Reversal of left ventricular hypertrophy by propranolol in hypertensive rats

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ABSTRACT

Background: Hypertension contributes significantly to the development of left ventricular hypertrophy. Left ventricular hypertrophy is associated with increased incidence of sudden cardiac death. Recognition and management of hypertension is, therefore, imperative.

Objective: To establish whether propranolol can reverse left ventricular hypertrophy in hypertensive rats.

Methods: Hypertension was induced in male albino rats by giving them 1% NaCl solution as their only drink for four weeks. Propranolol was then administered orally to one of the four groups of rats used in this study. Systolic blood pressure of each rat was measured twice a week using a modified tail-cuff method. Each rat was then sacrificed, its heart excised from the chest cavity and geometric studies carried on the left ventricle.

Results: Excessive intake of sodium salt by the rats caused an increase in their systolic blood pressure which was accompanied by left ventricular hypertrophy. The elevated blood pressure (139.4± 0.5 mm Hg) was, however, brought back to normal (108.4 ± 0.2 mm Hg) by propranolol. Data on weight, thickness, and volume of the left ventricle strongly indicated that propranolol can reverse ventricular hypertrophy.

Conclusion: Propranolol reverses left ventricular hypertrophy besides lowering elevated systolic blood pressure in rats.

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INTRODUCTION

Hypertension, commonly called high blood pressure, is the commonest of all cardiovascular diseases and is recognized as a major health problem. It causes 12.4 million deaths annually, with most of these deaths (9.6 million) occurring in developing countries[1]. The disease takes its toll by causing vascular complications that affect vital organs of the body particularly the brain, heart, and kidneys.

There is compelling evidence that many hypertensive individuals are unaware of their disease and far too few realize what the risks are or what can be done. On the basis of the known hypertensive population, only one half or even less receives adequate treatment and, out of these, only one half has satisfactory control of their hypertension[2].

Hypertension itself is not a problem *per se*; rather it is the arterial and arteriolar diseases produced by the high blood pressure that cause morbidity and mortality. In Kenya, since it is only the immediate cause of death that is recorded on death certificates, hypertension as a contributing factor is often overlooked.

Many of the complications of hypertension, for example, stroke, heart attack, and chronic heart failure, create major social, personal, and financial problems. For instance, hypertension and its complications were estimated to cost the American people over 25 billion dollars in direct medical expenditures and in income lost through illness, disability, premature loss of productivity, and death; besides an enormous, though incalculable toll of social disruption and personal and family agony[3]. Perhaps the greatest fiscal impact of hypertension and its complications upon the national economy, of a country like Kenya, is the premature withdrawal of productive individuals from the workforce. This withdrawal is not only attributable to death from coronary disease, stroke, and heart failure, but also to the morbidity from these events that are non-fatal. Recognition and management of hypertension is, therefore, imperative.

Left ventricular hypertrophy is one of the pathological hallmarks of hypertension. It is the most common and important adaptation of the heart to repeated increases in afterload[4,5]. Left ventricular hypertrophy develops as a compensatory mechanism designed to maintain a normal cardiac output in the presence of an increased arterial pressure. For a time, the

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ventricular hypertrophy produces a stable compensation for the increased afterload but, sooner or later, a stage of decompensation occurs and the ventricle fails to meet the demands placed upon it. Heart failure then occurs and the animal dies[5,6].

The efficiency of a hypertrophied heart has been widely studied in man and other experimental animals[6,7,8,9,10]. The findings support the conclusion that hypertrophy is, in fact, associated with diminished performance.

On the other hand, a hypertensive patient with left ventricular hypertrophy has four times the chance of developing heart attack compared to a patient with similar blood pressure level but no hypertrophy; also such a patient has a risk of stroke increased twelvefold and a threefold higher risk of intermittent claudication[11]. Besides, since a hypertrophied heart is associated with diminished performance, a drug that both lowers blood pressure and reverses ventricular hypertrophy is more preferable to one that only lowers blood pressure. The present study was hence carried out to establish whether the drug propranolol, a beta-adrenergic blocker, can reverse left ventricular hypertrophy in rats.

MATERIALS AND METHODS

Male albino rats aged 18-20 weeks were used in this study. The rats were divided into four groups of eight animals each. The rats had free access to rat pellets (Unga Feeds Ltd.). Normal control rats (Group I) were given distilled water while Group II rats were given 1% sodium chloride solution *ad libidum*, throughout the study period. Group III and Group IV rats were given 1% sodium chloride solution as their only drink for the first four weeks, and then distilled water and propranolol (Inderal® - AstraZeneca Pharmaceuticals LP.), respectively, for the remaining four weeks. The drug was dissolved in distilled water and administered orally (10mg/kg/day).

The systolic blood pressure of each rat was measured, twice a week, using a modified tail-cuff method[12]. To avoid variations in blood pressure due to day cycle, all measurements were carried out between 9.00am and 11.00am.

Each rat was anaesthetized with ether and then thoracotomized. The beating heart was excised from the chest cavity and immersed briefly in three changes of Tyrode's solution at room temperature in order to wash out blood from the chambers. The heart was then immersed in ice cold glutaraldehyde (2%)-paraformaldehyde (2%) fixative and fixed for at least 24 hours.

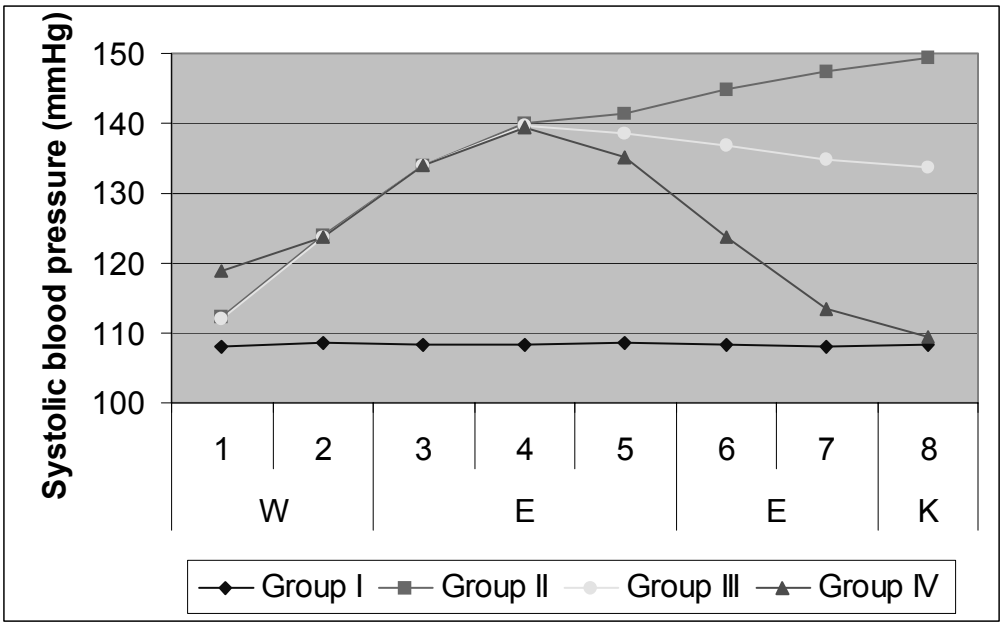
Later on, each heart was removed from the fixative and excessive fat trimmed off. The atria were separated completely from the ventricles. The right and left ventricles were then separated such that the left ventricle was composed of the left ventricular free wall plus the septum. The weight and height of the left ventricle were taken. The left ventricle was then serially cut into two halves. The thickness of the left ventricular free wall was measured using a Vernier caliper gauge (E.T. Monks and Co. Ltd.). The ventricle was then further sectioned, with a sharp blade, into approximately eight 1mm thick slices. The slices were cut at right angle to the basal-tip of apex axis. The luminal surface area of each slice was determined by planimetry. The luminal volume of the left ventricle was determined by multiplying the sum of the luminal surface areas of the slices by the height of the left ventricle.

RESULTS AND DISCUSSION

Systolic blood pressure of Group I (control) rats remained almost the same (108.4 ± 0.2 mm Hg) throughout the entire study period, while that of Group II (saline only) rats rose steadily from 112.3 ± 0.4 mm Hg to 149.3 ± 0.5 mm Hg, over the same period. This indicated that increased intake of sodium salt causes a rise in the rat's systolic blood pressure. This finding agrees with those of others (13,14) that excess dietary salt is a major factor contributing to the development of hypertension in both humans and animal models. The systolic blood pressure of Group III and Group IV rats rose steadily (from 112 to 139 mm Hg, average) in the first four weeks and then declined slightly (to 133 mm Hg) for Group III and, steeply (to 108 mm Hg) for Group IV rats, in the last four weeks of the study period (Figure 1).

The difference in systolic blood pressure between Group I and Group IV rats was statistically significant ($p<0.05$) in week 4, but was not significant in week 8. This implied that propranolol lowered the elevated systolic blood pressure (139.4 ± 0.5 mm Hg) back to normal (108.4 ± 0.2 mm Hg). This finding is similar to previous observations (15,16,17) that propranolol lowers hypertension in rats, and also in man. However, just as Skelton (18) found out, substitution of water for saline after hypertension has developed results in a modest decline in blood pressure (Figure 1, Group III).

Figure 1. Weekly mean systolic blood pressure of rats in Groups I to IV.



Data on left ventricular weight, thickness, and volume is presented in Table 1. Group II recorded the highest left ventricular weight (581.6 ± 8.4mg), and the lowest ventricular volume (214.3 ± 2.4mm^3). It also recorded the thickest ventricular wall (6.6 ± 0.1mm). This is an indication that the elevated systolic blood pressure was accompanied by development of left ventricular hypertrophy. Other investigators[6,19], have also reported that left ventricular hypertrophy, a form of end-organ damage, usually accompanies hypertension.

Table 1. Weight (W), thickness (T), and volume (V) of the left ventricle of rats in Groups I to IV. (Values are mean ± SE)

	W (mg)	T (mm)	V (mm^3)
Group I	481.9 ± 8.8	4.5 ± 0.1	404.4 ± 4.3
Group II	581.6 ± 8.4	6.6 ± 0.1	214.3 ± 2.4
Group III	555.5 ± 6.7	6.5 ± 0.1	256.6 ± 2.7
Group IV	483.3 ± 1.0	4.8 ± 0.1	414.9 ± 1.4

Hypertension makes the cardiac muscle to work harder. The resulting hypertrophy, as observed here, is the product of the thickening and shortening of the muscle fibers of the heart. The end result is a heart that is less able to meet the circulatory need of the body.

Whereas the difference in left ventricular weight was significant ($P<0.05$) between Group II and Group IV (581.6 ± 8.4 vs 483.3 ± 1.0), it was not significant between Group I and Group IV (481.9 ± 8.8 vs 483.3 ± 1.0). There was also no significant difference ($P<0.05$) in left ventricular wall thickness between Group I and IV (4.5 ± 0.1 vs 4.8 ± 0.1); however, the difference was significant between Group II and Group IV (6.6 ± 0.1 vs 4.8 ± 0.1). The same applied to ventricular volume. These observations strongly indicate that propranolol is capable of reversing left ventricular hypertrophy in rats.

Propranolol has been widely used as an antihypertensive drug since Pritchard and Gillam[20] first introduced it in 1964. Propranolol blocks beta-1 receptors predominantly in the cardiac muscle. This blockade decreases heart rate, myocardial contractility, and cardiac

output. In addition atrio-ventricular conduction is slowed. These effects lead to a decrease in blood pressure[21]. There is need for future work to investigate the mechanism by which propranolol reverses left ventricular hypertrophy.

CONCLUSION

This study has established that increased intake of sodium salt leads to an elevation of systolic blood pressure in rats, which, in turn, is accompanied by left ventricular hypertrophy. The elevated blood pressure can, however, be effectively brought back to normal, and ventricular hypertrophy reversed, by propranolol. Since a hypertrophied ventricle is associated with diminished performance, there is need to carry out further research on the ability of the available, and new, antihypertensive drugs to reverse ventricular hypertrophy.

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