# A Study of Lithium Sodium Countertransport in Erythrocytes of Patients with Essential Hypertension.

Z H Tanvir, S J Khan,F Munawar
Department of Physiology, K.E.M.C. Lahore and
Nishter Medical College, Multan.
*Correspondence to : Dr Zafar Hussain*

*Lithium-sodium countertransport activity in erythrocytes was studied in 15 mild and 15 moderate essential hypertensives and 20 age and sex matched control subjects. There was statistically highly significant (P <0.001) increase in Vmax of lithium-sodium countertransport in essential hypertensives as compared to that of controls. The difference in Vmax of countertransport activity between mild and moderate essential hypertensives was also highly significant (P< 0.001). There was a highly significant correlation (P<0.001, r=0.75, 0.89, 0.92) between Vmax and parameters like diastolic blood pressure, age and body weight of moderate essential hypertensives. The correlation of these parameters with Vmax in mild essential hypertensives. The correlation of these parameters with Vmax in mild essential hypertensives was significant (P<0.05, r=0.70, 0.50)*

*Key Word: Lithium-sodium countertransport, Maximal transport rate (Vmax) Essential hypertension.*

In the vast majority of patients with essential hypertension, the aetiology is unknown and they are classified as having essential hypertension. Approximately 90% of all persons suffering from hypertension are cases of essential hypertension.[1]

Essential hypertension appears to result from a combination of genetic and environmental factors, of which an excess of sodium intake is the most important.[2,3] Sodium is transported through several pathways across the human red cell membrane. One of these modes of sodium movement in human red cell is lithium-sodium countertransport. This system promotes the exchange of sodium for sodium lithium for lithium, or lithium for sodium and appears to be an operational mode of sodium-hydrogen exchange.[4,5,6,7,8.]

As this system can produce lithium against its electrochemical potential gradient, which is driven by an oppositely directed electrochemical potential gradient of sodium, it is called the lithium-sodium countertransport system. Canessa et al (1980)[9] explored the relation between the distribution of the maximum rate Vmax of red cell lithium-sodium countertransport and the distribution of essential hypertension in the human population. They found that this system is more than twice as active in the red cells of patients with essential hypertension as in those of normal control subjects. Elevated Vmax of lithium countertransport among hypertensive subjects and their children was also reported in several other studies. [10,11,12,13,14,15]

Although this consistent finding raises the possibility that this abnormality of ion transport is the cause of essential hypertension which may prove to be valuable diagnostic marker for the disease, yet the relationship between elevated red cell sodium countertransport and the pathogenesis of essential hypertension is still obscure and requires further research.[10] It is therefore, hoped that this study will certainly prove useful in exploring further the relationship between sodium countertransport and essential hypertension.

## Material and Methods:

The study was conducted on 15 (8 males and 7 females) cases of mild essential hypertension (diastolic blood pressure between 90-104 mmHg) and 15 cases of moderate essential hypertension (diastolic blood pressure between 105-114 mmHg). All cases were diagnosed carefully after taking detailed history, complete physical examination and laboratory investigations.

In the control group, 20 (10 males and 10 females) normotensive subjects were included. They were labeled normotensive after taking detailed history, complete physical examination and blood pressure recording with diastolic blood pressure less than 90 mm Hg (average of three readings) on two separate occasions at least one week apart.

Lithium sodium countertransport in the subjects' red cells was measured according to the method

described by Woods et at (1982).[16] Blood for analysis was drawn into tubes containing ammonium salts of ethylenediamine tetra-acetic acid (EDTA) and was processed. The red cells were separated, washed and loaded with lithium by suspending in a medium containing lithium chloride. The lithium loaded cells were incubated in sodium free and sodium enriched media for measurement of lithium efflux.

Portions of cell suspension were diluted with distilled water and lithium countertransport was measured by flame phosomesex. Vmax of countertransport (millimoles of lithium efflux per litre of red blood cells per hour) was computed from the linear regression of lithium loss as a function of time.

## Results:

There was a highly significant (P<0.001) increase in Vmax of lithium sodium countertransport both in mild and moderate essential hypertensives as compared to that in controls. The elevation in Vmax of countertransport activity was also highly significant (P<0.001) in moderate essential hypertensives than that in mild cases (Tables 1 and 2, Figures 1and 2).

**Table - 1** Comparison of Mean Lithium Efflux mmol/l RBCs(means ± SD)

| Time (hrs) | G1 | G2 | G3 | P Value |
|---|---|---|---|---|
| 0 | 0.009±0.010 | 0.003±0.005 | 0.005±0.080 | P>0.05(NS*) |
| 2 | 0.36±0.03 | 0.75 ± 0.02 | 0.86 ± 0.06 | P>0.001(HS**) |
| 4 | 0.72 ±0.04 | 1.52 ± 0.04 | 1.67 ± 0.09 | P>0.01(HS**) |

NS* Non significant (G2,G3 vs G1)
HS** Highly significant (G2,G3 vs G1)

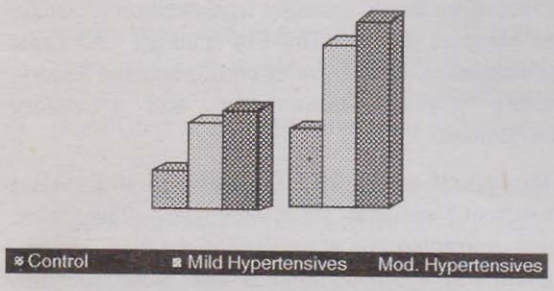


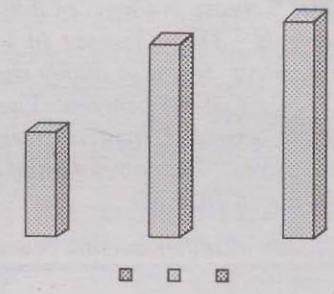

Fig.1: Comparison of mean lithium efflux between controls, mild and moderate essential hypertensives.

There was highly significant (P<0.001) correlation between Vmax and parameters of diastolic blood pressure (r=0.75), age (r=0.89) and body weight (r=0.92) in moderate essential hypertensives while it was significant (P<0.05, r=0.63, 0.70, 0.50) in mild essential hypertensives.

**Table-2** Comparison of Vmax of Lithium sodium counteransport(mean ± SD)

| G1 | G2 | G3 | P value |
|---|---|---|---|
| 0.18 ± 0.01 | 0.38 ± 0.01 | 0.42 ± 0.02 | P>0.001(HS*) |

Vmax in millimoles per litre of red blood cells per hour.
HS* Highly significant (G2, G3 vs G1; G3 vs G2)



G1. Controls
G2 Mild essential hypertensives
G3 Moderate essential hypertensives

Fig.2 Comparison of Vmax of Lithium sodium countertransport between controls, mild and moderate essential hypertensives.

The correlation of V Max with diastolic blood pressure (r=0.02), age (r= 0.09) and body weight (r=0.25) was non-significant (P>0.05) in control subjects.

## Discussion

Abnormalities in erythrocyte membrane sodium transport in patients with essential hypertension have been recognized for many years. It is suggested that such studies can help to differentiate between essential and secondary hypertension.

Increase in lithium sodium countertransport activity reflects the abnormal kinetic properties of sodium-hydrogen exchange either functional or structural. Functional disturbance can be either phosphorylation of the transporter or increased cytoplasmi : calcium both of which are genetically determined.

Abnormally raised sodium-hydrogen exchange and hence lithium sodium countertransport induce sodium and water retention, facilitates smooth muscle contraction, increases total peripheral resistance and causes hypertension .[7,13,14]

In our study, we observed that increase in Vmax of countertransport activity in mild and moderate essential hypertensives was highly significant (P<0.001), as compared to that of controls. The difference in Vmax of lithium sodium

countertransport between mild and moderate essential hypertensives was also highly significant (P<0.001).

Our results are in accordance with those of Semplicini et al (1992 b),[8] Canessa (1994),[14] Carr et al (1995),[15] Canessa et al(1991),[17]. Nosadini et al (1991), [18] Trevisan et al (1992) [19] and petrov et al (1994). [20]

The correlation of Vmax with blood pressure, age and body weight of moderate essential hypertensives was highly significant (P<0.001),while in case of mild essential hypertensives, it was significant (P <0.05).Vmax was non-significantly (P> 0.05) correlated to blood pressure, age and body weight of the control subjects.Thus, it is evident that Vmax of countertransport activity increases with increase in blood pressure, age and body weight in essential hypertensives. Several other studies yielded the same findings.[7,13,17,21]

In conclusion, lithium sodium countertransport, a mode of operation of sodium hydrogen exchange can be regarded as a dependable marker for essential hypertension. It is positively correlated to blood pressure, age and body weight of essential hypertensives.
Moreover, it is genetically determined and is not affected by dietary intake of sodium.

**References**


1. Garay RP, Meyer P. A new test showing abnormal net Na+ And K+ fluxes in erythrocytes of essential hypertensive patients. Lancet 1979; 1: 349-53.
2. Watt GCM, Foy CJW, Hart JT. Comparison of blood pressure, sodium intake, and other variables in offspring with and without a family history of high blood pressure. Lancet 1983; 1: 1245-48.
3. Garay RP. Kinetic Aspects of Red Blood Cell sodium Transport Systems in Essential Hypertension. Hypertension 1987; 10 (Suppl II): I.11-I.14.
4. Garay R, Roasti C, Meyer P. Sodium transport in primary hypertension. Klin Wochenschr 1987; 65 (Suppl 8): 66-68.
5. Wiley JS, Cooper RA. A Furosemide-Sensitive Cotransport of Sodium plus Potassium in the Human Red Cell. J Clin Invest 1974; 53: 745-55.
6. Sarkadi B, Alifimoff JK, Gunn RB, Tosteson DC. Kinetics and Stoichiometry of Na-Dependent Li Transport in Human Red Blood Cells. J Gen Physiol 1974;72:249-65.
7. Semplicini A, Marzola M, Mozzato MG, Ceolotto G, Campagnolo M, Giusto M, Pessina AC. Red cell Li+ /Na+ countertransport and cardiovascular risk factors in hypertension. Ital J Mineral Electrolyte Metab 1992a; 6:207-15.
8. Semplicini A, Lusiani L, Marzola, M, Ceolotto G, Mozzato MG, Zanette G, Donadon V, Stefanini MG, Zanuttini D, Pessina AC. Erythrocyte Li+/Na+ and Na+/H+ exchange, cardiac anatomy and function insulin-dependent diabetics. Eur J Clin Invest 19992b;254-59.
9. Canessa M, Adragna N, Solomon HS, Connolly TM, Tosteson DC. increased sodium-lithium countertransport in red cells of patients with essential hypertension. N Engl J Med 1980;302: 772-76.
10. Cusi D, Barlassina C, Variants M, Lupi P, Ferrari P, Bianchi G. Familial Aggregation of cation transport abnormalities and essential hypertension. Clin Exp Hypertens 1981;3(4): 871-84.
11. Smith JB. Ash KO, Hunt SC, Hentschel WM, Sprowell W, Dadone MM, Williams RR. Three Red Cell Sodium Transport Systems in Hypertensive and Normotensive Utah Adults. Hypertension 1984; 6: 159-66.
12. Weder AB. red-cell lithium-sodium countertransport and renal lithium clearance in hypertension. N Engl J Med 1986; 314(4): 198-201.
13. Semplicini A, Marzola M, Mozzato MG, Ceoloto G, Pessina AC. Red blood Cell Li+ /Na+ Exchange in Patients with Diabetic Nephropathy and Essential Hypertension: Therapeutic Implications. Renal Failure 1993; 15(3): 333-40.
14. Canessa M. Erythrocyte sodium-lithium contertransport: another link between essential hyppertension and diabetes. Curr Opin Nephrol Hypertens 1994; 3(5): 511-17.
15. Carr SJ, Sikand K, Moore D, Norman RI. Altered membrane microviscosity in essential hypertension: relationship with family history of hypertension and sodium-lithium countertransport activity. J Hypertens 1995; 13(1): 139-46.
16. Woods JW, falk RJ, Pittman AW, Klemmer PJ, Watson Bs, Namboodiri K. increased red-cell sodium-lithium countertransport in normotensive sons of hypertensive parents. N Engl J Med 1982; 306(10): 5993-95.
17. Canessa M, Morgan K, Goldszer, R, Moore TJ, Spalvins A. Kinetic Abnormalities of the Red blood Cell Sodium-Proteon Exchange in Hypertensive Patients. Hypertension 1991; 17 340-48.

18. Nosadini R, Semplicini A, Fioretto P, Lusiani L, Trevisan R, Donadon V, Zanette G, Nicolosi GL, Algio VD, Zanuttini D, Viberti GC. Sodium-lithium Countertransport and Cardiorenal Abnormalities in Essential Hypertension. Hypertension 1991; 18: 191-98.
19. Trevisan R, Nosadini R, Fioretto P, Semplicini A, Donadon V, Doria A, Nicolosi G, Zanuttini D, Cipollina MR, Lusiani L, Avogaro A, Crepaldi G, Viberti GC. Clustering of risk factors in hypertensive insulin-dependent diabetics with high sodium-lithium countertransport. Kidney Int 1992; 41: 855-61.
20. Petrov VV, Britov AN, Levitsky DO, Minchenko BI, Konstantinov EN, Svidersky VD, Novikow ID, Grishenkov EA, Lijnen PJ. Nonlinear relationship between erythrocyte sodium lithium countertransport and blood pressure in man. Methods Find Exp Clin Pharmacol 1994; 16(9): 661-66.
21. Kzesinski JM, Saint-Remy A, Du F, Rorive G. Red blood cell Na-Li countertransport, hypertensive heredity, and cardiovascular risk in young adults. Am J Hypertens 1993; 6(4): 314-16.