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Melatonin prevents adverse myocardial infarction injury via Notch1/Mfn2 pathway

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OBJECTIVES Myocardial infarction (MI) caused by coronary atherosclerosis or spasm takes an important role in the progression of cardiac hypertrophy, heart failure and arrhythmia. Notch signaling has been proved to be crucial for cell-to-cell interaction and involve in human development and diseases. Most importantly, mitochondrial dysfunction is linked with MI in which Notch1 has attracted more attention. However, Notch1's function on mitochondrial impairment in post-MI is poorly defined, no matter the role of mitochondrial fusion-associated protein 2 (Mfn2) in it. Moreover, whether melatonin potentiates Notch1/Mfn2 pathway in post-MI remains unclear. The present study was to investigate the effect of melatonin treatment on the Notch1/Mfn2 pathway in post-MI.

METHODS Small interfering RNA (siRNA, 20 μg per heart) against Notch1 or Mfn2 and Jagged1 were delivered via intramyocardial injection. 3 days later, MI was established by ligation of anterior descending branch. C57 mice were randomly assigned to the following experimental groups (n=10): (1) Sham; (2) MI; (3) Control; (4) NKD; (5) MKD; (6) Vehicle; (7) Jagged1; (8) Jagged1 + Control; (9) Jagged1+ MKD; (10) Mel: (10 mg/kg/day, 14 days before MI; 20 mg/kg/day, 2 days after MI) with MI; (11) Mel + Luz: (1 mg/kg/day, 14 days before MI; 2 mg/kg/day, 2 days after MI) with MI; (12) Vehicle + Control; (13) Mel + Control; (14) Mel + NKD; (15) Mel + MKD. Myocardial function, fibrosis, apoptosis, reactive oxygen species (ROS) and mitochondrial disorder were determined through echocardiography, masson-trichrome, caspase-3 kit, lucigenin-enhanced luminescence, transmission electron microscopy and ATP kit, respectively.

RESULTS The genetic ablation of Notch1 or Mfn2 aggravated post-MI injury, along with worse mitochondrial damage and more ROS generation, when compared with control group ($P<0.01$). In contrast, Jagged1 improved mitochondrial structure and function, reduced ROS production, and attenuated post-MI injury ($P<0.05$). Interestingly, although Mfn2 expression was slightly regulated by Notch1 signaling in myocardium, Mfn2 deficiency was able to largely eliminate Jagged1's cardioprotection, evidenced by suppressed cardiac function, aggravated myocardial fibrosis, increased cell apoptosis, worsened mitochondrial impairment and enhanced oxidative stress ($P<0.01$). These reveal an indispensable role of Mfn2 in Notch1's protection against MI injury, perhaps by breaking the positive feedback loop of mitochondrial impairment and ROS production. Furthermore, melatonin activated Notch1 signaling and increased Mfn2 expression, all of which were reversed by luzindole (a nonselective antagonist of melatonin receptor) ($P<0.05$). Notably, melatonin attenuated post-MI injury in normal mice, but not in Notch1 or Mfn2 deficiency mice.

CONCLUSIONS Melatonin attenuates post-MI injury through Notch1/Mfn2 pathway in a receptor-dependent manner, perhaps by blocking the vicious circle of mitochondrial impairment and ROS generation.

Key Words: Myocardial infarction; Mitochondria; Melatonin; Notch1; Mfn2; ROS

GW27-e0676

Application of Holter ECG for screening sleep disordered breathing in coronary slow flow phenomenon

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OBJECTIVES To study the correlation between sleep disordered breathing (SDB) and coronary slow flow phenomenon (CSFP). Holter ECG is, to some extent, valuable for screening SDB in CSFP.

METHODS Select patients who undergwent coronary angiography for being suspected of coronary heart disease during the period from January 2015 to April 2016, divide them into CSFP Group and Control Group according to the coronary angiography results. Holter ECG inspection was conducted on both groups of patients to initially select SDB patients.

RESULTS The coronary angiography results indicated 29 confirmed CSFP cases and 36 normal cases. According to the Holter heart rate variability (HRV) analysis, sleep apnea risk score higher than 4 would be regarded as the positive diagnostic criteria. SDB incidence rate in the CSFP group (41.2%) was higher than that in the control group (11.9%), and the difference was of statistic value ($p < 0.05$). Body mass index (BMI), smoking, diabetes, history of snoring, the athletic flat test positive rate and sleep apnea risk score were all higher in the CSFP group than those in the control group ($P < 0.05$). After adjusting with other variables by logistic regression test, it was found that BMI and sleep apnea risk indexes were the risk factors of CSFP, with OR value of 1.142(1.002 ~ 1.433), 3.39 (1.078 ~ 10.291) respectively (both $P<0.05$).

CONCLUSIONS SDB, an independent factor resulting in CSFP and impairing coronary flow, is thus associated with CSFP. Holter is a simple and quick non-invasive means of assessing and filtrating SDB. Correcting SDB boasts a guiding significance on the recovery of CSFP.

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The Association Between Insulin Resistance and Coronary Collateral Circulation in Patients with Impaired Glucose Tolerance

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OBJECTIVES To study the relationship between insulin resistance and coronary collateral vessel formation in patients with impaired glucose tolerance.

METHODS This study enrolled 20 control subjects, and 187 patients with impaired glucose tolerance, who underwent coronary angiography. We prospectively selected all patients who had at least one total occlusion of a major coronary. The homeostasis model assessment of insulin resistance and quantitative insulin sensitivity check index were used to quantify insulin resistance (HOMA2-IR). The severity scale of coronary artery stenosis was quantitatively assessed according to coronary angiography by Gensini scoring system. The collateral scoring system developed by Rentrop and Cohen was used. All statistic work was carried out with software of SPSS 13.0.

RESULTS HbA1c, Fasting insulin (FINS) and HOMA2-IR were (5.16±1.15)%, (7.45±1.31) pmol/L and 0.17±0.10 in control, (5.67±1.21)%, (7.85±1.41) pmol/L and 0.23±0.15 in Rentrop 3 group, (5.75±1.24)%, (8.06±1.50) pmol/L and 0.24±0.16 in Rentrop 2 group, (6.11±1.31)%, (8.19±1.57) pmol/L and 0.27±0.18 in Rentrop 1 group, (6.38±1.40)%, (8.89±1.66) pmol/L and 0.32±0.21 in Rentrop 0 group. Compared with good collateral group and control, HbA1c, FINS and HOMA2-IR were significantly higher in poor collateral group ($P<0.05$). The stepwise multivariable regression analysis shown that HOMA2-IR ($R=6.518$, $P<0.05$), HbA1c ($R=1.916$, $P<0.05$), 2h-PBG ($R=1.130$, $P<0.05$) and FINS ($R=1.547$, $P<0.05$) were significant independent predictor for the severity scale of coronary artery stenosis. The binary regression analysis shown, HOMA2-IR (OR=1.679, 95% CI: 1.101-2.558, $P=0.016$) enter the coronary collateral grade regression equation eventually. HOMA2-IR was the significantly independent predictor for poor coronary collateral.

CONCLUSIONS This study shows that insulin resistance is significantly higher in impaired glucose tolerance patients with coronary occlusion. The severity scale of coronary artery stenosis and the poor coronary collateral are partly related to insulin resistance.

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Value of Tei index and Brain Natriuretic Peptide on Predicting long-term Outcome in Ischemic Cardiomyopathy Patients

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OBJECTIVES To explore the value of Tei index and brain natriuretic peptide (BNP) on predicting major adverse cardiovascular events (MACE) in ischemic cardiomyopathy patients with two years long-term follow up.

METHODS The study enrolled 238 patients with ischemic cardiomyopathy. The patients were further divided into four groups according to the median of Tei index and BNP. G1 group (Tei≤0.66, BNP≤532.6 ng/ml, n=70), G2 group (Tei≤0.66, BNP > 532.6 ng/ml, n=51), G3 group (Tei > 0.66, BNP≤532.6 ng/ml, n=50), G4 group (Tei > 0.66, BNP > 532.6 ng/ml, n=67). Incidence of MACE was observed during