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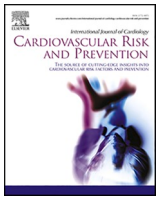

Renal denervation ameliorated salt-induced hypertension by improving cardiac work, cardiac enzyme and oxidative balance in Sprague-Dawley rats

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ABSTRACT

Background: Hypertension is associated with cardiovascular dysfunction, dysregulation of the antioxidant system and alteration of the level of some enzymes in the metabolic pathway. The possible modulatory effect of acute renal denervation (ARD) on cardiovascular function and the antioxidant system is still a subject of intense debate. This study sought to ascertain the ameliorative effects of ARD on cardiovascular parameters, antioxidant system, creatine kinase and lactate dehydrogenase levels.

Methods: Thirty-six Sprague-Dawley rats (5–6 weeks old) were divided into 6 groups of 6 animals each consisting of Normal Salt, High Salt, Normal Salt + Sham Denervation, High Salt + Sham Denervation, Normal Salt + Renal Denervation and High Salt + Renal Denervation. Induction of hypertension with 8 % salt in the diet lasted for 8 weeks. Renal or Sham denervation was thereafter done on selected groups. At the end of the experimental period, cardiovascular parameters, plasma antioxidant status, plasma creatine kinase (CK) and lactate dehydrogenase (LDH) levels were assessed. Significance level was set at $p < 0.05$.

Results: Salt-loading significantly increased systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MABP), rate pressure product (RPP) while reducing superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT). Acute renal denervation significantly ($p < 0.0001$) reduced SBP, DBP, MABP, RPP, LDH and norepinephrine level while increasing SOD, GSH and CAT. ARD did not significantly alter CK level.

Conclusion: Acute renal denervation, by reducing sympathetic activity, ameliorates cardiovascular and antioxidant functions as well as reduces LDH level without significantly altering CK level in salt-induced hypertension.

1. Introduction

Hypertension remains one of the most prevalent cardiovascular risk factors [1] in many cardiac pathologies like heart failure, cardiac arrest and cardiac arrhythmias [2,3]. In the year 2000 alone, close to 30 % of the world adult population was affected and according to some projections, by 2025, this might still increase, affecting about 1.5 billion people [4] worldwide. The overall prevalence of hypertension in Nigeria ranges between 8 % and 46.4 % [5] depending on the cut-off value used for defining hypertension. However, in blacks, salt-sensitive hypertension appears to be more prevalent [6]. High-salt diet has been reported to cause hypertension in humans and several species of laboratory animals [7–9]. Some of the suggested mechanisms include impairment of vascular function [8–10], modulation of reflex function, impairment of contractile properties of the vascular smooth muscle [11], increased cardiac oxygen demand [12] and effects on several factors and secretions from the endothelium which modulate both constriction and dilatation [7].

It is well established that sustained high blood pressure has very strong direct correlation with sympathetic hyperactivity which often leads to increased central sympathetic output [13]. Hypertension is also associated with an elevation of reactive oxygen species (ROS) and frequently also with an impairment of endogenous antioxidant mechanisms [14]. NAD(P)H oxidase-derived ROS for example plays a physiological role in the regulation of endothelial function and vascular tone and a pathophysiological role in endothelial dysfunction, inflammation,

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hypertrophy, apoptosis and many other processes underlying cardiovascular and renal remodeling in hypertension and diabetes mellitus [15]. Elevation of ROS affects multiple tissues, either directly or through nitric oxide depletion, induction of contraction and endothelial dysfunction in the vasculature, hypertrophic remodeling in blood vessels and myocardium, increased salt reabsorption in the kidneys that often lead to damage of many tissues and eventual death [14].

The rate pressure product (RPP), also called the double product is an established indicator of cardiac work [16]. It is one of the primary indicators of maximum consumption of oxygen by the myocardial cells [17]. Myocardial oxygen consumption correlates strongly with the rate pressure product and has been shown to follow a circadian pattern similar to what is observed in cardiovascular events [18]. Furthermore, high blood pressure and elevated myocardial oxygen demand have been shown to have positive association with the severity of cardiovascular disease [19].

Plasma creatine kinase (CK) activity has been postulated to be a good marker of CK activity from the fast twitch striated skeletal muscles. This enzyme has been shown to be of importance in hypertension [20,21]. Patients with high vascular reactivity and contractility also presented with high CK activity [22]. High blood pressure had also been correlated with increased CK mRNA levels [23]. It had also been proposed that high CK activity enhanced adenosine triphosphate (ATP) availability for the process of vascular contractions in the resistance arterial vessels [24]. The level of LDH is usually very high in some cardiovascular morbidities like myocardial infarction [25]. Unfortunately, there appeared to be a general lack of literature on the possible diagnostic value of LDH and CK in cardiovascular emergencies [26,27].

In the past, numerous experimental models including spontaneously hypertensive rats (SHR) [28], 2-kidney 1-clip Goldblatt rats, deoxycorticosterone acetate (DOCA)-salt rats [29], 1-kidney, 1-clip (1K1C) Goldblatt rats [11], Dahl salt-sensitive rats and humans with secondary hypertension [30] have been used to study the cause and progression of human cardiovascular disease. For salt-sensitive hypertension, an animal model may be obtained through the feeding of weanling rats with 8 % salt diet [7,8].

Several authors had reported the crucial role of bilateral renal denervation in the development and regulation of blood pressure [31,32]. Bilateral renal denervation inhibits both renal and systemic sympathetic activity [33]. It was reported to also improve arterial stiffness and provide ventricular rate control in a patient with permanent atrial fibrillation [34]. Recently, renal sympathetic denervation has been developed for treatment of resistant hypertension [35]. Although it has been shown to produce significant and sustained reduction in blood pressure for up to 36 months after denervation [33], there are limitations to its use.

While hypertension is associated with sympathetic hyperactivity, dysregulation of the antioxidant system, increased cardiac work and endothelial dysfunction, there are conflicting results on the likely ameliorative effects of renal denervation on these functions. Precisely, the effect of acute bilateral renal denervation on cardiovascular functions, antioxidant status, creatine kinase and lactate dehydrogenase levels have not been reported. Even though renal denervation is used for resistant hypertension, its possible ameliorative effects on other forms of hypertension cannot be ruled out. This study therefore sought to ascertain the precise effect of acute bilateral renal artery denervation on cardiovascular functions, antioxidant status, creatine kinase and lactate dehydrogenase levels in a rat model of salt-induced hypertension.

2. Methods

Ethical approval

This study was performed in accordance with the guidelines for animal experimentations at College of Medicine of the University of Lagos. Protocol for this study was approved by the College of Medicine of the University of Lagos Animal Care and Use Research Ethics Committee (CMUL-ACUREC) with registration number: CM/HREC/12/16/080. All procedures for this study were carried out in strict adherence to the National Institutes of Health Guide for the care and use of laboratory animals.

2.1. Grouping of animals

Thirty-six (36) weanling Sprague-Dawley (SD) rats (5–6 weeks old) weighing between 90 and 110 g were used. They were divided into six (6) groups of six (6) animals each as follows: Group I was fed normal rat chow and served as the Normal Salt (NS) group. Group II was fed with high salt diet containing 8 % NaCl and served as the High Salt (HS) group. Groups III and IV were fed normal and high salt diet respectively then sham-denervated without any treatment. These groups served as Normal Salt + Sham Denervation (NS + SD) and High Salt + Sham Denervation (HS + SD) respectively. Groups V and VI were fed normal and high salt diet respectively then renal-denervated. They served as Normal Salt + Renal Denervation (NS + RD) and High Salt + Renal Denervation (HS + RD) respectively. Induction of hypertension lasted for 8 weeks and renal denervation was for a week. Thus, the experimental period lasted for nine weeks before the animals were sacrificed for assessment of cardiovascular, antioxidant and cardiac markers. The grouping is as shown in Table 1.

2.2. Bilateral renal denervation

Rats in groups V and VI underwent bilateral renal denervation to reduce the neural influence on renal functions. Rats were anaesthetized with ketamine (100 mg/kg body weight) intra-muscularly. The left kidney was exposed via a flank incision. The renal artery and vein were stripped of surrounding adventitia and all visible renal nerves that run on the renal artery were cut. The renal arteries were then treated with absolute alcohol containing 15 % phenol. After renal denervation, the flank incision was sutured and the procedure was repeated on the opposite side to denervate the right kidney. Rats in groups III and IV underwent sham denervation with the use of normal saline instead of phenol-alcohol preparation used for renal denervation. All surgical procedures were performed after the period of induction of hypertension. All rats were maintained on their respective diets till the period of the sacrifice. All operated rats (groups III, IV, V, and VI) received an injection of penicillin of 300 000IU· (kg body weight^{-1}) at the time of surgery to prevent infection. This method had been shown to ablate the afferent and efferent renal nerves [35]. After recovery from anesthesia, all animals were returned to their cages.

2.3. Measurement of blood pressure and calculation of rate pressure product

At the end of the 9 week-experimental period, animals for invasive

Table 1
Grouping of animals.

Groups	Induction (Weeks 1–8)	Treatment (Week 8)	Group Name
Group I	Normal rat chow (0.3 % NaCl)	No treatment	Normal Salt (NS)
Group II	Rat chow with 8 % NaCl	No treatment	High Salt (HS)
Group III	Normal rat chow (0.3 % NaCl)	Sham Denervated	NS + Sham (NS + SD)
Group IV	Rat chow with 8 % NaCl	Sham Denervated	HS + Sham (HS + SD)
Group V	Normal rat chow (0.3 % NaCl)	Renal Denervated	NS + RD
Group VI	Rat chow with 8 % NaCl	Renal Denervated	HS + RD

RD- Renal Denervation.

blood pressure measurement were anaesthetized with a solution of 25 % (w/v) urethane and 1 % (w/v) α-chloralose injected intraperitoneally at a dose of 5 ml/kg body weight. The anaesthetized rat was placed on its back on the operating table, the limbs were fastened to the table and the trachea was exposed and cannulated for adequate ventilation. The blood pressure measurements were obtained by cannulation of one carotid artery. A polyethylene cannula filled with 1 % heparinised saline was inserted into the artery, tied in place, and connected via a pressure transducer (model SP 844, Physiological Pressure Transducer. AD Instruments) that was attached through MLAC11 Grass adapter cable to a computerized data acquisition system with LabChart-7 pro software (Power Lab-4/24T, model MLT844/P; AD Instruments Pty Ltd., Castle Hill, Australia). The heart rate was determined by counting the number of arterial pulses. The rate pressure product (RPP) was calculated as a product of systolic blood pressure and heart rate for each of the animals [12]. The mean values were determined and used as an indirect indicator of cardiac work.

2.4. Oxidative stress studies

The levels of superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT) and malondialdehyde (MDA) were assessed. Following measurement of blood pressure parameters, blood samples from each animal were collected in plain bottles and centrifuged at 3000 rpm for 15 min to get plasma samples for oxidative stress studies using previously described standard methods [36]. The reduced glutathione (GSH) content of the plasma was determined using the method described by VanDooran et al. [37]. The GSH determination method is based on the reaction of Ellman's reagent 5,5′ dithiobis (2-nitrobenzoic acid) DNTB) with the thiol group of GSH at pH 8.0 to produce 5-thiol-2-nitrobenzoate which is yellow at 412 nm. The level of the SOD enzyme was determined according to the method described by Sun and Zigman [38]. The reaction was carried out in 0.05 M sodium carbonate buffer pH 10.3 and was initiated by the addition of epinephrine in 0.005 N HCl. Catalase (CAT) activity was determined by measuring the exponential disappearance of H_2O_2 at 240 nm and expressed in units/mg of protein as described by Aebi [39]. Absorbance was recorded using Shimadzu recording spectrophotometer (UV 160) in all measurement. Malondialdehyde (MDA) was estimated with the method of Uchiyama and Mihara [40] which is based on its interaction with thiobarbituric acid (TBA) to form a pink complex with absorption maximum at 535 nm. Absorbance was recorded using Shimadzu recording spectrophotometer (UV 160) in all measurements.

2.5. Assessment of cardiac markers

Creakine kinase: The catalytic concentration was determined from the rate of formation of NADPH, measured at 340 nm, by means of the hexokinase (HK) and glucose-6-phosphate dehydrogenase (G6P-DH) coupled reactions [41].

Lactate dehydrogenase (LDH): The catalytic concentration was determined from the rate of decrease of NADH measured at 340 nm. For the estimation, plasma was separated by centrifugation and the enzyme levels were estimated according to the procedure reported by Rajadurai and Prince [42].

2.6. Assessment of norepinephrine levels

Using previously described standard methods [43,44], norepinephrine level was measured from the kidney homogenates to validate renal denervation procedure.

2.7. Statistical analyses

The data were summarized and expressed as means ± SEM. The data were analyzed using one-way ANOVA. The Student–Newman–Keuls post-hoc test was used to identify differences between individual means. The confidence interval was set at 95 %, so that in all cases, results with a value of $p < 0.05$ were considered significant (GraphPad Prism 6, GraphPad Software, Inc., La Jolla, Calif., USA).

3. Results

3.1. Effect on cardiovascular parameters

3.1.1. Effect of high salt diet on cardiovascular parameters

Systolic blood pressure was significantly higher ($p < 0.001$) in the High Salt (HS) diet group (149.40 ± 4.78 mmHg) and High Salt + Sham Denervation (HS + SD) group (152.10 ± 5.75 mmHg) when compared with the Normal Salt (NS) diet group (106.30 ± 7.56 mmHg) and Normal Salt + Sham Denervation (NS + SD) group (100.80 ± 4.91 mmHg) respectively. Also, diastolic blood pressure was significantly higher ($p < 0.001$) in the HS diet group (115.60 ± 6.39 mmHg) and HS + SD group (102.90 ± 4.22 mmHg) when compared with the NS diet group (73.64 ± 5.96 mmHg) and NS + SD group (66.88 ± 2.68 mmHg) respectively. See Table 2. Pulse pressure was not significantly different between the HS diet group and the NS diet group and also between the HS + SD diet group and the NS + SD diet group. See Table 2. Mean arterial blood pressure was significantly higher ($p < 0.001$) in the HS diet group (126.90 ± 5.82 mmHg) and HS + SD group (116.50 ± 3.99 mmHg) than in the NS diet group (84.52 ± 6.48 mmHg) and NS + SD group (78.89 ± 3.39 mmHg) respectively. Heart rate was not significantly different between the HS diet group and the NS diet group and also between the HS + SD diet group and the NS + SD diet group. Rate pressure product which was used as an indirect indicator of cardiac work was significantly higher ($p < 0.01$) in the HS diet group (60547 ± 2468 AU) and HS + SD group (58366 ± 2072 AU) than in the NS diet group (40973 ± 4812 AU) and NS + SD group (41549 ± 2226 AU) respectively. Also see Table 2.

3.1.2. Effect of renal denervation alone on cardiovascular parameters

Renal denervation in rats fed the normal diet caused a significant increase ($p < 0.05$) in systolic blood pressure in NS + RD group compared to the NS group (122.30 ± 1.86 vs 106.30 ± 7.56 mmHg). It however did not cause a significant change ($p > 0.05$) in diastolic blood pressure, pulse pressure, mean arterial blood pressure, heart rate and rate pressure product in the NS + RD group compared to the NS group.

3.1.3. Effect of renal denervation following high salt diet on cardiovascular parameters

Renal denervation significantly ($p < 0.01$) reduced the systolic blood pressure in High Salt + Renal Denervation (HS + RD) group (105.70 ± 6.04 mmHg) compared to the HS group (149.40 ± 4.78 mmHg). It also significantly ($p < 0.001$) reduced diastolic blood pressure (73.24 ± 4.32 vs 115.60 ± 6.39 mmHg, $p < 0.01$), mean arterial blood pressure (84.06 ± 4.79 vs 126.90 ± 5.82 mmHg, $p < 0.01$) and rate pressure product (41366 ± 3744 AU vs 60547 ± 2468 AU, $p < 0.01$). Results are shown in Table 2.

3.2. Antioxidant levels

3.2.1. Effect of high salt diet on antioxidant parameters

Superoxide dismutase, reduced glutathione (GSH) and catalase were significantly lower in the HS diet and HS + SD groups than in the NS diet group and NS + SD groups ($p < 0.01$ in each case). Catalase was similar ($p > 0.05$) in NS + SD and HS + SD. Malondialdehyde (MDA) was used to assess the level of lipid peroxidation. MDA level was significantly higher in the HS diet group (6.34 ± 0.48 μmol, $p < 0.05$) when compared with the NS diet group (5.61 ± 0.55 μmol). See Table 3.

3.2.2. Effect of renal denervation alone on antioxidant parameters

Renal denervation in rats fed the normal diet caused a significant

Table 2
Effect of salt-loading and renal denervation on cardiovascular parameters.

	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse Pressure (mmHg)	Mean Arterial BP (mmHg)	Heart Rate (beats/min)	Rate Pressure Product (AU)
Normal Salt (NS)	106.30 ± 7.56	73.64 ± 5.96	32.65 ± 1.85	84.52 ± 6.48	374.50 ± 23.36	40973 ± 4812
High Salt (HS)	149.40 ± 4.78***	115.60 ± 6.39***	33.80 ± 2.01	126.90 ± 5.82***	405.40 ± 12.49	60547 ± 2468**
Normal Salt + Sham Denervation (NS + SD)	100.80 ± 4.91	66.88 ± 2.68	36.01 ± 4.32	78.89 ± 3.39	404.50 ± 6.01	41549 ± 2226
High Salt + Sham Denervation (HS + SD)	152.10 ± 5.75***	102.90 ± 4.22***	40.80 ± 4.56	116.50 ± 3.99***	407.30 ± 11.30	58366 ± 2072**
Normal Salt + Renal Denervation (NS + RD)	122.30 ± 1.86α	82.85 ± 3.22	39.44 ± 2.00	96.00 ± 2.68	410.30 ± 13.17	50250 ± 2121
High Salt + Renal Denervation (HS + RD)	105.70 ± 6.04*μ	73.24 ± 4.32*μ	32.48 ± 2.63	84.06 ± 4.79*μ	386.90 ± 18.41	41366 ± 3744*μ

Values represent Mean ± SEM. Significant (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ vs corresponding normal diet group, α = $p < 0.05$ vs NS group, μ = $p < 0.01$ vs HS group).

Table 3
Effect of salt-loading and renal denervation on antioxidant levels.

	Superoxide dismutase (SOD) (μmol/mg/pro)	Reduced glutathione (GSH) (μmol/mg prot)	Catalase (μmol/mg/pro)	Malondialdehyde MDA (μmol/mg prot)
Normal Salt (NS)	2.50 ± 0.24	27.21 ± 1.65	6.29 ± 0.42	5.61 ± 0.55
High Salt (HS)	1.01 ± 0.13***	16.14 ± 1.18***	3.99 ± 0.23***	6.34 ± 0.48*
Normal Salt + Sham Denervation (NS + SD)	2.20 ± 0.18	28.62 ± 1.25	5.00 ± 0.26	5.16 ± 0.30
High Salt + Sham Denervation (HS + SD)	1.54 ± 0.28**	15.27 ± 0.67***	4.54 ± 0.52	6.30 ± 0.29*
Normal Salt + Renal Denervation (NS + RD)	6.00 ± 0.82	28.45 ± 1.85	6.81 ± 0.30	5.19 ± 0.59
High Salt + Renal Denervation (HS + RD)	4.56 ± 0.28*μ	32.17 ± 2.09*μ	5.54 ± 0.37*β	3.34 ± 0.38**μ

Values represent Mean ± SEM. Significant (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ vs corresponding normal diet group, α = $p < 0.01$ vs NS group, μ = $p < 0.001$, β = $p < 0.05$ vs HS group).

increase ($p < 0.01$) in superoxide dismutase level in NS + RD group compared to the NS group (6.00 ± 0.82 vs 2.50 ± 0.24 μmol/mg/pro). There was no statistically significant change ($p > 0.05$) in the levels of GSH, catalase and malondialdehyde in the NS + RD group compared to the NS group. Also, in Table 3.

3.2.3. Effect of renal denervation following high salt diet on antioxidant parameters

Superoxide dismutase and GSH were significantly higher in the HS + RD group than in the HS diet group ($p < 0.001$ in each case). In a similar manner, the level of catalase was significantly higher ($p < 0.05$) while that of MDA level was significantly lower ($p < 0.001$) in the HS + RD group when compared with the respective HS groups. See Table 3.

3.3. Cardiac markers

3.3.1. Effect of high salt diet on cardiac markers

There was no significant difference ($p > 0.05$) in the creatine kinase level between the HS diet group and the NS diet group. It was also similar ($p > 0.05$) in HS + SD group and the NS + SD group. This is illustrated in Fig. 1. There was no significant difference ($p > 0.05$) in the lactate dehydrogenase level between the HS group and the NS group as well. There was also no significant difference ($p > 0.05$) in the lactate dehydrogenase level between the HS + SD diet group and the NS + SD diet group. See Fig. 2.

3.3.2. Effect of renal denervation alone on cardiac markers

While there appears to be a reduction in creatine kinase in NS + RD compared to NS group, the slight reduction was not statistically significant ($p > 0.05$). There was also no statistically significant difference ($p > 0.05$) in the lactate dehydrogenase level in NS + RD compared to the NS group.

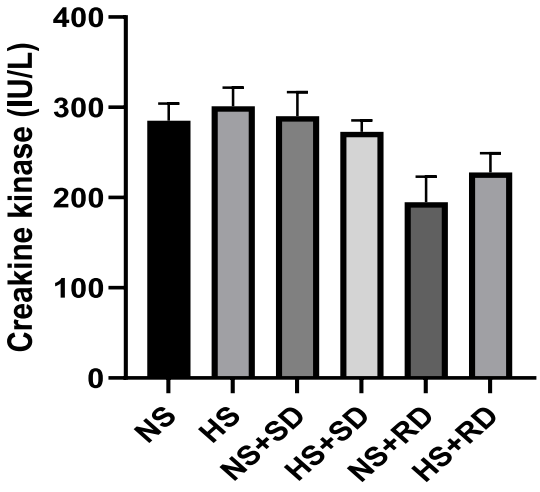

Fig. 1. Creatine kinase level across the groups.

3.3.3. Effect of renal denervation following high salt diet on cardiac markers

While renal denervation did not significantly change the creatine kinase level in the HS + RD group (227.70 ± 21.58 IU/L) compared the HS group (301.00 ± 20.73 IU/L), it significantly ($p < 0.05$) reduced the lactate dehydrogenase level in HS + RD group (266.70 ± 27.79 IU/L) compared to the HS group 634.10 ± 87.23 IU/L as shown in Fig. 2.

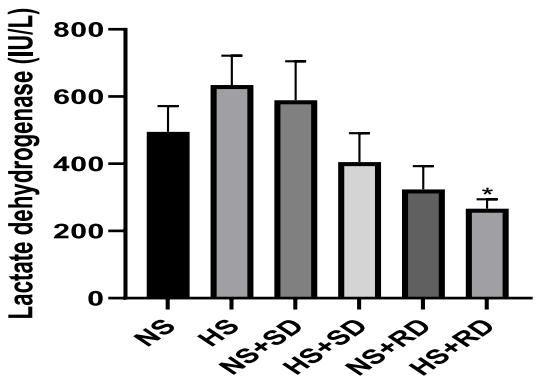

Fig. 2. Lactate dehydrogenase level across the groups Bars represent Mean ± SEM. Significant (* = $p < 0.05$ vs HS diet group).

3.4. Norepinephrine level

3.4.1. Effect of high salt diet on norepinephrine level

There was no significant difference between norepinephrine level in the HS group when compared with the NS group (0.97 ± 0.04 pmol/ml vs 0.94 ± 0.04 pmol/ml, $p > 0.05$). There was equally no significant difference between the norepinephrine level in the HS + SD group and the NS + SD diet group (0.91 ± 0.02 pmol/ml vs 0.96 ± 0.05 pmol/ml, $p > 0.05$) as illustrated in Fig. 3.

3.4.2. Effect of renal denervation alone on norepinephrine level

Renal denervation significantly reduced ($p < 0.01$) norepinephrine level in NS + RD (0.63 ± 0.07 pmol/ml) compared to NS (0.94 ± 0.04 pmol/ml) group. This is illustrated in Fig. 3.

3.4.3. Effect of renal denervation following high salt diet on norepinephrine level

Renal denervation significantly reduced ($p < 0.01$) norepinephrine level in HS + RD (0.64 ± 0.06 pmol/ml) group compared to HS (0.97 ± 0.04 pmol/ml) group as illustrated in Fig. 3 as well.

4. Discussion

Hypertension continues to be investigated because its genesis and underlying mechanisms remain elusive [45]. Part of the suggested mechanisms involve causing hyperactivity of the sympathetic nervous system [46]. A prudent approach to hypertension management will involve attempting to reduce this hyperactivity and that is exactly the central idea of this research work. In this study, the ameliorative effects on the cardiovascular functions, antioxidant status, creatine kinase and lactate dehydrogenase levels are clearly elucidated.

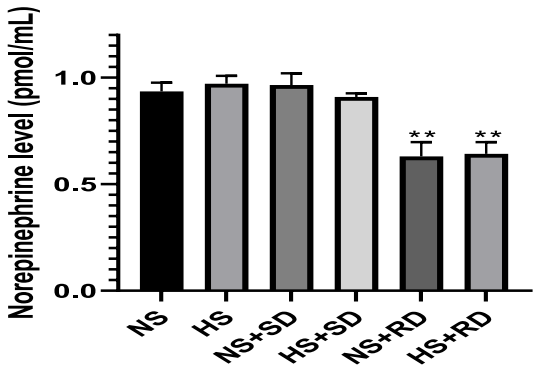

Fig. 3. Norepinephrine level across the groups. Bars represent Mean ± SEM. Significant (* = $p < 0.05$ vs HS diet group).

4.1. Effect of high salt diet on cardiovascular parameters, antioxidant level and cardiac biomarkers

The modern living lifestyle is known to produce physical and psychological stress resulting in increased blood pressure (BP) and heart rate (HR). This may result in increased myocardial oxygen demand (MOD). Myocardial oxygen demand correlated best with rate pressure product (RPP) and it's a better marker of predicting cardiovascular disease (CVD) [12,47]. In this study, the marked increase in the magnitude of the rate pressure product following salt-loading implies that the demand for oxygen in the salt-loaded group was higher when compared with the control. This is likely to put more pressure on the heart to perform its function. Inability to supply oxygen to the myocardium when demand is high appears to be related to several cardiovascular events, including transient myocardial ischemia, acute myocardial infarction, and sudden death [18,48]. Thus, our result is in line with these earlier observations. At the same time, salt-loading of normal Sprague-Dawley rats not only caused increased blood pressure but also led to increase in oxidative stress markers in this study. The plasma superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT) were all observed to be significantly reduced in the salt-loaded animals. This caused the observed imbalance often referred to as oxidative stress [49,50]. The degree of tissue destruction was also found to be higher in the salt-loaded rats as evidenced from the higher level of malondialdehyde (MDA), a marker of lipid peroxidation in tissues. These observations agree with earlier studies [49,51]. Oxidative stress has been shown to be strongly associated with hypertension [49,52,53]. It is still not clear whether it is a causative agent or results from some other coexisting pathologies in hypertension. Some other studies had indicated the possibility of increased norepinephrine level to increase oxidative stress [54,55]. Clinical and experimental studies indicate that oxidative stress contributes to the development of hypertension in human beings [56] and animals [57]. Several studies have demonstrated that oxidative stress is involved in the pathogenesis of arterial hypertension in genetic animal models [57] and in secondary forms of arterial hypertension [58,59]. Taken together, these findings in salt-dependent hypertension suggest that oxidative stress is secondary to increased salt intake and contributes to increased blood pressure.

Importantly, while salt diet in this study increased myocardial oxygen demand and oxidative stress, it did not cause any significant change in the cardiac biomarkers. Creatine kinase (CK) and lactate dehydrogenase (LDH) are two prominent diagnostic cardiac biomarker enzymes that are released into the plasma once the heart is overworked or damaged [60,61]. Lactate dehydrogenase (LDH) is a ubiquitous cytoplasmic enzyme in all cells of the body. It catalyses the reversible conversion of pyruvate to lactate as a part of the lactic acid cycle and following cellular injury, it is released from impaired cells into plasma [62]. It has been shown that plasma LDH is elevated in hypertensive rats induced by sodium fluoride indicating induction of oxidative stress, renal, and cardiac damage after exposure [63,64]. The level of LDH is usually very high in some cardiovascular morbidities like myocardial infarction [25]. Unfortunately, there appeared to be a general lack of literature on the possible diagnostic value of LDH and CK in cardiovascular emergencies [26,27]. Creatine kinase (CK) has been hypothesized to have independent dose-response association with blood pressure [65,66]. High creatine kinase is also correlated with failure of antihypertensive therapy [67].

4.2. Effect of renal denervation following high salt diet on cardiovascular parameters, antioxidant level and cardiac biomarkers

In this study, acute renal denervation completely reversed the increased systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and rate pressure product in salt-loaded animals. The findings of the present study showed a significant reduction in RPP in rats fed the salt diet following denervation. This implies that the demand

for oxygen by the myocardial cells is partially under the control of the renal sympathetic nerves. Acute renal denervation however did not alter the pulse pressure and heart rate in the animals. In line with our observation, radio-frequency renal denervation was also observed not to have any significant effect on heart rate [68]. The concomitant reduction in the plasma norepinephrine level shows that while salt-loading may not directly increase the sympathetic nerve activity to cause increase in blood pressure as evidenced from the lack of significant change in the plasma norepinephrine level between the normal and salt-loaded rats, acute renal denervation may counteract the salt-loading effects by reducing the level of sympathetic nerve activity. Our results are in consonance with earlier reports in other hypertension models [69,70]. This further confirms the multifaceted nature of the mechanisms that regulate blood pressure [71]. It is a known fact that the renal nerve regulates the activity of the sympathetic nervous system [72] which in turn helps to regulate blood pressure parameters [73].

However, there was a report of significant reduction in heart rate following renal denervation in a clinical trial [74]. Recent clinical studies show that renal denervation significantly attenuates muscle sympathetic nerve activity [75] and reduces cardiac hypertrophy and function. Renal denervation was reported to prevent the development of deoxycorticosterone acetate (DOCA)-salt-induced left and right ventricular hypertrophy despite preventing the high level of hypertension caused by DOCA-salt rats [76]. There is dearth of information on the direct effect of renal denervation on rate pressure product and thus the demand for oxygen. Contrary to this observation, Bhatt et al. [77] reported no significant change in blood pressure and heart rate, the two components of myocardial oxygen demand, in animals and humans following renal denervation. However, our results agree with what was reported in other models of hypertension as complete renal denervation delays the rise in blood pressure in spontaneously hypertensive, chronic L-NAME-induced hypertensive rats and New Zealand rat strains and hypertension induced by angiotensin-II [78]. Bilateral renal denervation also effectively prevented the elevation of blood pressure due to insulin infusion. After hyperinsulinemia-induced hypertension had been fully established, subsequent denervation of both kidneys precipitously reduced the blood pressure, which returned to normotensive levels within 2 weeks [79]. Rodriguez-Leor et al. [80] was however of the opinion that the variation in the results could be due to different population or strain of animal used in the studies. Incomplete normalization of elevated blood pressure may be explained by the assumption that other blood pressure-increasing mechanisms may remain operational [81] and the process occurs independently of the state of the extracellular fluid volume [82]. Our present result indicates that the integrity of the renal nerves is essential for the correction of high demand for oxygen by the heart in salt-induced hypertension in Sprague-Dawley rats.

Renal denervation in this study caused significant increase in superoxide dismutase (SOD) level in the salt-loaded and control rats. Reduced glutathione (GSH)(GSH) and catalase levels were significantly increased in only the salt-loaded group. Malondialdehyde level was found to be reduced in the salt-loaded group as well. This represents a general improvement in the antioxidant system. In consonance with our findings, Kudoh et al. [83] reported amelioration of oxidative stress in the cortex, white matter and paraventricular nucleus of high salt-loaded spontaneously hypertensive rats following renal denervation. In the present study, we observed that renal denervation, attenuated salt-induced reduction in antioxidant levels [84,85] and lipid peroxidation and thus further showcases a likely crosstalk between increased blood pressure, increased activity of the sympathetic nervous system and reduced antioxidant system of the body. Radio-frequency renal denervation (RF-RDN) upregulated mRNA and protein expression of key antioxidants, superoxide dismutase 1 (SOD1) and glutathione peroxidase (GPX-1), in the heart, providing strong evidence that RF-RDN attenuates oxidative stress associated with severe hypertension [86]. Renal denervation in this study was carried out to reduce the hyper-activation of the sympathetic nervous system that is associated with hypertension, but it appears to have effects beyond just reducing this hyperactivity [87].

Another key finding of this study is the significant reduction in LDH in the rats fed the high salt diet following acute renal denervation. Further studies would need to be conducted to unravel the mechanisms behind this observation.

In conclusion, in salt-induced hypertension, acute renal denervation reduced sympathetic activity, cardiovascular function and LDH level, elevated antioxidant enzymes without significantly altering CK level.

CRediT authorship contribution statement

Abdullahi Adejare: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ahmed Oloyo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis. **Yusuf Dahud:** Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Morufat Adeshina:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Abiola Agbaje:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Clinton Ejim:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Khadijah Ismail-Badmus:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Smith Jaja:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis.

Declaration of generative AI and AI-assisted technologies in the writing process

None to declare as no AI-tool was used in drafting the content of the manuscript.

Declaration of competing interest

None.

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