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ORIGINAL ARTICLE

Plasma and erythrocyte relationship of catecholamines in haemodialysis patients

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Abstract

The function of the autonomic nervous system is based on reciprocal interaction between the sympathetic and parasympathetic parts, most frequently in the form of antagonistic action on target organs. The main mediators of the sympathetic nervous system in the effectors part are catecholamines (CA), which are involved in various physiological processes. Moreover, CA also has a profound effect on the kidneys, being factors that impact on renal haemodynamics, and have been reported to be altered in pathological disorders, e.g. extracellular volume expression, hypertension and cardiovascular complications. The increased sympathetic nerve activity, at least in part, can explain the raised in plasma CA observed in chronic kidney diseases. Furthermore, plasma CA levels in ureamic patients cannot be considered a reliable index of sympathetic activity, due to existence of many factors which may affect their values. In addition, CA released into the circulation, as one of many substances, may penetrate across the cellular membranes of erytrocytes (RBC). Taking these observations together, the aim of the presented study was to investigate for the first time the plasma and erythrocyte relationship of catecholamines in haemodialysis. The studies were performed among 37 haemodialysed patients who were inhabitants of the Lublin commune. Plasma and intracellular concentration of CA were measured prior to and following haemodialysis by high performance liquid chromatography with electrochemical detection. The results suggest that RBC are able to accumulate CA at the stage of terminal renal failure; in addition, the levels of adrenaline and dopamine in RBC depend on the accumulation of urea in plasma. It was also found that the dynamic changes in concentration of RBC adrenaline are an independent predictor of mortality in haemodialysis patients.

Key words

chronic kidney disease, catecholamines, erythrocytes, hemodialysis

INTRODUCTION

Chronic kidney disease (CKD) is a syndrome developing as a result of congenital or acquired diseases of the urinary tract, which is a consequence of end-stage renal failure. Nowadays, CKD is a critical and rapidly growing global health problem. The prevalence of chronic kidney disease is about 10–16%, mainly in the elderly [1, 2]. Clinical manifestations of CKD may include a variety of metabolic dysfunctions, such as accumulation of uraemic toxic substances leading to neurological disorders, in particular, sympathetic dysfunction.

The function of the autonomic nervous system is based on reciprocal interaction between the sympathetic and parasympathetic parts, most frequently in the form of antagonistic action on target organs. The main mediators of the sympathetic nervous system in the effectors part are catecholamines (CA): noradrenaline (NA), adrenaline (A) and dopamine (DA). Neurotransmitters are biogenic amines derived from the amino acid tyrosine and possess a catechol group with an attached amino group [3, 4]. Ther are synthesized both in the brain and in the peripheral organs and cells, such as the adrenal medulla, non-neuronal gut cells, platelets and lymphocytes [4].

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These molecules involved in various physiological process, *inter alia,* respond to stress. Moreover, CA also has profound effects on the kidney [5], being factors that impact on renal haemodynamic, and have been reported to be altered in pathological disorders, e.g. extracellular volume expression, hypertension and cardiovascular complications [6].

The increased sympathetic nerve activity, at least in part, can explain the increased in plasma catecholamines observed in CKD. It is also known that catecholamines clearance is decreased in CKD. For example, NA clearance is reduced by 20% in mild renal failure and by up to 40% in patients on haemodialysis (HD) [7, 8]. Catecholamines released into the circulation, as one of many substances, may penetrate across the cellular membranes as passive diffusion, active transport, sodium and potassium pump or anion changing system [3, 9, 10, 11]. In the literature [9, 12, 13], there have been some reports about the role and transport of circulating catecholamines in human red blood cells (RBC). Many authors [9, 12, 14, 15] in their series of experiments have confirmed that human erythrocytes could transport CA from their sites of release to their sites of elimination, or are subsequently inactivated by the red cells. Moreover, red blood cells may contribute to extraneuronal metabolism of CA by the processes of methylation or sulfoconjugation, although the nature and magnitude of this phenomenon still remains unclear. Especially little is known about the role and transport of circulating CA in RBC patients who have CKD. Furthermore, plasma CA levels in uraemic patients

cannot be considered a reliable index of sympathetic activity; studies using microneurographic techniques confirmed that sympathetic overactivity is often present in uraemia [16].

Therefore, the aim of the presented study was to investigate the plasma and erythrocyte relationship of catecholamines in haemodialysis.

MATERIALS AND METHOD

The studies were performed among 37 hemodialysed patients who were inhabitants of the commune Lublin – 17 women and 20 men, aged 26–85 years, with the median duration of haemodialysis of 3.5 years. The control group comprised 22 healthy subjects matched for age to the study group, undergoing prophylactic examinations at the Department of Laboratory Diagnostics at the Medical University in Lublin, south-east Poland. Standard phlebotomy techniques were used to obtain samples. The study protocol was approved by the local Ethics Committee at the Medical University in Lublin. Written informed consent was obtained from each patient qualified to participate in the study. All patients underwent a clinical examination at the Department of Nephrology of the Medical University in Lublin. Samples of venous blood were collected to dry tubes without anticoagulant, and centrifuged immediately. The samples were either used for measurements immediately or stored frozen at -80 °C. In the serum, concentration of creatinine, total protein, albumin and urea were measured prior to and following haemodialysis using routine laboratory methods. Similarly, haematology testing was performed with blood.

Sampling. Analysis of levels of catecholamines in biological fluids has necessitated the use of highly sensitive analytical techniques.

Extraction of catecholamines from erythrocytes. Blood was collected into K_3EDTA (7.5 ml) via intravenous catheter, after the patients had rested for 20 min in the supine position. To isolate erythrocytes, the blood samples were subjected to low speed centrifugation (225×g, 15 min) at +4 °C, and aspirated to the supernatant platelet rich plasma. The samples were then centrifuge at high speed (10,000×g, 10 min) and aspirate the platelets poor plasma and buffy coat layers. The erythrocytes were then washed with an equal volume of physiological saline and centrifuged (10,000×g, 10 min) three times at +4 °C. After that, 1 ml of densely-packed erythrocytes were added to 1 ml of ice-cold deionized water. The lysis of erythrocytes were resuspended in equal volumes (2 ml) into the tubes containing 120 µl of a preservative solution (900 mg of EGTA and 700 mg of reduction glutathione in 8 ml of 0.5 N NaOH). After vigorous agitation, the samples were stored at -80 °C until assayed. Extractions of catecholamines from plasma and erythrocytes lysate was carried out with a ChromSystems Reagent kit for HPLC analysis. Plasma and intracellular concentration of catecholamines were measured prior to and following haemodialysis by the method of high performance liquid chromatography with electrochemical detection (HPLC-ED).

Statistical analysis. All values are expressed as mean and standard deviations. Distributions of the analyzed variables were tested using the Shapiro-Wilk test. For a comparison of the obtained results of investigations in the case of normally distributed variables, the Student t-test was used. For variables that did not demonstrated compliance with the normal distribution, the non-parametric U Mann-Whitney test was used. Correlations between variables were investigated using Spearman`s test. In all tests, p-value <0.05 was considered significant. All statistical analyses were conducted using the Statistica 10.0 software. In order to investigate the diagnostic value of erythrocytes and plasma catecholamines were plotted by the ROC (Receiver Operating Characteristic) curve, and the area under the curve (AUC) was calculated to describe the capability of the markers to discriminate between dead and live haemodialysis patients during two years observation. For this, MedCalc ver. 11.4.3.0 software was used.

RESULTS

Baseline characteristics of the study population are shown in Table 1 and selected laboratory parameters in Table 2. In the examined group of haemodialysis patients, significant differences were found concerning creatinine, blood urea nitrogen (BUN), total protein (TP), albumin, hematocrit (HCT),haemoglobin (HGB), red blood cells (RBC), mean corpuscular haemoglobin concentration (MCHC) mean cell corpuscular volume (MCV), in comparision with the control group. Plasma and erythrocyte catecholamines of the analysed population are shown in Table 3. As a result of the conducted studies, it was found that the plasma levels of noradrenaline (550.36 pg/ml) was significantly elevated in comparison with the control group (234.93 pg/ml p<0.001),

Table 1. Baseline characteristics of the study population

Parameter	HD patients N = 37	Reference group N = 22
Age (years)	67.02 ± 12.89	58.2 ± 13.1
BMI (kg/m^2)	26.4 ± 4.57	21.5 ± 4.1
Systolic blond pressure (mmHg)	124.64 ± 12.49	121.8 ± 12.3
Diastolic blood pressure (mmHg)	74.41 ± 11.59	73.6 ± 6.7
Pulse pressure (mmHg)	50.23 ± 13.28	50.1 ± 10.2

Table 2. Selected biochemical and haematological parameters of HD patients and reference group

Parameter	HD patients N = 37	Reference group N = 22
Creatinine (mg/dl)	9.1 ± 1.8***	0.8 ± 0.2
BUN (mmol/l)	19.95 ± 4.72***	4.23 ± 1.24
TP (g/dl)	6.75 ± 0.75**	7.2 ± 0.3
Albumin (g/dl)	3.76 ± 0.43**	4.3 ± 0.4
HCT (%)	31.91 ± 3.34***	41.28 ± 2.82
HGB (g/dl)	10.50 ± 1.21***	14.09 ± 0.7
RBC (10^{12}/l)	3.47 ± 0.39***	4.58 ± 0.032
MCV (fl)	90.42 ± 10.62	90.15 ± 2.65
MCH (pg)	30.26 ± 2.15	30.8 ± 1.33
MCHC (g/dl)	32.88 ± 1.56***	34.18 ± 1.13
Dialysis period (h)	4.6 ± 0.2	

*** p<0.001 **p<0.01 * p<0.05 – HD patients vs. reference group

Table 3. Plasma and erythrocyte catecholamines of the analyse population

	HD patients N = 37	Reference group N = 22	P
NA [pg/ml] Me			
Plasma	550.36	234.93	<0.001
RBC	153.21***	234.89***	>0.05
E/P	0.25	1.07	<0.001
A [pg/ml] Me			
Plasma	56.49	45.01	>0.05
RBC	263.36***	132.18***	<0.001
E/P	3.92	2.88	>0.05
DA [pg/ml] Me			
Plasma	39.04	39.94	>0.05
RBC	126.05***	294.1***	<0.001
E/P	2.75	7.8	<0.01

*** p<0.001 **p<0.01 * p<0.05 – RBC vs. Plasma

whereas plasma concentration of adrenaline (56.49 pg/ml; p>0.05) and dopamine (39.04 pg/ml, p>0.05) were not elevated. Furthermore, no significant differences were found between the level of NA in erythrocytes (p>0.05) in both study population, as opposed to values of A (p<0.001) and DA in RBC (p<0.001) (Tab. 3). The results presented in Table 3 indicate statistically significant differences between CA in RBC and plasma (p<0.001). In other words, the concentration of A, DA in RBC were higher than those found in plasma. Accumulation of circulating catecholamines in erythrocytes was compared to rising plasma levels of catecholamines. Accumulation of CA in RBC was estimated by the ratio of their erythrocytes/plasma (E/P) concentration. The ratio of NA (0.25; p<0.001) and DA (2.75; p<0.01) in the group of haemodialysis patients were significantly lower than those observed in the control group (NA 1.7; DA 7.8) (Tab. 3). After taking into consideration the patients gender, no significant differences were found in the plasma and erythrocytes CA depending on the patients gender. CA concentration before and after HD treatment are presented in Table 4. The results indicated that NA (550.36 pg/ml) in plasma had a significantly lower concentration after haemodialysis treatment (417.98 pg/ml p<0.001). However, values for NA (153.21 pg/ml) and A (263.36 pg/ml) in RBC before haemodialysis were higher than after haemodialysis (NA 144.32 pg/ml A 253.14 pg/ml), whereas an inverse relationship was noted for DA before HD (126.05 pg/ml) and after HD (142.07 pg/ml). The observed differences were slight and not statistically significant. Univariate correlations of circulating CA concentrations are presented in Table 5. According to the correlations analysis, the plasma levels of A were directly proportional to the concentration of urea before and after haemodialysis (r_s= 0.33 p<0.05 and r_s= 0.34 p<0.05). Therefore, it was confirmed that there was a negative correlation between the values of A, DA in RBC and levels of urea before and after haemodialysis (Tab. 5). A statistically significant negative correlation was found to exist between the E/P ratio of A (before and after HD) and urea values (r_s= -0.38 p<0.01;r_s= -0.37 p<0.01). Changes in the value of catecholamines induced by haemodialysis treatment are

Table 4. Catecholamines concentration before and after HD treatment

	Before HD N = 37	After HD N = 37	P
NA [pg/ml] Me			
Plasma	550.36	417.98	<0.001
RBC	153.21	144.32	>0.05
E/P	0.25	0.35	>0.05
A [pg/ml] Me			
Plasma	56.49	40.70	>0.05
RBC	263.36	253.14	>0.05
E/P	3.92	4.88	>0.05
DA [pg/ml] Me			
Plasma	39.04	43.64	>0.05
RBC	126.05	142.07	>0.05
E/P	2.75	2.72	>0.05

Table 5. Univariate correlations of serum urea in the study population

Correlates	rs	P*
Before HD RBC A [pg/ml] vs. After HD Urea [mmol/l]	–0.39	< 0.01
Before HD RBC A [pg/ml] vs. After HD Urea [mmol/l]	–0.40	< 0.01
Before HD RBC DA [pg/ml] vs. After HD Urea [mmol/l]	–0.36	< 0.01
Before HD Plasma A [pg/ml] vs. After HD Urea [mmol/l]	0.33	< 0.01
Before HD Plasma A [pg/ml] vs. After HD Urea [mmol/l]	0.34	< 0.01
Before HD R/P A vs. Before HD Urea [mmol/l]	–0.38	< 0.01
Before HD R/P A vs. Before HD Urea [mmol/l]	–0.37	< 0.01

*Significant correlations assessed by Spearman correlation method

Table 6. Changes in value of catecholamines induced by haemodialysis treatment among dead and living patients during two-year observation

	CA	Dead N = 28 $\bar{x} \pm SD$ Me	Living N = 9 $\bar{x} \pm SD$ Me	P
Plasma	Δ NA	–249.19 ± 345.7 –257.34	–92.58 ± 411.4 –226.09	> 0.05
	Δ A	–31.85 ± 124.39 –10.9	7.14 ± 30.66 10.51	> 0.05
	Δ DA	2.12 ± 22.54 2.64	–1.77 ± 31.33 –4.74	> 0.05
RBC	Δ NA	–142.94 ± 475.54 –31.58	24.8 ± 165.4 –2.09	< 0.01
	Δ A	–91.41 ± 564.57 –21.225	165.39 ± 438.19 75.56	< 0.01
	Δ DA	15.97 ± 194.92 –10.37	–42.57 ± 243.27 –13.57	> 0.05

presented as the delta values (Δ) among the dead and living patients (Tab. 6). This ratio was calculated based on the difference in concentrations of catecholamines determined before and after haemodialysis treatment. Significant differences were observed between Δ NA RBC (p<0.01) and Δ A RBC (p<0.01) among dead and living patients during two years of observation. In contrast, no significant differences were observed in the other values of E/P. Figure 1 shows the ROC curve for the delta RBC adrenaline values. Diagnostic sensitivity and specificity of delta A RBC positive and negative

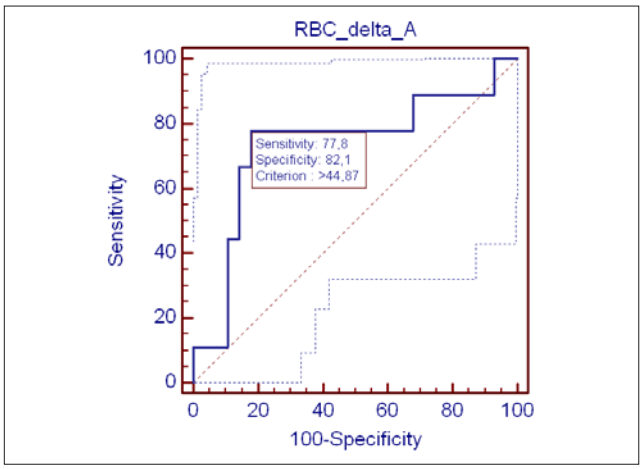

Figure 1. Receiver-operating characteristics curie for Δ A RBC in haemodialysis patients

predictive values for cut-off value 44.87 pg/ml were 77.8% and 82.1%, respectively. The area under the curve equal to 0.74 ($p<0.01$) indicates a good diagnostic usefulness of RBC adrenaline as an independent predictor of mortality.

DISCUSSION

The majority of reports [17, 18] on CA in haemodialysis patients describe disturbances of the plasma levels of CA. The presented study confirms the results of previous studies in which plasma catecholamines are increased in HD patients. It has to be pointed out that an increased level of CA in plasma is common and due to impaired central dopaminergic control. Recently, research on metabolizes circulating CA have focused on renalase. This is a new, flavin-adenin dinucleotide (FAD) containing hormone secreted by the kidneys and circulates in the blood, and may play a key role in metabolizing CA [19,20,21]. As blood levels are markedly reduced in end-stage renal disease, this suggests a higher concentration of plasma catecholamines [22]. Renalase deficiency may contribute to the heightened sympathetic tone observed in CKD. What is interestingly is that various stressors are able to stimulate levels and production of CA in adipocytes [23]. However, there is still a lack of information concerning the full characterization of adipocytes and CA production.

As mentioned earlier, plasma CA levels in uraemic patients cannot be considered a reliable index of sympathetic activity [16]. Thus, in the presented study, level of CA in RBC were determined for the first time in haemodialysis patients. Likewise, the accumulation of catecholamines in erythrocytes was compared to plasma levels of catecholamines. This demonstrated that in haemodialysis patients the levels of A and DA in RBC were significantly elevated compared to plasma concentration, while NA values in RBC were lower than in plasma. This suggests that RBC are able to uptake plasma CA. In addition, this is confirms by the ratio of their erythrocytes/plasma concentration (E/P), with no assumption as to whether CA cross the RBC membrane or remain absorbed at their surface. Thus, the response of human RBC to increased concentrations of CA in plasma is dependent on the amine structure and on the plasma concentration. However, the data presented here are consistent with a study by Alexander [24] which found that under physiological conditions, DA, NA and A concentrations in blood cells are higher than those in plasma. This fact might reflect homeostasis due to the adaptive mechanism of the accumulation of CA in RBC. As a matter of fact, the increased ability of erythrocytes to accumulate dopamine and adrenaline confirms the existence of active transport [9].

Analysis of the results obtained in the control group indicated a slight difference between RBC and plasma concentration of NA (RBC NA 234.89 pg/ml; plasma NA 234.93 pg/ml). This suggests that passive transport is involved in the transmission of NA through the cell membrane. Taken together, the accumulation CA in RBC markedly reduced the level of renalase in plasma patients with end-stage renal disease [25], and the presence of processes of methylation or sulfoconjugation in RBC [26], it seems that RBC might play a role in metabolizing CA. In the haemodialysis patients in the presented study, a significant relationship was noted between concentrations of A and DA in RBC and the level of urea in plasma (Tab. 5). These studies support the notion that levels of DA and A in RBC might be part of the mechanism of uraemic toxins. Urea is the main uraemic toxin and the nitrogenous end-product of protein metabolism; it is also the most abundant nitrogenous product that accumulates in CKD. Thus, it is possible that urea could cause a significant reduction in CA transport from plasma to RBC during HD. As confirmed by the results, in haemodialysis patients the level of CA in RBC are decreased, compared with the values of CA in RBC of the control group. It is interesting to note that in the research by Bonomini and Sirolli [27], the uremic toxins were significantly influenced by the viability of RBC. Thus, uraemic toxins induce and modify the quantity and quality composition of phospholipids of red blood cells membrane. On the other hand, the oxidative stress accompanying chronic renal failure and haemodialysis processes may cause a number of interferences [28, 29, 30, 31]. Disturbances of the chemical composition of the erythrocyte membrane, anomaly of the haemoglobin structure, disturbances of glycolytion and oxidation reduction enzymes, in general leads to a shorter RBC lifespan and contributes to renal anaemia.

Raised sympathetic activity is now recognized as an important mechanism involved in cardiovascular complication in humans. During two years observation, nine deaths were observed through a cardiac event. In agreement with data from the medical literature, that in the course of chronic kidney insufficiency due to renal impairment, nearly 50% of deaths among patients with end-stage renal disease were due to cardiovascular diseases [32]. The risk of death is higher in the haemodialysed than the general population [1]. In the presented study, diagnostic sensitivity and specificity of Δ A RBC for the cut-off value 44.87 pg/ml were calculated on the basis of this result, and it can be supposed that the dynamic change in the concentration of adrenaline in RBC of HD is an independent predictor of mortality. It may also be speculated that the CA release from RBC would participate in the regulation of the immune processes and inflammatory responses contributing myocardial remodeling. This hypothesis is similar to that in which T cells also can release catecholamines, and are an integral part and potent modulators of these neuro-endocrine-immune and inflammatory interactive networks [4, 33, 34]. Nonetheless, the presented data should be cautiously interpreted because

the development of cardiovascular complications are complex processes. We are at the beginning of solving the problem of whether dynamic change in the concentration of adrenaline is a causative factor of mortality, or just an 'innocent bystander'. On the other hand, it is known for sure that the role of plasma CA, especially NA as an indicator of cardiovascular events in HD patients, was previously well established [35]. In Mallamaci`s study, interactions between NA and Asymmetric Dimethyl Arginine (ADMA) levels among patients with end-stage renal disease, remains an independent risk factor for predicting adverse cardiovascular outcomes, and are strongly associated with left ventricular concentric hypertrophy and left ventricular systolic dysfunction [35]. Prospective studies are needed to better elucidate the role of RBC in the metabolic CA of haemodialysis patients.

CONCLUSIONS

The presented results suggest that RBC are able to accumulate CA at the stage of terminal renal failure; in addition, the levels of A, DA in RBC depend on the accumulation of urea in plasma. It was also found that the dynamic changes in concentration of RBC adrenaline are an independent predictor of mortality in haemodialysis patients.

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