Intracoronary pressure gradient measurement in acute myocardial infarction patients with the no-reflow phenomenon during primary percutaneous coronary intervention

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Abstract

Background: Various experimental and clinical studies have reported on coronary microcirculatory dysfunction ("no-reflow" phenomenon). Nevertheless, pathogenesis and effective treatment are yet to be fully elucidated. This study aimed to measure the intracoronary pressure gradient in the no-reflow artery during emergent percutaneous coronary intervention and explore the potential mechanism of no-reflow.

Methods: From September 1st, 2018 to June 30th, 2019, intracoronary pressure in acute myocardial infarction patient was continuously measured by aspiration catheter from distal to proximal segment in the Department of Coronary Care Unit, Tianjin Chest Hospital, respectively in no-reflow arteries (no-reflow group) and arteries with thrombolysis in myocardial infarction-3 flow (control group). At least 12 cardiac cycles were consecutively recorded when the catheter was pulled back. The forward systolic pressure gradient was calculated as proximal systolic pressure minus distal systolic pressure. Comparison between groups was made using the Student t test, Mann-Whitney U-test or Chi-square test, as appropriate.

Results: Intracoronary pressure in 33 no-reflow group and 26 in control group were measured. The intracoronary forward systolic pressure gradient was $-1.3$ ($-4.8, 0.7$) and $3.8 (0.8, 8.8)$ mmHg in no-reflow group and control group ($Z = -3.989, P < 0.001$), respectively, while the forward diastolic pressure gradient was $-1.0$ ($-3.2, 0$) and $4.6 (0, 16.5)$ mmHg in respective groups ($Z = -3.851, P < 0.001$). Moreover, the intracoronary forward pressure gradient showed significant difference between that before and after nicorandil medication ($Z = -3.668, P < 0.001$ in systolic pressure gradient and $Z = -3.530, P < 0.001$ in diastolic pressure gradient).

Conclusions: No reflow during emergent coronary revascularization is significantly associated with local hemodynamic abnormalities in the coronary arteries. Intracoronary nicorandil administration at the distal segment of a coronary artery with an aspiration catheter could improve the microcirculatory dysfunction and resume normal coronary pressure gradient.

Clinical trial registration: www.ClinicalTrials.gov (No. NCT 03600259).

Keywords: Acute myocardial infarction; Coronary hemodynamics; Intracoronary pressure gradient; No-reflow; Primary percutaneous coronary intervention

Introduction

The no-reflow phenomenon is defined as a lack of the myocardial reperfusion after prolonged ischemia despite opening of the infarct-related artery (IRA), which may occur due to multiple factors, including mechanical obstruction by embolisms, vascular auto-regulation (sympathetic reflex), the extrinsic coagulation pathway, leukocyte adherence, platelet thrombi, free radicals, microvascular ischemia, and edema. A study from wave intensity analysis showed that both distal (myocardial) and proximal (aortic) ends of the coronary system can exert a dynamic influence on blood flow, which is different from the systemic circulation. There are six cyclic waves per cardiac cycle with an ascription to particular cardiac activities, among which three originate proximally (forward compression wave; forward decompression wave; late forward compression wave) and three distally (early backward compression wave, late backward compression wave, backward decompression wave). No reflow after primary percutaneous coronary intervention (pPCI) often leads to increased myocardial necrosis, coronary endothelial dysfunction, cardiac dysfunction, and microcirculatory dysfunction, which in turn can lead to stronger blood flow in the opposite direction.© 2020 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the Creative Commons Attribution-NonCommercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. Edited by: Ning-Ning Wang

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To date, studies on the treatment of no-reflow phenomenon have mainly focused on vasodilator agents, which are often used for emergent revascularization of the no-reflow phenomenon via guiding catheter, peripheral vein, and arterial sheath. Intracoronary nicorandil and adenosine are both efficient and safe as adjunctive treatments to pPCI after thrombus aspiration. The coronary flow velocity pattern assessed by Doppler guidewires in the no-reflow coronary artery is characterized by the appearance of systolic retrograde flow, a diminished systolic antegrade flow plus a rapid deceleration of diastolic flow. In theory, blood flows from the chamber with high pressure to the chamber with low pressure; hence, we hypothesized that intracoronary pressure in the distal segment of the no-reflow artery would be higher than the proximal segment after coronary recanalization. In other words, contradictory pressure gradients are involved in the occurrence of the no-reflow phenomenon. Therefore, we attempted to continuously measure the intracoronary pressure from distal to proximal in the no-reflow coronary artery during emergent PCI.

Methods

Ethical approval

Our research was approved by the Ethics Committee of Tianjin Chest Hospital (No. 2017LW-002). All the patients received pPCI approved the possibility that they may be enrolled into our research before procedure. Written informed consent was obtained from each participant according to federal and institutional guidelines.

Patient population

Inclusion criteria were the onset of ST segment elevation myocardial infarction less than 12 h before admission and successful coronary stent implantation from September 1st, 2018 to June 30th, 2019. Exclusion criteria included significant cardiac insufficiency (left ventricular ejection fraction <40%); ostium, extremely bifurcation or tortuous coronary lesions. Among them, 33 patients suffering no-reflow (thrombolysis in myocardial infarction [TIMI] grade 0–1) were assigned to the no-reflow group, while 26 patients who directly obtained TIMI grade 3 blood flow in the same period were randomly selected with a ratio of 1:30 into the control group. Continuous intracoronary pressure was successfully measured in 59 patients via the top of the aspiration catheter.

Coronary angiography and pressure measurements

Aspirin (300 mg) and clopidogrel (300 mg) were orally taken before coronary angiography. Intravenous heparin (routine dose 100 U/kg) was given before angioplasty. All digital angiography images were obtained at a speed of 25 frames/s. Left and right coronary angiograms were assessed by at least two experienced interventional cardiologists. The guiding catheter and percutaneous transluminal coronary angioplasty (PTCA) guidewire were chosen according to the characteristics of the lesion and operator’s experience. Thrombus suction was routinely performed before balloon angioplasty when the artery was completely occluded, and the blood flow was lower than TIMI grade 2, or the thrombus could be seen on X-ray images. Thrombus suction was deemed effective when the thrombus completely disappeared and blood flow returned to a TIMI grade 3, thus allowing for exclusion of severe stenosis. Stenting was performed following balloon angioplasty. No filter wire protection was used.

The no-reflow diagnosis was confirmed after successful stent implantation without mechanical complications, for example, dissection, spasm, or obvious distal embolization if the flow of the target vessel was less than TIMI grade 3 if it presented as abnormal runoff of contrast, retrograde movement or cessation of motion during systole. To rule out atypical cases and atypical changes, the patients suffering slow flow (TIMI grade 2) were excluded, and only those with no-reflow (TIMI grade 0–1) after stent were enrolled into the no-reflow group. The thrombus aspiration catheter (ZEEK, Zeon Medical Inc, Tokyo, Japan) was inserted into the no-reflow vessel again along the PTCA wire. After contrast was injected through an aspiration catheter to confirm the patency of the distal artery, the catheter was rinsed with heparin saline. Then, the pressure-monitoring device that comes with the machine (Mac-Lab IT, GE Healthcare, WI, USA) was connected to the end of the aspiration catheter. The tip of the aspiration catheter was positioned to the distal segment at the no-reflow artery. After the position for measuring coronary pressure was optimized and jam-free pressure graphics were shown, the operator slowly pulled back the aspiration catheter until the tip was back into the guiding catheter. Systolic and diastolic pressure of 12 cardiac cycles were recorded with the speed of 23 mm per second; including the systolic and diastolic pressures of a far segment, middle segment, near segment, and each heartbeat.

The aspiration catheter was advanced again over the no-reflow region, and nicorandil was bolus-injected into the distal coronary at a dose of 2 to 6 mg (Beijing Sihuan Kebao Pharmaceutical Co. Ltd., Beijing, China) through the end of the aspiration catheter. The repeated injection and combination with sodium nitroglycerin or nitroprusside injection were allowed until TIMI grade 3 flow was achieved. The cases with ideal TIMI 3 grade flow after stent implantation were assigned to the control group. Two radiologists blinded to patient data evaluated the blood flow of the IRA according to the existing TIMI criteria.

The pressure graphics and systolic or diastolic pressure values are shown in Figures 1 and 2.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (range interquartile), whereas categorical variables are expressed as a percentage. Comparison between groups was made using the Student t test, Mann–Whitney U test, or Chi-square test, as appropriate. All data were analyzed using SPSS 24.0 (SPSS, Inc. Chicago, IL, USA). A value of P < 0.05 was considered statistically significant. The proximal systolic and diastolic pressure were respectively regarded as the average of the
last three peaks and value before the aspiration catheter was pulled back into guiding catheter tip, while the distal systolic and diastolic pressure were the mean value of the first three systolic and diastolic pressures measured at the distal segment of culprit artery. The forward systolic pressure gradient was calculated as proximal systolic pressure minus distal systolic pressure, while the forward diastolic pressure gradient was the gap between proximal diastolic pressure and distal diastolic pressure.

**Results**

A total of 59 consecutive patients were enrolled in the clinical observational research; 33 were in the no-reflow group and 26 were in the control group. Table 1 shows the basic characteristics and angiographic features. In the no-reflow group, ten patients presented as TIMI flow grade 1 and others were of grade 0. The culprit lesion was left anterior descending artery in 15 patients, right coronary artery in 14 patients, and left circumflex artery in four patients.

The intracoronary systolic/diastolic pressures accord with the Gaussian Distribution, while the forward systolic/diastolic pressure not. The intracoronary systolic pressures at the distal and proximal segments were 114.6 ± 25.1 and 112.1 ± 24.1 mmHg in the no-reflow group, while 110.9 ± 16.2 and 113.7 ± 14.9 mmHg in the control group, respectively, with a forward systolic pressure gradient of −1.3 (−4.8, 0.7) and 3.8 (0.8, 8.8) mmHg in respective groups (Z = −3.989, P < 0.001). The intracoronary diastolic pressures at the distal and proximal segments were 71.2 ± 14.8 and 69.4 ± 13.6 mmHg in the no-reflow group, and 62.6 ± 12.3 and 70.2 ± 10.7 mmHg in the control group, respectively, with a forward diastolic pressure gradient −1.0 (−3.2, 0) and 4.6 (0, 16.5) mmHg in respective groups (Z = −3.851, P < 0.001) as shown in Table 2.

The intracoronary forward pressure gradient showed significant difference between that before and after nicorandil medication (Z = −3.668, P < 0.001 in systolic pressure gradient and Z = −3.530, P < 0.001 in diastolic pressure gradient) [Table 3]. The pressure gradients in some patients from control and no-reflow group are respectively shown in Figures 1 and 2.

All pressure values of 12 cardiac cycles from distal to proximal were recorded, and trend curves were shown for systolic pressure and diastolic pressure. The trend was consistent with the pressure changes observed in the previous two groups (P < 0.05, both in Figure 3).

**Discussion**

In the present study, we found that both the systolic and diastolic intracoronary pressures at the distal segment of the no-reflow artery were higher than those at the proximal...
Table 2: Intracoronary pressure and pressure gradient measurement in respective groups (mmHg).

| Items                              | No-reflow group (n = 33) | Control group (n = 26) | t/Z value | P   |
|------------------------------------|--------------------------|------------------------|-----------|-----|
| Proximal systolic pressure         | 112.1 ± 24.1             | 113.7 ± 14.9           | 3.238     | 0.077|
| Distal systolic pressure           | 114.6 ± 25.1             | 110.9 ± 16.2           | 3.199     | 0.079|
| Systolic pressure gradient         | -1.3 (-4.8, 0.7)         | 3.8 (0.8, 8.8)         | -3.989    | 0.000|
| Proximal diastolic pressure        | 69.4 ± 13.6              | 70.2 ± 10.7            | 0.874     | 0.354|
| Distal diastolic pressure          | 71.2 ± 14.8              | 62.6 ± 12.3            | 0.252     | 0.618|
| Diastolic pressure gradient        | -1.0 (-3.2, 0.0)         | 4.6 (0.0, 16.5)        | -3.851    | <0.001|

Figure 2: Intracoronary pressure chart monitoring continuously by thrombus aspiration catheter when pulled back from distal to proximal segment in LAD after no-reflow. In this case, distal segment (waves on the left) showed relatively higher systolic and diastolic pressure, while proximal segment (waves on the right) showed relatively lower systolic and diastolic pressure. Both systolic and diastolic pressure showed a gradual downward trend from distal to proximal segments. The vertical axis represents the real-time intracoronary pressure while the abscissa axis represents the cardiac cycle during pulling back catheter. LAD: Left anterior descending artery.

Table 1: Basic information and angiographic data of patients in no-reflow and control group.

| Items                              | No-reflow group (n = 33) | Control group (n = 26) | t/F value | P   |
|------------------------------------|--------------------------|------------------------|-----------|-----|
| Male                               | 22 (67)                  | 17 (65)                | 0.011     | 0.918|
| Age (years)                        | 59.8 ± 10.3              | 56.8 ± 9.4             | 0.441     | 0.509|
| D-to-B (min)                       | 71.2 ± 16.7              | 59.8 ± 17.2            | 0         | 0.987|
| EH                                 | 21 (64)                  | 16 (62)                | 0.027     | 0.869|
| DM                                 | 19 (58)                  | 13 (50)                | 0.336     | 0.562|
| LDL (mmol/L)                       | 3.56 ± 0.90              | 4.25 ± 0.71            | 3.178     | 0.080|
| Current smoker                     | 17 (52)                  | 12 (46)                | 0.167     | 0.683|
| Culprit vessels                    |                          |                        | 0.344     | 0.842|
| LAD                                | 15 (46)                  | 13 (50)                |           |     |
| RCA                                | 14 (42)                  | 11 (42)                |           |     |
| LCX                                | 4 (12)                   | 2 (8)                  |           |     |
| Stent diameter (mm)                | 3.12 ± 0.28              | 3.06 ± 0.38            | 1.786     | 0.187|
| Stent length (mm)                  | 36.8 ± 16.7              | 45.9 ± 14.9            | 0.133     | 0.716|

Data was presented as n(%) and mean ± SD. D-to-B: Time of door to balloon dilation; EH: Essential hypertension; DM: Diabetes mellitus; LDL: Low-density lipoprotein; LAD: Left anterior descending artery; RCA: Right coronary artery; LCX: Left circumflex coronary artery; SD: Standard deviation.
segment, leading to an inverse pressure gradient in the no-reflow artery and limiting the antegrade flow. Intracoronary distal drug administration can effectively restore forward flow and forward pressure gradient. These findings are consistent with our hypothesis and also consistent with the results from Doppler guidewire in no-reflow coronary artery,\textsuperscript{16-18} showing a low systolic antegrade, low velocity, the appearance of early systolic retrograde flow, and a steep deceleration slope of the diastolic flow velocity. No reflow during emergency revascularization was significantly associated with local hemodynamic abnormalities in the coronary arteries. The reverse pressure gradient disappeared and TIMI grade 3 flow was restored after nicorandil was injected intracoronary into the distal segment.

Key factors that led to abnormal contrast runoff (retrograde or stopped) during no-reflow included reduced systolic antegrade flow volume, shorter duration of diastolic antegrade flow, lower systolic-to-diastolic peak velocity ratio, and markedly higher diastolic deceleration rate in no-reflow arteries.\textsuperscript{19} Therefore, vasoactive drugs, especially vasodilators, should be administrated through an aspiration catheter in case of failing to reach the distal vascular bed and enter the aortic circulatory system. Movahed et al.\textsuperscript{20} recommend that distal administration of high doses of intracoronary vasodilators could be used to treat resistant no-reflow arteries. In the present study, we precisely provided the theoretical basis for this mode of administration. Chen et al.\textsuperscript{21} have reported that low intracoronary diastolic blood pressure measured by invasive catheterization is the independent risk factor for poor myocardial reperfusion, while combined medication of anisodamine and nicorandil before PCI is beneficial for optimal myocardial reperfusion following the procedure. Another randomized research revealed a significant improvement of corrected TIMI frame count after drug infusion, as well as higher heart rate and systolic blood pressure drop in the verapamil group compared with that of the nitroglycerin group after intracoronary administration through selective microcatheter, which indirectly demonstrated the role of abnormal intracoronary pressure gradient in the development of no-reflow phenomenon.\textsuperscript{22}

However, distinct from intracoronary pressure, a recent animal experiment revealed that discreetly elevated systematic blood pressure during reperfusion, assessed as aortic pressure and regarded as reperfusion resistance, was associated with an increased no-reflow area and in infarct size in a clinically relevant porcine model of ischemia-reperfusion.\textsuperscript{23}

Microcirculatory dysfunction is a common cause of slow blood flow. Our study results could not distinguish the causes of no-reflow from microcirculation obstruction, myocardial edema, or cardiac insufficiency. Therefore, we excluded patients experiencing chest pain for more
than 12 h or those with significant cardiac insufficiency. The improvement in microcirculation relies on the regression of myocardial edema and the disappearance of microcirculatory compression.\(^{[24]}\) If microcirculatory dysfunction was caused by microvascular obstruction, repeated and effective thrombus aspiration could obviously minimize invisible microthrombus pre- or post-stent implantation. Although the magnitude of the pressure is difficult to calculate, the negative pressure in the distal segment of the coronary artery formed by repeated aspiration is beneficial to the formation of the forward pressure gradient and recovery of the forward blood flow.

Intracoronary administration of nicorandil after primary PCI improves microvascular function by reducing the microvascular resistance index and increasing coronary flow reserve,\(^{[25]}\) whereas abnormal pressure gradient in our study could only be regarded as indirect evidence of microcirculatory disorders of the no-reflow artery post-reperfusion. Perhaps the wave density analysis in the IRA could explain the abnormal pressure gradient. Besides, capillary pericytes were regarded as mediating coronary no-reflow after myocardial ischemia by constraining coronary capillaries and reducing microvascular blood flow, despite re-opening of the culprit artery. Cardiac pericytes are therefore a novel therapeutic target in ischemic heart disease.\(^{[26]}\)

Limitations

The present study can only partly explain the mechanism of intracoronary hemodynamic changes. To our knowledge, this is the first observational study that used a simple pressure monitor and distal administration of nicorandil via catheter aspiration during primary PCI. However, our study was a single-center study with a small sample. Based on our findings, we assume that most of the vasodilator administration in the distal segment would reach a more significant beneficial effect on no-reflow coronary arteries compared to conventional drug delivery through guiding catheter, which should be further verified in the subsequent researches. While Doppler guidewire is the best choice for measuring blood flow velocity, as well as flow and pressure before and after coronary stenosis, the slow blood flow often has no fixed stenosis and the pressure gradient results as a change from the beginning of coronary to the end. The patient’s condition is often unstable during emergent interventional therapy, where the state of an illness may be further aggravated if it is not possible to quickly correct blood flow status. In the present study, we could not repeat the measurement at multiple positions in the IRA.

Conclusions

No reflow during emergent coronary revascularization is significantly associated with local hemodynamic abnormalities in the coronary arteries. Intracoronary nicorandil administration at the distal segment of a coronary artery with an aspiration catheter could improve the microcirculatory dysfunction and resume normal coronary pressure gradient.

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Conflicts of interest

None.

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