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CARDIOPROTECTIVE EFFECT OF IVABRADINE VERSUS CARVEDILOL IN RATS

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ABSTRACT: The discovery of the f-channel and its role in regulating pacemaker activity lead to the development of new pharmacological agents such as ivabradine, which target these f-channels causing a reduction in heart rate by inhibiting the f_{current} . The aim of the present work was designed to evaluate the cardioprotective effect of ivabradine on experimentally- induced myocardial infarction and adrenaline-induced arrhythmia in rats. In addition, the present work studied the effect of ivabradine on isolated rabbit's aortic spiral strip and isolated rabbit's heart. Acute myocardial infarction in rats was induced by isoperameline (150mg/kg subcutaneous injection, once) 24 rats were divided into the following groups: group (I) control normal rats, group (II) myocardial infarction – induced rats with no previous treatment, group (III) myocardial infarction – induced rats pretreated with ivabradine (10mg/kg/day) for one week and group (IV) myocardial infarction – induced rats pretreated with carvedilol (1mg/kg/day) for one week. Electrophysiological, biochemical and histopathological parameters were estimated. pretreatment with either ivabradine or carvedilol show significant improvement in all these parameters with insignificant difference between them. In the current work 20 rats were used to investigate the protective effects of ivabradine (10mg/kg) and carvedilol (1mg/kg) on adrenaline- induced arrhythmia in anaesthetized rats and the results revealed that both drugs had a prophylactic effect. Also data obtained in the present work pointed out that ivabradine in gradually increasing doses produce no significant effect on the isolated rabbit's aortic strip and basal myocardial contractility of isolated rabbit's heart. Both ivabradine and carvedilol have cardioprotective effect against acute MI as well as adrenaline- induced arrhythmia with no significant difference between them, also ivabradine has no effect on contractility of the heart. So, the choice of either drug in these disease states depend on which of them has low side effects.

INTRODUCTION Ivabradine is a selective and specific inhibitor of the sinus node If current. It offers clear therapeutic benefits to stable coronary patients including those already being treated with B-blockers or those with contraindication or intolerance to B-blockers. It specifically binds to the f-channels that are located in the membrane of the sinoatrial cells, in the pacemaker node ¹.

Ivabradine preserves both small and large coronary artery vasodilatation, whatever the level of exercise, thus ensuring adequate endocardial blood perfusion during exercise ².

Pure heart rate reduction with ivabradine results in improved left ventricular function and increased stroke volume, and thus preserved cardiac output **3**. Ivabradine exerts no significant effect on myocardial contractility, either at rest or during exercise ⁴.

Carvedilol is non selective beta blocker with α_1 -blocking activity decreasing heart rate, decreasing contractility, vasodilator and has antioxidant effect ⁵.

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Heart rate reduction by both drugs through different mechanisms plays a role in the medical treatment of myocardial ischemia.

The present work was carried out to screen the cardioprotective effect of ivabradine and carvedilol on experimentally – induced myocardial infarction and adrenaline-induced cardiac arrhythmia.

MATERIALS AND METHODS:

This study was done in pharmacology department, Benha faculty of medicine, Benha university during February 2014.

Drugs and chemicals:

Ivabradine Hydrochloride (powder) [Servier, France]. Carvedilol (powder) [Marcyl Pharmaceutical Industries, Egypt]. Isoprenaline HcL (powder) [Sigma, U.S.A.]. Adrenaline Hydrochloride Tartrate (powder) [B.D.H, England]. Urethane (ethyl carbamat): (white crystals) [prolabo, Paris]. Hematoxylin & eosin stain [Biostain ready reagents, UK]. Formaline (solution) (neutral 10% formaline): El-Gomhoria Pharmaceutical Chemical Co., ARE.

In-vivo experiments:

Animals:

44 adult male albino rats (brought from Experimental Animal Breeding Farm, Helwan-Cairo) weighing 150-200gm. ,were used for in-vivo experiments. They have acclimatized for one week and were caged (6/ cage) in fully ventilated room (at room temperature). Rats were ad libitum access to water & balanced diet.

Experimental groups:

Model of experimentally induced myocardial infarction: 24 male rats weighing 150- 200 gm at the beginning of the study were used. After one week of acclimatization, rats were randomly subdivided into four groups to study the effect of ivabradine on myocardial infarction in comparison with carvedilol. **Group (I):** Control group: the rats of this group were given saline only by subcutaneous injection. **Group (II):** MI group: the rats of this group were given isoprenaline (150mg/kg) by subcutaneous injection⁶. **Group (III):** Ivabradine-treated group: the rats of this

group were given ivabradine (10mg/kg/day) by gavage⁷. For one week before subcutaneous injection of isoprenaline (150mg/kg). **Group (IV):** Carvedilol-treated group: the rats of this group were given Carvedilol (1mg/kg/day) by gavage⁸. For one week before subcutaneous injection of isoprenaline (150mg/kg).

Experimentally induced myocardial infarction⁶.

The animals were anaesthetized with urethane in a dose of 1.5- 1.75 gm/kg body weight. Half of the dose was injected intraperitoneally, to induce rapid onset and the other half subcutaneously, to insure long maintenance of the anaesthetic effect.

After complete anaesthesia, the rats were led on their back. ECG records were done using needle electrodes. The four limb electrodes. The animals were then injected subcutaneously in the abdominal region with freshly prepared solution of the isoprenaline (150mg/kg) then the following parameters were measured:

Electrophysiological parameter: The four limbs electrodes were fixed to the animal's four limbs and records were done using the standard lead II at rate 25mm/min. the animals were then injected subcutaneously in the abdominal region with freshly prepared solution of the isoprenaline (150mg/kg). E.C.G. tracings were recorded immediately, 30 minutes, 1, 2 and 4 hours after isoprenaline injection. The use of lead II was more informative (in rats) than other leads⁹.

Biochemical parameter: At the end of experiment after ECG records were done a blood sample of about 4 ml was withdrawn by heparinized cannula from right carotid artery¹⁰. The blood samples were centrifuged at 3000 rotation/minute and the sera were separated. Samples were stored at -20°C in dark containers and subjected to creatine phosphokinase-MB (CK-MB) and troponin-I measurement.

Histopathological examination:

After functional studies were completed, the chest was then rapidly opened and the heart was removed as a whole and was put into a buffered 4% formaline fixation solution and processed with paraffin wax for histopathological examination.

Transverse sections (2- μ m thick) of the LV free wall at the papillary muscle level were stained with hematoxylin and eosin then cardiac sections were examined for the presence of myocyte degenerative changes, infarct like necrosis¹⁰.

Model of experimentally adrenaline-induced arrhythmia¹¹:

20 male rats weighing 150- 200 gm were used. After complete anaesthesia, the rats were led on their back. ECG records were done using needle electrodes. Rats were randomly subdivided into two groups to study the effect of ivabradine on arrhythmia in comparison with carvedilol.

Group I: Ivabradine-adrenaline treated group:

i-Adrenaline was given I.V in rats in gradually increasing doses starting by 5 μ g/kg, then the dose was increased gradually by the same amount every 15 min. until arrhythmia (in the form of at least 3 consecutive ventricular ectopic beats) had occurred. The minimal arrhythmogenic dose of adrenaline was determined.

ii- Ivabradine was given I.V at dose of 10mg/kg¹².

iii- After 15 min., adrenaline was injected again beginning with the minimal arrhythmogenic dose and the dose was gradually increased every 15 min. until occurrence of arrhythmia again after ivabradine. The arrhythmogenic doses of adrenaline before and after ivabradine were compared statistically.

Group II: Carvedilol-adrenaline treated group:

i- Adrenaline was given I.V in rats in gradually increasing doses starting by 5 μ g/kg, then the dose was increased gradually by the same amount every 15 min. until arrhythmia (in the form of at least 3 consecutive ventricular ectopic beats) had occurred. The minimal arrhythmogenic dose of adrenaline was determined.

ii- Carvedilol was given I.V at dose of 1mg/kg¹³.

iii- After 15 min., adrenaline was injected again beginning with the minimal arrhythmogenic dose and the dose was gradually increased every 15 min. until occurrence of arrhythmia again after carvedilol. The arrhythmogenic doses of adrenaline before and after carvedilol were compared statistically.

II- *In-vitro* experiments:

The following isolated preparations were used to investigate the possible effects and site of action of ivabradine:

1. Isolated perfused rabbit's heart¹⁴

2. Isolated perfused rabbit's aortic spiral strip¹⁵

Statistical Analysis:

All data were expressed as Mean + SEM. Difference between the groups were compared by student T-test with P- value < 0.05 selected as the level of statistical significance¹⁶. SPSS version 16 was used for statistical analysis.

RESULTS:

In-vivo experiments:

Effect of ivabradine and carvedilol on myocardial infarction in rats:

T-wave voltage changes:

1- MI group:

The mean of T- wave voltage (mV) at 0 time (immediately before isoprenaline injection) was 0.29 \pm 0.02. After isoprenaline injection, the T wave voltage tend to be elevated reaching a maximum level after 4 hours with mean of 0.71 \pm 0.02 (mV), when this value was compared with the value of T-wave voltage at zero time it revealed a significant increase (p < 0.001) (**Fig. 1**)

2- Ivabradine-treated group:

The mean value of T-wave voltage at zero time was 0.36 \pm 0.03 (mV), after 4 hours the mean T-wave voltage was 0.42 \pm 0.03 mV. When this value was compared to corresponding value in MI group, there was a significant decrease (p < 0.001).(**Fig. 2**)

3- Carvedilol-treated group:

The mean value of T-wave voltage at zero time was 0.31 \pm 0.03 (mV), after 4 hours the mean T-wave voltage was 0.41 \pm 0.04 mV. When this value was compared to corresponding value in MI group, there was a significant decrease (p < 0.001).(**Fig.3**) Comparing the results of ivabradine-treated group to that of carvedilol-treated group, there was insignificant (p > 0.05) difference between them.

The effect on heart rate (HR):

1- MI group: The heart rate at the start of experiment (0 time) was 304.2 \pm 18.3 beat/min,

while at 4 hours after isoprenaline injection, it was 461.7 ± 13.1 beat/min. When both values were compared to each other, there was significant increase ($p < 0.001$). (Fig.1)

2- Ivabradine-treated group:

The heart rate at the start of experiment (0 time) was 286.6 ± 25.6 beat/min, while at 4 hours after isoprenaline injection, it was 330.8 ± 15.8 beat/min. When these values were compared to the corresponding values of MI group, there was significant decrease ($p < 0.001$). (Fig.2)

3- Carvedilol-treated group:

The heart rate at the start of experiment (0 time) was 298.3 ± 14.2 beat/min, while at 4 hours after isoprenaline injection, it was 340.8 ± 21.2 beat/min. When these values were compared to the corresponding values of MI group, there was significant decrease ($p < 0.001$). (Fig.3)

Comparing the results of ivabradine-treated group to that of carvedilol-treated group, there was insignificant ($p > 0.05$) difference between them.

Serum level of CK-MB (Fig.4).

1- Control group:

The mean level of serum CK in normal rats was 589 ± 15.5 U/L.

2- MI group:

The mean serum CK level 4 hours after isoprenaline injection was 1495 ± 30.9 U/L. This level was highly significantly ($p < 0.001$) increased when compared to mean value of CK level of normal rats.

3- Ivabradine-treated group:

The mean CK level was 845 ± 61.9 U/L at 4 hours after isoprenaline injection. When this value was compared to corresponding value in MI group, there was a significant decrease ($p < 0.001$).

4- Carvedilol-treated group:

The mean CK level was 1019.7 ± 54.8 U/L at 4 hours after isoprenaline injection. When this value was compared to corresponding value in MI group, there was a significant decrease ($p < 0.001$). Comparing the results of ivabradine-treated group

to that of carvedilol-treated group, there was insignificant ($P > 0.05$) difference between them.

Serum level of Troponin-I (Fig.5).

1- Control group:

The mean level of serum troponin-I in normal rats was 0.24 ± 0.06 ng/ml.

2- MI group:

The mean serum troponin-I level 4 hours after isoprenaline injection was 1.97 ± 0.27 ng/ml. This level was highly significantly ($p < 0.001$) increased when compared to mean value of troponin-I level of normal rats.

3- Ivabradine-treated group:

The mean troponin-I level was 0.46 ± 0.01 ng/ml at 4 hours after isoprenaline injection. When this value was compared to corresponding value in MI group, there was a significant decrease ($p < 0.001$).

4- Carvedilol-treated group:

The mean troponin-I level was 0.54 ± 0.13 ng/ml at 4 hours after isoprenaline injection. When this value was compared to corresponding value in MI group, there was a significant decrease ($p < 0.001$). Comparing the results of ivabradine-treated group to that of carvedilol-treated group, there was insignificant ($p > 0.05$) difference between them.

Histopathological examination:

Histopathological examination of the heart for detection of manifestation of acute ischemia and inflammation was done at the end of the experiment with comparison of signs of acute infarction (changes in cardiomyocyte bundles, nuclear shape) in different groups.

1-Control group:

There are interlacing bundles of cardiomyocytes with spindle shaped nucleus with abundant eosinophilic cytoplasm. (Fig 6).

2-MI group:

Isoprenaline induced acute ischemia and infarction in form of degenerative changes in cardiomyocyte bundles, nuclear shape. (Fig.7).

3- Ivabradine-treated group: There are little signs of infarction in form of slight atrophic cardiomyocytes. (Fig.8).

4- Carvedilol-treated group:

There are little signs of infarction in form of scattered foci of necrotic areas.(Fig.9).

Effect of ivabradine and carvedilol on adrenaline-induced arrhythmia in rats (Fig.10).

1-Ivabradine-adrenaline treated group (Fig.11a-d).

In rats receiving adrenaline before injection of ivabradine, the mean minimal arrhythmogenic dose of adrenaline that could produce arrhythmia was $12 \pm 6 \mu\text{g}/\text{kg}$.

After restoration of normal rhythm and injection of ivabradine (10mg/kg IV) for 15 min., the mean dose of adrenaline that could produce arrhythmia after ivabradine was $1000 \pm 81.6 \mu\text{g}/\text{kg}$.

When the dose of adrenaline that could produce arrhythmia after ivabradine was compared to that dose of adrenaline that could produce arrhythmia before ivabradine injection, there was highly significant increase ($p < 0.001$).

2- Carvedilol-adrenaline treated group (Fig.12a-d).

In rats receiving adrenaline before injection of carvedilol, the mean minimal arrhythmogenic dose of adrenaline that could produce arrhythmia was $20 \pm 4.08 \mu\text{g}/\text{kg}$.

After restoration of normal rhythm and injection of carvedilol (1mg/kg IV) for 15 min., the mean dose of adrenaline that could produce arrhythmia after carvedilol was $1125 \pm 47.8 \mu\text{g}/\text{kg}$.

When the dose of adrenaline that could produce arrhythmia after carvedilol was compared to that dose of adrenaline that could produce arrhythmia before carvedilol injection, there was highly significant increase ($p < 0.001$).

Comparing the results of ivabradine-adrenaline treated group to that of carvedilol-adrenaline treated group, there was insignificant ($p > 0.05$) difference between them.

II. In vitro experiments:

1. Effects on isolated perfused rabbit's heart: To show the effect of ivabradine on basal cardiac

contractility in isolated rabbit heart, ivabradine was added in gradually increasing doses (2, 4, 8, 16, and 32 μg). It was observed that ivabradine produced no change in the amplitude of contraction of isolated rabbit's heart (Fig.13)

2. Effect on isolated rabbit's aortic spiral strip:

Ivabradine added in gradually increasing doses (2, 4, 8, 16, and 32 $\mu\text{g}/25\text{ml}$ organ bath). It was observed that ivabradine produced no change on isolated rabbit's aortic spiral strip (Fig.14).

Also the drug had no effect on nor adrenaline precontracted isolated rabbit aortic strip (40 $\mu\text{g}/25\text{ml}$ organ bath) by increasing doses of the drug.(Fig.15)



FIGURE (1): ECG TRACING (LEAD II) OF INFARCTED RAT RECEIVED ISOPRENALINE S.C INJECTION (4 HOURS AFTER ISOPRENALINE).

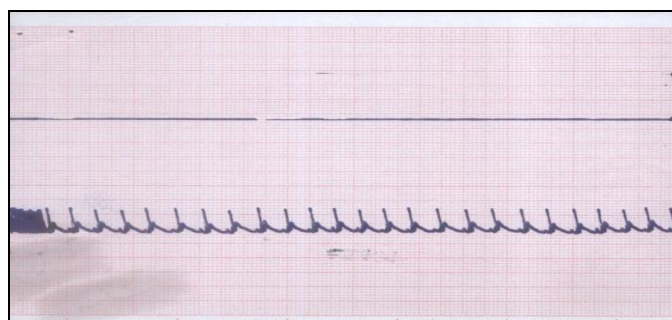


FIGURE (2): ECG TRACING (LEAD II) OF IVABRADINE-TREATED RAT RECEIVED ISOPRENALINE S.C INJECTION (4 HOURS AFTER ISOPRENALINE).

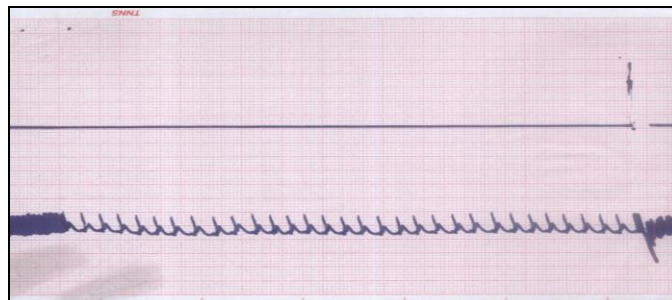


FIGURE (3): ECG TRACING (LEAD II) OF CARVEDILOL-TREATED RAT RECEIVED ISOPRENALINE S.C INJECTION (4 HOURS AFTER ISOPRENALINE).

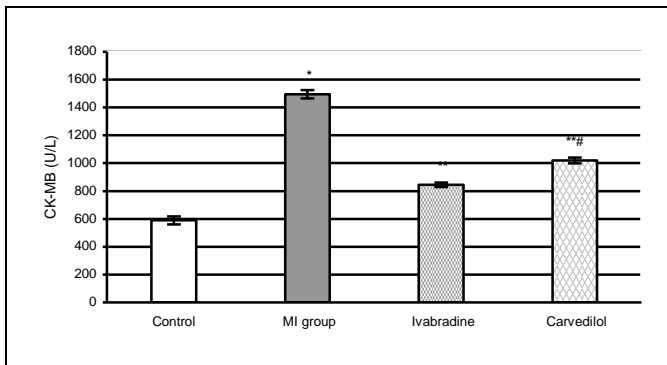


FIG. 4: HISTOGRAM SHOWING THE EFFECT OF IVABRADINE (10mg/kg/day BY GAVAGE) AND CARVEDILOL (1mg/kg/day BY GAVAGE) FOR ONE WEEK ON CK-MB LEVEL OF MYOCARDIAL INFARCTION INDUCED BY ISOPERNALINE (150mg/kg s.c INJECTION) IN RATS IN VARIOUS GROUPS.

*Significant (P<0.001) compared to control group

**Significant (P<0.001) compared to MI group

#Insignificant (P>0.05) compared to Ivabradine-treated group

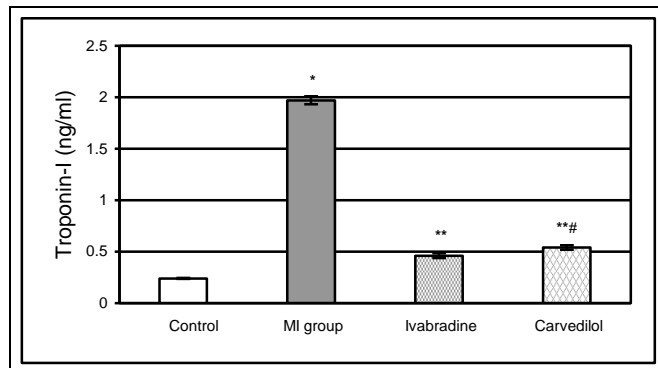


FIG. 5: HISTOGRAM SHOWING THE EFFECT OF IVABRADINE (10mg/kg/day by gavage) AND CARVEDILOL (1mg/kg/day by gavage) FOR ONE WEEK ON TROPONIN-I LEVEL OF MYOCARDIAL INFARCTION INDUCED BY ISOPERNALINE (150mg/kg s.c INJECTION) IN RATS IN VARIOUS GROUPS.

*Significant (P<0.001) compared to control group

**Significant (P<0.001) compared to MI group

#Insignificant (P>0.05) compared to Ivabradine-treated group

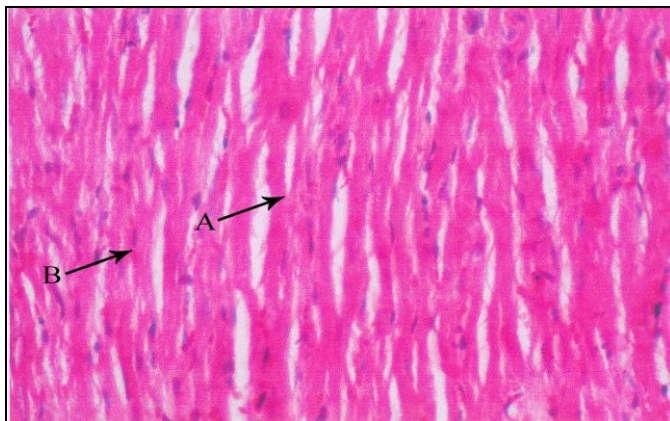


FIG. 6: A PHOTOMICROGRAPH OF A CUT SECTION IN THE HEART OF CONTROL GROUP SHOWING (A) INTERLACING BUNDLES OF CARDIOMYOCYTES WITH (B) SPINDLE SHAPED NUCLEUS WITH ABUNDANT EOSINOPHILIC CYTOPLASM (H&EX40).

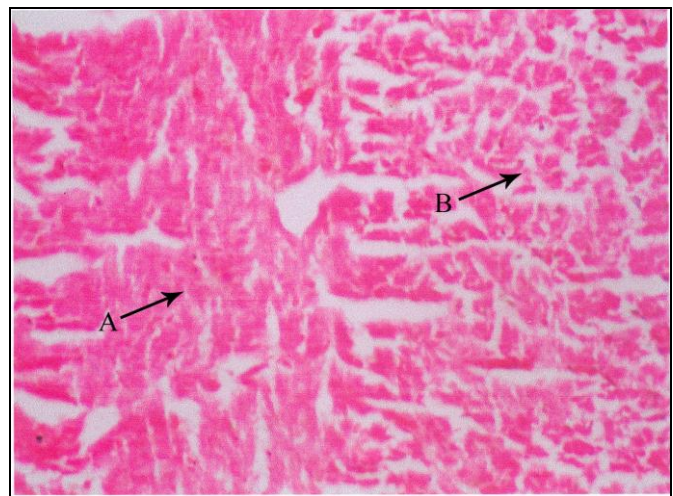


FIG 7: A PHOTOMICROGRAPH OF A CUT SECTION IN THE HEART OF MI GROUP SHOWING (A) CARDIOMYOCYTES WITH LOST CELLULAR DETAILS. (B) NUCLEI SHOWING PYKNOTIC CHANGES (H&EX40).

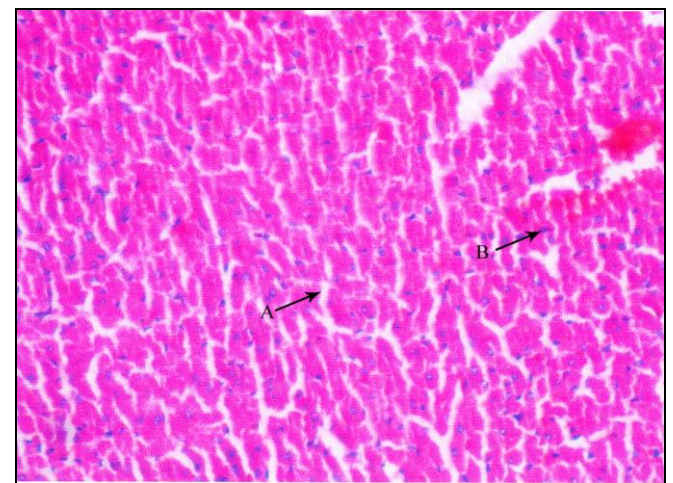


FIG. 8: A PHOTOMICROGRAPH OF A CUT SECTION IN THE HEART OF IVABRADINE-TREATED GROUP SHOWING SLIGHT ATROPHIC CARDIOMYOCYTES (H&EX40).

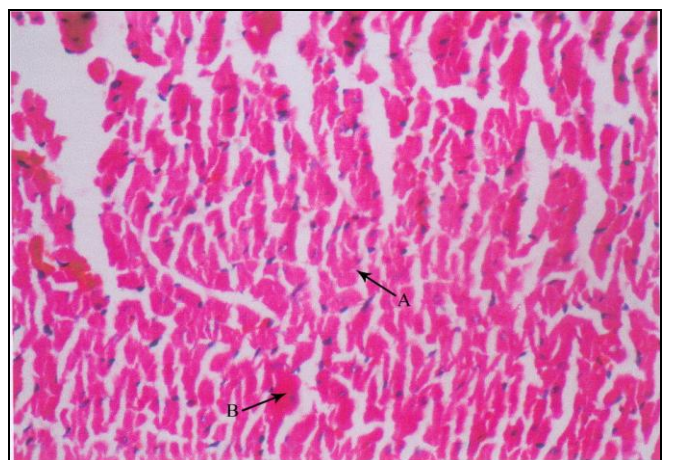


FIG. 9: A PHOTOMICROGRAPH OF A CUT SECTION IN THE HEART OF CARVEDILOL-TREATED GROUP SHOWING (A) NORMAL APPEARING CARDIOMYOCYTES WITH (B) SCATTERED FOCI OF NECROTIC AREAS (H&EX40).

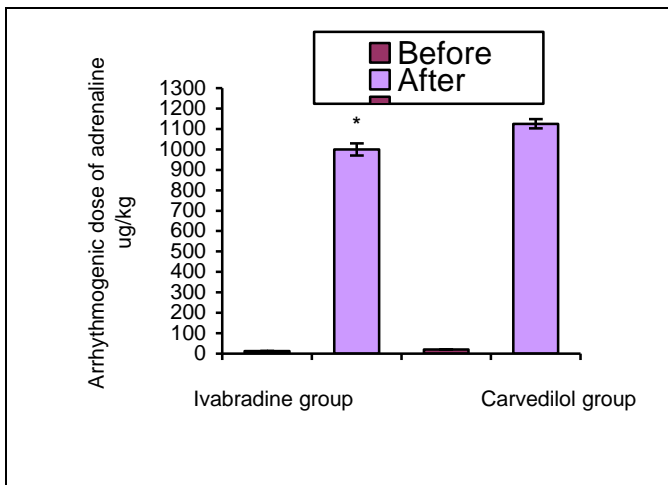


FIG. 10: HISTOGRAM SHOWING THE EFFECT OF IVABRADINE (10mg/kg IV INJECTION) AND CARVEDILOL (1mg/kg IV INJECTION) ON ARRHYTHMOGENIC DOSE OF ADRENALINE IN RATS.

Before = before ivabradine or carvedilol injection

After = after ivabradine or carvedilol injection

*Significant at (P<0.001) compared to the dose before ivabradine or carvedilol

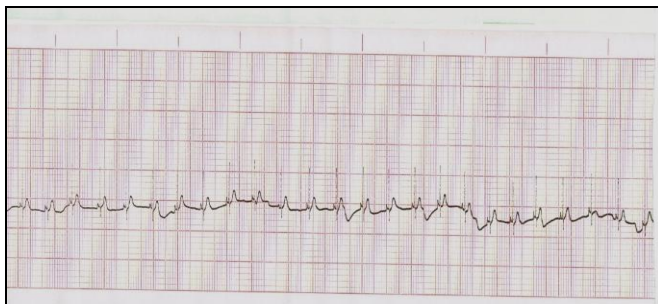


FIG. 11A: ECG TRACING (LEAD II) OF CONTROL NORMAL RAT

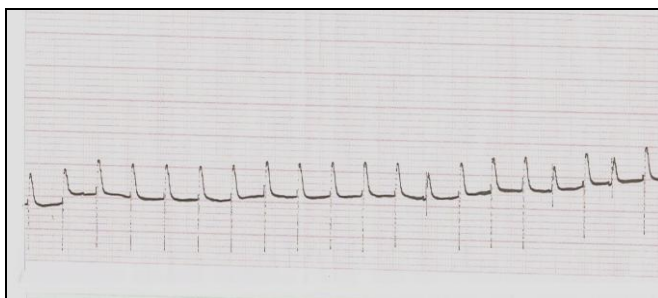


FIG. 11B: ECG TRACING (LEAD II) AFTER ADRENALINE 10µg/Kg I.V. INJECTION

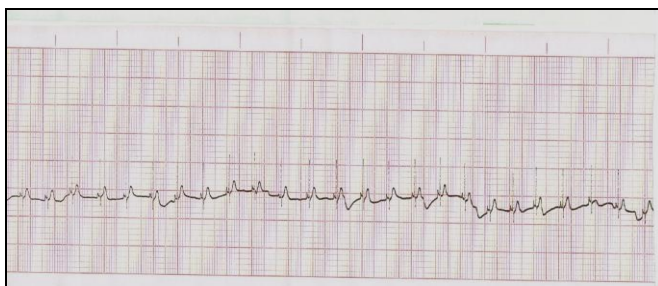


FIG.11C: ECG TRACING (LEAD II) AFTER IVABRADINE 10mg/kg I.V. INJECTION

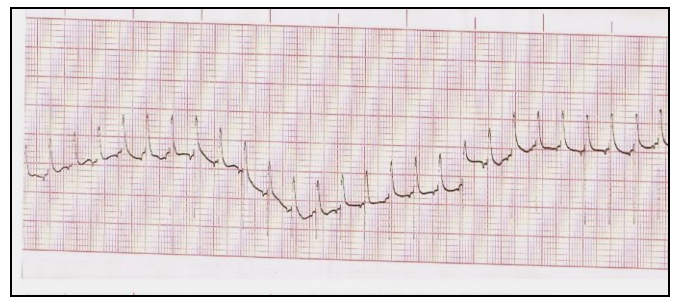


FIG. 11D: ECG TRACING (LEAD II) OF ADRENALINE 1000µg/Kg I.V. INJECTION AFTER IVABRADINE 10mg/Kg I.V. INJECTION



FIG. 12A: ECG TRACING (LEAD II) OF CONTROL NORMAL RAT



FIG. 12B: ECG TRACING (LEAD II) AFTER ADRENALINE 30µg/Kg I.V. INJECTION

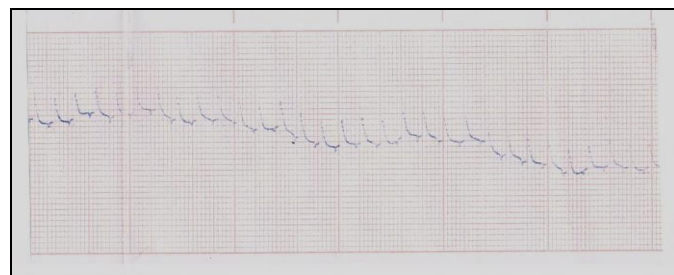


FIG. 12C: ECG TRACING (LEAD II) AFTER CARVEDILOL 1mg/kg I.V. INJECTION

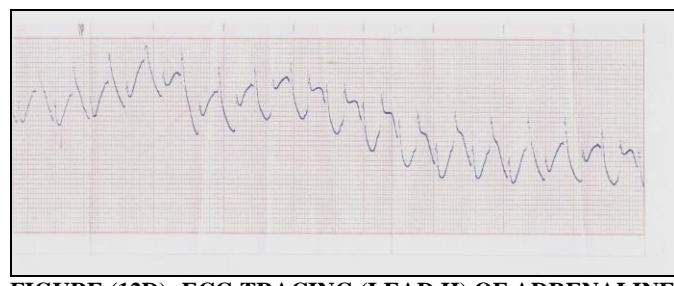


FIGURE (12D): ECG TRACING (LEAD II) OF ADRENALINE 1100µg/kg I.V. INJECTION AFTER CARVEDILOL 1mg/kg I.V. INJECTION



FIG. 13: A RECORD DEMONSTRATING THE EFFECT OF GRADUALLY INCREASING DOSES OF IVABRADINE ON THE ISOLATED PERFUSED RABBIT'S HEART CONTRACTIONS.

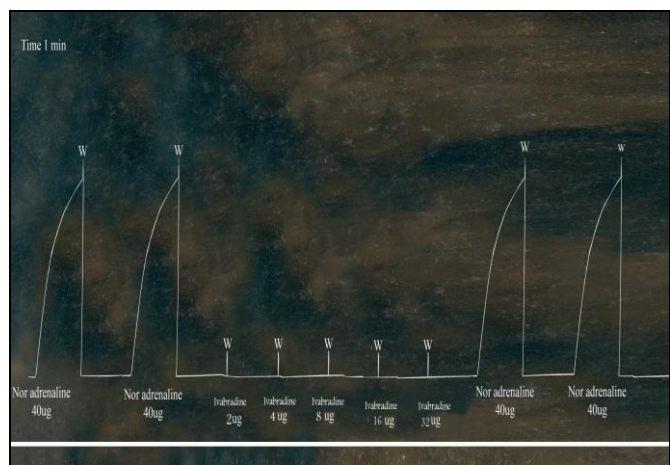


FIG.14: A RECORD DEMONSTRATING THE EFFECT OF IVABRADINE ON ISOLATED RABBIT'S AORTIC SPIRAL STRIP.

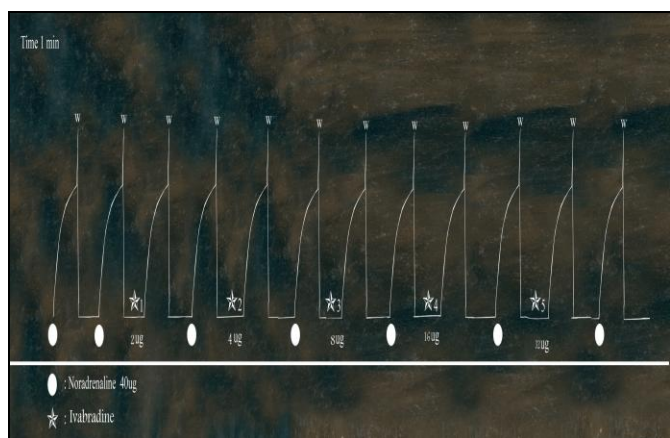


FIG. 15: A RECORD DEMONSTRATING THE EFFECT OF IVABRADINE ON NOR ADRENALINE PRECONTRACTED ISOLATED RABBIT AORTIC STRIP.

DISCUSSION: The present study was designed to evaluate the cardioprotective effect of ivabradine and carvedilol on experimentally-induced

myocardial infarction and adrenaline-induced arrhythmia in rats.

The cardioprotective effect of ivabradine and carvedilol on isoprenaline induced acute myocardial infarction in rats was investigated by ECG changes (T-wave and HR), biochemical changes (CK-MB and troponin-I) and histopathological changes of cardiac muscles.

Myocardial infarction in rat was a result of disturbance in physiological balance between production of free radicals and antioxidative defense system¹⁷.

Some of the mechanisms proposed to explain isoprenaline induced damage to cardiac myocytes include hypoxia due to myocardial hyperactivity, coronary hypotension, calcium overload and hypertrophy, depletion of energy reserve and excessive production of free radicals¹⁸.

Panda and Naik¹⁹ documented that generation of highly cytotoxic free radicals through isoprenaline auto-oxidation stimulates lipid per-oxidation and causes irreversible damage to the myocardial membrane.

Regarding ECG changes, the results of the present study revealed that, the myocardial infarction group showed significant ($P < 0.001$) increase in T-wave voltage in all animals subjected to isoprenaline injection.

These results are in agreement with those of Surawicz,²⁰ who reported that the "T" wave was elevated in rats immediately after coronary ischemia and remained elevated for 5 hours after ischemia.

The ECG tracing showed sinus tachycardia in addition to the injury current in form of highly peaked T-wave. These results were in agreement with the observation of²¹.

Similar results were obtained from²² who proved marked increase of heart rate in isoprenaline injected rats with changes in ECG findings.

In the present study both ivabradine (10mg/kg/day) and carvedilol (1mg/kg/day) administration for one

week produced significant decrease in T-wave voltage as well as heart rate with insignificant ($p > 0.05$) difference between them.

Du et al.,²³ demonstrated that oral treatment with ivabradine significantly reduced HR in a rat with sympathoadrenergic activation induced by β_1 -agonist isoproterenol.

Same results were obtained by Vilaine¹² in conscious Wistar rats after single or repeated oral dose of ivabradine. The author demonstrated that ivabradine selectively reduced the heart rate both at rest and during exercise by inhibiting the If pacemaker current of the sinus node without modification of myocardial contractility, atrioventricular conduction or ventricular repolarization offering great protection of regional myocardial contractility.

Ciobotaru et al.,²⁴ proved that ivabradine treatment for three months induced heart rate reduction in a rat model of MI with aortic banding.

Steg et al.,²⁵ reported that i.v ivabradine may be of potential value in ST-segment elevation myocardial infarction (STEMI), by allowing rapid heart rate control without affecting blood pressure or hemodynamics.

The results of the present study are in consistence with Maćzewski and Maćkiewicz²⁶ who proved that ivabradine and metoprolol attenuated heart rate increase in a rat model of myocardial infarction (MI) with coronary artery ligation and also decreased mortality rate in both groups. Also⁷ showed that both metoprolol and ivabradine produced nearly comparable heart rate reduction either in early or late treatment in a model of MI.

The effects of either metoprolol or ivabradine once 15min after experimental occlusion of a coronary artery (CAO) and another time after 28 days of treatment in a rabbit model of MI were studied by²⁵ who showed that ST displacement and the Q waves appeared in MI group had disappeared in ivabradine and metoprolol groups associated with significant reduction of heart rate and mortality rate.

Halkin et al.,²⁸ reported that β -blockers reduce the risk of re-infarction and death following acute myocardial infarction.

Cuculi et al.,²⁹ proved that patients with acute coronary syndrome pretreated with β -blockers and presented with MI should further receive their β -blocker if they are hemodynamically stable for its potential to prevent re-infarction and sudden cardiac death during the later period of the hospital stay. Patients without β -blocker pretreatment who are hemodynamically stable should start this therapy soon after presentation for MI, especially when there is tachycardia, hypertension or even with normotensive patient.

Fonarow³⁰ reported that carvedilol has been proposed to ameliorate the adverse effects of ischemia and reperfusion by its properties involving antioxidation, inhibition of adhesion and activation of neutrophils, protection of endothelial function and direct vasodilation.

A study by Basu³¹ investigated the effects of acute (intravenous) and long-term (oral medications for 6 months) treatment with carvedilol versus placebo in 151 patients with AMI. Carvedilol was found to significantly reduce cardiac events compared with placebo.

These data are in line with Svetlana et al.,³² who reported that the advantage of carvedilol over other beta blockers can also be found in the fact that the acute beta blockade in AMI can cause a deeper ischemia caused by neurohormonal activation and vascular constriction through the non-blocked alpha-receptors. With the simultaneous beta and alpha blockade carvedilol improves the subendocardial flow and reduces the myocardial ischemia. With its antiischemic effect carvedilol reduces the seriousness and the number of anginal attacks, increases the threshold for the effort-induced ischemia and improves the functional capacity of the coronary patient.³²

The biochemical parameters studied in the present work revealed elevation in the level of serum creatine kinase MB-isoform (CK-MB) and troponin-I in MI group.

Myocardium contains an abundant amount of diagnostic marker enzymes for MI and once metabolically damaged it releases its intracellular contents into the extracellular fluid³³. Hence, the serum levels of these markers enzymes reflect the alterations in membrane integrity and/or permeability.³⁴

During myocardial infarction, damaged heart tissue releases cardiac enzymes such as creatine kinase (CK). CK is found in the heart muscle, liver, skeletal muscles, and in the brain. CK-MB is a subtype of CK that is found only in heart muscle. Low level of the enzyme is normally found in the blood stream. Assay of MB isoenzyme of CK (CK-MB) activity in blood to obtain the magnitude and persistence of elevations is useful in estimating the extent of infarction³⁵.

Initial studies demonstrated that the distribution of CK was found to correlate with the distribution of reduced blood flow in heart of rabbit. Also, it was found to be correlated to ST-segment elevation that histologically demonstrates necrosis and with electron microscopic changes associated with cell death³⁶.

CK is an enzyme that catalyzes the transphosphorylation of ADP to ATP. CK is an intracellular enzyme which controls the concentration of ATP in such a way that it is retained in the cell at a constant level. This action of CK is extremely important if very high ATP turnover rate in the heart is considered³⁷.

Lefer et al.,³⁸ has found that serum CK correlates with myocardial CK depletion in cats with acute myocardial infarction.

The obtained data are in harmony with previous studies concluded that infarction leads to cardiac abnormalities and increase in the level of CK-MB³⁹.

Troponin is a protein released from myocytes when irreversible myocardial damage occurs. It is highly specific to cardiac tissue and accurately diagnoses myocardial infarction with a history of ischaemic pain or ECG changes reflecting ischaemia. Cardiac troponin level is dependent on infarct size, thus

giving clinicians an idea of the prognosis following an infarct⁴⁰.

In the year of 2000, Cardiac troponin replaced CK-MB as the biomarker of choice for diagnosing a myocardial infarction⁴¹.

The present study show that in both ivabradine and carvedilol groups of rats, the serum CK-MB and troponin-I levels 4 hours after isoprenaline injection was significantly decreased ($P < 0.001$) compared to MI group with insignificant ($P > 0.05$) difference between them.

The results of the present study are in keeping with results achieved in the clinical trial done in patients with early phases of reperfused anterior myocardial infarction with impaired left ventricular function done by Fasullo et al.,⁴² who demonstrated the beneficial effect of ivabradine and metoprolol with significant reduction of serum cardiac enzyme creatine kinase. Same results were obtained by Gerd Heusch et al.,⁴³ in patients with heart failure accompanying acute anterior wall MI, ivabradine effectively controls heart rate preventing excessive sinus tachycardia, reduces infarct size and troponin-I level probably secondary to control of heart rate.

Nageh et al.,⁴⁴; Cavallini et al.,⁴⁵ and Okmen et al.,⁴⁶ reported that the serum level of troponin I and CK-MB increase considerably after percutaneous coronary interventions (PCI) in patients who undergo elective PCI. This observation may suggest some degrees of myocardial injury during PCI.

Moloudiet al.,⁴⁷ demonstrated that administering 12.5 mg carvedilol prior to PCI prevented the rise of troponin I and CK-MB after the process considerably, with its effect most pronounced at 24 hours after PCI.

Histopathological study indicated that in ivabradine and carvedilol groups there are little signs of acute infarction (changes in cardiomyocyte bundles, nuclear shape and nuclear cytoplasm) compared to MI group. Isoprenaline, a potent synthetic catecholamine produced "infarct-like" lesions in the heart of experimental rats, which were similar

to those found in acute myocardial infarction (AMI) and sudden death in man.⁴⁸

Upaganlawar et al.,¹⁸ demonstrated that isoprenaline elicited cardiac damage evidenced by focal confluent necrosis of muscle fibers with inflammatory cell infiltration, and edema with fragmentation of muscle fibers.

In agreement with the present study Heusch et al.,⁴⁹ demonstrated that ivabradine pretreatment in anaesthetized pigs subjected to 90min controlled left anterior descending coronary artery hypoperfusion and 120min reperfusion significantly reduced the infarct size.

This was referred to the antioxidative effects of ivabradine. The in-vivo effects of ivabradine were absent at a dose that did not lower heart rate that correlates the HR reduction with corresponding anti-atherosclerotic effects and decrease oxidative stress⁵⁰. These results may, in part, explain the significant decrease of myocardial infarction (MI) size observed in patients treated with ivabradine⁵¹.

As far as comparing the efficacy of different β -blockers in preventing LV remodeling after AMI, Tang⁵² reported an effective attenuation of LV remodeling by carvedilol and improvement of hemodynamics and LV function after AMI in rats. Metoprolol exhibited similar benefits regarding hemodynamics, LV dilatation and function, but not LV hypertrophy. Therefore, in instances where the use of β -blockers is indicated such as during the peri- and post-MI period, carvedilol may be superior to other medications in the same class.

Yuejin et al.,⁸ added that Cilazapril, carvedilol and their combination are all effective in preventing LV remodeling after AMI in rats, and in improving haemodynamics and LV function, with the combination therapy being superior to monotherapy in all respects.

Same results were obtained by Svetlana et al.,³² in the group of AMI patients, treated with carvedilol the frequency of serious cardiac events (reinfarctions, unstable angina, urgent revascularization) was reduced for 42%, which was

a significantly larger percentage compared to the placebo-treated group.

Beta-blocker therapy has been found to produce significant reductions in the risk of sudden cardiac death after MI⁵³.

In the current work, the protective effects of ivabradine (10mg/kg) and carvedilol (1mg/kg) in adrenaline-induced arrhythmia in anaesthetized rats were investigated. The results revealed that both ivabradine and carvedilol had a prophylactic effect against adrenaline-induced arrhythmias.

The result of this study is in consistence with Koncz et al.,⁵⁴ who studied the effects of ivabradine on maximum rate of depolarization (V_{max}), repolarization and spontaneous depolarization using micro-electrode technique and by applying patch-clamp technique in large animal (dog) to examine action potential characteristics and ionic currents respectively. Ivabradine exerted decrease in the amplitude of spontaneous diastolic depolarization, reduction in spontaneous rate of firing of action potentials and produced a concentration- and frequency-dependent (V_{max}) block in dog Purkinje fibers and ventricular muscle.

In agreement with the present study Vaillant et al.,⁵⁵ reported that in a model of myocardial ischaemia which induced in pigs by complete and brief (1-min) occlusion of the proximal left anterior descending coronary artery. Repeated abrupt coronary occlusions were performed at 15-min intervals. Ventricular fibrillation threshold (VFT) determinations were performed at the end of each coronary occlusion, before and after i.v. administration of ivabradine (0.25mg/kg). VFT was significantly increased in ivabradine treated animals, this increase in VFT was explained by an increase in duration of monophasic action potential, and reduction of the hypoxic area.

Luminita and Roxana⁵⁶ considered the ivabradine efficacy and safety profile, the heart rate reduction in the early postoperative period after coronary surgery in patients with conduction abnormalities or left ventricular dysfunction with ivabradine therapy emerged as the best treatment.

In agreement with the present study in case of inappropriate sinus tachycardia (IST) which characterized by paroxysmal tachycardia originating in the sinus nodal area. Zellerhoff et al.,⁵⁷ demonstrated that ivabradine appears effective and safe in patients with symptomatic inappropriate sinus tachycardia.

The same results were obtained by Mackiewicz et al.,⁵⁸ who reported that potential mechanisms of ivabradine as antiarrhythmic agent in acute MI in rat include prevention of diastolic Ca^{2+} leak from sarcoplasmic reticulum and upregulation of If current in left ventricle.

The result of this study is in consistence with Fu Siong et al.,⁵⁹ who found that ivabradine, which is licensed for chronic stable angina and chronic heart failure, may be useful in the clinical setting to prevent reperfusion arrhythmias if given early enough during the course of acute ischaemia-infarction before primary percutaneous coronary interventions (PCI), and may also be protective against reperfusion arrhythmias in unstable angina and coronary vasospasm.

There is also evidence suggesting that beta blocker administration is associated with a better prognosis in patients with sustained ventricular tachyarrhythmias and in patients successfully resuscitated from cardiac arrest⁶⁰. The protective effect of beta blockers may be exerted via their anti-adrenergic effects; some authors believe that additional mechanisms are involved including a possible membrane-stabilizing effect⁶¹.

Storstein⁶² added that carvedilol exerts a weak blockade of the slow-type calcium channel. As a class, calcium channel-blockers inhibit the inwardly directed Ca^{2+} current, delaying conduction through the atrial and atrioventricular nodes. The ability to depress this particular calcium-ion current is the basis for use of carvedilol in the management of supraventricular arrhythmias, ischemia and reperfusion-induced arrhythmias.

Takusagawa et al.,⁶³ reported that carvedilol has the inhibitory effect against reperfusion arrhythmias in rats and suggest that the mechanism

of action of this compound is related to the combined effects of beta-blocking and antioxidant. Also⁶⁴ demonstrated the beneficial effect of carvedilol on arrhythmias when taken with an ACE inhibitor. As, carvedilol significantly reduced supraventricular arrhythmias and atrial flutter or fibrillation. Also, carvedilol significantly reduced 'any ventricular arrhythmia' by 63% and 'malignant ventricular arrhythmias' by 70%. Moreover, treatment with carvedilol lead to an increase in time to first occurrence of atrial flutter or fibrillation and first malignant ventricular arrhythmia.

Same results were obtained by Carol et al.,⁶⁵ in a 6-month, randomized, placebo-controlled study of 168 patients with heart failure due to ischemic etiology or idiopathic dilated cardiomyopathy, carvedilol administered at 12.5-50mg twice daily lead to reduced ventricular arrhythmia activity and improved ventricular function.

The results of current work are similar to those of Acikel et al.,⁶⁶ in a randomized clinical trial of 110 patients investigating the efficacy of carvedilol compared with metoprolol succinate in preventing postoperative atrial fibrillation in the first 3 days after coronary artery bypass graft, 20 patients (36%) in the metoprolol group and 9 patients (16%) in the carvedilol group developed AF.

The data of the present work revealed that ivabradine in gradually increasing doses produced no effect on the amplitude of spontaneous contractions of isolated perfused rabbit's heart.

Same result was obtained by Berdeaux⁶⁷ who reported that selective inhibition of If current by ivabradine was found to reduce heart rate both at rest and during exercise in experimental animals, without any inotropic effects or effect on left ventricular systolic function or coronary vasomotor activity. Also Savelieva⁶⁸ reported that ivabradine reduces the heart rate without altering myocardial contractility or other hemodynamics.

The present results showed that ivabradine produced no effect on nor adrenaline induced contractions in isolated rabbit's aortic spiral strip. This result is consistent with that obtained by Drouin et al.,⁶⁹ who showed that 3-months treatment

of young dyslipidaemic mice with ivabradine had a protective effect on endothelial function with no effect on lipid profile. On the other hand, acute ivabradine treatment had no effect on endothelial dysfunction. One of the possible explanations is that chronic treatment with ivabradine potently inhibits vascular oxidative stress. The authors excluded the endothelial protective effects of ivabradine to be secondary to the reduction of heart rate.

CONCLUSION: We can assume that both ivabradine and carvedilol have cardioprotective effect against acute MI as well as adrenaline-induced arrhythmia with no significant difference between both drugs. The present experimental study supports the concept that increased heart rate is deleterious to the cardiovascular system. So, the choice of either drug in these disease states depend on which of them has low side effects.

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