Original Article

Pre-Exposure to Normobaric Hyperoxia Has No Effect on Myocardial Injury Biomarkers after Percutaneous Transluminal Coronary Angioplasty

Asghar Mohammadi[1], MS; Shahin Raoufi[1], MS; Mehrdad Namdari[1*], MD; Amir Raoufi[1], MD; Khatereh Anbari[1], MD; Shiba Tahzibi[1], BS; Mohammad Almasian[1], MA; Bahram Rasoulian[2], MD, PhD

ABSTRACT

Background: It has been determined in animal models that hyperoxia-induced preconditioning could reduce the ischemia/reperfusion injury of the heart tissue. Short-term ischemia and the subsequent reperfusion occur unavoidably in coronary angioplasty. The purpose of the present study was to determine the possible effects of oxygen pretreatment in inducing preconditioning during percutaneous transluminal coronary angioplasty (PTCA).

Methods: Thirty-two patients, referred for elective angioplasty, were randomly divided into the control group and the oxygen group. The subjects in the oxygen group were exposed to normobaric oxygen (nearly 70% O_2) via non-rebreathing masks for 1 hour at 12 and 2 hours before PTCA. One hour after the last oxygen pre-exposure period, the patients underwent PTCA (20 s of balloon inflation and 2 min of reperfusion). The chest pain score and cardiac injury biomarkers were assessed 12 hours after coronary angioplasty. The biomarker data and the chest pain scores were analyzed using the Mann–Whitney test and the Wilcoxon *t*-test. Also, the ratio of patients with positive C-reactive protein results was compared between the groups using the Fisher exact test.

Results: The troponin I and CKMB levels were elevated in both groups after angioplasty, but there was no significant difference between the groups in this regard (P=0.23 and P=0.47, respectively). The average pain score during balloon inflation in the oxygen group was lower than that in the control group (2.8±1.2 vs. 4.11±1.21; P=0.008).

Conclusions: Two episodes of 1-hour pre-exposure to normobaric hyperoxia (nearly 70% O_2) at 12 and 2 hours before PTCA had no significant effect on myocardial injury biomarkers, troponin I, and CKMB. ***(Iranian Heart Journal 2016; 17(3):18-26)***

Keywords: Chest pain ■ Coronary angioplasty ■ Hyperoxia ■ Oxygen■ Preconditioning

[1] Department of Cardiology, Madani Hospital, Lorestan University of Medical Sciences, Khorramabad, I.R. Iran.
[2] Razi Herbal Medicines Research Center and Department of Physiology and Pharmacology, Lorestan University of Medical Sciences, Khorramabad, I.R. Iran.

Corresponding Author: Mehrdad Namdari, MD; Madani Hospital, Lorestan University of Medical Sciences, Khorramabad, I.R. Iran.
E-mail: namdari_m@yahoo.com **Tel:** 06633315100

Received: January 9, 2016 **Accepted:** June 14, 2016

Heart ischemia/reperfusion (I/R) not only occurs after myocardial infarction but also some degree of I/R may occur as a result of elective procedures such as cardiac surgery and coronary angioplasty.[1] Ischemic preconditioning (IPC) was originally introduced by Murry et al.,[2] who reported that short periods of cardiac I/R in dogs increased myocardial tolerance to more prolonged subsequent ischemia and the consequent reperfusion. Preconditioning consists of 2 windows of protection. The 1st window begins immediately and the 2nd one commences about 12 hours after ischemia.[3] Many agents have been proven to induce preconditioning or to be involved in IPC mechanism; these include bradykinin, adenosine, opioids, and reactive oxygen species (ROS).[4-7] Although excess amounts of ROS produced during the reperfusion period are involved in myocardial injury, a small amount of ROS released during a short period of ischemia or short term hyperoxic pre-exposure can induce cardiac preconditioning, while the cardioprotective effects of IPC are canceled out by free radical scavengers.[7-9] Additionally, many pharmacological agents that generate ROS are able to reduce the myocardial infarct size.[8-10] Several animal studies have shown that normobaric oxygen pretreatment could reduce heart I/R injury.[8-12] Moreover, it has been demonstrated in human studies that hyperoxic pre-exposure improves renal function in patients undergoing kidney transplantation and that the administration of hyperbaric oxygen improves myocardial function after coronary artery bypass grafting surgery (CABG).[13,14] Percutaneous transluminal coronary angioplasty (PTCA) is a clinical setting with inevitable periods of I/R and provides an excellent situation to assess the effects of different possible protective protocols in the human myocardium.[15] Based on previous animal studies on the effects of oxygen pre-exposure on reducing cardiac I/R injury and the role of ROS in the mechanism of IPC, the present study for the 1st time aimed to assess the effects of hyperoxic preconditioning on heart injury biomarkers and the chest pain score of patients undergoing coronary angioplasty. It should be noted that short-term hyperoxic pre-exposure is a benign protocol, which leads only to a sub-lethal increase in ROS production and works as a possible inducer of cellular endogenous defense mechanisms.

METHODS

Study Population

In this randomized clinical trial, 32 patients—referred for elective PTCA—were randomly divided into the oxygen group and the control group. The study was carried out in Shahid Madani Heart Hospital in Khorramabad, Iran, between February 2013 and December 2014. The study protocol was approved by the Medical Ethics Research Committee of Lorestan University of Medical Sciences. First, the method of study was explained to each patient and then a written informed consent was obtained from each patient. All the patients had stable angina when undergoing coronary angioplasty. Patients were included if they had isolated obstructive lesions in at least 1 coronary artery branch with ≥70% reductions in the luminal diameter. Patients who had chronic obstructive lung disease, exposure to oxygen 3 days prior to the commencement of PTCA, episode(s) of chest pain 48 hours before PTCA, Prinzmetal angina, or upper respiratory infection were excluded from the study. Both the control group and the oxygen group consisted of 16 patients (10 men and 6 women, mean age =53±11 y and 53±9 y, respectively). The mean ejection fraction was 52±5% in the control group and 49±1% in the oxygen group. The last episode of chest pain in all the patients occurred 48 hours prior to PTCA.

Study Protocol

In this single-blinded randomized clinical trial, each patient in the intervention (oxygen) group was exposed to normobaric oxygen twice (about 70% O_2 in the inspired air) via a

non-rebreathing mask at 12 and 2 hours before PTCA. Each episode of oxygen pretreatment lasted for 1 hour. One hour after the last period of oxygen pre-exposure, diagnostic angiography was performed and a nonionic contrast agent (Visipaque GE, Healthcare Ireland, osmolality: 320 mg/mL) was administrated intravenously to each patient. After diagnostic angiography, the patients who had isolated obstructive lesions in at least 1 coronary artery branch with ≥70% reductions in the luminal diameter underwent coronary angioplasty. The PTCA procedure was performed via a routine technique using the femoral approach. After prep and drape, heparin (2000 IU) was administered intravenously before coronary angioplasty. Subsequently, the balloon was positioned across the lesion and 1 session of balloon inflation was done for 20 seconds. The stent was thereafter inserted into the narrowed coronary artery, and then there was a 2-minute period of reperfusion. The balloon inflation pressure ranged from 11 to 14 atm. At the end of the procedure, the angioplasty balloon was deflated and was withdrawn from the stenotic site; and after 2 minutes, the reperfusion study protocol was finished. Similar procedures were carried out for the control group patients, except that they were not exposed to normobaric oxygen pretreatment with oxygen masks. The cardiologist who did the angiography and angioplasty procedures was not aware of the patients' group and did not know whether the patients had been subjected to oxygen pretreatment or not.

Laboratory Measurements

Venous blood samples were obtained from each patient before and 12 hours following the PTCA procedure to measure troponin I and CKMB levels and C-reactive protein (CRP) as biomarkers of cardiac cell injury. Troponin I and CKMB activities were measured with standard kits (RAMP Vancouver, Canada) using an auto-analyzer and expressed as nanograms per milliliter (ng/mL). Also, the level of highly sensitive C-reactive protein (hs-CRP) was determined with a standard kit (Enison, Iran) and expressed as positive or negative. The normal values of CKMB and cTnI were considered to be ≤5 ng/mL and ≤0.1 ng/mL, respectively.

Assessment of Chest Pain

At the end of balloon inflation, the severity of chest pain was assessed with visual analog scores by a nurse, who had no knowledge of the patients' group. The patients were asked to indicate the severity of chest pain on a scale of 0 (no pain) to 10 (severe pain).

Statistical Analysis

The biomarker data are expressed as means ± SDs. All the chest pain score data are shown in the relevant figure, and the median has also been presented. The data were analyzed with SPSS, version 21, and the comparisons between the groups were analyzed with the Mann–Whitney test and the changes within the groups were analyzed with the Wilcoxon *t*-test. The ratio of cases with positive CRP results was compared between the 2 groups using the Fisher exact test. A P value <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the control and oxygen groups are summarized in Table 1. There were no statistically significant differences between the 2 groups in terms of the determined parameters. Angioplasty was successfully performed in all the patients.

Chest Pain

The average pain score during balloon inflation in the oxygen group was lower than that in the control group (2.8±1.2 vs. 4.11±1.21; P=0.008). The chest pain score data are depicted in Figure 1.

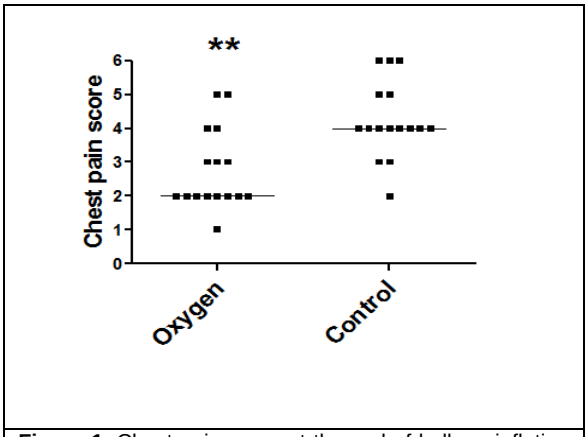

Figure 1. Chest pain score at the end of balloon inflation in the control and oxygen groups. The chest pain score was higher in the control group than in the oxygen group. The line shows the median in each group. **, *P*=0.008

Cardiac Biomarkers

Troponin level: The troponin level changed from 0.001±0.0001 ng/mL to 0.039±0.062 ng/mL in the oxygen group and from 0.0055±0.012 ng/mL to 0.061±0.21 ng/mL in the control group. The changes were not significant in either group (*P*=0.068 and *P*=0.28, respectively). There were no significant differences in the values of troponin I between the 2 groups before and after angioplasty (*P*=0.23) (Table 2).

CKMB level: The CKMB level changed from 1.44±1.18 ng/mL to 3.04±2.56 ng/mL in the oxygen group and from 1.8±1.16 ng/mL to 3.78±3.61 ng/mL in the control group. The changes were significant in both groups (*P*=0.034 and *P*=0.017, respectively). There were no significant differences in the values of CKMB between the 2 groups before and also after angioplasty (*P*=0.47) (Table 3).

CRP value: According to the Fisher exact test, there was no significant difference in terms of positivity between the 2 groups (*P*=0.57) (Table 4).

Table 1. Demographic and clinical characteristics of the patients in the 2 groups

Variable	Control Group (n=16)	Oxygen Group (n=16)
Age (y) (mean± SD)	53±11	53±9
Gender, M/F	10/6	10/6
Hypertension, n	3	5
Smoking, n	5	5
Diabetes mellitus, n	3	9
Previous CABG , n	0	2
Previous PTCA , n	4	0
Left ventricular ejection fraction, %, (mean± SD)	52%±5	49%±1
Use of Long-acting nitrates, n	5	10
Use of β-blocker agents, n	9	8
Glibenclamide usage, n	3	7
Opioid usage, n	3	2

CABG, Coronary artery bypass graft surgery; PTCA, Percutaneous transluminal coronary angioplasty
There were no statistically significant differences between the 2 groups in terms of the determined parameters.

Table 2. Serum troponin values before and after PTCA in the 2 groups

Group Value (Within each group)	Before PTCA (mean ± SD) ng/mL	After PTCA (mean ± SD) ng/mL	*P*
Oxygen group	0.001±0.0001	0.039±0.062	0.068
Control group	0.0055±0.012	0.061±0.2	0.280

**P*<0.05 significant
PTC, Percutaneous transluminal coronary angioplasty

Table 3. Serum CKMB values before and after PTCA in the 2 groups

Group Value (Within each group)	Before PTCA (mean ± SD), ng/mL	After PTCA (mean ± SD), ng/mL	*P*
Oxygen group	1.44±1.18	3.04±2.56	0.034
Control group	1.8±1.16	3.78±3.61	0.017

**P*<0.05
PTC, Percutaneous transluminal coronary angioplasty

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Table 4. CRP changes following PTCA in the 2 groups

Group	Positive CRP before PTCA n (%)	Positive CRP after PTCA n (%)	*P*
Oxygen group	0(0%)	0(0%)	>0.050
Control group	0(0%)	1(6.3%) 0/317	

CRP, C-reactive protein; PTCA, Percutaneous transluminal coronary angioplasty

DISCUSSION

The results of the present study showed that 2 episodes of 1-hour pre-exposure to nearly 70% normobaric hyperoxia before PTCA had no significant effect on the release of cardiac injury biomarkers.

In some studies, cardiac biomarkers such as troponin I and CKMB have been assessed before and after angioplasty as the hallmarks of cardiac cell injury.[19,20] Of course, the purpose of these studies was to determine the relationship between biomarker changes after PTCA and the patients' outcome.[21-23] Also in a study, the beneficial effects of IPC during PTCA on CKMB release were determined.[24] Accordingly, in the present study, alongside the chest pain score, cardiac biomarker changes were measured as a sign of cardiac cell injury to assess the possible cardioprotective effects of hyperoxic pre-exposure in coronary angioplasty. In addition to oxygen, a number of pharmacological agents like estrogen, nitroglycerine, bradykinin, and enalaprilat have been shown to be cardioprotective in patients undergoing PTCA as determined by ST-segment changes, echocardiographic findings, and severity of chest pain.[16-18] Oxygen therapy is a common treatment for patients who experience respiratory and/or cardiac failure, but oxygen is a double-edged sword in this regard. Hyperoxia worsens systolic myocardial performance in healthy volunteers.[25] It also leads to the impairment of cardiac relaxation and increased left ventricular filling pressures in patients with and without congestive heart failure.[26] In addition, hyperoxia results in a reduced cardiac output and increased peripheral vascular resistance in patients with acute myocardial infarction.[27] Additionally, a large number of studies have shown that oxygen usage in normoxemic patients with acute myocardial infarction has no beneficial effects and that oxygen therapy is indicated only in patients who are hypoxemic.[28] Besides these minor side effects of hyperoxia on cardiovascular disease, atelectasis is a pulmonary complication that occurs after a short-term administration of high oxygen fraction in the clinical setting. Of course, the severity of atelectasis is much less pronounced in patients who are pre-oxygenated with 80% O_2 as compared with 100% O_2; and in patients breathing 60% O_2, atelectasis almost is not found.[29] Oxygen toxicity is the most important pulmonary complication that occurs only after long-time exposure and up to 24 hours for 80% O_2 and 6 hours for 100% O_2 is considered safe in clinical practice.[30] Moreover, it is well-known that hyperoxia could also have beneficial effects on patients because of its so-far documented preconditioning-like effects on the myocardium. For example, several experimental studies have demonstrated that the normobaric oxygen pretreatment of rats reduces the infarct size and the incidence of I/R-induced cardiac arrhythmias.[11, 12, 31-33] Also, Sharifi et al.[34] showed that hyperbaric oxygen therapy was able to inhibit restenosis after coronary angioplasty in patients who had experienced acute myocardial infarction. On the other hand, Karu et al.[35] demonstrated that pre-exposure to oxygen for 120 minutes immediately before cardioplegia could not significantly affect the release of troponin I and CKMB after CABG. In another study, Karu et al.[36] again showed that 1 hour's oxygen pre-treatment, 30 minutes before cardioplegia, did not have cardioprotective effects against myocardial injury after CABG. Although the hyperoxia protocol implemented

in these studies was different, the results of these studies were similar and no cardioprotective effects were found for hyperoxia. In our study, we tested 2 episodes of 1-hour pre-treatment with oxygen, 12 and 2 hours before PTCA, to induce both early and late phases of IPC; this protocol of hyperoxia, however, did not significantly reduce myocardial injury biomarkers (troponin I and CKMB) after PTCA. Therefore, the results of our study chime in with the results reported by Karu et al. in cardiac surgery. In contrast, Yogaratnam et al.[13] used hyperbaric oxygen preconditioning in patients undergoing CABG and found lower levels of troponin in the oxygen-pretreated group as a sign of less damage to the cardiac cells. Moreover, the authors reported that blood loss, blood transfusion, and length of the intensive care stay decreased in their intervention group. Of course Yogarantam et al. used hyperbaric rather than normobaric oxygen and this factor probably can explain the difference of results between these studies. There are possible reasons that may explain the different results of the studies by Karu et al. in CABG and our study in PTCA: The hyperoxic pre-exposure protocol (i.e., 1 or 2 episodes of 1 or 2 hours of oxygen pretreatment) may not be sufficient to activate intrinsic cardiac protective pathways in humans. On the other hand, inspiratory concentrations of oxygen are another important factor in the induction of preconditioning-like effects. For example, Tähepõld et al.[33] showed in their isolated heart model study that 60 or 180 minutes of ≥80% O_2 was able to reduce I/R-induced infarct size in the rat heart and exposure to 95% O_2, 80% O_2, and 60% O_2, but not 40% O_2, immediately before heart isolation improved post-ischemic heart functional parameters. Also, it has been shown in other organs like the kidney that the protective effects of hyperoxic pretreatment relate to the oxygen exposure timing protocol.[37] Animal studies also have shown that there are interspecies differences in terms of response to pre-exposure to oxygen for the activation of protective mechanisms. Therefore, further studies are needed to determine the optimal hyperoxia protocol (duration of exposure and concentration of oxygen) in humans. It could also be proposed that the preconditioning phenomenon may not be induced by hyperoxia in the human heart. This hypothesis has already been considered in a study.[36] However, thus far, there is not sufficient evidence to support this idea. Another issue examined in our study is that in contrast to cardiac biomarkers, which exhibited no significant changes between the 2 groups, the chest pain scores decreased slightly in the oxygen-pretreated group. Nonetheless, there is a limitation that could affect the validity of the chest pain score in our study. The duration of balloon inflation was short (20 s), because 2 minutes of balloon inflation used in some clinical studies[16-18] was not approved by the Medical Research Ethics Committee of Lorestan University of Medical Sciences. Thus, balloon inflation for a 20-second duration was performed. This duration of balloon inflation did not induce considerable chest pain in all the patients.

In conclusion, 2 episodes of 1-hour pre-exposure to normobaric hyperoxia (nearly 70% O_2) at 12 and 2 hours before PTCA did not induce cardioprotective effects in the human heart as was determined by the absence of significant differences in terms of myocardial injury biomarkers, troponin I, and CKMB between the oxygen-pretreated and control groups. We suggest that further studies be undertaken with a view to determining the possible optimal oxygen usage protocol before cardiac interventions to activate preconditioning pathways in the human heart.

Acknowledgments

The present study was supported by the Vice Chancellorship for Research, Lorestan University of Medical Sciences. The authors would like to thank the staff of the CCU ward in Shahid Madani Hospital.

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