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Research Article

Myocardial hypertrophy induced by nephrectomy alters cardiovascular parameters and cardiac GLUT-4 expression in rats.

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Abstract
Given the discrepancies on the role of glucose in cardiac hypertrophy, the present study was designed to evaluate cardiac Glucose Transporter-4 (GLUT-4) expression during hypertension-induced myocardial hypertrophy, and exercise-induced myocardial hypertrophy in rats.Twenty Wistar rats were divided into four groups of five rats for studies on myocardial hypertrophy induced by unilateral nephrectomy–induced myocardial overload, and exercise-induced hypertrophy. Systolic, diastolic, mean arterial pressure and heart rate were measured along with QRS-interval and R-amplitude. Immunohistochemistry of paraffin embedded myocardial tissues were carried out to estimate the expression of GLUT-4.The systolic, diastolic and mean arterial pressure of unilateral nephrectomy-induced hypertensive rats were significantly increased compared to control. The QRS-interval was significantly prolonged when compared with the control rats. Nephrectomy-induced myocardial hypertrophy caused a significant decrease in the expression of GLUT-4 compared to control. There was no significant difference in blood pressure parameters of exercise-induced cardiac hypertrophy. The QRS interval of the rats subjected to swimming exercise was prolonged significantly but not the R-amplitude. There was no significant difference in the cardiac tissue expression of GLUT-4 exercise-induced hypertrophy rats and control rats.In conclusion, the present study suggest that a decrease in GLUT-4 expression is associated with myocardial hypertrophy arising from unilateral nephrectomy-induced hypertension.

Key Words: unilateral nephrectomy; cardiac hypertrophy; GLUT-4; myocardial overload

INTRODUCTION

Cardiac hypertrophy is central to most cardiovascular related diseases because it represents the response of the myocardial tissue to overload that is secondary to conditions like hypertension, chronic renal disease, myocardial infarction, cardiomyopathy, and valvular disease (Marian et al., 2017). These conditions are known to cause pressure and volume overload that results in maladaptive increased ventricular wall thickness that is not proportional to ventricular chamber (Hallow et al., 2021; Berenji et al., 2005). Physiologically, hemodynamic stress can result in volume overload and adaptive ventricular muscle mass dilatation in exercise and pregnancy (Chung et al., 2014; Ellison et al., 2012). This is often referred to as physiological hypertrophy associated with proportional increase in ventricular muscle mass and ventricular chamber (Carreno et al., 2006; Kemi and Ellingsen, 2021). Cardiac hypertrophy is known to induce a shift in substrate preference for the production of energy and this metabolic change has been attributed to the loss of myocardial activity (Doenst et al., 2013). Under resting condition, the heart depend to a large extent on the mitochondrial oxidation of fatty acid (60-70%) for the generation of energy in form of ATP, while glucose and lactate contribute the remaining 30-40% (Ma and Li, 2015; Stanley et al., 2005). During post-prandial state, glucose was revealed to contribute 60-70% ATP required for myocardial activity through enhanced activity of insulin (Bertrand et al., 2008; Ormazabal et al., 2018). Previous studies revealed that cardiac hypertrophy alter myocyte energy substrate preference from predominantly fatty acid to glucose. This change in energy substrate is thought to be associated with increased activity of glucose transporter-1,-4 (GLUT-1 and GLUT-4) although GLUT-4 is more predominant in the adult myocardium (Chadt et al., 2020). GLUT-4 remains inactive in myocardial cytoplasm until factors like hemodynamic stress and insulin activate the translocation of these transporters to the plasma

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membrane (Becker et al., 2001) during pressure overload and volume overload.

However, there are contradictory reports concerning the influence of ventricular hypertrophy on glucose uptake in the myocardial tissue. Previous studies revealed elevated uptake and use of glucose in the hypertrophied heart of humans and animals while fatty acid use was reduced (Diem and Zhao, 2019). Previous report by Hamirani et al., (2016) revealed no significant difference in the glucose uptake between hypertensive patients with and without left ventricular hypertrophy (LVH) and normotensive patients. In addition, the presence of myocardial insulin resistance was unraveled in cardiac hypertrophy patients due to aortic stenosis independent of diabetes, coronary artery disease or hypertension (Jia et al., 2016). Wende et al., (2017) further revealed that mice with cardiac hypertrophy and decreased life span are GLUT-4 deficient.
Given the discrepancies on the role of glucose in cardiac hypertrophy, this study was designed to evaluate the myocardial expression of GLUT-4 in volume overload- and exercise-induced cardiac hypertrophy in rats.

MATERIALS AND METHODS

Reagents: Normal goat serum, biotinylated secondary antibody and streptavidin peroxidase (KPL, Inc., Gaithersburg, Maryland, USA). GLUT-4 protein antibody (bioss Inc. Woburn, Massachusetts, USA).

Experimental design and animal treatment: Twenty male Wistar rats, weighing 120-150 g were divided into four groups of five rats each to carry out the study on pathological cardiac hypertrophy induced by unilateral nephrectomy–induced myocardial overload, and exercise-induced cardiac hypertrophy. They were fed with commercial rat chow and water ad libitum. Acclimatization was done for 1 week before the commencement of this study. The Wistar rats were subjected to humane care based on the guideline for the care and use of laboratory animals, and ethics regulations as provided in National Institute guidelines of animals' welfare during experiment, National Health Institute, 1996.

Pathological hypertrophy: Ten Wistar rats were grouped (n=5) into control and unilateral nephrectomy-induced myocardial overload -induced cardiac hypertrophy rats.

Unilateral nephrectomy-induced myocardial overload procedure
Ketamine 75 mg/kg in combination with xylazine 10 mg/kg were administered intraperitoneally. The abdominal region was shaved, and incision was made to expose the abdominal viscera. The left kidney was located, its blood supply and ureter are then exposed. The renal blood supply was identified and isolated with two ligatures, artery and vein were both tied off together at the hilum of the kidney and at the aorta/inferior vena-cava using sterile 4–0 silk ligature. The kidney was carefully removed out of retro-peritoneal cavity. The abdominal contents in all rats were carefully returned, and the wound closed using sterile continous 3–0 chromic gut suture. Thereafter, high NaCl loading was done with 4% NaCl in diet of the rats for 6 weeks (Dizaye et al., 2011). The control rats had sham nephrectomy with brief exposure of the left kidney and subsequent closure of the abdomen with continuous 3-0 chromic catgut suture.

Exercise-induced hypertrophy: Ten Wistar rats were grouped (n=5) into control and exercise-induced hypertrophy rats.
Exercise training protocol
The exercised rats were taken through a six weeks swim training regimen. Exercise training was performed in a swimming tank (112cm×680cm×650cm) filled with tap water that was warmed to approximately 27˚C, and the exercise intensity was progressively increased. In the first week, the rats swam for ten minutes every day. In the second week, the swimming time was increased each day until the animals could swim for 60 min while wearing a caudal dumbbell weighing 5% of their body weight (Medeiros et al., 2000).

Blood pressure and ECG measurement: Blood pressure parameters like systolic, diastolic, mean arterial pressure and heart rate were determined in non-invasive, non-anaesthetized rats, through tail plethysmography with the use of an electrosphygnomanometer (CODA, Kent Scientific, USA). ECG parameters like QRS-interval and R-amplitude were measured by attaching standard lead II electrodes subcutaneously in conscious rats using a seven-lead ECG machine (EDAN VE-1010, Shanghai, China). The machine was calibrated at 20 mm/mV amplitude and 50 mm/s paper speed.

Immunohistochemistry of GLUT-4: Immunohistochemistry of paraffin embedded myocardial tissues were carried out after the tissues were preserved with formalin as described earlier by Alabi et al., (2020).

Statistical Analysis: All values were reported as the mean ± standard error of mean. The differences between two groups were compared using paired t-test, and analysis of variance was used to compare the differences within the group along with Dunnett's post-test. Statistical analysis was done using GraphPad Prism® 5.0, and all statistical significance set as $p < 0.05$.

RESULTS

Unilateral nephrectomy-induced myocardial hypertrophy
In this study, the systolic, diastolic and mean arterial pressure of unilateral nephrectomy-induced hypertensive rats were significantly increased compared to control (Table 1). The heart weight to tail length ratio of the nephrectomy-induced hypertensive rats was also increased significantly ($p<0.05$) compared to the control group. The QRS-interval of the hypertension-induced myocardial hypertrophy rats was prolonged significantly when compared with the control although there was no difference in R-amplitude and plasma glucose level of the two groups in this study (Table 1). Nephrectomy-induced myocardial hypertrophy caused a significant decrease in the expression of GLUT-4 compared to control (Plate A & Figure 1A).

Table 1:
The effect of hypertension-induced cardiac hypertrophy on hemodynamicparameters, ECG parameters, plasma glucose and cardiac hypertrophy index

Parameters	**Control**	**Hypertension**
Systolic Blood Pressure (mmHG)	125.21 ± 4.6	140.52 ± 3.5*
Diastolic Blood Pressure (mmHG)	90.70 ± 5.2	118.37 ± 2.7*
Mean Arterial Pressure (mmHG)	100.30 ± 3.8	125.66 ± 3.7*
QRS-interval (m/s)	10.67 ± 1.5	18.33 ± 0.7*
R-amplitude (mV)	0.38 ± 0.09	0.33 ± 0.04
Heart Weight/Tail Length (gm/cm)	0.030 ± 0.0024	0.065 ± 0.0031*
Plasma glucose level (mg/dl)	94.60 ± 2.5	99.60 ± 1.6

The results are expressed as mean ± SEM, for five animals in each group. *Values differ significantly from normal control (*p< 0.05).

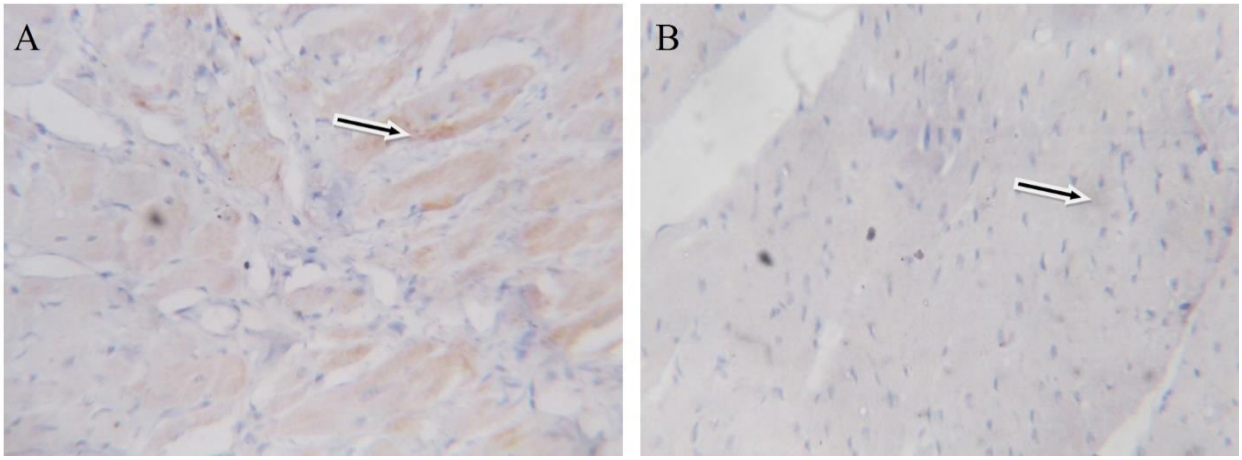

Plate A:
Photomicrons photomicrograph showing cardiac GLUT-4 expression in rats (x 100). **A** represents Immunohistochemical staining in control rats. **B** represents Immunohistochemical staining in hypertension-induced myocardial hypertrophy rats

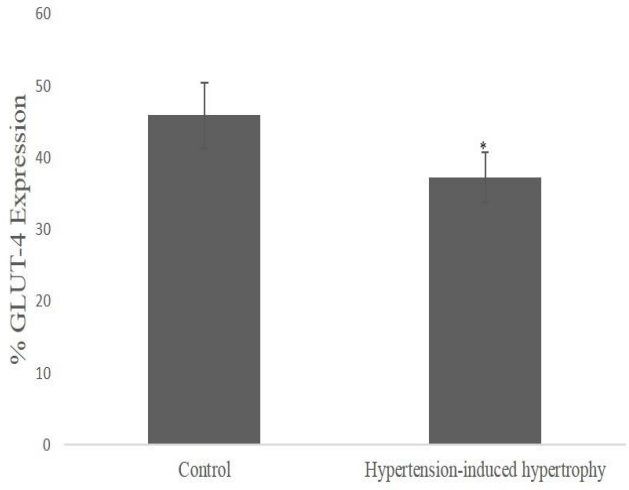

Figure 1A:
Bar chart showing the GLUT-4 expression as mean ± SEM. *p<0.05 is considered significant compared with control

Exercise-induced hypertrophy

From table 2, there was no significant difference in blood pressure parameters of exercise-induced cardiac hypertrophy and control rats. The QRS interval of the exercise rats was prolonged significantly but the R-amplitude that was increased in the exercise-induced hypertrophy rats was not significant when compared with control. The heart weight/tail length was significantly increased in the exercise-induced hypertrophy rats compared to control rats. The heart beat/minute of physiological hypertrophy group was slightly but insignificantly reduced compared to normal. There was no significant difference in the cardiac tissue expression of GLUT-4 exercise-induced hypertrophy rats and control (Plate B& Figure 2A).

Table 2:
The effect of exercise-induced cardiac hypertrophy on hemodynamic parameters, ECG parameters, and cardiac hypertrophy index

Parameters	**Control**	**Exercise**
Systolic Blood Pressure (mmHG)	128.41 ± 3.3	120.52 ± 3.2
Diastolic Blood Pressure (mmHG)	100.20 ± 1.2	108.27 ± 3.8
Mean Arterial Pressure (mmHG)	115.56 ± 1.6	125.76 ± 2.9
QRS-interval (m/s)	11.57 ± 4.2	15.33 ± 2.3*
R-amplitude (mV)	0.45 ± 0.04	0.78 ± 0.02
Heart Weight/Tail Length (gm/cm)	0.047 ± 0.0062	0.078 ± 0.0024*
Heart rate (beat/min)	260 ± 7.6	225 ± 4.5

The results are expressed as mean ± SEM, for five animals in each group. *Values differ significantly from normal control (*p< 0.05).

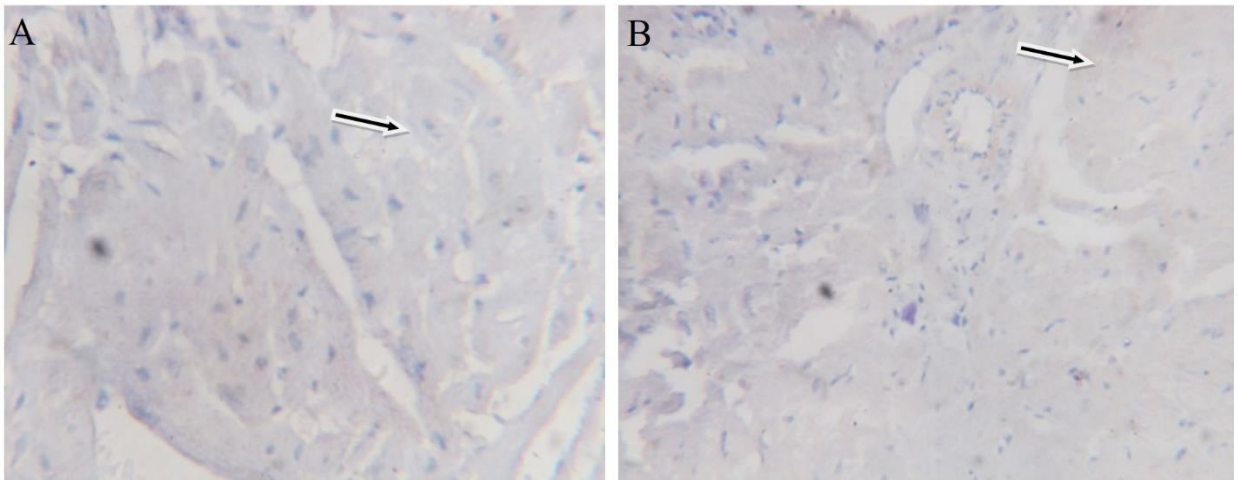

Plate B:
Photomicrons photomicrograph showing cardiac GLUT-4 expression in rats (x 100). **A** represents Immunohistochemical staining in control rats. **B** represents Immunohistochemical staining in exercise-induced myocardial hypertrophy rats **.**

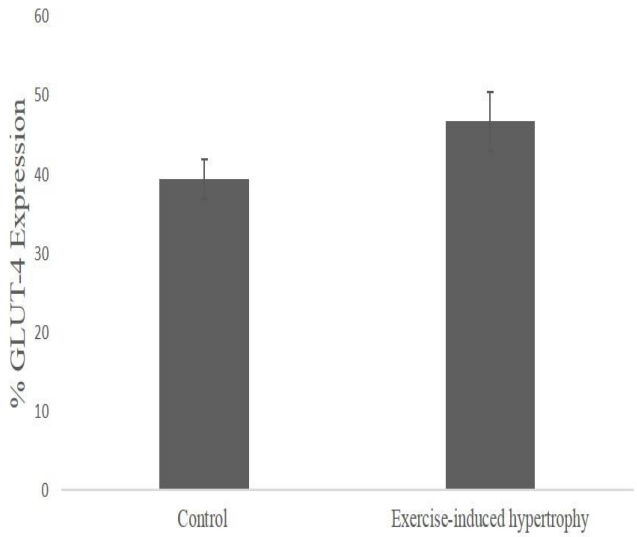

Figure 2A: Bar chart showing the GLUT-4 expression as mean ± SEM. *p<0.05 is considered significant compared with control

DISCUSSION

Hypertension is a major cause of concentric or pathological myocardial hypertrophy. Pressure overload that results from hypertension is directly related to increase in afterload of aorta and peripheral resistance (Pagoulatou et al., 2021). From the present study, unilateral nephrectomy caused systolic pressure, diastolic pressure, mean arterial pressure and heart weight to tail length ratio to increase significantly compared to control rats. The increased resting blood pressure parameters support previous study on unilateral nephrectomy-induced hypertension (Hung et al., 2015). In response to unilateral nephrectomy, the body activate compensatory mechanisms like sympathetic reflex and renin-angiotensin II-aldosterone system leading to increased preload and afterload (Chong et al., 2018). Sustained increase in preload and afterload for long time usually leads to maladaptive or

pathological hypertrophy. The significant increase in heart weight/tail length of unilateral nephrectomy-induced hypertensive rats fed with 4% NaCl diet for 6 weeks compared with control rats in this study suggest that pressure overload and volume overload caused myocardial hypertrophy. This result agrees with findings previously reported on myocardial overload leading to hypertrophy (Rafael et al., 2020, Lin et al., 2015 and Wang et al., 2017).

Previous researches have shown that resting blood pressure and heart rate of an athlete that perform dynamic exercise like swimming, running or cycling were moderately low compared with a normal untrained person or static athletes (Barbara et al., 2011). Similar result was observed in this study, there was a slight but insignificant decrease in the systole, diastole, mean arterial blood pressure and heart rate. The mechanism of low BP seems unclear but was linked with modified resting autonomic nervous system balance (Pavlik et al., 2002), baro-receptor reflex reset (Lenard et al., 2005) and modified effect of vasoactive substance. Similar to unilateral nephrectomy-induced myocardial hypertrophy, heart weight/tail length was significantly increased in the exercise-induced hypertrophy. Enlargement of left ventricle during exercise-induced hypertrophy is known to be caused by volume overload, which is associated with increase in ventricular mass that is proportional to ventricular chamber. Although there was a significant increase in heart weight/tail length and prolongation of QRS-complex (ventricular depolarization) in the pathological and physiological myocardial hypertrophy model of this study, the R-amplitude of hypertension-induced overload was low while that of exercise-induced overload was high compared to normal rats. The low R-amplitude in the hypertension-induced hypertrophy compared with exercise-induced hypertrophy may be a useful ECG parameter to differentiate these two types of hypertrophy.

Glucose transporter 4 (GLUT-4) are predominant cardiac tissue membrane proteins that assist in moving glucose into myocardial cytosol through facilitated diffusion (Szablewski, 2017). During resting phase, GLUT-4 are found mainly in myocardial tissue cytoplasm, but translocate to the cell membrane in response to membrane receptor- signal transduction pathway like IRS1/2-PIK3- protein kinase Akt pathway (Chabowski et al., 2006). From the present study, myocardial tissue expression of GLUT-4 in control rats was significantly increased when compared with hypertension-induced myocardial hypertrophy rats. This result contradict previous studies that revealed an increase in glucose uptake and expression of GLUT-4 during abnormal heart condition like myocardial hypertrophy (Aerni-Flessner et al., 2012). The reduced GLUT-4 expression observed in this study agrees with the study of Hamiriani et al., (2016), that showed myocardial decrease in the uptake of glucose in hypertensive patient with hypertrophy compared to normal patients. Decreased GLUT-4 expression in this study also correlate with the findings of Jameel and Zhang, (2009) that revealed a decrease in myocardial glucose uptake and GLUT-4 expression in patient with aortic stenosis-induced hypertrophy compared with normal patients. From the study of Jameel and Zhang, (2009), decrease in myocardial tissue expression of GLUT-4 correlate with insulin resistance that is different from the hyperglycemic whole body insulin resistance and thus suggest that myocardial hypertrophy is associated with its peculiar insulin resistance independent of diabetes. Myocardial hypertrophy-induced insulin resistance was explained to be caused by hemodynamic stress during myocardial overload and this stress has been suggested to cause reduced insulin sensitivity through desensitization of IRS-protein kinase Akt pathway and also involve activation of p38 MAPK (Lausten et al., 2007; Qi et al., 2013). Further studies carried out by Witteles and Fowler, (2008), Liling et al., (2019) revealed similar decrease in myocardial GLUT-4 expression during cardiac hypertrophy and also concluded that myocardial insulin resistance is independent of systemic insulin resistance.

Further investigation on the expression of GLUT-4 in physiological hypertrophy was carried out in the present study to confirm the correlation between myocardial hypertrophy and insulin resistance. From the result obtained, there was a slight but insignificant increase in myocardial GLUT-4 expression in the exercise-induced myocardial hypertrophy rats compared with normal control rats. Also, the insignificant difference in GLUT-4 expression between exercise-induced hypertrophy and normal control rats confirm the cardiovascular adjustment that was observed in the blood pressure parameters measured.

In conclusion, the present study suggest that a decrease in GLUT-4 expression is associated with myocardial hypertrophy that arise from unilateral nephrectomy-induced hypertension.

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