ARTERIAL HYPERTENSION

ARTERIAL HYPERTENSION
THE RED CELL IN HUMAN

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SUMMARY
A survey of the current state of some haemodynamic factors and red cell involvement in arterial hypertension is presented. Blood viscosity, as one of the major determinants of flow resistance, may play a significant role in blood pressure regulation. Red cell rigidity, in addition to some other rheologic abnormalities, might contribute to the elevation of blood viscosity and consequently to worsening flow conditions, either in hypertensive human or experimental animal models. Structural disturbances in red cell membrane and abnormalities in transmembrane ionic fluxes may assume great pathophysiological significance, where affecting red cell deformability and consequently blood viscosity.

INTRODUCTION
In the light of the classic pathophysiological concepts, any tentative to associate the pathogenic mechanisms of arterial hypertension to some red cell features would be a little less than heretic.

According to far distant viewpoints, the increase in blood pressure was claimed to result from an isolated dysfunction that, centered on the kidney, would determine an increase on the vascular resistance.1 This apparently convincing relationship could be linked by the renin-angiotensine system and its functional interaction with aldosterone secretion and the sympathetic nervous system. Due to some contradictory results, where emerged the individualization of several types of arterial hypertension, it was realized that the increase on blood pressure could not be the consequence of hyperactivity of the renin-angiotensine alone (for reviews, see 2-4).

In the present, the mosaic theory of hypertension of Page 5, 6 is no more the fuzzy thinking as it was looked some years ago. According to this concept, a number of regulatory components may be interrelated to control blood pressure and tissue perfusion.

However, the cause for the elevated arterial pressure in 90-95% of patients cannot be determined. These patients have essential (or primary) hypertension (EH), in opposition to the secondary hypertension of a well-known established cause. Since EH is not an homogeneous entity (where some inherited defects seems to be involved), the mechanisms underlying blood control deregulation may differ between clinically similar patients. Whatever the number of factors involved in EH, this pathologic disorder must be recognized as a chronically consequence of vascular changes (Fig. 1), that are associated to increased blood pressure (for reviews, see 4, 7).

Haemodynamic factors are amongst these possible regulatory participants, being the total peripheral resistance and cardiac output believed as the major physiologic determinants of arterial pressure (for reviews, see 7,8). The resistance to blood flow in turn depends on the product of blood viscosity and vascular hindrance.

Although the significance of changes in the blood rheology has been generally neglected, there is strong evidence that such disturbances might increase flow resistance (for review, see 9). In part, these abnormalities could reflect a decrease in red cell deformability.

A great deal of interest about the possible importance of red cell in essential hypertension was derived since abnormalities in sodium transport were first reported in 1960, in erythrocytes from hypertensive subjects.10 The consequence was a flood of reports (and a great deal of controversy) showing marked changes in transmembrane fluxes of Na+, K+ and Li+ in erythrocytes from both essential hypertension humans (EH) and genetically spontaneous hypertensive rats (SHR, for review see 11). Comparable alterations have been also detected in other circulating cells or tissue (e.g. vascular smooth muscle).11, 12

The pathophysiological meaning of these changes is still poorly understood. As some of them appear frequently in families with a high propensity to EH, they might be used to identify subjects that have or are destined to have EH. This perspective, still questionably, would be in line with recent epidemiological observations that have demonstrated a relatively strong genetic component on the determination of the blood pressure.13

Generally, the alterations observed in red cell transport systems would represent part of a more widespread abnormality involving different cell membranes.14 A series of facts suggest that cell membranes may be considered a basic determinant affecting the regulation of blood pressure.15 The availability and ease of manipulation

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Fig. 1: Proposed common pathway that leads to increased arterial pressure in most forms of hypertension. According to recent views, a complex interaction of multiple factors may account to the increased total peripheral resistance that results in established hypertension. Vasoactive stimuli (e.g. neurogenic, hormonal and/or miogenic changes) might be the cause of functional alterations in vascular smooth muscle (pressure independent) that precedes the development of high blood pressure. The maintenance of increased wall stress and/or lesions in the cellular components in the vessel wall might result in structural abnormalities in vasculature and subsequent impairment of pathological conditions which account for sustained hypertension.

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would make the cells an excellent representative of more difficulty accessible tissues.

Although a direct causal relationship between red cell ion transport and hypertension seems unlikely, there are reasons to believe that an increase in arteriolar tone, and consequently the development of hypertension, might be linked to previous alterations in cation involvements (Na⁺, Ca²⁺, + exchange) or vascular smooth muscle. In any case, those ion transport abnormalities might indicate localized changes in membrane organization (possibly involving lipid-protein interactions) or the effect of circulating factors.

The ability of circulating red blood cells to deform is determined by the physical properties of the cell membrane, in addition to the internal viscosity of the cell and its shape/volume relationship. Therefore, changes in membrane fluidity and rigidity may have some influence on the rheologic properties of the erythrocytes in hypertension. Whether some rheologic alterations will contribute to the development of hypertension is still open to further discussion.

In this overview some essential features of the pathogenic mechanisms of hypertension are outlined, an attempt is made to correlate blood viscosity with vascular resistance, and the rheologic behavior of red blood cells is emphasized in connection with structural disturbances in red cell membrane and transmembrane ionic fluxes.

**HAEMODYNAMICS AND BLOOD VISCOSITY FACTORS**

Beyond a diversity of pathogenic factors, elevated pressure in EH patients or its best experimental animal model, the spontaneously hypertensive rat (SHR), is mostly associated with haemodynamic disturbances. In this terms, the abnormal and progressive increase in arterial pressure must be dependent by either an elevated total peripheral resistance and/or increased cardiac output.

Although in most forms of hypertension (including the restrict group of secondary forms) cardiac output remains normal, all show increased total peripheral resistance to blood flow (for reviews, see 23).

In macrocirculation, the overall vascular resistance (R) is primarily determined by a relation between the arterial-venous pressure drop (ΔP, equivalent to the arterial pressure) and the forward flow, of blood, given by the cardiac output (Q), as follows: \( R = \frac{\Delta P}{Q} \). As blood flows in the microcirculation (consisting of arterioles, capillaries and venules) a different species of restriction appears, affecting the delivery of oxygen and nutritive substances to tissues. At this vascular territory, when the major portion of the pressure drop occurs, the resistance through a simple vessel or vascular network is equal to the product of vascular hindrance (Z) and blood viscosity (\( \eta \)).

Vascular hindrance, representing the contribution of vessel geometric factors (without blood viscosity interference) is expressed by the Poiseuille-Hagen law, where Z is proportional to the inverse fourth power of the vessel radius: \( Z = \frac{1}{r^4} \). Therefore vasoconstriction causes an increase in Z whereas vasodilation leads to lower Z (for review, see 16).

Although the effects of slight modifications in blood viscosity have been considered insufficient to explain the elevated pressure in certain forms of hypertension, significant variations in blood viscosity have been described in cardiovascular disorders 17-19 including sustained and borderline EH. Similar increases in blood viscosity was detected in SHR in studies of other groups. In these experiments the reduction of blood viscosity by isovolemic hemodilution was followed by a significant increase of high blood pressure in hypertensive rats. Moreover, blood viscosity in parallel with arterial pressure are reduced by some non-diuretic antihypertensive drugs, either in hypertensive patients 23, 29-31 or experimental animal models; a direct correlation between whole blood viscosity and mean arterial pressure could be observed.

These findings might indicate that rheological changes are associated with increased blood pressure, even at the stage preceding established hypertension.

The hemodynamic role of increased blood viscosity in the elevation of blood pressure was also attributed to a malfunction of hypothalamic vascular viscosity receptors. However, there is presently no clearly defined pathogenic relationship between such changes. Blood viscosity is a function of haematocrit, plasma viscosity, red cell aggregation and red cell deformability. The interplay between these variables and the extent of their contribution to overall blood viscosity depends on the local conditions of blood flow. Although some conflicting results have occasionally emerged, significant changes in all these major factors of blood viscosity have been described in EH patients.

In the early study of Tibblin and co-workers, the increase in haematocrit of hypertensive patients was correlated with the primary contributing factors to elevated blood viscosity; a possible role could be also suspected for fibrinogen. More recently, rheologic changes other than increased haematocrit were shown clearly responsible for the elevated blood viscosity in sustained 24, 30, 31, 35-38 and borderline 25, 31, 32 EH.

Blood viscosity remained higher even when evaluated in hypertensive patients with matched haematocrit values; thus the increase in haematocrit only partly could explain the observed blood hyper-viscosity in all patients. Moreover, the association of higher haematocrit with EH has not been confirmed in some other clinical studies, 25, 30, 35 where increased blood viscosity was also not detected, 29, 31 unless corrected to a standard haematocrit.

Either in borderline or established EH, the magnitude of blood viscosity elevation, as well as the factors determining such increase, were dependent upon the shear rates normally existing in the blood vessels. At high shear rates approximately equivalent to blood flow conditions in the microcirculation, the increase of blood viscosity was between 1/2 and 1/3 less than at lower shear rates prevailing in large vessels.

Whereas at these low shear rates the viscosity of blood was largely determined by increased haematocrit plus higher plasma viscosity and red cell aggregation, at higher shear rates the elevation of blood viscosity was due to higher haematocrit and plasma viscosity alone. 30, 34, 35

The increase in plasma viscosity and red cell aggregation was apparently due to the elevation of fibrinogen concentration both in borderline or established EH 24, 25, 30, 31 and SHR. 25, 27. In the sequence to these studies, it might be concluded that elevated haematocrit, plasma viscosity and red cell aggregation, by increasing blood viscosity, are potential determinants of higher blood pressure.

These findings might be supported by some clinical 35 and experimental studies, 27, 28 although being contested by others. 39, 37 The reasons for such discrepancies are not clear but could reflect the diversity of the patients studied or, more generally, the heterogenous pathogenic nature of the hypertensive disorder.

Whereas there is general agreement on the occurrence of increased plasma viscosity and fibrinogen concentration in association with arterial hypertension, conflicting reports have appeared upon the contribution of red cell deformability. A clear reduction of whole blood filterability, worsening with time, was observed in patients with malignant phase hypertension, 37 in apparent dependence of plasma proteins and other factors. Such findings in blood filterability are in accord with our previous results on whole blood filterability in moderate EH patients and studies of other groups. 35, 38, 39

As whole blood filterability depends on the external fluid viscosity acting on cell surface, haematocrit and red cell aggregation, in addition to the degree of erythrocyte deformation, filterability tests recently assessed by us on red cell suspensions; even so, a clear decrease in erythrocyte filterability was observed in a group of hypertensive subjects.

In other report, using the measurement of erythrocyte internal viscosity (Tk), the presence of low deformable red cells was suggested as an associated cause of hypertension. 33 Red cell deformability, as measured by a filtration technique, is also impaired in experimentally hypertensive dogs.

In contrast to these findings some reports on EH 29 and SHR 26, 27 did not show significant differences in red cell deformability between hypertensive and normotensive groups.

Beyond the contribution of decreased cell deformability to the viscous resistance of blood to flow, an elevation of red cell 2,3,-diphosphoglycerate concentration is claimed for hypertensive patients. 56, 41. 2,3-diphosphoglycerate levels were significantly, correlated with systolic, mean and diastolic blood pressures. If such increase of 2,3-diphosphoglycerate reflects a compensation 44 for tissue underperfusion associated with establish-
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Cation transport systems in normal erythrocytes.

Fig. 2: Cation transport systems in normal erythrocytes.

TRANSPORT ABNORMALITIES

In the sequence of the original demonstration of increased red cell sodium concentration and potassium to-potassium ratio in patients with essential hypertension, 10 similar abnormalities in sodium transport were detected in white blood cells 47 and proposed to other tissues for this type of pathology. 11, 47, 49

Since then, and in despite to some recent uncertainty and doubts about methodology and adequacy of matching hypertensive to normotensive subjects, 50 a variety of abnormalities on red (and white) blood cells have been associated to E-H, and also partly sustained in SHR. 12 Similar alterations have been also observed in the normotensive relatives of such patients. 11

The three pathways for sodium transport that have received the greatest attention are the sodium pump 51, sodium-potassium cotransport 52 and sodium-lithium countertransport 53. The mechanisms of these different Na+ transport pathways in human erythrocytes (represented in Fig. 2) are briefly described in following.

As in all other cells, most of the extrusion of Na+ from the red cell is carried out by a ouabain-sensitive complex functional protein, the Na+, K+ ATPase. This active transport mechanism of Na+, closely coupled with K+, generates a Na+ and K+ electrochemical gradient across the cell membrane, in dependence of the energy supplied by the metabolism of glucose; the same pump unit that extrudes Na+ carries K+ inward, in a approximate ratio of 3Na+/2K+; in the stationary state, the K+ gradient is about 30/1 (intracellular/external), being the intracellular Na+ concentration about 15 times lower than the external Na+ concentration. Failure in red cell ATP concentration impairs the transport of Na+ and so diminishes the gradients.

The Na+, K+ pump-activity is also dependent on the concentration of both cations: an increase on Na+ internally or an excess of external K+ stimulates pump activity until a maximum is reached. In vivo and under normal conditions, the pump is in a steady-state, determined by the extra- and intracellular Na+ and K+ concentrations, that corresponding to a submaximum stimulation. Due to the continuous Na+ and K+ leaks through the lipid bilayer (passive permeability) both cation gradients tend to be dissipated unless the pump activity is preserved 51.

The remaining two Na+ transport systems do no derive energy from the hydrolysis of ATP but rather from the electrochemical gradient of another participating ion. Both pathways are responsible for 10 to 20 percent of the total residual fraction of the Na+ and K+ fluxes. If the participating ion must be situated on the opposite side of the membrane, the system is called countertransport; if it is in the same side of the membrane, it is called cotransport.

The Na+-cotransport system (ouabain-resistant and furosemide-sensitive) promotes a coupled efflux or influx of both Na+ and K+ ions, driven by an appropriate transmembrane electrochemical gradient of the co-ion. Thus the net-outward uphill Na+ transport is stimulated by internal Na+, whereas the inward cotransport is stimulated by external K+. Under basal conditions, the inward and outward ion cotransport movements compensate for each other. 52

In human erythrocyte the cotransport fluxes are about 10 times lower than those dependent from the Na+, K+ pump. It has been suggested that the pathway remains inactive whereas the intracellular sodium concentration is kept at acceptable levels by the pump; above a critical level, when the Na+ pump is maximally stimulated, any increase on intracellular Na+ concentration activates the Na+, K+-cotransport. More generally, these systems might participate as a gradient regulator, where any change in internal Na+ or external K+ levels activates a cotransport flux to the opposite membrane side of the ionic alteration.

The Na+-K+ (Li+) countertransport pathways involves a 1:1 exchange of internal for external Na+ ion. This system (ouabain-resistant and phloretin-sensitive) may accept Li+ ions to exchange for Na+ or other Li+ cations. As the countertransport pathway hardly effects the overall distribution of Na+ across the cell membrane, it seems unlikely to be of any physiological relevance. 53

Flux changes across the red cell membranes and involving all
described systems have been reported in human hypertensives and SHR. These abnormalities would agree with the described increase in intraerythrocyte Na⁺ concentration, if recent studies have not questioned the findings. In contrast to the decreased pump activity described in leukocytes of patients with EH, conflicting results emerge from studies on red cells (Fig. 3)

![Diagram of sodium transport systems in human and experimental hypertension](https://example.com/diagram)

**Legend**
- EH: essential hypertension
- SH: secondary hypertension
- SHR: spontaneously hypertensive rats
- †: values higher, equal or lower than normal controls

Preliminary results in erythrocytes of EH patients showed that the Na⁺, K⁺-ATPase activity was normal or slightly increased. No differences on the red cell ouabain-sensitive pump were also detected between hypertensives (with and without medication) and normotensives. Such observations are in conflict with the data of Postnov et al. and some of our results.

According to Postnov et al., the decrease of Na⁺, K⁺-ATPase activity in hypertensive erythrocytes (mostly from subjects with recently stopped medication) could be due to a decrease of the binding ability of the inner part of the red cell membrane for calcium. This membrane defect was suggested as a local manifestation of a more general cell membrane alteration affecting the control mechanism of EH.

In a previous study of our laboratory, the decrease in red cell ouabain-sensitive Na⁺, K⁺-ATPase activity was shown in a group of hypertensive subjects, with and without medication. More recently, a significant decrease in that ATPase activity was limited to the untreated patients.

Furthermore, in the plasma of patients with EH, an inhibitor of the Na⁺, K⁺-ATPase was observed. However, it remains to be convincingly demonstrated that this inhibitor influences ion fluxes or Na⁺, K⁺-pump activity in the erythrocyte membrane.

According to the initial studies of Garay et al., the outward furosemide-sensitive Na⁺, K⁺ cotransport was decreased in erythrocytes of patients with EH, as compared to normotensives or patients with renovascular hypertension. These observations, initially confirmed by other groups, would suggest that the absence of the cotransport pathway in EH played an aetiological role in the development of the high intracellular Na⁺ concentration, and might represent a genetic marker for the disease. Other studies have not confirmed those findings, with some groups reporting an increase in Na⁺-K⁺cotransport and others observing no change.

Further investigation have shown that the Na⁺-Na⁺/Li⁺ countertransport across erythrocyte membranes is also increased in patients with EH but appears normal in secondary hypertension. This abnormality seems to be most pronounced in patients with a genetic predisposition to EH and shows an apparent dependence on a dialysable plasma factor.

In contrast, other studies have not confirmed any alterations in the countertransport pathway between essential hypertensive and normotensives. Therefore, the interaction of the various components of sodium transport in the red cell membrane from essential hypertensive subjects are complex and yet poorly understood. The effect of treatment of hypertension on these systems remains to be clarified, although some observations have already suggested that some medication in use might reverse the underlying changes in membrane transport.

**FUNCTIONAL AND STRUCTURAL ALTERATIONS OF THE MEMBRANE**

A common membrane defect has been proposed to explain some functional alterations demonstrated in erythrocytes and a variety of cell types in essential hypertension and spontaneously hypertensive rats. Such membrane concept may be considered the result of a vast accumulation of data, initially provoked by studies in the vascular smooth muscle.

In addition to the observed increase of water and sodium contents in the renal artery wall of hypertensive subjects, further observations showed that the levels of water and some ions (Na⁺, K⁺, Cl⁻, Ca²⁺) were also elevated in experimental hypertension. Proceeding from these observations, a relationship between vascular reactivity, vasoconstriction and ion balance changes was suggested.

Later on, increased K⁺ and Cl⁻ turnover and higher rate of
Na⁺ efflux 

were noted in arterial smooth muscle cells of hypertensive rats; a decrease in membrane calcium binding parallel to increased Ca²⁺, Mg²⁺-ATPase were also reported to normotensive rats.²⁷

Although attractive, the derived hypothesis that enhanced sodium concentration in vascular smooth muscle may increase intracellular calcium levels in hypertension, and so stimulate the vascular tone, is still questionable. In alternative to the Na⁺-Ca²⁺ exchange concept, the activation of the actomyosin complex in hypertension might derive primarily to an alteration of membrane regulation over intracellular Ca²⁺ binding and concentration (for review, see 12).

Later studies have demonstrated that such ionic alterations are not limited to the cardiovascular contracting cells but are indeed extensive to other cells, either in human or experimental hypertension. In addition to the described alterations in countertransport, cotontransport and sodium pump systems for univalent cations in erythrocytes of essential hypertensive patients (see Sodium Transport Abnormalities), similar membrane defects have been detected in SRH erythrocytes. Thus, erythrocyte membrane ouabain-independent permeability to Na⁺ and K⁺ is increased in SHR,⁷⁸,⁸²,⁸⁴ apparently due to an intrinsic defect in cell membrane ⁸⁵ genetically linked to the hypertensive process.⁶⁶,⁸⁷

Further studies suggested that such altered cation transport in SHR erythrocytes, as well as in essential hypertensive patients, is associated with an abnormal distribution of intracellular calcium.⁸⁲

(See Fig. 4). Furthermore, erythrocyte membrane of both the SHR and patients with EH differ from those of normotensive controls by their higher passive permeability to calcium and increased Ca²⁺ concentration. No such alteration were observed in steroid-induced hypertensive rats.⁸⁸

In fact, the properties of erythrocyte membranes seem dependent on the effects of calcium on membrane conformation.⁵⁵

The decrease in Ca²⁺ binding ability was also reported in plasma membrane of adipocytes,⁶⁶ cardiomycocytes, hepatocytes and synaptosomes,⁸⁶,⁹⁷ and in the microsomal fractions of arterial smooth muscle cells from spontaneously hypertensive rats, compared with normotensive controls. This could suggest that defective calcium handling by membranes (as well as other ionic transport abnormalities) being extensive to different cell types, indeed present great pathogenic importance.

The possible role of calcium and other divalent cations in the pathogenesis of essential hypertension has been receiving increasing support.⁹⁹ If such interaction do exist in excitable cells, as suggested for vascular smooth muscle of SHR,¹⁰¹,¹⁰² the resultant intracellular cationic changes (particularly calcium and sodium overload) could be involved in increased blood pressure.

The increased intracellular Ca²⁺ concentrations, as observed in erythrocytes of SHR and patients with EH,⁵⁵ may be due to enhanced passive calcium influx and/or to a decreased rate of active calcium extrusion. A defective interaction between calmodulin and the Ca²⁺-ATPase in erythrocyte membrane of SHR and patients with essential hypertension,⁵³,¹⁰⁴ also shown in plasma membranes of SHR brain tissue,¹⁰⁴ would support an increase of the intracellular Ca²⁺ pools not limited to erythrocytes.

However, the observation ⁸⁸ that the specific activity of Ca²⁺-ATPase is already increased in erythrocyte membranes from SHR suggests an higher rate of Ca²⁺ extrusion, parallel to an increase in passive calcium influx. According with this report, the elevated intracellular calcium concentration would induce a compensatory activation of the Ca²⁺-ATPase, as evidenced by a higher affinity of the enzyme for Ca²⁺. Such alterations might be related to some detected abnormalities of the phospholipid composition in SHR erythrocytes membranes, but absent in DOCA rats.⁸⁸

Although the Ca²⁺-ATPase activity of erythrocyte membranes did not differ between SHR and normotensive controls,⁸⁹ there are cumulative data that support the involvement of membrane lipid alterations in the described abnormalities of calcium transport in SHR erythrocytes.

Recent fluorescence polarization studies showed that the microviscosity of erythrocyte membranes from SHR is higher than in normotensive controls.⁶⁸ These findings, confirmed in patients with EH but inexistent in patients with renal hypertension,²⁷ are in agreement with our results in erythrocytes of essential hypertensive patients.⁶¹ Therefore, it seems reasonable to conclude that the erythrocyte membranes of SHR and essential hypertensive patients have increased rigidity of the lipid bilayer. This alteration seems to be also extensive to the plasma membrane of hepatocytes, cardiomycocytes and of synaptosomes from both SHR or hypertensive-prone rats.⁹⁷,¹⁰⁶ These last results would confirm a genetic abnormality in hypertensive rats leading to diffuse alterations of cell membrane structure.

In addition increased microviscosity, the polarization studies showed a decreased rate of lateral diffusion, both in the lipid bilayer and in sites of lipid-protein interactions in the erythrocyte membrane of essential hypertensive patients.⁸⁹ Such abnormalities might be related to specific defects in lipid or protein components of erythrocyte membranes, as well as altered ionic fluxes and enzymatic activities reported in EH patients and SHR.

Although contradictory, it has been recently reported that the content and/or metabolism of inositol phospholipids are altered in erythrocyte membranes of SHR, even before they became hypertensive.¹⁰⁷,¹⁰⁸ This fact acquires a special dimension as one realizes that such minor class of phospholipids may be involved in the Ca²⁺-transport system of plasma membrane that controls the transport of surface-bound Ca²⁺ ions into the cell.¹⁰⁹ Moreover, both the cation-transporting ATPases in the human erythrocyte membranes have been shown to depend upon the inner lipid monolayer, the Na⁺-, K⁺-ATPase activity being governed by phosphatidylerine alone whereas the activity of Ca²⁺-, Mg²⁺-ATPase is affected by the total glycosphingolipid content in plasma membrane phospholipids affecting cell membrane fluidity could modify cation ionic fluxes, as demonstrated in hypertension.

The exact functional repercussions of the well established interrelation of red cell AChE and phosphatidylinositol ¹¹² also requires further studies. Apparently, both the substrate and an inhibitor of

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**Legend**

- **SHR**
- **EH**
- **DOCA**
- **Ca²⁺**
- **Na⁺**
- **K⁺**
- **Ca²⁺ binding ability**
- **Membrane permeability**
- **RED CELL**
- **Calcium pump**
- **Co²⁺**
- **NO³⁻**
- **Ca²⁺**
- **Co²⁺ binding ability**

**Fig. 4: Proposed abnormalities of red calcium transport and activity in human and experimental hypertension.**

A decrease in Ca²⁺ binding by the cytoplasmic side of the membrane was shown, both in SHR and EH erythrocytes, but not observed in erythrocyte of patients with chronic renal hypertension.⁹² The decrease in Ca²⁺ binding ability, attributed to a reduction in the number of calcium binding sites on the inner surface of the membrane,⁹¹ might be directly related to the increased passive permeability of the erythrocyte membrane for Na⁺ and K⁺,⁸² and decreased Na⁺, K⁺-ATPase activity.⁸⁸ A similar decrease in sodium binding to the inner side of the membrane was observed in erythrocytes of essential hypertensive patients.⁸⁸ These data seem to indicate the presence of structural alterations in the erythrocyte membranes of EH patients and SHR, located in the inner part of the membrane that determines the permeability to univalent cations and probably enhance Ca²⁺ influx and intracellular concentration.
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![Diagram of Red Cell Transport Systems](image)

**Fig. 3: Sodium transport systems in human and experimental hypertension.** Legend: EH: essential hypertension; SH: secondary hypertension; SHR: spontaneously hypertensive rats; I = 1: values higher, equal or lower than normal controls.

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ACHE influence Ca\(^{2+}\) binding to erythrocytes of SHR and essential hypertensive subjects.\(^{10}\) If increased ACHE activity in erythrocytes of EH patients, \(^{46, 47}\) is related to altered calcium transport can not be presently ruled, in or out. The hypothesis suggesting the existence of localized changes in membrane organization, possibly involving lipid-protein interactions is in accord with results upon temperature-dependent cation fluxes in erythrocytes of patients with EH \(^{114}\) and spontaneously hypertensive rats.\(^{115}\) Beyond previously described differences in lipid composition, recent studies have also pointed to localized structural modification in the membrane protein of SHR erythrocytes, one group showing a decrease \(^{116}\) whereas another group claims for an increase of band 3 protein.\(^{117}\) In a preliminary work of our laboratory, \(^{40}\) also a decrease in band 3 protein in association with other minor abnormalities of the electrophoretogram pattern was evidenced in erythrocyte membranes of EH patients.

CONCLUSIONS

There in increasing evidence that changes in structural and functional properties of a diversity of cell membranes are associated with primary human and experimental hypertension and even observed at a prehypertensive stage.

In this concern, the disturbances observed in erythrocyte membranes would be acting as markers of such widespread abnormality, probably genetically determined. Such red cell membrane alterations may interfere with cell deformability during flow through capillary blood vessels; in association with some other modifications of blood composition, the resulting increase in whole blood viscosity would contribute to enhance vascular peripheral resistance.

However, the link between elevated arterial hypertension and occurring alterations in red cell membrane conformation and transport still wait further insight.

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