Scandinavian Cardiovascular Journal

ISSN: 1401-7431 (Print) 1651-2006 (Online) Journal homepage: https://www.tandfonline.com/loi/icdv20

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To cite this article: Ardavan Khoshnood, Mahin Akbarzadeh, Marcus Carlsson, David Sparv, Pallonji Bhiladvala, Arash Mokhtari, David Erlinge & Ulf Ekelund (2018) Effect of oxygen therapy on chest pain in patients with ST elevation myocardial infarction: results from the randomized SOCCER trial, Scandinavian Cardiovascular Journal, 52:2, 69-73, DOI: 10.1080/14017431.2018.1439183

To link to this article: https://doi.org/10.1080/14017431.2018.1439183

SCANDINAVIAN CARDIOVASCULAR JOURNAL, 2018
VOL. 52, NO. 2, 69–73
https://doi.org/10.1080/14017431.2018.1439183

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ORIGINAL ARTICLE

Effect of oxygen therapy on chest pain in patients with ST elevation myocardial infarction: results from the randomized SOCCER trial

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ABSTRACT

Objective. Oxygen (O_2) have been a cornerstone in the treatment of acute myocardial infarction. Studies have been inconclusive regarding the cardiovascular and analgesic effects of oxygen in these patients. In the SOCCER trial, we compared the effects of oxygen treatment versus room air in patients with ST-elevation myocardial infarction (STEMI). There was no difference in myocardial salvage index or infarct size assessed with cardiac magnetic resonance imaging. In the present subanalysis, we wanted to evaluate the effect of O_2 on chest pain in patients with STEMI. *Design*. Normoxic patients with first time STEMI were randomized in the ambulance to standard care with 10 l/min O_2 or room air until the end of the percutaneous coronary intervention (PCI). The ambulance personnel noted the patients´ chest pain on a visual analog scale (VAS; 1-10) before randomization and after the transport but before the start of the PCI, and also registered the amount of morphine given. *Results*. 160 patients were randomized to O_2 ($n = 85$) or room air ($n = 75$). The O_2 group had a higher median VAS at randomization than the air group (7.0 ± 2.3 vs 6.0 ± 2.9; $p = .02$) and also received a higher median total dose of morphine (5.0 mg ± 4.4 vs 4.0 mg ± 3.7; $p = .02$). There was no difference between the O_2 and air groups in VAS at the start of the PCI (4.0 ± 2.4 vs 3.0 ± 2.5; $p = .05$) or in the median VAS decrease from randomization to the start of the PCI (−2.0 ± 2.2 vs −1.0 ± 2.9; $p = .18$). *Conclusion*. Taken together with previously published data, these results do not support a significant analgesic effect of oxygen in patients with STEMI.

European Clinical Trials Database (EudraCT): 2011-001452-11.
ClinicalTrials.gov Identifier: NCT01423929

ARTICLE HISTORY
Received 6 December 2017
Revised 1 February 2018
Accepted 3 February 2018

KEYWORDS
Cardiology; emergency medicine; STEMI; oxygen treatment; pain

Introduction

Ever since Dr. Charles Steele in 1900 published [1] that one of his patients with angina pectoris was relieved by oxygen (O_2) therapy, supplemental O_2 has been a cornerstone in the treatment of patients with suspected acute myocardial infarction (AMI) and recommended by many guidelines [2,3]. O_2 therapy is believed to reduce ischemia in the myocardium and the risk of arrhythmias [4] and acute heart failure, and to decrease the ischemic chest pain.

Some of the first studies suggested that O_2 therapy may have positive circulatory effects in AMI patients [5,6], but many modern studies indicate that O_2 therapy is more likely to have negative cardiovascular effects and that it may even increase infarct size [7–9]. Recently, however, both Ranchord et al. [10] and Khoshnood et al. [11,12] found no effect of O_2 therapy on infarct size in patients with ST elevation myocardial infarction (STEMI).

The analgesic effect of O_2 therapy observed by Steele was also supported by early studies. In 1939 Boothby et al. [13] stated that administration of 100% O_2 has a rapid pain-relieving effect in angina pectoris, and in 1940, Boland [5] concluded that O_2 therapy effectively decreases chest pain in AMI patients, even when opiates fail to help. A decade later, however, Russek et al. [14] declared that supplemental O_2 to patients with angina had no effect on the circulation, AMI development or chest pain. More recent studies suggest that there is no analgesic effect of O_2 therapy in patients undergoing elective percutaneous coronary intervention (PCI) [15] or AMI patients and relief of angina [8].

In the present substudy of the Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) trial, we assessed the effect of O_2 therapy vs room air on chest pain in STEMI patients transported to acute PCI.

Methods

The SOCCER study was a dual-center, single blinded randomized controlled trial conducted in Lund and Malmö

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Supplemental data for this article can be accessed here.

in Sweden between January 2012 and August 2015. Regarding the design and method, the reader is referred to previous publications [11,12,16]. The trial was approved by both the Regional Ethical Review Board and the Swedish Medical Products Agency (EudraCT No 2011-001452-11). This study is reported in accordance with the CONSORT statement [17].

Patient inclusion and management

In brief, patients with first time STEMI, symptom duration of <6 hours and a normal blood oxygen saturation (≥94%) were, after verbal consent, included in the ambulance and randomized to either 10 L/min supplemental O_2 therapy (O_2 group) or room air (air group). All patients had an OxyMask fitted and were blinded to the study intervention which lasted until the end of the percutaneous coronary intervention (PCI).

Except for the study intervention, all patients were treated according to local and international guidelines with dual antiplatelet therapy, as well as beta-blockers and morphine as needed. If blood oxygen saturation fell under 94%, the study intervention was terminated and standard care O_2 treatment with 10 l/min started. The ambulance personnel used case report forms to note vital parameters and patient management, including medications given.

After the PCI, the patients were informed by a study physician and consented to participation in writing.

This study was a planned secondary analysis of data from the SOCCER trial, and there was no formal sample size calculation.

Visual analog scale

The visual analog scale (VAS) is an easy, reliable, widely used and validated tool to measure the intensity of acute pain [18–20]. The VAS consists of a numeric scale between 0-10 (0-100 mm) on which the patient indicates his or her level of pain. Zero (0) corresponds to "no pain" and ten (10) to the "worst imaginable pain".

In this study, the ambulance personnel reported the patients' assessment of their chest pain, i.e. their VAS score, on case report forms both at randomization and at arrival at the PCI-center.

Statistical analysis

We compared the study groups with respect to VAS score using a 2-sided Mann-Whitney test because the data were not normally distributed, with a $p < .05$ considered statistically significant. The null hypothesis was that there was no difference in VAS score between the groups. All data were analyzed using Microsoft Excel and IBM SPSS Statistics V22.

Results

The study profile is outlined in Figure 1. Of 229 patients assessed for eligibility, 160 were randomized to the O_2 group or the air group. After excluding patients with missing VAS values in the two groups, 111 patients were included in the final analysis; 60 patients randomized to the O_2 group and 51 randomized to the air group. The missed VAS scores were often because the patients were not able to use the scale for scoring their pain due to language barriers or cognitive difficulties.

The Supplemental Tables 1 and 2 show patient and PCI procedural characteristics for the first 160 patients included. For the 111 patients included in the final analysis, both patient characteristics (Table 1) and PCI procedural characteristics (Table 2) were similar. By randomization, patients

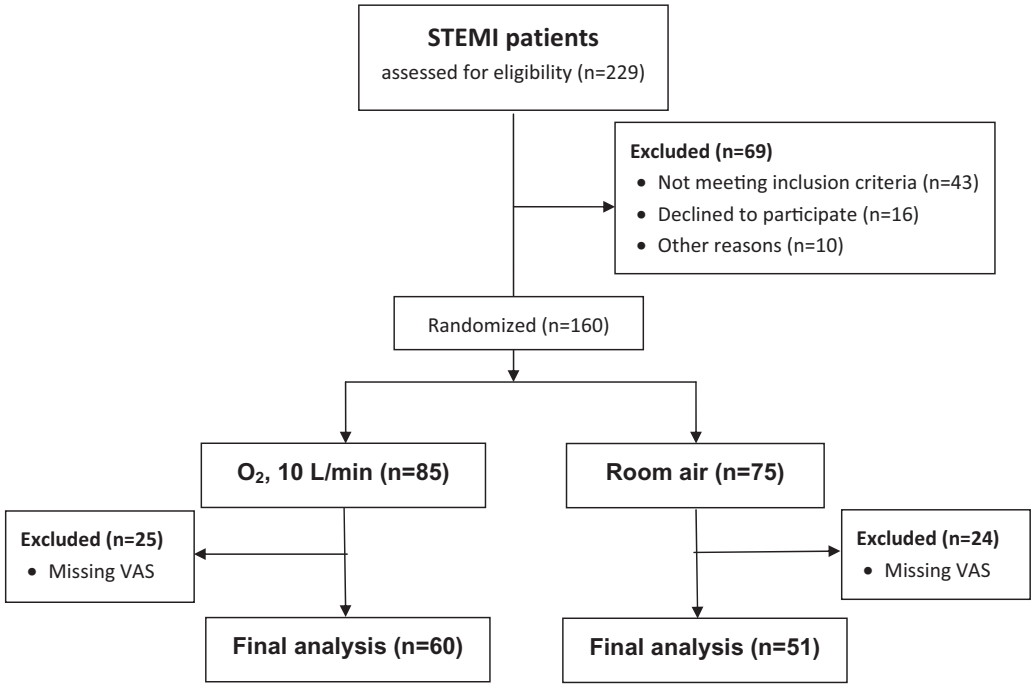

Figure 1. Patient flow diagram. A total of 111 patients were included in the final analyses.

Table 1. Patient characteristics at randomization for those included in the final analysis.

Characteristics	O_2 group ($n = 60$)	Air group ($n = 51$)	p value
Demographics			
Male gender, n (%)	37 (62)	37 (72)	.228
Mean age, year (SD)	64.4 (13)	67.7 (12.0)	.224
Current smoker, n (%)	20 (33)	18 (35)	.829
Past smoker, n (%)	23 (38)	30 (39)	*.032*
Medical history, n (%)			
Diabetes	9 (15)	8 (16)	.921
Hypertension	19 (32)	24 (47)	.099
Previous stroke/TIA	0 (0)	3 (6)	.058
Prior medication, n (%)			
ACEi	10 (17)	7 (14)	.805
Anticoagulant	1 (2)	1 (2)	1.000
Antidiabetic medication, oral	8 (13)	5 (10)	.569
ARBs	2 (3)	5 (10)	.227
Aspirin	5 (8)	8 (16)	.288
Betablocker	1 (2)	10 (20)	.007
CCB	2 (3)	7 (14)	.086
Diuretics	2 (3)	10 (20)	*.017*
Insulin	1 (2)	3 (6)	.373
Nitrates	0 (0)	3 (6)	.167
Statins	4 (7)	8 (16)	.176
Duration of study intervention (O_2 or room air)			
Mean time, min (SD)	86.3 (31)	92.6 (43)	.568
Findings at inclusion			
Mean heart rate, BPM (SD)	85.2 (19)	87.3 (17)	.396
Mean systolic BP, mm Hg (SD)	151.2 (34)	147.9 (31)	.606
Mean diastolic BP, mm Hg (SD)	82.1 (35)	79.9 (29)	.247
Mean blood oxygen saturation, % (SD)	98.1 (2)	97.7 (2)	.258

ACEi: angiotensin converting enzyme inhibitor; ARBs: angiotensin II receptor blockers; BP: blood pressure; BPM: beats per minute; CCB: calcium channel blockers; O_2: oxygen; PCI: percutaneous coronary intervention; TIA: transient ischemic attack.

Table 2. Procedural characteristics for those included in the final analysis.

Characteristics	O_2 group ($n = 60$)	Air group ($n = 51$)
Killip class at arrival to the PCI laboratory, n (%)		
Class I	57 (95)	49 (96)
Class II	3 (5)	2 (4)
Culprit lesion, n (%)		
Left Anterior Descending artery	32 (53)	23 (45)
Left Circumflex Artery	3 (5)	4 (8)
Right Coronary Artery	21 (35)	18 (35)
Other	4 (7)	6 (12)
Coronary disease, n (%)		
Single vessel	28 (47)	28 (55)
Multivessel	27 (45)	16 (31)
Left main coronary artery	3 (5)	4 (8)
Other[a]	2 (3)	3 (6)
Findings at arrival to the PCI laboratory		
Mean heart rate, BPM (SD)	75.6 (16)	73.4 (16)
Mean systolic BP, mm Hg (SD)	140.5 (25)	138.0 (28)
Mean diastolic BP, mm Hg (SD)	83.2 (16)	82.1 (16)
Cardiogenic shock, n (%)	1 (2)	2 (4)
Mean blood oxygen saturation, % (SD)[b]	99.0 (1)	97.2 (2)

CABG: coronary artery bypass grafting; IV: intravenous; O_2: oxygen; PCI: percutaneous coronary intervention; SC: subcutaneous.
[a]Other indicates normal/atheromatous vessels.
[b]$p = 0.00$.

in the air group were significantly more often treated with diuretics and past smokers than those in the O_2 group. Supplemental Tables 3 and 4 outline patient characteristics and PCI procedural characteristics for the excluded patients in the two groups. The excluded patients to a great degree shares the same characteristics as the patients included in the final analysis.

Table 3. Pain management and VAS in patients included in the final analyses.

	O_2 ($n = 60$)	Air ($n = 51$)	p value
Number of patients receiving Morphine, (%)	49 (82)	32 (63)	.026
Median amount of Morphine given, mg (SD)	6.0 (5)	4.0 (4)	.007
Median VAS at randomization, (SD)	7.0 (2)	6.0 (3)	.020
Median VAS at the start of PCI, (SD)	4.0 (2)	3.0 (2)	.050
Median VAS difference from randomization until the start of PCI, (SD)	−2.0 (2)	−1.0 (3)	.183

Table 3 shows both the pain management and VAS for the 111 included patients. A significantly higher amount of the patients included in the O_2 group received intravenous morphine in comparison with the air group (81.7% respective 62.7%; p = .026). The median amount of morphine given were also significantly higher in the O_2 group compared with the air group (6.0 mg ± 4.6 respective 4.0 mg ± 3.9; p = .007).

The O_2 group had also a significantly higher median VAS in comparison with the air group at randomization (7.0 ± 2.3 respective 6.0 ± 2.9; p = .020) but not at arrival to the PCI-center (4.0 ± 2.4 respective 3.0 ± 2.5; p = .050). When comparing the median difference in VAS from randomization to the beginning of the PCI, between the O_2 group and the air group, the difference was not significant (−2.0 ± 2.2 respective −1.0 ± 2.9; p = .183).

Discussion

In this sub-study we aimed to evaluate the effect of O_2 therapy on chest pain in STEMI patients undergoing PCI. We found that patients in the O_2 group had already before the randomization a significantly higher VAS and most likely because of that, also received significantly more morphine in comparison with the air group.

Although some studies state that O_2 therapy diminish chest pain [5,13], other studies have shown no effect of O_2 therapy on chest pain [8,14,15]. In a Cochrane review on the effects of O_2 therapy in patients with AMI [21], only two studies were identified which discussed the question of pain; Rawles and Kenmure [7] as well as Wilson and Channer [22]. Both these studies reported the use of opiates as a measurement for pain and showed no difference between patients receiving O_2 therapy or air. However, the authors of the Cochrane report [21] conclude that the risk of bias were high in these two studies, and that no conclusions should be drawn. Similarly, no effect of O_2 therapy on chest pain was observed in the OXYPAIN trial [15], where a total of 305 patients with stable angina or acute coronary syndrome (ACS) undergoing PCI was included. The study measured chest pain during PCI by using the VAS and showed no effect on chest pain in patients being randomized to O_2 instead of air. A limitation of this study may have been that it included patients with stable angina who may have had less pain during the PCI compared to STEMI patients who often chest pain also before balloon inflation. Also the AVOID study [8,9], the results of which suggested a larger IS in patients treated with O_2 compared to air, did not show any difference between the two arms when

discussing pain or the use of analgesics; the median pain scores were equal for the groups.

Our finding of a higher median VAS value for the patients in the O_2 group before intervention is probably a play of chance. Because of the higher VAS value, the patients in the O_2 group also received significantly more morphine. During the study intervention, the median VAS value fell in both groups, and neither the decrease nor the values at PCI start were significantly different between the groups. Since most patients in both groups received morphine, and since the decreases in VAS values were similar in comparing the two groups, we could not discern a significant effect of O_2 on the chest pain. Many studies, e.g. [23–25], describe the analgesic effect of morphine in AMI patients, and we believe that the observed diminished pain was explained by the fact that the majority of our patients were given iv morphine.

Study limitations

As our results include STEMI patients from two university hospitals only, they may not be representative for all STEMI patients. However, the patients included in the present study have similar characteristics and were managed in a similar way as STEMI patients in other studies [26–30]. We believe that the randomization-induced difference in diuretic use and previous smoking between the study groups (Table 1) was without significant effect on the results.

The patientś VAS and morphine injections were all managed by the paramedics who were aware of the patient́s group allocation. It is unclear whether this may have influenced the patient management, but with respect to our data and results in our previous publications [11,12], such influence is deemed to be small if at all existent.

Conclusion

Patients in the O_2 group had a significantly higher median VAS before randomization, in comparison with patients in the air group. However, this might be the result of play of chance. In discussing the analgesic effect of O_2, a major analgesic effect does not seem to exist. Larger studies are needed to fully answer the question of oxygen as an analgesic agent. This present study, taken together with previously published data, do not support a significant analgesic effect of O_2 in patients with STEMI.

Disclosure statement

The authors report no conflicts of interest.

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