

Sodium and potassium concentrations in red blood cells and plasma in children with congenital heart defect

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The sodium and potassium concentrations of the red blood cells and plasma were investigated in 93 children with cardiac disease, most of them with congenital heart defect, and in 48 healthy children of the same age. The red blood cell sodium and potassium concentrations were constant within a narrow range in normal subjects, but varied profoundly in pathological conditions. Digitalis treatment caused RBC Na^+ and plasma K^+ levels to increase and the RBC K^+ level to decrease by blocking the Na^+-K^+ pump. The highest RBC Na^+ concentration was observed in critically ill patients with congestive heart failure treated with digoxin. An augmented RBC sodium value was found in heart malformations with left to right shunt and in congestive cardiomyopathy that was not treated, whereas in patients with right to left shunt lower RBC sodium, higher RBC potassium and plasma potassium values were registered without any treatment. In cases of hyperkinetic circulation without any congenital heart defect the value of RBC sodium was definitely low. A low sodium and a high potassium level of the RBC were found after total correcting heart surgery. It is concluded that measurement of changes in sodium and potassium concentrations of the red blood cells is not a reliable method for assessment of the efficacy of digitalis treatment. The results point to the accompanying phenomena at a cellular level in heart disease.

One of the essential properties of living organisms is that they are capable of maintaining a non-uniform distribution of material by means of their biological limiting membranes. One indication of this is the difference to be observed between the electrolyte concentrations of the extra- and intracellular spaces, which can be maintained only through the active metabolism of the cells. The process of ion exchange across the cell membrane consists of a number of components, the most important of which is the active ion transport [27]. In the cases

of Na^+ and K^+ , this is performed by the $\text{Na}-\text{K}$ pump [27, 28, 29, 33].

This phenomenon has been studied by many authors in connection with heart diseases, but mainly from the aspect of the cardiac glycosides acting specifically on Na^+ , K^+ -ATPase corresponding to the $\text{Na}-\text{K}$ pump [1, 22, 36]. At the same time, independently of the drug effect, the phenomenon has been investigated in congestive circulatory failure almost exclusively in adulthood [9, 14, 21, 30]. Such examinations in childhood, particularly in congenital heart disease, have

scarcely been done [32]. We therefore considered it interesting to study the Na^+ and K^+ concentrations of red blood cells (RBCs) in a large number of paediatric heart patients, mainly with congenital heart disease, in order to establish correlations between the changes and the type of the underlying disease or the characteristic pathological process.

PATIENTS AND METHODS

Examinations were made on the plasma and RBC electrolytes in 93 children with heart disease. The vast majority of the cases were diagnosed by haemodynamic examination. The results were compared with those for 48 healthy control children. The latter were of various ages and both sexes, in whom the examinations did not reveal any disease; they had not been subjected to any treatment.

The Na^+ and K^+ concentrations of the plasma and the RBCs were determined with a digital flame photometer. RBC electrolytes were measured with the method of Fortes-Mayer and Starkey [13]: RBCs were washed with an isoosmotic

MgCl_2 containing solution and haemolysed with saponin, and the electrolytes were examined flame photometrically. The results were expressed with reference to 1 litre plasma or 1 litre RBCs.

RESULTS

Table I gives the Na^+ and K^+ concentrations of the plasma and the RBCs for the controls. The plasma levels lay between the standard limits, while the RBC levels were found within a very narrow range and were fairly constant independently of age.

TABLE I

Plasma and red blood cell Na^+ and K^+ concentrations in 48 healthy children

	$\bar{x} \pm \text{SD}$
Plasma	$\text{Na}^+ = 139 \pm 3 \text{ mmol/l}$
Plasma	$\text{K}^+ = 4.2 \pm 0.5 \text{ mmol/l}$
Red blood cell	$\text{Na}^+ = 6.2 \pm 0.8 \text{ mmol/l}$
Red blood cell	$\text{K}^+ = 95.1 \pm 3.5 \text{ mmol/l}$

Table II lists the RBC and plasma Na^+ and K^+ concentrations of the

TABLE II

Red blood cell and plasma Na^+ and K^+ concentrations in children with heart disease in correlation with the severity of the condition and with the application of digoxin treatment

	Red blood cell		Plasma	
	Na^+ (mmol/l)	K^+ (mmol/l)	Na^+ (mmol/l)	K^+ (mmol/l)
	$\bar{x} \pm \text{SD}$	$\bar{x} \pm \text{SD}$	$\bar{x} \pm \text{SD}$	$\bar{x} \pm \text{SD}$
Controls (n = 48)	6.2 ± 0.8	95.1 ± 3.5	139 ± 3	4.2 ± 0.5
Patients without congestive heart failure, no digoxin treatment (n = 75)	6.5 ± 1.9	95.4 ± 5.0	139 ± 4	4.3 ± 0.6
Patients without congestive heart failure, digoxin treatment (n = 5)	8.7 ± 1.5	93.0 ± 4.4	137 ± 4	4.9 ± 0.5
Patients with congestive heart failure, digoxin not yet administered (n = 3)	7.7 ± 0.7	94.7 ± 3.7	138 ± 3	4.5 ± 0.4
Patients with congestive heart failure, digoxin treatment (n = 10)	15.0 ± 5.9	93.8 ± 7.2	140 ± 4	4.7 ± 0.5

heart patients, broken down into groups on the basis of the severity of the condition and the administration or not of digoxin. The patients in a compensated or subcompensated state who did not receive digoxin did not exhibit differences from those for the controls. An elevated RBC Na^+ level was observed in the compensated patients treated with digoxin and in the untreated patients with congestive heart failure, and the highest level was found in the digoxin-treated patients with congestive heart failure. In digoxin treated cases we received a slightly lower K^+ value of the RBCs and a higher value of K^+ of the plasma. Likewise the level of K^+ of the plasma was higher in cases with congestive heart failure that had not been treated with digoxin.

In Table III the results of digoxin-treated patients are presented. In every case the characteristics of acid-base conditions, other treatments and remarks concerning the patients are given. Every digoxin-treated patient received in addition furosemide and KCl. A higher Na^+ concentration of RBCs was found in every group, especially in the patients with left to right shunt and congestive heart failure. In every group there was a slight elevation in the plasma K^+ level. The K^+ level of the RBCs was lower in the group of patients with left to right shunt who were compensated, in those with congestive heart failure and those who were after surgery, but was elevated in the group with right to left shunt and who had congestive heart failure. The concentration of plasma

Na^+ was slightly lower in patients with cardiomyopathy and those after surgery. There were not significant changes in acid-base conditions; mostly alkaline changes were seen, although the measured alkalosis in those with a right to left shunt was the result of a strong replacement of NaHCO_3 .

Table IV shows the RBC and plasma Na^+ , K^+ concentrations of heart patients, broken down into groups on basis of the diagnosis. In patients with large left to right shunt the RBC Na^+ concentration was elevated. This was marked in patients who were receiving digoxin treatment, but an even higher concentration of RBC Na^+ was found in patients with congestive heart failure taking digoxin. In the two latter groups a lower RBC K^+ and higher plasma K^+ concentration was observed. (In the cases with large left to right shunt the ratio of pulmonary: systemic output was more than 2:1.) In patients with a right to left shunt who did not receive digoxin a lower level of Na^+ of the RBC and higher level of K^+ of the RBC and of the plasma was measured. Patients with congestive heart failure and right to left shunt who were treated with digoxin showed an elevated K^+ concentration in the RBC and the plasma, but in these cases the concentration of RBC Na^+ was also higher. In cases of hyperkinetic circulation without any congenital heart disease there was a definitely lower sodium concentration of the RBC and higher sodium concentration of the plasma. A lower level of K^+ and

TABLE III

Electrolyte and acid-base values in patients treated with digoxin

I. No congestive heart failure (n = 5)

1. Left to right shunt (n = 2)

Patient	Plasma (mmol/l)		Red blood cell (mmol/l)		pH	Standard bicarbonate (mEq/l)	pCO ₂ (kPa)	Diuretic treatment
	Na ⁺	K ⁺	Na ⁺	K ⁺				
K. J.	143	4.3	10.6	88.3	7.35	21.6	5.9	Furosemide
T. A.	137	4.9	7.9	97.5	7.38	23.0	5.5	Furosemide
\bar{x}	140	4.6	9.3	92.9	7.37	22.3	5.7	
\pm SD	4	0.4	1.9	6.5	0.02	1.0	0.3	

2) After total surgical correction (n = 3)

B. Z.	134	5.1	7.4	95.3	7.44	21.2	3.9	Furosemide Spironolacton
K. G.	135	5.5	7.8	88.2	7.41	24.6	5.5	Furosemide
M. E.	136	4.6	10.0	95.9	7.45	25.0	4.7	Furosemide Spironolacton
\bar{x}	135	5.1	8.4	93.1	7.43	23.6	4.7	
\pm SD	1	0.5	1.4	4.2	0.02	2.1	0.8	

II. Congestive heart failure (n = 10)

1) Left to right shunt (n = 6)

T. K.	144	4.9	16.1	91.3	7.46	22.2	4.0	Furosemide
K. M.	137	5.0	13.7	94.6	7.43	23.5	4.5	Furosemide
Sz. Cs.*	137	5.1	27.6	76.7	7.38	21.8	4.9	Furosemide
Á. A.	144	4.4	9.5	92.5	7.37	23.2	5.1	Furosemide
T. G.	137	4.8	19.9	93.3	7.39	24.6	5.6	Furosemide
F. J.	137	4.0	18.1	98.5	7.36	24.0	6.0	Furosemide
\bar{x}	139	4.7	17.5	91.2	7.39	23.2	5.0	
\pm SD	4	0.4	6.1	7.5	0.04	1.1	0.7	

* 6 hours before death

2) Right to left shunt (n = 2)

M. E.	131	5.0	8.5	105.0	7.40	25.5	4.4	Spironolacton Furosemide
L. K.	139	4.7	9.2	97.1	7.37	18.7	3.9	Spironolacton
\bar{x}	135	4.9	8.9	101.0	7.38	22.1	4.2	
\pm SD	6	0.2	0.5	5.7	0.02	4.8	0.4	

TABLE III (cont.)

Patient	Plasma (mmol/l)		Red blood cell (mmol/l)		pH	Standard bicarbonate (mEq/l)	pCO ₂ (kPa)	Diuretic treatment
	Na ⁺	K ⁺	Na ⁺	K ⁺				
3) <i>Cardiomyopathic patients</i> (n = 2)								
L. J.	136	3.8	12.0	93.4	7.42	24.1	4.7	Furosemide
R.M.	137	5.0	14.9	95.5	7.47	23.1	4.1	Furosemide
\bar{x}	137	4.4	13.5	94.4	7.44	23.6	4.4	
\pm SD	0.7	0.8	2.1	1.5	0.04	0.7	0.4	

higher level of Na⁺ of the RBC was observed in patients with cardiomyopathy and congestive heart failure. The latter difference was even more striking in cases of cardiomyopathy treated with digoxin. In postoperative cases where digoxin treatment was unnecessary, a low Na⁺ and a high K⁺ level of the RBC was seen. In contradiction to this, digoxin treated patients after total corrective surgical intervention showed an elevated RBC Na⁺, plasma K⁺ level and a depressed RBC K⁺ level.

DISCUSSION

The starting point of the present work was the assumption that the intracellular electrolytes do not always vary in parallel with the plasma electrolytes. Thus, the intracellular space, too, must definitely be taken into consideration in an assessment of the total electrolyte content of the organism (a possible deficiency or excess) [6]. The RBCs are a good model for studying the intracellular space, though their composition cannot be identified with that of other cells. The RBC is an atypical cell as it has no

nucleus and has a specialized function, but in numerous other investigations it has proved a useful model for studying both membrane transport and the intracellular electrolytes [1, 27, 29, 33].

The normal RBC electrolyte values differ to some extent in the various publications, especially in earlier works. Sieberth [31] compared the normal values in 27 reports between 1952 and 1978. The Na⁺ and K⁺ concentrations varied in the ranges of 6.2–24 mmol/l and 81–104 ml/l, respectively. Uniformly lower Na⁺ values have been reported in recent years and our present data were also low.

One of the aims of the present work was to detect the effect of digoxin on the Na–K pump (Tables II and III). Besides digoxin treatment, determining roles are played in the RBC electrolyte changes by the severity of the basic process and by the momentary situation of the patient's general condition. If there is a serious disturbance of the energy supply to the organism, a process begins to equal the ion difference between the cell and its environment. In a critically severe

TABLE IV

Red blood cell and plasma Na⁺ and K⁺ concentrations in children with heart diseases, classified according to the diagnosis

	Red blood cell				Plasma			
	Na ⁺ (mmol/l)		K ⁺ (mmol/l)		Na ⁺ (mmol/l)		K ⁺ (mmol/l)	
	\bar{x}	SD	\bar{x}	SD	\bar{x}	SD	\bar{x}	SD
CONTROLS (n = 48)	6.2±0.8		95.1±3.5		139±3		4.2±0.5	
PATIENTS WITH CONGENITAL HEART DEFECT								
1) without shunt								
1/a no congestive heart failure no digoxin treatment (n = 17)	7.0±3.2		94.0±4.5		140±3		4.2±0.6	
1/b congestive heart failure, digoxin not yet administered (n = 1)	7.0		96.8		135		4.9	
2) large left to right shunt								
2/a no congestive heart failure, no digoxin treatment (n = 16)	8.3±2.5		95.0±5.0		140±3		4.3±0.5	
2/b no congestive heart failure, digoxin treatment (n = 2)	9.3±1.9		92.9±6.5		140±4		4.6±0.4	
2/c congestive heart failure, digoxin treatment (n = 6)	17.5±6.1		91.2±7.5		139±4		4.7±0.4	
3) small left to right shunt;								
no congestive heart failure, no digoxin treatment (n = 14)	5.8±1.2		93.9±3.5		141±3		4.0±0.4	
4) right to left shunt								
4/a no congestive heart failure, no digoxin treatment (n = 12)	5.6±1.3		100.9±4.8		139±2		5.0±0.8	
4/b congestive heart failure, digoxin treatment (n = 2)	8.9±0.5		101.0±5.6		135±5		4.9±0.2	
HYPERKINETIC PATIENTS (n = 5)	4.0±0.8		95.3±3.9		144±2		4.3±0.3	
CARDIOMYOPATHIC PATIENTS								
a) congestive heart failure, digoxin not yet administered (n = 2)	8.0±0.6		93.7±4.5		139±1		4.3±0.3	
b) congestive heart failure, digoxin treatment (n = 2)	13.5±2.1		94.4±1.5		137±1		4.4±0.8	
PATIENTS WITH CONDUCTION DISTURBANCE (n = 5)	5.9±0.6		95.2±4.7		139±2		3.8±0.1	
Congenital heart defect after surgical correction								
a) no congestive heart failure, no digoxin treatment (n = 6)	5.7±0.9		99.2±4.0		137±5		4.3±0.4	
b) no congestive heart failure, digoxin treatment (n = 3)	8.4±1.4		93.1±4.2		135±1		5.1±0.5	

state it is necessary to take into account the possibility that the cell cannot ensure the energy needed for the continuous functioning of the Na-K pump which is about 20-30% of the total cell energy requirement [27, 33]. When our patients were classified according to severity, this showed up mainly in an increased RBC Na^+ level in the serious cases (Tables II and III). Most of these patients participated in digitalis treatment. Digitalis therapy is extensively used in childhood, especially in cases of congestive heart failure and supra-ventricular paroxysmal tachycardia [2, 4, 5, 18, 19]. Each of the digitalis treated patients with congestive heart failure also received furosemide and KCl. Furosemide blocks the membrane transport of Na^+ , K^+ directly [20] and affects $\text{Na}^+-\text{K}^+-\text{ATP-ase}$ [35]. Moreover the K^+ loss due to furosemide [2, 18, 19] has a direct effect on the cation membrane transport [8, 10, 26]. On the whole a strong increase of RBC Na^+ was found beside the increase of plasma K^+ and the decrease of RBC K^+ in all of the patients treated with digoxin, furosemide and KCl. Digoxin decreases the RBC K^+ level by blocking the Na^+-K^+ pump, augments the plasma K^+ level and also the RBC Na^+ concentration. In our investigated cases the plasma K^+ level increased due to digoxin and KCl therapy: this was dominant in relation to the antagonistic furosemide therapy. A moderate plasma Na^+ decrease was caused by furosemide in cardiomyopathic and post-operative cases (Table III).

Normal or rather alkaline tendencies in the acid-base balance were observed, although in cases with right to left shunt, the intensive NaHCO_3 substitution played an important role. Digitalis therapy is more effective in cases of alkalosis and hypokalaemia than in cases of acidosis and hyperkalaemia [19]. Table III shows that patients with left to right shunt, where a moderate alkalosis was found, displayed a higher RBC Na^+ and lower RBC K^+ . Acidosis and hyperkalaemia were characteristic of patients with right to left shunt; in these cases a moderate rise of RBC Na^+ was seen and the level of RBC K^+ was higher than normal. This might be interpreted in a way that digitalis is more effective in cases with left to right shunt, at least as regards the blocking of the Na^+-K^+ pump of the RBC membrane. Patients with congestive heart failure not treated with digitalis received individual therapy with antibiotics, diuretics and KCl. They did not display any essential acid-base changes. In some authors' opinion the concentration of Na^+ and K^+ in the RBC reflects digitalis treatment or intoxication better than does the level of digoxin in serum [11, 12, 23, 24].

Table II and III reveal the elevation of RBC Na^+ concentration as a consequence of digitalis treatment in both the compensated patients and patients with congestive heart failure. In comparison to RBC Na^+ increase in response to digitalis treatment alone, a still higher level was found in response to combined congestive heart

failure and digitalis treatment. An RBC Na^+ increase was also observed in some patients with congestive heart failure who had not received digitalis. Accordingly, the Na^+ elevation does not only result from digitalis treatment. Further, the data of Ford and Pedersen [12, 23] indicate that the RBC electrolyte situation has normalized after more than 2 months of digitalis treatment, through a compensatory mechanism, as we, too, could observe this in two patients. These data suggest that examination of the RBC Na^+ and K^+ concentrations and the finding of an elevated Na^+ concentration do not provide reliable signs of the effect of digitalis therapy.

As regards the explanation of the individual changes, the cause of the elevated RBC Na^+ concentrations in cardiomyopathies and in congenital diseases accompanied by a left to right shunt is presumably the weaker Na-K pump activity due to the poor oxygenization. Moreover, in cases with left to right shunt the occurrence of an alkaline tendency (most by in connection with diuretic therapy) may be an important factor. Alkalosis may cause the RBC Na^+ level to rise [1, 15, 16]. Two of the cardiomyopathic patients also showed metabolic alkalosis. We may assume that the low RBC Na^+ concentrations observed in children with hyperkinetic circulation might be related to the cause of the hyperkinesia, e.g. an enhanced beta-adrenergic reactivity. These children did not receive treatment, neither were there acid-base changes. One of the causes of the low RBC Na^+ and

the high RBC K^+ and plasma K^+ level in patients with right to left shunt could be due to the metabolic acidosis existing in these patients. The RBC Na^+ level is low in acidosis, but in the literature there are few data concerning this phenomenon [15]. The hyperkalaemia found in the plasma may also be brought in connection with this fact. Accordingly, the poorer oxygenization is compensated by the acidosis connected with the Na^+ and K^+ of the RBC. The rise of the RBC Na^+ level found in patients with right to left shunt who were treated with digoxin was probably due to the effect of digoxin and of the congestive heart failure.

Children with congenital heart defect after corrective heart surgery showed a low RBC Na^+ and a high RBC K^+ level 2-3 weeks after the operation. This RBC cation distribution is characteristic of young RBCs and those that have a higher energy level [3]. The pathologic electrolyte distribution found before the operation discontinued after total correction. In digoxin treated patients after surgery the well known effects of digoxin were seen: RBC Na^+ and plasma K^+ showed a higher, RBC K^+ a lower level.

Naturally, other factors, too, may have an influence on the intracellular electrolyte composition. Gárdos [17] showed the role of intracellular Ca^{2+} in the migration of K^+ across the cell membrane. The cell electrolyte composition is known to be affected by the intracellular pH, the membrane structure, certain hormones, the pros-

taglandins, the cyclic nucleotides, oxidant effects and various drugs. The role of some of these has been elucidated but the details are far from clear. Moreover, the newly discovered natriuretic hormone may also play a role in the pathophysiology of various heart diseases, mostly where atrial pressure is affected by stenosis, shunt or tachycardia [7, 25]. In the regulation of Na^+ membrane transport, however, the part of the natriuretic hormone is uncertain [34].

Our data permit a number of conclusions. Changes in the RBC ion composition occur with different characteristics in the various heart patient groups but partly independently of the plasma. The change in the plasma Na^+ or K^+ level was in excess of ± 2 SD in 11 cases, compared with 42 cases for the RBC Na^+ or K^+ level. In those patients where the value of plasma Na^+ or K^+ was over ± 2 SD in every case, the change of RBC Na^+ or K^+ was of the same degree. It looks as if the changes in the RBC Na^+ or K^+ levels were more distinct and characteristic than those of the plasma. The 11 cases where changes in the plasma Na^+ or K^+ levels were observed were divided between various groups of patients, so no conclusion could be drawn from these.

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