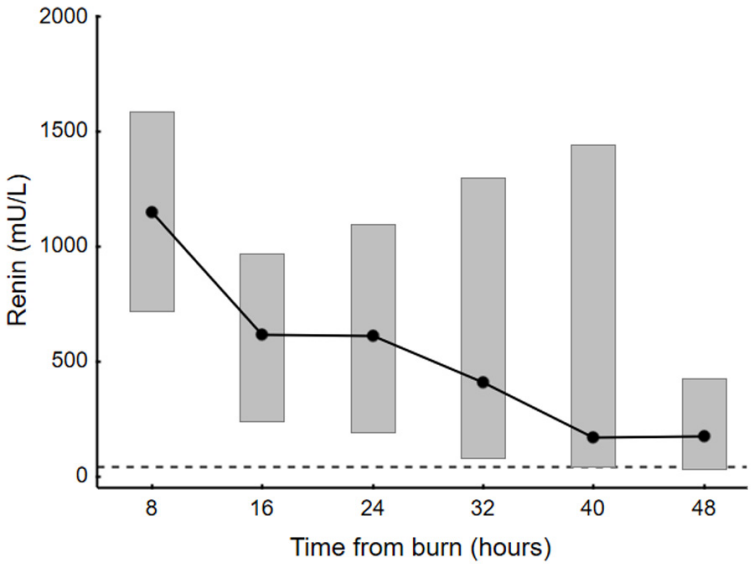


**Figure 2.** Plasma renin levels at eight-hourly intervals during the first 48 hours after burn. The dashed line indicates the upper reference value of 40 mU/L. Data are presented as median and IQR.

We have studied the concentration of circulating plasma renin, which is determined by the balance between secretion and clearance of renin. It is well known that renin release from the kidneys is stimulated by three different mechanisms; 1) decreased pressure in the afferent arteriole, 2) increased sympathetic stimulation and 3) decreased concentration of sodium chloride at macula densa [23-25].

The very high renin levels seen in this study could be a result of the kidneys' normal physiological response to hypoperfusion. If so, this raises concerns about whether resuscitation according to the Parkland for-

**Table 2.** Multivariable linear regression for plasma renin

| | Coefficient | p | 95% CI |
|---|---|---|---|
| Lactate | 76.7 | 0.002 | 28.2 to 125.2 |
| Age, years | 2.3 | 0.50 | -4.3 to 8.8 |
| TBSA% | 12.2 | 0.02 | 2.3 to 22.1 |
| Norepinephrine | 829.2 | 0.45 | -1319.5 to 2977.9 |
| Mean arterial pressure | 3.5 | 0.65 | -11.6 to 18.6 |
| Urinary output | -107.2 | 0.13 | -244.8 to 30.3 |
| Constant | -443.6 | 0.53 | -1817.3 to 930.2 |

Model $R^2$ 0.44, P 0.002.

mula may lead to a relative hypoperfusion of the kidneys. This could be a possible mechanism behind the early kidney injury commonly seen in patients with severe burns [8-10].

Another possible explanation for the very high renin levels seen in this study could be the increased sympathetic stimulation secondary to the severe burn. However, the contribution of stress as a factor increasing the renin levels in the present model was not specifically evaluated and needs to be explored further.

To investigate the third mechanism for renin release (the decreased concentration of sodium chloride at macula densa) is not easy in a clinical study. It is difficult to know to what extent this mechanism contributed to the high renin levels seen in our study. Possibly, this could be due to the large sodium load usually given (Ringer acetate) during fluid resuscitation.

The clearance of renin has been less well studied than the secretion of renin. The plasma half-life of rat renin varies with different glycosylation of renin [26]. Human renin can be separated into different forms with different half-lives [27]. To which amount decreased clearance contributes to our findings of very high plasma renin concentrations early after burns is unclear. One possible contributing mechanism could be that mediators released in response to the burn influences glycosylation of renin and thereby alters its clearance.

There are several important limitations in this study that needs to be addressed. One important limitation is the small number of patients. It must, however, be stressed that the burns were substantial in size (median TBSA 36%). In addition, the change in the variable, i.e. renin, was seen in all patients and the size of the change was very large (25 times above upper reference value). Furthermore, the study was observational and hypothesis generating, thus no causal relationships were investigated.

Lactate is a well-documented and often used indicator of tissue hypoperfusion [11, 12]. We did find an association between plasma renin and plasma lactate, but it needs to be emphasized that lactate was still within the reference range and therefore the value of this observation may be reduced.

A confounding factor complicating the interpretation of the data in this study was the early use of norepinephrine to increase MAP. However, we did not find any association between plasma renin levels and the dose of norepinephrine.

Urinary output is a well-known indicator for renal perfusion. How can it be advocated that there is renal hypoperfusion despite acceptable urinary output? A possible contributing factor to such a finding could be the glomerular hyperfiltration that has previously been shown during resuscitation using the Parkland formula [28, 29].

The hypovolaemic period during Parkland resuscitation is well documented and was also assumed to be present in this study [4-7]. Although we had early ITBVI measurements from three patients only, the recorded values were in line with previous publications, thus indicating a similar period of controlled hypovolaemia in this study [4-7].

During the late 20$^{th}$ century, studies on plasma renin activity in burns were published [14-17]. Plasma renin activity, however, was later thought to be less accurate for estimating plasma renin concentration, as it depends not only on renin concentration but also on the concentration of angiotensinogen [30, 31]. We therefore opted to study the actual renin concentration as opposed to the plasma renin activity. We have not been able to find any other studies on specifically renin concentration after burns.

The renin angiotensin system has recently evoked new interest. In 2017 the ATHOS-3 in-

vestigators showed that Angiotensin II effectively raised blood pressure in refractory vasodilatory shock [32]. In recent decades, the concept of tissue renin angiotensin system has evolved, with the discovery of other enzymes (besides renin) capable of converting angiotensinogen to angiotensin I [24]. To avoid confounding our measurements of actual renin concentration with these other enzymes, we chose to study plasma renin concentration as opposed to plasma renin activity.

While plasma renin concentration was raised to more than 25 times above upper reference value, the traditionally used endpoints for fluid resuscitation remained within or close to reference. In combination with the fact that acute kidney injury is a common complication after Parkland fluid resuscitation, this raises concerns about whether resuscitation using the Parkland formula may lead to renal hypoperfusion [8, 9].

It would have been interesting to address the association between renin levels and clinical outcome (such as the development of organ dysfunction and prolonged healing time) but the current study was not powered for this.

## Conclusion

In this prospective longitudinal cohort study we found that median plasma renin eight hours after burn was 25 times the upper reference value, reducing to four times the upper reference value at 48 hours. The finding may suggest a transient kidney hypoperfusion, but this needs to be explored further.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Rosa Vieweg, Department of Anaesthesiology and Intensive Care, Linköping University Hospital, Linköping 581 85, Sweden. E-mail: Rosa.Vieweg@regionostergotland.se; rosavieweg@me.com

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