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EXPERIMENTAL STUDY

Effect of dexmedetomidine on erythrocyte deformability during ischemia-reperfusion injury of liver in diabetic rats

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Abstract: *Aim:* The aim of this study is to evaluate the effect of dexmedetomidine on erythrocyte deformability during IR injury of liver in diabetic rats.
Methods: Twenty- eight Wistar Albino rats were included in the study after a 4 week streptozocin (65 mg/kg) treatment to observe the existence of diabetes. The animals were randomly assigned to one of the four experimental groups: GroupC and DC (sham-control group): The abdomen was dissected with a median laparotomy and the liver was collected. GroupDIR: The liver was collected after IR following the abdominal median laparotomy. GroupDIRD: The liver was collected after IR following the abdominal median laparotomy and 30 min of infusion of dexmedetomidine 100 μg/kg ip
The deformability measurements were performed in erythrocyte suspensions containing Htc 5% in PBS buffer.
Results: The deformability index was significantly increased in diabetic rats, however it was similar in the GroupC and DIRD. It was significantly increased in the GroupDIR when compared to the GroupC, DIRD and DC. The relative resistance was increased in IR models.
Conclusion: Erythrocyte deformability was damaged in rats having diabetes and IR injury. This injury might lead to further problems in microcirculation. It was shown that dexmedetomidine may be useful in enhancing the adverse effects of this injury *(Tab. 1, Fig. 2, Ref. 41)*. Full Text in PDF *www.elis.sk.*
Key words: erythrocyte deformability, ischemia reperfusion, α_2 agonist, experimental diabetes, dexmedetomidine, rat.

In the recent two or three decades, the prevalence of diabetes mellitus (DM) has rapidly increased throughout the world, with the estimation that it will increase by 200 % in the next several decades (1–4). As a result, physicians will be encountered with an increasing population of diabetic patients undergoing anesthesia and surgery and also the patients may have serious complications, such as hypertension, ischemic heart disease in association with significant increases in length of stay and mortality rates in hospital, as well as nephropathy, and autonomic neuropathy (1–3). Moreover, the diabetics have as much as two to three fold higher frequency of cardiovascular disorders and three times higher mortality rates in comparison to the healthy population (4). Thus, a more careful perioperative care is necessary for these patients (5).

Previous clinical and experimental studies have investigated several aspects of hepatic ischemia – reperfusion (I/R) injury, which is a common problem in trauma, hepatic surgery, and transplantation. (6–9). Intraoperative temporary interruption of liver blood flow and subsequent reperfusion during surgical procedures can lead to liver dysfunction or severe hepatic failure, depending on the severity and duration of the ischemia (9).

Many tissues and cells can be damaged by free radicals, with red blood cells (RBC) being one of the most susceptible. During I/R, the increased oxidative stress (OS) can cause an augmented RBC membrane lipid peroxidation with the consequent alteration of cellular deformability. Erythrocyte deformability is of crucial importance for the maintenance of normal circulation as it facilitates the passage of RBC through narrow capillaries in the microcirculation and reduces blood viscosity at high shear rates in large blood vessels (10).

Hemorheological parameters, which include (but are not limited to) hematocrit, plasma proteins, erythrocyte aggregation, and erythrocyte deformability in DM, are often disturbed (11).

Several drugs in anesthesia have been used to prevent I/R injury, including sevoflurane, dexmedetomidine, isoflurane, ketamine (9, 12–14).

Dexmedetomidine, a selective and potent α2-adrenoceptor agonist, was approved by the U.S. Food and Drug Administration in 1999 for sedation of patients hospitalized in intensive care settings. Since then, a growing number of research articles have emerged and reported other possible indications, such as regional and general anesthesia (15, 16). Dexmedetomidine was reported to be effective in protection against focal ischemia in rabbits, in cardiac I/R injury in rats in kidney I/R injury in rats, and in incom-

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plete forebrain ischemia in rats (12, 17–19). Despite its increased clinical use, especially, in critically ill patients, the effect of dexmedetomidine on liver I/R injury has not been investigated yet (20).

The primary aim of this study was to investigate the deformability changes and the preventive role of dexmedetomidine against them in erythrocytes of diabetic rats on an experimental model of hepatic I/R injury.

Materials and methods

Animals and experimental protocol

This study was conducted in the Physiology Laboratory of Kirikkale University upon the consent of the Experimental Animals Ethics Committee of Kirikkale University. All of the procedures were performed according to the accepted standards of the Guide for the Care and Use of Laboratory Animals.

In the study, 28 male Wistar Albino rats weighing between 250 and 300 g, raised under the same environmental conditions, were used. The rats were kept under 20–21 °C at cycles of 12-hour daylight and 12-hour darkness and had free access to food until 2 hours before the anesthesia procedure. The animals were randomly separated into the four groups, each containing 7 rats.

Diabetes was induced by a single intraperitoneal injection of streptozotocin (Sigma Chemical, St. Louis, MO, USA) at a dose of 65 $mg.kg^{-1}$ body weight. The blood glucose levels were measured at 72 h following this injection. Rats were classified as diabetic if their fasting blood glucose (FBG) levels exceeded 250 $mg.dl^{-1}$, and only animals with FBGs of > 250 $mg.dl^{-1}$ were included in the diabetic groups (diabetes only, diabetes plus ischemia-reperfusion and diabetes plus Dexmedetomidine-ischemia-reperfusion). The rats were kept alive for 4 weeks after the streptozotocin injection to allow development of chronic diabetes before they were exposed to ischemia-reperfusion (21). The rats were weighed before the study.

Rats were anesthetized with the intraperitoneal ketamine 100 $mg.kg^{-1}$. The chest and abdomen were shaved and each animal was fixed in a supine position on the operating table. The abdomen was cleaned with 1 % polyvinyl iodine and when dry, the operating field was covered with a sterile drape and median laparotomy was performed. There were four experimental groups (Group C (sham-control; n=7), (Group DC (diabetes-sham-control; n=7), Group DI/R (diabetes-ischemia-reperfusion; n=7), and Group DI/R-D (diabetes- ischemia-reperfusion -Dexmedetomidine; n=7).

The abdomen was dissected with a median laparotomy and the liver was collected in all groups. Sham operation was performed on the rats in Group C and Group DC. The sham operation consisted of mobilization of the hepatic pedicle only. The rats in this group were sacrificed 90 min after the procedure. Hepatic I/R injury was induced in Groups DI/R and DI/R-D respectively with a hepatic pedicle clampage using a vascular clamp as in the previous study of Yaylak et al (8). After an ischemia period of 45 min, the vascular clamp was removed. A reperfusion period was maintained for 45 min. In Group DI/R-D, dexmedetomidine hydrochloride 100 $mg.kg^{-1}$, (Precedex 100 µg/2 ml, Abbott®, Abbott Laboratory, North Chicago, Illinois, USA) was administrated via intraperitoneal route 30 minutes before clampage (22).

All the rats were given ketamine 100 $mg.kg^{-1}$ intraperitoneally and intracardiac blood samples were obtained. Heparinized total blood samples were used to prepare erythrocyte packs. Deformability measurements were done using erythrocyte suspensions with 5 % hematocrit in phosphate buffered saline (PBS) buffer.

Deformability measurements

Blood samples were taken very crefully and the measurement process was as fast as possible to avoid hemolysis of erythrocytes. The collected blood was centrifuged at 1000 rpm for ten minutes. Serum and buffy coat on erythrocytes were removed. Isotonic PBS buffer was added to collapsing erythrocytes and this was centrifuged at 1000 rpm for ten minutes. Liquid on the upper surface was removed. Finally pure red cell packs were obtained from the washing process, which was repeated three times. Erythrocytes packs were mixed with PBS buffer to generate a suspension with the value of 5%Htc. Those erythrocyte suspensions were used for the measurement of deformability. Collection and deformability measurements of erytrocytes were done at 22 °C.

The constant-current filtrometre system was used for the measurement of erytrocytes deformability. Samples to be measured were prepared as 10 ml of erytrocytes suspension and PBS buffer. The flow rate was held constant at 1.5 ml/min with an infusion pump. A 28 mm nucleoporin polycabonate fitler with a 5 µm pore diameter was prefered. The changes in pressure while the erythroctes were passing through the filter were detected by the pressure transducer and the data was transferred to computer with the help of MP 30 data equation systems (Biopac Systems Inc, Commat, USA). The necessary calculations were performed with the related computer programs by measuring the pressure changes at various times. The pressure calibration of the system was performed each time before measuring the samples. At first, buffer (P_T) and then erythrocytes (P_E) passed through the filtration system and the changes in pressure were measured. The relative refractory period value (Rrel) was calculated by relating the pressure value of erythroctes suspension to pressure value of buffer. An increase in Rrel as the deformability index was interpreted as the adverse effect on erythrocytes deformability (23, 24).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) 12.0 programm was used for statistical analysis. The variations in blood glucose level, erythrocyte deformability and rat weight between the study groups were assessed by using the Kruskal–Wallis test. The Bonferroni adjusted Mann–Whitney U test was used after the significant Kruskal–Wallis to determine, which group differs from the other. The results were expressed as the mean± standard deviation (Mean ± SD). Statistical significance was set at the p value <0.05 for all analysis and $p< 0.033$ (0.1/3) for the Bonferroni adjusted Mann–Whitney U.

Results

During the study period, 4 of the diabetic rats died (2 in the Group DC, 1 in the Group DIR, and 1 in the Group DIR-D).

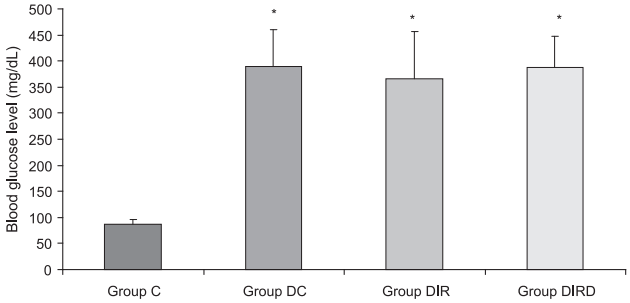

Fig. 1. Blood glucose level of the groups. Each bar represents the mean ± SD. * p<0.05 compared to the Group C.

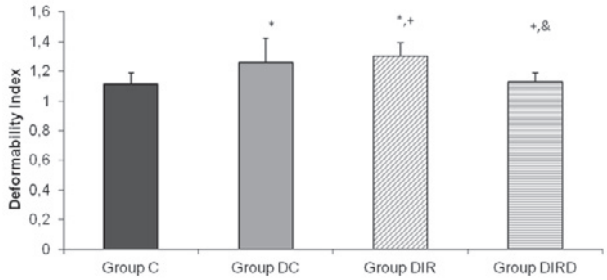

Fig. 2. Erythrocyte deformability values of the groups. Each bar represents the mean ± SD. * p<0.05 compared to the Group C; + p< 0.05 compared to the Group DC; & p< 0.05 compared to the Group DIR.

Blood glucose measurements were 87.4 ± 8.1, 389.3± 71.6, 366.3 ± 89.7, 386.9 ± 61.2 mg /dL for the Group C, DC, DI/R and DI/R-D, respectively (Fig. 1). Serum glucose was detected to be significantly lower in the Group C, when compared to the Groups DC, DI/R and DI/R-D (p=0.001, p=0.002, p=0.001, respectively).

There was no statistically significant difference observed in body weights of rats at the beginning of the study between the groups. Rats' weight measurements were 305.0 ± 12.6, 181.7± 13.7, 188.6 ± 18.9, 185.2 ± 14.8 g for the Group C, DC, DI/R and DI/R-D, respectively (Tab. 1). The weight measurements were significantly higher in the Group C in comparison to the Groups DC, DI/R and DI/R-D (p=0.002, p=0.004, p=0.004, respectively).

Deformability index was significantly increased as a result of induced DM in the Groups DC, DI/R and DI/R-D when compared to the Group C (p=0.007). I/R augmented the relative resistance, which was an indicator of rat erythrocyte deformability (p=0.001). Deformability indices were found to be similar in the Group C and Group DI/R-D (p=0.225). However, it was significantly higher in the Group DI/R in comparison to the Group C, Grup DC and the Group DI/R-D (p=0.002, p=0.025, p=0.001, respectively) (Fig. 2).

Discussion

Diabetes mellitus (DM) is a metabolic disorder characterized by an abnormally high blood sugar (hyperglycemia) resulting from either low insulin level or insulin resistance at most of the body cells. Diabetes mellitus has a high social and economic importance as the number of the diabetes patients continues to grow at an unprecedented rate throughout the world (25).

We induced diabetes by an injection of a single dose of 65 $mg.kg^{-1}$ STZ in 20 mM of sodium citrate buffer solution stored on ice, via the intraperitoneal (ip) route (26). Following the induction of diabetes, 4 of the rats died. In literature, we found that STZ has been used at two different doses in two recent publications (27). In one of these studies, 60 $mg.kg^{-1}$ STZ buffered in 0.1 M citrate (pH: 4.5) was injected and the rats were grouped according to the blood glucose levels measured after 72 hr, so that rats with a blood glucose level > 350 $mg.dL^{-1}$ were included in the study (27). In the other study, the investigator used 50 $mg.kg^{-1}$ STZ and studied the rats with a blood glucose level >250 $mg.dL^{-1}$ (28). The cause of death of four rats in our study may bea higher dose (65 $mg.kg^{-1}$) of STZ. Therefore, it is possible that lower doses of STZ might have been adequate for diabetes induction.

Hemorheological parameters, such as; hematocrit, plasma proteins, erythrocyte aggregation, and erythrocyte deformability; are often disturbed in DM (29). For the migration of oxygen and vital molecules to the final organ capillaries and clearance of metabolic wastes, erythrocytes must be able to extend and curve and have the capability to move in these areas. This capacity, termed as "deformability" becomes more important in microcirculation. Altered erythrocyte deformability not only changes the oxygen delivery capacity of the erythrocytes but also the survival of the circulating erythrocytes (30–32).

Additionally, it has been suggested that the impaired perfusion at the tissue level observed as a complication of diabetes mellitus is primarily due to the reduced erythrocyte deformability (33, 34). Besides, metabolic changes and tissue perfusion due to cardiovascular problems may lead to an inadequate recovery in plasma viscosity (35).

Cho et al demonstrated that blood viscosity significantly increased in diabetes. These results suggest that the consequent elevation of glucose in the blood plasma affects primarily RBCs and the vascular endothelial cells, including the walls of capillaries. The impaired glucose tolerance or uncontrolled blood glucose levels often result in microvascular complications of diabetes (11). Moreover, the impairment of erythrocyte deformability is attributed to the specific changes in the membrane structure. The oxidative stress due to high glucose concentrations causes damage to the erythrocyte membrane proteins, even in a relatively short exposure time (36).

Barnes et al (37) showed that erythrocyte deformability was lower in 14 diabetes patients with an extensive micro-angiopathy

Tab. 1. Comparison of body weights at the beginning and end of study.

Weight (g)	Group C (n=7)	Group DC (n=7)	Group DI/R (n=7)	Group DI/R-D (n=7)	P
Beginning	271.42±16.51	278.57±13.75	277.14±15.24	274.24±19.02	0.849
End	305.00±12.60	181.75±13.74*	188.65±18.93*	185.23±14.89*	<0.0001

* p<0.05 compared to the Group C

than in 22 diabetes patients with slight or no complications or in controls. They suggested that hyperviscosity and reduced erythrocyte deformability might well be important and potentially treatable factors in the etiology or progression of microcirculatory disease in diabetes. Similar to the previous studies, we also found that erythrocyte deformability was decreased in diabetes induced rats.

Erythrocyte deformability and erythrocyte membrane rigidity have been reported to be affected by several agents, which induce lipid peroxidation. In this study, dexmedetomidine treatment was shown to have protective effects against hepatic I/R injury induced changes of erythrocyte deformability. Ischemia-reperfusion damage develops when liver blood flow is interrupted, or severely diminished, for a long period of time and then restarted (38).

In this study, for the first time to our knowledge, we have reported that IR of the diabetic rat liver resulted in a significant negative changes of the erythrocyte deformability, and the administration of dexmedetomidine, a highly potent and selective α2-adrenoreceptor agonist, administered at the start of ischemia, can provide a varying degree of protection against negative effects on erythrocyte deformability.

The effect of dexmedetomidine in I/R models depends on several factors, such as the route of administration (intravenous (39), intraperitoneal (12, 19), dosage, type of ischemic tissue or organ, duration and temperature of ischemia, timing of administration (before (12, 19, 22) or after (18) ischemia) and the species itself.

In one of the studies regarding α2 agonists, Belhoula et al (40) reported that the premedication of type 2 diabetic patients with clonidine 90 min before the surgery improved blood glucose control and decreased insulin requirements during ophthalmic surgery, because clonidine decreased circulating catecholamines despite having no effect on cortisol concentrations and GH secretion. However, Venn et al (41) reported that dexmedetomidine, a highly selective and potent α2 agonist, decreased insulin secretion after major surgery without exacerbating the glycemic response. This report suggested that impaired insulin secretion was balanced by a reduced sympathetic activity. At present, it would be reasonable to accept that α2 agonists, such as clonidine or dexmedetomidine, modify insulin secretion without exacerbating the glycemic response.

As a conclusion, the results of this study clearly demonstrated that erythrocyte deformability is significantly altered in experimental hepatic I/R injury in the diabetic rat. This might lead to further problems in microcirculation. Thus, measurement of erythrocyte deformability might have an important impact in follow-up of I/R injury. Additionally, dexmedetomidine administered before induction of ischemia, was observed to have protective effects on these alterations in hepatic I/R injury. Other aspects of these findings including clinical significance and practical applications merit further experimental and clinical investigation.

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