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Observations on the activity of the renin–angiotensin–aldosterone (RAA) system after low volume colloid resuscitation for burn injury

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Summary

Studies of plasma renin activity (PRA) and plasma aldosterone in burn patients treated with a low volume colloid resuscitation regimen revealed very high levels of both hormones.

Highest hormone levels occurred in the 5 days post burn with the correlation between PRA and plasma aldosterone $r = +0.787$ $(p<0.001)$.

The negative correlation between 24 hour urinary sodium excretion and PRA $(r = -0.671, p<0.001)$, *was closer than that between 24 hour sodium excretion and plasma aldosterone* $(r = -0.556, p<0.01)$.

Secondary elevations of PRA and plasma aldosterone occurred in 2 patients (7–14 days after injury) associated with clinical deterioration and systemic sepsis.

Introduction

Plasma renin activity (PRA) and plasma aldosterone are known to increase following the stress of both haemorrhage *(1)* and surgical operations *(2)*. Renin converts a circulating alpha$_2$ globulin to angiotensin I and the relatively inactive angiotensin I is converted into the vasoconstrictor angiotensin II) act to enhance renal tubular resorption of enzyme (found in greatest amount in the pulmonary blood vessels). Angiotensin II stimulates aldosterone release from the adrenal cortex after which aldosterone (and possibly also agiotensin II) act to enhance renal tubular resorption of sodium *(3)*.

Several studies have demonstrated marked activation of the renin–angiotensin–aldosterone system (RAA) after burn injury *(4–7)*. The level of PRA has been proposed as a sensitive index of the effect of a burn and its subsequent treatment *(5)*. Accordingly the present study seeks to describe the RAA responses in patients treated exclusively with a low volume colloid burn resuscitation regimen *(8)*.

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Materials and methods

Burn injured adult patients were studied soon after their admission to the Burn Centre, with all studies initiated within 24 hours of injury. During the resuscitation phase (36 hours post burn) intravenous colloid replacement was related to the patient's estimated blood volume and to the observed clinical response during colloid infusion *(8)*.

THE COLLOID REGIMEN

At admission the patient's blood volume was estimated as 7.5% of body weight (kilograms). It was then considered that one third of the blood volume should represent the likely upper limit of infusion need in the 0–8 hours post burn, with a second third the upper limit of colloid need in the 8–20 hours post burn, and the final third for the 20–36 hour period. Whilst these volumes were guides to likely upper limits of infusion need, the actual volumes of colloid (plasma protein fraction) infused were related to the clinical response of the patient.

Venous blood samples were drawn as soon as possible after admission, and further venous blood samples were taken between 9 am and 12 noon on all subsequent days of study *(9)*. Blood taken by peripheral vein venepuncture (patient supine) was placed in heparinised tubes and the plasma immediately separated in a refrigerated centrifuge and stored at $-20\,^{\circ}C$ prior to hormone assay. Standard radioimmunoassay techniques were used to measure PRA *(10)*, plasma aldosterone *(11)*, and plasma cortisol (WHO Method Manual Annex 6, Human Reproduction Unit, WHO, Geneva).

Twenty-four hour urine collections were made from 9 am to 9 am for measurement of urine volume and urine sodium content. Correlations between plasma hormone levels and these indices of renal function were calculated using the Spearman rank correlation, with the level of significance determined from the corresponding value of t in a two tailed test.

Results

Fifteen patients (11 male and 4 female) were studied. The mean time of admission post burn was 3.7 hours (range 1.0–24.0 hours), mean age 36.6 years (range 14–83 years), and mean extent of burn injury 38% body surface area (BSA) (range 10%–80% BSA). Individual details for these 15 patients together with the outcome of their injury are given in Table I.

TABLE I *Clinical details of patients*

Patient	*Sex*	*% BSA burn*	*Age*	*Comments and outcome*
MJ	M	10	34	Healed, discharged 8 days post burn (PB)
JP	M	15	20	Healed, discharged 18 days PB
ST	M	19	18	Grafted 24 days PB, discharged 72 days PB
SC	M	20	14	Grafted 23 and 32 days PB, discharged 49 days PB
KE	M	21	61	Grafted 23 days PB, DIED 28 days PB
AS	M	27	32	Healed, discharged 22 days PB
DV	M	30	50	Inhalation burn/self inflicted flame burn, DIED 8 hours PB
DA	F	32	26	Healed, discharged 32 days PB
BA	F	32	83	DIED 58 hours PB
BU	F	35	77	DIED 56 hours PB
WI	M	39	19	Septicaemia 9th PB day, transfer at 22 days PB to a military hospital
WA	M	50	32	25% healed, 25% grafted at 24 and 38 days PB, discharged 79 days PB
OL	M	80	20	DIED 7 hours PB
FA	F	80	23	Self inflicted DIED 21 days PB
ME	M	80	40	Self inflicted DIED 48 hours PB

Seven patients died, mean age 50.5 years (range 20–83 years), and mean burn extent 51.5% BSA (range 21%–80% BSA).

PRA ranged 0.5–103.0 ng/ml/hour (mean 23.0 ng/ml/hour), whilst plasma aldosterone ranged 102.0–3950.0 pg/ml (mean 936.6 pg/ml) and plasma cortisol ranged 86.0–>1000.0 ng/ml.† Highest hormone levels were observed within the first 12 days after burn injury (Fig. 1), although the scatter for values of PRA and plasma aldosterone was wide, and the degree of elevation of plasma hormone levels was not clearly related to the extent of the burn injury. Although generally high levels of both hormones were seen to accompany larger burn injuries, very high levels of both hormones, PRA 80.0 ng/ml/hour and plasma aldosterone 3950.0 pg/ml, were found on the second post burn day in a patient who had only sustained a 19% BSA burn. Forty-seven simultaneous measurements of PRA and aldosterone in these 15 patients showed a highly significant positive correlation $r = +0.787$ ($p<0.001$).

Four patients illustrate differing patterns of hormone response in relation to varying extent of injury (Fig. 2). The extent of burn ranged 15%–80% BSA and plasma hormone levels were highest in the first 5 days post burn. The fluid volumes received by these patients, together with their urine volume outputs are given (Table II). Only moderate increases in PRA and aldosterone were observed in the patient

† For this laboratory normal values (subjects supine):
PRA 0.25–2.20 ng/ml/hour.
Plasma aldosterone 49.0–215.0 pg/ml.
Plasma cortisol (9 am–1 pm) 70.7–223.4 ng/ml.

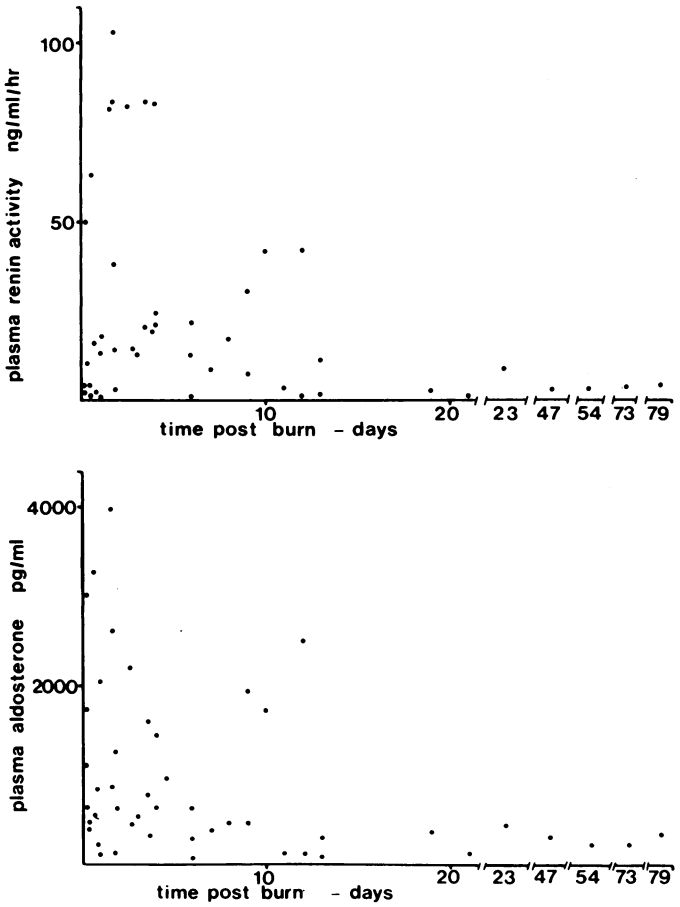

FIG. 1 The relationship of PRA and plasma aldosterone to the time post burn injury.

with the 15% BSA burn, and even in response to a 50% BSA burn the initial high hormone levels had returned almost to normal before the 10th post burn day. For the patient with the 50% BSA burn these low hormone levels than persisted (despite intervening skin grafting operations) until his discharge from hospital 79 days post burn. A secondary rise in both PRA and plasma aldosterone was seen in 2 of the 4 patients between 7 and 14 days after injury. In one patient with a 39% BSA burn this was associated clinically with a septicaemia, and in the other patient with an 80% BSA burn this secondary rise in hormone levels was associated with a deteriorating clinical condition prior to death 21 days after injury.

Complete 24 hour urine collections throughout the study period were made in 9 patients (all urine was collected after spontaneous voiding and urinary catheters were not used), and hormone values were correlated with 24 hour sodium excretion for the period during which the blood samples had been taken. Urinary sodium excretion and plasma hormone values were compared over the 14 days following burn injury. A significant negative correlation was found between the 24 hour urinary sodium excretion and both PRA $r = -0.671$ ($p<0.001$) and plasma aldosterone $r = -0.556$ ($p<0.01$).

Discussion

This study of burn patients treated with a low volume colloid intravenous fluid replacement regimen has revealed substantial increases in both PRA and plasma aldosterone particularly in the immediate post burn period, with a highly significant positive correlation between plasma levels of the two hormones. There was, however, no clear relationship between the extent of hormonal response and the size of burn injury. Significant negative correlations existed between 24 hour urine sodium excretion and plasma levels of both

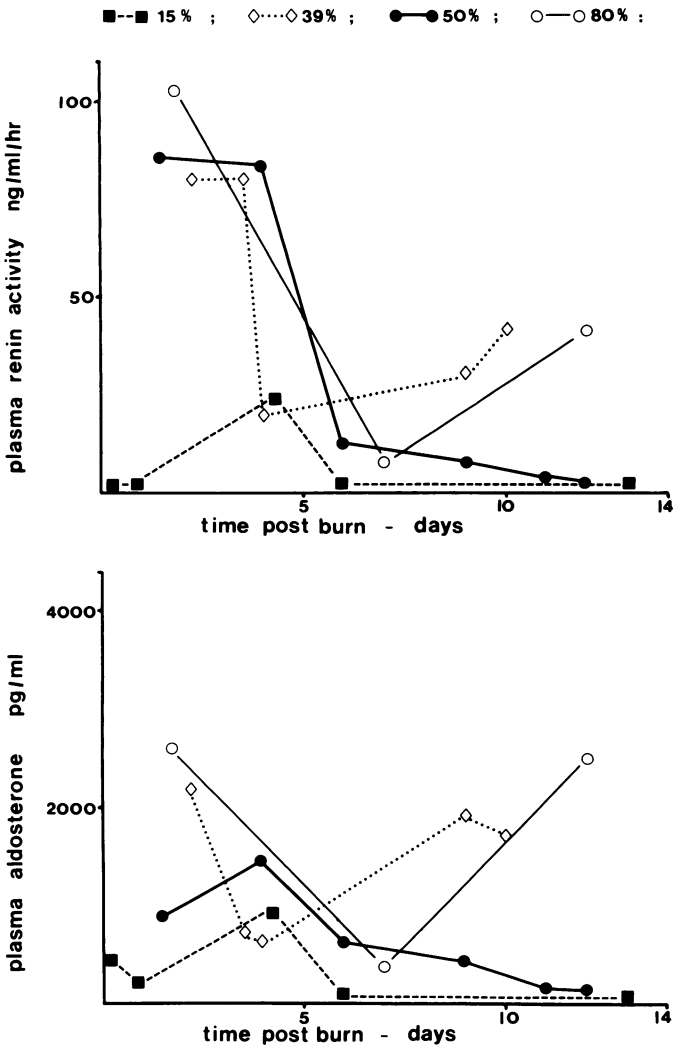

FIG. 2 Plasma hormone changes in the 14 days post burn in 4 patients with differing extent of burn injury.

TABLE II *Fluid balance details in four patients with burns ranging from 15% to 80% BSA*

Patient	% BSA burn	Estimated blood volume (litres)	Fluid balance in 24 hours post burn		
			Intravenous	Oral (litres)	Urine
MJ	15	5.1	3.25	1.20	2.00
WI	39	5.1	3.45	3.88	2.58
WA	50	5.4	4.12	2.40	1.31
FA	80	3.2	2.66	2.79	0.43

hormones. The stronger negative correlation between sodium excretion and PRA than between sodium excretion and plasma aldosterone may relate to the fact that renin action results in the formation not only of aldosterone but also by an intermediate step angiotensin II; aldosterone (and possibly angiotensin II) are both active in promoting sodium resorption by cells of the kidney tubule *(3)*.

Previous studies have documented changes in plasma aldosterone *(12)* and PRA *(4–7, 13)* after burn injury. In the study by Bane *et al. (12)* of 7 patients (burn extents not given) plasma aldosterone values did not exceed 608 pg/ml, although elevated levels continued until the 60th post burn day in one patient. Bozovic *et al. (4)* reported 18 patients with burns of 5%–95% BSA treated with intravenous fluid infusions of 1.5 ml of colloid and 1.0 ml of water and electrolytes per kilogram per % BSA burn per 24 hours, and noted a maximum increase in renin activity (just prior to death) of × 110 of normal. Dolecek *et al. (5, 14)* recorded PRA and angiotensin II changes in 46 patients up to 9 weeks post burn. Highest values for both hormones accompanied the larger injuries with peak PRA reaching 32.0 ng/ml/hour and maximum angiotensin II plasma level 660 pg/ml (normal 153.2 ± 55.5 pg/ml).

In a more recent report on 10 patients treated with Ringer's lactate crystalloid resuscitation, 4 ml/kg/% BSA burn/24 hours (mean age 36.8 years, mean burn extent 37.7% BSA), Molteni *et al. (13)* describe PRA values of < 8 ng/ml/hour on the day of burn injury, rising to 40–50 ng/ml/hour by the 5th day. In patients with 80%–90% BSA burns PRA reached 80–100 ng/ml/hour and aldosterone 600–900 pg/ml (these patients died on the 8th post burn day).

The increases in PRA detected in the present study were of a similar order to those reported for another group of burn patients of similar mean age and mean extent of burn injury *(13)*; however, increases in plasma aldosterone levels in the present study are generally considerably greater than those reported by other workers *(12, 13)*. The earliest elevation for PRA was at 2 hours (PRA 50.2 ng/ml/hour for a patient with an 80% BSA burn) and 6 hours (PRA 10.3 ng/ml/hour for a patient with a 30% BSA burn). In this context for the patients reported by Molteni *et al. (13)* treated with large volumes of crystalloid PRA did not exceed 8 ng/ml/hour in the first 24 hours post burn. With similar mean ages and mean burn extents between the present study and that reported by Molteni *et al.*, it suggests that an earlier and more marked renin and aldosterone response may occur in patients treated with low volume colloid resuscitation. The findings in the present study demonstrate the substantial and prolonged elevations in PRA and plasma aldosterone consequent upon burn injury, although the time for which these elevations are noted appears to be shorter than reported in other series. Both increased secretion and reduced metabolic clearance are likely to contribute to the rise in plasma levels of both hormones. Whilst these findings agree closely at least in the general pattern of response with those reported from other studies, it is difficult to elucidate the quantitative differences from other studies since the lack of standardisation of the assays may introduce bias into any interpretation. However, the possibility exists at least that some of the variation from study to study may be the result of the influence of different treatment regimens employed—both of resuscitation and wound management.

There may be considerable variation in the duration and intensity of sodium and water retention in patients with similar size burn injuries, with the relationship between urinary sodium output and urine volume not only variable, but in some instances completely dissociated *(15)*. Recognition of these patterns of post traumatic antidiuresis and sodium retention has led some workers to advise limitation of intravenous fluid loads in burn resuscitation *(16–18)*, although others continue to advocate relatively large volumes of intravenous resuscitative fluids *(19–21)*. The inverse relationship between PRA or aldosterone and sodium excretion in the present study indicates that these hormones have a significant role in affecting the sodium retention that is observed after thermal injury coupled with low volume colloid resuscitation. In the absence of strict balance studies of sodium intake during the study period it could obviously not be claimed that the hormones are necessarily the major effectors of this response. Measurement of 24 hour endogenous creatinine clearance rates during this study (Griffiths *et al.*, unpublished observations) did suggest that variations in glomerular filtration rate (GFR) were not responsible for the salt and water retention observed after the first 48 hours post burn injury. However, the difficulties involved in the interpretation of the results of this type of GFR measurement do not permit a substantive assessment of the relative con-

tribution of haemodynamic and hormonal factors to the retention of fluid and electrolytes.

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