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Original Article

The Effects of Olive Leaf Extract Administration on the Cerebral Hypoperfusion-Induced Electrophysiological Alterations in Rat Heart

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Abstract

Background and Aim: In the present study, the role of ethanolic extract of olive (*Olea europaea*) leaf administration against the cerebral hypoperfusion-induced electrophysiological alterations and left ventricular thickness in rat heart was studied.

Materials and Methods: The right carotid artery was occluded with a 5-0 silk suture and the left carotid artery was occluded after a week. The olive (Olea europaea) leaf extract was administered orally (by gavage) to three experimental groups of rats in 100, 200 and 300 mg/kg/day for two weeks after the left carotid artery occlusion and processed in 25 days. The sham and hypoperfusion groups were fed with normal saline. Each group had 6 rats. After 25 days, electrophysiological heart parameters, i.e. HR, QTc, QRS duration, QT interval, PR interval, RR interval, ST amplitude, T wave amplitude and also the thickness of left ventricle (TLV) were assessed.

Results: The administration of olive leaf extract (100, 200 and 300 mg/kg) exhibited its cardioprotective effect by both stabilizing heart rate and preventing ECG changes (such as shortening of PR, QRS, QT and QTc intervals, prominent T waves and ST elevation). Moreover, olive leaf extract (100, 200 and 300 mg/kg) prevented cardiac hypertrophy after cerebral hypoperfusion.

Conclusion: Our results indicated that post-treatment with ethanolic extract of olive leaves could prove beneficial effects in managing the cerebral hypoperfusion-induced cardiac abnormality in rats.

Keywords: Electrocardiogram, Cerebral hypoperfusion, Left ventricle, Olive leaf extract

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Introduction

Cardiovascular complications commonly happen after brain injury and are associated with increased mortality and morbidity (1, 2). There are a wide range of abnormalities including ECG changes, hypotension, hypertension, cardiac arrhythmias, release of biomarkers of cardiac injury and left ventricular (LV) dysfunction (3). A research has demonstrated that carotid artery stenosis is an important risk factor for cerebrovascular diseases such as transient ischemic attack and cerebral infarction (4). The abnormalities are usually reversible, hence, the management should focus on general supportive care and also on treatment of the underlying brain injury (3). Neurotic stunned myocardium used to be associated with covert coronary artery disease or myocardial ischemia secondary to systemic, catecholamine-induced hypertension and tachycardia. Nevertheless, animal and human studies have confirmed that it is induced by excessive norepinephrine release from myocardial sympathetic nerve terminals, and it is after all, independent of plasma catecholamine levels (5). The release of catecholamines into the myocardial interstitium results in the long-term opening of beta1-adrenergic receptor-controlled calcium channels and rapid depletion of adenosine triphosphate. This results in mitochondrial dysfunction and cell death and is associated with a classic histological picture called myocardial contraction band necrosis that is characterized by focal myocytolysis, myofibrillar degeneration, and irregular cross-band formation. The greatest degree of histological changes can be observed in subendocardial regions of the heart, with relative apical sparing, associated with areas of sympathetic innervation rather than specific vascular territories (6). The leaves of the olive plant have been used for decades in folk (traditional) medicine to treat cardiovascular complications (7). The medicinal capacities of olive products have centralized in recent years, on its polyphenols (particularly oleuropein and hydroxytyrosol), which have been proved in animal and in vitro studies to have antioxidant, antimicrobial, hypoglycemic, antihypertensive, and anti-atherosclerotic properties (8-15). Oleuropein is one of the polyphenols which are found abundantly in olive leaf compounds. This polyphenol can prohibit the membrane lipid oxidation and cardiovascular diseases. Furthermore, it is effective in improving coronary artery disease. Moreover, it has antiarrhythmic effect and improves lipid metabolism (16-18). One of the significant properties of olive leaf extract is that it is capable of reducing infarct volume, brain edema, blood brain permeability and neurobehavioral deficit scores in a reliable and reproducible animal model of stroke followed by reperfusion when it is utilized as a pretreatment (11). Therefore, this study was undertaken to investigate the possible effects of Olive leaf extract post-treatment on cerebral hypoperfusion-induced electrophysiological changes in rat heart.

Materials and Methods

Plant Collection and Extract Preparation

Olive leaves were collected from trees in the west lands of Iran (Lorestan Province) in February. The leaves were washed from external matters, then dried at room temperature in shade and were ground in a blender (sunny SC80) to form powder. Thereafter, 100 g of the powder was added to 1000 ml (70%) ethanol and permitted to extract. Using rotary evaporator (Rontegen, Germany), the solvent was separated. Then dried powder was yielded by using freeze dryer (Hidolf, Germany).

The resultant ethanol extract was stored in closed dark glass container in refrigerator until the time of its use. The extract, on the basis of its dose, in a required amount was dissolved in physiologic saline and was given orally to the animals. Using HPLC technique, the oleuropein amount of the extract was assessed, which was reported as 14%. The oleuropein amount of olive leaves was determined by HPLC method as previously described (19).

Animals

In this experimental study, 30 male Wistar rats, weighing on average 200-300 grams, were housed under standard conditions (22–25°C, 12-hour light–dark cycle) with free access to food and water. The rats were divided into 5 groups (n=6), (Table 1). The animal care was conducted in accordance with the

institutional guidelines of Lorestan University of Medical Sciences (I.R.) and the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals.

Surgical Preparation

The animals were anesthetized by intraperitoneal administration of chloral hydrate (400 mg/kg body weight). Body temperatures were maintained at 37 ± 1◦C by the use of a blanket. The right carotid artery was occluded with a 5-0 silk suture and then the left carotid artery was occluded after a week. The olive (Olea europaea) leaf extract was administered orally (gavage) to three experimental groups of rats in 100, 200 and 300 mg/kg/day for two weeks after the left carotid artery occlusion and processed in 25 days. The sham (control) and hypoperfusion groups were fed with normal saline (Figure 1) (Table 1).

The Registration and Evaluation of ECG Parameters

The ECG tracings were analyzed via Power monitoring system (ML750 Power Lab/4sp) and then the following ECG parameters were examined:

1) RR interval (the interval between the apex of two consecutive adjacent R waves),

2) QT interval (the interval between beginning of Q wave and T wave apex),

3) Corrected QT interval (QTc), defined as the QT interval corrected for the heart rate by means

Of Bazett's equation: $QTc = QT\ (ms)/\ [RR\ (s)]^{1/2}$

4) HR

5) QRS duration

6) ST amplitude

7) T wave amplitude

The Evaluation of the Ventricle Thickness

After recording the ECG parameters, the rats were killed and their hearts were excised (chest was opened via left thoracotomy in the fifth intercostal space to expose and dissect the heart after incision of the pericardium) and then the left ventricle (LV) was washed with sodium chloride and fixed in 10% phosphate-buffered formalin. Subsequently, it was divided into transverse slices of 2 mm thickness from the apex to the base. It was finally incubated with a 1% solution of hematoxylin and eosinophil (H&E), stained for 20 minutes at 37◦C and then the thickness of left ventricle (TLV) was measured by Motic Images Plus 2.0 system.

Statistical Analysis

Data are presented as means±S.E.M. The statistical comparison of means between groups was performed by one-way ANOVA and a subsequent Tukey test using SPSS Statistics. The value of $p< 0.05$ was considered to be significant.

Results and Discussion

The Effects of Different Doses of Olive Extract on HR and Electrophysiologic Parameters

The administration of different concentrations of olive extract (100, 200 and 300 mg/kg/day) resulted in significant distinctions in the rats' HR, QT interval, PR and RR interval and QRS duration among the hypoperfusion group and the experimental groups (Figure 2A).

HR was significantly higher ($p<0.05$) in hypoperfusion group than 300mg+H group (410±10 vs 305±40 beats/min in 300mg+H group). While in 100mg+H and 200mg+H groups, HR returned to sham values. In 300mg+H group (305±40 beats/min*)*, HR was significantly lower ($p<0.05$) than hypoperfusion (410±10 beats/min*)* and 100mg+H groups (360±25 beats/min) (Figure 2A).

In the hypoperfusion rats, the induction of cerebral hypoperfusion significantly reduced the QRS (11.11±0.35vs 15.06±0.55 ms –$p<0.01$), RR (127.25±5.13vs 183.8±10.45 ms –$p<0.001$) and QT interval (37.67±2.19vs 61.67±2.81 ms –$p<0.001$) when compared to the sham group. The QT interval in

Table 1: A summary of experimental groups and the diet/drug treatment protocols.

Groups	Treatment protocols
sham	normal saline (gavage)
100mg+H	hypoperfusion +100 mg/kg/day olive leaf extract
200mg+H	hypoperfusion +200 mg/kg/day olive leaf extract
300mg+H	hypoperfusion +300 mg/kg/day olive leaf extract
hypoperfusion	hypoperfusion + normal saline

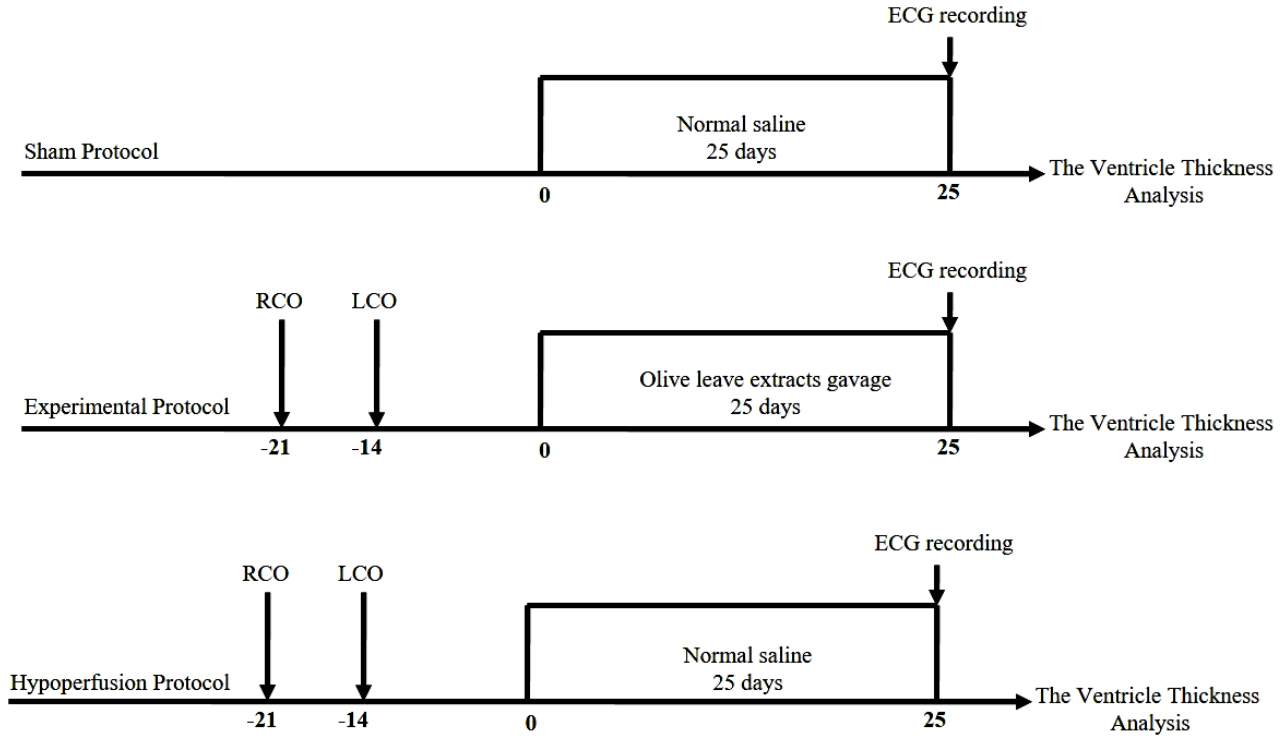

Figure 1. Illustration of the experimental protocols. The right carotid artery was occluded and then the left carotid artery was occluded after a week. In Experimental protocol, the Olive (Olea Europaea) leaf extract was administered orally (gavage) to three experimental groups of rats in 100, 200 and 300 mg/kg/day for two weeks after the last surgery and processed in 25 days. Animals in the sham control and hypoperfusion protocols were fed with normal saline. RCO = Right Carotid Occlusion, LCO = Left Carotid Occlusion.

100mg+H (58.83±2.68 ms) and 200mg+H (55.33±3.32 ms) groups were prolonged and returned to the sham group (Fig. 5). Through the administration of different concentrations of olive leaf extract (100, 200 and 300 mg/kg/day), the RR (175.07±4.56 ms, 164.5±9.08 ms and 158.35±4.97 ms respectively) and QRS duration (16.22±0.88 ms, 17.46±0.64 ms and 16.16±1.11 ms, respectively) was prolonged and returned to the sham group (Fig. 2 B, C and D).

In the hypoperfusion group, the induction of hypoperfusion significantly reduced the P-R interval (38±6 ms) compared to the sham (55.5±4.5 ms) and other groups ($p<0.05$). Through the administration of different concentrations of olive extract (100, 200 and 300 mg/kg/day), the P-R duration (52±4 ms, 54±5 ms and 53±2.5 ms, respectively) was prolonged and returned to the sham group (Figure 3A).

The results of the measuring of the ST amplitude (mv) demonstrated a significant decrease ($p\leq0.001$) in the experimental (100mg+H, 200mg+H and 300mg+H) groups (20.2±0.58 mv, 16.4±1.89 mv and 13±1 mv, respectively) in comparison with the hypoperfusion group (48±2.17 mv). The greatest reduction was observed in the 300mg+H group (Fig. 3B).

The results of the measuring of the T amplitude (mv), demonstrated a significant decrease ($p\leq0.001$) in the experimental (100mg+H, 200mg+H and 300mg+H) groups (53.2±1.7 mv, 52.6±2.42 mv and 46±2.77 mv, respectively) in comparison with the hypoperfusion group (78.2±3.14 mv) (Fig. 3C).

The Effect of Different Doses of Olive Extract on Corrected QT (QTc) Interval

The change in QTc interval (ms) was measured in the groups (Figure 3D). In the hypoperfusion rats (10.83±0.95 ms), the cerebral hypoperfusion induction significantly reduced the QTc interval compared to sham (15.5±0.45 ms –$p<0.01$). Through the administration of different concentrations of olive leaf extract (100, 200 and 300 mg/kg), the QTc interval (13.6±0.93 ms, 14.2±0.86 ms and 16.8±0.73 ms, respectively) significantly altered compared to the

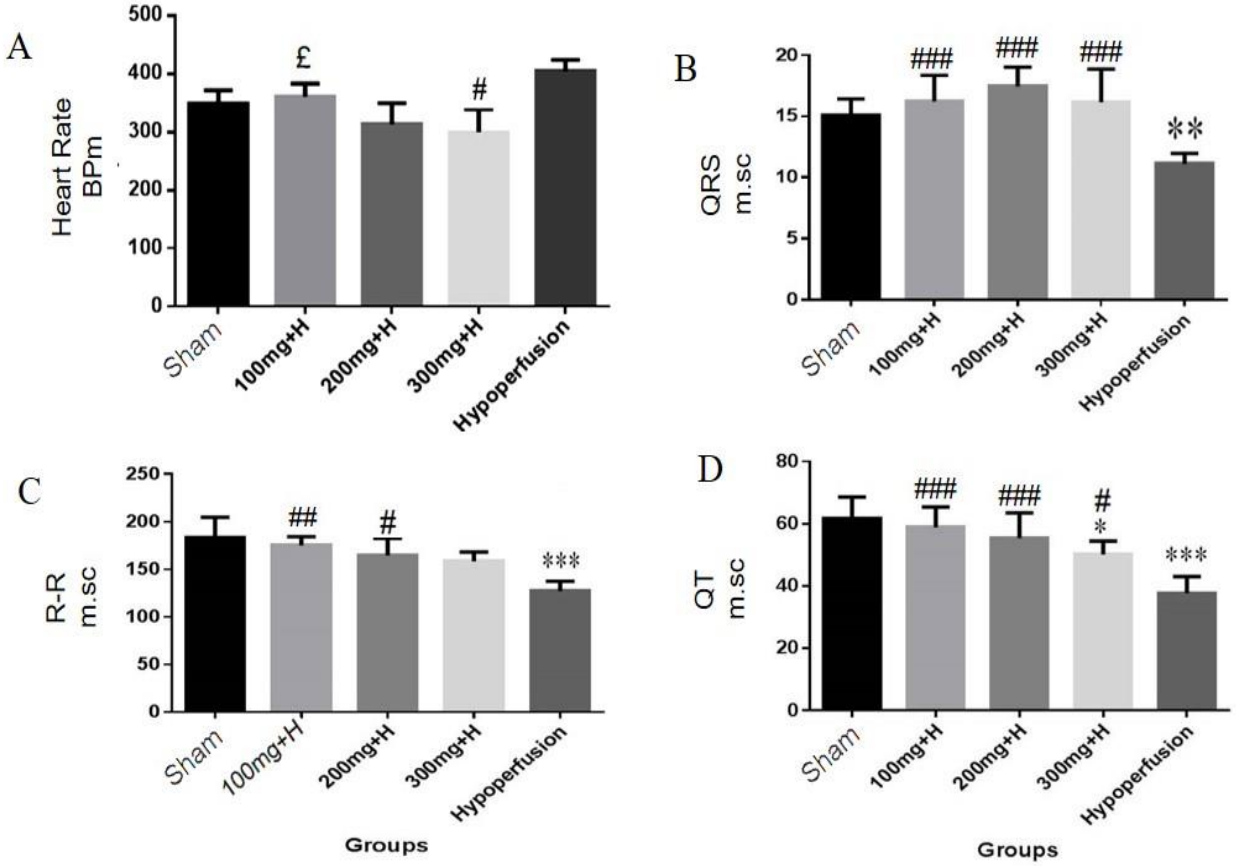

Figure 2. The effects of cerebral hypoperfusion and olive leaf extract on A) heart rate, B) QRS interval, C) R-R interval and D) QT interval parameters in different groups. The values are mean ± SEM; HR = heart rate (beats/min); sham = normal saline (gavage), 100mg+H= hypopefusion+100 mg/kg/day olive leaf extract, 200mg+H= hypoperfusion + 200 mg/kg/day olive leaf extract, 300mg+H= hypoperfusion + 300 mg/kg/day olive extract, hypoperfusion= hypoperfusion+ normal saline (gavage); *: p<0.05 vs the sham group, **: p<0.01 vs the sham group, ***: p<0.001 vs the sham group, #: P < 0.05 vs Hypoperfusion group, ## p<0.01 vs Hypoperfusion group, ### p<0.001 vs Hypoperfusion group, £ p<0. 05 vs 300mg +H group.

sham group, and the QTc interval significantly increased in 300mg+H group compared to the hypoperfusion group (p<0.001) (Figure 3D).

The Effect of Different Doses of Olive Leaf Extract on the "Thickness of Left Ventricle (TLV)" in Rat Heart

After the induction of cerebral hypoperfusion, TLV (2.5±0.08 mm) was significantly increased compared to the sham group (1.2±0.04 mm). Furthermore, post-treatment with different concentrations of olive leaf extract (100, 200 and 300 mg/kg) significantly decreased the TLV (1.42±0.06 mm, 1.62±0.1 mm and 1.3±0.13 mm, respectively) compared to the hypoperfusion group (Fig. 4 A and B) (p<0.05).

In the present study, the Olive leaf ethanol extract significantly reduced the HR, ST amplitude and T amplitude, prolonging QT, PR and RR interval, QRS duration and QTc, and decreased the thickness of left ventricle in rats with cerebral hypoperfusion**.** The increased HR and the reduced R-R intervals in hypoperfusion group were in line with previous studies reporting that the sympathetic hyperactivity associated with traumatic brain and ischaemic injury could cause direct injury to the myocardium (20). Catecholamine-induced vasoconstriction is an acute complication leading to tachycardia and a secondary increase in myocardial oxygen demand. In this study, R-R interval shortening and in 300mg+H group, HR elevation after hypoperfusion were prevented via the administration of different concentrations of olive leaf extracts (100, 200 and 300 mg/kg/day). Our study indicated that olive leaf extract could have a protective role in heart pathology related to cerebral hypoperfusion. Cardiac arrhythmias and ECG

abnormalities occur frequently in patients with acute stroke, either with or without coexisting cardiac diseases. The incidence and prevalence of arrhythmias and highly abnormal type of ECGs depend on the types and onset of stroke, the duration and equipment used for cardiac monitoring and criteria used for determination and classification of arrhythmias. Ischemic and hemorrhagic lesions in some particular areas of brain, such as the insular cortex, can cause imbalances in central autonomic control of the heart, disrupt the heart's ability to adjust during stress, increase hormones of the sympathoadrenal system and bring about damage to the cardiac tissue that is similar to histopathology found in sympathetic over activity. Identification of high-risk patients after stroke is important, because appropriate cardiac monitoring for early detection of ECG abnormalities and arrhythmias and effective management, including supportive and specific treatment of arrhythmias, can prevent cardiac morbidity and mortality after acute stroke (21). The findings related to cerebral hypoperfusion in our study concerned ST segment elevation, prominent T waves, and shortening of P-R**,** QRS, QT and QTc intervals. The release of catecholamines into the myocardial interstitium leads to prolonged opening of β1-adrenergic receptor-controlled calcium channels which causes shortening of P-R, QRS, QT and QTc intervals and prominent T waves. In our study, the shortening of P-R, QRS, QT and QTc intervals and prominent T waves after hypoperfusion were prevented via the administration of different concentrations of olive extract (100, 200 and 300 mg/kg/day), similar to heart rate. Neurogenic ECG changes such as ST segment change can be linked to some factors including the development of a prolonged ischaemic neurological

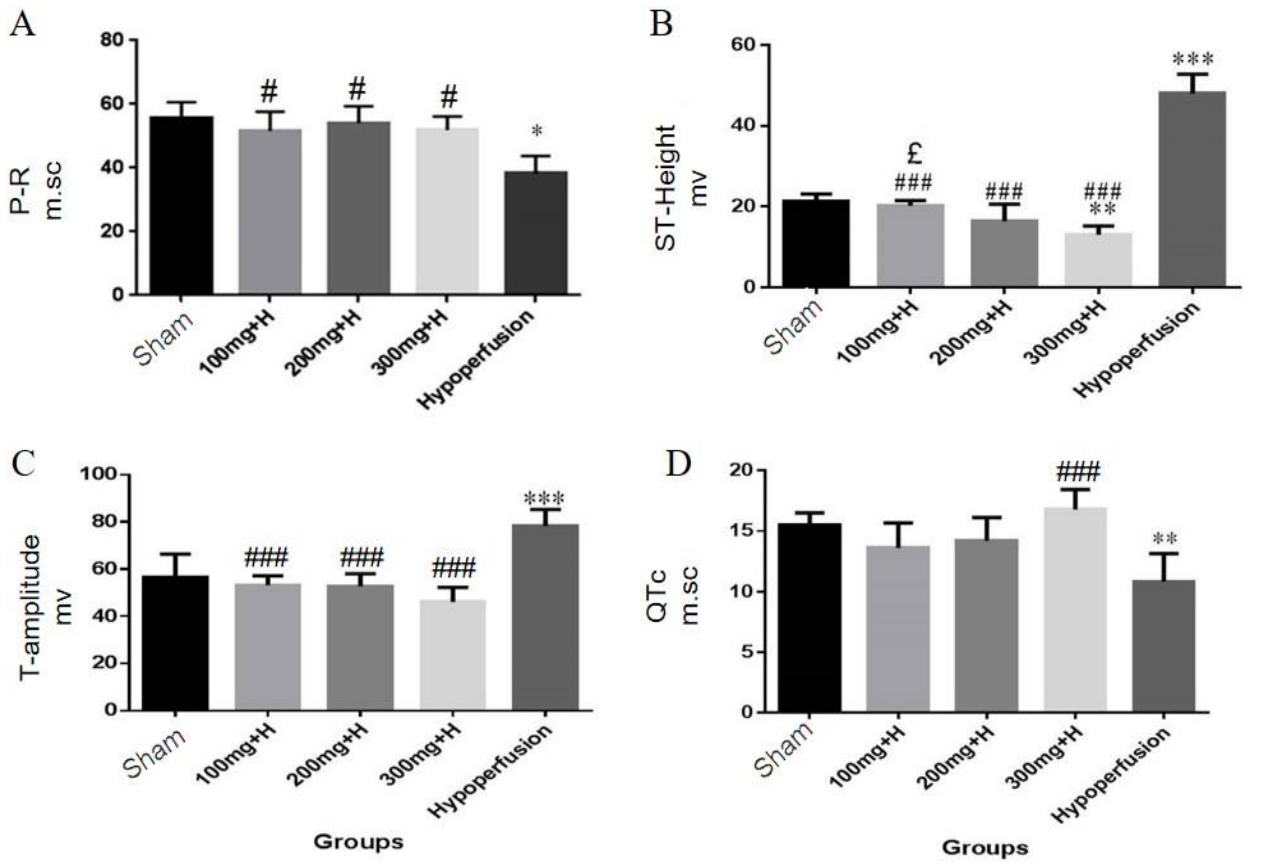

Figure 3. The effects of cerebral hypoperfusion and olive leaf extract on A) P-R interval, B) ST-Height, C) T-amplitude and D) QTc interval parameters in different groups. The values are mean ± SEM; sham = normal saline (gavage), 100mg+H= hypopefusion+100 mg/kg/day olive leaf extract, 200mg+H= hypoperfusion + 200 mg/kg/day olive leaf extract, 300mg+H= hypoperfusion + 300 mg/kg/day olive extract, hypoperfusion= hypoperfusion+ normal saline (gavage); *: p<0.05 vs the sham group, **: p<0.01 vs the sham group, ***: p<0.001 vs the sham group, # p<0.05 vs Hypoperfusion group, ### p<0.001 vs Hypoperfusion group, £ p<0. 05 vs 300mg +H group.

deficit, poor outcome, and death after subarachnoid haemorrhage (3). It has been demonstrated that the increased incidence of stroke or transient ischemic attack is associated not only with the hypertensive condition but also with hypertension-induced cardiac injury or left ventricular hypertrophy (22). Giulio Selvetella et al. have shown that the possibility of cardiac hypertrophy could be explored in hypertension and cardiac damage (22).

Our findings have indicated that the thickness of left ventricle significantly increased after cerebral hypoperfusion, and Post-treatment with 300mg/kg/day of olive leaf extract significantly decreased the thickness of left ventricle. According to Iran's traditional medicine, the leaves of olive tree are of value for the treatment of hypertension. A number of experimental studies have reported the hypotensive effects of olive leaf extract by different solvent and methods, ranging from hot water extracts glycerol/ethanol extracts and ethanol extract. Moreover, the consumption of aqueous extract of olive leaves for 3 months led to the reduction of blood

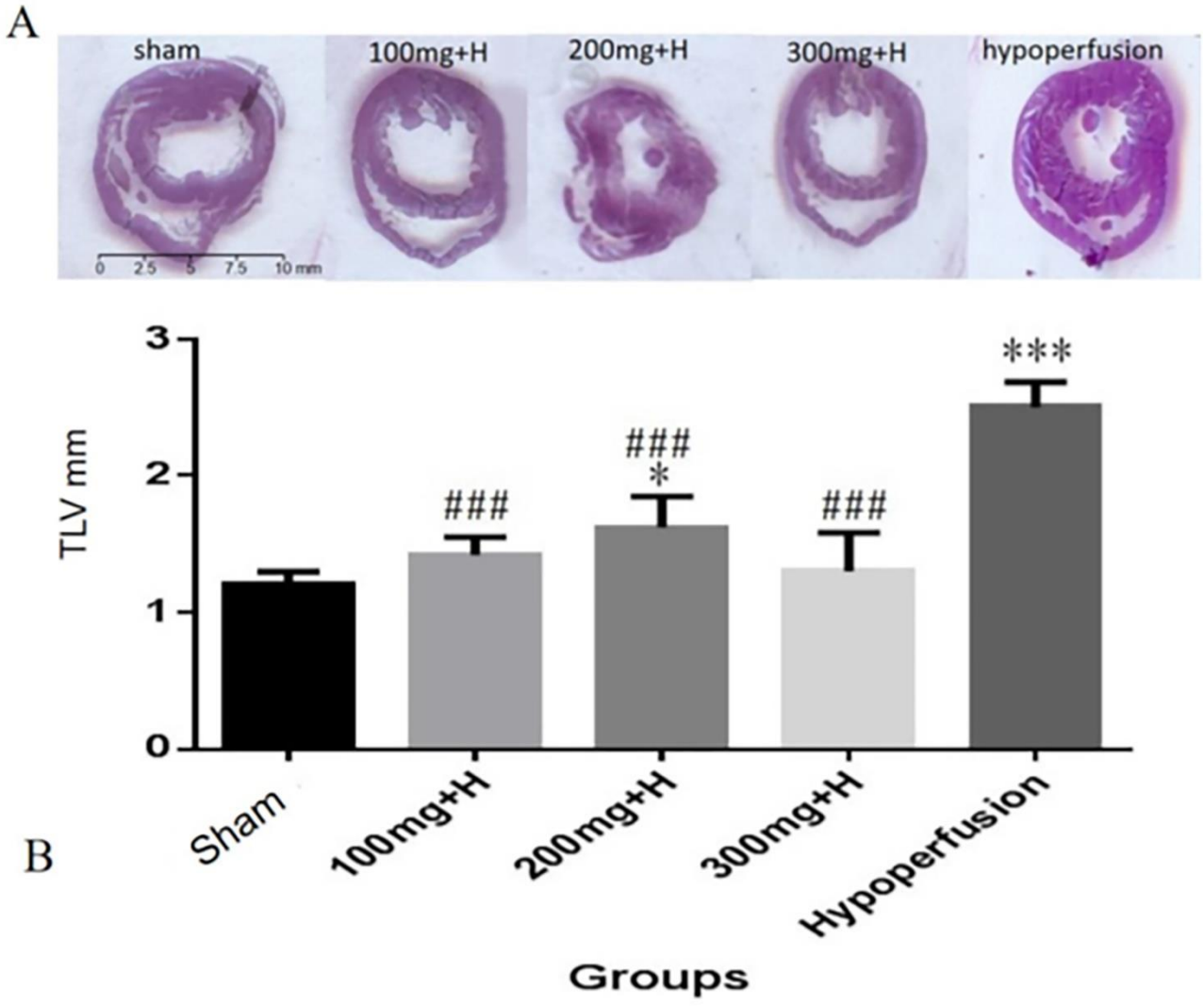

Figure 4. A) Digital scans of hearts in cross-section taken at midventricle along the short axis. These images illustrate the amount of left ventricular free wall thickening and chamber narrowing in different groups. B) The effects of cerebral hypoperfusion and olive leaf extract on the thickness of left ventricle (TLV) parameter. The values are mean ± SEM; sham = normal saline (gavage), 100mg+H= hypoperfusion+100 mg/kg/day olive leaf extract, 200mg+H= hypoperfusion +200 mg/kg/day olive leaf extract, 300mg+H= hypoperfusion +300 mg/kg/day olive leaf extract, hypoperfusion= hypoperfusion + normal saline (gavage); *: $p<0.05$ vs the sham the group, ***: $p<0.001$ vs Control, ### $p<0.001$ vs hypoperfusion group.

pressure in hypertensive patients (23). The findings of the present study confirm the beneficial effect of olive leaf extract against cerebral hypoperfusion induced left ventricular hypertrophy in rats that may be due to its Blood pressure lowering and antihypertensive effect. Further studies are under way to further elucidate its mechanism of action. Furthermore, it has been suggested that the generation of a large quantity of free radicals plays an important role in the establishment of arrhythmia. Hence, the administration of free radical scavengers has antiarrhythmic effects (24). Since the heart has low regenerative ability (25), increasing the antioxidant defense system of the myocardium has a great relevance. In this study, our aim was to know whether the administration of different doses of olive leaf extract could have cardioprotective effect against cerebral hypoperfusion-induced electrophysiological changes in rat hearts. Epidemiological data have indicated that the lower incidence of cardiovascular diseases and cancers in Mediterranean area is associated with high consumption of natural phenolic antioxidants, especially olive, through their traditional diet (26). Oleuropein is the main constituent of olive leaf extracts that has anti-inflammatory, antidiabetic, anti-atherosclerotic, antimicrobial and antitumoral effects (27).

Conclusion

In our study, the administration of different concentrations of olive leaf extract (100, 200 and 300 mg/kg/day), exhibited its cardioprotective effect by stabilizing heart rate and preventing ECG abnormalities (such as shortening of P-R, QRS, QT and QTc intervals, prominent T waves and ST elevation). In addition, olive leaf extract in different doses (100,200 and 300 mg/kg) prevented cardiac hypertrophy after cerebral hypoperfusion. The possibility of anti-cardiac hypertrophy effect of olive leaf extract may be explored in its anti-hypertension effects that require more investigation. S0ince patients with a more severe neurological deficit are more likely to develop cardiac dysfunction, increased vigilance is required in those with the most severe brain injury. The spectrum of abnormalities includes hypertension, ECG changes, cardiac arrhythmias and left ventricular (LV) dysfunction. The abnormalities are usually reversible. Hence, it is likely that future studies could prove the beneficial effects of olive leaf extract in managing the neurogenic cardiac injury in human beings.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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