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Research Article

Sodium bicarbonate supplementation prevents cardiac hypertrophy in male rats exposed to high intensity swim exercise via inhibition of lactate dehydrogenase activity

[1]A.O. Afolabi and [2]*S.T. Shittu

Department of Physiology, Faculty of Basic Medical Sciences, [1]Ladoke Akintola University of Technology, Ogbomosho, Nigeria; [2]University of Ibadan, Ibadan, Nigeria

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ABSTRACT

Background: Cardiac hypertrophy is linked with ventricular arrhythmia and can be fatal among athletes engaged in high intensity exercise. This study investigates the effect of sodium bicarbonate on cardiac hypertrophy induced by swim exercise in male Wistar rats. **Methods**: Forty male Wistar (100-150 g) randomly divided into 5 groups 1-5 (n =8) were used. Group 1 was the control sedentary animals while groups 2-3 and 4-5 were exercised at low or high intensity, respectively. Groups 1,2 and 4 received distilled water while groups 3 and 5 received sodium bicarbonate (250 mg/kg, p.o) daily. Exercise was carried out by swimming in a temperature regulated water tank 5 days/ week for 8 weeks. The intensity was varied by attaching 5% body weight load to the tail of the high intensity exercise groups while the low intensity groups were unloaded. Body weight was monitored weekly. Blood samples were obtained for plasma lipid profile, C-Reactive Protein (CRP) and Lactate Dehydrogenase (LDH) concentration. Cardiac hypertrophy was determined from the heart weight to tail length (HW:TL) ratio. Data were presented as Mean ± SEM. **Results**: Final body weights of all exercised groups were not different when compared with their initial weight. Cholesterol and low-density lipoprotein were decreased in the high intensity exercise group treated with sodium bicarbonate. Triglyceride level was not different across all groups while High-density lipoprotein increased in the low intensity untreated and low intensity treated groups. CRP level was not different across all groups while LDH activity was significantly decreased in the high intensity exercised group treated with sodium bicarbonate. Sodium bicarbonate treatment also caused significant decrease in HW:TL ratio in the treated high intensity exercise group compared with their corresponding untreated group. **Conclusion**: Sodium bicarbonate supplementation ameliorated swim exercise-induced cardiac hypertrophy in male Wistar rats through a mechanism that probably involves lactate dehydrogenase activity.

INTRODUCTION

Acidosis is a well-documented consequence of intense exercise and this contributes largely to exercise-induced fatigue (Fittz, 1994). The traditionally held belief is that lactate accumulation is responsible for the acidosis but current evidence tend to disprove this (Gladdens, 2004) as lactate is a proton acceptor rather than a donor of proton to reduce pH, thus, the acidosis is of metabolic origin pooled from the increased glycolysis and ATP hydrolysis (Robergs, 2001; Robergs et al., 2004). Nonetheless, increased blood lactate exists during metabolic acidosis and its use as an indirect marker of acidosis remains acceptable for clinical diagnosis (Meerhaeghe and Velkeniers, 2005). Interestingly, lactate has been implicated as the signaling molecule for cardiomyocyte growth leading to cardiac hypertrophy (Dai et al., 2020). Through the stabilization of N-myc downregulated gene family 3 and stimulation of extracellular signal-regulated kinase, lactate supplementation to rats with knockout Lactate Dehydrogenase A activity significantly reversed defects in adaptive cardiomyocyte growth in response to hemodynamic stress (Dai et al., 2020). Hemodynamic

*Address for correspondence:
Email: st.shittu@ui.edu.ng

stress condition is typical during exercise (Kounoupis et al., 2020).

Cardiac hypertrophy in trained athletes is unarguably physiological, being an adaptive measure to meet increased metabolic demand during exercise and to enhance cardiac function at rest (Richey and Brown, 1998; Iemtsu et al., 2003). Exercise-induced cardiac adaptations in addition to ventricular hypertrophy include enhanced aerobic capacity and diastolic cardiac enlargement resulting in increased ventricular stroke volume and cardiac output (Buttrick and Scheuer, 1987; Pellicia et al., 1996;1999; Dorn, 2007). However, at extreme conditions such as severely intensified exercise, cardiac hypertrophy could cause sudden death among athletes (Hart, 2003) due to the associated ventricular arrhythmia (Abdollahi et al., 2016; Yılmaz et al., 2018; Gazdag et al., 2020). It may be speculated that engaging in long term high intensity sports results in premature deaths of the athletes. Since excessive lactic acid production invariably accompanies such high intensity unremitting exercise, this may be detrimental to normal cardiac hypertrophy. Therefore, preventing or minimizing extreme exercise-induced cardiac hypertrophy in athletes may well be life-saving. Sodium bicarbonate supplementation during exercise has been shown to buffer increased lactate production (Beaver et al., 1986; Ardévol et al., 1987; Valenza et al., 2012), enhance muscular strength (Materko et al., 2008) and improve performance in runners (Gledhill, 1984), swimmers (Gao et al., 1988) and sprint cyclist (Lavander and Bird, 1989). Modulation of pyruvate-lactate axis has been found beneficial in prevention of cardiac hypertrophy and heart failure (Tran and Wang, 2019; Cluntun et al., 2021), it is however not known if sodium bicarbonate supplementation with its consequent effect on lactate production could be beneficial in the prevention of cardiac hypertrophy. The current study was therefore designed to investigates the effect of sodium bicarbonate on cardiac hypertrophy *in* rats following low and high intensity exercise.

MATERIALS AND METHODS

Forty male Wistar rats weighing between 100 and 150 g were used for the study. They were housed in plastic cages in the animal house of the Department of Physiology, Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, Ogbomosho under controlled environmental condition of 22 ± 3ºC temperature, 12 hours -12 hours light/ dark cycle and a relative humidity of 60 ± 5%. The rats were allowed free access to standard pelletized rat feed and water. Acclimatization was carried out for two weeks prior to the experiment. All experimental protocol and handling of the rats were done in accordance with standard ethical guideline as contained in the NIH publication No. 85-23 guidelines.

Experimental design

The animals were randomly divided into 5 groups of 8 rats each and treated as follows:

1. Sedentary Control (Control): Non-exercised normal rats administered 1ml/Kg distilled water daily
2. Low intensity Untreated (LU): The rats were exercised at low intensity and administered 1ml/Kg distilled water daily.
3. Low intensity Treated (LT): The rats were exercised at low intensity and orally administered 250 mg/kg body weight of Sodium Bicarbonate daily
4. High intensity Untreated (HU): The rats were exercised at high intensity and administered 1ml/Kg distilled water daily
5. High intensity Treated (HT): The rats were exercised at high intensity orally administered 250 mg/kg body weight of Sodium Bicarbonate daily.

Exercise and treatments were done between 9 am and 10 am daily for 8 weeks. The body weights were monitored weekly.

Exercise Protocol

Exercise was carried out using the swimming protocol described by Evangelista et al (2003). This protocol has been verified to induce cardiac hypertrophy in rats (dos Reis et al., 2018). Briefly, a swimming chamber made from a 100 cm deep circular water tank filled with water up to 50 cm mark was used. The water temperature was maintained at 31 ± 1^0C. The animals were initially trained to swim for 5 days by dropping them into the water for incremental duration until the 60 minutes/ day was attained. After the adaptation training, the rats were exercised for 60 minutes/ day, 5 consecutive times a week for the 8 weeks period of the study. The high intensity exercise was done by attaching a load which is equivalent to 5% body weight of the rats to their tail while the low intensity exercise did not bear any weight. The animals were immediately wrapped and drained in towel after removal from swimming chamber before being returned to their cages.

Determination of Cardiac hypertrophy and biochemical assays

After eight weeks, the animals were sacrificed through cervical dislocation and blood was collected through the retro-orbital sinus into heparinized bottle for plasma

lipid profile, C-Reactive Peptide and lactate dehydrogenase activity using standard commercially available kits. The heart weight to tail length ratio was used as an index of cardiac hypertrophy (Yin et al., 1982; Syed et al., 2016; Ferridooni et al., 2017)

Statistical Analysis

Data were presented as Mean ± Standard Error of Mean. Difference in mean values were assessed by Analysis of Variance (ANOVA) followed by Tukey's posthoc analysis and P< 0.05 was considered significant.

RESULTS

Effect of sodium bicarbonate supplementation on body weight of exercised male Wistar rats

As shown in table 1, the sedentary non-exercised rats had significant weight gain while, there was no significant change in the body weight of all exercised rats when their initial weights were compared with their final weights at 8 weeks. However, all exercised groups had significantly reduced weights compared with the control. Sodium bicarbonate supplementation in the LT and HT animals did not have any effect on their weights when compared with the untreated and the control groups.

Table 1: Effect of sodium bicarbonate supplementation on body weight of exercised male Wistar rats

Bodyweight (g)	**Group**				
	Control	**LU**	**LT**	**HU**	**HT**
4th week	104.25±2.90	108.75±5.87	103.88±4.81	115.67±7.37	108.63±5.93
6th week	115.88±3.0	107.38 ±5.78	105.88±7.63	111.4±7.58	104±4.87
7th week	124.88±2.72	105.5±5.64	107.57±6.94	112.63±7.8	105.13±4.47
8th week	132.75±2.35*	99.5±5.13	113.86±6.25	107.38±7.83	102.43±3.07

Data are expressed as Mean ±SEM (n=8). * P < 0.05 when the initial weight was compared with the final weight. LU=Low intensity Untreated, LT= Low Intensity Treated, HU=High intensity Untreated, HT= High Intensity Treated.

Table 2: Effect of sodium bicarbonate supplementation on plasma lipid profiles of exercised male Wistar rats

Lipid Profile (Mmol/L)	**Group**				
	Control	**LU**	**LT**	**HU**	**HT**
Cholesterol	0.23 ± 0.02	0.20 ± 0.03	0.21 ± 0.04	0.22 ± 0.07	0.14 ±0.03$^{*\#}$
LDL	0.23 ± 0.02	0.17 ± 0.03	0.14 ± 0.05	0.20 ± 0.07	0.13 ± 0.03*
HDL (x 10^{-1})	0.04 ± 0.01	0.19 ± 0.02*	0.55 ± 0.04$^{*\#}$	0.04 ± 0.01	0.02 ± 0.00$^{*\#}$
TG	0.07 ± 0.03	0.04 ± 0.02	0.05 ± 0.01	0.03 ± 0.01	0.03 ± 0.01

Data are expressed as Mean ±SEM (n=8). * P < 0.05 Vs Control, $^{\#}$ P < 0.05 Vs Untreated LU=Low intensity Untreated, LT= Low Intensity Treated, HU=High intensity Untreated, HT= High Intensity Treated, LDL=Low Density Lipoprotein, HDL= Low Density Lipoprotein, TG=Triglyceride.

Effect of sodium bicarbonate supplementation on lipid profile of exercised male Wistar rats

The lipid profiles of the rats were shown in table 2, exercise did not cause any significant change in the cholesterol and Low-density cholesterol (LDL) levels of the LU and HU rats when compared with the control. However, bicarbonate supplementation in the HT group caused significant decrease in both cholesterol and LDL levels. Triglyceride level was not different across all groups while High-density cholesterol increased in LU and LT groups.

Effect of sodium bicarbonate supplementation on C-Reactive protein and lactate dehydrogenase levels of exercised male Wistar rats

C-Reactive protein level was not different across all groups (figure 1) while lactate dehydrogenase activity (figure 2) was significantly decreased in the HT group compared with the control.

Effect of sodium bicarbonate supplementation on cardiac hypertrophy of exercised male Wistar rats

As shown in figure 3, the heart weight: tail length ratio was significantly increased in the HU group when

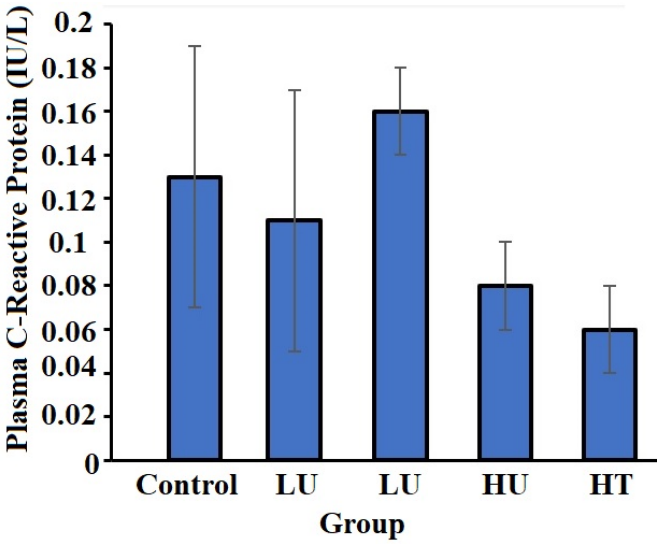

Fig. 1. Effect of sodium bicarbonate supplementation on plasma C-Reactive protein level of exercised male Wistar rats. Data are expressed as Mean ±SEM (n=8). LU=Low intensity Untreated, LT= Low Intensity Treated, HU=High intensity Untreated, HT= High Intensity Treated.

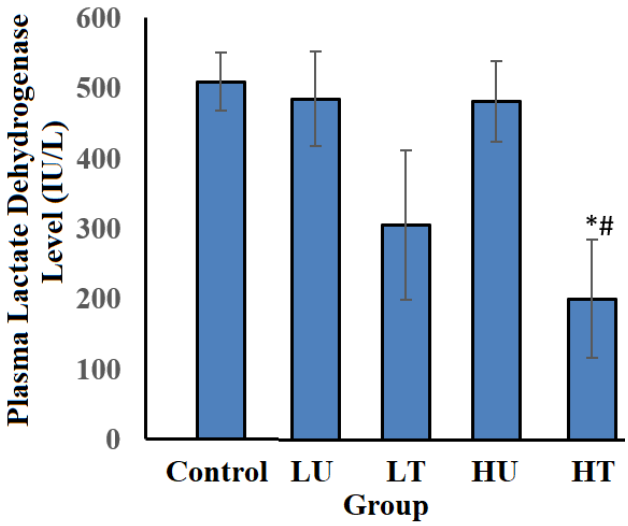

Figure 2. Effect of sodium bicarbonate supplementation on plasma lactate dehydrogenase level of exercised male Wistar rats. Data are expressed as Mean ±SEM (n=8). * P < 0.05 Vs Control, # P < 0.05 Vs Untreated LU=Low intensity Untreated, LT= Low Intensity Treated, HU=High intensity Untreated, HT= High Intensity Treated.

compared with the control. The increased heart weight: tail length ratio was however ameliorated by sodium bicarbonate supplementation in the HT compared with HU. This indicates that in the HU group, there was cardiac hypertrophy compared with the control and these was ameliorated in the HT group.

DISCUSSION

The effect of sodium bicarbonate supplementation on cardiac hypertrophy was studied in swim exercised rats. The lack of body weight gain observed in all the exercised rats is in accordance with the documented effect of swim exercise on weight gain in rats (Hart et al., 2001; Speretta et al., 2012; Svidnicki et al., 2013). A plausible explanation for the lack of weight gain is the increased fat oxidation to meet up with the increased energy expenditure during exercise (Venables et al., 2005). The observed effect of exercise on body weight which was not reversed by sodium bicarbonate supplementation is consistent with the report of Movilli et al (2005) that oral sodium bicarbonate supplementation prevents weight gain in patients undergoing dialysis.

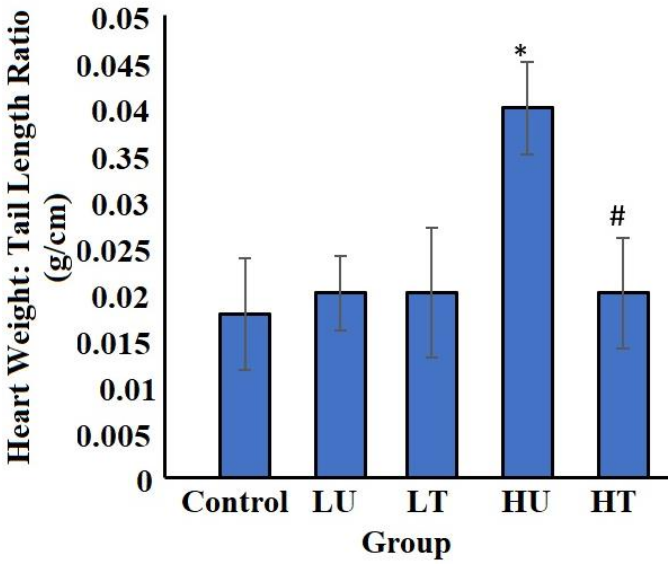

Fig. 3. Effect of sodium bicarbonate supplementation on heart weight: tail length ratio of exercised male Wistar rats. Data are expressed as Mean ±SEM (n=8). * P < 0.05 Vs Control, # P < 0.05 Vs Untreated LU=Low intensity Untreated, LT= Low Intensity Treated, HU=High intensity Untreated, HT= High Intensity Treated.

Cholesterol and LDL level which were not different in the exercised untreated groups compared with the control is consistent with an earlier report that swim exercise does not have hypocholesterolemic effect on the blood of rats fed normal diet (Gollnick, 1963; Guerra et al., 2007). However, in obese and high-fat fed rats, exercise has been shown to reduce blood cholesterol and LDL levels (Guerra et al., 2007; Karanth and Jeevaratnam, 2009; Speretta et al., 2012). In the HT group of this study, bicarbonate supplementation caused significant decreased cholesterol level when compared with control and HU groups, thus sodium bicarbonate probably potentiated the effect of exercise on plasma cholesterol level. Such potentiation by sodium bicarbonate treatment had been reported earlier (Dakam et al., 2007).

C-reactive protein (CRP) is a marker of chronic systemic inflammation frequently used in cardiovascular disease risk assessment (Fedewa et al., 2017). It is closely associated with obesity and factors that affect obesity can affect CRP level; for instance, weight loss regimens have been shown to cause significant decrease in CRP level and its predisposition to atherosclerosis (Tchernof et al., 2002; Okita et al., 2004). However, data on the effect of physical activity on CRP levels are conflicting. For instance, Abramson and Vaccarino (2002) and Ford (2002) reported that increase physical activity decreased CRP level while Rawson et al (2003) reported that there is no association between CRP level and physical activity. The lack of difference in the CRP level of all the groups in our study is in line with the report of Lakka et al (2005) that exercise can only reduce CRP level in obese individuals with basal elevated CRP level while it remained unchanged in individuals with normal basal level. The CRP levels of control rats was similar to the CRP levels of the exercised with/or without sodium bicarbonate supplementation in the current study. As it was observed in this study, sodium bicarbonate supplementation did not have any effect on CRP level in young active men after exhaustive exercise (Tofighi and Saedmocheshi, 2013).

Lactate dehydrogenase catalyzes the interconversion of pyruvate and lactate. It has been found to be elevated in the plasma/serum after muscular exertion in man (Rose et al., 1970) and following swim exercise in rats (Vander Tuig, 1976). The activity of LDH in the blood is very low at rest, but if muscle cells are damaged by high-intensity exercise, LDH is released from the cell, and LDH activity in the blood is elevated. It represents the degree of adaptation of metabolic function during energy metabolism, exercise intensity, muscle stiffness, fatigue recovery, and excessive training and histological damage analysis (Hooloszy and Booth, 1976; Apple and Rogers, 1986). Increased plasma LDH activity is a reflection of muscular damage (Lippi et al., 2008) and activities that reduce it has been shown to improve fatigue recovery in humans (Kim et al., 2020).

Sodium bicarbonate supplementation has been shown to decrease LDH activity after exercise in female non-athletes (Habibi Heghad et al., 2015) accordingly, sodium bicarbonate supplementation in the HT group of this study caused significant decrease in the plasma LDH level. An *in vitro* experiment on breast cancer cells posited that extracellular alkalinization as a result of sodium bicarbonate administration to culture media inhibits activity of LDHA, the isoenzyme of LDH which catalyzes pyruvate conversion to lactate (Neolaka et al., 2017). It is this isoenzyme of LDH that has been implicated in cardiac hypertrophy following hemodynamic stress (Dai et al., 2020). It is therefore not surprising that cardiac hypertrophy was significantly prevented in the HT group who had significant reduction in plasma LDH concentration following sodium bicarbonate supplementation in the current study. The suppression of LDHA activity and inhibition of cellular lactate exporter monocarboxylate transporter 4, MCT4 were recently shown to mitigate cardiac hypertrophy (Cluntun et al., 2021).

It was therefore concluded from this study that sodium bicarbonate supplementation to rats exposed to high intensity swim exercise prevents cardiac hypertrophy through the inhibition of lactate dehydrogenase activity. The influence of the observed decrease cardiac hypertrophy on cardiovascular variables and performances following sodium bicarbonate administration to the exercised rats requires further elucidation.

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