Original Article
Different expression of connexin 43 between culprit arteries and non-culprit arteries and role of angiotensin II on expression of connexin 43 in non-culprit arteries

Jian Wang[1], Zhong-Xian Li[2], Jing-Hua Liu[1], Shao-Ping Wang[1], Ming Zhang[1], Chang-Hua Wang[1], Ping Wang[1], Ze Zheng[1]

[1]Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, Beijing, China; [2]No. 371 Central-Hospital of PLA, Xinxiang, China

Abstract: *Introduction and objectives:* The purpose of the study was to observe different expression of connexin 43 between culprit arteries and nonculprit arteries in ischemia-reperfusion model and investigate on the mechanism of nonculprit arteries lesions progression. *Methods*: Rabbit hyperlipidemia ischemia-reperfusion model was established, vascular smooth muscles of culprit arteries and nonculprit arteries were divided into 4 groups: ① culprit arteries control group, ② nonculprit arteries control group, ③ culprit arteries ischemia-reperfusion group, ④ nonculprit arteries ischemia-reperfusion group. Immunohistochemistry analysis of connexin 43 was performed in each group. Smooth muscle cells of nonculprit arteries were divided into 4 groups: ① normal control group. ② hyperlipidemia control group. ③ angiotensin II intervention group. ④ mitogen-activated protein kinase pathway inhibitor pretreatment plus angiotensin II intervention group. Expression of connexin 43 was analysed in each group. Results: Fluorescence immunohistochemistry analysis of connexin 43 showed there was significant difference between culprit arteries ischemia-reperfusion group and nonculprit arteries ischemia-reperfusion group (1723.52±138.64 vs 2136.15±237.82, *P*<0.001). Expression of connexin 43 in angiotensin II intervention group was higher than that in hyperlipidemia control group (1.79±0.31 vs 1.25±0.21, *P*<0.05), expression of connexin 43 in mitogen-activated protein kinase pathway inhibitor pretreatment plus angiotensin II intervention group was lower than that in angiotensin II intervention group [(0.85±0.19 vs 1.79±0.31, *P*<0.05), (0.99±0.13 vs 1.79±0.31, *P*<0.05), (0.81±0.15 vs 1.79±0.31, *P*<0.05) respectively]. *Conclusions*: Expression of connexin 43 in nonculprit arteries was higher than that in culprit arteries, it may be involved in angiotensin II--mitogen-activated protein kinase pathway.

Keywords: Nonculprit arteries progression, connexin 43, angiotensin II, ischemia-reperfusion

Introduction

Although primary percutaneous coronary intervention (PCI) could salvage dying myocardium, reduce cardiovascular event, and improve prognosis in patients with acute myocardial infarction, recent studies showed that nonculprit arteries lesions may progress, and progression of nonculprit arteries lesions may be the important factor that influenced prognosis of patients with acute myocardial infarction after primary PCI [1]. The mechanism of nonculprit arteries progression was unclear. Our recent animal experiment showed that expression of connexin 43 (Cx43) was increased along with smooth muscle cells proliferation in nonculprit arteries, it indicated that expression of Cx43 was the key element of nonculprit arteries lesions progression. A recent research showed that angiotensin II (AgII) up-regulated expression of Cx43 via mitogen-activated protein kinase (MAPK) pathway and induced smooth muscle cells proliferation and migration in saphenous vein smooth muscle cells [2], we supposed that progression of nonculprit arteries may be due to up-regulation of expression of Cx43 in vascular smooth muscles via Ag II-MAPK pathway. Therefore, we planned to establish rabbit myocardium ischemia-reperfusion model, observed different expression of connexin 43 between culprit arteries and non-culprit arteries and investigated the role of AgII--MAPK--Cx43 pathway on progression of nonculprit arteries.

Methods

Hyperlipidemia model

Male Japanese white rabbits were fed with high fat diet for 80 days (free access to food and

water, 12 h light/dark cycle) and enrolled those total cholesterol >3 multiples of normal value (1~2 mmol/L) for ischemia-reperfusion model. hyperlipidemia rabbits were divided into four groups: ① culprit arteries control group (8 rabbits), ② nonculprit arteries control group (8 rabbits), ③ culprit arteries ischemia-reperfusion group (8 rabbits), ④ nonculprit arteries ischemia-reperfusion group (8 rabbits). Ischemia-reperfusion model was established as followed.

Ischaemia-reperfusion model

The animal experiments were conducted in accordance with guidelines of the Institutional Animal Care and Use Committee of Capital Medical University, and the study protocol was approved by the Institutional Ethics Committee of Capital Medical University. Rabbits possess double-deck pleura, they could survive even if unilateral pneumothorax happened during thoracotomy, so we selected rabbit for ischemia-reperfusion mode. Male Japanese white rabbits, weighing 2.5~3.0 kg were used in this study. The experimental animals were placed on an operating table. Sterile solutions were used to limit the inflammatory reaction to the surgical preparation. They were anaesthetised with pentobarbital sodium (40 mg/kg) administered via the marginal ear vein. Additional doses were given when required (10 mg/kg/h). A thoracotomy was performed at the 4th intercostal space and the pericardium was opened. A 3/0 silk 4th read was placed around left anterior descending coronary artery (LAD). Lead II of the surface electrocardiogram, heart rate and arterial pressure were continuous recorded on a computer (Mac Power PC) using a data acquisition system (MacLab 8 channels, AD Instruments). Heparin (2500 i.u.) was injected intravenous at the beginning of the experiment [3].

Experimental protocol

Experimental animals were allowed a 20 min stable period in order to reach a steady state after surgical preparation. Coronary artery occlusion was produced in the ischemia-reperfusion group by clamping the snare around the left anterior descending artery. Myocardial infarction was confirmed by elevation of the ST segment of surface electrocardiogram. The ligation was loosened after 30 min ischemia,

chest incision was closed with a three-layer suture, and then experimental animals were feed on ordinary diet for one week. Sterile solutions were used for 3 days to limit the inflammatory reaction to the surgical experiment. Lead II of the surface electrocardiogram was continuous recorded for 72 h. Experimental animals from the control group were submitted to the same surgical and experimental protocol, but coronary artery occlusion was not performed. All experimental animals that survived the experimental protocol were enrolled in this study [3]. Experimental animals were sacrificed to the marginal ear vein air embolism. Thereafter, animals from four groups (① culprit arteries control group (8 rabbits), ② nonculprit arteries control group (8 rabbits), ③ culprit arteries ischemia-reperfusion group (8 rabbits), ④ nonculprit arteries ischemia-reperfusion group (8 rabbits)) were submitted to either of the following protocols for tissue immunohistochemistry analysis and smooth muscular cells separation.

Reagents

Rabbit anti Cx43 monoclonal antibody (Cat. no. 35-5000), goat anti-rabbit IgG (H+L) second aintibody (Cat. no. 31460), 10% goat serum albumin, rabbit antiβ-actin monoclonal antibody (Cat. no. ZB001) (all from *Sigma-Aldrich Company* Ltd).

Coronary arteries staining

Culprit arteries were LAD, and nonculprit arteries were right coronary arteries (RCA). Coronary artery tissues (LAD and RCA) were collected. tissue blocks were fixed in tissue stationary liquid (Triangle Biomedical Sciences, Durham, NC), and cut into slices of thickness of 6 μm. Tissue slices were infused in methanol and 3% hydrogen peroxide solution for removal of endogenous peroxidase. Tissue slices were stained with HE for observing atherosclerosis lesions.

Cx43 immunohistochemistry analysis

Expression of Cx43 of vascular smooth muscles of culprit arteries and non-culprit arteries were quantitative analysed with immunohistochemical method [2], each tissue block was cut into 3 slices of thickness 3 μm, one slice was stained with hematoxylin-eosin for observing
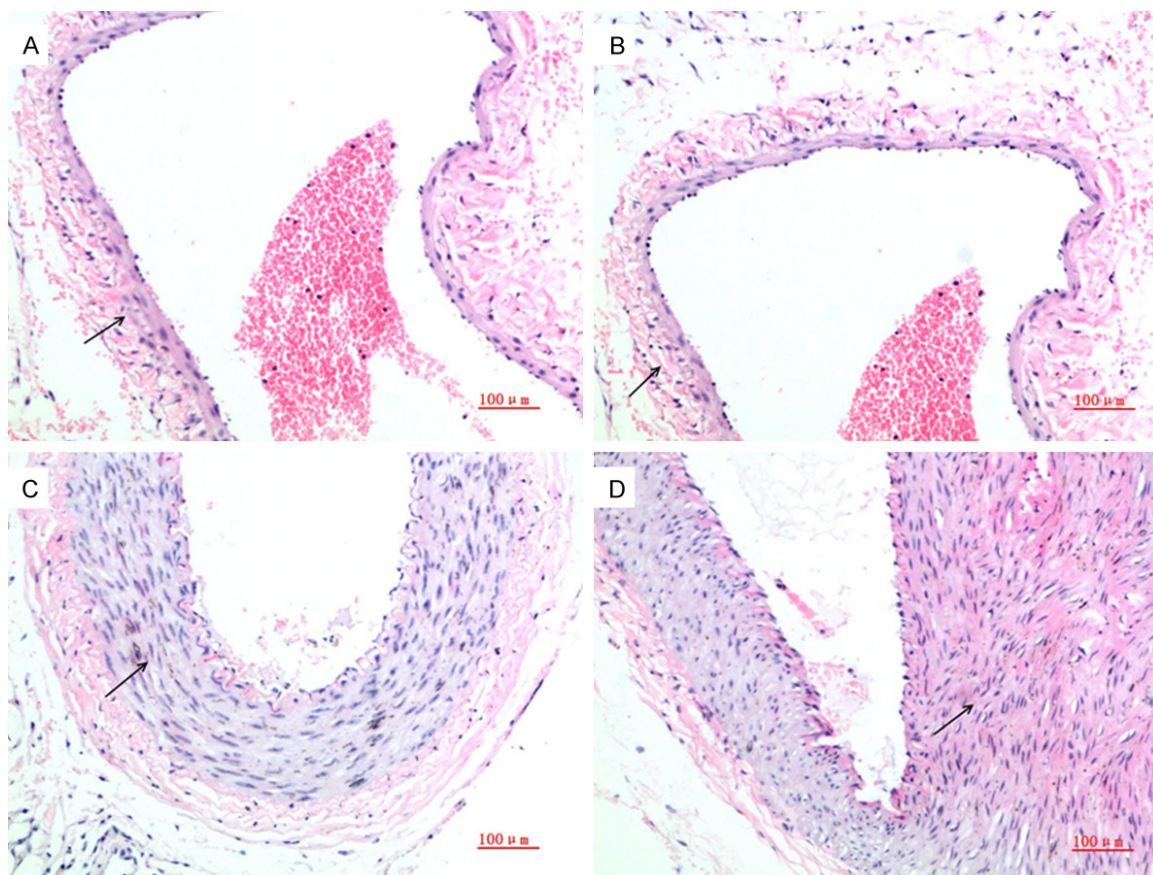
Figure 1. Histological changes of culprit arteries and non-culprit arteries. A. Culprit arteries control group; B. Nonculprit arteries control group; C. Culprit arteries ischemia-reperfusion group; D. Nonculprit arteries ischemia-reperfusion group. Note: arrow indicated coronary atherosclerosis plaque.

smooth muscle structure under light micro-scope. The other two slices were processed with immunohistochemistry method, they were dewaxed and dipped in 0.25% Triton X-100 solution for 30 min, digested by 0.1% tryp-sinase for 20 min in 37°C, rinsed by phosphate buffer solution (PBS, pH: 7.4, components: KH_2PO_4 0.2 g, $Na_2HPO_4 \bullet 12H_2O$ 2.9 g, NaCL 8.0 g, KCL 0.2 g added distilled water to 1000 ml), sealed by 10% goat seralbumin for 20 min, and decaed 1:400 anti Cx43 specific antibody in 4°C for incubation overnight (about 14 h). Next day slices were rewarming in room temperature for 1 h, and rinsed by phosphate buffer solu-tion, then were decaed 1:60 goat anti rabbit IgG antibody and incubation for 1 h, were mounted by 60% buffer glycerine. All process required protection from light. The color of Cx43 Immunohistostaining was yellow brown. Each slice was selected four Immunohistos-taining zone, 2 slices were selected for each rabbit, Cx43 was quantitative analysed by MIAS

image analysis system (Beijing University of Aeronautics and Astronautics).

Smooth muscle cells separation culture and subgroup

Rabbits (included normal control group (8 rab-bits) and hyperlipidemia group (8 rabbits)) were executed, left anterior descending arteries (cul-prit arteries) and left right coronary arteries (nonculprit arteries) were separated under as-epsis condition, and were moved to super clean bench, intima and tunica media were scraped off, smooth muscle cells were digested and separated by collagenase type I, smooth mus-cle cells were inoculated in a 100 mL culture bottle (concentration: 1×10^5/mL), cultivated by 20% solcoseryl DMEM/F12 culture medium, serial subcultivated to the fourth generation for reserve. Smooth muscle cells were divided into 4 groups (12 samples in each group): ① normal control group, smooth muscle cells supplied

Table 1. Thickness of coronary atherosclerosis plaque in each group

Group	n	Thickness (μm)
Culprit arteries control group	8	41.03±11.41
Nonculprit arteries control group	8	38.21±10.17[*]
Culprit arteries ischemia-reperfusion group	8	83.98±16.25[**]
Nonculprit arteries ischemia-reperfusion group	8	111.73±23.43[***]

Note: [*]compared with culprit artery control group, $P>0.05$; [**]compared with culprit artery control group, $P<0.001$; [***]compared with nonculprit artery control group and culprit artery ischemia-reperfusion group, $P<0.0001$, $P<0.001$ respectively.

Table 2. Cx43 of culprit arteries and non-culprit arteries immunohistochemistry analysis one week later after ischemia-reperfusion (mean integral optical density)

Group	n	Cx43 quantitative analysis
Culprit arteries control group	8	1315.21±151.47
Nonculprit arteries control group	8	1302.76±142.31[*]
Culprit arteries ischemia-reperfusion group	8	1723.52±138.64[**]
Nonculprit arteries ischemia-reperfusion group	8	2136.15±237.82[***]

Note: [*]compared with culprit arteries control group, $P>0.05$; [**]compared with culprit arteries control group, $P<0.001$; [***]compared with nonculprit arteries control group and culprit arteries ischemia-reperfusion group, $P<0.001$.

with phosphate buffer solution. ② hyperlipidemia control group, hyperlipidemia smooth muscle cells supplied with phosphate buffer solution. ③ angiotensin II intervention group, hyperlipidemia smooth muscle cells were cultivated in 6-well culture plates, 3 ml cell culture media was added to each well. Smooth muscle cells were intervened by Ang II ($1×10^{-7}$ mol/L) for 24 h. ④ MAPK pathway inhibitor pretreatment plus Angiotensin II intervention group, smooth muscle cells were pretreated by MARK pathway (ERKs, JNKs and P38MAP) inhibitor (PD98059 (100 μmol/L), SB203580 (25 μmol/L), SP600125 (25 μmol/L)) for 30 min respectively and intervened by Ang II ($1×10^{-7}$ mol/L) for 24 h.

Cx3 expression of smooth muscle cells in nonculprit arteries

Smooth muscle cells of four groups were separated and total proteins were isolated from smooth muscle cells, and equal amounts (20 μg) of protein samples were resolved by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto a nitrocellulose membrane. The membrane was blocked in 5% milk in TBS-T (Tris buffered saline and 0.1% Tween 20) for 1 h and then incubated with primary antibody against Cx43 (1:200; USCNLIFE) or β-actin (1:200; USCNLIFE) as an internal control overnight at 4°C, followed by incubation with horseradish peroxidase-conjugated secondary antibody (1:10,000; USCNLIFE) for 1 h at 25°C. After washing 3 times with TBS, the membrane was developed using an enhanced chemiluminescent detection system (Amersham, Piscataway, NJ, USA). Signal intensities were quantitated using the Quantity One software (Bio-Rad, Hercules, CA). Cx43 expression was quantitated by Cx43/β-actin optical absorption ratio.

Statistical analysis

All statistical analyses were carried out using the SPSS 11 software. Measurement data were present as mean ± SD, Statistical evaluations among groups (more than 2 groups) were done using analysis of variance (ANOVA) with the Tukey post hoc test, values of *p* less than 0.05 were considered as significant. Statistical evaluations between two groups were done using *t* test, values of *p* less than 0.05 were considered as significant.

Results

Atherosclerosis plaques were shown in culprit arteries and nonculprit arteries one week later after ischemia-reperfusion (**Figure 1**). Coronary artery tissues HE staining quantitative analysis showed that atherosclerosis plaque thickness was 41.03±11.41 μm in culprit arteries control group, 38.21±10.1 μm in nonculprit arteries control group (compared with culprit artery control group, $P>0.05$), 83.98±16.2 μm in culprit arteries ischemia-reperfusion group (compared with culprit arteries control group, $P<0.001$), 111.73±23.43 μm in nonculprit arteries ischemia-reperfusion group (compared with nonculprit arteries control group and culprit arteries ischemia-reperfusion group, $P<0.0001$, $P<0.001$ respectively) (**Table 1**).

Cx43 of culprit arteries and non-culprit arteries immunohistochemistry analysis showed that
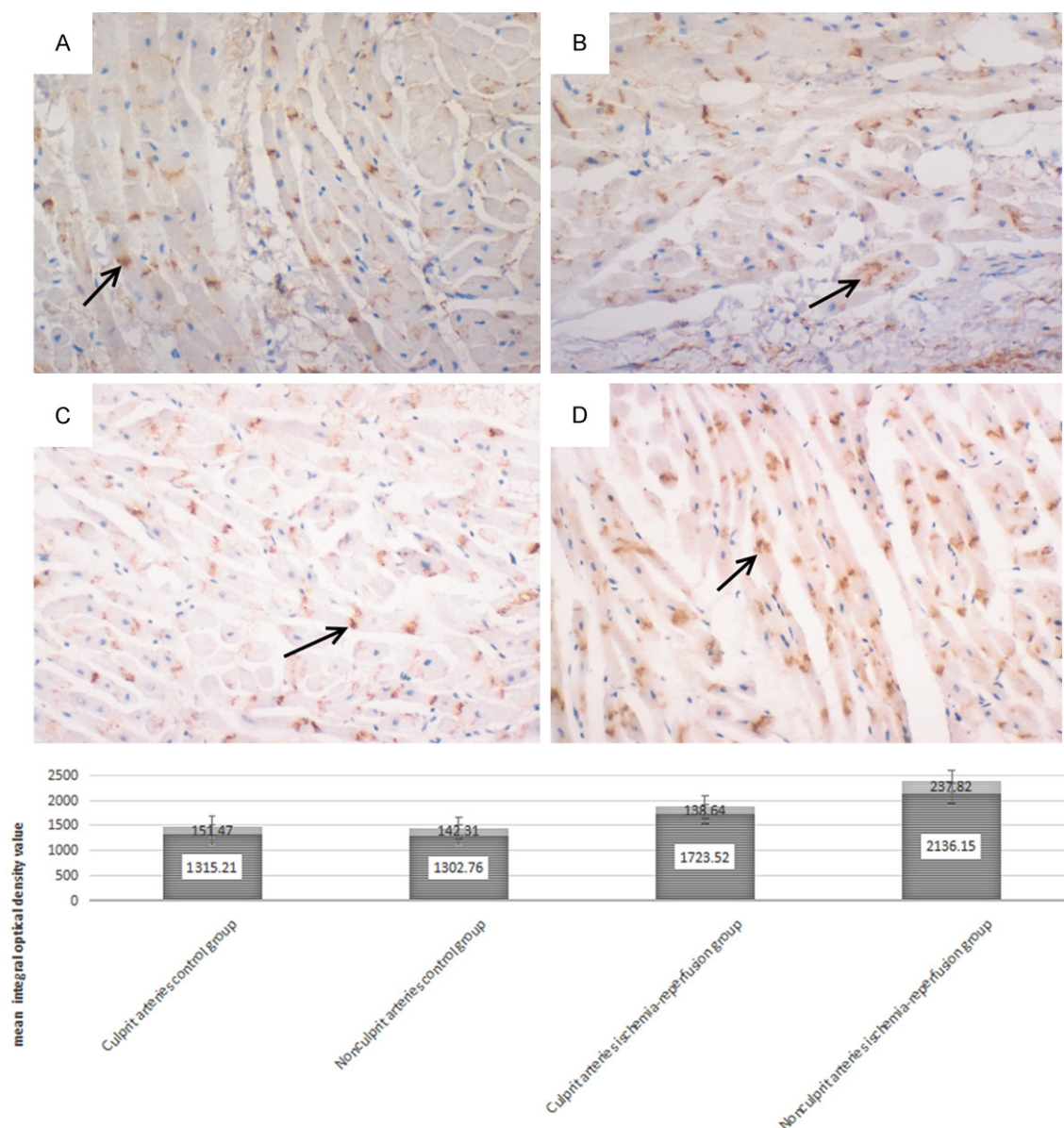
Figure 2. Immunohistostaining of Cx43 in culprit arteries and non-culprit arteries. A. Culprit arteries control group; B. Nonculprit arteries control group; C. Culprit arteries ischemia-reperfusion group; D. Nonculprit arteries ischemia-reperfusion group. Note: arrow indicated Cx43.

mean integral optical density of Cx43 was 1315.21±151.47 in culprit arteries control group, 1302.76±142.31 in nonculprit arteries control group; mean integral optical density of Cx43 was 1723.52±138.64 in culprit arteries ischemia-reperfusion group, and 2136.15±237.82 in nonculprit arteries ischemia-reperfusion group. it indicated that there was no significant difference between culprit arteries control group and nonculprit arteries control group ($P = 0.4084$), there was significant difference between culprit areries ischemia-reperfusion

group and nonculprit arteries ischemia-reperfusion group ($P<0.001$) (**Table 2**).

Isolating culture and subgroup study of smooth muscle cells showed that Cx43 expression in hyperlipidemia group was significant higher than that in normal control group [1.25±0.21 vs 0.62±0.14, $P<0.05$], Cx43 expression in Angiotensin II intervention group was significant higher than that in hyperlipidemia group [1.79±0.31 vs 1.25±0.21, $P<0.05$], Cx43 expression in MARK pathway inhibitor plus an-
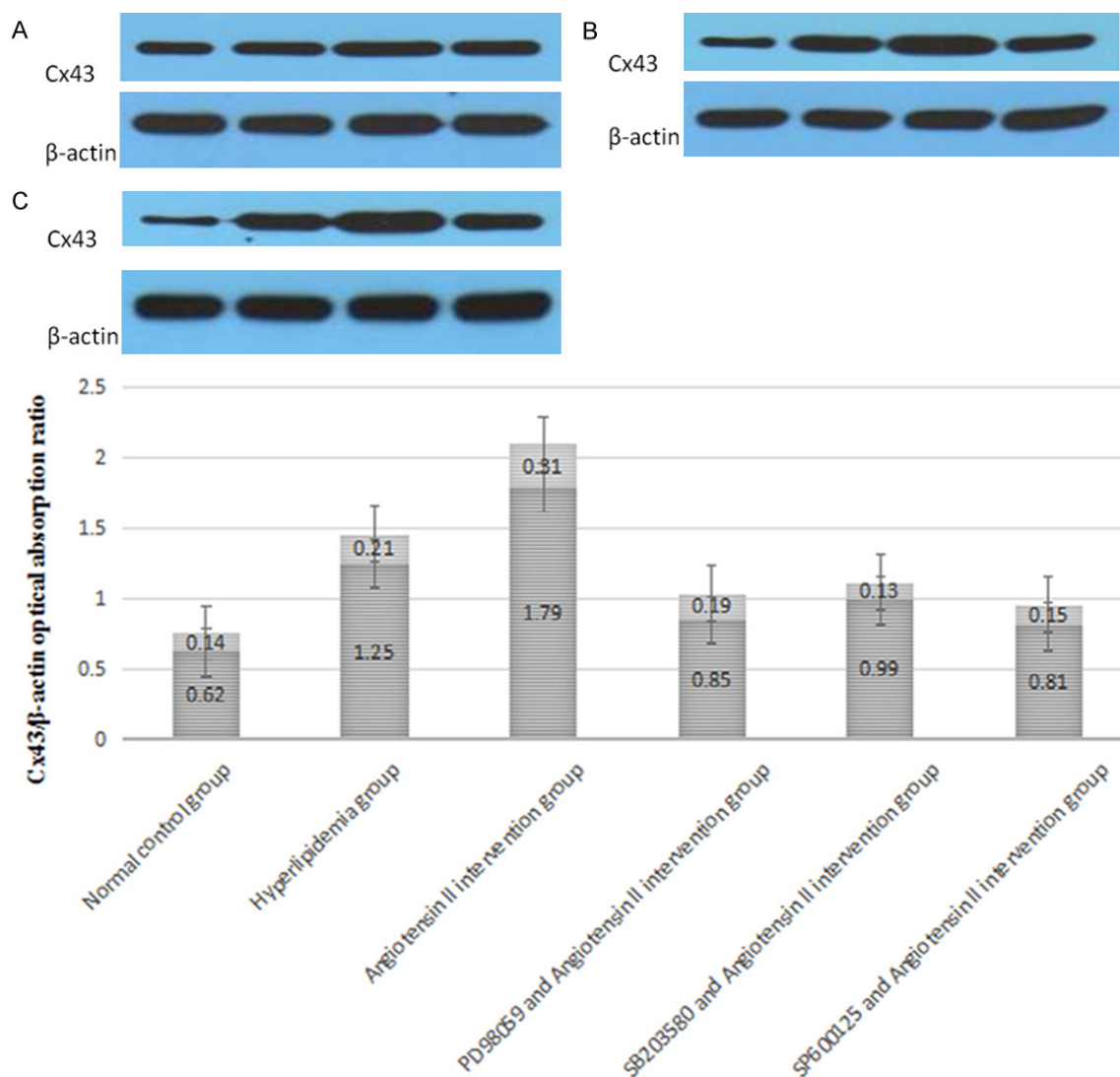
Figure 3. Effect of MAPK pathway inhibitor pretreatment and Angiotensin II intervention on Cx43 expression of non-culprit arteries. Notes: A. From left to right: normal control group, hyperlipidemia group, Angiotensin II intervention group, PD98059+ Angiotensin II intervention group; B. From left to right: normal control group, hyperlipidemia group, Angiotensin II intervention group, SB203580+ Angiotensin II intervention group; C. Note: from left to right: normal control group, hyperlipidemia group, Angiotensin II intervention group, SP600125+ Angiotensin II intervention group. *Compared with normal control group, $P<0.05$; **Compared with hyperlipidemia group, $P<0.05$; #Compared with Angiotensin II intervention group, $P<0.05$.

giotensin II intervention group was significant lower than t in angiotensin II intervention group [(0.85±0.19 vs 1.79±0.31, $P<0.05$), (0.99±0.13 vs 1.79±0.31, $P<0.05$), (0.81±0.15 vs 1.79±0.31, $P<0.05$) respectively] (**Figure 3**; **Table 2**).

Discussion

Nowadays there are few studies about nonculprit arteries progression in patients with acute ST elevation myocardial infarction. We have studied blood flow perfusion and myocardium tissue perfusion of non-culprit arteries in 117 patients with acute myocardial infarction, and found that blood flow perfusion and myocardium tissue perfusion of nonculprit arteries were correlation with those of culprit arteries [4, 5]. Moreover, we have performed a clinical follow-up study for 519 patients with STEMI underwent primary percutaneous coronary intervention, and found that recurrent PCI was mainly due to non-culprit arteries lesions progression. Chronic inflammation and sustained stress

Table 3. Effect of MAPK pathway inhibitor pretreatment and Angiotensin II intervention on Cx43 expression of non-culprit arteries (Cx43/β-actin optical absorption ratio)

$n = 12$	Normal control group	Hyperlipidemia group	Angiotensin II intervention group	PD98059 pretreatment and Angiotensin II intervention group	SB203580 pretreatment and Angiotensin II intervention group	SP600125 pretreatment and Angiotensin II intervention group
Cx43/β-actin optical absorption ratio	0.62±0.14	1.25±0.21*	1.79±0.31▲	0.85±0.19Δ	0.99±0.13Δ	0.81±0.15Δ

Note: *compared with normal control group, $P<0.05$; ▲compared with hyperlipidemia group, $P<0.05$; Δcompared with Angiotensin II intervention group, $P<0.05$.

may be involved in progression of non-culprit arteries lesions, catecholamine may play an important role on progression of nonculprit arteries lesions [6]. However, its specific mechanism was unknown.

In the recent years, the role of connexins (Cxs) on vascular smooth muscle cell (VSMC) proliferation and migration in atherosclerosis (AS) was more and more attractive. Cx43 was a transmembrane protein, it consists of four transmembrane domains, two extracellular and one intracellular loop. There is increasing evidence that connexins are involved in the development of intimal hyperplasia and restenosis involving mouse and human atherosclerotic lesions. Gap junctions provide an enclosed channel for direct exchange of signaling molecules, including ions and small metabolites. Evidence suggested that Cx43 participated in cell growth, differentiation, and the development of intimal hyperplasia [7]. In early atheromas, the expression of Cx43 in smooth muscle cells has been observed in the neointimal lesion. Cx43 was found in the endothelium covering the shoulder of the plaques and neointimal smooth muscle cells. Cx43 gene expression was also altered in rabbit arterial wall and plays a key role in neointimal formation after balloon injury. Deglise and colleagues observed coronary arteries samples in patients underwent heart transplantation, and found that expression of Cx43 in intima hyperplasia region was 10 fold higher than in the normal vessel in prophase stage of atherosclerosis. Along with atherosclerosis progression, expression of Cx-43 was decreased gradually, and in the end stage of atherosclerosis, expression of Cx43 was lower than that in the normal vessel. In the prophase stage of atherosclerosis, inhibiting expression of Cx43 in vessel smooth muscle may inhibit progression of atherosclerosis, it indicated that Cx43 participate in prophase progression of atherosclerosis [8].

As to Cx43 signal transduction pathway, Jia et al. observed that expression of Cx43 in smooth muscle cell of saphenous vein was up-regulation and lead to smooth muscle cell proliferation and migration after pretreated with angiotensin II. Up-regulation of Cx43 expression was depend on AP-1, and was regulated by ERK1/2, p38MAPK and JNK signal transduction pathway [9, 10]. It indicated that Ang II-MAPK-Cx43 pathway may participate in proliferation and migration of smooth muscle cells in vein. However, it was not clear that Ang II-MAPK-Cx43 pathway whether or not participate in proliferation and migration of smooth muscle cells in nonculprit arteries.

In view of above-mentioned study, we supposed that nonculprit arteries progression may be due to increased angiotensin II, and angiotensin II may induce up-regulation of expression of Cx43 by MAPK pathway.

Our study showed that atherosclerosis plaques were shown in nonculprit arteries one week later after ischemia-reperfusion (**Figure 1**; **Table 1**). Atherosclerosis plaque thickness in nonculprit arteries ischemia-reperfusion group was more than nonculprit arteries control group and culprit arteries ischemia-reperfusion group. It indicated that nonculprit arteries progress more quickly than culprit arteries (**Figure 1**; **Table 1**).

Cx43 of culprit arteries and non-culprit arteries immunohistochemistry analysis showed that mean integral optical density of Cx43 was 1315.21±151.47 in culprit arteries control group, 1302.76±142.31 in nonculprit arteries control group; mean integral optical density of Cx43 was 1723.52±138.64 in culprit arteries ischemia-reperfusion group, and 2136.15± 237.82 in nonculprit arteries ischemia-reperfusion group. There was no significant difference between culprit arteries control group and nonculprit arteries control group ($P = 0.4084$), and there was significant difference between culprit arteries ischemia-reperfusion group and nonculprit arteries ischemia-reperfusion group ($P< 0.001$) (**Figure 2**; **Table 2**). It indicated that

expression of Cx43 in nonculprit arteries was more than that in culprit arteries after ischemia-reperfusion, moreover, nonculprit arteries lesions progress more quickly than culprit arteries lesions after ischemia-reperfusion. It suggested that Cx43 may be the key element of nonculprit arteries progression. The reason that expression of Cx43 in nonculprit arteries was more than that in culprit arteries after ischemia-reperfusion may be involved in injure-repair mechanism: injure in culprit arteries was more than that in nonculprit arteries, but repair was similar in both culprit arteries and nonculprit arteries.

Isolation culture in vitro for smooth muscle cells in nonculprit arteries showed that expression of Cx43 (Cx43/β-actin photoabsorption ratio) in Hyperlipidemia group was higher than that in the control group [(0.86±0.17 vs 0.45±0.12, $P<0.05$), (1.25±0.21 vs 0.62±0.14, $P<0.05$), (0.85±0.18 vs 0.39±0.12, $P<0.05$) respectively]; expression of Cx43 in angiotensin II intervention group was higher than that in hyperlipidemia group [(1.26±0.34 vs 0.86±0.17, $P<0.05$), (1.79±0.31 vs 1.25±0.21, $P<0.05$), (1.28±0.37 vs 0.85±0.18, $P<0.05$) respectively]; Cx43 expression in MARK pathway inhibitor plus Angiotensin II intervention group was significant lower than that in Angiotensin II intervention group [(0.85±0.19 vs 1.79±0.31, $P<0.05$), (0.99±0.13 vs 1.79±0.31, $P<0.05$), (0.81±0.15 vs 1.79±0.31, $P<0.05$) respectively] (**Table 3**). It indicated that, as neuroendocrine was activated (serum catecholamine level was increased) and hemodynamics was altered in patients with acute ST elevation myocardium infarction after primary PCI [6] renin-angiotensin system was activated. Increased angiotensin II may affect signal transduction of MARK pathway via autocrine, paracrine, emiocytosis (or via concomitance microcirculation pathway between culprit artery and nonculprit artery), leaded to Cx43 expression upregulation, smooth muscle cells proliferation, migration, and atherosclerosis lesions progression [11, 12].

Conclusions

We concluded that expression of Cx43 in nonculprit arteries was more than that in culprit arteries after ischemia-reperfusion, moreover, nonculprit arteries lesions progress more quickly than culprit arteries lesions after ischemia-reperfusion. Sympathetic nerve--catecholamine--angiotonin II--Cx43 may participate in nonculprit arteries progression. Angiotensin-converting enzyme inhibitor (ACEI) may inhibit nonculprit arteries progression. It may provide new thinking and new therapy target for nonculprit arteries progression.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jian Wang, Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, 2 Anzhen Road, Chaoyang District, Beijing 100029, China. E-mail: 13671329282@139.com

References

[1] Tsiamis E, Toutouzas K, Synetos A, Karambelas J, Karanasos A, Demponeras C, Drakopoulou M, Stefanadi E, Tsioufis C, Tousoulis D, Stefanadis C. Prognostic clinical and angiographic characteristics for the development of a new significant lesion in remote segments after successful percutaneous coronary intervention. Int J Cardiol 2009; 72: 352-358.

[2] Jia G, Cheng G, Gangahar DM, Agrawal DK. Involvement of connexin 43 in angiotensin II-induced migration and proliferation of saphenous vein smooth muscle cells via the MAPK-AP-1 signaling pathway. J Mol Cell Cardiol 2008; 44: 882-890.

[3] Mazenot C, Loufrani L, Henrion D, Ribuot C, Müller-Esterl W, Godin-Ribuot D. Endothelial kinin B1-receptors are induced by myocardial ischaemia-reperfusion in the rabbit. J Physiol 2001; 530: 69-78.

[4] Wang J, Liu JH, Zheng B, Zhang M, Wang SP, Zheng Z. Impact of primary PCI on blood perfusion in nonculprit artery in patients with anterior STEMI. Chin Med J (Engl) 2013; 126: 22-26.

[5] Wang J, Yan HB, Zheng B, Song L, Wang SP, Zhang XJ, et al. The impact of primary PCI in culprit artery on epicardial blood flow of nonculprit artery in patients with anterior STEMI. Chin J Emerg Med 2011; 20: 971-975.

[6] Wang J, Liu JH, Zhu XL, Zhang M, Wang SP, Zheng Z. Nonculprit lesion progression in patients with ST elevation myocardial infarction after primary percutaneous coronary intervention. Int Heart J 2014; 55: 48-52.

[7] Chadjichristos CE, Morel S, Derouette JP, Sutter E, Roth I, Brisset AC, Bochaton-Piallat ML, Kwak BR. Targeting connexin 43 prevents platelet-derived growth factor-BB induced phenotypic change in porcine coronary artery smooth muscle cells. Circ Res 2008; 102: 653-660.

[8] Déglise S, Martin D, Probst H, Saucy F, Hayoz D, Waeber G, Nicod P, Ris HB, Corpataux JM, Haefliger JA. Increased connexin43 expression in human saphenous veins in culture is associated with intimal hyperplasia. J Vasc Surg 2005; 41: 1043-1052.

[9] Jia G, Mitra AK, Cheng G, Gangahar DM, Agrawal DK. Cross-talk between angiotensin II and IGF-1-induced connexin 43 expression in human saphenous vein smooth muscle cells. J Cell Mol Med 2010; 15: 1695-1702.

[10] Salameh A, Krautblatter S, Baessler S, Karl S, Rojas Gomez D, Dhein S, Pfeiffer D. Signal transduction and transcriptional control of cardiac connexin43 up-regulation after 1-adrenoceptor stimulation. J Pharmacol Exp Ther 2008; 326: 315-322.

[11] Pfenniger A, Chanson M, Kwak BR. Connexins in atherosclerosis. Biochim Biophysica Acta 2013; 1818: 157-166.

[12] Salameh A, Dhein S. Effect of mechanical forces and stretch on intercellular gap junction coupling. Biochim Biophys Acta 2011; 1818: 147-156.