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Molecular and Immunological Effect of Propofol in Relieving Myocardial Ischemia-Reperfusion Injury in Type 2 Diabetic Patients

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ABSTRACT

This study aimed to explore the clinical mechanism of propofol in relieving myocardial ischemia-reperfusion injury in type 2 diabetic patients. In the present study, 369 patients suffering from myocardial ischemia-reperfusion injury who were diagnosed with type 2 diabetes in our hospital from January 2018 to May 2019 were selected as study subjects and randomly divided into low-dose propofol group (n=123; intravenously injected with 25 mg before angiography), high-dose propofol group (n=123; intravenously injected with 50 mg before angiography) and control group (n=123; receiving local anesthesia before angiography, subcutaneously injected with 2% lidocaine 2.5 ml at puncture point). After coronary angiography in each group, the serum nitric oxide (NO), endothelin-1 (ET-1) and cardiac troponin (cTnT) contents in different treatment groups were detected by enzyme-linked immunosorbent assay. Coronary blood samples were obtained during coronary angiography. Expressions of interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF -α) were detected by Western blotting (WB). The protein contents of B-cell lymphoma factor 2 (Bcl-2), apoptosis-related genes Bax and caspase-3 were detected by WB. The contents of lactic dehydrogenase (LDH), creatine kinase (CK), superoxide dismutase (SOD) and malondialdehyde (MDA) were detected by enzyme-linked immunosorbent assay. Results showed that compared with the control group, the low-dose propofol group had increased NO, decreased ET-1 and cTnT contents ($P<0.05$), and high-dose propofol group had further increased NO and further decreased ET- 1 and cTnT contents compared with low-dose propofol group ($P<0.05$). Compared with the control group, the low-dose propofol group had reduced IL-1β, IL-6 and TNF-α expressions ($P<0.05$), and high-dose propofol group had further reduced IL-1β, IL-6 and TNF-α expressions compared with low-dose propofol group ($P<0.05$). Compared with the control group, the low-dose propofol group had increased Bcl-2 protein content, decreased Bax and Caspase-3 protein contents ($P<0.05$); compared with low-dose propofol group, high-dose propofol group had further increased Bcl-2 protein content, further decreased Bax and Caspase-3 protein contents ($P<0.05$). Compared with the control group, low-dose propofol group had decreased SOD content, increased LDH, CK, and MAD contents ($P<0.05$). Compared with low-dose propofol group, high-dose propofol group had further decreased SOD content, further increased LDH, CK and MAD contents ($P<0.05$). We conclude that, Propofol has a protective effect on myocardial ischemia-reperfusion injury in type 2 diabetic patients, the mechanism of which is to up-regulate serum NO, Bcl-2 and SOD, and down-regulate serum ET-1, cTnT, IL-1β, IL-6, TNF-α, BAX, LDA, CK, MAD, thus protecting cardiomyocytes.

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INTRODUCTION

Type 2 diabetic patients have a high incidence of cardiovascular complications, and cardiovascular accidents are considered as a high-risk cause of perioperative death in diabetic patients (Wang *et al*., 2017). Diabetic patients with acute myocardial infarction after ischemia-reperfusion injury have several times higher mortality than non-diabetic patients (Chen *et al*., 2017). The release of inflammatory mediators is closely related to type 2 diabetes and myocardial ischemia-reperfusion injury (Zykov *et al*., 2018). In the pathophysiological process of reperfusion, damage and dysfunction of endothelial cells in the coronary arteries may be an important early event that leads to subsequent apoptosis of myocardial cells during ischemia-reperfusion (Yu *et al*., 2018). Endothelial dysfunction is characterized by reduced NO bioavailability, which is an important cause of reperfusion injury (Hou *et al*., 2019; Paelestik *et al*., 2017). Propofol is a widely used intravenous anesthetic that has been used in various experimental models to reduce oxidative stress, protect mitochondrial function, and reduce inhibitory effect of apoptosis on I/R injury (Bradic *et al*., 2019). It is reported that propofol provides cardioprotection against I/R injury in type 1 diabetes (Hao *et al*., 2017; Suchal *et al*., 2017). Whether propofol has a protective effect on myocardial ischemia/reperfusion injury in type 2 diabetes

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remains unclear as this disease has high clinical incidence, and the potential mechanism of this protective effect waits to be determined. This study is designed to evaluate the mechanism of action of isopropofol on myocardial ischemia-reperfusion injury in type 2 diabetic patients.

MATERIALS AND METHODS

A total of 246 patients diagnosed with type 2 diabetes + myocardial ischemia-reperfusion injury in our hospital from January 2018 to May 2019 were selected as subjects and randomly divided into low-dose propofol group (n=123) and high-dose propofol group (n=123). Patients in the low-dose propofol group underwent coronary angiography under local anesthesia; patients in the high-dose propofol group underwent coronary angiography under propofol anesthesia (50 mg intravenously injected before angiography).Meanwhile, healthy examinees receiving coronary angiography in our hospital were selected as the control group (n=87).

Inclusion criteria: patients with prior myocardial ischemia or one or more coronary artery stenosis ≥50% during coronary angiography of percutaneous coronary intervention or coronary artery bypass grafting; type 2 diabetes is defined as the case where fasting blood glucose exceeds 7 mmol / l, or blood glucose exceeds 11 mmol / l two hours after oral administration of glucose 75 g. The oral glucose tolerance test confirmed the lack of type 2 diabetes in the CAD group.

Exclusion criteria: age> 80 years; acute myocardial infarction or unstable angina within 3 months before the experiment; Raynaud phenomenon in the forearm; arteriovenous shunt or other vascular abnormalities; any protocol that hinders completion of the study, participation in other study or unwillingness to participate in this study.

Medical ethics issues: This study was approved by the hospital ethics committee, and all participants signed informed consent.

Coronary angiography implementation plan

Perioperative coronary angiography detection

Clinical information obtained during the hospitalization (ECG, cTnT and hemoglobin serial laboratory measurements, perioperative and intraoperative vital signs monitoring, echocardiography, cardiac pressure and angiography detection of coronary artery disease) were followed. All perioperative myocardial injury met the cTn standard, so at least one of the following conditions was met: ischemic symptoms, new important ST-T wave changes or new left bundle branch block, pathological Q wave in ECG, loss of new viable myocardium or new regional wall motion abnormalities as indicated by imaging evidence, 30-day mortality rate in outcome end-point associated with primary event of coronary thrombosis identification, and 1-year mortality rate in the secondary outcome end-point. Death is classified into cardiovascular or non-cardiovascular death. Cardiovascular death includes death attributable to acute myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular surgery, cardiovascular hemorrhage (*e.g.,* ruptured or dissected aortic aneurysm), and pulmonary embolism. Unless there is evidence of non-cardiovascular causes, all deaths are assumed as cardiovascular deaths. Non-cardiovascular deaths include all deaths caused by clearly recorded non-cardiac and non-vascular factors.

Coronary angiography treatment procedure

If the absolute increase of cTnT exceeds the preoperative level ≥14ng/L, the structured response includes the assessment of possible symptoms associated with perioperative myocardial injury in patients diagnosed with perioperative myocardial injury. The researchers recorded the 12-leads ECG. In the pre-determined perioperative myocardial injury management plan, continuous guidance is given to all cardiologists who provide cardiac consultation after perioperative myocardial injury. All treatment decisions regarding perioperative myocardial injury are made jointly by the attending physician and the cardiologist.

Blood sample collection

A coronary blood sample (3ml) was obtained during coronary angiography and placed in a common plastic tube. 1.8 ml of this venous blood was transferred to an anticoagulant tube containing 0.2 ml of 3.8% sodium citrate. The sample was centrifuged (1200×g) for 10 min in 1 h, serum was extracted and stored in a 0.5 ml Eppendorf tube at a temperature of -30°C to be used within 1 month.

Determination of NO, ET-1 and cTnT

Nitric oxide (NO), endothelin-1 (ET-1) and cardiac troponin (cTnT) were determined by ELISA. All reagents in this study were from Wuhan Bosite Bioengineering Co., Ltd. (Wuhan, China) and were used according to the manufacturer's instructions.

Detection of IL-1β, IL-6, TNF-α, Bcl-2, Bax, Caspase-3 protein contents

The blood sample was centrifuged at 12000 ×g, 4°C for 30 min, and the supernatant was aspirated, diluted with equal amount of 5 × SDS loading buffer at 1:1 (V/V), boiled at 100°C for 5 min. The protein concentration of the sample was measured by BCA protein concentration determi-

nation kit. Take 15 μL of the sample to be tested for loading {glyceraldehyde-3- phosphate dehydrogenase (GAPDH) monoclonal antibody (1:500) as the standard for protein loading amount}, and the total protein loading amount in each lane is 30 μg. SDS-polyacrylamide gel electrophoresis (SDS-PAGE) was performed. The protein strips were charged and transferred to Immun-blot PVDF membrane by wet process, blocked with 50 g/L skim milk powder at 20°C for 3 h, and the corresponding antibodies were added (mouse anti-rat IL-1β monoclonal antibody,1:400, mouse anti-rat IL-6 monoclonal antibody, 1:400, mouse anti-rat TNF-α monoclonal antibody, 1:400, rabbit anti-rat Bcl-2 polyclonal antibody,1:400, rabbit anti-rat Bax, 1:400 polyclonal antibody, rabbit anti-rat Caspase-3, 1:400 polyclonal antibody for incubation at 4°C overnight. The strips were rinsed for 10 min×3 times with TBS buffer (Tris 50 mmol/L, NaCl 100 mmol/L, pH 7.5), incubated at 37°C for 2 h using the corresponding horseradish enzyme-labeled IgG (1:1000), and rinsed for 10 min×3 times. After luminescence development, the image was scanned with a Mieroteck scanner, and integrated optical density analysis was performed using Quantity-One software.

Detection of LDH, CK, SOD and MAD expression in coronary blood samples

Colorimetric detection kit was used to detect the expression levels of LDH, CK, SOD and MAD in the coronary blood samples; the experimental steps of the colorimetric detection followed the instructions.

Statistical analysis

This study adopted SPSS20.0 statistical analysis software (IBM, USA). The measurement data was expressed as "mean ± standard deviation" ($\bar{x} \pm s$). One-way analysis of variance or repeated measurement data analysis of variance was used for comparison between groups, LSD-t test was used for pairwise comparison. The count data was expressed as percentage (%), and χ^2 analysis was used for comparison between groups. $P<0.05$ indicates statistically significant difference.

RESULTS

Table I shows the general characteristics of the participants. In comparison between the control group and low-dose propofol group, age, gender, BMI, total cholesterol, high-density lipoprotein and low-density lipoprotein do not differ statistically (P>0.05). The low-dose propofol group has higher systolic pressure, diastolic pressure, MAP, hemoglobin, and glucose levels than the control group (P<0.05). All subjects well tolerated the experimental protocol. During the ischemia, the subjects felt forearm numbness, but no patient felt any pain or discomfort.

Table II shows the NO, ET-1 and cTnT contents by ELISA, IL-1β, IL-6, TNF –α, Bcl_2, Bax and Caspase-3 detected by western blotting and expression of *LDH, CK, SOD* and *MAD* in the blood of type 2 diabetic patients. Compared with the control group, the low-dose of propofol causes an increase in NO and Bcl_2, and decrease in all the remaining parameters ($P<0.05$). The high-dose of propofol further intensifies the effect of propofol ($P<0.05$).

Table I.- Statistics of basic characteristics.

Item	Control group (n=87)	Low-dose propofol group (n=123)	High-dose propofol group (n=123)	F value	P value
Age	58.73±5.82	58.24±6.17	57.18±5.53	4.875	0.178
Gender (Male: Female)	41:46	58:65	54:69	6.142	0.654
Systolic pressure (mmHg)	115.34±4.51	134.68±12.93	130.52±11.71	37.516	0.016
Diastolic pressure (mmHg)	75.22±6.18	83.15±8.26	81.26±9.05	15.135	0.013
MAP	91.37±7.28	101.58±11.18	98.65±8.66	11.764	0.028
BMI(kg/m^2)	26.14±3.54	26.23±2.72	27.53±2.32	2.376	0.463
Hemoglobin (%)	32.23±4.53	47.62±2.85	45.39±3.15	24.183	0.007
Glucose (mmol/L)	0.86±0.11	1.87±0.16	1.79±0.21	12.227	0.016
Total cholesterol (mmol/L)	4.35±0.16	4.78±0.14	4.68±0.37	0.186	0.568
High density lipoprotein (mmol/L)	1.38±0.15	1.26±0.13	1.32±0.10	3.563	0.429
Low density lipoprotein (mmol/L)	2.46±0.43	2.37±0.23	2.56±0.19	5.187	0.172

Table II.- Effect of low and high doses of propofol on levels of NO, ET-1 and cTnT contents detected by ELISA, IL-1β, IL-6, TNF –α, Bcl2, Bax and Caspase-3 proteins detected by western blotting and expression of LDH, CK, SOD and MAD using colorimetric detection kits in the blood of type 2 diabetic patients.

Control / Propofol Group	Control (n=87)	Low-dose (n=123)	High-dose (n=123)	F value	p value
NO (μmol/L)	58.73±10.15	75.34±9.26	87.54±5.37	35.347	0.012
ET-1 (μg/L)	63.75±0.32	55.56±0.37	37.14±0.22	12.175	0.024
cTnT (μg/L)	12.132±0.12	9.145±2.25	5.748±1.08	13.145	0.018
IL-1β (integrated optical density)	1324.57±36.28	1155.46±50.47	902.94±25.22	33.267	0.014
IL-6 (integrated optical density)	1623.22±39.53	1259.17±42.24	915.05±50.53	55.187	0.008
TNF-α (integrated optical density)	1589.13±59.26	1059.17±36.34	785.86±62.35	66.175	0.001
Bcl-2 (integrated optical density)	5.88±1.26	8.04±1.11	12.06±2.22	15.264	0.012
Bax (integrated optical density)	2.87±0.34	1.98±0.24	1.25±0.31	12.524	0.008
Caspase-3 (integrated optical density)	3.85±0.14	2.95±0.24	2.05±0.16	14.485	0.013
LDH (U/L)	1861.52±232.61	1652.57±150.54	1472.15±127.37	12.534	0.012
CK (U/L)	190.22±19.16	145.26±25.28	121.84±29.23	11.256	0.024
SOD (μmol/mL)	68.11±1.25	43.54±0.37	26.22±0.54	15.137	0.033
MAD (nmol/L)	15.13±2.87	10.37±2.24	7.22±1.48	10.185	0.008

Figure 1 shows the expression of IL-1β, IL-6 and TNF-α. Figure 2 shows the IL, Bcl-2, Bax and Caspase-3 protein contents in coronary blood samples by western blotting. Compared with the control group, the low-dose propofol group has reduced IL-1β, IL-6 and TNF-α expressions, Bax and Caspase-3 protein contents (P<0.05), and high-dose propofol group has further reduced expression compared with low-dose propofol group (P<0.05).

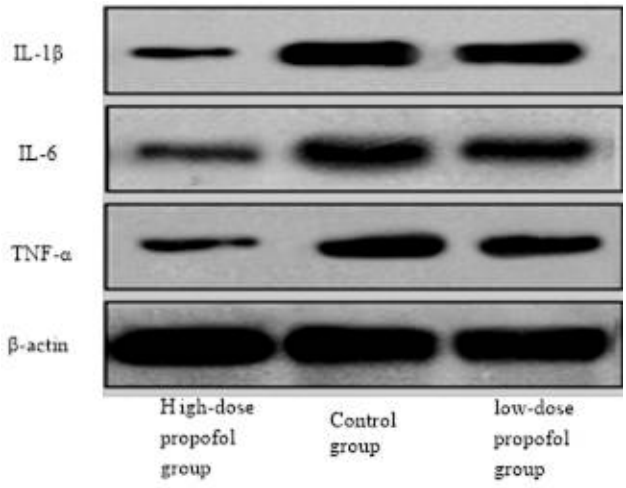

Fig. 1. Effect of propofol on expression of IL-1β, IL-6 and TNF-α detected by western blotting in blood serum of type 2 diabetic patients.

Table II also shows level of LDH, CK, SOD and MAD in coronary blood samples. Compared with the control group, low-dose propofol has decreased all the parameters (P<0.05). High-dose propofol group has further decreased the exzume levels (P<0.05).

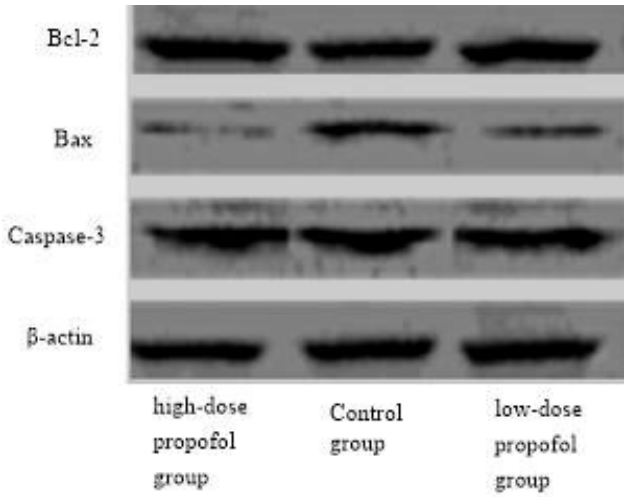

Fig. 2. Effect of propofol on expressions of Bcl-2, Bax and Caspase-3 protein detected by western blotting in blood serum of type 2 diabetic patients.

DISCUSSION

IR injury involves destruction and metabolic disorders of tissue structure. In clinical cardiac surgery,

infarction after coronary artery ligation was observed in the case of myocardial ischemia-reperfusion injury. Type 2 diabetes is one of the most common endocrine and metabolic diseases (Li *et al*., 2018). This study indicates that propofol improves heart function in type 2 diabetic patients, increases serum NO, and reduces the content of ET-1 and inflammatory mediators in myocardial ischemia-reperfusion injury.

There is evidence that intravenous narcotic propofol may inhibit lipid peroxidation, improve mitochondrial function, protect myocardium and reduce myocardial ischemia-reperfusion injury in patients (Fan and Yang, 2017). Several clinical and biochemical indicators can be used in diagnosis of myocardial injury. cTnT is considered as the "gold standard" for the diagnosis of myocardial injury (Huynh *et al*., 2019). In this study, propofol reduced cTnT concentration in the serum and improved heart function. During myocardial ischemia, changes in NO levels are controversial. Previous studies have shown that NO release is increased during myocardial ischemia of coronary artery (Sheng *et al*., 2017). By contrast, other authors found that NO release was reduced. Endothelial function plays an important role in maintaining stability and normal hemodynamics. The key factor to its function is NO (Zhang *et al*., 2017). NO exerts an anti-inflammatory effect by inhibiting the adhesion of neutrophilic granulocyte to endothelial cells and reducing the release of inflammatory factors. Appropriate amount of NO can protect cardiomyocytes, reduce damage, inhibit intimal hyperplasia and improve heart function after IR injury. As an important regulator of cardiovascular function, ET plays an important role in maintaining vascular tone and cardiovascular system stability. Epinephrine, thromboxane, angiotensin, insulin, inflammatory factors and hypoxia stimulate the synthesis of ET-1, while inhibitors of ET-1 synthesis include NO, PGI2, atrial natriuretic peptide and heparin (Jia *et al*., 2017). This experiment shows that propofol can increase NO levels and reduce serum ET-1 concentration, thereby exerting cardioprotective effects against myocardial ischemia-reperfusion injury in type 2 diabetic patients.

Type 2 diabetes and myocardial ischemia-reperfusion injury concern inflammatory mediators. Inflammatory factors may cause myocardial damage in type 2 diabetic patients. Therefore, inhibiting the release of inflammatory cytokines is an important strategy for protecting the heart of type 2 diabetic patients against myocardial damage. As an important inflammatory cytokine, TNF-α mainly produced by the activation of monocytes/macrophages is involved in certain autoimmune diseases (Liu *et al*., 2019). Therefore, it can stimulate NO synthase (i-NOS) synthesis to release large amounts of NO (Eroglu *et al*., 2017). This will exacerbate peroxidation of membrane lipid and tissue damage. IL-1β is mainly produced by macrophages, and it is found that systemic response is a result of injection and secretion of large amounts of IL-1β (Yu *et al*., 2018). IL-6 plays an important role in combating infection by enhancing the effects of other cytokines and regulating immune response, acute phase response and hematopoiesis (Wu *et al*., 2017). Inflammatory factors play an important role in myocardial ischemia-reperfusion injury. Inflammation caused by myocardial ischemia and hypoxia prompts monocytes and macrophages to release large amounts of IL. As a highly specific neutrophil chemotactic factor, interleukin causes adhesion and aggregation of large numbers of leukocytes (an obstacle that hinders microcirculation), increases active oxygen and damages cardiomyocytes (Yu and Gao, 2017). Inflammatory factors cause neutrophils to release cytotoxicity, aggravate the inflammatory response, block capillaries and vasoactive substances, leading to acute tissue injury. This study indicates that propofol reduces the expression of inflammatory cytokines such as IL-1β, IL-6, and TNF-α in serum.

Under conditions of diabetes and ischemia, hypoxia leads to anaerobic respiration, resulting in lactic acid production, ATP consumption, and intracellular pH decline. These effects induce oxidative stress, intracellular Ca2+ overload and cell membrane damage, and cause direct oxidative damage to DNA and mitochondria (Zhang *et al*., 2018). All these factors can lead to cell death through apoptosis, which is considered as one of the major causes of myocardial ischemia and reperfusion injury. Caspase-3 is one of the most important enzymes that regulate and execute apoptosis, which acts as an early marker of apoptosis (Ge *et al*., 2017). Bcl-2 protein family, through its pro-apoptotic and anti-apoptotic members, plays a vital role in controlling apoptosis mechanism of mammalian cells (Li *et al*., 2017). The ratio of Bcl-2 to Bax determines the fate of the cell. When the ratio is reduced, the cell tends to undergo apoptosis. Conversely, when this ratio increases, cells tend to survive. In addition, increased apoptosis is shown in cardiomyocytes of diabetic patients and STZ-induced diabetic animals. Studies have shown that cardiomyocyte apoptosis in diabetic patients is about 85 times that of non-diabetic patients (Cooper *et al*., 2018). Recent studies have found that propofol has a protective effect against ischemia-reperfusion injury in brain I/RI patient models and myocardial I/RI patient models. Our results revealed that propofol treatment increased Bcl-2 protein content and decreased the Bax and Caspase-3 protein contents (Meng *et al*., 2018).

CONCLUSION

To conclude, propofol has a protective effect on myocardial ischemia-reperfusion injury in type 2 diabetic patients by improving cardiac function, increasing serum NO, Bcl-2, and SOD, and decreasing serum ET-1, cTnT, and IL- 1β, IL-6, TNF-α, BAX, LDA, CK, MAD.

Statement of conflict of interest

The authors have declared no conflict of interests.

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