ORIGINAL ARTICLE

Role of Indapamide in Attenuating Pressure Overload-Induced Left Ventricular Hypertrophy through Modulation of the Cardiac Renin-Angiotensin System

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Abstract

In rat hearts under continuous pressure overload, the hypertension diuretic medication indapamide changed the structure of the left ventricle (LV). Banding the ascending aorta increased LV pressure and, consequently, LV mass throughout a 6-week period. For an extra 6 weeks, the mice were given either a low-dose (1 mg/kg/day, n = 9) or a high-dose (10 mg/kg/day, n = 9) of indapamide. When compared to vehicle-treated controls, low-dose indapamide treatment decreased LV weights. In addition, low-dose indapamide therapy improved molecular indicators of hypertrophy, such as LV atrial natriuretic factor mRNA expression, and decreased myocyte volume. Furthermore, LV angiotensin-converting enzyme and plasma were significantly reduced by low-dose indapamide (−65%). Despite the LV's continuous pressure overload and the fact that long-term low-dose indapamide therapy did not considerably change salt excretion, these changes were seen. LV mass, shape, or gene expression were not significantly affected by high-dose indapamide treatment. In conclusion, in rats with persistent LV pressure-overload, low-dose indapamide administration results in a slight regression of ventricular hypertrophy and a downregulation of cardiac renin-angiotensin system components.

Key words: Angiotensin system, diuretics, hypertrophy, indapamide, renin

INTRODUCTION

The most common cardiac reaction to aortic stenosis and arterial hypertension is left ventricular hypertrophy (LVH).[1] Cardiac expansion may be caused by stimulation of neurohormonal systems, such as the renin-angiotensin system, in addition to heart pressure overload.[2,3] The connection between the renin-angiotensin system and the left ventricle (LV) growth response is shown by the fact that inhibition of the system may cause LVH regression despite ongoing pressure overload.[4]

Antihypertensive medications that activate the renin-angiotensin system may be viewed as less beneficial given the compelling evidence that the system plays a crucial role in exacerbating LVH when pressure overload is present.[5,6] Indapamide is a diuretic that has been found to safely and successfully decrease blood pressure in patients with mild-to-moderate hypertension. Its diuretic activity is negligible at the indicated therapeutic dose; therefore, other mechanisms must account for its antihypertensive action.[7] In addition, in hypertensive individuals receiving indapamide, LVH seems to

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Received: 26-05-2026
Revised: 23-06-2026
Accepted: 30-06-2026

regress.[8] Therefore, we investigated the effects of indapamide in an experimental scenario where a fixed constriction of the ascending aorta prevents the LV from emptying. Angiotensin-converting enzyme (ACE) inhibition has been demonstrated to improve LVH in this scenario.[9,10] Sympathectomy did not improve LVH in rats with aortic stenosis, and no other therapeutic approach has been demonstrated to do so thus far. Thus, the goal of this investigation was to find out if indapamide may make rats with fixed ascending aortic stenosis experience LVH regression. We especially expected that this potential effect would only become apparent if a little amount of indapamide, which inhibits the activation of the systemic renin-angiotensin system, was given.[11]

MATERIALS AND METHODS

Yarrow Chemicals in Mumbai provided indapamide and other chemicals. The remaining compounds were all of analytical quality.

Animals

Under general anesthesia, male Wistar rats weighing between 104 g and 160 g were ventilated and intubated. By making a thoracic incision and attaching a silver clip with an internal diameter of 0.6 mm to the ascending aorta, aortic stenosis was produced. The ascending aorta was left unclipped, although age-matched controls underwent the same therapy. Rats were fed a typical rat diet and had unrestricted access to water. Each rat was kept separately in a room with a 12-h light/dark cycle. To collect urine, the animals were kept in metabolic cages during the final 5 days of the study. Every safety measure was implemented in compliance with the guidelines set forth by the Indian government's committee for control and supervision of experiments on animals.

Treatment

For 6 weeks following surgery, indapamide (1 or 10 mg/kg/day; $n=9$) or a placebo ($n=9$) was given once daily. Hydroxycellulose was only given to the vehicle (aortic stenosis with placebo treatment) and control (fake surgery, $n = 9$) groups. Before being applied, indapamide was dissolved in hydroxycellulose. Every week, the weight of each animal was measured in order to modify the dosage. The dosage was determined by prior research on indapamide in both short-term and long-term studies utilizing different models of animals with secondary types of hypertension or genetically hypertensive animals. It was frequently discovered that 3 mg/kg/24 h was the most effective oral dosage of indapamide to lower hypertension in spontaneously hypertensive rats. Similar to other natriuretic medications, indapamide has demonstrated a diuretic effect in several studies; however, its exact mode of action is yet unknown. Dehydrated rats are markedly diuretically affected by single oral doses of indapamide, starting at 0.5 mg/kg. Natriuresis was doubled, and kaliuresis was 1.2 times higher with a short dose of 1 mg/kg.[12]

Indirect systolic blood pressure measurement

An automated cuff inflator-pulse detection system was used to take indirect systolic blood pressure using the tail-cuff method before, 1 week following, and right before the end of treatment. The reported values are the average of four to six recordings made by the same investigator at the same time on 3 separate days, 4 h after the medication was given.

Tissue preparation

The rats were given anesthetic and then beheaded. The tissue was processed right away. The left and right ventricles were kept apart, and the ventricles were separated from the atria. After weighing each tissue, it was instantly frozen in liquid nitrogen and kept at −70°C until it was needed. Blood was drawn through the inferior vena cava, which is located between the liver and the peritoneum.

Biochemical measurements

Sodium, potassium, and creatinine concentrations in serum and urine were analyzed, and creatinine clearance was calculated using an automated analyzer. As previously stated, the ACE activity in the serum and heart was measured using a modified fluorometric approach. As directed by the manufacturer, commercially available kits were used to measure the levels of renin and aldosterone in plasma.

Statistical analysis

Groups were compared using analysis of variance. Statistical significance was defined as a $P < 0.05$

RESULTS

Blood pressure, LV pressure, and pressure gradient

Significant LV pressure overload was found in animals with aortic banding [Table 1]. Blood pressure, heart rate, aortic pressure gradient, and left ventricular pressure were all unaffected by indapamide. As a result, the drug had no discernible hemodynamic effects in this model.

Estimation of biochemical parameters (Sodium, potassium, and creatinine)

For the final 5 days of medication or vehicle treatment, the animals were housed in a metabolic cage. The serum levels

Table 1: Measurement of blood pressure, left ventricle pressure, and pressure gradient

Variable (6th week of treatment)	Control	Vehicle	Indapamide 1 mg/kg	Indapamide 10 mg/kg
Hear rate (Beats/min)	442±52	417±19	418±18	426±24
Blood pressure (mm/Hg)	126±9	128±12	125±10	127±12
Aortic pressure (mm/Hg)	116±15.27	128±32	126±8	128±21

Values are expressed as Mean±standard deviation $P<0.05$ compared with control

Table 2: Estimation of biochemical parameters (Sodium, potassium, and creatinine)

Parameter	Control	Vehicle	Indapamide 1 mg/kg	Indapamide 10 mg/kg
Sodium (mM)	162±28	148±76	142±60	125±35
Potassium (mM)	409±42	450±221	430±122	384±102
Creatinine (μM)	86.2±9.4	92.4±26.6	84.6±21.2	83.1±15.8
Urine volume (mL/day)	8.22±1.8	8.11±5.1	8.19±5.2	9.1±1.7

Values are expressed as Mean±standard deviation $P<0.05$ compared with control

of creatinine, potassium, and sodium did not differ across the four groups of rats at this time. These measurements were likewise similar in the urine of rats with aortic stenosis that were given a placebo and a fake therapy. Urine volumes were slightly greater, and salt concentrations were slightly lower in rats administered indapamide. The creatinine clearances of the four groups were similar [Table 2].

Heart weights

The animals showed notable cardiac hypertrophy following 12 weeks of aortic banding. Even after controlling for body weight, low-dose indapamide therapy resulted in a small but significant decrease in LV weight when compared to vehicle-treated aortic banding rats (−12%, $P = 0.008$; [Table 3]). In a similar vein, low-dose indapamide treatment resulted in a notable decrease in right ventricular mass.

CONCLUSION

Low-dose (1 mg/kg/day) indapamide treatment for LVH may cause a slight regression of LVH due to the downregulation of cardiac growth-regulatory genes such as cardiac ACE. Nevertheless, high-dosage indapamide (10 mg/kg/day) had no effect on LVH in this animal. This could be because, as was seen with the low dose, side effects, such as the activation of the circulatory renin-angiotensin system, exceeded the advantages of indapamide. The findings support the recommendation to treat arterial hypertension with cardiac hypertrophy using a lower dosage of indapamide.

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Source of Support: Nil. **Conflicts of Interest:** None declared.