Interrelationship among glomerular filtration rate, fractional sodium excretion and albuminuria in Russell's viper bite patients

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The interrelationship among Ccr, FENa% and Ualb were observed in 38 Russell's viper bite patients for 5-days clinical course. Degree of albuminuria had strong hyperbolic relation with glomerular filtration rate (Ccr) on day 1 after bite but not from day 2 onwards. The extent of albuminuria and fractional sodium excretion (FENa%) level was found to indicate the severity of renal insult. Albuminuria (Ualb) was associated with impaired Ccr and renal sodium handling. Ccr value below 40 ml/min or albuminuria (Ualb) above 2.07 g/24 hr on day 1 after bite was found in oliguric renal failure patients.

INTRODUCTION

Systemic envenoming causes acute renal failure in about 30% of patients following Russell's viper bite in Myanmar (1). A broad spectrum of renal lesions has been reported from histopathological studies, however, there was no information available on the functional changes of the kidneys in these patients. In this present communication the dynamic changes of renal function measured by creatinine clearance (Ccr), fractional sodium excretion (FENa%) and albuminuria (Ualb) are presented and these variables are also constructed in a three dimensional pattern for better inderstanding of interrelationship among these parameters in Russell's viper bite victims.

MATERIALS AND METHODS

Patients - Thirty-eight cases of proved Russell's viper bite victims admitted to Thayarwady township hospital were studied during 1984-85. Russell's viper bite was confirmed by positive venom antigen detected in their sera by enzyme-linked immunosorbant assay (2). Twelve apparently healthy normal subjects were also studied as a reference.

Methods - Twenty min: clotting test (3) was carried out on blood samples obtained from the snake bite patients. Daily serum and urine samples were collected for 5 days and frozen for biochemical measurements. Twenty four hr endogenous creatinine clearance for glomerular function, fractional sodium excretion test for renal handling of sodium and albuminuria were measured. The FENa is the quotient of the urine-plasma sodium and creatinine ratios multiplied by a factor of 100. Its derivation is as follows :

$$FENa = (U/P)_{Na} / (U/P)_{cr} \times 100\%$$

Creatinine by alkaline picrate method, albumin by bromocresol-green specific dye method and sodium by flamephotometry were used.

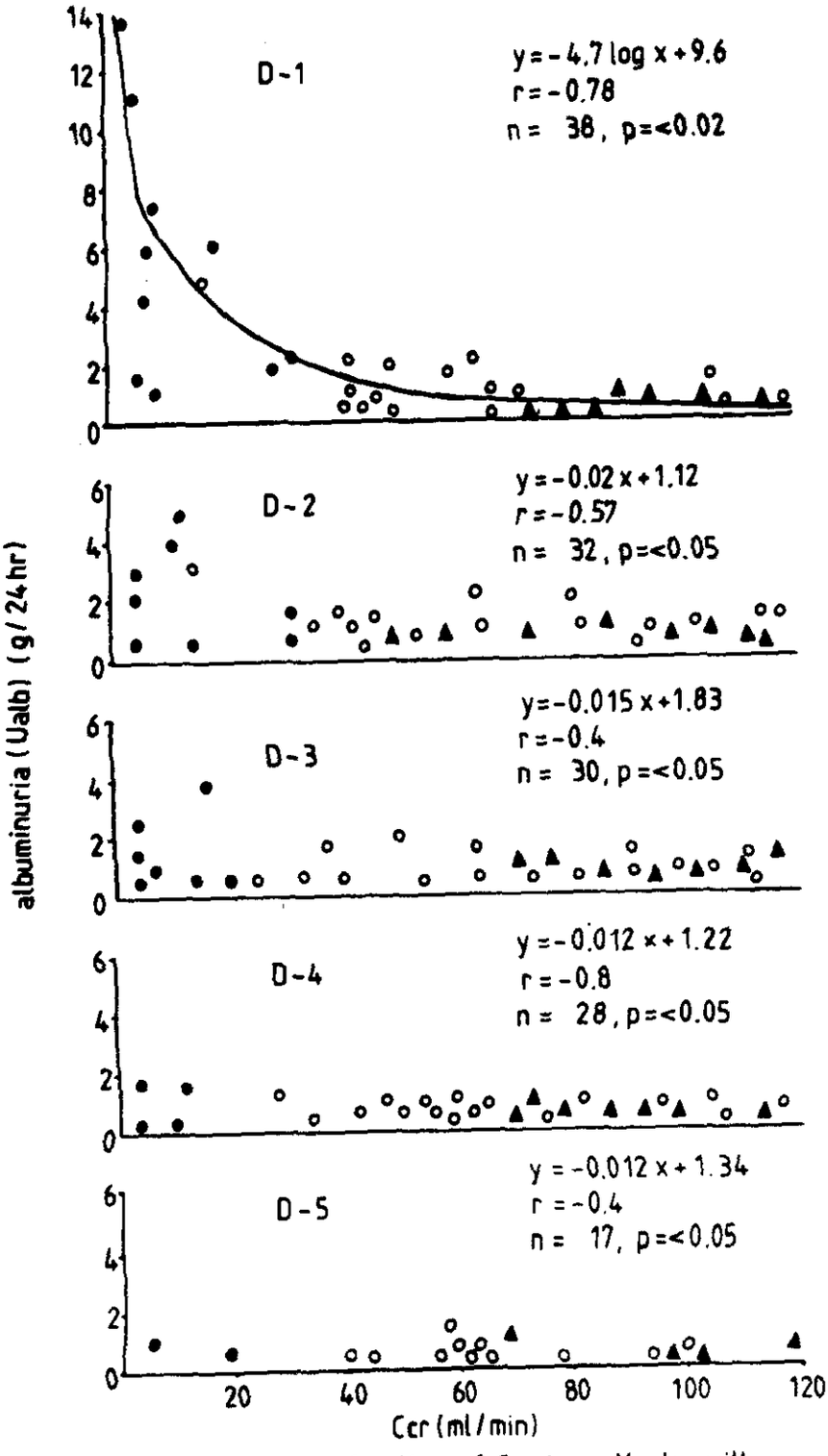
Treatment - Monospecific enzyme refined freeze-dried equine antivenom (BPI) was given as soon as the blood became incoagulable Patients who passed less than 400 ml of urine per 24 hr after rehydration were defined as oliguric renal failure. Fluid balance was strictly controlled.

Statistical analysis - Mathematical curve fitting was executed on the data by testing linear (y= 1 + bx), exponential

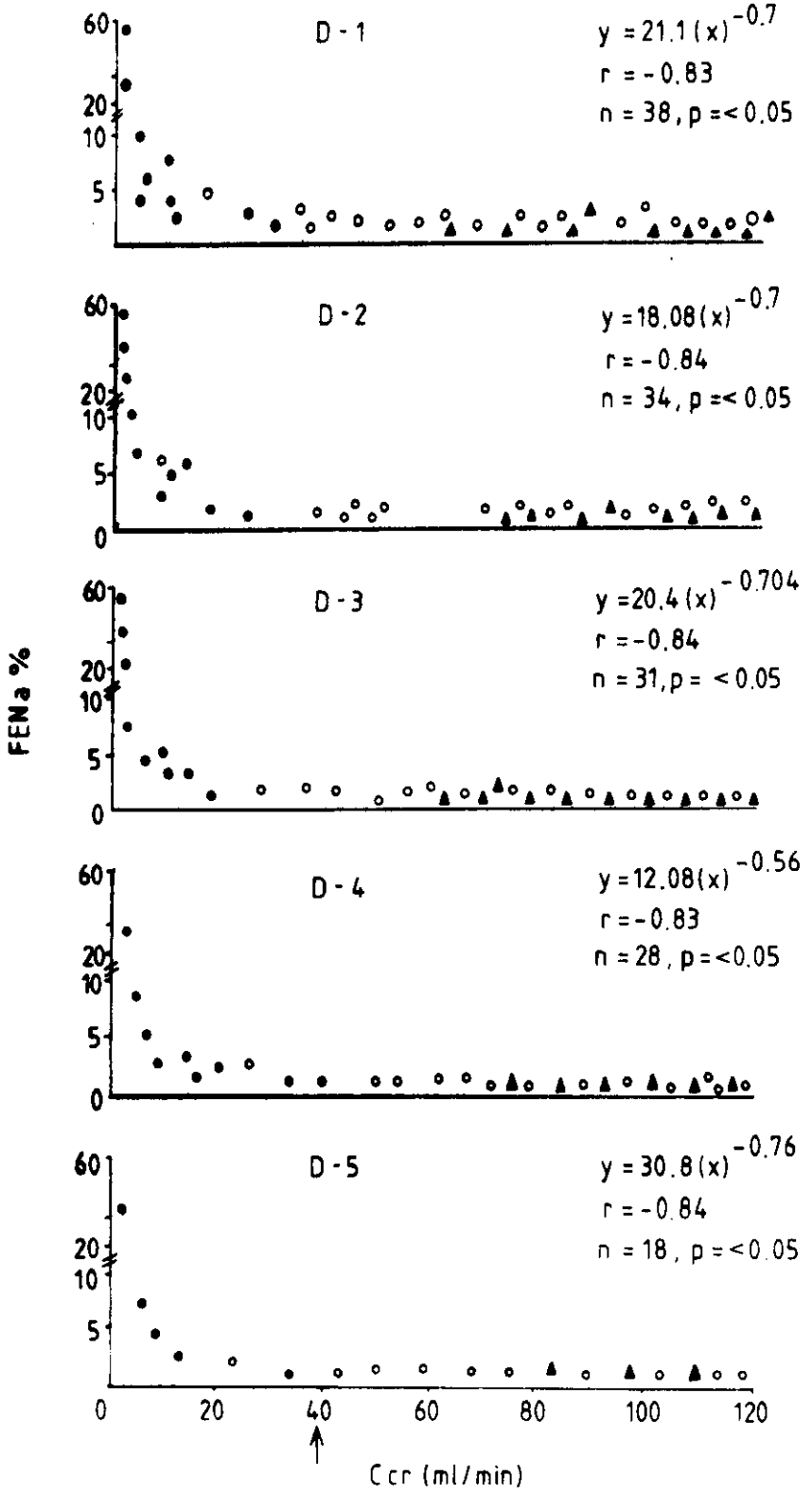
Table 1. Clinical and laboratory data in 38 patients following Russell's viper bite.

RV No.	Bite to admission (hr)	Bite to incoag : blood (hr)	Serum creatinine (mg/dl) adm/max	Oliguria ±	Clinical outcome
87	1.5	2.7	1.46/7.1	+	PD
127	2.0	4.3	1.56/8.0	+	R
151	1.1	2.4	1.1 /2.3	+	Ex
110	2.5	10.7	1.56/8.0	+	R
141	2.5	2.5	1.8 /4.0	+	Ex
157	2.7	2.7	0.86/3.6	+	PD
124	8.2	8.2	2.3 /5.4	+	R
93	2.8	2.8	1.5 /11.7	+	R
143	1.5	2.8	1.3 /6.12	+	R
73	6.5	6.5	1.0 /6.4	+	R
97	4.8	4.8	2.0 /5.3	+	Ex
94	1.8	5.5	2.0 /3.3	-	R
111	1.25	2.6	1.8 /4.3	-	R
123	3.25	8.3	2.7 /3.6	-	R
149	1.0	1.6	1.2 /2.4	-	R
79	2.0	2.0	1.3 /6.3	-	R
134	5.3	5.3	1.0 /6.0	-	R
81	2.2	2.2	1.8 /3.1	-	R
118	6.9	6.9	1.3 /3.0	-	R
78	1.2	4.0	1.3 /1.3	-	R
135	3.4	12.5	1.5 /1.5	-	R
159	1.2	17.2	1.1 /1.5	-	R
98	3.8	3.8	1.2 /1.3	-	R
74	2.7	2.7	1.3 /1.3	-	R
88	3.3	3.3	1.5 /1.8	-	R
130	0.75	16.0	1.1 /1.8	-	R
137	1.0	2.2	1.1 /2.0	-	R
154	0.92	13.4	0.86/1.3	-	R
106	2.7	2.7	1.3 /2.0	-	R
86	2.5	-	0.86/1.0	-	R
91	4.0	-	1.5 /1.8	-	R
92	2.0	-	1.0 /1.0	-	R
100	1.42	-	1.8 /1.8	-	R
107	1.5	-	1.5 /1.5	-	R
108	6.5	-	1.0 /1.0	-	R
115	1.75	-	1.3 /1.3	-	R
117	2.25	-	1.1 /1.1	-	R
145	3.7	-	1.2 /1.2	-	R

incoag : incoagulable, adm : admission, max : maximum,
R : recovered, PD : peritoneal dialysis, Ex : expired



Fig(1). Albuminuria as a function of Ccr in patients with incoagulabe blood[with oliguria(●) and without oliguria(○)]and patients with clotted blood (▲).



Fig(2). FENa % as a function of Ccr.
See figure(1) for symbol definitions.

($y = ae^{bx}$), log($y = 1 + b \log x$), and power($y = ax^b$) functions.

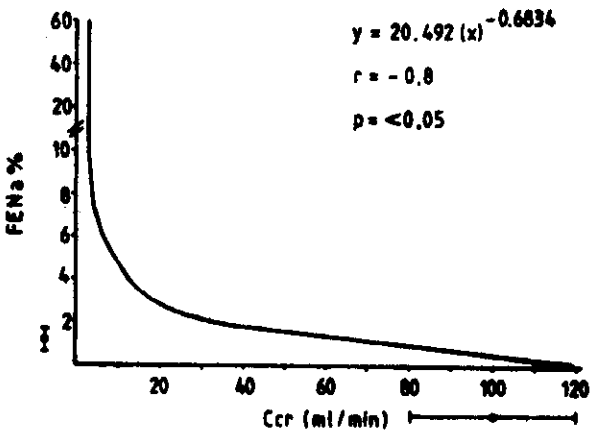
RESULTS

The clinical and laboratory data of all 38 Russell's viper bite patients are in Table (1). Of the 38 proved Russell's viper bite patients, 29(76.3%) developed incoagulable blood at mean 5.6 hr, range 1.6-17.2 hr after bite, their admission time was mean 2.78 hr, range 0.9-8.2 hr after bite and their blood became reclotted after antisera at mean 14.09 hr, range 6.0-25.2 hr after bite. 9(23.7%) had clotted blood throughout the whole clinical course of the study and they were admitted at mean 2.85 hr, range 1.42-6.5 hr after bite. Of 29 patients with incoagulable blood, 11 developed oliguria on day 1 after bite.

Albuminuria as a function of Ccr, Fig (1). Significant hyperbolic relationship between albuminuria and Ccr was observed ($r = -0.78$, $p = 0.02$) on day 1 after bite. Oliguria developed when Ccr fell below 40 ml/min and the corresponding albuminuria was about 2.07g/24hr in these patients. Very poor correlations between albuminuria and Ccr were observed on day 2 to day 5 after bite.

FENa% as a function of Ccr, Fig (2).

Constant hyperbolic function between Ccr and FENa% was observed throughout the whole clinical course of the study ($r=-0.8$ $p=<0.05$). As Ccr values decreased progressively, there was an increasing value of FENa%, the rate of FENa% rise being very gradual at first but became very steep when Ccr reached below 20 ml/min. From the mean relationship between FENa% and Ccr, four arbitrary hypothetical sequential stages of renal functional derangement can be discerned Fig (3).



STAGE	Ccr (ml/min)	FENa%
I	80-120	<1.0
II	30 - 80	1-2
III	16.6 - 30	2-3
IV	< 16.6	>3.0

Fig (3). mean relationship between FENa and Ccr. 95% confidence limits of controls (|—●—|)

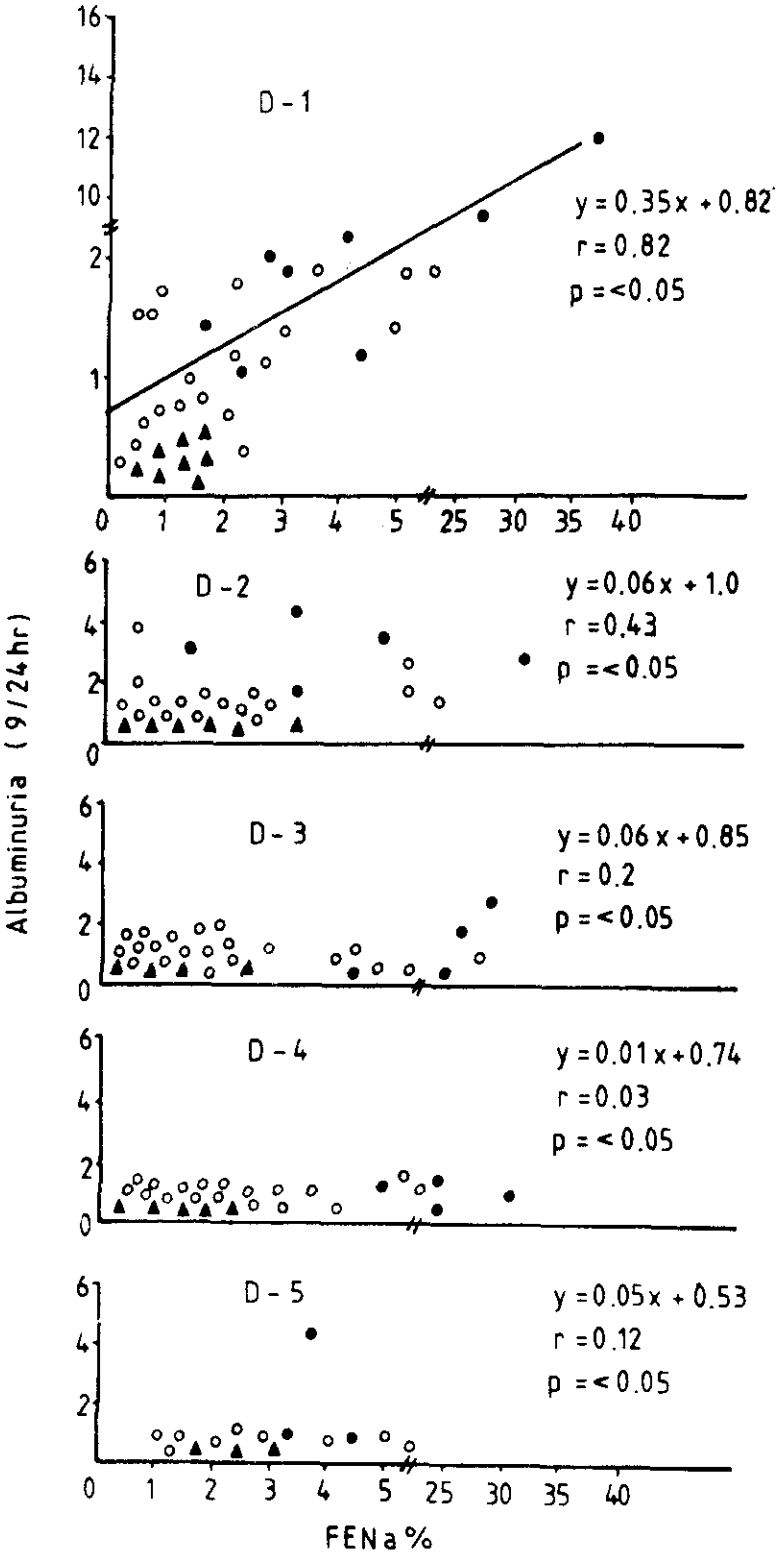
Stage I Ccr ranges within normal limits, ie 80-120 ml/min with FENa% less than 1%.

Stage II Ccr ranges from 30-80 ml/min with FENa 1-2%.

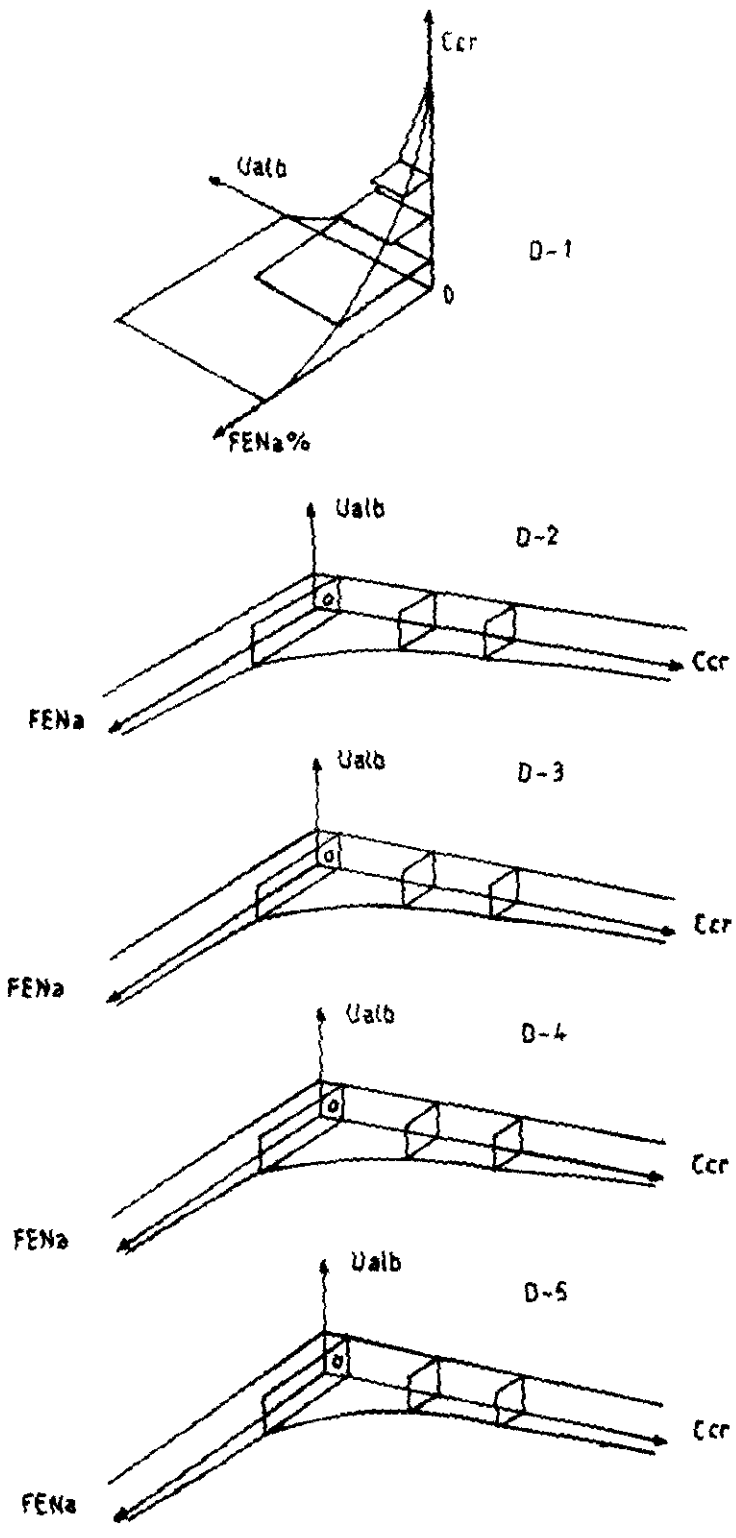
Stage III Ccr ranges from 16.6-30 ml/min with FENa 2-3%.

Stage IV Ccr ranges from 0.0-16.6 ml/min with FENa more than 3%.

Albuminuria as a function of FENa%, Fig (4).



Fig(4) Albuminuria as a function of FENa%
See figure(1) for symbol definations



Fig(5). Albuminuria(Ualb)-Ccr-FENa curves combined in a three dimensional construction, D-1 to D-5 after bite.

Significant positive linear function between albuminuria and FENa% was observed on day 1 after bite ($r=0.82$, $p=<0.05$). Nevertheless, during day 2 to day 5 after bite, there was no significant correlation between these two variables, which shows that impairment of sodium handling was not in parallel with the degree of albuminuria on these days.

Three dimensional pattern of albuminuria (U_{alb})-Ccr-FENa%, Fig (5).

Both FENa% and albuminuria increased expotentially with decreasing Ccr during day 1 after bite. Albuminuria in accordance with arbitary sequential phases of renal function derangement on day 1 was also presented in Table (2).

Table 2. Albuminuria (g/24 hr) calculated from the hyperbolic equation: albuminuria (g/24 hr)= 4.7 log (Ccr)+ 9.6, in accordance with arbitrary sequential stages of renal function derangement on day 1 after bite.

	Ccr ml/min	FENa%	albuminuria(g/24hr)
Controls*	80-120	0.9-1.5	0.0 -0.05
Stage I	80-120	< 1.0	0.2 -0.65
Stage II	30-80	1.0-2.0	0.65-2.66
Stage III	16.6-30	2.0-3.0	2.66-3.86
Stage IV	< 16.6	>3.0	> 3.86

*95% confidence limits

During day 2 to day 5 after bite, the above relationship changed into different pattern. As Ccr reduced progressively, expotential rise in FENa% persisted, but albuminuria no longer correlated with either falling Ccr or rising FENa% values.

DISCUSSION

The most striking biochemical changes found in the present study is the hyperbolic relationship between fall in Ccr and increase in amount of both albuminuria and FENa% during dayl after the bite. This relationship indicates the fact that albuminuria and FENa% levels can be used as a valuable marker in assessing the extent of glomerular filtration failure in early hours after Russell's viper bite. Since oliguria was observed as early as day I after the bite in most of the patients with severe envenoming, the finding of rising albuminuria and FENa% levels before Ccr fell below 40 ml/min, the critical level of GFR, at which oliguria starts to develop, signifies the fact that continuous monitoring of these two variables soon after the bite could detect patients at risk of developing severe renal insufficiency. Moreover, abnormal loss of albumin from the kidneys and FENa% less than 1% occurred before significant reduction of Ccr during stage I further intensifies this value. However, the interrelationship among these variables changed into different patterns on day 2 to 5 after the bite. Albuminuria no longer correlated with the change in both Ccr and FENa% despite constant hyperbolic relationship between Ccr and FENa% levels. The most likely cause of this observation might be either due to a decrease in glomerular capillary permeability to albumin and/or reduction in number of functioning glomeruli as a result of severe renal damage. Therefore, the finding of heavy albuminuria on day 1 followed by reduced excretion of albumin on subsequent days after the bite should be regarded as a sign of severe and progressive renal damage.

Although the exact pathogenic mechanism(s) that take part in Russell's viper venom nephropathy are not known, the histopathological studies revealed distinct morphological features. The salient feature in the kidney are intraglomerular depostion of fibrin, fibrin degrading products and coagulation(4). Myint Lwin et al(1) also reported that the very rapid development of oliguria supports the idea of massive occlusion of the renal micro-

vasculature with fibrin, resulting in renal ischemia. The other possible factor that should be considered is the direct nephrotoxic action of the venom (5).

The clinical course of acute renal failure may be divided into three stages: (1) stage of renal insult or initiating phase, (2) stage of renal insufficiency, and (3) stage of renal recovery. Stage of renal insult or initiating phase is the period where diagnosis and prevention have major roles(6). From the present study, it is possible that stage I and IV represent initiating and significant renal insufficiency stages respectively. In between these two stages, there is a gray zone which include stage II and III. During stage I, although glomerular injury had already started as indicated by abnormal loss of albumin from the kidneys, there was an intense resorption of sodium from the intact tubules. This might result from renin-angiotensin mechanism. FENa less than 1% indicates, sodium avid state, acute glomerulonephritis, intrarenal hemodynamic alteration and intrarenal obstruction (7). Since our patients received adequate fluid and electrolyte replacement at the time of admission,sodium avid state could not be a contributing factor in lowering FENa level. As glomerular injury advances, both glomerular filtration failure and inpaired renal sodium handling follows, resulting in significant renal insufficiency during stage IV.

It is possible that depending on the magnitute and duration of renal insult, renal failure may be maintained by: a decrease in glomerular capillary permeability, leakage of filtrate across damaged tubular epithelium, tubular obstruction and persistent renal vasoconstriction (8).

In summary the following points were noted:

(1) Albuminuria was associated with impaired Ccr and renal sodium handling.

(2) Degree of albuminuria had a strong correlation with impaired Ccr only on day 1, but not on subsequent days after the bite.

(3) Ccr value below 40ml/min or albuminuria level above 2.07 g/24 hr on day 1 after bite was found in oliguric renal failure patients.

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