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The Analgesic Effect of Oxygen in Suspected Acute Myocardial Infarction

A Substudy of the DETO2X-AMI Trial

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ABSTRACT

OBJECTIVES In this substudy of the DETO2X-AMI (An Efficacy and Outcome Study of Supplemental Oxygen Treatment in Patients With Suspected Myocardial Infarction) trial, the authors aimed to assess the analgesic effect of moderate-flow oxygen supplementation in patients with suspected acute myocardial infarction (AMI) treated with percutaneous coronary intervention (PCI) and to study the effect of oxygen supplementation on the use of opiates and sedatives during PCI.

BACKGROUND Routine oxygen in normoxemic patients with AMI does not provide clinical benefit. However, oxygen may relieve ischemic pain.

METHODS Patients were randomly allocated to oxygen or ambient air according to the main study protocol. After PCI, peak level of pain during PCI was measured by the Visual Analogue Scale. The total amount of opiates and sedatives was reported.

RESULTS A total of 622 patients were enrolled: 330 in the oxygen group and 292 in the ambient air group. There was no significant difference in peak level of pain (oxygen 4.0 [1.0 to 6.0] vs. air 3.0 [0.6 to 6.0]; $p = 0.37$), use of opiates (mg) (oxygen 0.0 [0.0 to 3.0] vs. air 0.0 [0.0 to 3.0]; $p = 0.31$), or use of sedatives between the groups (median [interquartile range]) (oxygen 2.5 [0.0 to 2.5] vs. air 2.5 [0.0 to 2.5]; $p = 0.74$).

CONCLUSIONS In the present study, the authors did not find any analgesic effect of routine oxygen as compared with ambient air, and no differences in the use of sedatives and opiates during PCI. Our results indicate that moderate-flow oxygen supplementation does not relieve pain in normoxemic patients with suspected AMI undergoing treatment with PCI and should thus not be used for this purpose. (J Am Coll Cardiol Intv 2018;11:1590–7) © 2018 by the American College of Cardiology Foundation.

The use of routine oxygen therapy in acute myocardial infarction (AMI) has recently been evaluated in several studies (1-3). Even though the use of oxygen in the treatment of hypoxemia is well established (4), the evidence in other indications remain sparse (5). The potential hazard of hyperoxemia has been investigated, and the risk-benefit ratio of routine oxygen remains

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unclear (6-8). A common use for oxygen in AMI is to relieve pain (5,9). Ischemic pain represents a visceral pain sensation primarily mediated by chemosensitive nociceptors in the heart muscle (10). In the presence of myocardial ischemia, a number of chemical mediators are released, which triggers the production of prostaglandins through a cyclooxygenase pathway (11). The chemical response stimulates nociceptors, mainly located in the epicardium, which results in a depolarization of the cardiac visceral spinal afferent fibers (12,13).

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Oxygen has been used to relieve ischemic symptoms for more than 100 years, which was the very first indication of oxygen therapy in suspected AMI (14). The rationale behind the use of oxygen as an analgesic agent is that oxygen is considered to improve oxygenation of the ischemic heart muscle and by this, diminish the effects of the chemical and mechanical response to ischemia (6). A small number of studies used the amount of analgesic pharmaceuticals as a proxy variable for pain estimation (15,16), but to our knowledge, only 2 randomized clinical trials have conducted a direct measurement of oxygen therapy in pain management, where the most recent study only measured pain as a screening tool for pre-hospital inclusion before intervention (1). The other trial was our previous study, the randomized, double-blind, placebo-controlled OXYPAIN (Analgesic effect of OXYgen during PercutAneous coronary INtervention) trial (17), in which 300 patients with coronary artery disease were treated by percutaneous coronary intervention (PCI). In this trial, oxygen was not superior to air in pain reduction. However, this was a single-center trial in which patients with

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

NSTEMI = non-ST-segment elevation myocardial infarction

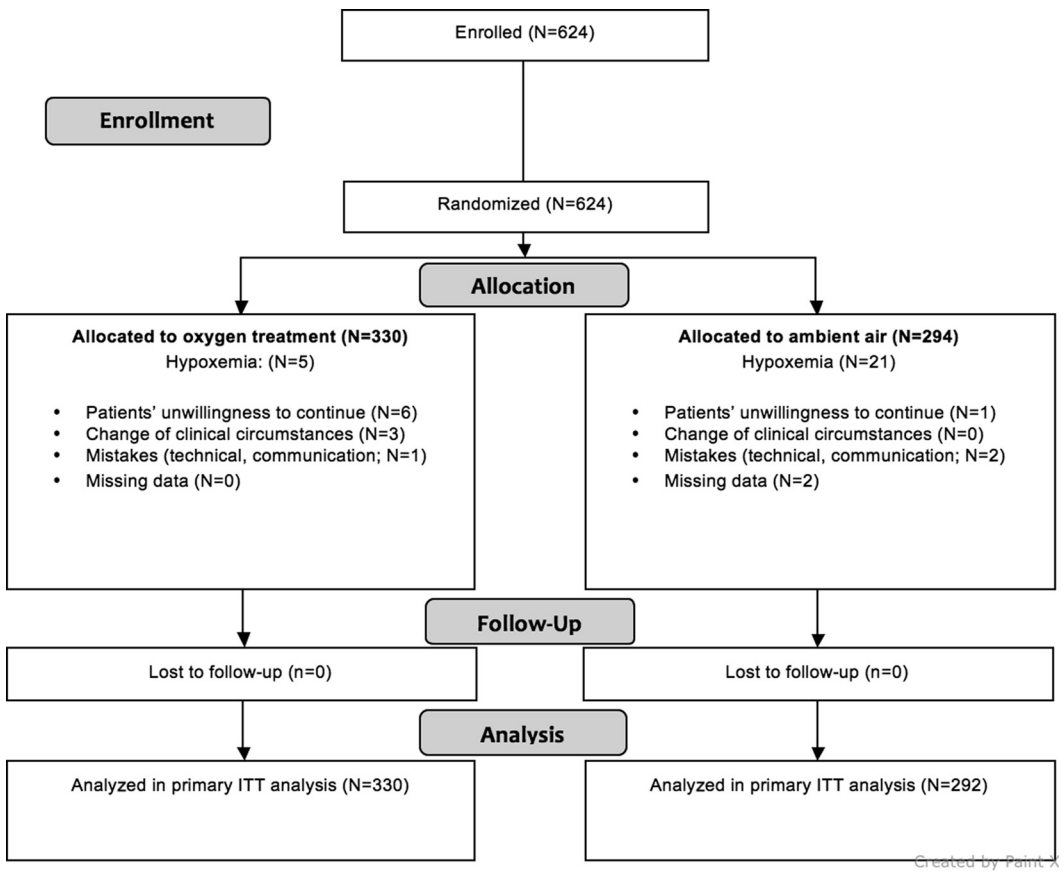
PCI = percutaneous coronary intervention

SaO_2 = arterial oxygen saturation

STEMI = ST-segment elevation myocardial infarction

VAS = Visual Analogue Scale

FIGURE 1 Patient Flow Chart of Enrollment, Randomization, and Analysis



Patients with suspected acute myocardial infarction included in the main trial were considered eligible for inclusion if percutaneous coronary intervention was carried out within the time frame of the main study intervention. ITT = intention-to-treat.

ST-segment elevation myocardial infarction (STEMI) were excluded. In the present substudy, we aimed to assess the analgesic effect of moderate-flow oxygen supplementation in a cohort of patients undergoing treatment with PCI and to study the effect of oxygen supplementation on the use of opiates and sedatives during PCI.

METHODS

DESIGN. The present study was a pre-specified substudy of the DETO2X-AMI (An Efficacy and Outcome Study of Supplemental Oxygen Treatment in Patients With Suspected Myocardial Infarction) trial (18). Patients with suspected AMI included in the main trial were considered eligible for inclusion if PCI was carried out within the time frame of the main study intervention. All Swedish cardiology departments with capacity for primary PCI and part of the main study (n =14) were asked for participation. Eight high-volume centers accepted.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE. The main study was approved by the ethical review board in Gothenburg (DNR 287-12) as well as by the Swedish Medical Products Agency (MPA) (EudraCT 2013-002882-20) and was registered at clinicaltrials.gov (NCT01787110). This substudy was approved by the ethical review board in Gothenburg as an amendment to the main study (DNR T510-14). All included patients gave oral consent followed by written confirmation within 24 h as described in the main publication (18).

PROCEDURE AND DATA COLLECTION. All patients followed the protocol of the main study (19). In the present cohort, 70 to 100 U/kg heparin was administered by an intra-arterial injection directly after the insertion of the arterial sheath. Oxygen saturation was measured continuously during the intervention by pulse oximetry. Five minutes after removal of the guiding catheter from the arterial sheath, the patients were asked to estimate the peak level of chest pain during the time span of the intervention, defined as the period from insertion to removal of the arterial sheath. The Visual Analogue Scale (VAS), a well-established and validated tool for determination of pain/discomfort (20–22), was used to estimate the level of pain. Furthermore, the total amount of opiates and sedative agents administered during the study period was reported.

SAMPLE SIZE AND STATISTICAL ANALYSIS. Based on previous VAS data from the OXYPAIN study (17), an estimated sample size of 150 in each group would result in 80% power with a significance level of 0.05 (2-tailed) to detect a relative difference of 15% between the study groups. Because we also included STEMI patients with possibly more severe pain and thus more variation in VAS score (23), we decided to increase the sample size to 250 in each arm. VAS

TABLE 1 Patient Baseline Characteristics, Clinical Presentation, and Final Diagnoses

	Oxygen Group	Ambient-Air Group
Median age, yrs	67.0 (59.0–74.0)	66.0 (58.0–73.0)
Male	246 (74.5)	213 (72.9)
Body mass index, kg/m^2	27.0 (4.1)	27.0 (4.2)
Current smoker	88 (26.7)	85 (29.1)
Hypertension	124 (37.6)	135 (46.2)
Hyperlipidemia	61 (18.5)	60 (20.5)
Diabetes mellitus	60 (18,1)	51 (17.4)
Renal failure*	40 (12.1)	45 (15.4)
Previous cardiovascular disease		
Myocardial infarction	41 (12.4)	42 (14.4)
PCI	38 (11.5)	34 (11.6)
CABG	16 (4.8)	9 (3.1)
Cause of admission		
Chest pain	315 (95.5)	279 (95.5)
Dyspnea	3 (0.9)	2 (0.7)
Medication at admission		
Aspirin	58 (17.6)	62 (21.2)
$P2Y_{12}$ receptor inhibitor	7 (2.1)	8 (2.8)
Beta-blocker	67 (20.3)	72 (24.7)
Statins	58 (17.6)	58 (19.9)
ACE inhibitor or angiotensin II blocker	78 (23.6)	88 (30.1)
Calcium blocker†	34 (10.3)	50 (17.1)†
Diuretic agent	25 (7.6)	31 (10.6)
Median time from symptom onset to randomization, min	188.0 (116.0–400.0)	210.0 (115.0–405.0)
Ambulance transportation	238 (72.1)	217 (74.3)
Vital signs at presentation		
Systolic blood pressure, mm Hg	147.8 (25.5)	144.9 (23.9)
Heart rate, beats/min	76.2 (18.2)	76.5 (17.3)
Median oxygen saturation, %	97 (96–99)	97 (95–99)
Final diagnosis		
Myocardial infarction	308 (93.3)	274 (93.8)
STEMI	238 (72.1)	203 (69.5)
NSTEMI	68 (20.6)	67 (22.9)
Angina pectoris	7 (2.1)	3 (1.0)
Other cardiac diagnosis	7 (2.1)	6 (2.1)
Unspecified chest pain	6 (1.8)	4 (1.4)
Other, noncardiovascular diagnosis	2 (0.6)	5 (1.7)
Missing data	2 (0.6)	4 (1.4)

Values are median (interquartile range) or n (%). *Renal failure was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2. †There were no significant differences between the groups with the exception of calcium blockers in benefit of ambient-air (p = 0.01).

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

was considered a continuous variable. VAS and the amount of analgesic agents were calculated and reported as median with interquartile range. The comparison between the supplemental oxygen and ambient air groups was computed by the Mann-Whitney *U* test (Wilcoxon rank-sum test). Categorical variables were analyzed using the chi-square test or Fisher exact test as appropriate. A p value of <0.05 was considered statistically significant. Explorative subgroup analyses were performed in the STEMI, non-ST-segment elevation myocardial infarction (NSTEMI), and sex groups, using the same statistical calculations/methods.

RESULTS

PATIENT CHARACTERISTICS AND PROCEDURAL DATA. Between December 1, 2014, and December 29, 2015, a total of 624 patients were enrolled (9.4% of the main study population and 14.7% of the main study population treated by PCI) (18). Of the 622 patients, 330 were randomized to receive supplemental oxygen at a moderate flow rate and 294 to ambient air. In the ambient air group, 2 patients were excluded from the analysis due to missing data (1 patient with a gastrointestinal bleeding without evidence of ischemia and 1 with inaccurate personal identification number). Five patients in the oxygen group and 21 in the ambient air group received additional oxygen due to development of hypoxemia. Thirteen additional patients did not complete the study intervention for miscellaneous reasons (Figure 1). A total of 594 patients (95%) were enrolled because of chest pain, and of those, 582 (93.6%) were diagnosed with myocardial infarction (Table 1). The most common finding on coronary angiography was 1-vessel disease (34.4%) involving the left anterior descending coronary artery as the culprit lesion. Ninety-four percent of the patients were classified as Killip class 1 (24), and interventional success rates were similar between the groups (Table 2).

CLINICAL OUTCOMES. There was no significant difference in the peak level of pain measured by VAS between the groups (median [interquartile range]: oxygen 4.0 [1.0 to 6.0] vs. air 3.0 [0.6 to 6.0]; p = 0.37) (Figure 2). Subgroup analyses of peak level of pain were performed in the groups of STEMI, NSTEMI, men, and women. There were no significant differences in any of the subgroup analyses (Table 3). Among all patients, 225 (36.1%) received opiates. The median dosage (mg) did not differ between the groups (oxygen 0.0 [0.0 to 3.0] vs. air 0.0 [0.0 to 3.0]; p = 0.31). Six hundred and twenty-one patients (99.8%) received sedatives (diazepam). There was no difference in dosage (mg) between the groups (oxygen 2.5 [0.0 to 2.5] vs. air 2.5 [0.0 to 2.5]; p = 0.74 (Table 3).

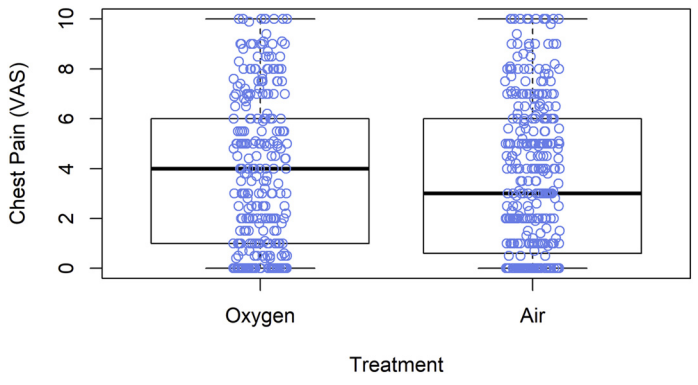
TABLE 2 Procedures, Medication, and Complications During Hospitalization

	Oxygen Group	Ambient-Air Group
Median duration of oxygen therapy, h	6.08 (6.00–11.93)	–
Received oxygen outside the protocol because of development of hypoxemia	5 (1.5)	21 (7.2)
Median oxygen saturation at end of treatment period, %	99 (97.0–100.0)	97 (95.0–98.0)
Procedures		
Coronary angiography	330 (100)	292 (100)
PCI	305 (92.4)	272 (93.2)
CABG	8 (2.4)	5 (1.7)
Median time from symptom onset to revascularization, min	187 (130.0–327.0)	180 (115.0–300.0)
Puncture site		
Radial artery	288 (87.3)	266 (91.1)
Femoral artery	42 (12.7)	28 (8.9)
PCI findings		
1-vessel disease	123 (37.3)	91 (31.2)
2-vessel disease	64 (19.4)	63 (21.6)
3-vessel disease	41 (12.4)	36 (12.3)
Culprit lesion*		
Right coronary artery	103 (31.2)	83 (28.4)
Left anterior descending artery	130 (39.4)	125 (42.8)
Left circumflex artery	54 (16.4)	50 (17.1)
Median radiation dose, Gy · cm^2	3,516 (1,781–3,516)	4,006 (1,970–6,994)
Median amount of contrast medium, ml	130 (100–170)	130 (100–180)
Median duration of hospital stay, days	3.0 (0–95)	3.0 (0–19)
Killip class I	312 (94.5)	276 (94.5)
Success rate†	290 (87.9)	257 (88.1)
Median highest measured level of highly sensitive troponin T, ng/l‡	1,104 (376.0–3,420)	1,134 (330.0–3,664.0)
Medication		
Intravenous diuretic agent	32 (9.7)	28 (9.6)
Intravenous inotrope	7 (2.1)	6 (2.1)
Intravenous nitroglycerin	17 (5.2)	16 (5.5)
Aspirin	297 (90.0)	265 (90.8)
$P2Y_{12}$ receptor inhibitor	301 (91.2)	266 (91.1)
Beta-blocker	288 (87.3)	254 (87.0)
Statin	309 (93.6)	263 (90.1)
ACE inhibitor or ARB	284 (86.1)	248 (84.9)
Calcium blocker	27 (8.2)	36 (12.3)
Diuretic agent	35 (10.6)	44 (15.1)
Complications		
Reinfarction	3 (0.9)	0 (0)
New-onset atrial fibrillation	11 (3.3)	9 (3.1)
Atrioventricular block, second-degree or third-degree	5 (1.5)	5 (1.7)
Cardiogenic shock	5 (1.5)	3 (1.0)
Cardiac arrest	12 (3.6)	11 (3.8)
Death	5 (1.5)	6 (2.1)

Values are median (interquartile range) or n (%). Comparison of continuous variables were calculated by the Mann-Whitney *U* test and categorical variables with Chi^2 test or Fisher exact test. There were no significant differences between the groups. *Data were available for 545 (87.6%) of the patients. †Success rate was defined as general success, and the strictly diagnostic procedures were excluded. ‡Data were available for 537 (86.3%) of the patients: 286 patients (86.7%) in the oxygen group and 251 patients (86.0%) in the ambient-air group (p = 0.81).

ARB = angiotensin-receptor blocker; other abbreviations as in Table 1.

FIGURE 2 Peak Level of Ischemic Chest Pain Measured by VAS



There was no significant difference in the peak level of pain measured by VAS between the groups (median [interquartile range]) (oxygen 4.0 [1.0 to 6.0] vs. air 3.0 [0.6 to 6.0]; p = 0.37). VAS = Visual Analogue Scale.

DISCUSSION

In this clinical trial, we assessed the analgesic effect of moderate-flow oxygen supplementation in patients with suspected AMI and normal oxygen saturation. Our results demonstrate no significant differences in the peak level of pain between the groups randomized to receive oxygen or ambient air, a finding consistent with previous studies (1,5,15–17). Furthermore, there were no differences in the use of opiates or sedatives between the groups.

The role of oxygen in the treatment of ischemic pain has been studied since the early 20th century (14,25,26). Existing evidence has been mainly empirical from small case series, based on the assumption that in the case of impaired oxygen supply in the myocardium, supplemental oxygen would increase oxygen delivery to the ischemic tissue by collateral circulation and thus, decrease ischemic pain (27,28). Similarly, oxygen therapy was believed to decrease myocardial injury and thereby reduce the risk of arrhythmias and, ultimately, morbidity and mortality (29). This assumption was further supported by animal models (30,31), studies of hyperbaric oxygen (32,33), and nonrandomized trials conducted before the era of myocardial revascularization (34,35). Rusek et al. (36) showed in 1950 that hyperoxemia causes a prolonging of the ischemic characteristics of the electrocardiogram, and does not relieve ischemic pain in AMI. Moreover, routine oxygen in normoxemic patients might be associated with potentially harmful effects that can worsen myocardial ischemia (1,37). The effects are considered to derive from the vasoactive properties of oxygen and caused by inadvertent hyperoxemia (8). Different underlying mechanisms have been proposed: increased production of reactive oxygen species decreasing the bioavailability of nitric oxide leading to subsequent vasoconstriction (38,39), direct vasoconstriction caused by closure of ATP-sensitive K^+-channels (40), direct effects on L-type $Ca2^+$-channels (41), increased production of the vasoconstrictor metabolite 20-HETE (42), and an increased engagement of the angiotensin I/II system (43). Furthermore, vasoconstriction and the subsequent hemodynamic responses may be associated with aggravated ischemia, as demonstrated by increased lactate levels during hyperoxemia (28,44). Even though the exact mechanisms are yet to be determined, the vasoactive capacity of oxygen is beyond doubt. On the basis of theoretical data, hyperoxemia could actually result in a more severe pain experience (7). However, our study demonstrates that supplemental oxygen at a moderate flowrate does not increase or decrease ischemic pain during AMI.

The estimation of pain remains a difficult task in the diagnostics and treatment of coronary artery disease (45). Nevertheless, in the recently updated European Society of Cardiology guidelines for AMI presenting with ST-segment elevation (46), the authors emphasize the importance of pain relief. Pain is associated with an increased sympathetic activity with a subsequent vasoconstriction and increased workload for the heart, and thus is important to manage. In the guidelines, titrated intravenous opiates and sedatives in anxious patients are recommended for pain relief (Class IIa, Level of Evidence: C). Routine oxygen is not recommended for patients with an arterial oxygen saturation (SaO_2) ≥90% (Class III, Level of Evidence: B) due to the possible harmful effects of hyperoxemia. In hypoxemia,

TABLE 3 Clinical Endpoints

	n	Oxygen Group	Ambient-Air Group	p Value
Peak level of pain estimated by VAS				
Main study cohort	622	4.0 (1.0-6.0)	3.0 (0.6-6.0)	0.37
ST-segment elevation myocardial infarction	465	4.0 (1.0-6.0)	4.0 (1.0-6.7)	0.97
Non-ST-segment elevation myocardial infarction	115	3.5 (1.6-6.0)	2.0 (0-5.0)	0.11
Male	456	3.5 (1.0-6.0)	2.8 (0.6-6.6)	0.35
Female	157	4.5 (1.0-6.5)	4 (1.0-6.0)	0.75
Use of opiates and sedatives				
Median use of opiates, mg	225	0.0 (0.0-3.0)	0.0 (0.0-3.0)	0.31
Median use of sedatives, mg	621	2.5 (0.0-2.5)	2.5 (0.0-2.5)	0.74

Values are median (interquartile range) unless noted otherwise. The p value for comparison was calculated by the Mann-Whitney *U* test (Wilcoxon rank-sum test).
VAS = Visual Analogue Scale.

defined as a partial arterial oxygen pressure of <60 mm Hg or an arterial SaO_2 of <90%, supplemental oxygen is recommended (Class 1, Level of Evidence: C). In addition, the American College of Cardiology Foundation/American Heart Association guidelines (47) state that oxygen is appropriate in SaO_2 <90%, and recommend that oxygen be used with caution due to the vasoconstrictive properties. Hence, our present results are in agreement with current clinical guidelines (46,47).

Our main study, the DETO2X-AMI trial (18), did not demonstrate any significant beneficial effect of oxygen as compared with ambient air on all-cause mortality at 1 year, infarct size measured by troponin T release, or on the incidence of rehospitalization with myocardial infarction. The results from this substudy further strengthen the recommendation that it is safe and reasonable to withhold oxygen from patients with suspected AMI and normal oxygen saturation, and that supplemental oxygen at a moderate flowrate is not associated with an analgesic effect. Also, combined with the results from our previous publication (17), the present findings are consistent in stable angina, unstable angina, NSTEMI, and STEMI. Even though we did not perform a pooled analysis of the results, we consider it reasonable and in accordance with guidelines to limit the use of oxygen in all patients during PCI to hypoxemic patients with a SaO_2 ≤90% only, irrespective of the level of pain.

STUDY LIMITATIONS. First, pain is a complex outcome to measure, mainly due to the high degree of subjectivity, but also because of a lack of objective methods to quantify individual pain experience. There are a considerable number of tools available for self-reported estimation of pain, where the VAS is associated with high reliability and validity for chronic pain conditions as well as in acute pain (20,21,48). However, pain estimation by any tool might be affected by interviewer bias where the research staff influences the response of the subject. Therefore, we used a standardized procedure that in some extent should adjust for this. Another limitation is that some patients in our study were already treated with opiates in the pre-hospital setting, which could influence pain experience during PCI. Furthermore, as the study was not double blinded or placebo controlled, we cannot rule out a potential placebo effect of oxygen. However, in our previous study (17) as well as in the SOCCER (Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion) trial (2), we used a placebo-controlled design with similar results. Also, in this study, we used oxygen with a moderate flowrate of 6 l/min. In several publications, higher doses of oxygen have been associated with an increase of vascular resistance, decrease in coronary blood flow, aggravated cardiac injury, and worsen long-term prognosis (1,8,49,50). The results of this study do not refute the risk of a dose-dependency, and it remains unclear whether the results would have been similar in a study of higher oxygen concentration. However, we designed this study to reflect current clinical practice in patients with suspected AMI without hypoxemia at baseline. By using a moderate dose of oxygen combined with a lower limit of SaO_2 of 90%, we increased oxygen saturation enough to diminish the risk of hypoxemia while avoiding excessive hyperoxemia and potential harm. Finally, in clinical practice, oxygen is commonly used to alleviate nausea. We did not specifically investigate this variable, which poses a limitation.

CONCLUSIONS

In this pragmatic, registry-based randomized clinical trial, we did not find any analgesic effect of oxygen as compared with ambient air, and no differences in the use of sedatives and opiates during PCI. Our results indicate that moderate-flow oxygen supplementation does not relieve pain in patients with suspected AMI and normal oxygen saturation undergoing treatment with PCI and thus should not be used for this purpose.

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PERSPECTIVES

WHAT IS KNOWN? Oxygen in normoxemic patients with AMI does not provide clinical benefit but may relieve ischemic pain.

WHAT IS NEW? Our findings do not demonstrate a significant analgesic effect of moderate oxygen flowrate supplementation. Oxygen should therefore not be used in normoxemic patients.

WHAT IS NEXT? The generalizability of our findings should be studied in high-concentration oxygen flowrate.

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