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Serum Adropin as a Biomarker for Cardiac Dysfunction in Experimentally Induced Male Albino Rat Heart Failure Model

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Abstract

Background: Heart Failure (HF) remains to be one of the major worldwide causes of mortality and morbidity. Adropin is a recent peptide hormone that may play a role in energy homeostasis and metabolism. Some studies revealed that adropin plays a crucial role in the pathogenesis of heart failure others suggesting that it may be important for maintaining cardiovascular system potency.

Aim of Study: To find out the possibility of using adropin as a biomarker for detection of cardiac dysfunction, in experimentally induced heart failure in male albino rats.

Material and Methods: This study was conducted on 2 groups of male albino rats (180-200g): Control group (I) (n=10), in which rats fed normal chow. Chronic heart failure group (II) (n=10), in which chronic heart failure was induced by subcutaneous injection of Isoproterenol at a dose of 5mg/kg once daily for 14 consecutive days. Echocardiographic measurements were done, whole Body Weight (BW) was measured, serum levels of adropin & brain natriuretic peptide were measured. Whole Heart Weight (WHW) were measured, then (WHW/BW ratio were calculated). Finally, histopathological examination of heart tissues was done to evaluate the cardiac tissue structural changes.

Results: Induction of heart failure resulted in cardiac function deterioration developed after 14 days, as proved by the significant increase in brain natriuretic peptide (4.4 ±0.02 vs. 1.4±0.06 $p<0.001$), reduction of ejection fraction (50.7 ±3.02 vs. 71.60±3.43 $p<0.001$) along with corresponding histopathological changes in ventricular tissues. There was a significant increase in adropin levels in heart failure group (4.8 ±0.15 vs. 2.7±0.10 $p<0.001$). Furthermore; those levels were positively correlated with the previously affected parameters.

Conclusion: This study suggested that adropin may act as a mediator in cardiac dysfunction and can be used as a marker for early diagnosis of cardiovascular system affection.

Key Words: *Adropin – Heart failure – Rats.*

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Introduction

ONE of the most common causes of morbidity and mortality around the world is Heart Failure (HF), its main risk factors are lifestyles changing, genetic tendency, stress, dietary habits, hypercholesterolemia, diabetes and risky behaviors, such as over nutrition, smoking, and alcohol consumption **[1]**.

Actuality, the end-stage of numerous cardiac disease thereby is HF, which leads eventually to overload over the cardiac muscles and subsequent injury resulting in insufficient blood supply to convene the metabolic requirements of the body. The most common features of heart failure are impairment of active relaxation & contraction of the left ventricle, ventricular remodeling followed by hypertrophy, and reduction of ejection fraction [2].

Adropin is a peptide hormone contains 76 amino acid. This name is originally come from the Latin word "aduro" (set fire) and "pinquis" (fats or oils) [3]. Adropin is encoded by (gene symbol: Enho). Which is the gene associated with energy homeostasis. The concentrations of Enho gene expression and circulating adropin are determined by dietary habits, energy status, and sugar consumption **[3,4]**.

The exact physiological roles of this peptide poorly understood. However, it was suggested that its function is associated with energy homeostasis and the control the metabolism of fatty acid and glucose **[3,5]**. Adropin is expressed predominantly in the, liver, brain, coronary arteries, vascular endothelium and heart (pericardium, myocardium and endocardium) **[6]**.

In 2011, Lian and his co-workers stated that increase adropin serum concentration plays a essential role in heart failure pathogenesis. Moreover, elevated plasma levels of adropin, with reduced ejection fraction in heart failure patients, were positively correlated with the severity of this disease [7].

Adropin also associated with regulation of angiogenesis, capillary density and increases blood flow in hind limb ischemia model, therefore, it may be vital for maintenance of cardiovascular integrity [4].

It was reported that when the ventricles are under high pressure and stress they produce Brain Natriuretic Peptide (BNP) which is a cardiac neurohormone biomarker. Furtheremore, it is proven to be effective in the diagnosis of heart injury and to recognize patients at high risk for cardiac disorders [8].

Further studies are needed to increase our knowledge about the association between adropin and cardiovascular diseases either for their prevention, or to be a promising biomarker for cardiovascular risk stratification.

Material and Methods

In the period from 2 1 th January to 8th of March 2019, at the Departments of Physiology, Anatomy and Cardiology, Faculty of Medicine, Zagazig, Egypt, this study was performed on twenty adult male albino rats (wister) weighting 190-200g. Rats were got from, the Animal House, Faculty of Veterinary Medicine, Zagazig University, Egypt.

Before the experiment, animals were subjected to 14 days for acclimatization to laboratory conditions under controlled temperature (24-26ºC), humidity (50-60%) and 12hrs. light dark cycle. All animals were fed on a standard diet with free access to water. The animals were randomly divided to 2 main groups: (I) Control group (n=10)) II) Chronic Heart failure group CHF (n=10). Induction of chronic heart failure was done by Isoproterenol (DL-Isoproterenol hydrochloride). Isoproterenol was dissolved in isotonic saline (Nacl 0.9%) and subcutaneously injected into rats in group (II) in a dose of 5mg/kg, single injection each day, for 14 consecutive days to create experimental HF [9,10]. The control rats in group (I) simultaneously received normal saline injections. Death rate in CHF rats was 8%, and dead animals were replaced.

The principles of care for the laboratory animals followed the recommendations of National Institutes of Health Guide for Care and Use of Laboratory Animals and Zagazig University, Faculty of Medicine Animal House Guide Instructions.

Echocardiographic measurement:

On the 14th day, after 12hrs of fasting, the animals were anesthetized with intraperitoneal injection of urethane (1200mg/kg) [11]. After anaesthesia, the chest wall of every isolated animal was shaved carefully, then animal was fixed in supine position with front legs stretched. After that, ultrasound gel was put to the precordium.

Transthoracic echocardiography was done using a GE ultrasonography and 7.5MHz. transducer. The heart firstly imaged in two-dimensional (2-D) mode in parasternal long axis view. From this view, the M-mode line was applied perpendicular to the interventricular septum and passed through the Left Ventricle (LV) structures, at the level of the chordae tendinea, just below Mitral valve, and M-mode images were collected [12].

All the following parameters were assessed: Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular End Systolic Diameter (LVESD) and the left ventricular mass (g). Function of the left ventricle was assessed by these following parameters:

1- Fractional shortening of the left ventricular wall (FS%) that was calculated from M-mode using this following equation (FS%): [(LVEDD-LVESD)/LVEDD] X 100.

2- The ejection fraction of the left ventricle (EF%) which was calculated automatically by echocardiographic machine according to Teicholz equation [13]. Measurements were obtained by averaging results of three heart beats for each animal.

Blood samples collection: After echocardiographic evaluation, Body Weight (BW) of each rat was recorded using an electronic balance (Germany). Blood samples were obtained, at the end of the experimental period, from sinus orbitus vein of each rat after inhalational anesthesia using (Diethyl ether, ADWIC Laboratory Chemicals, Egypt) [14]. The blood samples were allowed to form clot in the room temperature before centrifugation at 3000rpm for 15-20 minutes. The collected sera were kept at –20ºC until analysis. Repeated freezing and thawing was avoided.

Serum biochemical analysis:

1- Serum adropin level: By using (ELISA) kit {Enzyme-Linked Immunosorbent Assay} purchased from Biotechnology Co., Ltd, China, according to Zhao et al. [15].

2- Serum BNP level: By using enzyme-linked immunosorbent assay (ELISA) kit. Purchased from Dalian Pan-State Chemical Technology Co., China , according to Li et al. **[16]**.

Morphometric and histo -pathological assessment:

Morphometric measures were obtained including whole heart weight for each rat in both groups for assessing the development of cardiac hypertrophy. Then (WHW/BW ratio were calculated).

Histo -pathological examination: The hearts were excised then placed in 10% formalin after that left ventricle was cut into sections 1-2mm in thickness. Section was fixed in methanol & ethanol (1:1) ratio then processed in ascending grades of alcohol solution, immersed in paraffin wax finally, sectioned by microtome at 5 µm thickness followed by staining with hematoxylin & eosin dye also, with Masson's Trichrome stain. Sections were examined in Light Microscope Unit in Department of Anatomy and Embryology, Faculty of Medicine, Zagazige University.

Statistical analysis:

The data obtained in the present study were expressed as mean ± SD for quantitative variables and statistically analyzed by using the Statistical Package for the Social Sciences (SPSS) program (version 20) (SPSS Inc. Chicago, IL, USA. Independent samples *t*-test: Was used to compare means of 2 different groups. Pearson's correlation was used to detect the association between serum adropin levels and other parameters measured.

Test was considered significant at *p*-values <0.05. The smaller the *p*-value obtained the more significant are the results.

Results

This study revealed that serum levels of Adropin showed a significant increase in CHF group (II) ($p<0.001$) when compared to control group (I). Moreover, there was a significant increase in serum levels of BNP in CHF group (II) ($p<0.001$) when compared to control group (I). In addition, there was a significant increase in WHW/BW ratio in CHF group (II) ($p<0.001$) when compared to control group (I) (Table 1).

This study also demonstrated that LVESD; LVEDD & LVmass were significantly increased in CHF group (II) [($p<0.001$); ($p<0.001$) & ($p<0.001$)] respectively when compared to control group (I) while, there were a significant decrease in EF% & FS% in CHF group (II) [($p<0.001$); ($p<0.001$)] respectively when compared to control group (I). (Table 2). Also, serum adropin showed a significant positive correlation with serum BNP levels in CHF group (II) ($p<0.01$); WHW/BW ratio in CHF group (II) ($p<0.01$) (Table 1). Moreover, there was a significant positive correlation with LVESD in CHF group (II) ($p<0.01$) & LVEDD in CHF group (II) ($p<0.01$). On the other hand, serum adropin showed a significant negative correlation with EF% in CHF group (II) ($p<0.01$) & FS% in CHF group (II) ($p<0.01$) (Table 2).

Table (1): Shows serum adropin; BNP levels & Cardiac morphometric measures (mean ± SD) in two studied groups.

	Group (I) (control)	Group (II) (CHF)
Serum Adropin (ng/ml)	2.7±0.10	4.8±0.15*** **a**
Serum BNP (ng/ml)	1.4±0.06	4.4±0.02*** **a**
		r=+0.888**
Body weight (BW) (g)	207.4±9.77	186.5±7.84
Whole heart weight (WHW) (g)	1.03±0.02	1.21±0.07
WHW/BW ratio	0.48±0.04	0.63±0.03*** **a**
		r=+0.952**

a : Significant when compared with group (I).
r : Correlation coefficient with serum adropin.
*** : Significant ($p<0.001$). **: Significant ($p<0.01$).

Table (2): Showing echocardiographic measured parameters (mean ± SD) in the two studied groups.

	Group (I) (control)	Group (II) (CHF)
LVESD (mm)	3.60±0.45	5.57±0.63 *** **a**
		r=+0.886**
LVEDD (mm)	5.50±0.51	7.86±0.67*** **a**
		r=+0.951**
LV mass (g)	1.21±0.15	1.82±0.17*** **a**
EF %	71.60±3.43	50.7±3.02*** **a**
		r=–0.959**
FS %	35.92±3.08	22.02±3.39*** **a**
		r=–0.966**

a : Significant when compared with group (I).
r : Correlation coefficient with serum adropin.
*** : Significant ($p<0.001$). **: Significant ($p<0.01$).

Histopathological examination of the cardiac tissues:

Light microscope examination of left ventricle apical sections showed the followings:

In group (I) (control), myocardial fibers were arranged regularly with clear striations Fig. (1A,B). There was normal intermuscular spaces with no apparent necrosis or degeneration Fig. (2A,B). While, in group (II) (CHF), examination of cardiac tissues revealed fibroblastic hyperplasia with hypertrophy and subendocardial necrosis, along with enlarged edematous intramuscular space. Fig. (3 A-C). Moreover, there was edema and necrosis of myofibrils with inflammatory cells infiltration and red blood cells extravasations were also noticed Fig. (4A-C).

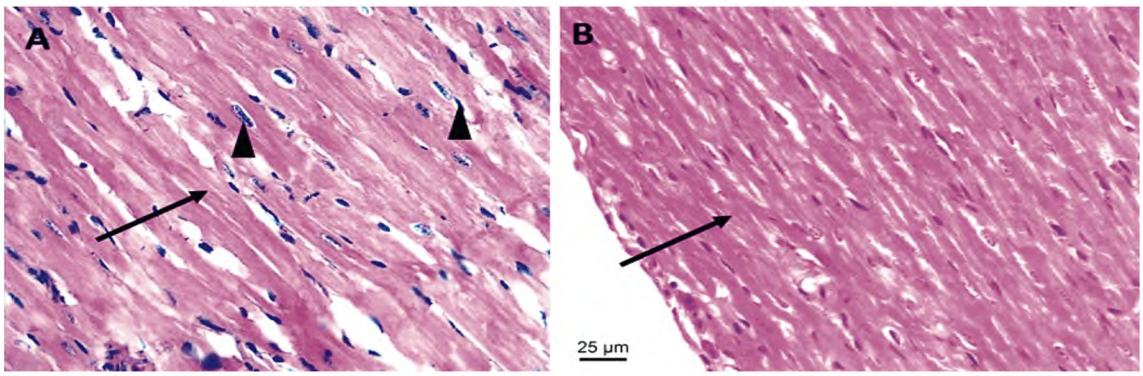

Fig. (1): (A, B): Photomicrograph of section of rat cardiac apexes in control group showing myocardial fibers was arranged regularly with clear striations with elongated nucleus (arrow head) (H & E X400).

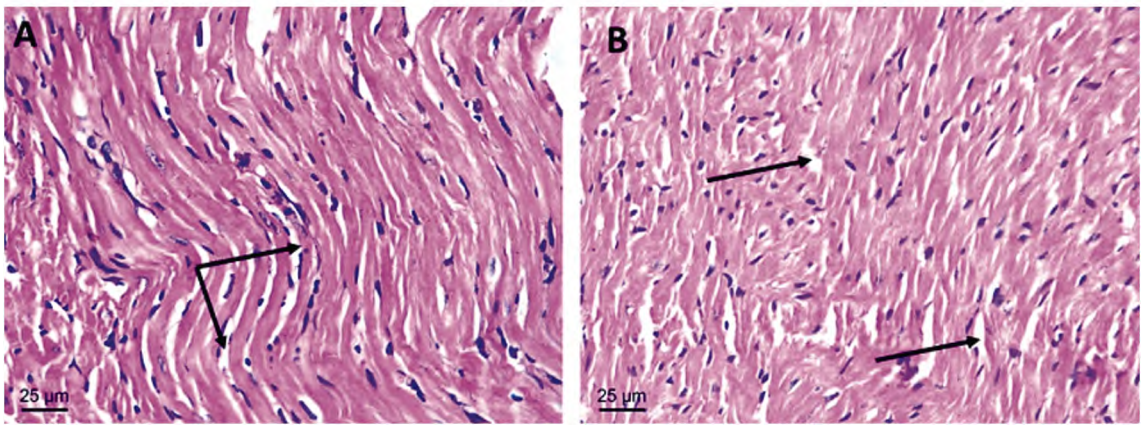

Fig. (2): (A, B): Photomicrograph of section of rat cardiac apexes in control group showing myocardial fibers was separated by normal intermuscular spaces (arrows). (H & E X400).

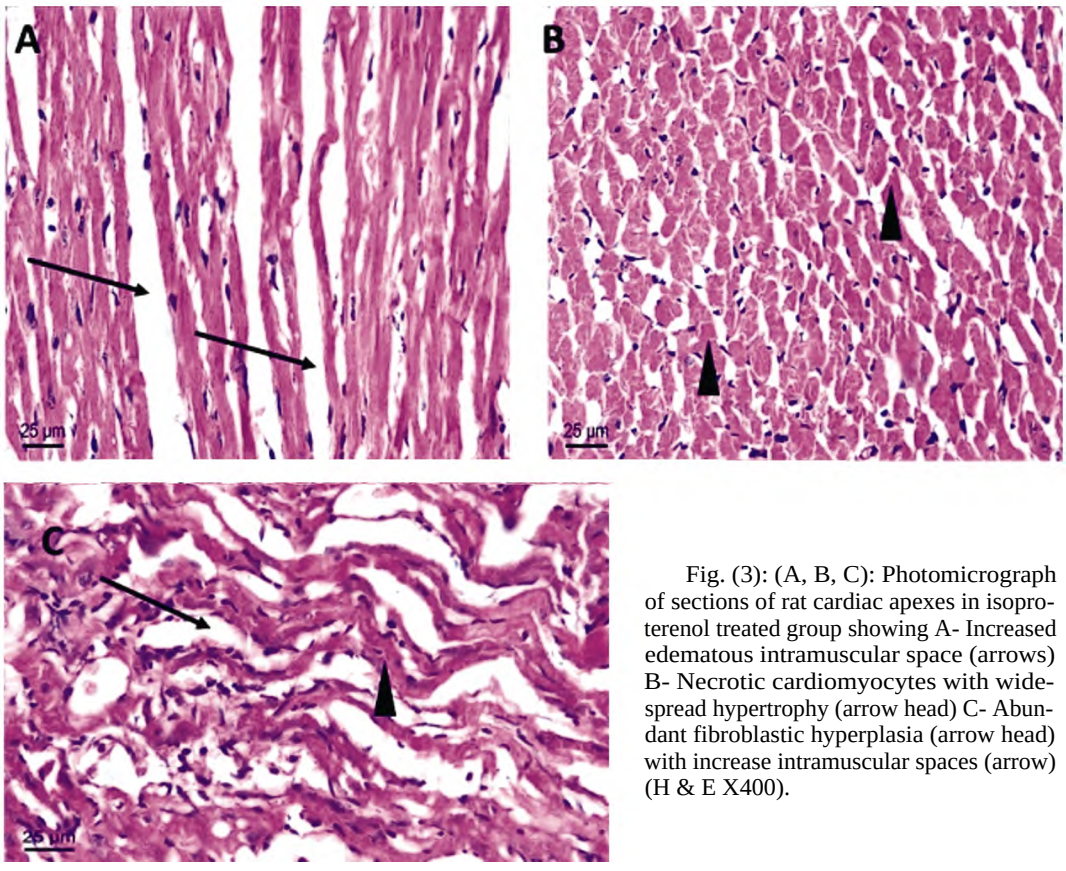

Fig. (3): (A, B, C): Photomicrograph of sections of rat cardiac apexes in isoproterenol treated group showing A- Increased edematous intramuscular space (arrows) B- Necrotic cardiomyocytes with widespread hypertrophy (arrow head) C- Abundant fibroblastic hyperplasia (arrow head) with increase intramuscular spaces (arrow) (H & E X400).

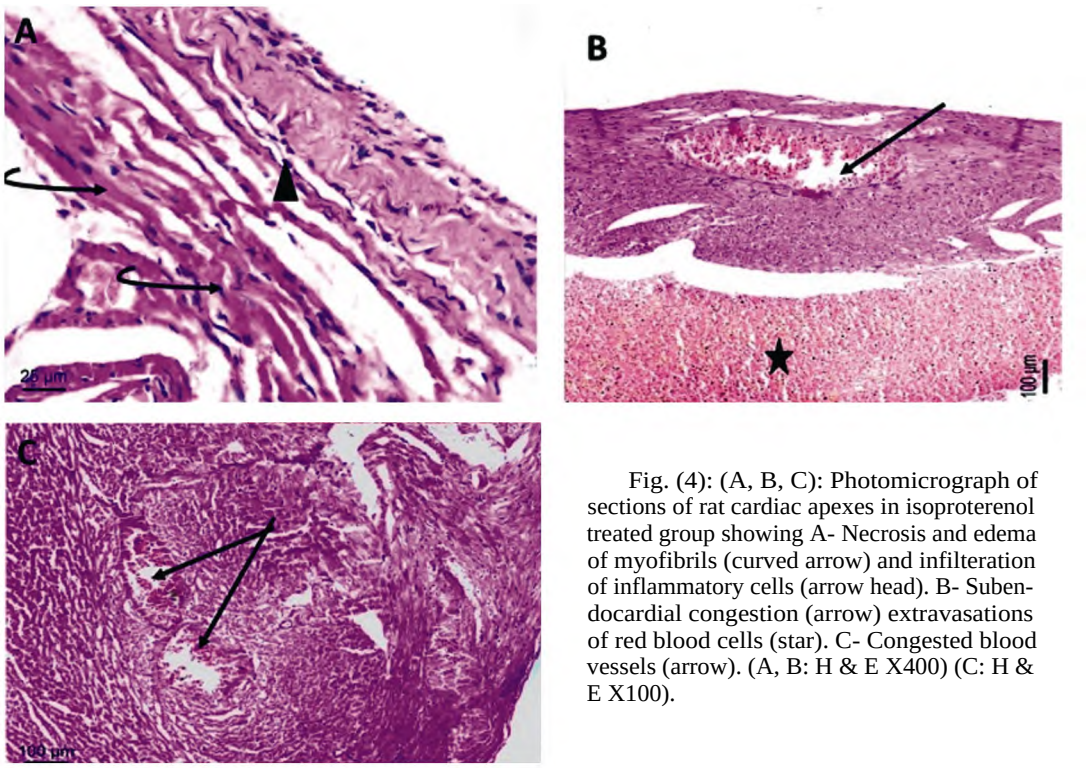

Fig. (4): (A, B, C): Photomicrograph of sections of rat cardiac apexes in isoproterenol treated group showing A- Necrosis and edema of myofibrils (curved arrow) and infilteration of inflammatory cells (arrow head). B- Subendocardial congestion (arrow) extravasations of red blood cells (star). C- Congested blood vessels (arrow). (A, B: H & E X400) (C: H & E X100).

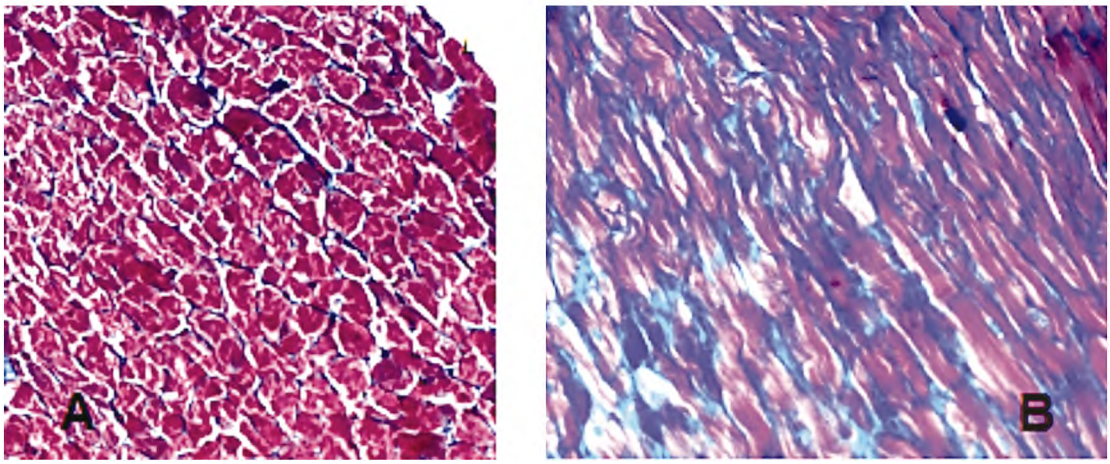

Fig. (5): (A, B): Photomicrographs of Masson's Trichrome-stained heart sections (A) Control rats showing normal little collagen distribution in the endocardium and myocardium (blue color). (B) ISO treated group showing wide areas of collagen deposition (blue color). (Masson's Trichrome X400).

Heart sections stained with Masson's Trichrome showed normal depositions of collagen fibers and cardiac fibrous tissue in between cardiomyocytes in control group Fig. (5A). On the other hand, ISO-treated rats exhibited remarkable depositions of collagen fibers and fibrous tissue in between cardiomyocytes Fig. (5B).

Discussion

In spite of the significant progress that has been made over the past 3 decades in health promotion field, heart failure remains one of the most important leading causes to morbidity and mortality in the developed countries and that problem significantly contributes to the economic burden of modern health care systems **[17]**.

Nevertheless, heart failure remains the chronic progressing and debilitating syndrome with a prevalence of about 10% among population who are over 70 years old, depending on geographic place **[18]**.

Adropin level in the circulation is highly regulated by the amount of energy intake as well as its involvement in the cardiovascular function, especially in endothelium function [4].

The aim of this study was to find out the possibility of using serum adropin as a biomarker for cardiac dysfunction in isoprotrenol induced chronic heart failure.

Isoproterenol considered as a 0-adrenergic receptor agonist. The heart failure animal model that induced by isoproterenol has been widely used to evaluate the effects of several protective agents on cardiac dysfunction that caused by myocardial ischemia [19,20]. The pathophysiologic and morphologic alterations of this non-invasive model are comparable with those of heart failure in humans [21].

Isoproterenol could increase the expression of angiotensin H plus impairment of pump function of myocardium in rats. The possible mechanism may be diffuse acute necrosis of myocardium that caused by sharp increase of catecholamine level [22]. ISO may cause a relative lack of blood flow for myocardium. In addition, chronic inflammatory reaction plus activation of renin-angiotensin-aldosterone system might be involved in the progress of chronic heart failure and myocardium remodeling [23].

In the present study, according to our results, a significant increase in circulating adropin levels were found in ISO induced heart failure group when compared to controls. These finding is in agreement with Aydin and his co-workers animal study in which they evaluated adropin level in cardiac tissue. In addition, other parameters were estimated in serum, including adropin, troponin-1, and creatine kinase. Adropin synthesis in the hearts of rats exposed to myocardial infarction was higher than in the control group. Also, serum concentrations of adropin increased at 30 minutes after the cardiac attack and reached its peak at 2 hours. When myocardium cells become damaged, adropin is released into the bloodstream. However, there was a positive correlation between the concentrations of adropin and troponin-1 [24].

In addition, the present study revealed that injection of isoproterenol (5mg/kg/day, s.c.) for 14 days caused myocardium hypertrophy in rats. Secondary to that hypertrophy of both ventricles, the heart weight was much more in the ISO group than in control group. In addition, ISO group showed higher heart weight/body weight ratio when compared with control group. These findings are in consistency with Karagöz et al., [10] who used 30 male Wistar albino rats divided into three groups: Control, isoproterenol-induced heart failure group (ISO), and isoproterenol-induced heart failure positive album treated group (VA) then parameters of heart failure were compared among the studied groups.

B- Type natriuretic peptide (BNP) is considered as a neurohormone primarily secreted from cardiac ventricles. Now it is used as a marker for diagnosis of CHF as it is easy to obtain and rapidly detected [25]. BNP is an endogenous antagonist of the Renin-Angiotensin-Aldosterone System (RAAS). It not only reduces systemic vascular resistance and central venous pressure, but also decreases volume of blood and cardiac output [26].

As the level of BNP is correlated with the degree of left ventricle dysfunction, measurement of BNP could help in diagnosis and evaluation of Heart Failure (HF). BNP measurement has become a routine for diagnosis of CHF [27].

The present study revealed a significant increase in serum BNP in Chronic Heart Failure group (CHF). Furthermore, a significant positive correlation between adropin and BNP levels in (CHF) group was found. These data are in consistency with Lian et al., [7] who showed that the level of adropin in plasma correlated positively with the level of BNP. They reported also that plasma adropin level was increased significantly according to the degree of HF. They studied on a group of 56 comprised patients with CHF and 20 of healthy control subjects, they were divided into 4 subgroups according to New York Heart Association (NYHA) functional classification. At the end of the experiment the Plasma levels of both adropin, & Brain Natriuretic Peptide (BNP) beside cardiac hemodynamics were determined.

In addition, Kalkan et al., [28] reported that adropin and irisin levels in serum were correlated positively with BNP level and New York Heart Association (NYHA) classification while its level negatively correlated with both Body Mass Index (BMI) and serum albumin levels.

The elevation of BNP level in plasma could has both diuretic & natriuretic action in the kidney also, it could produce vasodilation in the vascular beds, all these effects help preservation of cardiac function in HF [28,29].

The emergence and development of the echocardiogram was a great advancement for in vivo assessment of the heart. In small animals used in

experimental laboratories, this method enabled the follow-up of the effect of injuries and/or treatment on the heart, in an unlimited fashion as regards the number of times the exam is repeated.

Induction of heart failure in the present study by isoproterenol (5mg/kg/day, s.c.) for 14 days causes progressive impairment of heart function characterized by increased LVESD, LVEDD & LV mass as well as significant decrease in EF% & FS% when compared to that of control group. Furthermore, a significant positive correlation was found between LVESD & LVEDD in CHF group and serum adropin levels in the same group. However, serum adropin showed a significant negative correlation with EF% & FS% in CHF group. Several scholars have reported that isoproterenol induced impairment of heart function **[30-32]**.

Regarding histopathological findings, the present study revealed that the control group shows no histopathological changes (normal appearance myocardial muscle fiber) no myocyte damage or inflammation. While, in isoproterenol treated group shows diffused myocyte necrosis with marked inflammation. ISO induces structural and functional variations in cardiac tissue leading to subendocardial myocardial ischemia, hypoxia then necrosis and finally hyperplasia of fibroblastic cells with decreased myocardial compliance and marked diminish of both diastolic and systolic functions of the heart that change resembles nearly local myocardial pathological changes that occure in human myocardial infarction **[33]**.

Cardiac hypertrophy is considered as a compensatory response of the cardiac tissue to acute onset of myocardial infarction also, in injury or hemodynamic stress **[34]**.

Adrenergic stimulation is a land mark of the maladaptive cardiac hypertrophy. The agonist of β 1-adrenergic receptor like ISO could cause cardiac hypertrophy resemble the compensatory hypertrophy that occures due to myocardial infarction so, it represents the mostly used model **[35]** in addition, ISO has been known to produce infarction-like necrosis of the cardiac muscle **[36]**. ISO has been reported to generate free radicals and stimulate lipid peroxidation that all leading to irreversible damage of the myocardium structure **[37]**.

Moreover, activation of 0-adrenergic receptor could provoke different mechanisms like, enhancing protein synthesis, stimulating phosphotidyl inositol-3 kinases & mitogen-activated protein kinases which all contribute to the hypertrophy **[38]**.

Our study demonstrated that on the 14 th day of ISO administration, animal models exhibited myocardial hypertrophy that proved by the significant increase in WHW & WHW/BW ratio. In consistency with Taylor and Tang **[39]** who reported that optimal WHW could be gained on the 8 th day of ISO administration subcutaneously. Moreover histopathological examination of myocardial tissue in normal control animals revealed an intact and united cell membrane with no sign of edema, inflammation and infiltration of inflammatory cells. Whereas histological examination of rats myocardium injected ISO revealed coagulative myonecrosis, edema and infiltration of inflammatory cells. Those observations are in consistancy with many studies on ISO-administered in rats **[32,40]**.

The noticed increase in WHW in ISO treated rats could be referred to the water content expansion, edema of intramuscular spaces, and spread of inflammatory cells followed by extensive necrosis of cardiac muscle fibers **[41]**. The cardiac hypertrophy induced by ISO injection is confirmed by the observed mononuclear cells infiltration, aggrevation in fibrous tissue content & thickness of the myocardium of the left ventricle, inaddition, the massive fibrous tissue deposition in endomysium among cardiomyocytes of the left ventricle.

In conclusion, adropin may act as a mediator in cardiac dysfunction and can be used as a marker for early diagnosis of cardiovascular system affection.

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Declaration of interest statement: The authors declare that there is no conflict of interests regarding the publication of this paper.

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مستوى الآدروبين بمصل الدم كمؤشر حيوى لإختلال وظائف القلب فى نموذج قصور القلب التجريبى المحدث بذكور الجرذان البيضاء

الخلفية: يظل قصور القلب أحد أهم أسباب الوفيات فى جميع أنحاء العالم. الآدروبين هو من الببتيد الحديثة التى قد تلعب دوراً فى توازن الطاقة والتمثيل الغذائى. قد كشفت بعض الدراسات أن الآدروبين يلعب دوراً حاسماً فى التسبب فى قصور القلب، فى حين يشير البعض الآخر إلى أنه قد يكون مهم للحفاظ على فعالية نظان القلب والأوعية الدموية.

الهدف: معرفة إمكانية إستخدام الآدروبين كمؤشر حيوى للكشف عن قصور القلب، فى قصور القلب المحدث تجريبياً فى ذكور الفئران البيضاء.

المواد والطرق: قد أجريت هذه الدراسة على مجموعتين من ذكور الفئران البيضاء (١٨٠–٢٠٠جم): المجموعة الضابطة (I) (ن=١٠)، حيث أطعمت الفئران الطعام المعتاد. ومجموعة قصور القلب المزمن (II) (ن=١٠)، والتى أحدث فيها قصور القلب المزمن عن طريق الحقن تحت الجلد من الأيزوبروترينول بجرعة ٥مغ/كغ مرة واحدة يومياً لمدة ١٤ يوماً متتالياً. وقد أجريت الأشعة التليفزيونية للقلب وتم قياس وزن الجسم بالكامل، وتم قياس مستويات مصل الدم من الببتيد الناتريوتريك الدماغى. وتم قياس الوزن الكلى للقلب، ثم (تم حساب نسبة وزن القلب لوزن الجسم. أخيراً، تم إجراء فحص مجهرى لأنسجة القلب لتقييم التغيرات الهيكلية فى الأنسجة القلبية.

النتائج: أدى إحداث قصور القلب إلى تدهور وظائف القلب بعد ١٤ يوماً، كما ثبت من خلال الزيادة الكبيرة فى الببتيد الناتريوتريك الدماغى (4.4±0.02 مقابل 1.4±0.06 $p<0.001$)، وتقليل فى نسبة ضخ الدم من القلب (50.7±3.02 مقابل 71.60±3.43 $p<0.001$) جنباً إلى جنب مع التغيرات النسيجية الميكروسكوبية المقابلة فى أنسجة البطين. وقد كانت هناك زيادة كبيرة فى مستويات الآدوربين فى مجموعة قصور القلب (4.8±0.15 مقابل 2.7±0.10 $p<0.001$) علاوة على ذلك، كانت هذه المستويات مرتبطة بشكل إيجابى مع سبق قياسه من متغيرات.

الخلاصة: أقترحت هذه الدراسة أن الآدروبين قد يكون بمثابة وسيط فى الخلل الوظيفى للقلب ويمكن إستخدامه كعلامة للتشخيص المبكر لإعتلال نظام القلب والأوعية الدموية.