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# SALT-INDUCED HYPERTENSION IMPAIRS OSMOTIC FRAGILITY, HEMORHEOLOGICAL FACTORS, AND ANGIOGENESIS IN MALE WISTAR RATS

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**Abstract**
Plasma tonicity plays a vital role in the regulation and maintenance of erythrocytes' structural, behavioral and functional composition. When the cellular environment is hypotonic, there is a tendency for red blood cell lysis. Erythrocyte osmotic fragility is used to evaluate the rate of lysis in erythrocytes in living tissues. Hemorheology deals with blood flow mechanics in relation to the blood plasma composition and its formed elements. This is usually presented as the blood viscosity, which is inversely proportional to the flow rate of blood and tissue perfusion. The vascular endothelium produces vascular endothelial growth factor which plays a vital role in angiogenesis and helps regulate blood flow and vascular resistance. Alterations in blood viscosity can alter blood flow rate, tissue perfusion, and angiogenesis. This can result in metabolic disorders and hypertension. Therefore, this study aimed to investigate the effects of salt-induced hypertensive impairment on osmotic fragility, hemorheological factors, and angiogenesis in male wistar rats.

A total of 15 male Wistar rats (150g-180g)) were obtained, acclimatized for 14 days, and distributed into three groups of five animals per group was used for this study. The groups are: Negative Control (Zero salt in diet); Positive Control (Normal salt diet i.e 0.3% salt); and high salt diet (8% salt) = HSD group. A high-salt diet was developed by adding 8-g table salt to 92-g rat feed. The animals were kept for 4 weeks with access to developed rations for each group and water ad libitum. Osmotic fragility was measured using a spectrophotometer. Systolic/Diastolic Blood Pressure (SBP/DBP), Mean Arterial Pressure (MAP), Heart Rate (HR), and flow rate (FR) were measured using the tail cuff method, blood viscosity was

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calculated using the standard method, and vascular endothelial growth factor (VEGF) was determined using ELISA. Statistical analysis was performed using one-way ANOVA, and the level of significance was determined at $p<0.05$.

There was an increase ($p<0.05$) rate of erythrocyte hemolysis in the HSD group compared with the negative and positive control groups. There was also an increase ($p<0.05$) in the systolic, diastolic, and mean arterial pressure and heart rate in the HSD group, indicating salt-induced hypertension. There was a reported increase in the hematocrit, platelet estimates, and fibrinogen concentrations, which contributed to the increased blood viscosity and decreased flow rate as well as tissue perfusion ($p<0.05$) when the HSD group was compared with the positive and negative control groups. There was a significant decrease in the vascular endothelial growth factor in the HSD group compared to the negative and positive control groups.

The findings of this study reveal the rate of red blood cell hemolysis, hemorheological disturbance, and vascular endothelial impairment in male Wistar rats exposed to high salt dietary intake.

**Introduction**

Salt is an ionic compound composed of sodium chloride (40% sodium and 60% chloride). Salt is readily soluble in water and can be separated into $Na^+$ and $Cl^-$ ions. Salt (sodium chloride) is the main source of sodium intake, accounting for 95% of daily intake with the vast majority (>85%) being excreted by the kidneys. Sodium is an important nutrient in the body and helps nerves and muscles function correctly. It is also involved in the auto-regulation of the water and fluid balance of the body (Sung, 2014). Total body sodium is tightly regulated to maintain extracellular sodium concentrations within a narrow range, which involves the engagement of multiple physiological mechanisms (Kotchen *et al*., 2013). Salt is essential for life in general, and saltiness is one of the basic tastes of humans.

The Global Burden of Disease Study on Salt (Mozaffarian *et al*., 2014) estimates that 1.65 million deaths from cardiovascular causes that occurred in 2010 can be attributed to salt consumption above a reference level of 2.0 g of sodium (equivalent to 5 g of salt) per day, and that a moderate population reduction in salt consumption could have prevented these deaths. Several studies published in recent years have revealed increased salt consumption in the general population worldwide. Cardiovascular system has been noted to be one of the major organ systems vulnerable to the adverse effects of high salt intake. Regarding public health, such increased salt consumption may result in higher cardiovascular morbidity and mortality (Marcelo *et al*., 2015). The World Health Organization (WHO) has highlighted the important role of sodium intake on cardiovascular health and blood pressure levels, and diets rich in salt are now widely seen as one of the main causes of CVD worldwide (WHO, 2007).

Osmotic fragility increases in essential hypertension and normotensive humans subjects with family history of hypertension (Tsuda *et al.*, 1984). The osmotic fragility *of* erythrocytes reflects functional or structural abnormalities of cell membranes and could be one of the genetic markers of hypertensive predisposition (Tsuda *et al.*, 1984) and may be used as a screening tool for monitoring treatment in patients with hypertension

(Fasanmade, 1999). Certain structural changes in the erythrocytes observed in patients with essential hypertension might be responsible for the increased lability of the erythrocyte membrane. These may include the following: inhibition of sodium transport in erythrocytes (Marx, 1981); reducing calcium binding ability which causes accumulation of intracellular calcium (Lake, 1977); prostaglandin $E_2$ (Allen, 1974); and reduced membrane cholesterol of erythrocytes (Yamori *et al*., 1980).

Hemorheology deals with blood flow mechanics, deformation, and viscosity of blood under the action of stresses. Viscosity can be simply defined as the property of a rheological material (fluid) to flow. In non-Newtonian fluids, such as blood, viscosity in rheological terms is the ratio of shear stress to shear rate (MacRury *et al*., 2009). In other words, blood viscosity is shear-dependent, such that the apparent viscosity increases at low flow rates and decreases with an increase in the shear stress rate. The viscosity of blood varies because of its multi-composition (blood cells, carbohydrates, proteins, electrolytes etc), according to the environment in which the flow occurs. There is more evidence to show that the flow properties of blood are important determinants of effective tissue perfusion, and when these factors are altered, disease processes can occur (Mohan *et al.*, 2001). Blood viscosity is directly linked to the hemoconcentration and inversely proportional to the flow rate. This implies that factors that increase blood constituents and decrease plasma will elevate blood viscosity, which will decrease the flow rate and alter tissue perfusion and angiogenesis (Chang *et al*., 2017).

Hence, this study aimed to investigate the impact of high salt intake on blood pressure, osmotic fragility, rheological properties, and angiogenesis in male Wistar rats.

## Materials and Methods

### Experimental design

Fifteen male wistar rats (150-180g) were obtained, acclimatized for 14 days, and grouped into three groups with five animals per group was used for this study. The groups are: Negative Control (Zero salt in diet); Positive Control (Normal salt diet i.e 0.3% salt); and high salt diet (8% salt) = HSD.

### Preparation of Feed Rations

Three different rations were used in this study. The high-salt diet comprises of 8-g table salt mixed with 92g of standard rat chow. The HSD group was given this ration and water *ad libitum*. The normal salt diet was prepared by mixing 0.30g of table salt with 99.70g of standard rat chow and water ad libitum, which was given to the positive control group. The zero salt diet was given to the negative control group.

### Blood Pressure and Heart Rate

Blood pressure and heart rate measurements were performed at the Small Animal Ward of the Vertinary Clinic University of Ibadan, Ibadan, Nigeria. Systolic Blood Pressure (SBP) was measured indirectly in a conscious and slightly restrained rat using the tail cuff plethysmography method (Kent Scientific, USA). Heart Rate tracings were observed and recorded during BP measurement. For these measurements, rats were conditioned to the restraint (cone) and the warming chamber for about 20 minutes before the measurement. SBP and HR measurements were performed in a silent environment to avoid sound interference by the same investigator. Two sensors were used to measure BP and Vascular Peripheral Resistance. After stabilization in the chamber, an acclimatization run was performed for 5 cycles which was immediately followed by a typical run involving 10 repetitions of the automated inflation-deflation cycle.

### Examination of Blood Samples

At the end of the fourth week, blood samples were collected by cardiac puncture and stored in heparinized bottles. These were used to evaluate the effect of a high-salt diet and diabetes mellitus on hematology, osmotic fragility, and rheology. Five animals from each group were used for analysis (N=5).

### Rheological Analysis

Whole blood viscosity and relative plasma viscosity were estimated using the method described by Reid and Ugwu (1987), and the flow rate was calculated. The plasma fibrinogen concentration was estimated using the clot weight method of Ingram (1952). Hematocrit was estimated using microhaematocrit reader.

$$\text{Relative Plasma Viscosity (mPa.s)} = \frac{\text{Flow Rate of Plasma (ml/secs)}}{\text{Flow Rate of Distilled water (ml/secs)}}$$

**Statistical Analysis**

Data were analyzed using GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA) and expressed as the means ±SE. One-way ANOVA was used for comparisons, followed by the post hoc Newman-Keuls Multiple Comparison test. $P < 0.05$ was considered statistically significant.

**Results**

**Osmotic Fragility**

Figure 1 presents the osmotic fragility rate (%). The percentage of erythrocyte osmotic fragility decreased significantly with an increase in NaCl concentration. Complete (100%) hemolysis at 0.0% NaCl. Moreover, no significant changes in erythrocyte osmotic fragility were observed at 0.0% and 0.1% NaCl concentration in all control and experimental groups when compared. However, significant ($P < 0.05$) changes in percentage erythrocyte fragility were recorded at 0.3%, 0.5%, 0.7% and 0.9% of NaCl concentrations, when the HSD group were compared with the control groups. *a, *b, *c, and *d $p<0.05$ at 0.3%, 0.5%, 0.7% and 0.9% of NaCl concentrations.

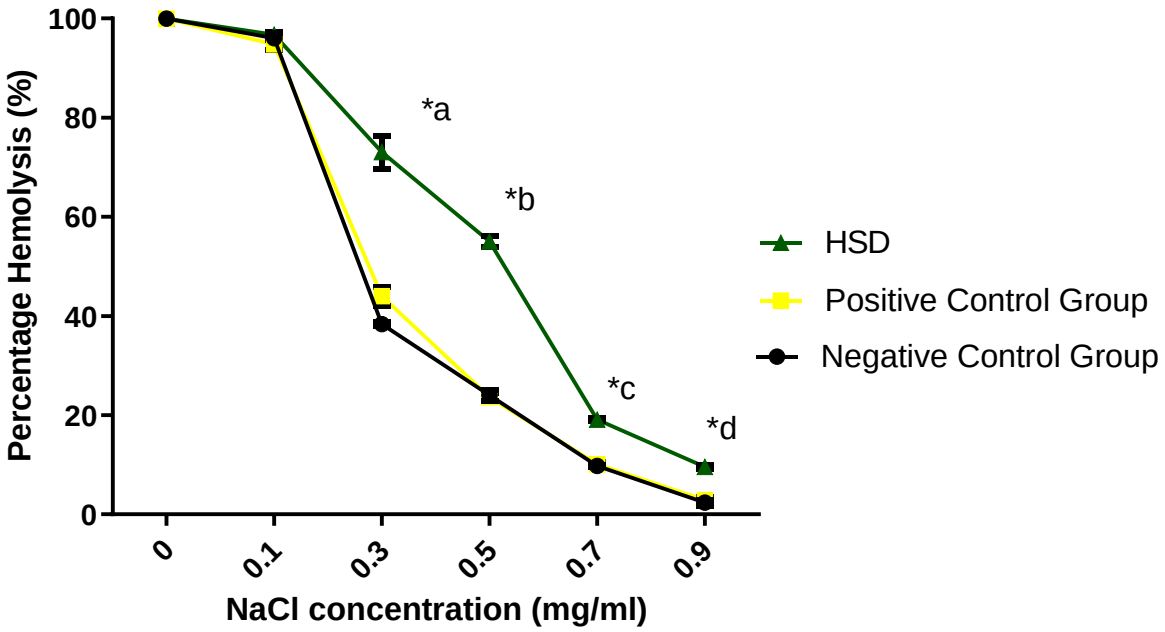


**Fig. 1:** Rate of erythrocyte osmotic fragility (%) 4th week after high-salt diet intake.

**Blood Pressure measurement results**

**Table 1:** Effect of high salt diet on Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Pressure and Heart Rate.

| Groups | SBP (mmHg) | DBP (mmHg) | MAP (mmHg) | Heart Rate (bt/min) |
|---|---|---|---|---|
| Neg. Cont. | 91.28±3.21 | 65.51±1.31 | 96.03±0.41 | 339.42±5.54 |
| Pos. Cont. | 94.24±0.12 | 69.23±1.52 | 101.21±0.12 | 346.67±5.42 |
| HSD | 106.08±0.25* | 73.04±2.32* | 119.43±0.25* | 391.26±7.32* |

Neg. Cont. = Negative control, Pos. Cont. = Positive Control, HSD = High Salt Diet, * = $p<0.05$ compared with negative and positive control groups. Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Heart Rate (HR).

**Result of Hemorheology**

**Table 2:** Effect of a high-salt diet on Whole blood viscosity, Relative plasma viscosity, Plasma flow rate, hematocrit, and fibrinogen.

| Groups | WBV (mPa.s) | RPV (mPa.s) | Flow Rate (cm/sec) | Hematocrit (%) | Fibrinogen ($mm^3$) |
|---|---|---|---|---|---|
| Neg. Cont. | 3.74±0.21 | 2.01±0.11 | 6.24±0.25 | 33.42±0.35 | 200±62 |
| Pos. Cont. | 4.24±0.12 | 2.31±0.41 | 6.89±0.35 | 34.67±0.32 | 185±56 |
| HSD | 6.08±0.25* | 3.74±0.12* | 4.29±0.34* | 37.26±0.51* | 220±56 |

Neg. Cont. = Negative control, Pos. Cont. = Positive Control, HSD = High Salt Diet, * = $p<0.05$ compared with negative and positive control groups. Whole blood viscosity (WBV) and relative plasma viscosity (RPV).

**Vascular endothelial growth factor**

There was a significant decrease in serum vascular endothelial growth factor ($p<0.05$) when the HSD group was compared with the negative and positive control groups (Figure 2.

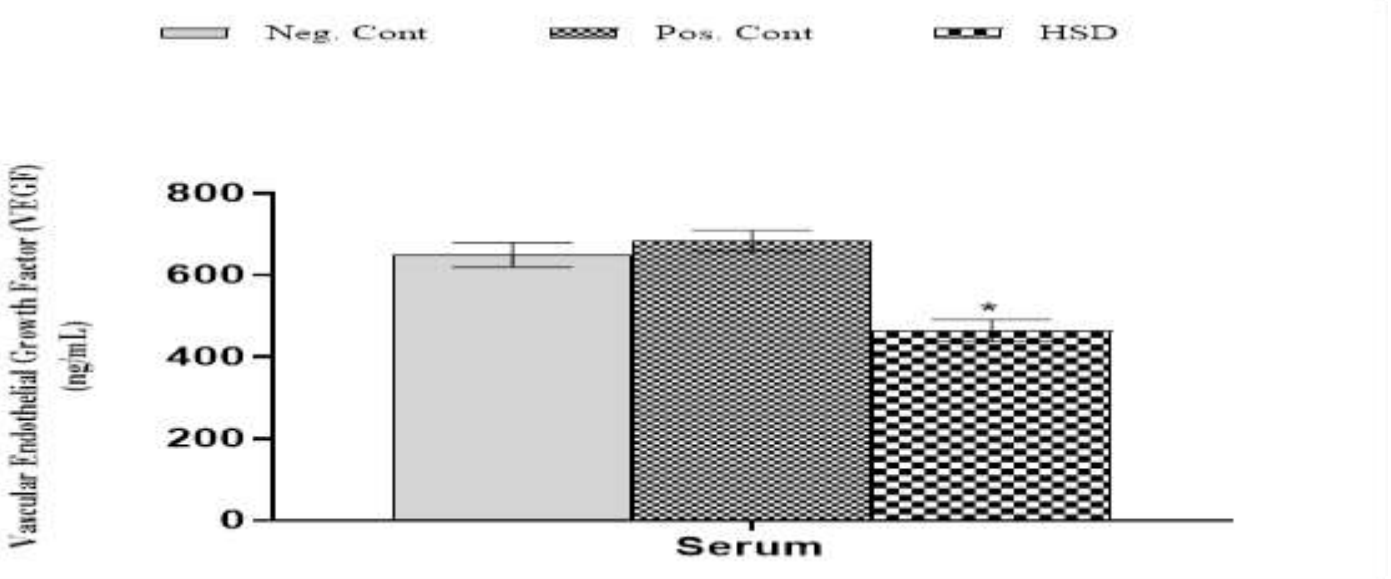


**Fig. 2:** Serum vascular endothelial growth factor after high-salt diet intake.

**Discussion**

This study reported a significant increase in the hemolysis rate of erythrocytes in the HSD group compared with the negative and positive control groups. Osmotic fragility is the shift in the hemolysis curve, which represents the measurement of absorbance versus NaCl concentration, and it is established at 50% of the hemolysis points (Bogner *et al*., 2005). During osmotic hemolysis, the volume of a RBC increases about 1.5 to 1.6 times higher than the discocyte in an isotonic solution. The osmolality of blood plasma is fairly regulated between 270 and 310 mosmol range. The major substances that regulate osmolality are sodium (136-145 mM), potassium (3.6–5.4 mM), chloride, hydrogen carbonate, urea, glucose, and plasma proteins (Bogner *et al*., 2005). The degree of resistance of red blood cells (RBC) to lysis because of a decrease in the NaCl concentration of their environment

is the basis of the osmotic fragility test. The osmotic fragility test is used in diagnosing hematological diseases like hemolytic anemia, hereditary spherocytosis, elliptocytosis, sickle cell anemia, as well as for RBCs from uremic or diabetic patients (Bartosz, 1990; Massaldi *et al.*, 1988). Osmotic fragility has been linked to an increase in essential hypertension and normotensive human subjects with a family history of hypertension (Tsuda *et al.*, 1984). The findings of this study are similar to the reported literature of Okonofua *et al* (2023), who documented an increase in the rate of osmotic fragility in diabetic and hypertensive male Wistar rats. However, Finaud *et al.*, (2006), Radak *et al.*, (1991), and Tsuda *et al.* (1984) reported that the osmotic fragility of red blood cells may not be affected by the short-term intake of a salt diet in human subject.

High salt intake was also able to actuate an increase in systolic and diastolic blood pressure, with a corresponding increase in mean arterial pressure and heart rate when the HSD group was compared to the control groups. Increased salt intake is a risk factor for hypertension (Strazzullo *et al*., 2009), stroke (O'Donnell *et al*., 2013), left ventricular hypertrophy (Rodriguez *et al*., 2011, Go *et al*., 2013), ischemic heart disease (Katsuyuki *et al*., 2013), heart failure (Marcelo *et al*., 2015), anemia (Zhou *et al*., 2013), and kidney-related disorders. The mechanism through which salt can induce hypertension is through sodium retention. Salt sensitivity is closely associated with renal Na metabolism. Renal Na excretion depends on filtration, which depends on the glomerular filtration rate, and tubular reabsorption, which is influenced by various factors (Zhu *et al.*¸2007; Drenjancevic *et al.*, 2010). Na reabsorption-promoting factors include the renin–angiotensin–aldosterone system (angiotensin II, aldosterone), sympathetic nervous system (alpha/beta receptor stimulation), insulin, and oxidative stress (Wang *et al.*, 2003; Huang *et al.*, 2006). Na reabsorption-inhibiting factors include atrial natriuretic peptide, prostaglandin, nitric oxide, and dopamine. Na retention alone does not increase blood pressure (Katsuyuki *et al*., 2013). Retaining Na is necessary to increase the circulating blood volume to increase blood pressure, leading to an elevation of the cardiac output and increase in vascular resistance. In addition, venous vasoconstriction mechanisms, such as sympathetic nervous system enhancement, are important. Some studies have indicated that salt directly acts on the central nervous system, increasing sympathetic nerve activity (Takahashi *et al*., 2011).

Hemorheology is concerned with the flow properties of blood and its dissolved elements (Baskurt, 2007). Blood flow is a vital determinant of tissue perfusion, and when flow patterns are disrupted there will be the development of diseases (Lowe *et al.*, 1980). In this study, hemorheological determinants included blood and plasma viscosity, flow rate, packed cell volume, and fibrinogen concentration. There was a significant elevation in the markers of hemorheological variables when the HSD group was compared with the negative and positive control groups. Blood and plasma viscosity is determined by hematocrit (Cho *et al,* 2008, Rabai 2012), plasma proteins (fibrinogen and globulin), and water (Mohan *et al.*, 2001*).* This finding is consistent with the work of Okomafe *et al*. (2017). The decrease in the flow rate in the HSD group could be linked to the increased blood viscosity, increased hematocrit, and hyperfribrinogenemia (Okonofua *et al.*, 2022). Decreased flow rate leads to decreased perfusion pressure and vascular modifications. The decrease in angiogenesis (vascular endothelial growth factor) in the HSD group could be linked to the determinants of blood flow mechanics that showed a distortion in tissue perfusion. Increased salt intake has been linked to the development of cardiac tissue remodeling and left ventricular hypertrophy (Marcelo *et al*., 2015). Several studies have documented that high salt intake deteriorates left ventricular hypertrophy (He and MacGregor, 2009; Rodriguez *et al*., 2011). A possible explanation lies in the volume expansion, which, combined with endothelial function impairment and enhanced arterial stiffness, increases the afterload (Starmans-Kool *et al.*, 2011).

**Conclusion**

This study demonstrates that high salt consumption in male Wistar rats can induce hypertension through sodium retention and sympathetic stimulation. It can also increase the breakdown of erythrocytes by increasing plasma tonicity. The increased blood and plasma viscosity, hyperfibrinogenemia, and increased hematocrit will lead to a decreased blood flow rate, which in-turn will impair tissue perfusion and angiogenesis.

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