SALT INTAKE AND HYPERTENSION

By

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- Salt or sodium chloride has been used over the years as food condiment as well as preservative.
- Its sources include
  - sea water,
  - rock salt and
  - recently, manufactured industrially.
- Consumption level of salt varies in many different communities.
- Sodium in salt is the major cation in the body fluids and blood.
- Sodium, because of Its osmotic property in ECF elevates blood pressure or causes hypertension.

- Thus, there is extreme interest in the relationship between the level of salt consumption in food and the level of blood pressure.
- The recommended average daily intake is about
  - 5gm (about 86 mmol) per day, equivalent to about 1 teaspoon but can range between 1 gm per day to as high as over 10 – 12gm in same populations *(1)*.
- Epidemiological studies have then showed a correlation between the level of salt intake and the incidence of hypertension.
  - For example, communities that consume very little or no salt in their diet such have incidence of hypertension which is virtually zero
  - whereas those that consume a high salt in their diet such do have incidence as high as 40% of the population *(2)*.

- A large scale study that involved 52 centres in 32 countries and
  - involving 10,500 subjects,
  - the INTERSALT study *(3)*,
- Found a correlation between the quantity of salt consumption and the level of blood pressure.
- By contrast, another study that looked into the effect of salt restriction in the diet, the Dietary Approach to Stop Hypertension (DASH)
  - showed that reduction of salt intake in the diet served resulted in the lowering of blood pressure in both normotensive and hypertensive subjects *(4)*.
- The results show significant beneficial effects on not only blood pressure but also on cardiovascular well being.
- A recent meta-analysis of studies on salt and blood pressure
  - estimated that reduction in salt intake of 5 gm (1 teaspoon) could result in 25% fewer strokes and other cardiovascular events *(1)*.

- The above observations became an impetus for us to embark on studies to find out the
  - mechanisms by which high salt in the diet can result in elevation of blood pressure.
  - Our group therefore embarked on studies on experimental animals.
- Previously, Dahl *(5)* had developed genetically-selected rats that developed hypertension when subjected to a high salt diet –
  - the so called Dahl Salt Sensitive (Dahl-SS) rats,
  - as well as the subset of salt resistant strains or Dahl-SR rats.
- However, in our studies we have used normal or non-genetically selected Sprague – Dawley (SD) rats.
  - If weaning SD rats of 4 – 6 weeks of age are fed a high salt diet containing 8% sodium chloride, for about 6 – 8 weeks, they often developed high blood pressure *(6, 7)*.
- Other animal studies involving chimpanzees, dogs fed with high salt diet have also been reported to develop elevated blood pressure *(8)*.

- In our rat studies, high dietary salt intake resulted in
  - high blood pressure which can be attributed to vascular mechanism.
- We therefore set out to investigate the responses of isolated blood vessels of rats and dogs that have been fed a diet that has a high salt content.
- In arterial vessels, which we studied by using
  - isolated aortic ring segments (Figs 1 & 2),
  - or the pressurized mesenteric artery preparation (Fig 3),
- A high salt diet resulted in
  - enhanced constriction tone *(6, 9)*
  - as well as reduction in relaxation responses to agonists.
    - Both factors that will increase vascular resistance and hence blood pressure.
- In addition, the veins which act as conduit vessels that return blood to the heart also show enhanced constriction tone after a high salt diet in the dog.
  - The result of this is that venous return to the heart will be accentuated leading to high cardiac output and hence high blood pressure.

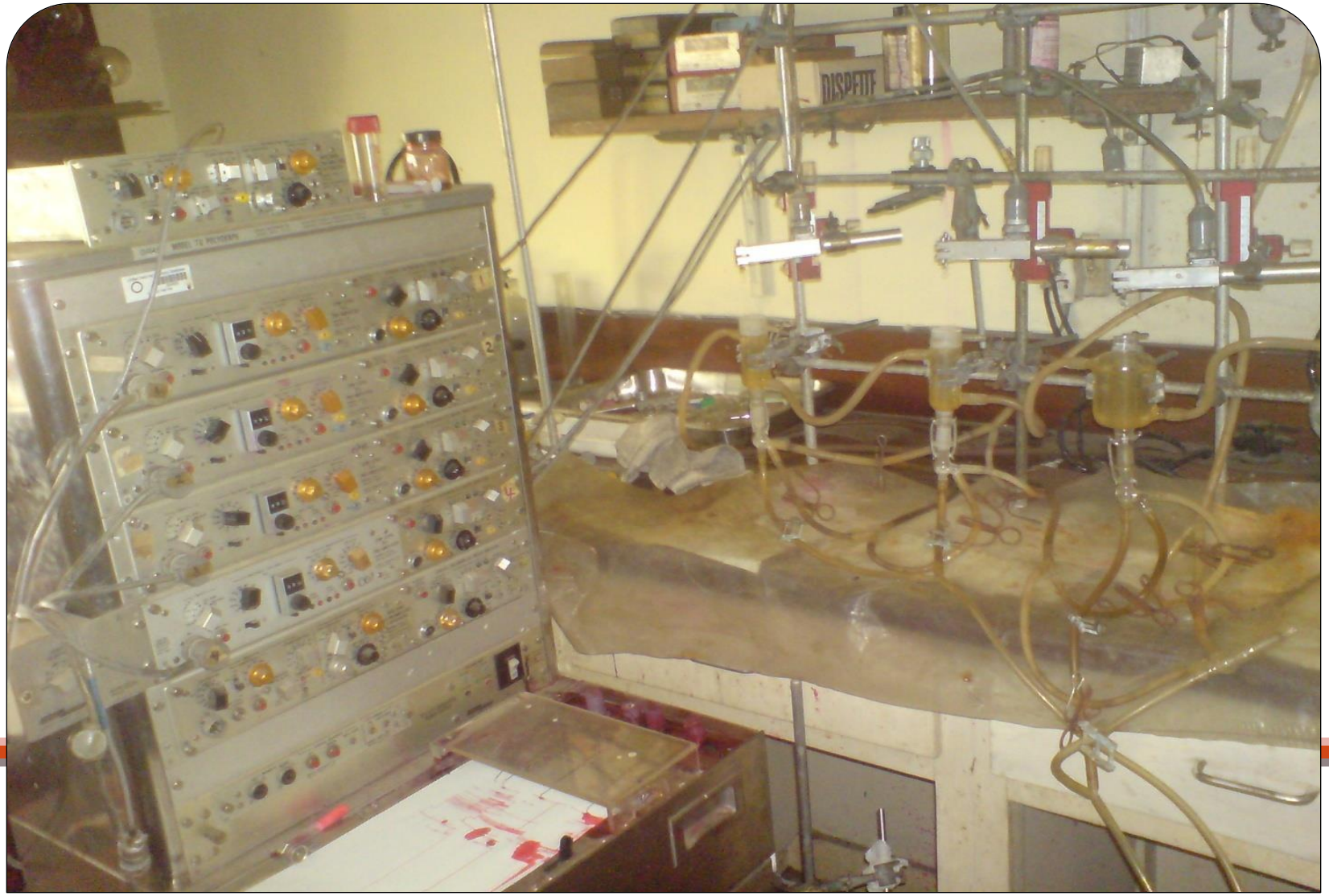

Fig. 1.Grass Polygraph Recorder and Organ Baths

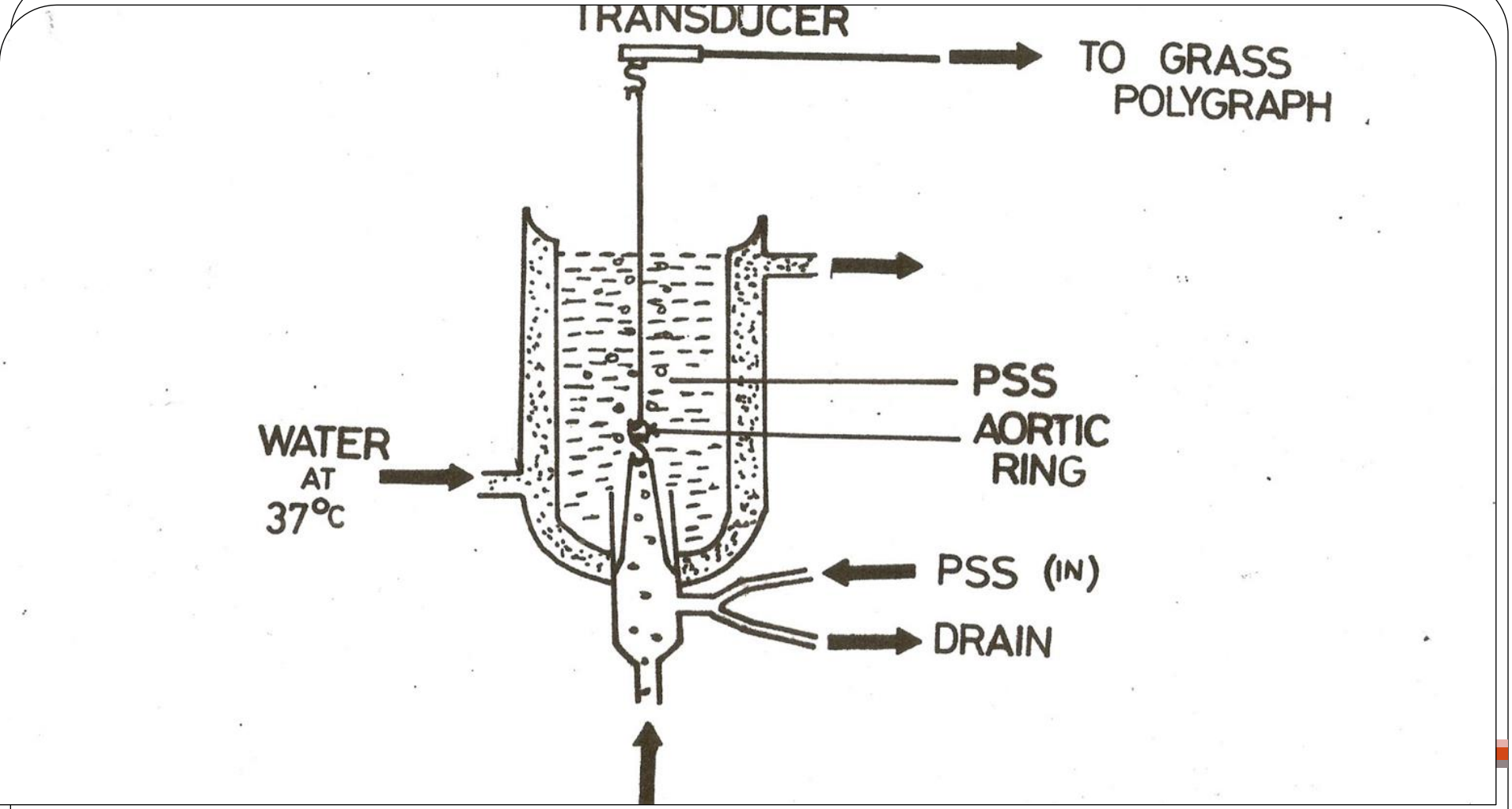

Fig. 2. Schematic diagram of an Organ Bath

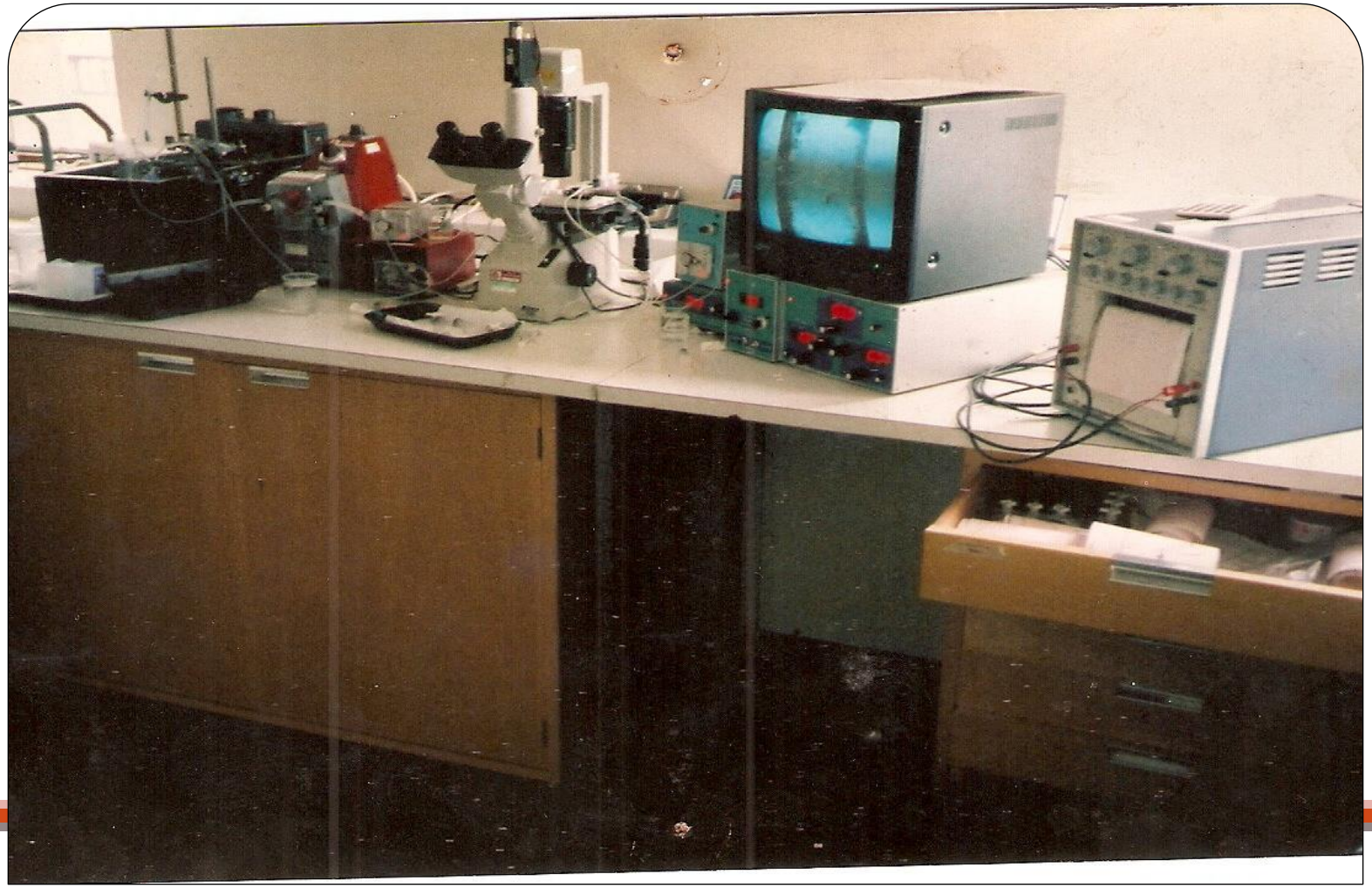

Fig. 3. Pressurized vessel set up

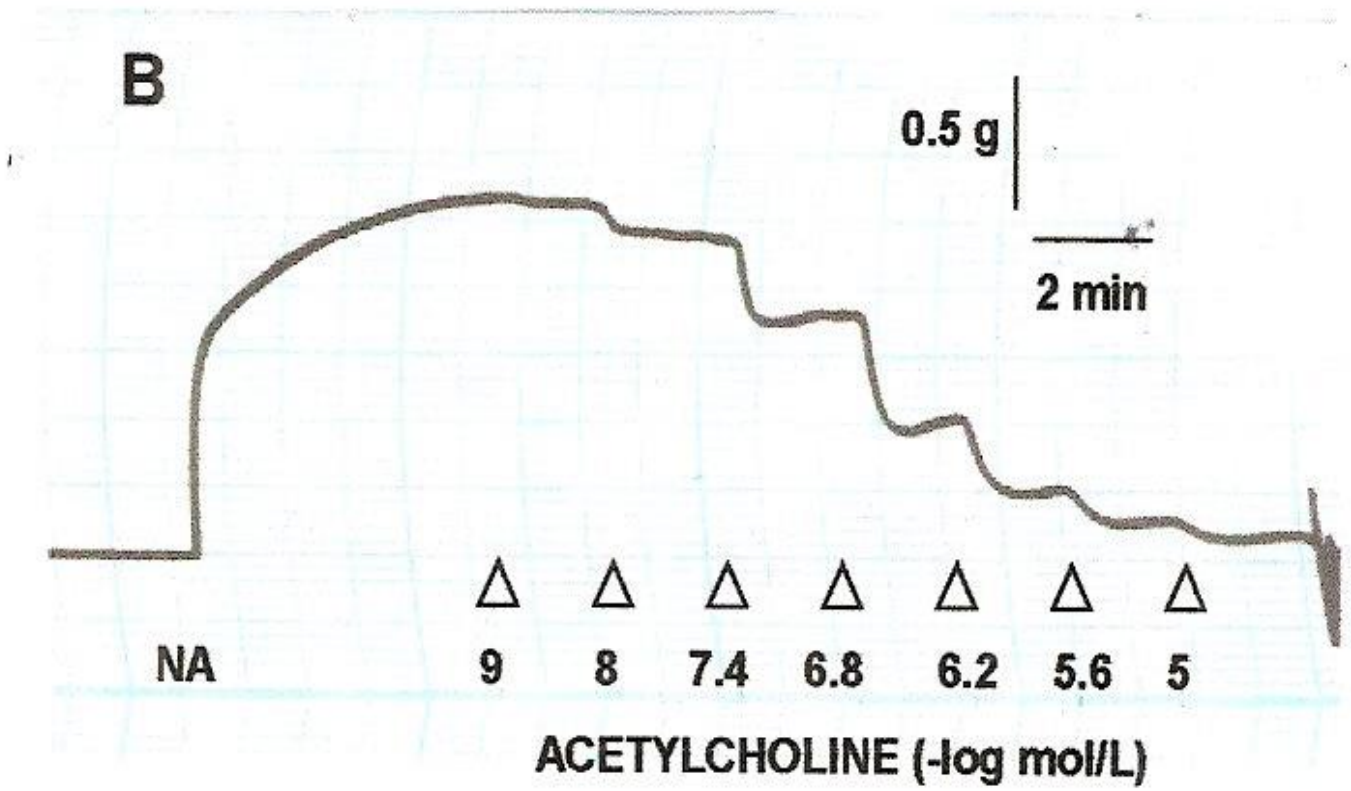

Fig. 4. Representative relaxation response to an agonist tracing

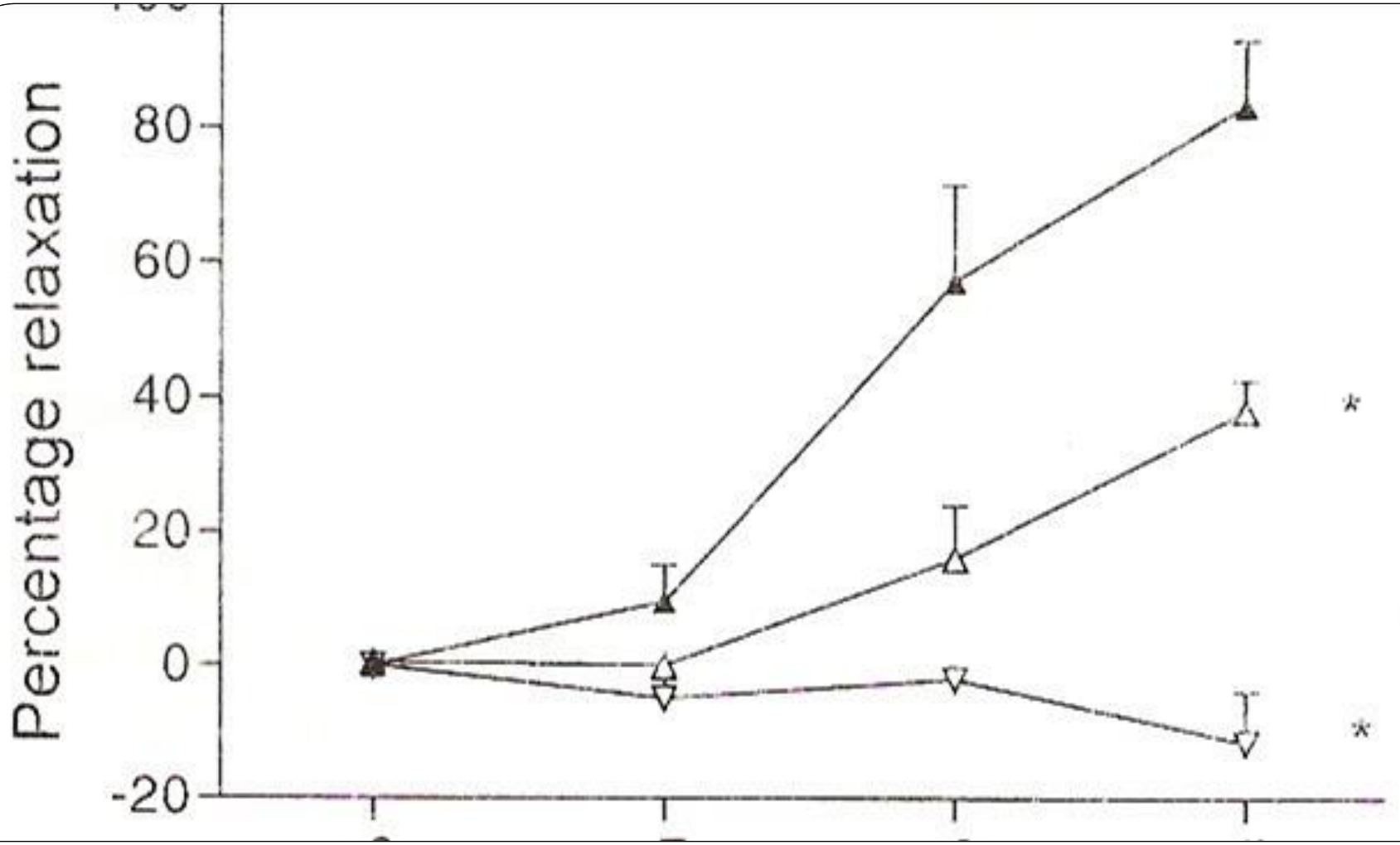

Fig. 5. Concentration –response relaxation curves in rats fed low salt diet before and after blockers , a) Control, b) + L-NAME, c) + Apamin & Charib (Sk + Bk)

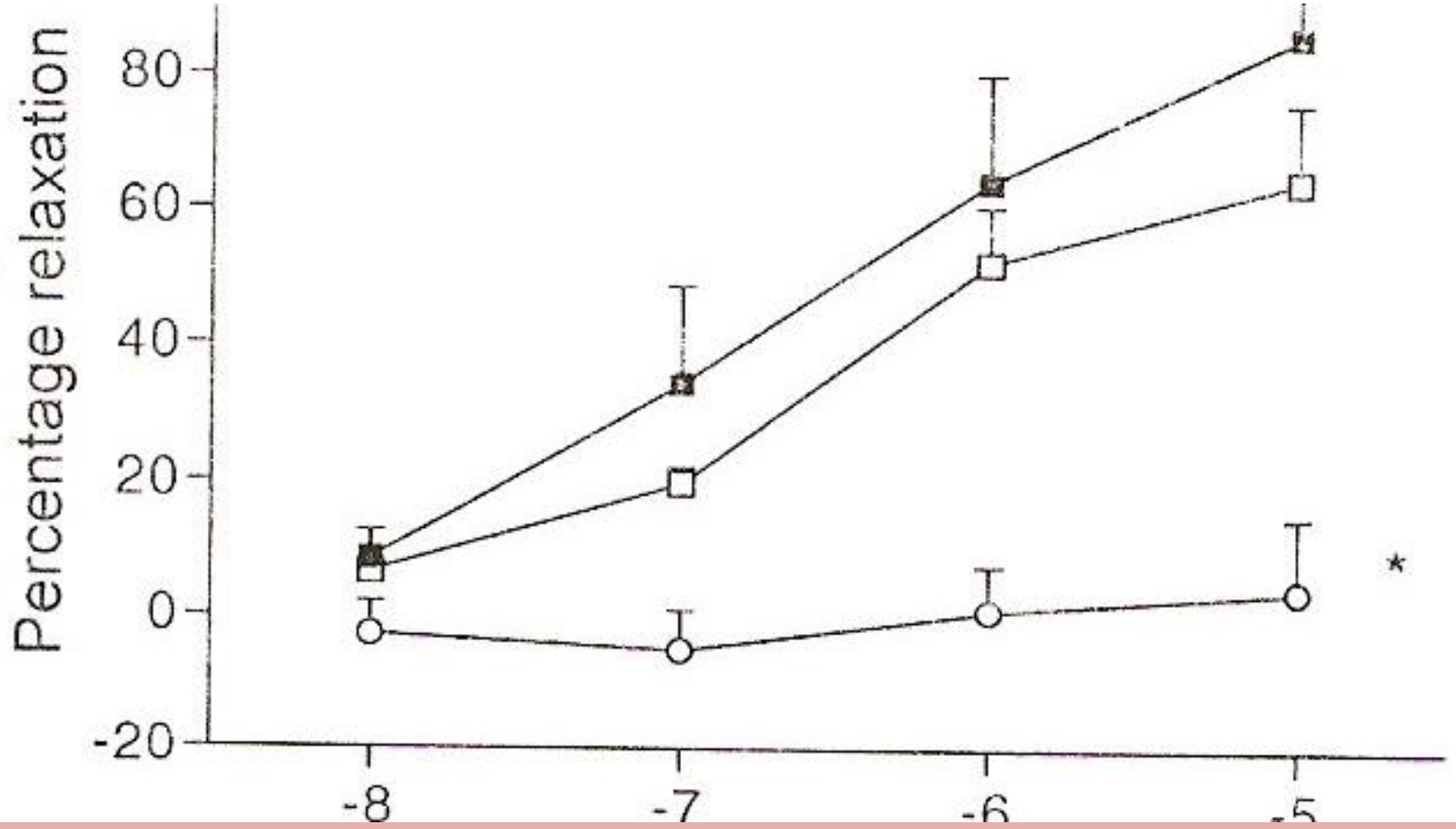

Fig. 6. Concentration –response relaxation curves in rats fed high salt diet before and after blockers

- The enhanced relaxation response that we reported in arterial resistance vessels was shown to be mediated by changes in the signaling mechanism in the vessel where the usual vasodilator agent –
  - The Endothelium Derived Relaxing Factor (EDRF) i.e. NO (Nitric Oxide) is replaced by
  - another vasodilator agent, the Endothelium Derived Hyperpolarizing Factor (EDHF) *(9)*.
- We have also reported reduction in cyclic – AMP mediated relaxation responses in isolated aortic ring preparation (10).

- Concurrent administration of potassium ions (K+) or the drug spironolactone, a potassium-sparing agent, have been shown to
  - reverse or inhibit the constriction responses of blood vessels to agonists following a high salt diet *(10)*.
- This observation is important in that it has been well reported that intake of potassium e.g. in fruits helps to lower blood pressure.
- Also recently, in addition, we have reported that
  - the male hormone, Testosterone, may actually reduce the tendency for blood vessels to relax (Fig 6) and
  - so promote development of hypertension which is consistent with the higher incidence of hypertension in males (11).

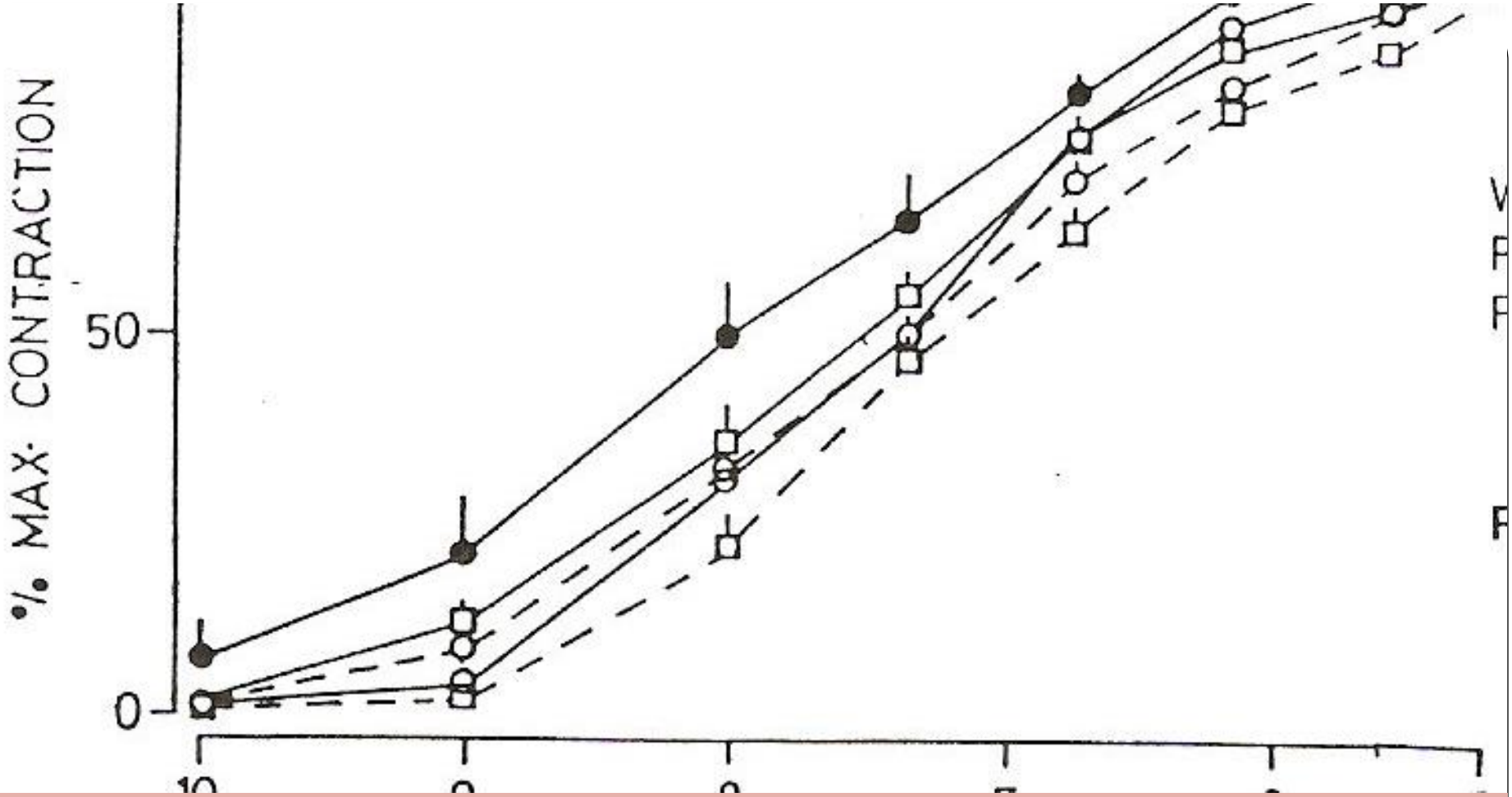

Fig. 7. Concentration response curves for norepinepherine in aortic rings from control, salt loaded, salt loaded potassium fed and salt loaded spironolactone fed rats

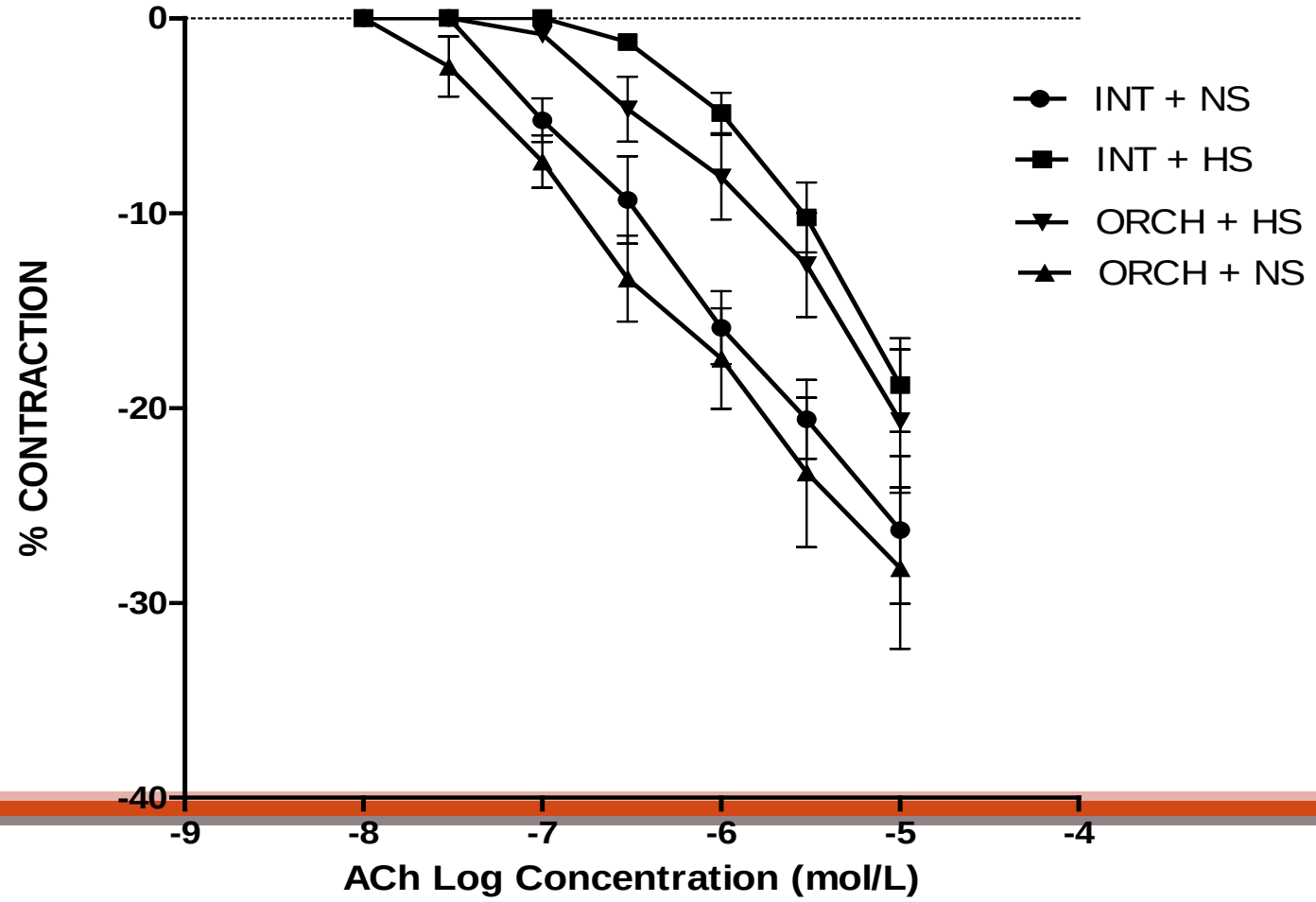

Fig. 8. Effect of testosterone on aortic rings relaxation response to acetylcholine in rats fed a high salt diet

- Following our several reports and experiments in laboratory animals, we are now shifting our focus to studies in humans.
  - As mentioned earlier, dietary salt intake can be evaluated from the 24 hour urinary excretion of sodium ion.
- We decided to carry out experiments in which oral salt of 200 – 400 mmol (about 11 – 22 gm of salt) was given to subjects over a 3 – 5 day period and we then monitored Blood Pressure and other parameters.
- The background to these series of studies is based on reports that blacks e.g. African Americans or native Africans do have a higher incidence of hypertension when compared with Caucasians.
- Furthermore, it has been shown conclusively that blacks tended to respond with a higher level of blood pressure in response to salt than their Caucasian counterparts.

- The incidence of salt sensitivity in
  - normotensive and hypertensive Caucasians in the United States is about 29% and 56% respectively compared with
  - 43% and 72% respectively in normotensive and hypertensive African Americans (13).
- In Nigeria, the incidence of hypertension often reported is
  - about 12–15% (14), which may be an under-estimation.
  - In a study in Britain, the incidence of hypertension in blacks has been reported to be as high as 50% *(15)*
- There thus appears to be a higher relationship between the salt intake and hypertension in blacks.
- This may have some relationship to salt sensitivity.
  - In salt sensitive individuals, the increase in BP in response to a loading dose of salt is greater than 5mmHg (16).

- Salt sensitivity in blacks has historical and scientific backgrounds.
- The historical background on bio-history of slavery suggests that surviving "slaves" after the transatlantic shipment did survive because of their
  - possessing inherent sodium conserving mechanisms to heat exposure and this trait was then transferred to later generations (**17**).
- However, lately it has been shown that salt sensitivity in blacks is possibly related to
  - defective Epithelial Sodium Channel (ENaC), which is the
  - membrane channel mechanism which handles the final adjustments of sodium homeostasis at the kidneys.

- A defective channel that results in excessive sodium reabsorption will lead to its accumulation and hence the tendency for blood pressure to increase.
- This defect in ENaC channel occurs in
  - about 5% of hypertensive blacks in the United State
  - compared with less than 1% of Caucasians (**18**).
- The defect has been linked to a transmutation of T594M gene, where Threonine is exchanged for Methionine, especially in the ß submit of the genes.
- The ENac channel is regulated by Aldosterone and is Amiloride-sensitive.
- Thus the drug Amiloride can be useful in cases of hypertension with defective ENaC (**18**).

- Our current studies are thus looking at:
  - The role of ENaC in salt sensitivity in Nigeria – nomotensives and hypertensives.
  - Blood pressure responses to neurally-mediated sympathetic challenges such as the Cold Pressure Test and
  - Salt Taste Threshold variability in individuals.

- Salt Taste threshold (STT) examines individual perception of salt taste at different salt concentrations.
  - A high salt taste threshold will suggest tendency to a high salt consumption because of the reduced taste perception for salt which can then lead to increase consumption and hence a rise in blood pressure.
- Some studies in our environment have reported a correlation between a high salt taste threshold and hypertension (**19**).
- Also, Preliminary results among Nigerians following salt loading with 200mmol sodium daily for 5 days have shown that
  - 44% of normotensive subjects are salt–sensitive
  - while 59% of an age-matched hypertensive group of subjects were salt-sensitive (Table 1).
- Salt sensitivity is determined when the Mean Arterial Pressure (MAP) increases by ≥5mmHg [16, 20].

- The Cold Pressor Test (CPT) has been carried out in normotensive and hypertensive subjects before and after salt loading with 200mmol of sodium daily for 5 days.
- The CPT allows categorization of vascular reactivity in subjects.
  - Hyper-reactivity occurs when the blood pressure response to the CPT is ≥15 mmHg, systolic or diastolic [21, 22].
- Our recent preliminary results have shown that
  - 71% of normotensive subjects and
  - 68.2% hypertensive subjects are hyper-reactive.
- Results from our laboratory also show that
  - salt sensitivity among normotensive and hypertensive subjects is positively correlated to systolic reactivity
- Being a predictor of the tendency to develop hypertension, this Cold Pressor Test is being developed
  - as a screening test for pre-hypertensive subjects among our populace.

Table. 1. Salt-sensitivity in Normotensive and Hypertensive Subjects

	Salt-Sensitive [SS]	Salt-Resistant [SR]	Total
Normotensive [NT] n = 18	44.4% (8)	55.6% (10)	100% (18)
Hypertensive [HTN] n = 22	59% (13)	41% (9)	100% (22)

Table. 2. Reactivity Status of Normotensive and Hypertensive Subjects Before and After Salt-loading

NORMOTENSIVE [n = 18]

	Hyper-reactive [HP]	Normo-reactive [NR]
B4 Salt	61% [11]	39% [7]
Aft Salt	72.2% [13]	27.8% [5]

HYPERTENSIVE [n = 22]

		Hyper-reactive [HP]	Normo-reactive [NR]
	B4 Salt	68.2% [15]	31.8% [7]
	Aft Salt	54.5% [12]	45.5% [10]

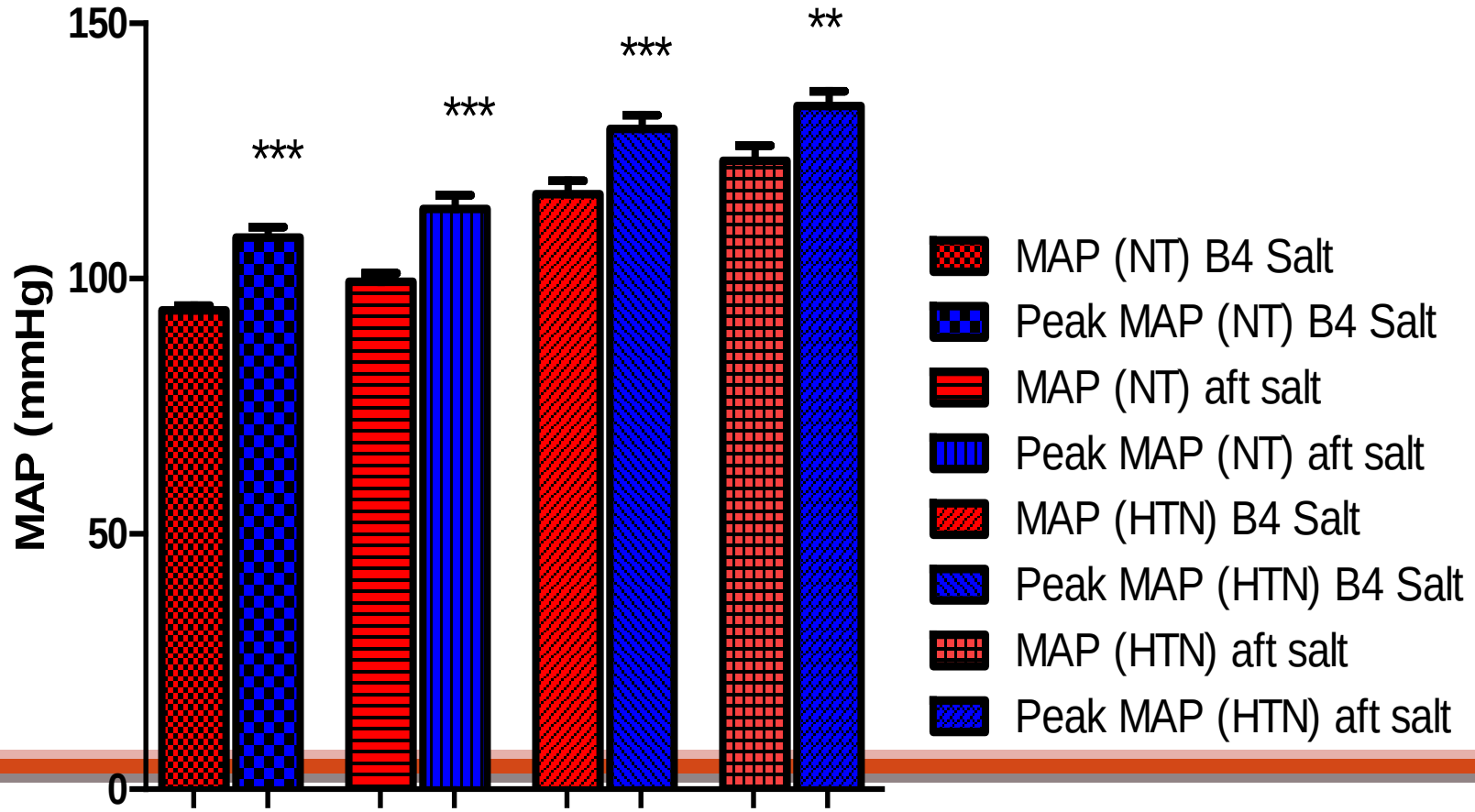

Figure. 9. Effect of Cold Pressor Test on Mean Arterial Pressure (MAP) mmHg in normotensive and hypertensive subjects before and after salt-loading. ANOVA $p < 0.0001$ ** $p<0.01$; *** $p<0.001$

- Our current on-going work seeks to eventually develop scientifically based criteria for
  - determining salt-sensitivity in an individual
  - and therefore the prediction of hypertension in Nigerians.
- So if we know this, we can therefore carry out dietary counseling to susceptible individuals so as to reduce the tendency towards high blood pressure.
- Our experiments on the assessment of ENaC will also allow us eventually to develop a possible genetic marker for identifying those with defective ENaC gene.

- In conclusion, the large numbers of studies on experimental animals and man have
  - linked a high intake of salt with the possibility of developing hypertension.
- However, not everyone will develop hypertension from salt but a large proportion of people that are salt sensitive will do so. Therefore:
  - a) a reduction in the quantity of salt in cooked food for both normotensives and hypertensives,
  - b) avoidance of high consumption of processed food,
  - c) development of the habit of NOT adding extra salt to table food,
  - d) identifying genetic markers and
  - e) identification of salt sensitive individuals
- Their counselling will go a long way in reducing significantly, the incidence of hypertension as a result of salt intake in Nigerians.

- Thank you.

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