Non-invasive ventilation improves hemorheology status in hypoxic patients with acute myocardial infarction after PCI

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Abstract

Background Hypoxemia sometimes occurs in the emergency room in the patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI), even in those with administration of conventional high-flow oxygen inhalation. The objective of the present study was to evaluate the effectiveness of non-invasive ventilation (NIV) in improving blood oxygen content and hemorheology in patients with AMI and hypoxemia. Methods This prospective study enrolled 50 consecutive eligible patients with AMI (aged 72.3 ± 9.5 years), who had undergone PCI and been administered high-flow oxygen but still had hypoxemia. Blood was taken before NIV and at 0.5, 1, and 2 h after NIV. Blood gases, hemorheological variables including erythrocyte deformability, erythrocyte aggregation, erythrocyte osmotic fragility, membrane fluidity, and oxidative stress level were measured. Results Blood PaO₂ increased to normal by 1 h after NIV. Assessed hemorheological variables had all improved and plasma malondialdehyde concentration decreased significantly after 2 h of NIV. Conclusions Our data suggest that NIV can help to improve blood oxygen content, hemorheological status, and minimize plasma lipid peroxidation injury in hypoxic patients with AMI who have undergone PCI.

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1 Introduction

Acute myocardial infarction is rapidly increasing in China, and coronary stent implantation is an effective and widely used treatment.¹ However, some patients who undergo emergency percutaneous coronary intervention (PCI) remain hypoxic even when receiving conventional high-flow oxygen. Persistent hypoxemia both decreases myocardial tissue perfusion and exacerbates cardiac dysfunction.

Non-invasive ventilation (NIV) is widely used in treating episodes of acute left ventricular failure with the aims to improve tissue oxygenation by increasing pulmonary and alveolar ventilation,² to reduce interstitial exudates and the thickness of respiratory membranes,³ to lower intrapleural and left ventricular transmural pressure, and to decrease cardiac afterload as well as preload, resulting in reduced cardiac oxygen consumption and cardiac work, which is helpful for the recovery of function of residual cardiomyocytes.⁴-⁶

Hemorheology variables are critical to oxygen transportation, especially erythrocyte deformability. And abnormal hemorheology has been demonstrated in various cardiovascular and cerebrovascular diseases, such as hypertension, coronary heart disease, and cerebral infarction.⁷,⁸

In the present prospective study, we enrolled 50 acute myocardial infarction (AMI) patients who had hypoxemia after emergency PCI that was not corrected by conventional high-flow oxygen inhalation and administered NIV to all of them. To evaluate the effectiveness of NIV, blood gases, hemorheological variables, and plasma oxidative stress level were measured before and 30 min, 1 h, 2 h after institution of NIV. Our findings indicate that NIV treatment is an effective means of correcting hypoxemia and improving hemorheology parameter in patients with AMI.

2 Methods

2.1 Subjects

From June 2009 to December 2015, 50 consecutive pa-
patients attending Shougang Hospital of Peking University and Beijing Anzhen Hospital of Capital Medical University with AMI (aged 72.3 ± 9.5 years) who had hypoxemia after undergoing emergency PCI even when receiving high-flow oxygen inhalation were recruited into this study. Myocardial infarction was diagnosed according to the Joint European Society of Cardiology/American College of Cardiology criteria, with inclusion criteria are as follows: (1) continuous chest pain for longer than 30 min; (2) ST-segments of more than two adjacent leads higher than baseline (limb leads > 0.1 mV; chest leads > 0.2 mV); (3) more than double normal serum concentrations of the myocardial enzyme, creatine kinase isoenzyme; (4) time of onset of AMI no more than 12 hours prior to presentation; (5) emergency PCI performed; and (6) patients’ peripheral oxygen saturation (SpO2) still < 90% 30 min later despite administration of high-flow oxygen before and after the procedure. Exclusion criteria were as follows: (1) pulmonary ventilation dysfunction caused by chronic obstructive pulmonary disease; (2) serious liver or kidney dysfunction, neurological diseases and severe lung infections.

Forty of the participating patients had anterior myocardial infarction, coronary arteriography showing that the culprit vessel was the proximal segment of the left anterior descending (LAD) artery. The other ten had combined anterior wall and inferior myocardial infarction. Five of these 10 patients had chronic occlusion of the right coronary artery (RCA), which was supplied by the LAD; thus, the culprit vessel was the LAD artery. The other five patients had chronic occlusion of the LAD, which was supplied by the RCA, the latter being the culprit vessel. Relevant patient characteristics are listed in Table 1. The patients were treated with NIV by covering their noses with the mask of a non-invasive ventilator that applied positive pressure, thus assisting them to take full breaths. Written informed consent was obtained from all subjects. The whole study was approved by the ethics committees of Capital Medical University and Peking University.

2.2 Monitored variables

All patients were managed in a critical care unit after the PCI, where their blood pressure, heart rate, respiratory rate, and peripheral oxygen saturation (SpO2%) were measured. Blood gases, including arterial pH, partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide in arterial blood (PaCO2) were monitored before and 30 min, 1 h, and 2 h after institution of NIV.

2.3 Measurements of erythrocyte deformation index (DI) and aggregation index (AI)

Venous blood (1 mL) was drawn and anti-coagulated with heparin before and 30 min, 1 h, and 2 h after commencement of NIV. Forty microliter blood was suspended in 1 mL of 15% polyvinyl pyrrolidone buffer (w/v, pH = 7.4, 295 mOsm/kg, viscosity = 15 mPa/s) and the DI at shear rates of 50–1000 s−1 were measured in a traditional ektacytometer (LG-B-190; Steellex, Beijing, China). The DI at 1000 s−1 was used for data analysis. Additionally, 800 µL of whole blood was loaded in the ektacytometer and the AI measured.

2.4 Measurement of erythrocyte osmotic fragility

Osmotic fragility tests were performed on blood taken before and 30 min, 1 h, and 2 h after commencement of NIV. Fifty microliter of blood was washed three times with PBS and resuspended in different concentrations of phosphate-buffered saline of osmolality ranging from 0–295 mOsm/kg. The mixtures were incubated at room temperature for 0.5 h and then centrifuged (3000 r/min). The absorbance of the supernatants was measured at 540 nm with a spectrophotometer (UNICO Instruments, Shanghai, China). The hemolysis rates were calculated.

2.5 Measurement of erythrocyte membrane fluidity

Membrane fluidity was measured by determining fluorescence polarization (p) and membrane microviscosity (η). The washed erythrocytes were incubated with 2 × 10−6 mol/L 1,6-di-phenyl-1,3,5-hexatriene (Fluka Chemie AG, Buchs, Switzerland) that was dissolved in tetrahydrofuran at 37°C for 30 min. Fluorescence polarization was determined by using a spectrophotofluorometer (Hitachi, Tokyo, Japan).
The excitation and emission wavelengths were 360 nm and 430 nm, respectively. Fluorescence polarization ($p$) was determined.[10] Membrane microviscosity ($\eta$) was calculated according to the formula: $\eta = 2p/(0.46 - p)$. The values for $p$ and $\eta$ are inversely related to membrane fluidity.

### 2.6 Measurement of plasma MDA concentrations

Malondialdehyde (MDA), the last product of lipid breakdown caused by oxidative stress, is an indicator of cell membrane injury.[11] MDA concentrations were determined by spectrophotometric measurement of the condensation product formed from MDA and 2-thiobarbituric acid. Concentrations of MDA were obtained by measuring the absorbance at 532 nm after the reaction and are expressed as µmol/L.

### 2.7 Statistical analyses

Data were expressed as mean ± SD. Statistical analyses were performed using SPSS13.0 software. Differences between groups were analyzed by one way ANOVA supplemented with Turkey’s HSD post-hoc test. $P < 0.05$ was considered to denote statistical significance.

### 3 Results

#### 3.1 Changes in symptoms, blood pressure, heart rate, and blood gas analysis after NIV

To evaluate the efficacy of NIV in patients with AMI and hypoxemia, all participants were managed in a Coronary Care Unit after PCI. Blood pressure, heart rate, respiratory rate, PaO2, blood gas analysis, and electrocardiogram changes were monitored. These data are shown in Table 2. All patients’ precordial discomfort improved within 30 min of commencement of NIV. Their SpO2 increased to more than 90% and their PaO2 reached the lower limit of normal. Additionally, their heart rate and respiratory rate were significantly lower ($P < 0.05$) than when on high-flow oxygen inhalation (HFOI) only, that is, before NIV was commenced. By 1 h after commencement of NIV, PaO2 reached normal levels. The arterial pH, blood pressure, and PaCO2 did not change before and after NIV.

#### 3.2 Erythrocyte DI improves after commencement of NIV

To investigate the effect of NIV on erythrocytes and its impact on oxygen provision in the microcirculation, erythrocyte DI was examined using a traditional ektacytometer before and 30 min, 1 h, and 2 h after commencement of NIV (Figure 1). DI at 1000/s tended to increase, this increase not being statistically significant at 30 min and 1 h compared with before NIV. However, 2 h after commencement of NIV, DI was significantly greater than pre-NIV ($P < 0.05$), indicating that NIV improves erythrocyte deformability in hypoxemic patients with AMI.

#### 3.3 AI increases after commencement of NIV

AI was measured using an ektacytometer. Aggregates in the blood are broken by high shear stress at 1000/s; the erythrocytes aggregate again when shearing stops. Changes in intensity of transmitted light were recorded and the AI calculated. It was found that the AI was high before NIV but decreased after its commencement (Figure 2). By 2 h after commencement of NIV, the AI was significantly lower than before NIV ($P < 0.05$). These data suggests that NIV reduces the tendency of blood to aggregate.

#### 3.4 Erythrocyte osmotic fragility improves after commencement of NIV

Erythrocyte osmotic fragility is a measure of the mechanical properties of erythrocyte membranes that enable erythrocytes to withstand hypotonic stress. Figure 3 shows that, in a solution of 145 mOsm/kg, the hemolysis rate was

### Table 2. Major clinical outcomes.

| Variable               | High-flow oxygen inhalation | Non-invasive ventilation |
|------------------------|-----------------------------|--------------------------|
|                        | 30 min later                | 1 h later                | 2 h later                |
| SpO2, %                | 83.27 ± 3.58               | 90.62 ± 4.23#           | 94.51 ± 5.02*           | 97.83 ± 4.06*               |
| pH                     | 7.39 ± 0.97                | 7.38 ± 0.85             | 7.40 ± 0.76             | 7.40 ± 0.72                 |
| PaO2, mmHg             | 70.65 ± 6.89               | 79.21 ± 7.28#           | 83.85 ± 9.11*           | 91.42 ± 10.01*              |
| PaCO2, mmHg            | 40.28 ± 3.25               | 39.65 ± 5.47            | 41.25 ± 3.87            | 39.21 ± 4.51                |
| P, respirations/min    | 26.51 ± 1.82               | 21.09 ± 2.13#           | 19.12 ± 3.08#           | 18.09 ± 3.11#               |
| HR, beats/min          | 107.08 ± 11.07             | 85.16 ± 9.05*           | 80.39 ± 7.53*           | 78.45 ± 5.08*               |
| SBP, mmHg              | 106.53 ± 10.08             | 110.21 ± 9.52           | 115.06 ± 10.21          | 109.82 ± 9.41               |
| DBP, mmHg              | 58.12 ± 5.13               | 59.56 ± 7.02            | 61.23 ± 6.15            | 60.21 ± 5.31                |

Data were presented as mean ± SD. $#P < 0.05$; *$P < 0.01$, compared with high-flow oxygen inhalation. DBP: diastolic blood pressure; HR: heart rate; P: respiratory rate; PaCO2: partial pressure of carbon dioxide in arterial blood; PaO2: partial pressure of oxygen; SBP: systolic blood pressure; SpO2: peripheral oxygen saturation.

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Figure 1. Changes in erythrocyte deformation index before and 30 min, 1 h, and 2 h after commencement of NIV. *P < 0.05 compared with deformation index before NIV, that is, when the patient was receiving only high-flow oxygen inhalation. DI: deformation index; HFOI: high-flow oxygen inhalation; NIV: non-invasive ventilation.

Figure 2. Aggregation indices before and 30 min, 1 h, and 2 h after commencement of NIV. †P < 0.05 compared with the aggregation index before commencement of NIV (patient receiving high-flow oxygen inhalation). HFOI: high-flow oxygen inhalation; NIV: non-invasive ventilation.

Figure 3. Erythrocyte osmotic fragility before and 30 min, 1 h, and 2 h after commencement of NIV. The hemolysis rate at 145 mOsm/kg is shown. ‡P < 0.05 compared with the hemolysis rate before commencement of NIV (patient receiving high-flow oxygen inhalation). HFOI: high-flow oxygen inhalation; NIV: non-invasive ventilation.

the highest before commencement of NIV and was markedly lower 1 h and 2 h after (P < 0.05), suggesting that the mechanical properties of erythrocytes improved after commencement of NIV.

3.5 Erythrocyte membrane fluidity increases after commencement of NIV

Membrane fluidity is related to the mechanical properties of erythrocyte membranes. Fluorescence polarization of the erythrocytes was measured and the microviscosity calculated. These data (Figure 4) showed that the microviscosity was 1.67 ± 0.21 before NIV was given. NIV for 1 h and 2 h significantly reduced the microviscosity to 1.27 ± 0.11 and 1.03 ± 0.09, respectively (P < 0.05). These data indicate that membrane fluidity increased after commencement of NIV.

Figure 4. Microviscosity before and 30 min, 1 h, and 2 h after commencement of NIV. ‡P < 0.05 compared with microviscosity before commencement of NIV (patient receiving high-flow oxygen inhalation). HFOI: high-flow oxygen inhalation; NIV: non-invasive ventilation.

3.6 Plasma lipid peroxidation decreases after commencement of NIV

The severity of plasma lipid peroxidation injury and changes in plasma peroxidation with increased blood oxygen content were investigated in NIV-treated patients by measuring plasma MDA concentrations (Figure 5). Plasma MDA concentrations showed a descending trend after commencement of NIV, being significantly lower at 2 h, indicating that NIV ameliorates lipid peroxidation injury.

Figure 5. Plasma MDA concentrations before and 30 min, 1 h, and 2 h after commencement of NIV. ‡P < 0.05 compared with plasma MDA concentration before commencement of NIV (patient receiving high-flow oxygen inhalation). HFOI: high-flow oxygen inhalation; NIV: non-invasive ventilation.

4 Discussion

Because of differences in time to presentation to a medical facility, culprit vessel, and infarction myocardial microcirculation perfusion, emergency PCI also has some complications that affect recovery and even threaten the patient’s life. Therefore, timely and effective treatment of
complications and achieving stability of vital signs are important in helping patients to get through the critical stage as quickly as possible and improving their subsequent quality of life.

Hypoxemia is a common complication of some serious internal diseases, being the main reason for tissue and organ oxygen deprivation. Oxygen therapy is an important adjunct to treatment of AMI and is routinely administered by nasal inhalation of oxygen. This study included 50 patients with AMI and subnormal SpO2 and PaO2 even after receiving conventional HFOI for 30 min. Reasons for their poor oxygenation may have included that they had large areas of myocardial infarction and myocardial microcirculation hypoperfusion resulting in reduced cardiomyocyte systolic function and pulmonary interstitial and alveolar edema, which are not conducive to optimal gas exchange. In addition, most of the 50 patients had blocked LAD arteries. There seems to be a correlation between LAD lesions and development of hypoxia, possibly because the LAD artery controls the blood supply to the ventricular anterior wall, the cardiomyocytes of which are closely related to ventricular ejection function. After a sudden decrease in blood supply from the LAD, the ensuing reduction in left ventricular ejection fraction would cause pulmonary congestion, directly resulting in hypoxia. We found that the patient’s SpO2 and PaO2 started to increase after they were given NIV, returning to normal within 2 h. This may have been attributable to improvements in: (1) tissue oxygenation by increasing pulmonary and alveolar ventilation; (2) pulmonary exchange by reducing interstitial exudates; and (3) reductions in intrapleural pressure, left ventricular transmural pressure, and cardiac afterload.

In this study, we also found that hemorheological variables improved to varying degrees with increases in oxygen content. DI, AI, membrane fluidity, and osmotic fragility are the important indicators of red blood cell rheological status. At high shear stress, erythrocyte deformability is an important determinant of whole blood viscosity, whereas at low shear stress, erythrocyte AI is the more important determinant of whole blood viscosity. In the present study we found that, with increasing oxygen content, erythrocyte DI increased whereas AI decreased, suggesting improvement in whole blood viscosity at both high and low shear stress. This is one of the ways in which NIV is beneficial because whole blood viscosity influences resistance to blood flow. High blood viscosity is associated with increased resistance to blood flow and thus slowing of blood flow, which both reduces tissue perfusion and enhances leukocyte adhesion to endothelial cells, which in turn promotes inflammation and tissue damage. Increases in erythrocyte deformability enhance their capacity to pass through tiny blood vessels, thus delivering more oxygen to the ischemic myocardial tissue and facilitating restoration of cardiomyocyte function. Membrane fluidity reflects membrane biomechanics. Decreased membrane fluidity decreases erythrocyte deformability and increases erythrocyte aggregation, resulting in an increase in whole blood viscosity. Studies have also shown that reduction in red cell membrane fluidity decreases the activity of membrane Na+/K+-ATPase, which results in changes in osmotic fragility.

Lipid peroxidation, a complex process that involves interaction between oxygen-derived free radicals and polyunsaturated fatty acids, results in a variety of highly reactive electrophilic aldehydes. Many studies have shown that lipid peroxidation injury participates in the pathogenesis of many diseases. MDA, a decomposition product of lipid peroxidation, reflects the degree of lipid peroxidation injury. It has been shown that the levels of hemoglobin oxygenation and lipid peroxidation are related to erythrocyte deformability. In our study, we found that erythrocyte DI increased in parallel with decreasing plasma lipid peroxidation after commencement of NIV. This improvement in hemorheological status is presumably related to increased oxygen content and decreased plasma lipid peroxidation injury.

Our data indicate that the use of NIV to manage hypoxemia after AMI warrants attention. The following points are crucial: (1) timely detection of hypoxemia after AMI, especially when SpO2% remains low even when HFOI is given. Older patients and those with a smoking history, diabetes mellitus, hyperlipidemia, and anterior myocardial infarction are particularly prone to this phenomenon. (2) When a ventilator is used, inspiratory pressure should start as low as possible (10 cmH2O) to minimize patient discomfort. The
pressure can then be adjusted to 14–16 cmH2O according to patient’s status. Positive end-expiration pressure is usually 4–6 cmH2O. The mode of ventilator is S/T. The duration of NIV can be adjusted according to whether the patient has clinical indications of cardiac insufficiency and how well the hypoxia is corrected. The inspiratory variables should be adjusted according to SpO2%. (3) High-flow oxygen (10 L/min) should be administered initially until SpO2 reaches above 90%, after which oxygen flow should be turned down (≤ 5 L/min) to maintain the SpO2% above 94%.

In summary, our study showed that NIV improves both oxygen content and blood flow in patients with AMI, thereby reducing resistance to blood flow and increasing tissue perfusion, which facilitates functional recovery after myocardial injury.

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