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The Relationship between Liver Dysfunction, Electrocardiographic Abnormalities and Metabolism in Rat

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Abstract

Introduction: Liver disorders may lead to many critical complications such as electrical heart abnormalities. The aim of this study was to investigate the relationship between the severity of liver dysfunctions, electrocardiogram variables and oxygen consumption.

Methods: Female Sprague Dawley rats were divided into 4 groups of sham, partial portal vein ligation (PPVL), common bile duct ligation (CBDL), and combination of them (CBDL+ PPVL). 28 days after the first surgery, animals were anesthetized; ECG recorded and right femoral artery and vein cannulated. Blood gas parameters and complete blood count were measured and the arterial-venous oxygen content difference (A-VO_2) calculated.

Results: QT interval and QTc in the CBDL+PPVL and CBDL groups were longer than those of the sham and PPVL groups. Furthermore, there were abnormal and bizarre T waves in the CBDL and CBDL+PPVL groups. In the CBDL+PPVL group, arterial O_2 pressure was lower while arterial CO_2 pressure and plasma concentration of HCO_3- were higher than those of the other groups. A-VO_2 in the CBDL+PPVL group was also lower than those of the other groups, and in the CBDL group was less than that of the PPVL group.

Conclusions: In this study, we detected bizarre T waves and increased QT interval and QTc in the ECG of cirrhotic rats, which could be partly linked to the severity of liver dysfunction and reduction of metabolism.

Keywords: Cirrhosis; QTc; T wave; Oxygen consumption

Introduction

Liver cirrhosis may lead to cardiac abnormalities with high incidence of sudden death around the world [1-3]. ECG analysis is done to predict the outcome of involved patients [4]. In several investigations, QT prolongation with or without alteration in heart rate have been reported in the patients with cirrhosis [5-7]. Even liver transplantation may not improve the abnormal QT, cardiomyopathy and arrhythmias [2,5,8,9]. In animal models of cirrhosis, prolonged QT interval, decreased PR interval and constant heart rate have been described [10]. However, these studies focus on the changes of QT interval and QTc with little attention to the other electrocardiogram abnormalities.

Chronic liver disorders may decrease the arterial oxygen pressure because either the impairment of gas exchange through respiratory membrane or intrapulmonary shunting caused by pulmonary vasodilation, angiogenesis and arteriovenous communication [11]. The arterial-venous oxygen difference also decreases in liver cirrhosis [12] which may be linked to decreased metabolism of organ tissues [13,14]. However, the relationship between ECG abnormalities and body's metabolism has not been disclosed in cirrhosis yet.

With the above background, in the present study, we investigated effects of three experimental models of liver dysfunctions including partial portal vein ligation, common bile duct ligation, and combination of them on electrocardiogram alterations and right lower limb's oxygen consumption in rat to find out whether or not there is a connection between the severity of liver disorders, ECG abnormalities and the body metabolism.

Materials and Methods

Ethical Clearance

All procedures were approved by the Center for Comparative and Experimental Medicine and the Ethical Committee of Animal Care at our university, according to the provisions of the declaration of Helsinki. Female Sprague-Dawley rats were housed in standard cages under the controlled laboratory temperature, humidity and 12:12 hour's light/dark cycles. They had free access to water and standard food a few days before starting the experiments. Animals were randomly divided into 4 groups of sham, partial portal vein ligation (PPVL), common bile duct ligation (CBDL) and combinations of them (CBDL+PPVL).

Experimental designs and protocols

Experiments were designed in two phases. At the first phase, animals were anesthetized by intraperitoneal injection of 60 mg/kg Ketamine hydrochloride and 10 mg/kg Xylazine [15]. The liver was exposed by blunt dissection of skin, fascia and muscle layers of the upper abdomen. In the PPVL group, portal vein was partially ligated.

In the CBDL group, common bile duct was ligated entirely. These procedures were performed according to the methods of previous studies [16]. In the CBDL+PPVL group, combinations of CBDL and PPVL were carried out. All surgical procedures were achieved under aseptic conditions. Also, in order to rule out effects of diurnal variations on ECG and metabolism [2,17] all experiments were performed during 11am-16 pm. After surgery, conscious animals were returned back to animal house in the cleaned and separated cages, and had free access to water and food.

28 days after the first surgery, animals were anesthetized by intraperitoneal injection of 60 mg/Kg sodium thiopental [18]. 1 ml of tail blood sample was taken in microcentrifuge tubes containing EDTA, centrifuged with 1200 rpm for 3 mins. Plasma was separated and stored at -70 °C in order to measure liver enzymes, direct and total bilirubins and Malondialdehyde (MDA), as an indicator of lipid peroxidation and inflammation. Also, blood was taken for measurement of blood cell counts and hemoglobin concentration. The ECG of lead II was then recorded while animals located on a wooden plate to prevent additional electrical signal which could interfere with our recording. Intervals of RR, JT (distance between S wave and the end of T wave) and QT, durations and voltages of P as well as QRS waves, and heart rate were analyzed by ECG analyzing software of a Power Lab system (AD instruments, Australia) (Figure 3 and Table 2). QT interval was corrected using normalized Bazett's equation $QTc=QT/(RR/f)^{1/2}$, where f is normalization factor according to RR duration in the sham group [19]. Duration of RR was 164.95 ± 4.99 ms corresponded to the heart rate of 367.1 ± 11.45 BPM. As a result, we considered the value of 164 ms in order to normalize the corrected QT. After a steady state period of 30 min, the arterial and venous blood gases were analyzed by blood samples taken from the right femoral artery and vein cannulas. At the end of the experiments, animals were sacrificed under deep anesthesia by intravenous injection of KCl.

Plasma and blood parameters

Plasma was analyzed for aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct and total bilirubins spectrophotometrically using an automated analyzer. Plasma MDA measured by TBARS assay method according the previous studies [15]. Also, blood hemoglobin (Hb) concentration was evaluated by autoanalzing device for hematology. Blood gas variables were assessed by easylyte blood gas analyzer (Medica, USA). The oxygen pressures of arterial (PaO_2) and venous (PvO_2) blood were measured, and the arterial-venous PO_2 differences, arterial (CaO_2) and venous (CvO_2) oxygen contents and arterial-venous O_2 content differences ($A\text{-}VO_2$) calculated and considered as an indicator for O_2 consumption and metabolism.

Statistical analysis

Data are given as mean ± SE. Analysis of variance (ANOVA) with the Tukey post hoc test was used for comparison of the experimental groups. All analysis was performed using the software of SPSS 18. Significance was assumed when P<0.05 and the confidence limits used were the 95% intervals.

Results

Plasma AST in the CBDL+PPVL group was higher than those of the sham, PPVL (p<0.001) and CBDL (p<0.01) groups, and in the CBDL group was more than those of the sham and PPVL groups (p<0.05) (Figure 1a). Furthermore, plasma ALT in the CBDL+PPVL group was more than the ones in the sham and PPVL groups (p<0.01) (Figure 1b).

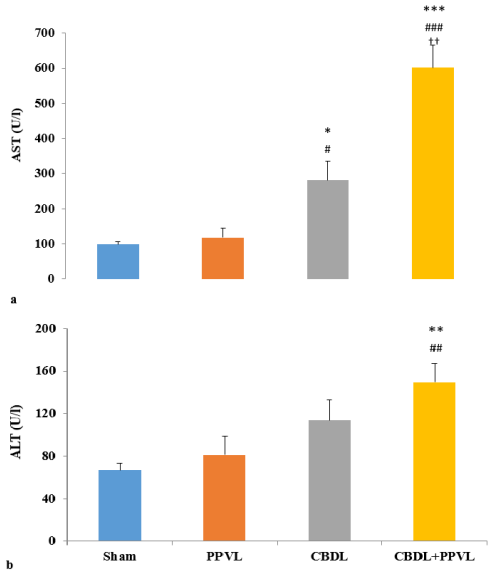

Figure 1: Plasma AST (a) and ALT (b) in the groups of sham, CBDL, PPVL and CBDL+PPVL. n=8 in each group. Data are presented as mean ± SE. ***(p<0.001), ** (p<0.01), * (p<0.05) vs. the sham group., $^{###}$(p<0.001), $^{##}$(p<0.01) and $^{#}$(p<0.05) *vs.* the PPVL group., ††(p<0.01) *vs.* the CBDL group.

Both direct and total bilirubins in the CBDL and CBDL+PPVL groups were significantly higher than the ones in the sham and PPVL groups (p<0.001) (Figures 2a and 2b).

In the CBDL+PPVL group, PaO_2 was lower than those of the sham (p<0.01) and PPVL (p<0.001) groups. $PaCO_2$ was more than that of the CBDL group (p<0.01), and HCO_3- concentration was higher than those of the other groups (p<0.01) (Table 1).

Groups	PaO2	PaCO2	HCO3-	pH
Sham	59.9 ± 1.89	38.9 ± 0.89	24.8 ± 0.53	7.40 ± 0.01
PPVL	60.7 ± 0.60	38.1 ± 1.79	24.7 ± 0.60	7.42 ± 0.01
CBDL	55.4 ± 1.64	34.02 ± 1.77	24.4 ± 0.57	7.46 ± 0.01
CBDL +PPVL	48.9 ± 1.79$^{**###}$	44.5 ± 2.18††	27.7 ± 0.57$^{**##††}$	7.41 ± 0.01

Table 1: Blood gas parameters of the arterial blood in the experimental groups, n=9-10 in each group. Data are presented as mean ± SE. Barometric pressure of atmosphere in our place is about 630 mmHg.

**(P<0.01) vs. the sham group., ### (P<0.001) and ## (P<0.01) vs. the PPVL group., †† (P<0.01) vs. the CBDL group.

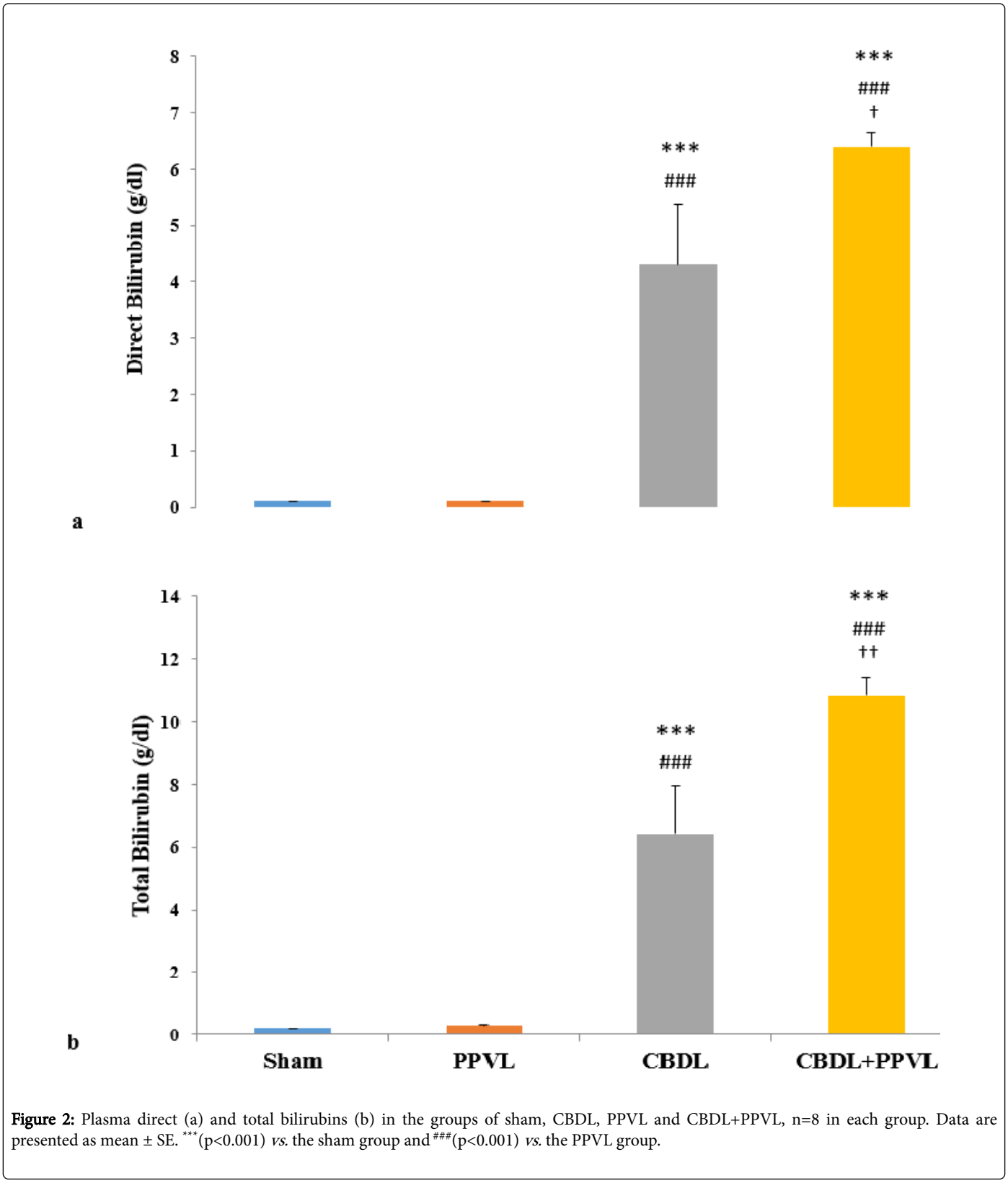

Figure 2: Plasma direct (a) and total bilirubins (b) in the groups of sham, CBDL, PPVL and CBDL+PPVL, n=8 in each group. Data are presented as mean ± SE. ***(p<0.001) *vs.* the sham group and ###(p<0.001) *vs.* the PPVL group.

RR interval in the CBDL group was less than the ones in the sham and PPVL groups. QT interval in the CBDL+PPVL group was longer than those of the sham and PPVL groups ($p<0.01$), and in the CBDL group was more than that of the sham group ($p<0.01$). In addition, JT interval in the CBDL+PPVL and CBDL groups were more than that of the sham group ($p<0.01$) (Figure 3 and Table 2).

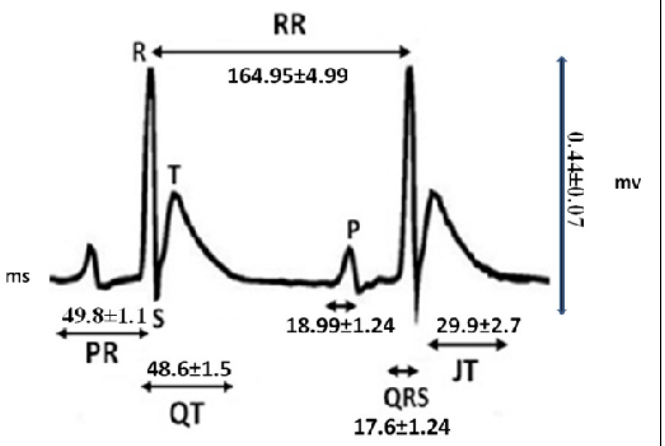

Figure 3: Schematic presentation of ECG waves of sham groups. Durations (ms) and voltages (mv) are expressed as mean ± SE (n=10).

Blood Hb concentration in the PPVL group was higher than those of the CBDL+PPVL CBDL and sham groups ($p<0.01$). It was followed by a higher CaO_2 in this group compared to the other groups ($p<0.001$). Also, CvO_2 in the PPVL group was more than that of the sham group ($p<0.01$).

Both PvO_2 and CvO_2 in CBDL+PPVL group were more than that of the sham group ($p<0.01$) (Table 3). QTc in the CBDL and CBDL +PPVL groups were more than the sham ($p<0.01$) and PPVL ($P<0.05$) groups.

There was no difference in the values of QTc in the CBDL and CBDL+PPVL groups. Moreover, A-VO_2 of the right femoral lower limb in the CBDL group was less than that of the sham ($p=0.051$) and PPVL ($p<0.05$) groups, and in the CBDL+PPVL group were less than those of the sham, PPVL ($p<0.001$) and CBDL ($p<0.05$) groups (Figure 4).

Plasma MDA in the CBDL and CBDL+PPVL groups were higher than those of the Sham and PPVL groups ($p<0.001$) (Figure 5). Furthermore, WBC in these two groups were more than the ones in the Sham and PPVL groups ($p<0.001$), and in the CBDL+PPVL group was more than that of the CBDL group ($p<0.05$) (Table 3).

Figure 6 indicates the real traces of ECG in all experimental groups. It shows changes in the shapes of T waves in both CBDL and CBDL +PPVL group which are different than the sham and PPVL groups. There are also additional P waves in the CBDL+PPVL group which are not detected in the other groups.

	Sham	PPVL	CBDL	CBDL+PPVL
RR Interval (ms)	164.95 ± 4.99	164.98 ± 4.9	155.36 ± 3.59	167.23 ± 4.98
Heart Rate (BPM)	367.1 ± 11.45	366.74 ± 10.77	388.09 ± 8.6	361.67 ± 11.4
P (ms)	18.99 ± 1.24	18.15 ± 1.06	16.56 ± 1.04	17.83 ± 1.26
QRS (ms)	17.62 ± 1.24	15.61 ± 0.31	16.2 ± 0.35	17.99 ± 1.2
QT Interval (ms)	48.56 ± 1.45	51.39 ± 2.3	64.36 ± 4.87 **#	67.8 ± 3.12 ** ##
JT Interval (ms)	29.92 ± 2.72	35.78 ± 2.36	48.15 ± 4.86 **	48.96 ± 3.58 **

Table 2: EKG parameters of lead 2 in the experimental groups, n=10 in each group. Data are presented as mean ± SE. **($p<0.01$) vs. the sham group, ##($p<0.01$) and #($p<0.05$) *vs.* the PPVL group.

	Sham	PPVL	CBDL	CBDL+PPVL
Hb (g/dl)	11.41 ± 0.47	14.11 ± 0.38**	10.85 ± 0.30##	11.74 ± 0.36##
PaO_2 (mmHg)	59.9 ± 1.89	60.66 ± 0.6	55.4 ± 1.64	48.89 ± 1.79 **###
PvO_2 (mmHg)	28.8 ± 1.02	31.78 ± 1.87	30.2 ± 1.25	36.4 ± 1.53 **†
RBC (10^6/µl)	5.33 ± 0.28	5.39 ± 0.21	5.22 ± 0.53	5.52 ± 0.23
WBC (10^3/µl)	5.52 ± 0.12	3.96 ± 0.67	13.52 ± 1.55 ***###	16.42 ± 0.59 ***†###
PaO_2-PvO_2 (mmHg)	31.1 ± 1.88	28.89±1.78	24.4±2.4	12.44 ± 0.81 ***††###
CaO_2 (ml/100ml)	13.53 ± 0.61	17.01 ± 0.46 ***	13.07 ± 0.40 ###	13.13 ± 0.38 ##

CvO_2 (ml/100ml)	8.08 ± 0.58	11.09 ± 0.0.69 **	8.76 ± 0.63	10.97 ± 0.25 **

Table 3: Hb, oxygen pressure and oxygen content in the arterial and venous blood, n=9-10 in each group. Data are presented as mean ± SE. ***(p<0.001) and **(p<0.01) *vs.* the sham group., ### (p<0.001) and ## (p<0.01) *vs.* the PPVL group., †† (p<0.01), † (p<0.05) *vs.* the CBDL group.

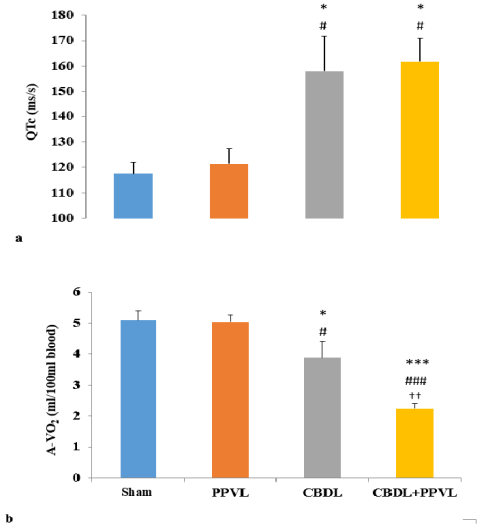

Figure 4: QTc (a) and A-VO2 (b) in the groups of sham, CBDL, PPVL and CBDL+PPVL. n=8 in each group. Data are presented as mean ± SE. ***(p<0.001) and **(p<0.01) *vs.* the sham group, ###(p<0.001) and #(p<0.05) *vs.* the PPVL group., † (p<0.05) *vs.* the CBDL group.

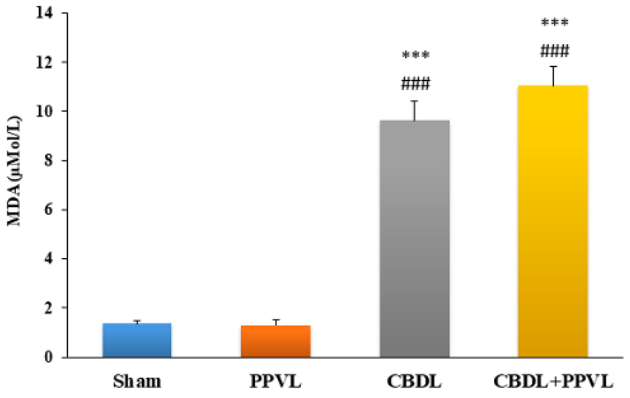

Figure 5: Plasma MDA in the groups of sham, CBDL, PPVL and CBDL+PPVL (Data are presented as mean ± SE. *** (p<0.001) *vs.* the sham group, ###(p<0.001) *vs.* the PPVL group).

Discussion

ECG analysis in the animal models of cirrhosis has not been fully discussed yet. In this study, we found alterations in the shape of T waves in both CBDL and CBDL+PPVL groups. Furthermore, we indicated similar QTc but lower A-VO_2 and therefore lower metabolism in the CBDL+PPVL group compared to the CBDL group.

The result of the liver enzymes and bilirubin indicate the establishment of liver cirrhosis in the CBDL and CBDL+PPVL groups. Furthermore, the severity of liver dysfunction seems to be higher in the CBDL+PPVL group compared with the CBDL group. In addition, significant inflammations were detected in the CBDL and CBDL +PPVL groups.

Prolonged QT and increased QTc in the CBDL and CBDL+PPVL groups are similar to the other studies of liver cirrhosis [2,17]. The increase in QT interval and QTc in the CBDL+PPVL group was not associated with significant alteration in heart rate, which are comparable with the data of others in CBDL model [10]. Our study was the first to indicate bizarre T waves in both groups of CBDL and CBDL+PPVL groups. In normal rats, ST segment is not detectable and T wave is along with the S wave (Figure 3). However, in our CBDL and CBDL+PPVL groups, the initial part of the T wave is flat, but at a higher level than that of the J point which continues with the rest dome shape of the T wave (Figure 6).

We haven't found the same result in the literature. This alteration may be related to the mechanisms involved in QT prolongation in cirrhosis. It has been suggested that increased QT may be caused by the decrease of the number and activities of potassium and calcium channels, sympathetic activity and local and general hormones [2,17]. It may also be linked to cardiac dilatation following hyperdynamic circulation in cirrhosis [20].

The arterial oxygen content in the PPVL group was higher than that of the other group. This may be related to a higher hemoglobin concentration in this group. Also, A-VO_2 of the right lower limb in the CBDL and CBDL+PPVL groups were significantly lower than those of the sham and PPVL groups. Our results agreed with others that oxygen consumption decreases in the patient with liver cirrhosis [14]. Moreover, the lower A-VO_2 in the CBDL+PPVL group compared with the CBDL group may be caused by more liver damage in this group.

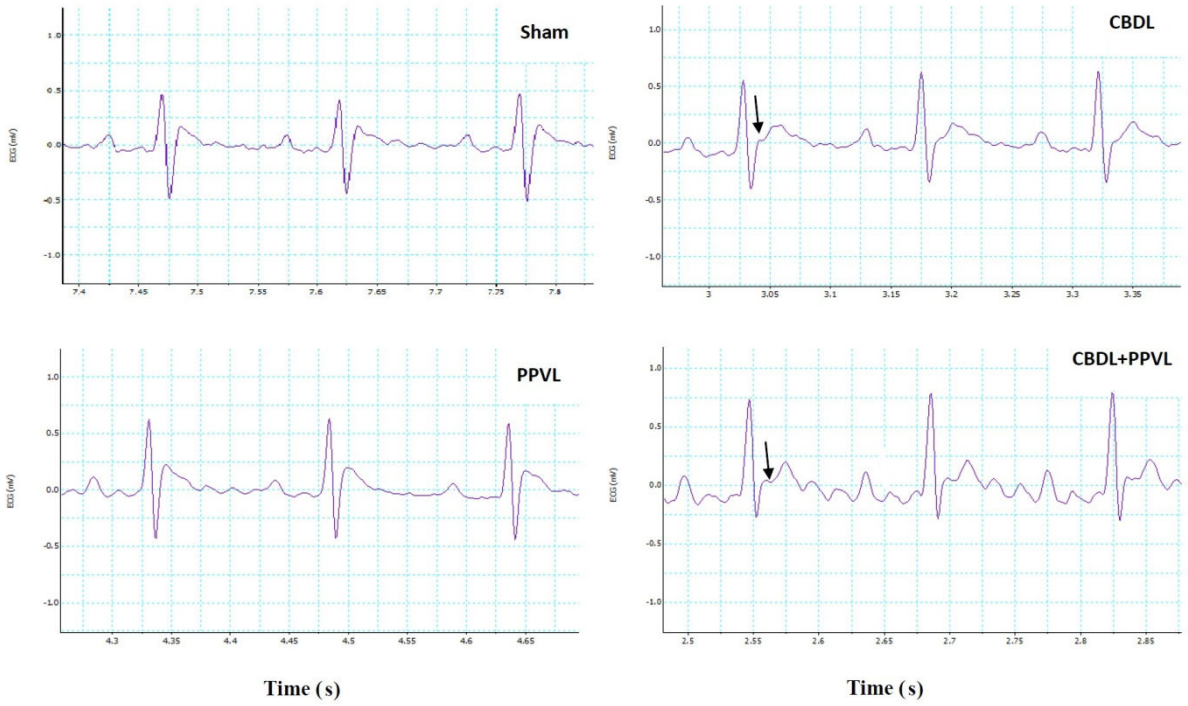

Figure 6: The real traces of ECG recording in the experimental groups. Arrows show T wave abnormalities in the CBDL and CBDL+PPVL groups.

We considered A-VO_2 of one organ as an indicator of total oxygen consumption, even though the metabolisms of different body tissues are not identical [21]. In addition, the alteration of oxygen consumption in cirrhosis may not be similar in different organs. Also, we haven't used a swan ganz or jugular vein catheter in our study because some limitations, and didn't measure the mixed venous blood which is necessary for the measurement of total oxygen consumption.

Portosystemic shunt is one of the complications of chronic liver cirrhosis [12]. Although our observation showed abdominal collateral vessels in the CBDL+PPVL group, we haven't measured this parameter quantitatively. It may probably be linked to portosystemic shunt and the bypass of blood from the portal vein, which prevents of more oxygen consumption by the liver. However, this issue could not be influential for the measurements of A-VO_2 in this study because the arterial and venous blood samples were taken by the femoral vessels.

QT and QTc were identical in the CBDL+CBDL and CBDL groups in spite of differences in their oxygen consumptions. As a result, only a partial relation between the QT interval, QTc and the body's metabolism is suggested. Sertiun 1 (SIRT1) produced by fat tissues has an important role in the maintenance of metabolic homeostasis and cardiac function. The inflammatory reactions of the body may be associated with the reduction in SIRT1, which consequently affects the myocardial performance [22,23]. We did not measure SIRT1. However, data of MDA and WBC in our study specify significant inflammations in the CBDL and CBDL+PPVL groups. These data can suggest further damage in the heart caused by the less expression of *SIRT1* in the fat tissue and direct effects of inflammatory mediators on cardiovascular function in the CBDL+PPVL group compared to the CBDL group [24]. The effect of metabolism on the cardiac function has been investigated in the other metabolic disorders such as metabolic syndrome in which the recurrence rate of premature ventricular contraction beat (PVCs) increases even after catheter ablation [25]. The metabolic syndrome may also lead to liver cirrhosis and increases the cardiovascular disease and mortality rate as a results of the effects of metabolism and inflammation [26,27]. All these data suggest a close relationship between electrocardiogram abnormality, cardiac dysfunction, inflammation and the reduction of body metabolism in liver cirrhosis.

We detected additional P waves in the CBDL+PPVL group. This may increase the risk of atrial fibrillation like those occur in cirrhotic patients [2,28]. Atrial fibrillation may also be linked to inflammatory reactions, even though the results of other investigation in this regard are controversial [29,30].

Conclusion

In this study, we detected ECG abnormalities, including bizarre T waves, increased QT interval and QTc in cirrhotic rat models which may be partially linked to the severity of liver dysfunction and the reduction of the oxygen consumption as an indicator of metabolism. Although ECG in human and rat are partly different, the investigation of these abnormalities in animal models may open the ways for the treatment of ECG abnormalities in cirrhotic patients.

Conflict of Interests

The Authors declare that they have no competing interests.

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