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Effect of Cadmium Chloride Administration and Restraint Stress Model on Cardiac Function of Female Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Psychological stress which is becoming an epidemic due to continental economic meltdown, wars, climate change, disasters has reached a point of global health concern and can be mimicked in rats by restraint stress model. Cadmium chloride is a heavy metal salt whose exposure can be through inhalation, drinking contaminated water, sheltering and watering. This study therefore evaluated the combined effects of restraint stress and cadmium chloride on cardiac function of female Wistar rats.

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Twenty four female Wistar rats were randomly divided into four groups of six rats each. Control (CTL) group received only water and animal feed *ad libitum*. Restraint stress (RSS) group was restrained using wire mesh for 30 minutes each day for 21 days. Cadmium chloride (CDC) group received 100mg/kg b.w of Cadmium chloride orally and daily for 21 days. Restraint stress and Cadmium chloride group (RSC) was restrained for 30 minutes and received Cadmium chloride (100mg/kg) daily for 21days. Twenty four hours after the last procedures, the ECG of the rats was taken and then all rats were anesthetized and their blood collected for biochemical assay. Their hearts were also removed for histology studies. The result showed that restraint stress and cadmium chloride caused an altered electrical conductivity of the heart independently and their combination caused an exacerbated effect. The serum troponin I (cTnI), Lactate dehydrogenase (LDH), Creatine kinase (CK) were significantly ($p<0.05$) higher in RSS and CDC groups when compared with the control however the LDH level was significantly higher in the RSC group when compared with other groups. Histology of the hearts of the rats indicated that both restraint stress and cadmium chloride caused necrosis in the hearts of the rats. In conclusion, the combined exposures to cadmium chloride administration and restraint stress have exacerbated deleterious effects on cardiac function of female Wistar rats.

Keywords: Lactate dehydrogenase; climate change; psychological stress; electrical conductivity.

1. INTRODUCTION

Environmental pollution is the contamination of the natural environment such as water, soil and air by a pollutant. This pollution creates bioavailability of the pollutant to the living organisms in the environment and may therefore have adverse effects on the organisms (Manisalidis et al., 2020). Environmental pollution is a major global concern with far-reaching consequences for human health, ecosystems, and the economy. Pollution can take many forms, including air pollution from industrial emissions and vehicle exhaust, water pollution from industrial effluents, agricultural runoff, soil pollution from pesticides, heavy metals, and improper waste disposal. The contributions of heavy metals as one of the major environmental pollutants have reached the level of global concerns (Mitra et al., 2022).

Cadmium (Cd), commonly considered a toxicant that does not have any reported physiological function (Genchi et al., 2020). Occupational and environmental exposure are the major route through which cd can be contacted majorly through contaminated food and smoking (Charkiewicz et al., 2023). In ocean water, the level of Cd has been shown to be <5 to 110 ng/l (Stannard et al., 2024). It can also be emitted to the environment through volcanic activity, weathering of Cd-containing rocks, sea spray, mining, fossil fuel combustion (Davidova et al., 2024) corrosive reagent, as well as its use as a stabilizer in PVC products, color pigments. Ni-Cd batteries are one of the heavy metals with the highest level of bioavailability to humans and animals through food, water, inhalation, skin and other routes. Cadmium chloride has been reported to have various deleterious effects on several body systems (Owolabi et al., 2024a; Owolabi et al., 2024b).

Restraint stress is a laboratory form of psychological stress. The utilization of restraint stress and immobilization is a commonly used method in laboratory settings to induce behavioral and physiological alterations related with stress in rats (Molina et al., 2023). These alterations have been observed to lead to the manifestations of dysfunctions in various organ systems. Since restraint stress is a form stress, it typically triggers the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenomedullary system which ultimately leads the release of corticosterone and epinephrine/norepinephrine respectively. These end-point hormones would eventually be responsible for most of the cellular stress responses (Herman et al., 2016). Studies have shown that restraint stress disrupted gastrointestinal system, altered feeding behavior and caused body weight fluctuations (Yau & Potenza, 2013) male reproductive system dysfunction (Procópio et al., 2023), neurobehavioral impairments (Chu et al., 2016). Chronic stress have been reported to exhibit physiological responses similar to those present in depression (Wang et al., 2017).

The heart is a muscular pumping organ. It receives blood from various systems of the body and also pumps blood to the different systems of

the body. The blood pumped by the heart contains the various elements needed for the survival of the components of the body systems and also contains the waste products of metabolism to be transported to the excretory organs (Mollova et al., 2013). The survival of the systems therefore depends heavily on the ability of the heart to receive blood from these organ systems and to pump blood to them. Reduced activity of the heart will therefore cause a disruption in the supply of adequate blood to these organ systems and could lead to adverse consequences (Huang, 2019). This study therefore is to assess the combined impact of psychological stress model and heavy metal pollutant on the cardiac function of female Wistar rats.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Cadmium Chloride, Normal saline, Distilled water, Methylated spirit, Formosaline, Phosphate buffer saline were obtained from the Central Laboratory Complex, LAUTECH, Oyo State, Nigeria.

Twenty four (24) female Wistar rats were obtained from a reputable commercial rat seller in ogbomoso, Nigeria and randomly grouped into four with six (6) rats in each group. The rats were acclimatized for 14 days at the site of the experiment and the experiment was conducted for 21 days thereafter. The control group (CTL) rats received animal feed and water only *ad libitum* throughout the period of the experiment. Restraint stress alone group rats (RSS) were each restraint for 30 minutes daily for 21 days. Cadmium Chloride alone group (CCC) rats each received Cadmium Chloride (100 mg/kg) orally and daily for 21 days. Restraint stress and Cadmium Chloride group (RSC) rats each received Cadmium Chloride (100 mg/kg) orally and daily and also restraint for 30 minutes daily for 21 days.

Procedure: The animals were restraint according to the method described by Thongrong et al. (2023). Each rat was placed in a carved wire mesh which is according to the length of each rat in a prone position. The mesh was carved such that it does not cause compression and pain to the rats. The mesh was worn round the rat such that head and tail of the rat can move freely in the wire mesh.

Cadmium Chloride was prepared daily by dissolving 10 grams of cadmium chloride in 100 milliliters of distilled water and administered orally according to the dosage (100 mg/kg b.w) using an oral cannula daily.

Twenty four hours after the last administration and restraint stress exposure, the Electrocardiograph (ECG) of each rat was determined using digital ECG machine, EDAN 10 Veterinary ECG. Each rat was anaesthetized with Ketamine and Xylazin. Each electrode was attached to their corresponding positions. Right and left legs, right and left arms and the heart. The resting ECG recording was done in one minute for each of the rats and the recording was saved. Cardiac puncture was then conducted on each of the anaesthetized rat to collect blood into plain sample bottles for biochemical analysis. The clotted blood was thereafter placed in a centrifuge where they were spun at a revolution of 2,500 revolutions/ minute for 10 minutes to obtain the serum upon which the biochemical assays were performed. The hearts of the rats were each removed, washed and prepared for Hematoxylin and Eosin (H&E) staining.

Data analysis: Data is expressed as Mean±SEM. Results were analysed using one-way ANOVA followed by duncan *posthoc* test. Differences were considered significant at $p<0.05$.

3. RESULTS

Figures showing the effects of restraint stress and cadmium chloride on the ECG of female Wistar rats.

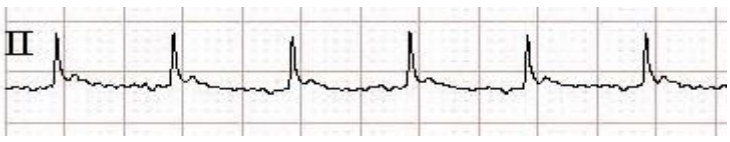


Fig. 1a. Control group: RR interval is regular, P and QRS are within normal range

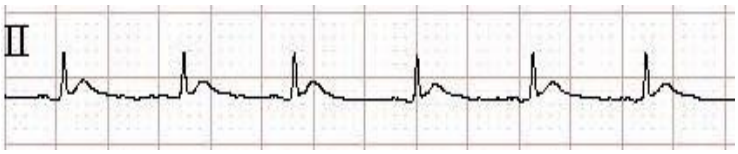


Fig. 1b. Cadmium chloride alone, QRS reduced P height is low indicating mitral valve impairment

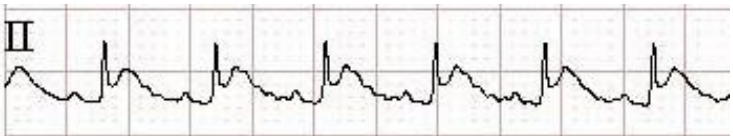


Fig. 1c. Restraint stress alone group: P is taller indicating delay in atrial depolarization, T height increased indicating myocardial infarction. Increase in the mean heart rate

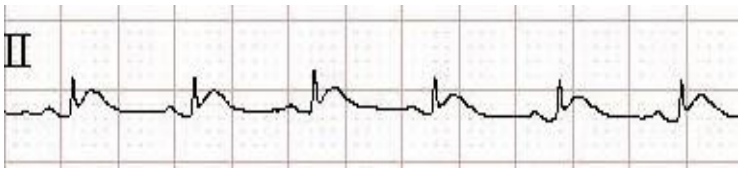


Fig. 1d. Cadmium chloride and Restraint Stress group: Height of P increased, T taller than normal in myocardial infarction. Tachycardia seen is as a result of Cadmium chloride and Restraint Stress

Figures showing the effect of Cadmium chloride and Restraint Stress on the serum cardiac function biomarkers in female Wistar rats

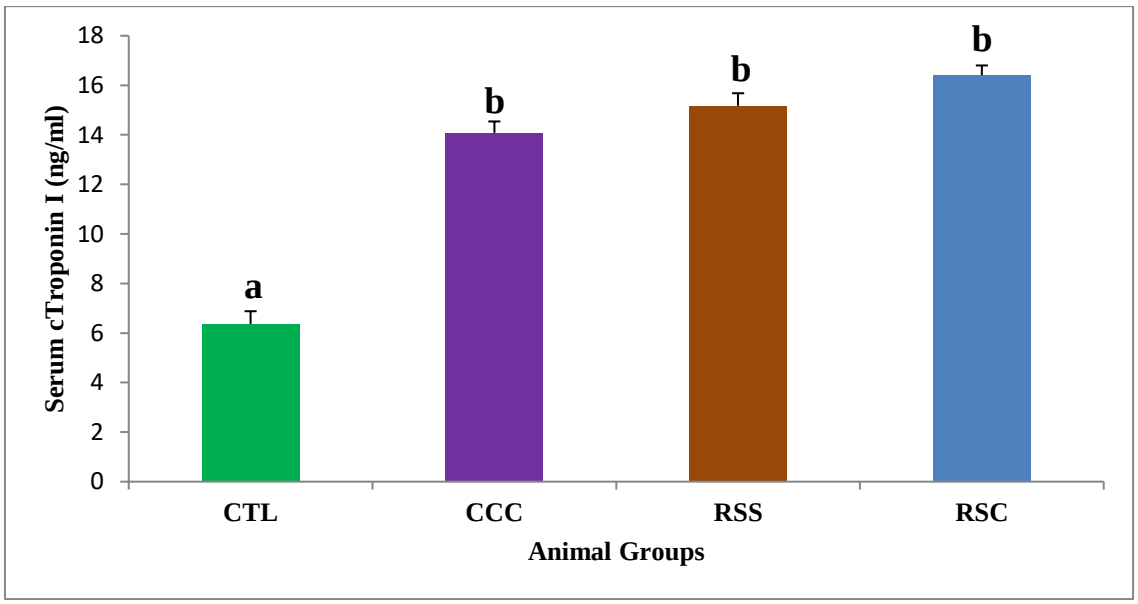


Fig. 2. Effect of cadmium chloride and restraint stress on the serum troponin I levels of female Wistar rats

n=6. Values are expressed as Mean±SEM. Serum cTI levels in the CCC, RSS and RSC groups were independently significantly ($p<0.05$) higher than the CTL. However no significant ($p<0.05$) difference was observed among these groups

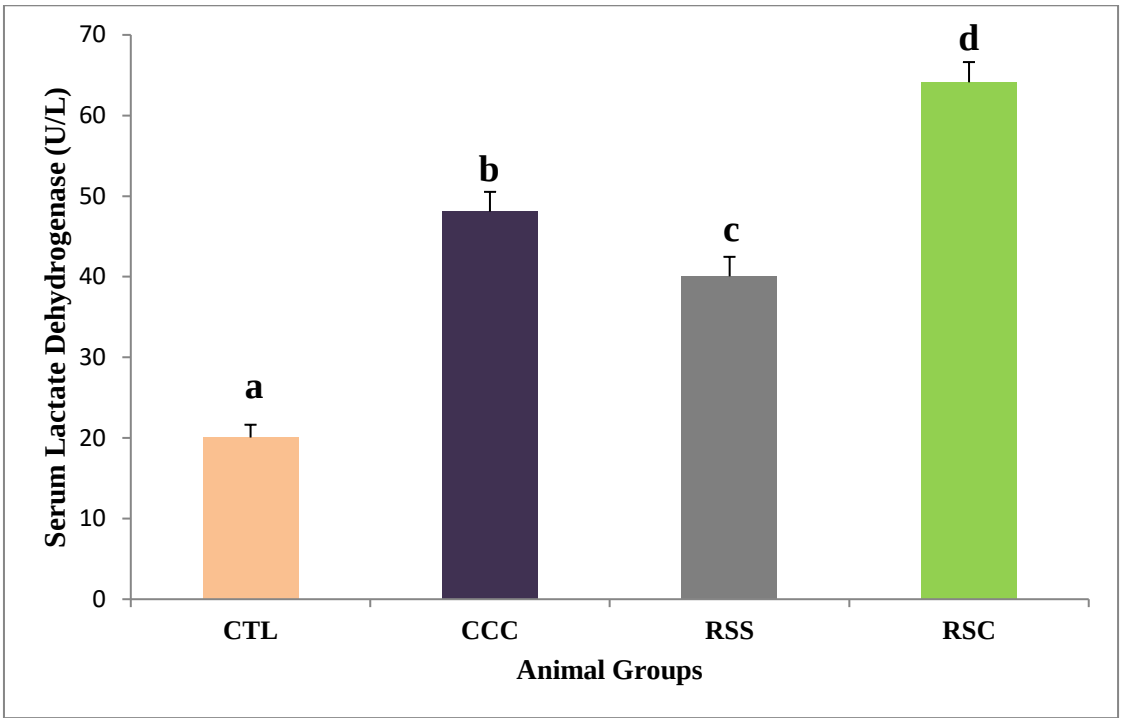


Fig. 3. Effect of cadmium chloride and restraint stress on the serum lactate dehydrogenase levels of female Wistar rats

n=6. Values are expressed as Mean±SEM. Serum LD levels in the CCC, RSS and RSC groups were independently significantly (p<0.05) higher than the CTL, However serum LD levels in RSC group was found to be significantly (p<0.05) higher than both RSS and CCC groups. Also the serum LD levels in CCC group was found to be significantly (p<0.05) higher than that of RSS

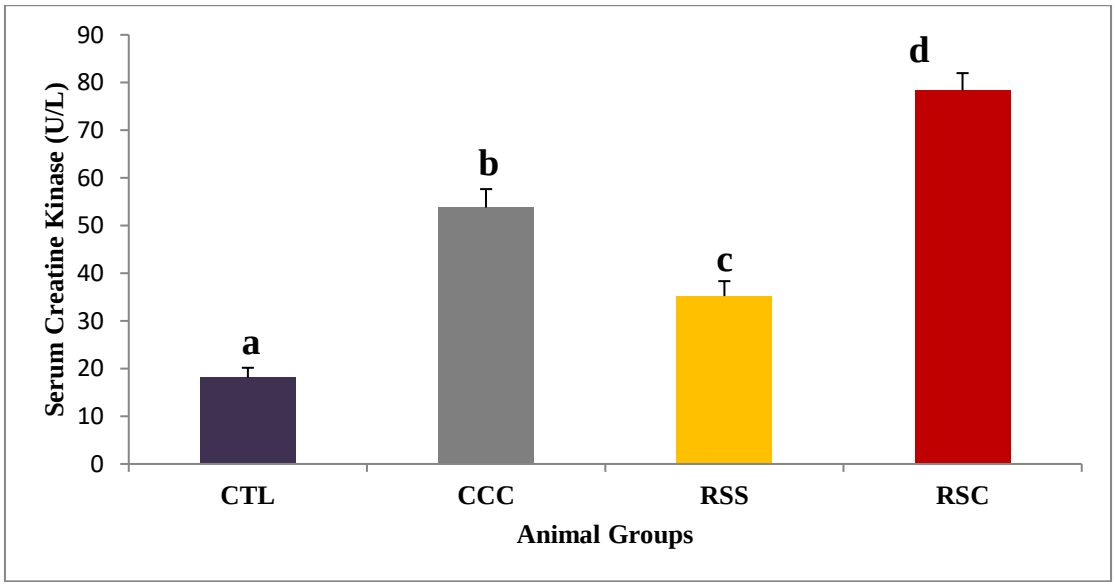
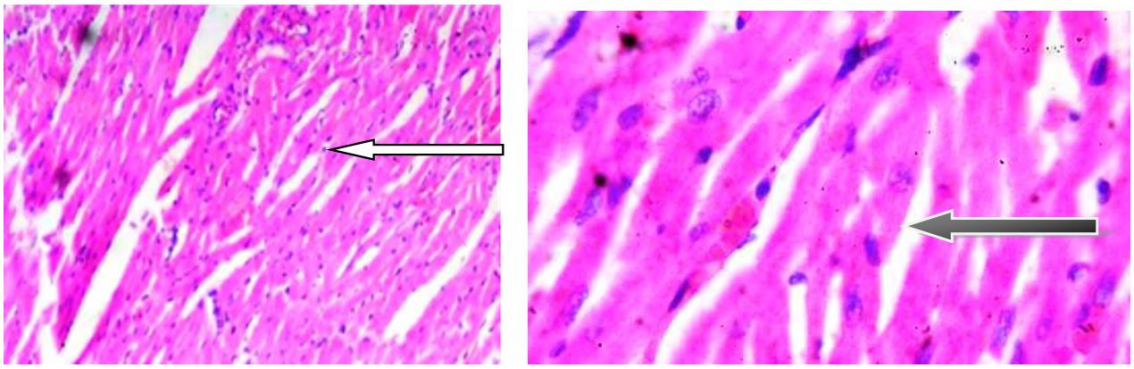


Fig. 4. Effect of cadmium chloride and restraint stress on the serum creatine kinase levels of female Wistar rats

n=6. Values are expressed as Mean±SEM. Serum CK levels in the CCC, RSS and RSC groups were independently significantly (p<0.05) higher than the CTL, However serum CK levels in RSC group was found to be significantly (p<0.05) higher than both RSS and CCC groups. Also the serum CK levels of CCC group was found to be significantly (p<0.05) higher than that of RSS

Histology of the Heart

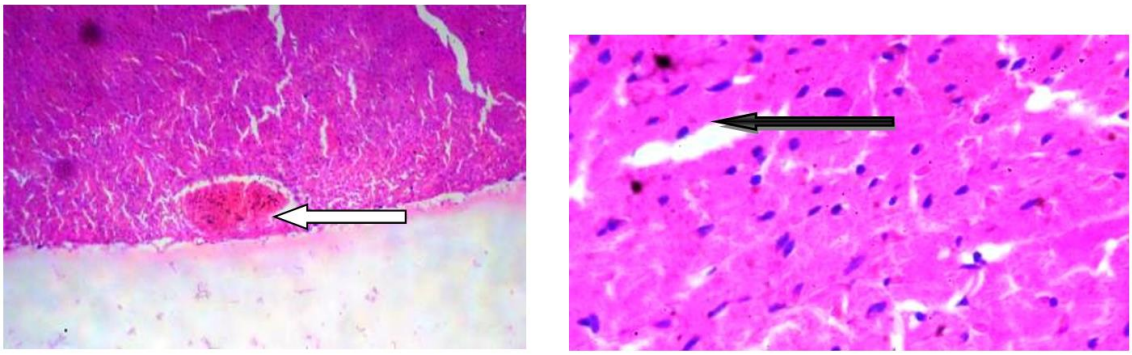
Control



X100 **X400**

Fig. 5a. Photomicrograph of a heart section stained by Haematoxylin and Eosin showing normal epicardial layer (white arrow) and normal myocardial layer seen (black arrow), the myocytes are normal

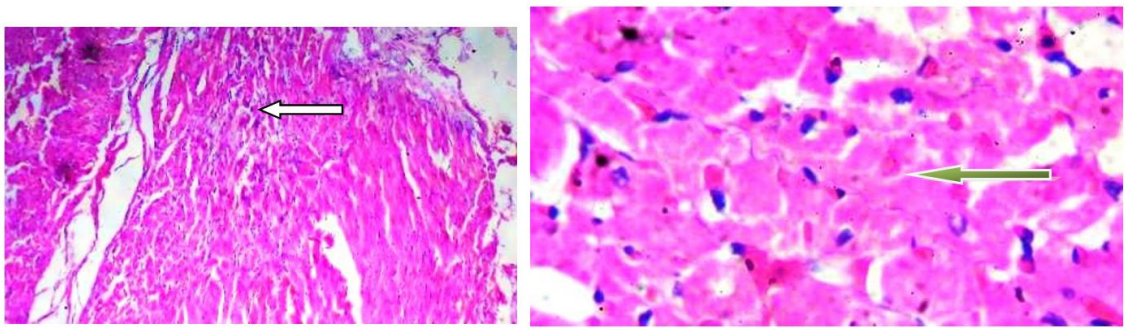
Restraint Stress alone



X100 **X400**

Fig. 5b. Photomicrograph of a heart section stained by Haematoxylin and Eosin showing epicardial layer with mild vascular congestion (white arrow) and myocardial layer appear normal (black arrow), the myocytes are normal

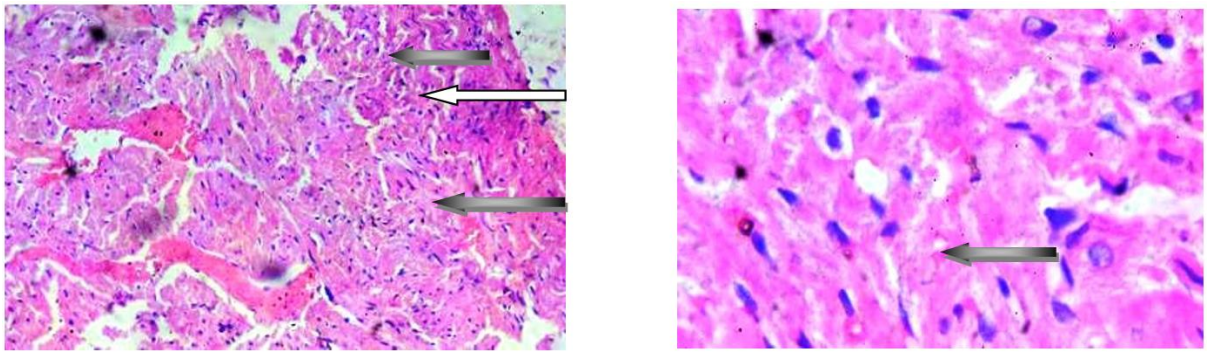
Cadmium Chloride alone



X100 **X400**

Fig. 5c. Photomicrograph of a heart section stained by Haematoxylin and Eosin showing mild epicarditis; (white arrow) and there are myocytes with necrosis seen (green arrow)

Restraint Stress and Cadmium Chloride



X100 **X400**

Fig. 5d. Photomicrograph of a heart section stained by Haematoxylin and Eosin showing epicardial layer with mild infiltrates (white arrow) and myocardial layer show moderately degenerated myocytes with necrosis (black arrow)

4. DISCUSSION

The ECG result of this study showed that QRS complex was reduced, P height was low in the CCC group (Fig. 1b). This ECG result indicates mitral valve impairment. Mitral valve impairment, also known as mitral regurgitation or mitral valve insufficiency is characterized by the reversal of blood flow from the left ventricle to the left atrium typically in the systolic phase of the cardiac cycle which could be as a result of myocardial infarction or dilated cardiomyopathy (Mc Carthy & Collier, 2018). Low P height indicates decreased P-wave amplitude which is correlated with a previous study of Protsenko et al. (2020) where decreased in P-wave amplitude and myocardial stiffness was observed following cadmium intoxication in rats. Cadmium induces reactive oxygen species (ROS) production, which triggers inflammatory signaling pathways (Saedi et al., 2024). Chronic inflammation promotes cardiac fibrosis (Turkcan et al., 2015), characterized by excessive extracellular matrix (ECM) deposition. This occurs due to the activation of cardiac fibroblasts into myofibroblasts, which secrete collagen and other ECM components. In a healthy state, resident CFs maintain a relatively quiescent state, which is responsible for preserving the homeostasis of the ECM cardiac structure and aiding in electrophysiological conduction (Travers et al., 2016). However, under pathological conditions, such as MI or chronic pressure overload, CFs undergo phenotypic changes, become activated, and contribute to cardiac remodeling and fibrosis (Chen et al., 2016). Over time, this leads to stiffening of the myocardium, reduced compliance, and impaired valve dynamics.

Restraint Stress increased P-wave, taller T and increased heart rate. Taller P Wave is indicative of atrial hypertrophy and its associated with increased heart rate (Fig. 1c). This phenomenon can be correlated to a previous study where acute mental stress induced abnormal P Wave and increases heart rate in women but not in men (Almuwaqqat et al., 2020). Exposure to stress activates the sympathetic nerve system (SNS) which in response increases heart rate, contractility, vasoconstriction, the level of epinephrine and norepinephrine secreted by the adrenal medulla and sympathetic nerves, respectively. Cardiac hypertrophy serves as an adaptive response to increased workload. However, when this increased workload becomes chronic, the compensatory hypertrophy transitions into pathological hypertrophy (Caturano et al., 2022). The result in the Cadmium chloride and Restraint Stress group showed Height of P increased, T taller than normal in myocardial infarction (Fig. 1d). Tachycardia seen is as a result of Cadmium chloride and Restraint Stress. This result suggests that the combined exposure to cadmium and restraint stress significantly altered cardiac conductivity.

The result of the current study showed that the troponin I level of the restraint stress alone group was significantly ($p<0.05$) higher than the control (Fig. 2). Troponin I is the inhibitory component of the troponin regulatory protein complex which

actually comprised of three subunits; other component subunits are troponin C and troponin T. All the troponin components are involved in the contractile process of both skeletal and cardiac muscle. However, cardiac troponin I (cTnI) is specific to the heart (Câmara et al., 2020). Though troponin can be detected in the blood of healthy individual at small amounts, when cardiac damage occurs particularly to irreversible levels, cardiomyocytes undergo metabolic changes that eventually lead to further release of troponin (Chaulin, 2022). Based on its specificity, troponin has been considered a potential marker of tissue damage (Lazar et al., 2022) and has been recommended by several international scientific societies as a diagnostic marker for acute myocardial infarction. Restraint stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamic-adrenomedullary axis leading to the release of cortisol and epinephrine and norepinephrine respectively. Both of these hormones increase the availability of glucose and rate of oxidative phosphorylation in the mitochondria of cardiomyocytes leading to the generation of reactive oxygen species (ROS). This is then followed by the release of troponin I by any of these possibilities as shown in Fig. 6.

The result of the current study also indicated that the serum LD (Fig. 3) and CK (Fig. 4) level of the restraint stress alone was significantly ($p<0.05$) higher than the control. This is indicative of myocardial infarction. Lactate dehydrogenase is an essential enzyme in the anaerobic pathway involved in the conversion of pyruvate to lactate and back (Zhu et al., 2022) while CK is an enzyme that catalyses the transfer of phosphate groups from high-energy phosphocreatine to ADP thereby regenerating ATP and their leakage from the cardiomyocytes into the blood can be caused by various factors including cell membrane damage, increased membrane permeability, cell necrosis, apoptosis. These factors can be triggered by hypoxia, inflammation and excessive catecholamine exposure. Interestingly, restraint stress has been reported to lead to hypoxia, inflammation and excessive catecholamine exposure (Krizanova et al., 2016) through the activation of hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-adrenomedullary axes. The activation of these axes can also lead to ATP depletion in the cardiomyoctes which further impairs the cellular membrane function. Excessive release of cathecholamine can also cause excessive calcium overload in the cardiomyocytes which could disrupts the cell membrane integrity (Wu et al., 2021). MAPK signaling, NF-kB activation, PI3K/Akt pathway disruption are also involved in the leakage of LD and CK.

The result of the current study also indicated that CC administration lead to the significant ($p<0.05$) elevation of the cTn, LD and CK in CC alone group when compared with the control (Figs. 2, 3, 4). The release of these three parameters is basically due to their leakage from the cardiomyocytes into the blood. This result further supports the reports of Hassanein et al. (2023) where it was observed that Cd injection resulted in remarkable increase in CK-MB, LDH and troponin-I levels. The marked increase in CK activity indicates impairment of enegetic homestasis and tissue damage (Baldissera & Baldisserotto, 2023). Increased LDH activity reflects increased dependence on anaerobic carbohydrate metabolism. The significant elevation of cTnI by cadmium signifies the possible induction of heart attack (myocardial infarction). This assertion is so because the cTnI has been identified as a superior marker for the left ventricular malfunction (Buiten et al., 2015) and that in most cases, wherever there is a rise in CTP, it is indicative of heart damage or a very recent myocardial infarction.

The histological result showed that restraint stress of 30 minutes daily for 21 days has epicardial layer with mild vascular congestion while the myocardial layer appeared normal (Fig. 5b). This mildness might have resulted from the degree, intensity and duration of the restraint. Subsequent experiment of this kind involving higher intensity and longer duration might probably produce more deleterious effects on the myocytes of the restraint stress group rats.

The examination of the heart of cadmium-exposed group showed mild epicarditis and myocytes with necrosis (Fig. 5c). This result is consistent with a previous study where early necrosis, apoptosis of the cardiomyocyte, disarrayed myofibrils, and ultrastructural changes in sarcomeres were observed in the Cd exposure group in mice (Chou et al., 2023). Studies have indicated that Cd damages cardiac tissues by causing oxidative damage in DNA, lipids, and proteins and inducing inflammation in the cardiac tissues which may impair cardiomyocyte function and trigger necrosis (Lei et al., 2011). Cd-induced increase in the levels of reactive oxygen species may promote the activation of phosphoinositide 3-kinase (PI3K)-Akt and P38

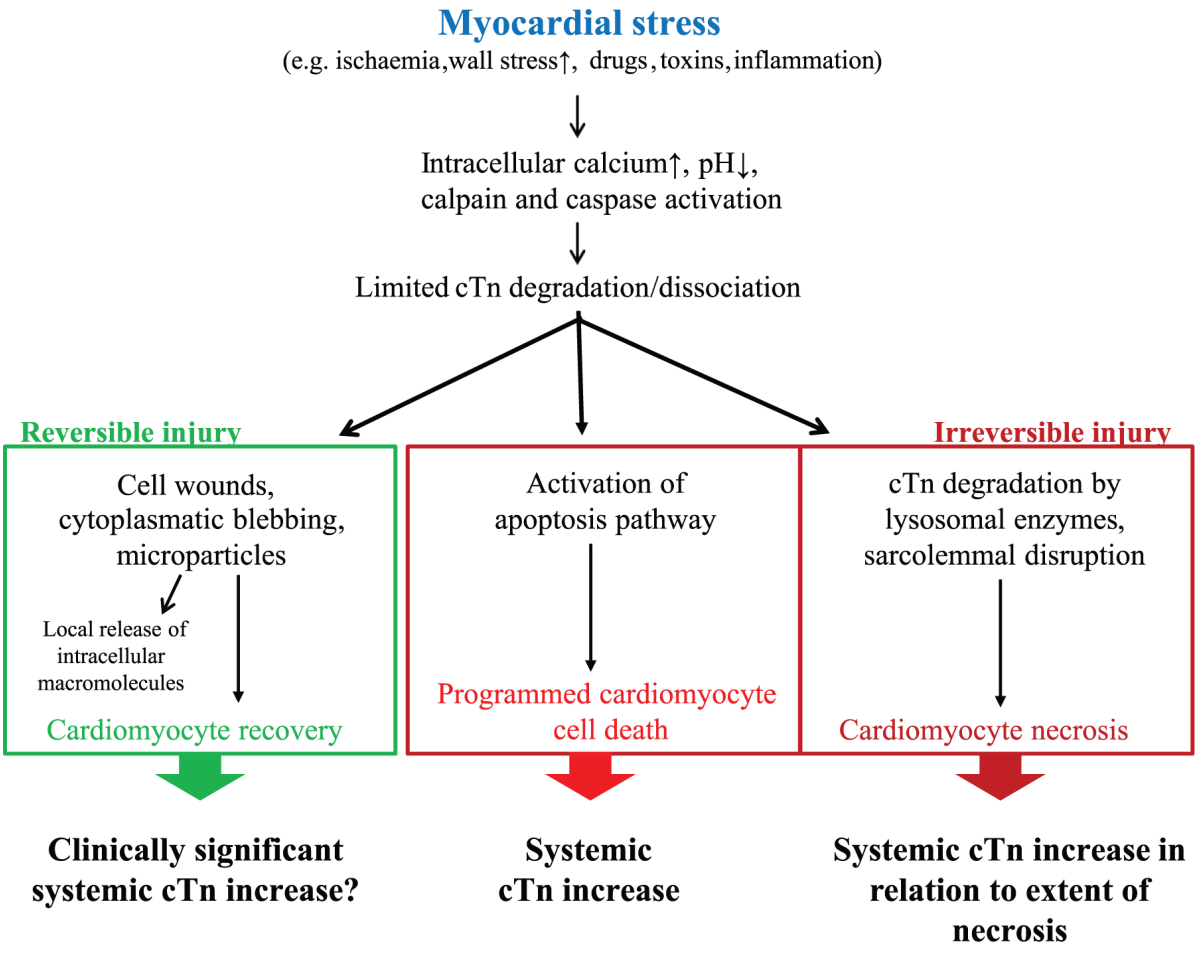


Fig. 6. Possible mechanism of Troponin I release from stressed myocardium (Mair et al., 2018)

mitogen-activated protein kinase signaling pathways, which are in a stress-adaptative response (Hu et al., 2015). However, sustained activation of these pathways, combined with mitochondrial dysfunction, calcium overload, and oxidative damage, overwhelms cardiomyocyte survival mechanisms. This ultimately culminates in necrosis characterized by cell swelling, loss of membrane integrity, and inflammatory damage.

The Restraint and Cadmium group showed the combined mechanisms of restraint stress and cadmium exposure induced adverse effects on the heart (Fig. 5d). However, the mild effects can be due to the duration of the study. Longer duration might promote more pronounced cardiotoxic effects owing the combined exposure of both stressors.

5. CONCLUSION

Cadmium chloride administration alone seems to produce a more deleterious effect on cardiac function of female Wistar rats than the restraint stress exposure alone. This is reflected in the altered electrical conductivity, increased serum levels of biochemical cardiac function markers and distorted myocytic histological presentations of these female rats. However the exposure of female rats to both cadmium chloride administration and restraint stress produced a higher alteration in the cardiac function of these female rats.

DISCLAMIER (ARTIFICAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as large language models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscript.

ETHICAL APPROVAL

This study was conducted following the Institutional Animal Care and Use Committee

(IACUC) guidelines, in strict compliance with the National Institutes of Health (NIH) guideline for the care and use of laboratory animals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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