The African Journal of MEDICAL SCIENCES

Editor: A. Olufemi Williams

Assistant Editors: O. O. Akinkugbe and B. O. Osuntokun

Volume 4

1973

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Melbourne

Afr. J. med. Sci. (1973) **4**, 307–312.

Functional Homogeneity of Nephron Population in the Sickle Cell Patient

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(*Received* 5 *September* 1972; *accepted* 6 *December* 1972)

Summary. Sickle cell patients (SCP) and normals were exposed to 20°C and 40°C and certain renal functions studied. The results are interpreted to indicate that in the normal human kidney the cortical nephrons predominate in activity at 20°C while the juxtamedullary nephrons predominate at 40°C and that in the SCP the nephron population is functionally homogeneous.

Résumé. Des malades atteints d'hematie falciforme et des malades qui n'en sont pas atteints, ont été soumis à des températures de 20° centigrade et de 40°C et certaines de leurs fonctions rénales étudiées. Les résultats de l'expérience montrent que dans le rein humain normal, les tubes urinifères corticaux sont plus actifs quand la température est de 20°C tandisque les tubes urinifères juxtamédulaires sont plus actifs quand la température est de 40°C. Chez le malade atteint d'hématie falciforme, tous les tubes urinifères fonctionnent de façon homogène.

INTRODUCTION

It is becoming increasingly clear that the mammalian nephron population is not functionally homogeneous. In 1968, Horster & Thurau suggested on the basis of micropuncture studies on single rat glomeruli that haemodynamic factors might alter sodium excretion through the redistribution of filtrate between juxtamedullary nephrons with loops having a high sodium reabsorptive capacity and superficial nephrons with low capacity loops (Horster & Thurau, 1968). Other studies have been interpreted to indicate that the cortical and juxtamedullary nephrons exhibit quantitative differences in sodium and water reabsorption (Barton *et al.*, 1968; Jamison & Lacy, 1971; Pomerantz, Birtch & Barger, 1968) and that shifts in the blood flow and filtration might occur between the two nehron populations (Bovee & Webster, 1971; Gauer, Henry & Behn, 1970; Pomerantz, Birtch & Barger, 1968).

No information however appears to exist in the literature regarding the functional heterogeneity of the human nephron population. The human nephron cannot be micro-

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punctured. Therefore evidence for functional heterogeneity must necessarily remain indirect. However nature has performed an experiment on the sickle cell patient (Haemoglobin SS) in whom the juxtamedullary nephrons and the vasa recta have been shown to be either abnormal or destroyed leaving intact for the most part the cortical nephrons (Bernstein & Whitten, 1960; van Eps *et al.*, 1970a, b). Therefore the renal handling of solute and water was studied in the sickle cell patient (SCP) and normals (Haemoglobin AA) during acute exposure to 20°C and 40°C. This methodological approach was adopted because a change in intrarenal sympathetic activity occurs during temperature change (Kenney, 1952, 1963; Radigan & Robinson, 1949) and this has been shown to associate with the redistribution of blood flow between cortical and juxtamedullary areas and changes in sodium excretion (Pomerantz, Birtch & Barger, 1968). The data are interpreted to indicate that in the normal human kidney the cortical nephrons predominate in activity at 20°C while the juxtamedullary nephrons predominate at 40°C and that in the SCP the nephron population is homogeneous.

MATERIALS AND METHODS

Nineteen male SCP (nine haemoglobin SS and ten haemoglobin SC) and ten normal healthy male Ghanaians with normal haemoglobin genotype (AA) between the ages 17 and 27 were acutely exposed to 20°C and 40°C in an environmental room. None of the subjects had any evidence of renal disease except the hyposthenuria of the SCP. The SCP were symptom-free at the time of study and none had had a crisis the previous 3 months. Half the subjects were exposed first to 20°C and then to 40°C and the order reversed in the other half. The period of exposure was 3 hr for each temperature. A relative thermal equilibration was achieved within the first hour as indicated by the steady record of the temperature obtained near the ear drum by means of a thermistor probe. The subject then ingested tap water initially at 20 ml/kg followed by half hourly ingestion of a volume equal to the urine output plus 50 ml to allow for insensible water losses. At the beginning of the second hour an infusion of 0·28 M mannitol delivered at 4 ml/min was started which was continued throughout the study. Timing of urine collection started at the beginning of the third hour, for an hour's duration, at half-hourly intervals, the subject changing from the recumbent to the upright position to empty the bladder. Blood was obtained from the antecubital vein of the arm opposite the infusion arm at the middle of the urine collection period. The urine flow rate was measured. The urinary and plasma osmolalities were measured with an Advanced osmometer on 2 ml samples. Total solute excretion, osmolar clearance and free water clearance were calculated using conventional formulae. The regression lines and correlation coefficients were calculated.

RESULTS

The results are shown in Figs. 1 and 2. In both figures, solute excretion (U osm.V) and free water clearance (V–C osm) were separately plotted against urine flow rate (V). It is evident from the admixture of points in Fig. 1 for the SS and SC that both groups responded in a similar manner to the stress of temperature change; no clear segregation between these two groups appears possible in Fig. 1. This observation is in keeping with that of van Eps *et al.* (1970a) that the destruction of the medullary vasa recta (with, presumably, secondarily

atrophic juxtaglomerular nephrons) which occurs in the SS, is also demonstrable, in the SC; in the latter group however destruction is less complete. Moreover, van Eps *et al.* (1970b) have shown unequivocally that the SC subject, like the SS, has a reduced ability to concentrate his urine, though the degree of this deficiency is less than in the SS. Therefore it appears entirely reasonable to consider the SS and SC in the study reported here as a single group (SCP) and compare it with the normal controls (AA).

It is clear from Fig. 2a that at urine flows greater than 10 ml/min (this corresponds to values obtained only at 20°C) the excretion of solute rose linearly with urine flow in the normal AA subjects with a high degree of correlation between the two parameters ($r = +0{\cdot}7$), the regression equation being $y = 0{\cdot}07x + 3{\cdot}0$. At urine flows less than 10 ml/min

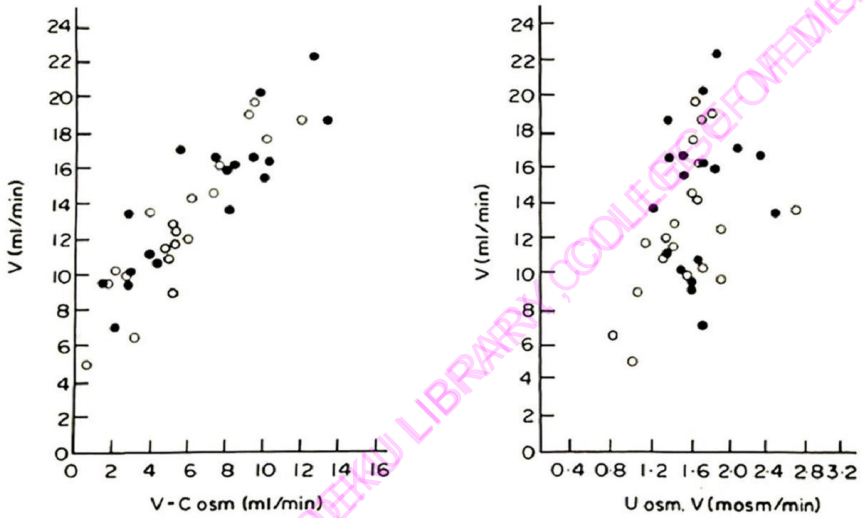

FIG. 1. Relationship between U osm.V, V–C osm and V in the SS and SC at 20°C and 40°C. Open circles, SC; closed circles, SS. Values for each group were plotted without distinguishing between 20° and 40° values. Note the complete admixture of points for SS and SC. Note also the fairly linear relationship between V and U osm.V.

(all points corresponding to values obtained only at 40°C) solute excretion changed without impressive alteration in urine flow. In the SCP on the other hand values for 20°C and 40°C could not be segregated because they were quite completely intermixed. In general solute excretion and urine flow rates appeared to change in the same direction (see also Fig. 1), the correlation coefficient being $+0{\cdot}34$ and the regression equation, $y = 0{\cdot}04x + 4{\cdot}94$.

In the AA, (Fig. 2b) a composite linear relationship was obtained, one for 20°C and another for 40°C, when V was plotted against V–C osm. The correlation between V and V–C osm was high at both 20°C ($r = +0{\cdot}96$) and 40°C ($r = +0{\cdot}86$), the corresponding regression equations being $y = 1{\cdot}29x + 2{\cdot}9$ for 20°C and $y = 0{\cdot}39x + 7{\cdot}3$ for 40°C. In the SCP no segregation occurred between 20° and 40° values, the correlation between V and and V–C osm high ($r = +0{\cdot}91$) and the regression equation being $y = 1{\cdot}01x + 5{\cdot}8$. It is of interest that the regression lines for the SCP at 20°C+40°C was nearly parallel to that in the AA at 20°, the slopes being 1·01 and 1·29 respectively.

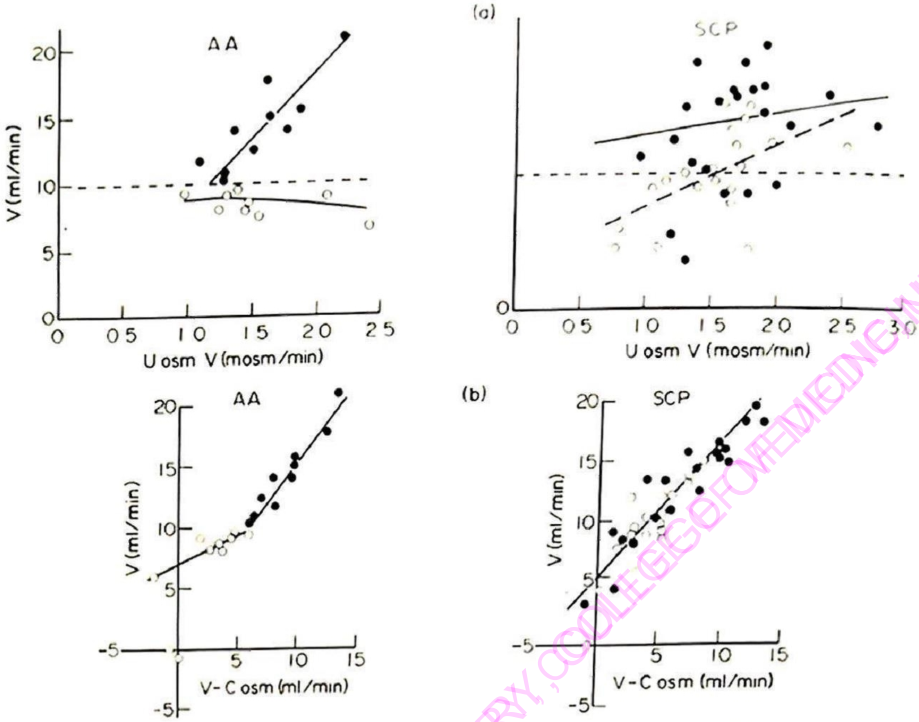

FIG. 2. (a) Composite relationship between U osm. V, and V in the AA at 20° and 40°. Absence of such relationship in the SCP (SS+SC). 20° and 40° values could not be segregated in the SCP (See also Fig. 1). Open circles, 40°C; closed circles, 20°C. Regression equations: AA at 20°C; $y = 0{\cdot}068x + 3{\cdot}0$. $r = +0{\cdot}70$. SCP at 20°C+40°C; $y = 0{\cdot}04x + 4{\cdot}94$. $r = +0{\cdot}34$. SCP at 20° only; $y = 2{\cdot}42x + 11{\cdot}37$. $r = +0{\cdot}24$. SCP at 40° only; $y = 4{\cdot}4x + 3{\cdot}02$. $r = +0{\cdot}55$. SCP. Solid line, regression line for all SCP at 20°C; broken line, regression line for 40°C.

(b) Relationship between V and V-C osm. Open circles, values at 40°C; closed circles, values at 20°C. Regression equations as follows: AA at 20°C; $y = 1{\cdot}29x + 2{\cdot}9$. $r = +0{\cdot}96$. AA at 40°C; $y = 0{\cdot}39x + 7{\cdot}3$. $r = +0{\cdot}86$.

Note: No differentiation between 20° and 40° values possible (see also Fig. 1) in the SCP Equation for pooled 20° and 40° data: $y = 1{\cdot}01x + 5{\cdot}8$. $r = +0{\cdot}91$.

DISCUSSION

Because a brisk combined water and osmotic diuresis was produced and maintained throughout the study, V is used here as a rough estimation of the rate of delivery of filtrate to the distal nephron and V–C osm to approximate sodium reabsorption in the ascending limb of the loop of Henle. In Fig. 2b, the lower slope at 40° compared with that at 20° in the AA subjects suggests a greater rate of sodium reabsorption per unit volume fluid delivery at this site at 40° than at 20°C. This, it is suggested, is probably secondary to the higher titre of circulating vasopression. The enhanced vasopression secretion in the heat has been clearly demonstrated by Segar & Moore (1968). Whether indeed vasopressin enhances sodium transport in the nephron is debatable (Berliner & Bennett, 1967).

It is suggested that the curve for the AA at 40°C represents largely juxtamedullary nephron activity. This interpretation is based on the following considerations: (1) Radigan & Robinson (1949) and also Kenney (1952, 1963) have shown that the intrarenal sympathetic activity increases in the heat. Since increased sympathetic tonus has been held to be as-

sociated with an increased juxtamedullary blood flow (Gauer, Henry & Behn, 1970; Pomerantz, Birtch & Barger, 1968), it is conceivable that filtration would also shift from cortical to juxtamedullary glomeruli. It is conceivable consequently, that juxtamedullary nephron activity preponderates at the 40°C employed in these studies. (2) Pomerantz, Birtch & Barger (1968) suggest that shift of filtration from long juxtamedullary nephrons to short cortical ones could occur during volume expansion and the reverse during an increased sympathetic drive. 20°C corresponds to volume expansion, for in the cold there is a shift of blood from skin and other peripheral areas to central vascular compartments (Glaser, Berridge & Prior, 1950; Hayward & Baker, 1968). 40°C corresponds to constriction of blood volume for blood moves from the central vascular compartments to the skin (Glasser *et al.*, 1950; Grayson, 1952; Sjostrand, 1953). Therefore the curve for the AA at 20° could represent mainly cortical nephron activity and at 40° mainly juxtamedullary nephron activity.

In the sickle cell patients, the lack of segregation between 20° and 40° values in Fig. 2b suggests that they have a functionally uniform population of nephrons. The almost identical slopes for the SCP (20°+40°) and for the AA at 20°C suggest, moreover, that the entire population in the SCP is functionally similar to the cortical nephrons in the AA. This interpretation is in keeping with the demonstration by van Eps *et al.* (1970a) in microangiographic studies that the vasa recta of the SCP are either absent or grossly abnormal and the observation of Bernstein and Whitten (1960) that pathological changes occur in the juxtamedullary nephrons early in life in the SCP. Indeed, van Eps *et al.* (1970b) have stated that the kidney of the SCP is like that of the beaver in lacking, functionally, the long-looped nephrons.

Figure 2a indicates further that the kidney of the SCP at either temperature behaves, with respect to the handling of solute and water, like that of the AA at 20°C for in both groups (AA at 20°; SCP at 20°+40°) solute excretion increased with the rate of delivery of fluid into the distal nephron. In the AA, at 40°C, varying amounts of solute could be excreted with little change in urine flow.

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