Patients with Type 2 Diabetes Exhibit Impaired Mobilisation of Endothelial Progenitor Cells after Acute Myocardial Infarction Mediated by VEGF/Akt/ENOS/MMP9 Pathway

Shen Yu, Lu Wen, Gu Rong, Wan Kun, Kang Lina. Department of Cardiology, Nanjing Gulou Hospital

Objective
The aim of this study is to investigate EPC mobilisation after acute myocardial infarction (AMI) in T2DM patients for the impairment of neovascularisation. We hypothesised that it is mediated by the downregulation of vascular endothelial growth factor (VEGF) pathway in bone marrow.

Research design and methods
We recruited 22 patients who were growth factor (VEGF) pathway in bone marrow.

Methods
Following AMI, patients with T2DM exhibited a delay (peak time: Day 7 vs Day 5) and a decrease in magnitude (peak level: 140±48/10^6 mononuclear cells (MNCs) vs 246±100/10^6 MNCs, p<0.05) of EPC mobilisation as compared to non-diabetic patients. This is similar to what we found in the T2DM rat model following AMI surgery. The first peak of EPC mobilisation in diabetic rats occurred 2 days later (Day 3 vs Day 1), and lower than nondiabetic rats (101±44/10^6 MNCs vs 260±64/10^6 MNCs respectively, p<0.05).

Conclusions
This is the first demonstration that bone marrow-derived EPC mobilisation following AMI is impaired in patients with T2DM. Such impairment is likely to have important contribution to the poor collateralization observed in such patients in response to vascular occlusive disease.

Increased Expression of Integrin-Linked Kinase Improves Cardiac Function after Myocardial Infarction in the Swine

Wen Lu, Wen Lu, Biao Xu

Objective and background
Left Cardiac remodelling is generally accepted as a determinant of the clinical course of heartfailure (HF). After myocardial infarction, cardiomyocyte loss and increased load trigger genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape and function of the heart. Prevention or attenuation of these signalling processes is an important goal of anti-remodelling therapy. Integrin-linked kinase (ILK), a widely expressed in mammalian tissues serine/threonine protein kinase, plays an important role in transducing cell–matrix interaction-induced biomechanical signals which regulate cytoskeletal remodelling, angiogenesis, cell growth, proliferation, survival and differentiation. Recently, ILK has been reported to be an critical component of the cardiac stretch sensor which regulates cardiac contractility, compensatory hypertrophy, survival and repair. In the previously study, we have found ILK could attenuate LV remodelling and improve the heart function after myocardial infarction in rats. In the present study, we investigated whether ILK could act a same role after acute myocardial infarction in swine.

Methods
Recombinant adenoviral vector containing both human wild-type ILK and humanised recombinant green fluorescent protein.
(hrGFP), as well as null-content adenoviral vector, was prepared. Swine of both genders were percutaneous intracoronary injected with adenoviral vector expressing ILK or empty ad-null in left anterior descending coronary artery (LAD) following left anterior descending coronary artery occlusion. ILK and report gene (hrGFP) expression were confirmed by western blotting and immunohistochemistry in both noninfarcted and infarcted hearts. Echocardiographic and PET-CT/SPECT analyses were performed 4 weeks after transfection. Then myocardial tissues were harvested and fixed for subsequent histological, immunohistochemical and TUNEL examination. Histological analysis of left ventricle was performed using H&E staining. Angiogenesis was evaluated by microvessel density using vwf staining. Apoptosis was measured by TUNEL analysis. Cardiomyocyte proliferation was estimated by proliferating cell nuclear antigen (PCNA) staining. Microvessel density was evaluated using CD105 and CD31 staining. Apoptosis was evaluated by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Echocardiographic and PET-CT/SPECT analyses were performed 4 weeks after transfection. Then myocardial tissues were harvested and fixed for subsequent histological, immunohistochemical and TUNEL examination.

**Results**

Western blotting and immunohistochemistry analysis revealed higher expression of ILK and hrGFP in infarct area of ad-ILK heart compared with ad-null controls after 4-week adenoviral delivery; the ectopic gene was mainly expressed in cardiomyocytes and partly in cardiac fibroblasts. Four weeks after transfection, echocardiographic and PET-CT/SPECT analysis demonstrated relatively preserved cardiac function in the ILK group. ILK treatment was associated with reduced infarct scar size, preserved LV geometry (including LV diameter, LV wall thickness, cardiomyocyte size). Enhanced angiogenesis was observed in ad-ILK animals. TUNEL analysis also revealed a reduction in apoptosis in the ILK group. Moreover, in vitro ILK increased cardiomyocyte proliferation was found through phospho-histone H3, decreased cardiomyocyte apoptosis, and increased VEGF expression.

**Conclusions**

ILK gene therapy improves cardiac remodelling and function in swines following myocardial infarction, and is associated with increased angiogenesis, reduced apoptosis and increased cardiomyocyte proliferation. These results may deliver a new approach to the treatment of post-infarct remodelling and subsequent heart failure.

**AN ESSENTIAL ROLE OF SERUM B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH ACUTE INFERIOR MYOCARDIAL INFARCTION**

**Objective**

To investigate the relationship between the level of serum B-type natriuretic peptide (BNP) and right ventricular infarction in patient with acute inferior myocardial infarction (AIMI).

**Method**

The serum BNP level was measured in 213 consecutive patients with acute inferior myocardial infarction and right ventricular infarction group; control group; left inferior myocardial infarction and right ventricular infarction group; control group; left anterior descending coronary artery (LAD) following left anterior descending coronary artery occlusion. ILK and report gene (hrGFP) expression were confirmed by western blotting and immunohistochemistry in both noninfarcted and infarcted hearts. Echocardiographic and PET-CT/SPECT analyses were performed 4 weeks after transfection. Then myocardial tissues were harvested and fixed for subsequent histological, immunohistochemical and TUNEL examination. Histological analysis of left ventricle was performed using H&E staining. Angiogenesis was evaluated by microvessel density using vwf staining. Apoptosis was measured by TUNEL analysis. Cardiomyocyte proliferation was estimated by proliferating cell nuclear antigen (PCNA) staining. Microvessel density was evaluated using CD105 and CD31 staining. Apoptosis was evaluated by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining. Echocardiographic and PET-CT/SPECT analyses were performed 4 weeks after transfection. Then myocardial tissues were harvested and fixed for subsequent histological, immunohistochemical and TUNEL examination.

**Results**

BNP level in the acute inferior myocardial infarction and right ventricular infarction group was significantly higher than that in acute inferior myocardial infarction group (p<0.101). The level in the proximal2mid segment of RCA group was higher than that in the LXC group (p<0.101). Additionally, logistic regression analysis showed that the level of BNP was an independent predictor of MACE in the 30 days and 3 months in acute inferior myocardial infarction patient (r=0.701, 95% CI <0.01 to 0.615, p<0.101).

**Conclusion**

We demonstrated the level of BNP in patients with acute inferior myocardial infarction or/and right ventricular infarction, and BNP could be a good predictor for patients with acute inferior myocardial infarction and right ventricular infarction.

**EFFECT OF ATROVASTATIN THERAPY ON BORDERLINE VULNERABLE LESIONS IN PATIENTS WITH ACUTE CORONARY SYNDROME**

**Objective**

To evaluate the effect of atrovastatin therapy on borderline vulnerable lesions in patients with acute coronary syndrome (ACS) and to investigate the relationship between lesion reversion and the level of MMP-9, TIMP-1, hs-CRP respectively.

**Methods**

Patients with ACS whose serum LDL-C is lower than 2.1 mmol/L underwent coronary angiography (CAG) and intravascular ultrasound (IVUS) investigation. If the culprit lesions were demonstrated to be borderline lesions (coronary artery stenosis between 50-70%) by CAG and minimal lumen cross-sectional area (CSA) >4.0 mm² by IVUS, the patients were enrolled in the present study. Intravascular ultrasound was performed to assess coronary atheroma at baseline and 12 months after atrovastatin therapy. The level of MMP-9, TIMP-1, hs-CRP were respectively measured by ELISA at baseline and 12 month-follow-up.

**Results**

No adverse events were reported during follow-up period. Comparing with baseline data, the level of ApoB decreased significantly at the end of the study (0.589±0.136 g/l vs 0.681±0.152 g/l, p=0.05). At 12 month IVUS follow-ups, minimal lumen CSA increased ((6.32±1.42) mm² vs (4.63±0.51) mm², p<0.01), the plaque/media (P&M) area decreased (6.70±1.19 mm² vs 8.17±1.55 mm²), p<0.05; Plaque Burden decreased (56.94±8.47 vs 61.4±10.34, p<0.01). A total of 25 soft plaques (50%) transformed into fibrous plaque. Comparing with baseline data, level of MMP-9 and hs-CRP decreased at the end of the study, ((1636±483) ng/ml vs (2241±554) ng/ml, p<0.001) and ((0.39+0.19 mg/l) vs (3.48±1.50 mg/l, p<0.001), respectively. TIMP-1 increased ((788±110) ng/ml vs (664±102) ng/ml, p<0.001). In stepwise multivariate linear regression analysis, the only independent predictor of changes in P&M area per year was decrement of MMP-9 and hs-CRP (γ=0.85, p<0.01, and γ=0.85, p<0.01, respectively). Regression equation is Annual Change of P&M area =−1.327+0.003 Annual Change of MMP-9+0.344 Annual Change of hs-CRP, R Square=0.830, Adjusted R Square=0.819, F=78.152, p=0.000.

**Conclusions**

Atrovastatin therapy stabilises borderline vulnerable plaque and reverses atherosclerosis progression in patients with ACS. Reversion of the atherosclerotic progression of vulnerable plaque is accompanied by the decrement of the level of plasma MMP-9 and hs-CRP. Changes in the level of MMP-9 and hs-CRP could predict the stabilisation of vulnerable plaque.