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Research article

Dexmedetomidine protects against myocardial ischaemia/reperfusion-induced renal damage in rats

Osama M. Assad[a,*], Dina A. Aly Labib[b], Laila Ahmed Rashed[c]

[a] Department of Anesthesiology, Faculty of Medicine, Cairo University, Egypt
[b] Department of Medical Pharmacology, Faculty of Medicine, Cairo University, Egypt
[c] Department of Medical Biochemistery and Molecular Biology, Faculty of Medicine, Cairo University, Egypt

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ABSTRACT

Background: Myocardial ischaemia/reperfusion (MI/R) may induce renal damage. Our aim was to investigate the effects of dexmedetomidine (DEX) administration at two different timings either before or after ischaemia on renal damage induced by MI/R.

Methods: MI/R injury was induced in a rat model. we ligated the left anterior descending coronary artery for 30 min (ischaemic period), then reperfusion occurred for 2 h (reperfusion period). A single dose of DEX (100 μg/kg) was given intraperitoneally, either 30 min before myocardial ischaemia or 5 min after reperfusion. With the end of reperfusion period, rats were sacrificed, then we collected the blood and removed both kidneys quickly for biochemical and histopathological analysis.

Results: MI/R caused an elevation in serum urea and creatinine, significant elevation in malondialdehyde (MDA) release and decrease in superoxide dismutase (SOD) activity in the rat kidney. There were also higher levels of serum tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). Treatment with dexmedetomidine, 30 min before induction of myocardial ischaemia, succeeded to improve all the tested parameters. The valuable changes in these biochemical parameters were linked with similar enhancement in the histopathological appearance of the kidney. Meanwhile, DEX given 5 min after reperfusion improved serum urea and creatinine only.

Conclusion: These findings imply that MI/R plays a fundamental role in kidney damage through increased production of oxygen radicals or deficiency in antioxidants, and DEX given before ischaemia exerts reno-protective effects probably by its radical scavenging antioxidant activity and anti-inflammatory mechanism.

1. Introduction

Among the common causes of death occurring perioperatively are the renal or cardiac injuries following cardiac surgery [1]. Lipid peroxidation, inflammatory reaction or oxidative stress following myocardial ischaemia/reperfusion (MI/R) may be leading causes of distant organs' damage after myocardial ischaemia [2]. An organ as the heart if exposed to severe ischaemia and then reperfused can affect a distant organ that was not exposed to the initial ischaemic event or cause multiple organ damage [3]. Because of its anatomical and unique structure, the kidney is considered a very sensitive organ affected easily by ischemia–reperfusion (I/R) [4]. Though, benefits of coronary revascularization or related techniques as thrombolysis or angioplasty may be life-saving from irreversible renal necrosis, still it is a double-edged sword because reperfusion may even augment renal damage [5].

The mechanisms behind the decline in renal function following coronary ischaemia then revascularization is most probably multifactorial and can be explained by decrease in renal blood flow, absence of perfusion in pulsatile manner, rupture of traumatized red blood cells (RBCs) or inflammatory reaction [6]. Also, apoptosis share in the pathophysiology of I/R insult. There is meaningful increase in the oxygen free radicals (FR) and reactive oxygen species (ROS) in the kidney. FR in turn initiate an inflammatory response. The most affected structures by the ROS are proteins, membrane lipids, and deoxyribonucleic acids. The endogenous antioxidant system includes enzymes as superoxide dismutase (SOD) and catalase which act to minimize the I/R insult [7]. Ongoing researches and studies are being developed to introduce new agents to alleviate organs' reperfusion-mediated insult. The anesthetic agents have impact on endogenous antioxidant systems and formation of free oxygen radical formation [8].

Dexmedetomidine (DEX) is a strong alpha 2 agonist. It is an anxiolytic which can be used pre-operatively as a preanaesthetic agent to

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* Corresponding author at: Department of Anesthesiology, Faculty of Medicine, Cairo University, Kaseralini, Cairo, Egypt.
E-mail addresses: osamaasaad72@yahoo.com (O.M. Assad), labibd5@gmail.com (D.A. Aly Labib), Lailaahmedrashed@gmail.com (L. Ahmed Rashed).

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help reduction of the dose of anaesthetics [9]. It has anti-inflammatory potentials and cardioprotective effects [10]. Previous studies have demonstrated that dexmedetomidine could alleviate direct organ damage secondery to exposure to I/R in different animal groups and can decrease the deleterious effects of I/R insult [11,12]. But, no studies have investigated the effects of dexmedetomidine on indirect renal damage developping after myocardial I/R. The objective of our study was to evaluate if DEX can improve the remote kidney damage following myocardial ischaemia reperfusion and clarify its potential protective effects on MI/R-induced renal damage, and investigate whether the timing of its administration, 30 minutes before and 5 minutes after ischaemia play a role or not. Several parameters were assessed including biochemical measurements of kidney function (serum urea and creatinine) and assessment of its anti-oxidant effect using biochemical markers as tissue malondialdehyde (MDA) and SOD and investigated its anti-inflammatory effect by measuring serum TNF-α and IL-1β. Changes in the heart rate were recorded during different periods and histopathological examination of the renal tissue was also done.

2. Material and methods

2.1. Animal grouping

A total of 40 healthy male wistar rats weighing between 200–250 gm were housed in separate cages in temperature- adjusted room with 12 h. light/dark cycle. They were adapted to the new atmosphere for one week before experiment and all animals had free access to water. The study protocol was permitted by the Institutional Reviewer Board of Faculty of Medicine, Cairo University and the animal experiments were done in agreement with the ethical guidelines of animal welfare. We randomly divided them into five groups, 8 rats in each group. Group I: control group, received normal saline. Group II: sham-operated, where isolation of left anterior descending (LAD) was performed but with no ligation and the rats received only normal saline. Group III: (I/R, untreated) in which myocardial I/R was induced after thoracotomy, by ligating LAD for 30 min, then followed by deligation and reperfusion for 2 h. Group IV (DEX before): in which Dexmedetomidine (Precedex 200 μg/2 ml, Hospira®, Illinois, USA) was injected at a dose of 100 μg/Kg by intraperitoneal (I.P.) route 30 minutes earlier than induction of ischaemia [13,14]. Group V (DEX after): in which rats received DEX at a dose of 100 μg/Kg I.P after ischaemia (5 minutes from the beginning of reperfusion). The timing of giving DEX 5 min after reperfusion was taken from a previous study investigating its effect on renal ischaemia by Gonullu et al. [14].

2.2. Experimental design

2.2.1. Myocardial ischaemia reperfusion

Rats were anesthetized with 100 mg/kg of ketamine hydrochloride (sigma-Aldrich, Inc, Canada) I.P. A cannula was introduced in the trachea for positive-pressure ventilation using room air. All animals were artificially ventilated with a standard tidal volume ventilation protocol. After shaving the chest, it was opened through a midline incision, the pericardium was incised and a loose 6/0 braided prolene suture was placed around the left anterior descending coronary artery (LAD) for 30 min in groups III, IV and V to induce ischaemia. The ends of the suture were threaded through a propylene tube to form a snare, to facilitate the successive removal of the suture to start reperfusion for 120 min. The body temperature was maintained throughout the experiment by using a heating pad and heat lamps. Subcutaneous electrocardiogram (ECG) leads (Suzuken, Kenz - ECG-102) placed in the rat's limbs to allow measurement of heart rates [15].

2.2.2. Biochemical studies

Following 2 hours of reperfusion, blood was withdrawn. The whole blood was centrifuged at 3500 rpm for 15 min, then we separated the serum and stored it at -20 °C for further biochemical studies to measure urea, creatinine, TNF α and IL-1β. Rats were then sacrificed. The left kidney was instantly fixed with 10% neutral buffered-formalin solution for 2 h at 20–25 °C, dehydrated, then embedded in paraffin for further histopathological analysis. The right kidney was snap frozen at -80 °C and used for determination of tissue MDA and SOD.

2.2.2.1. Measurement of serum urea and creatinine. Serum urea and creatinine levels were estimated using a commercial kit in an autoanalyzer. The results were expressed as mg/dl.

2.2.2.2. Measurement of serum TNF-α and IL-1β. Serum levels of IL-1β and TNF-α were evaluated using enzyme-linked immunosorbent assay [ELISA] Kit (Biomed, Diepenbeek, Belgium), based on the manufacturer's instructions and the values were presented as pg/ml.

2.2.2.3. Measurement of tissue MDA. MDA levels in the renal tissue homogenate were determined spectrophotometrically according to the protocol of Van Ye et al. [16] using thiobarbituric acid reactive substances (TBARS) assay kit from Zepto Metrix Inc. (USA). Values were expressed as nmol/mg protein.

2.2.2.4. Measurement of tissue SOD. The activities of SOD in the renal tissue homogenate were determined spectrophotometrically as previously described by Xie et al. [17], with the use of commercial SOD assay kits (Nanjing jiancheng Bioengineering, China). The results were expressed as U/mg protein.

2.2.3. Histopathological examination

Kidney tissue samples were kept in 10% neutral buffered formalin, embedded in paraffin, sectioned and lastly stained by hematoxylin and eosin (H & E), according to Bancroft et al. [18]. The EGTI (Endothelial, Glomerular, Tubular, and Interstitial) scoring system is created exactly for animal research on renal tissue in the setting of injury (Table 1). The scoring system entails histological damage in four discrete components: Endothelial, Glomerular, Tubular, and Interstitial. EGTI scoring was applied in both the intact and injured parts of the renal cortex [19].

Table 1
The EGTI histology scoring system.

Tissue type	Damage	Score
Tubular	• No damage	0
	• Loss of Brush Border (BB) in less than 25% of tubular cells • Integrity of basal membrane	1
	• Loss of BB in more than 25% of tubular cells, Thickened basal membrane	2
	• (Plus) Inflammation, Cast formation, Necrosis up to 60% of tubular cells	3
	• (Plus) Necrosis in more than 60% of tubular cells	4
Endothelial	• No damage	0
	• Endothelial swelling	1
	• Endothelial disruption	2
	• Endothelial loss	3
Glomerular	• No damage	0
	• Thickening of Bowman capsule	1
	• Retraction of glomerular tuft	2
	• Glomerular fibrosis	3
Tissue type	Damage	Score
Tubulo/Interstitial	• No damage	0
	• Inflammation, Hemorrhage in less than 25% of tissue	1
	• (Plus) necrosis in less than 25% of tissue	2
	• Necrosis up to 60%	3
	• Necrosis more than 60%	4

EGTI: Endothelial, Glomerular, Tubular, and Interstitial.

2.2.4. Measurement of heart rate

The rats' heart rate (HR) values were recorded from the ECG monitoring and compared among groups at the following time points; HR1. base line; HR2. start of ischemia; HR3. End of ischemia and start of reperfusion; HR4. 30 min after reperfusion; HR5. 60 min after reperfusion.

2.3. Statistical analysis

Data were coded and analyzed using the program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA, version 24). We presented the data as mean and standard deviation for quantitative variables. When we compared between groups, we used analysis of variance (ANOVA) with multiple comparisons post hoc test. *P*-values were considered as statistically significant if less than 0.05.

3. Results

In all the results, rats of sham-operated group (group II) did not show any significant change in all the tested parameters compared with control group (group I).

3.1. Biochemical results (Table 2)

3.1.1. Serum urea and creatinine

In comparison to control and sham-operated groups, I/R group was associated with significantly higher levels of serum urea and creatinine ($P < 0.05$). On the other hand, there was no significant difference in urea and creatinine between group IV (DEX before) and group V (DEX after) ($P > 0.05$). Meanwhile, both groups were significantly lower than group I/R ($P < 0.05$).

3.1.2. Serum TNF-α and IL-1β

The I/R group showed a significant rise in serum TNF-α and IL-1β levels compared to both control and sham operated groups ($P < 0.05$). DEX given before ischaemia significantly reduced both the serum TNF-α and IL-1β levels compared to the I/R group ($P < 0.05$). Meanwhile, when DEX was received after ischaemia, it did not demonstrate any significant changes from I/R group ($P > 0.05$). In both TNF-α and IL-1β, results of the DEX after group showed significant change from the (DEX before) group.

3.1.3. Tissue SOD

In the I/R group, there was significant decrease in tissue SOD activity compared to both control and sham-operated groups ($P < 0.05$). DEX administration before ischaemia significantly improved the SOD activity in the kidney compared to the I/R group ($P < 0.05$). Meanwhile, DEX given after ischaemia had no significant changes from I/R group ($P > 0.05$).

3.1.4. Tissue MDA

MI/R caused a significant increase in tissue MDA levels compared with both control and the sham-operated groups ($P < 0.05$). DEX given before ischaemia statistically decreased the MDA levels compared to the I/R group ($P < 0.05$). Unfortunately, administration of DEX after ischaemia failed to cause any significant changes compared to I/R group. There was significant difference between the results of the (DEX before) and the (DEX after) groups.

3.2. Histopathological findings

3.2.1. Control and sham groups

The renal cortex of the control and sham groups looked normal, showing complete brush border of the tubular cells with no thickening of the basal membrane. No evidence of inflammation or necrosis could be detected (Tubular score 0) fig.1A. There was no abnormality within the interstitial compartment (Interstitial score 0) fig.2A. The blood vessels showed an even endothelium with no bulge or disruption of the endothelial cells (Endothelial score 0) fig. 3A. The glomerulus looked complete with thin walled Bowman's capsule and no tuft retraction (Glomerular score 0) fig. 4A.

3.2.2. I/R group

Renal cortex of the I/R group showed varying degrees of damage after ischaemia/reperfusion in rats. Renal tubules showed coagulative necrosis, epithelial lining and interstitial cellular compartments. Intratubular albuminus casts were seen (Tubular score 4) fig 1B. The renal blood vessel showed loss of endothelial lining and perivascular edema (Endothelial score 3) fig 2B. Glomeruli showed retraction of capillary tufts and widening of Bowman's space (Glomerular score 2) fig 3B. Inflammatory reaction presented as congestion of blood capillaries and mononuclear cell infiltration of the interstitial compartment associated with necrosis up to 60% of the cells (Interstitial score 3) fig 4B.

3.2.3. DEX before group

In the DEX before group, renal cortex exhibited different degrees of damage after 30 minutes ischaemia then reperfusion in rats. Renal tubules showed loss of Brush Border (BB) in less than 25% of tubular cells with integrity of basal membrane (Tubular score 1) fig 1C. The renal blood vessel showed endothelial disruption (Endothelial score 2) fig 2C. Glomeruli showed thickening of Bowman capsule with mild hypercellularity of glomerular tufts (Glomerular score 1) fig 3C. Inflammation and haemorrhage were seen in less than 25% of tissue (Interstitial score 1) fig 4C (see Fig. 1).

3.2.4. DEX after group

In the DEX after group, renal cortex presented variable degrees of injury due to ischaemia reperfusion injury (IRI) rats. Renal tubules showed Loss of Brush Border (BB), cast formation, necrosis up to 60% of

Table 2
Serum urea, creatinine, TNF-α, IL-1β and tissue SOD, MDA in the different studied groups.

Group	Control	Sham	I/R	DEX before	DEX after
Tissue SOD (u/mg protein)	3.09 ± 0.90	3.10 ± 0.92	0.56 ± 0.07 [*,#]	1.71 ± 0.36 [$]	0.6 ± 0.0 9
Tissue MDA (nmol/mg protein)	1.03 ± 0.02	1.02 ± 0.01	13.72 ± 0.59 [*,#]	3.45 ± 0.93 [$]	12.78 ± 3.31 [@]
Serum TNF-α (pg/ml)	31.53 ± 1.05	30.91 ± 0.98	140.92 ± 7.9 [*,#]	61.51 ± 5.78 [$]	130.74 ± 4.1 [@]
Serum IL-1β (pg/ml)	29.32 ± 1.75	28.79 ± 1.49	114.19 ± 7.8 [*,#]	71.82 ± 6.67 [$]	106.59 ± 5.5 [@]
Serum creatinine (mg/dl)	0.19 ± 0.04	0.17 ± 0.05	1.15 ± 0.26 [*,#]	0.27 ± 0.07 [$]	0.43 ± 0.12 [$]
Serum urea (mg/dl)	42.22 ± 1.73	42.59 ± 2.86	78.09 ± 2.91 [*,#]	51.91 ± 5.14 [$]	52.41 ± 7.3 [$]

Values are presented as mean ± SD.

I/R, ischemia reperfusion; DEX, dexmedetomidine; SOD, superoxide dismutase; MDA, Malondialdehyde; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta.

[*] Statistically significant compared to corresponding value in control group ($P < 0.05$).

[#] Statistically significant compared to corresponding value in sham group ($P < 0.05$).

[$] Statistically significant compared to corresponding value in I/R group ($P < 0.05$).

[@] Statistically significant compared to corresponding value in DEX before group ($P < 0.05$).

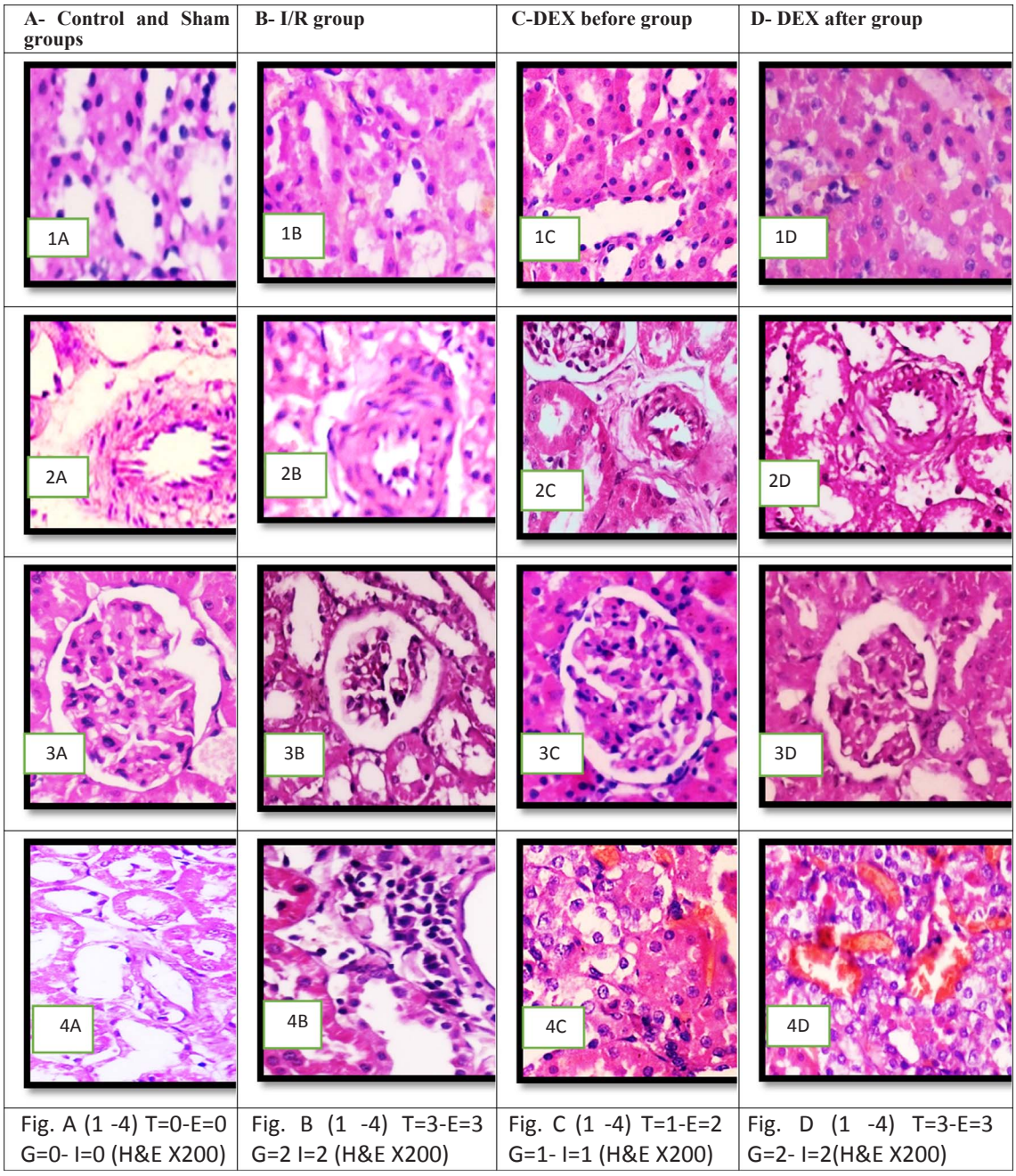

Fig. 1. Histopathological findings in the different studied groups.

tubular cells (Tubular score 3) fig 1D. The renal blood vessel showed loss of endothelial lining and perivascular edema (Endothelial score 3) fig 2D. Glomeruli showed thickening of Bowman capsule retraction of capillary tufts (Glomerular score 2) fig 3D. Inflammation, congestion of blood capillaries, hemorrhage and tubular necrosis were seen in less than 25% of tissue (Interstitial score 2) fig 4D.

3.3. Effect of dexmedetomidine on heart rates

As shown in Fig. 2, in I/R group, there was an initial significant increase in HR in comparison to sham and control groups at HR2 (326.1 ± 7.0) followed by highly significant decrease at the end of ischemia (HR3) (202.5 ± 7.3) ($P < 0.01$), then showed a significant increase again during reperfusion (HR4 and HR5) ($P < 0.05$). Dexmedetomidine in DEX before group showed statistically significant reduction in HR at HR2 (214.6 ± 7.3) ($P < 0.01$) as a direct effect on the heart then decreased the HR again at HR3 (176.3 ± 6.3) as a reflection to ischemia. Finally, Dexmedetomidine when given 5 min after reperfusion (HR4), showed statistically reduction in HR as expected (184.0 ± 6.9) ($P < 0.01$), when compared to other groups.

4. Discussion

The ischaemia reperfusion process occurring in cardiac surgeries as cardiopulmonary bypass most probably causes distant organ damage [13]. Renal damage is considered serious complication of coronary revascularization and may cause postoperative morbidity and mortality and a prolonged hospital stay [20]. To our knowledge, this is the first study to investigate the reno-protective effect of dexmedetomidine against renal damage induced by myocardial I/R following ligation of the left ascending coronary artery for 30 minutes then reperfusion for two hours. We compared the effects of DEX in the same dose at two

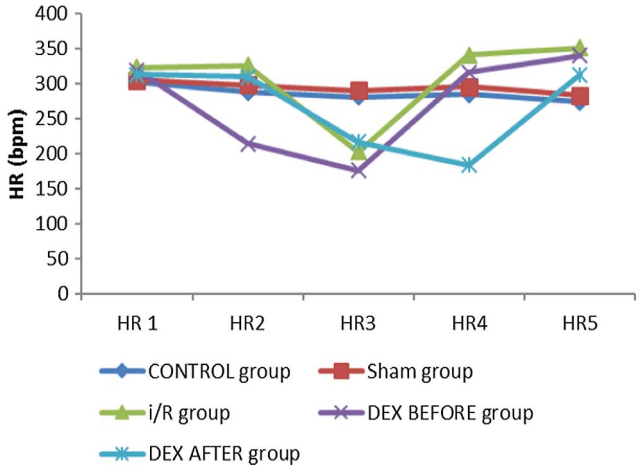

Fig. 2. The effects of dexmedetomidine infusion on heart rate during the study period. HR1, base line; HR2, start of ischemia; HR3, End of ischemia and start of reperfusion; HR4, 30 min after reperfusion; HR5, 60 min after reperfusion. In I/R group, there was an initial significant increase in HR in comparison to sham and control groups at HR2 (326.1 ± 7.0) followed by highly significant decrease at end of ischemia (HR3) (202.5 ± 7.3) ($P < 0.01$), then showed a significant increase again during reperfusion (HR4 and HR5) ($P < 0.05$). DEX before group showed significant reduction in HR at HR2 (214.6 ± 7.3) ($P < 0.01$) then decreased the HR again at HR3 (176.3 ± 6.3). Finally, DEX when given 5 min after reperfusion (HR4), it showed significant reduction in HR (184.0 ± 6.9) ($P < 0.01$), when compared to others.

different timings, either before or after ischaemia on several parameters.

In our experimental study, rats of sham-operated group (group II) did not show any significant changes in all the tested parameters compared with control group (group I). Myocardial I/R caused severe renal dysfunction. This was reflected in our study by a significant increase in the serum levels of urea and creatinine in the I/R group when compared to the control and sham groups. Moreover, it caused significant elevation in serum IL-1β and TNF-α compared to both sham-operated and control groups. The MI/R group showed also significant increase in renal tissue MDA levels compared to control and sham groups. Similarly, Parlakpinar et al. [21] and Ozer et al. [22] found elevated renal MDA levels after induction of myocardial ischaemia for 30 minutes and followed by 120 minutes of reperfusion and found also severe renal damage during histological examination. Moreover, in the I/R group, in our study, we found decrease in renal SOD activity.

The renal damage due to MI/R may be a direct cause of ischaemia and hypoperfusion. This may be explained by the fact that renal ischaemia initiates a series of events that can ultimately lead to cellular dysfunction and necrosis as reduced renal blood flow, tubular endothelial injury and renal tubular blockage [23]. Ischaemia can also promote expression of proinflammatory genes and suppress protective genes. Therefore, it induces a pro-inflammatory state. However, coronary revascularization can paradoxically create more tissue damage by its injurious effects on renal function including renal emboli; whether microembolus or macroembolus, release of hemoglobin from ruptured RBCs, elevated levels of catecholamines, abnormal renal function, inflammatory reactions and release of inflammatory mediators of the ischaemic tissue into the systemic circulation with disturbed cell metabolism [24]. During the period of IR injury, cells produce inflammatory cytokines as IL-1β, IL-8, TNF-α and so on, with increased expression of vascular adhesion molecules (VAM). These in turn mediate adhesion of leukocytes to the endothelium [25]. Experimental studies whether human or animal have been conducted on this subject [26,27]. Vasoactive mediators as eicosanoids and nitric oxide may also be responsible for I/R damaging effects.

However, in endogenous or exogenous renal injury such as MI/R, apoptosis is considered an important factor in the pathophysiology of I/R injury. These factors may increase reactive oxygen species (ROS), also known as free radicals, prominently in the kidneys. ROS are considered the main step in the reperfusion injury, which if excessively produced may cause acute renal damage. Oxygen free radicals (FR) in a damaged tissue are produced from various sources such as the xanthine oxidase system, activated neutrophils, mitochondrial electron transport chain, and arachidonic acid pathways [28]. The structures which are most sensitive to FR in the cells are membrane lipids, proteins and deoxyribonucleic acids. ROS-induced lipid peroxidation is responsible for I/R injury in all body organs. Cytotoxicity may be a contributing factor of the reperfusion injury due to rapid restoration of the acidotic pH of ischaemic phase to normal physiological pH of reperfusion [29].

In the current study, group IV (Dex before) and group V (Dex after) showed significant decrease in serum urea and creatinine compared to I/R group but without significant difference between both groups. Si et al. [30] concluded that, DEX could save the kidneys from I/R injury. Our results also went hand in hand with those of Liu et al. [31] who found that DEX improved renal functional recovery and decreased serum creatinine levels in rats.

Moreover, our results showed that only dexmedetomidine before ischaemia, significantly lowered serum levels of pro-inflammatory cytokines (TNF-α and IL-1β) compared to the I/R group. These findings were previously supported by the studies of Ammar et al. [1] in patients and Zhang et al. [32] in rats. Similarly, our results showed that only dexmedetomidine given before ischaemia significantly reduced levels of MDA, when compared to I/R group. MDA is an important end product of lipid peroxidation. Plasma and tissue levels of MDA are considered golden markers of the oxidative stress and the systemic response that follow I/R [33]. Cakir et al. [34], similarly noticed that DEX before ischaemia succeeded to lower renal MDA levels. As for the tissue SOD, Dex administration before ischaemia succeeded to increase the activity of SOD compared to I/R group. Whereas, DEX after ischaemia failed to attenuate the increases of TNF-α and IL-1β. Similarly, it did not reduce renal MDA concentration or increase SOD activity, when compared to myocardial I/R group.

These findings coincide with those of Zhang et al. [32] who found that different timings of dexmedetomidine administration affected its results. When given before ischaemia, it decreased the intestinal I/R insult in a dose-dependent manner and is therefore critical for intestinal protection. However, the initiation of dexmedetomidine after ischaemia, operation or in the ICU, produced no beneficial effect. Our results seem to be similar also to previous investigations studying the effects of dexmedetomidine on myocardial I/R injury in which dexmedetomidine given before induction of ischemia can help significantly to reduce the size of myocardial infarct in rats [35]. On the contrary, giving dexmedetomidine after ischaemia, at the beginning of reperfusion in the same dose increased the myocardial infarct size and failed to protect the cardiac muscle against I/R injury [36]. Similar studies done previously on the intestine showed that early reperfusion, not more 3 min is critical and can cause intestinal protection [37,38]. All these findings suggested that, although the exact mechanisms are not clear, the timing of treatment in relation to perfusion is critically important for protection against I/R injury.

Regarding the histopathological findings, administration of DEX before ischaemia, improved the renal damage as shown by the EGTI scoring system. A histopathologic study was done by Kocoglu et al. [39] to study the effects of dexmedetomidine on kidney I/R injury in rats. Their results confirmed that treatment with dexmedetomidine could improve the histopathologic findings that may associate renal I/R injury, and the authors concluded that dexmedetomidine is useful in improving the tolerance of the kidney against I/R injury. Also, Si et al. [40] proved that dexmedetomidine ameliorated the histopathological findings of the kidneys exposed to I/R and attenuated renal damage.

The protective mechanism of dexmedetomidine against ischaemia/reperfusion is not clearly identified. However, dexmedetomidine might cause renal protection by inhibiting inflammatory reaction [41]. Similar studies have demonstrated that dexmedetomidine could minimize

the effects of I/R injury in several organs, which was thought to be due to its anti-oxidant and anti-inflammatory properties [42,11]. İnci et al. [43] concluded that dexmedetomidine infusion can prevent the increase in ROS during mesenteric I/R injury in rats.

DEX was proved to increase the expression of the tight junction protein; zonula occludens-1(ZO-1) and occludin which confer renal protection [31]. Tight junctions are considered the key structures for good functioning of the epithelial cells, the process of renal development and nephron formation [44]. Ischemia-reperfusion injury is the main reason for acute kidney injury, altering the assembly of tight junction, initiating apoptosis and disturbing renal tubular cell. Similarly, Engelhard et al., [45] proved that DEX had anti apoptotic effect after partial cerebral ischaemia reperfusion in rats.

Khajuria et al. [46] explained the reno-protection of dexmedetomidine through α 2 receptor with subsequent initiation of phosphoinositide- 3 kinase (PI3K) that activated antiapoptotic proteins such as B-cell lymphoma 2 (BCL-2) and BCL-xl and therefore decreased renal cell death and high-mobility group protein B-1 (HMGB-1) release and inhibition of toll-like receptor 4 (TLR4) signaling. Moreover, it suppressed Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway which is involved in signal transduction for a number of cytokines. A Similar experimental study on rats noticed that dexmedetomidine reduced apoptosis through suppression of injury-mediated activation of JAK/STAT signaling pathway [40].

Another postulated renoprotective mechanism is that dexmedetomidine as an α2 receptor agonist could sustain or preserve renal medulla blood flow [47]. Also, it activates the adrenergic receptors on presynaptic membrane of central and peripheral sympathetic nerve, hence reducing the stress induced by surgery and plasma levels of catecholamines and inhibit ischaemia-induced release of noradrenaline [52]. Thus, it reduced release of presynaptic noradrenaline so minimized the complications of norepinephrine-induced vasoconstriction [48].

Regarding the effect of DEX on HR in our study, it was clear that DEX showed statistically significant reduction in HR at HR2 in DEX before group and again when given 5 min after reperfusion (HR4) in DEX after group. This is due to the fact that DEX inhibited sympathetic activity, thus induced decrease in heart rate [32]. Halaszynski et al. [49] found that DEX preserved hemodynamic and redistributed cardiac output in the conditions of reduced blood volume, thus maintained the perfusion to vital organs especially renal blood flow.

Taken together, our biochemical, histopathological and hemodynamic results help to hypothesize an anti-oxidant and anti-inflammatory caring properties for dexmedetomidine against renal damage during myocardial I/R injury in rats

5. Conclusion

Our study showed that perioperative use of dexmedetomidine reduced renal injury induced by myocardial ischemia reperfusion in rats. Dexmedetomine improved kidney function, attenuated proinflammatory cytokines (TNF-α and IL-1β), exerted anti-oxidant effects and prevented remarkable morphological alterations in kidney tissue. Taken together, our data indicate that dexmedetomidine may be helpful in reducing renal injury, as an example of a distant organ damage following myocardial I/R injury. This is most probably attributed to its antioxidant and anti-inflammatory effects. However, A limitation of this study is that we did not measure the blood pressure as another haemodynamic parameter in addition to the HR. Different doses of dexmedetomine could be used to study the dose- effect relationship in the future.

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Conflict of interest

The authors declare that they have no conflict of interest.

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