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Full-Length Research Article

Vincristine Prevents Hematological and Plasma Biochemical Alterations in Isoprenaline-Treated Rats

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Summary: Sustained adrenergic stimulation is linked to altered plasma biochemistry and haematological functions. However, whether vincristine (VCR), a vinca alkaloid with acclaimed cardioprotective property, can protect against biological alteration remains unknown. Hence, this present study investigated the protective impact of vincristine against plasma biochemical alteration caused by sustained beta-adrenergic stimulation induced by isoprenaline exposure in male Wistar rat. Animals were randomly divided into four groups; Group 1 received saline and was used as control. Group 2 received ISO (1 mg/kg, i.p.) for 14 days. Group 3 received ISO (1 mg/kg, i.p.) concurrently with vincristine (VCR) (25 µg/kg, i.p.) for 14 days. Group 4 was pre-treated (Pre-VCR) with VCR (25 µg/kg, i.p.) for 14 days before ISO treatment from days 15 to 28. Vincristine treatment was done in a six-day cycle with two days off in between each cycle and all the experimentation lasted for 28 days. Following euthanasia, blood was used for haematological, liver and renal function marker assays and the resulting data were subjected to inferential statistics. Our results showed a significant ($p<0.05$) increase in erythrocyte, haematocrit, haemoglobin and leucocyte while there was a significant ($p<0.05$) decreased in lymphocyte and thrombocyte in ISO-treated animals when compared with the control animals. However, VCR pre-treatment reversed these haematological parameters to normal levels. Liver (ALP, AST and ALT) and kidney (Creatinine, BUN, globulin, albumin and total protein) function markers were greatly ($p<0.05$) altered in ISO-treated animals. However, pre-treatment with VCR significantly modulated these markers. Plasma electrolytes were also modulated by VCR pre-treatment against the derangement caused by ISO treatment. Finally, our study suggests that vincristine pre-treatment protected animals exposed to sustained β-adrenergic stimulation from haematological, liver and kidney function alterations.

Keywords*: Isoprenaline, Vincristine, β-adrenergic stimulation, Hematology, Plasma biochemistry*

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INTRODUCTION

A possible cause of ventricular fibrillation and sudden cardiac death is the stimulation of β-adrenergic receptors by catecholamines (Saadeh *et al*., 2020). Because of its amazing technical simplicity, high reproducibility and tolerably low morbidity, the sympathomimetic β-adrenergic receptor agonist isoproterenol (ISO), causes irreversible damage to the heart in experimental animals (Azevedo *et al*., 2021). More recently, ISO has been utilized to simulate disease states notably involving organ toxicity and its associated cardio-biological sequelae in animals, demonstrating its basic and clinical application as a reliable experimental tool for the study of cardiovascular disorders.

It has been proposed that excess intracellular Ca2+, changes in electrolyte contents, oxidative stress, haematological abnormalities resulting in functional hypoxia and ischemia are some of the patho-biological mechanisms by which ISO impairs cardiovascular functions (Zhou *et al*., 2022; Asiwe *et al*., 2023a). To detect tissue necrosis, myocyte destruction is reflected by aberrant levels of several proteins in the blood (Sharifi-Rad *et al*., 2020). Stimulation of β-adrenergic receptors has been shown to contribute to changes in electrolyte balance, which are thought to be crucial in cardiac death. When ISO is administered, the pathophysiological alterations are similar to those that occur in human cardiac damage (Abukhalil *et al*., 2021). Accordingly, free radicals generation by ISO notably inducing peroxidation of membrane-bound polyunsaturated fatty acids (PUFAs), has been largely reported as one of the key mechanisms of ISO-induced cardiac impairment (Abrescia *et al*., 2020; Dyall *et al*., 2022). In animal models, particularly rats, isoprenaline administration can influence hematological parameters by

altering red and white blood cell dynamics through oxidative stress and inflammatory responses. Moreover, the metabolic stress induced by isoprenaline may compromise hepatic and renal function, reflected by elevated serum transaminases, urea, and creatinine levels. These biochemical changes indicate tissue injury and disrupted metabolic homeostasis (Umoren *et al*., 2023; Agbatutu *et al*., 2025). Thus, evaluating the effects of isoprenaline on hematological indices and liver and kidney function markers provides valuable insight into its systemic toxicity and the pathophysiological mechanisms underlying β-adrenergic overstimulation

The goal of every treatment includes both tissue protection and injury prevention using phytochemicals or neutraceuticals (Fan *et al*., 2021). The effect of one of the vinca alkaloids such as vincristine (VCR), frequently used in chemotherapy to treat a variety of cancers (Mayer *et al*., 2021; Elshamy *et al*., 2022) remains unknown. Tissue destruction is one of the most significant side effects of chemotherapy for cancer patients, leading to significant morbidity and mortality (van der Zanden *et al*., 2021). Alleviation of haematological alterations such as anaemia, leukopenia, and thrombocytopenia are common manifestations of moderate dose of vincristine, reflecting its impact on bone marrow function (Agbatutu *et al*., 2025). In addition, vincristine may mitigate biochemical perturbations characterized by elevated liver enzymes, altered renal function markers and changes in lipid and glucose metabolism. However, it believed that vincristine improved blood circulation and lessen oxidative stress-mediated myocardial damage (Chen *et al*., 2020). Vincristine's ability to reverse the detrimental effects of prolonged β-adrenergic receptor activation on haematological and plasma biochemical indicators by ISO is however unknown. Hence, this study investigated the effects of vincristine on the haematological and biochemical alterations caused by ISO in rats.

MATERIALS AND METHOD

Reagents and chemicals: The assay kits for alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), albumin, globulin, sodium (Na+), potassium (K+), and chloride (Cl) were purchased from Randox Laboratories Ltd., Co. Antrim, UK. Vincristine and ketamine hydrochloride were purchased from Rotex-Medica in Germany. Other substances employed in this research were of the highest purity and analytical grade from their respective vendors.

Animals: The twenty (20) male Wistar rats utilized in this experiment were healthy animals, aged 9 weeks and weighing between 120-140g. The animals were purchased from the central animal housing facility, University of Ibadan. They were fed standard pelleted rat food (Ladokun feed®) and allowed to freely access tap water. The animals were kept and maintained under laboratory conditions of temperature (25±02ºC), humidity (45-55) and 12hr-light and 12hr darkness. The experimental animals were kept in a polyethene cages throughout the duration of the experiment and housed at Faculty of Veterinary Medicine Animal House, University of Ibadan, Nigeria. The University of Ibadan Ethical Approval Committee approved the use of animals and assigned it the approval code UI-ACUREC/028-0820/27. The experimental protocol complied with national guidelines for care and management of animals (NIH Publication No. 85-23).

Study design: The animals were divided into four groups at random after acclimating to the laboratory environment for seven days, and each group received the following care: Group 1 received saline and was used as control. Group 2 received ISO (1 mg/kg, i.p.) for 14 days. Group 3 received ISO (1 mg/kg, i.p.) concurrently with vincristine (VCR) (25 µg/kg, i.p.) for 14 days. Group 4 was pre-treated (Pre-VCR) with VCR (25 µg/kg, i.p.) for 14 days before ISO treatment from days 15 to 28. Vincristine treatment was done in a six-day cycle with two days off in between each cycle and all the experimentation lasted for 28 days. We obtained the doses for ISO and VCR according to studies of Choudhary *et al*. (2006) and Panda *et al*. (2014), respectively.

Experimental β-adrenergic stimulation induction: To generate sustained adrenergic stimulation in experimental animals, ISO was dissolved in distilled water and delivered intraperitoneally daily for two weeks (14 days) at a dose of 1 mg/kg/day as described by Choudhary *et al*. (2006) with minor adjustments.

Data collection: Blood was taken into EDTA bottles for haematology following euthanasia through the retro-orbital sinus. The samples were centrifuged for 10 min at a speed of 3000 revolutions per min, and the plasma that was produced was decanted and kept at -20°C for plasma biochemical analysis. Using the appropriate kits, all assays were performed in accordance with the accepted laboratory methodology.

Haematology: According to the procedures outlined previously by Okonofua *et al*. (2021), haematocrit (PCV), hemoglobin (Hb) concentration, erythrocytes (RBC) count, leukocyte (WBC) count, lymphocyte count, and thrombocyte count were all assayed. Blood samples were collected into EDTA tubes for hematological analysis. Packed cell volume (PCV) was determined by the microhematocrit method, while hemoglobin (Hb) concentration was measured using the cyanmethemoglobin method at 540 nm. Erythrocyte (RBC) and leukocyte (WBC) counts were obtained manually using the improved Neubauer hemocytometer with appropriate diluting fluids. Differential leukocyte (lymphocyte) counts were performed on Wright–Giemsa–stained blood smears. Platelet (thrombocyte) counts were estimated microscopically from peripheral smears and results were expressed in conventional units to assess haematological responses to experimental treatment.

Liver and kidney function markers

Measurement of plasma alkaline phosphate measurement (ALP): Different concentrations (0.05, 0.02, and 0.01 mL) of plasma were pipetted into each sample tubes, and 3.00 mL, 1.00 mL, and 0.50 mL of reagents were pipetted into the test tubes. The mixture was then read on

starting absorbance and start time simultaneously, and again after 1, 2, and 3 minutes on a wavelength of 405 nm.

Measurement of plasma aminotransferase for aspartate (AST): Distilled water and NaOH 4M were utilised to prepare for the testing, wherein R1 served as buffer phosphate L-aspartate, while R2 is a 2,4-dinitrophenylhydrazone. With the exception of the blank tube, all the sample tubes received 0.1mL of plasma. All test tubes received 0.5 mL of reagent 1, and the blank received 0.1 mL of distilled water. This mixture was then mixed and allowed to sit at 37 °C for 30 min. Next, 5.0 ml of NaOH was added to each sample tube. After 5 min., the absorbance of the samples was measured against the blank at 546 nm.

Determination of plasma alanine aminotransferase (ALT): We used 0.4M NaOH as R2 reagent and 2,4-dinitrophenylhydrazine as R1 reagent in the buffer solution to measure the plasma Alanine Aminotransferase (ALT). The sample tubes were filled with 0.1 millilitres of plasma, 0.5 millilitres of reagent 1, and only 0.1 millilitres of distilled water for the blank. For precisely 30 min, the sample vials were mixed and incubated at 37°C. After mixing reagent 2 with the samples and the blank, the mixture was let to stand for 20 min at 20 to 25°C. 5.0 cc of NaOH was applied to the samples and the blank. According to Rietman and Frankel (1957), it was mixed and the samples' absorbance was compared to the reagent blank after 5 minutes at 546nm.

Markers of renal function: Using the Randox test kit and the Reitman and Frankel procedure (1957), plasma concentrations of creatinine, BUN, albumin, globulin, and total protein were measured.

Plasma electrolyte concentration estimation: Using specialised commercial kits, the plasma electrolytes sodium, potassium, and chloride were measured. SpectraMAX PLUS, a microplate reader (a molecular Device product), was used for all tests.

Statistical evaluation

The data were expressed using means and standard error of the means. In GraphPad Prism (San Diego, CA, USA) version 8.0, the one-way analysis of variance (ANOVA) was applied to all data, and the post hoc Newman-Keuls test was used to compare groups. P-values of 0.05 or less were considered significant.

RESULTS

Vincristine pre-treatment modulates haematological imbalances: As presented in figure (1A-C), adrenergic stimulation resulted in a significant increase in erythrocytes [$F(3, 16)=58.2$, $p<0.0001$, $R^2=0.916$], haemoglobin [$F(3, 16)=94.5$, $p<0.0001$, $R^2=0.947$] as well as increased packed cell volume [$F(3, 16)=84.2$, $p<0.0001$, $R^2=0.940$]. However, VCR pre-treatment as well as VCR co-treatment with ISO significantly reduced these variables when compared with control as well as ISO-treated groups. Lymphocytopenia [$F(3, 16)=48.9$, $p<0.0001$, $R^2=0.902$] and thrombocytopenia [$F(3, 16)=37.7$, $p<0.0001$, $R^2=0.876$] as well as luekocytosis [$F(3, 16)=14.2$, $p<0.0001$, $R^2=0.727$] were also observed in sustained adrenergic stimulated rats but VCR either pre-treatment or co-treatment significantly increased lymphocyte count and thrombocyte count as well as reducing leukocyte count comparatively to the control or ISO-treated animals figure (2A-C).

Vincristine pre-treatment prevents liver cell membrane disruption: Sustained adrenergic stimulation causes liver cell membrane disruption resulting in the significant release of ALT [$F(3,16)=55.0$, $p<0.0001$, $R^2=0.912$], AST [$F(3,16)=246$, $p<0.0001$, $R^2=0.979$] and ALP [$F(3, 16)=126$, $p<0.0001$, $R^2=0.959$] as shown in figure (3A-C). However, these were prevented by VCR, either pre-treatment compared with the control, and by ISO treatment compared with the ISO-treated group.

Vincristine prevents tubuloglomerular dysfunction*:* As shown in figure (4A-E), the levels of total protein [$F(3, 16)=40.0$, $p<0.0001$, $R^2=0.882$], albumin [$F(3, 16)=15.2$, $P<0.0001$, $R^2=0.740$] and globulin [$F(3, 16)=84.0$, $p<0.0001$, $R^2=0.940$] significantly reduced following sustained adrenergic stimulation in animals. Also, concentrations of BUN [$F(3, 16)=69.1$, $p<0.0001$, $R^2=0.928$] and creatinine [$F(3, 16)=34.7$, $p<0.0001$, $R^2=0.867$] were significantly increased in ISO-treated animals when compared with control. However, VCR pre-treatment or co-treatment significantly elevated the plasma levels of total protein, albumin and globulin while reducing the level of BUN and creatinine when compared with ISO-treated group.

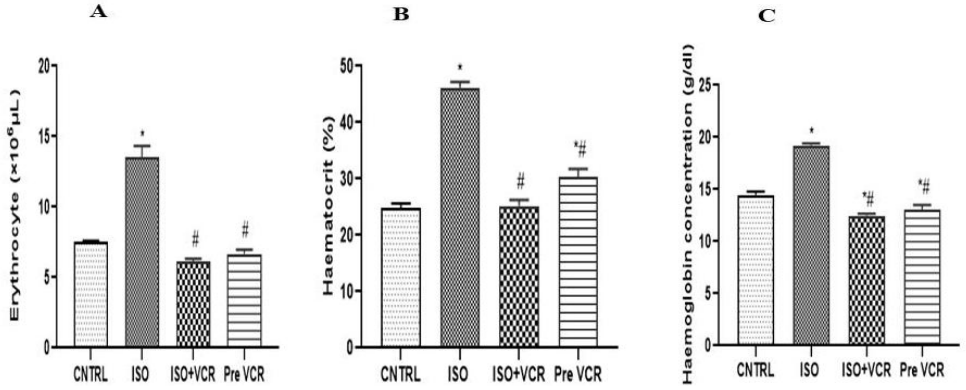

Figure 1:
Vincristine pre-treatment modulates haematological imbalances (A) Erythrocyte count (B) Haematocrit (C) Haemoglobin concentration. Values are expressed as Mean±SEM, n=5 and $^{*}p<0.05$ was significant when compared with the control group, while #p<0.05 was significant when compared with the ISO-treated group. CNTRL= control, ISO= Isoprenaline, VCR = Vincristine

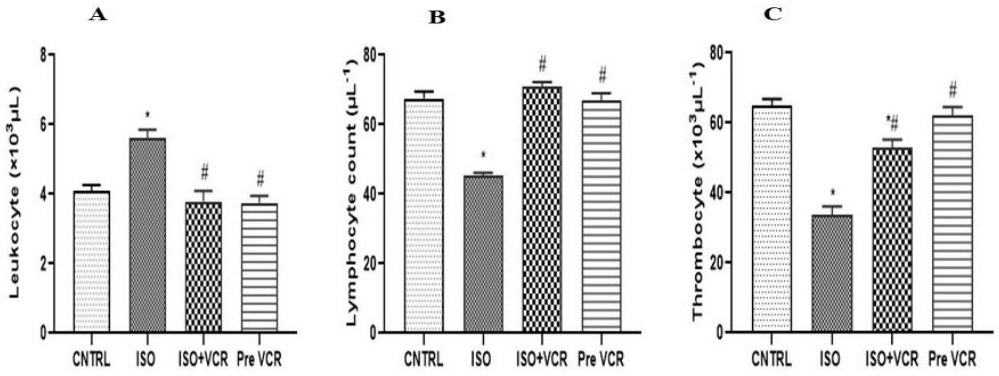

Figure 2:
Vincristine pre-treatment modulates haematological imbalances (A) Leukocyte count (B) Lymphocyte count (C) Thrombocyte count. Values are expressed as Mean±SEM, n=5 and $^{*}p<0.05$ was significant when compared with control group while $^{\#}p<0.05$ was significant when compared with ISO-treated group. CNTRL= control, ISO= Isoprenaline, VCR = Vincristine

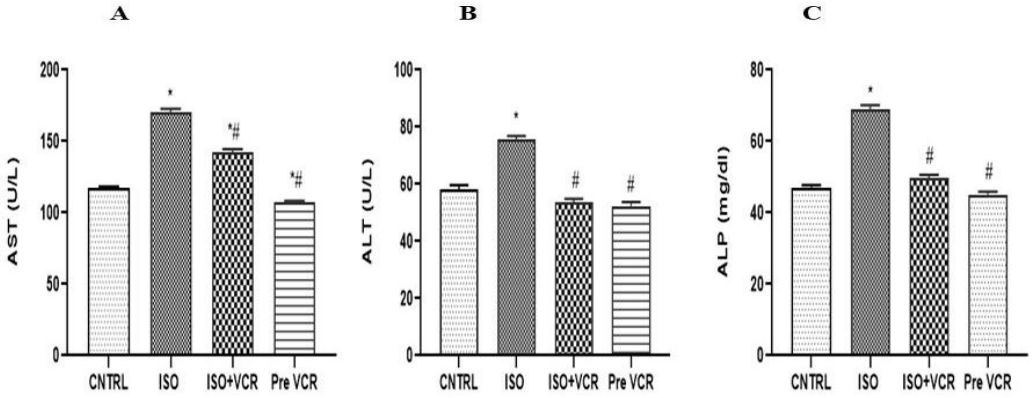

Figure 3:
Vincristine pre-treatment prevent liver cell membrane disruption (A) Aspartate aminotransferase (B) Alanine aminotransferase (C) Alkaline phosphatase. Values are expressed as Mean±SEM, n=5 and $^{*}p<0.05$ was significant when compared with the control group, while #p<0.05 was significant when compared with the ISO-treated group. CNTRL= control, ISO= Isoprenaline, VCR = Vincristine

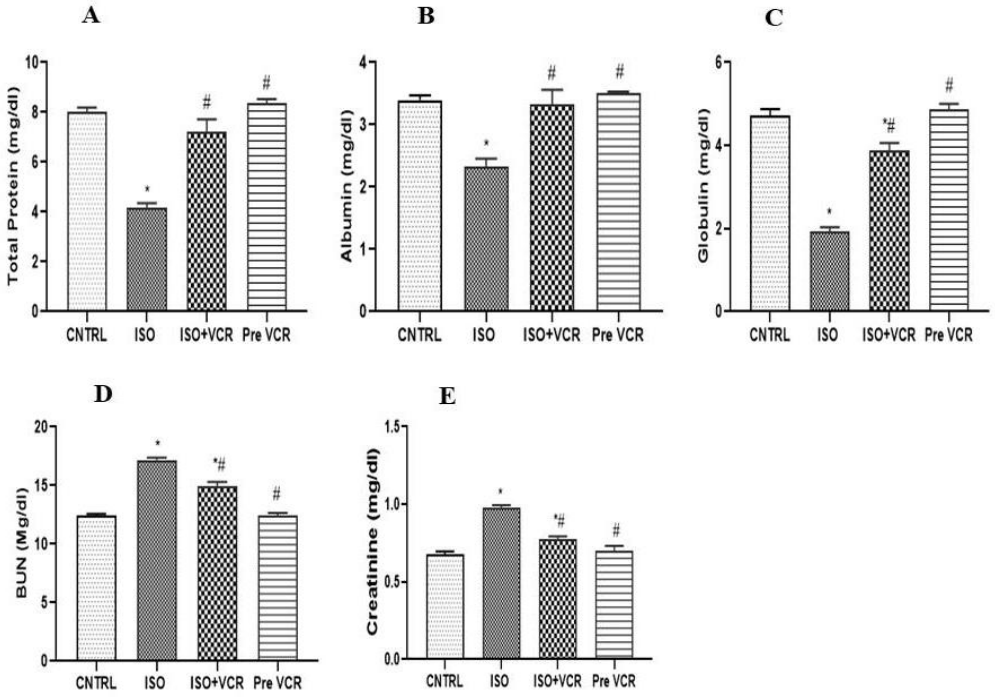

Figure 4:

Vincristine prevents tubuloglomerular dysfunction (A) Total protein (B) Albumin (C) Globulin (D) Blod Urea Nitrogen (BUN) (E) Creatinine. Values are expressed as Mean±SEM, n=5 and $^{*}p<0.05$ was significant when compared with control group while $^{\#}p<0.05$ was significant when compared with ISO-treated group. CNTRL= control, ISO= Isoprenaline, VCR = Vincristine

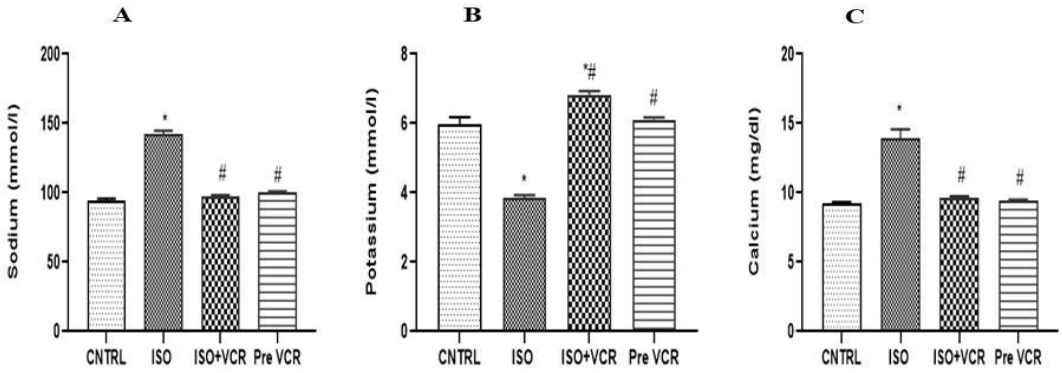

Figure 5:
Vincristine prevents electrolyte imbalance (A) Sodium ion (B) Potassium ion (C) Calcium ion. Values are expressed as Mean±SEM, n=5 and $^{*}p<0.05$ was significant when compared with control group while $^{\#}p<0.05$ was significant when compared with ISO-treated group. CNTRL= control, ISO= Isoprenaline, VCR = Vincristine

Vincristine prevents electrolyte imbalance: Sustained adrenergic stimulation significantly causes increased sodium ion [$F(3, 16)=277$, $p<0.0001$, $R^2=0.981$] and calcium ions [$F(3, 16)=49.1$, $p<0.0001$, $R^2=0.902$] while reducing potassium ion [$F(3, 16)=110$, $p<0.0001$, $R^2=0.954$] when compared with control groups as presented in figure (5A-C). However, vincristine pre-treatment as well as co-treatment normalises these electrolyte levels comparatively to the ISO-treated groups

DISCUSSION

By modifying the levels of plasma ALP, AST, ALT, creatinine, BUN, total protein, albumin, globulin, Na^+, Ca_2^+, K^+, and haematological parameters in ISO-treated rats, the study demonstrated that vincristine pre-treatment had a positive effect on animals exposed to sustained β-adrenergic stimulation.

Haematological characteristics primarily focus on the cellular components of blood, their quantity or concentration, the relative distribution of different cell types and structural or biochemical anomalies that encourage the onset of disease (Genchi *et al.,* 2020; Asiwe *et al.,* 2022a). It has been hypothesized that atherogenesis and blood rheology may share some characteristics due to the tight connection between cardiovascular disorders and haematology (Arkew *et al.,* 2022). Blood viscosity and variables including haematocrit, globulin, and total lipid concentration are found to be positively correlated (Huaman *et al.,* 2022). In rats exposed to ISO, higher levels of erythrocyte, haemoglobin and haematocrit were observed. According to Qiang *et al*. (2021), hypoxia, a state that causes erythrocytosis, may be the cause of the observed increase in erythrocytes. Accordingly, erythrocyte, haemoglobin, and haematocrit levels were decreased in rats treated with ISO and VCR concurrently, as well as pre-treatment with VCR.

A major risk factor for acute myocardial infarction (MI) has been linked to high leukocyte count (Klein *et al.,* 2020; Dey *et al.,* 2021). Additionally, alteration in neutrophils count may also contribute to tissue damage in myocardial infarction by releasing leukotrienes, free oxygen radicals and hydrolytic enzymes. Previous report has shown that leucocytosis, which is connected with necrotic process including its severity, may be the cause of the observed increase in leukocytes (Angelovski *et al.,* 2022). Following ISO and VCR co-treatment as well as VCR pre-treatment, the observed leukocytosis was reduced. In rats exposed to ISO, a measurable rise in thrombocyte count was seen. The atherothrombosis of MI is significantly influenced by thrombocytes (Asada *et al.,* 2020). Following MI, studies have shown increase in the production of small thrombocytes as well as a quick depletion of medium and large thrombocytes, leading to an overall increase in thrombocytes (Lordan *et al.,* 2021). In comparison with ISO-induced rats, VCR co-treatment as well as pre-treatment decreased the thrombocyte count. One indicator of prognosis in those with heart failure symptoms is connected with changes lymphocyte concentration (Li *et al.,* 2022). Functionally, T-lymphocytes regulate the growth of smooth muscle during vascular healing. Rats with lower T-lymphocyte numbers, however, exhibited greater myocardial lesions (Chen *et al.,* 2020). Therefore, during acute MI, a decrease in T-lymphocytes serves as both a marker and a contributing factor in the impairment of cardiac function. In this study, rats treated with ISO were shown to have lowered level of lymphocyte count. However, VCR co-treatment and pre-treatment protocols were found to improve the lymphocyte count.

The liver is a crucial organ that processes food and eliminates poisons that could jeopardize the body's normal functions (Qu *et al.,* 2022; Asiwe *et al.,* 2022b). Since a significant increase in their plasma concentration has been previously shown to suggest toxicity, the biomarkers ALT, ALP, and AST used in this study suggest impaired liver function (Qu *et al.,* 2022). Previous reports have shown that ISO administration, notably subcutaneously, causes an increase in hepatic enzyme release (Rathod *et al.,* 2022), a sign of liver cell damage and was complimentary to our findings. However, pre-treatment with VCR, as well as its co-treatment, resulted in a considerable decrease in the plasma concentration of these enzyme indicators. The kidneys are essential for removing waste products from

metabolism and toxins that endanger physiological homeostasis (Asiwe *et al.,* 2022b; Agbatutu *et al.,* 2022). As seen in rats treated with ISO, a sustained increase in adrenergic stimulation also causes a considerable rise in plasma levels of BUN and creatinine. Purine metabolites from ATP and ADP accumulate during ischemia, providing the necessary substrate, including hypoxanthine and the electron acceptor, oxygen, which results in the synthesis of urea and more critically, free O_2 and H_2O_2 (Saeb-Parsy *et al.,* 2021). In this study, BUN level was significantly reduced by co-treatment and pre-treatment of VCR. Plasma albumin's N-terminus undergoes structural alterations as a result of β-adrenergic stimulation, which lowers the protein's ability to bind cobalt cations (Asiwe *et al.,* 2023a; 2023b). Indeed, hypoxia, acidosis and the generation of reactive oxygen species during ischemia and/or reperfusion have all been put forth as possible causes of these alterations (Lu *et al.,* 2021). Increased free radical generation induced by sustained adrenergic stimulation may be responsible for the decline in serum total proteins and globulin. However, more studies are required to clarify this assertion. Interestingly, we found that rats co-treated or pre-treated with VCR demonstrated increased levels of plasma total protein and globulin levels, suggesting that vincristine might have played a homeostatic role. This beneficial effect might be linked to VCR's capacity to enhance *in vivo* antioxidant defense system, evidenced by reduced lipid peroxidation. In this context, it was previously revealed that VCR possesses anti-lipid peroxidative and antioxidant properties following β-adrenergic receptor activation in Wistar rats (Ge *et al.,* 2021; Yarmohammadi *et al.,* 2021). Furthermore, rats treated with ISO showed an electrolyte imbalance owing to increase in Na^+ and Ca_2^+ levels, and a reduction in K^+ levels. Increased levels of muscle free fatty acids (FFAs) have been linked to the non-competitive inhibition of numerous enzyme systems, including Na^+/K^+-ATPase (Wu *et al.,* 2021; Eruotor *et al.,* 2023). The blockage of the Na^+ pump was associated with excessive concentration of internal sodium and it is known to exacerbate cardiac excitotoxicity (Aksentijevi *et al.,* 2020). In this context, it was previously observed that rats treated with ISO had higher levels of FFAs (Wu *et al.,* 2021). Therefore, elevated amounts of FFAs may have caused disruption of Na^+/K^+-ATPase leading to increased sodium ion build-up observed in the ISO-treated rats, and this might be linked to altered ATP metabolism. Although adenylate cyclase activity has been shown to be boosted by adrenergic stimulation leading to an increase in the production of cyclic adenosine monophosphate (cAMP), cAMP is known to phosphorylate a number of locations during β-adrenergic stimulation, notably promoting excessive generation of ROS with increase Ca_{2+} concentration as we showed herein (Murakami *et al.,* 2021; Du *et al.,* 2021). However, co-treatment and pre-treatment with VCR lowered Na^+ and Ca_2^+ levels with increased K^+ level relative to ISO groups, effectively reducing the imbalance brought on by prolonged β-adrenergic stimulation.

In conclusion, the findings from this study showed that vincristine pre-treatment protected against haematological, liver and kidney function alterations achieved by isoprenaline-induced β-adrenergic stimulation. This is evidence in significant reduction of erythrocytosis, haemoglobinemia, leucocytosis, haematocrit, ALP, AST, ALT, creatinine, BUN, Na^+, Ca_2^+ with significant increase in lymphocytopenia, thrombocytopenia, K^+, albumin total proteins as well as globulin. The findings of this investigation support the previously noted cardio protective properties of VCR. However, to fully understand the mechanism underlying the hepato-renal protective effect of VCR on ISO-induced hematological derangements, more studies are required.

Ethical consideration: *the University of Ibadan Animal Care Research Ethics Committee approved the study (UI-ACUREC/028-0820/27) and the procedure closely complied with the ARRIVE recommendations as outlined in the 1996 revision of NIH Publication No. 85-23.*

Data accessibility statement: All the data associated with this study are included in this manuscript.

Contributions of Authors: *the study was conceptualised by JNA and AAF while data curation was managed by JNA, JCO and DEO. The first draft of the manuscript was written by JNA and revised by BB. The authors read and approved the final draft.*

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