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Supervisor: Ulf Ekelund, MD PhD consultant associate professor.

Examiner: Bertil Öhlin, MD PhD consultant.

Department of Emergency Medicine, Skåne University Hospital, Lund

Is high flow oxygen treatment beneficial or detrimental for normoxic patients undergoing percutaneous coronary intervention for first time ST-elevation myocardial infarction; an interim analysis of the SOCCER-study.

Martin Galeano, 871223-4114

Joakim Olofsson, 860203-2032

Populärvetenskaplig sammanfattning

Att ge syrgas till patienter som har en hjärtinfarkt har länge varit en del av standardbehandlingen, och många förväntar sig att det första som händer i en akut situation är att man får en mask med syrgas i. Detta fortsätter att ske trots att det saknas vetenskaplig grund. De studier som finns är av bristande kvalité och många av dem är från tiden innan man kunde göra ballongsprängning av proppar i hjärtats kranskärl. Dessutom pekar vissa av de studier som finns till och med på att syrgas till patienter utan syrebrist med hjärtinfarkt skulle kunna vara skadligt.

I den här uppsatsen, som är en föranalys av material från en större studie, jämför vi en grupp patienter som får syrgas i ambulansen på väg till sjukhuset för att göra ballongsprängning, mot en grupp som får andas rumsluft. I studien mätte vi först och främst hur hjärtmuskelns vägg rör sig efter hjärtinfarkten på hjärtultraljud. Vi mätte också mängden av ett protein som läcker ur hjärtmuskeln när den blir skadad och jämförde om det fanns någon skillnad mellan grupperna. Vi hittade ingen skillnad mellan de två grupperna i någon av undersökningarna.

Det är ännu en bit kvar tills vi har fått ett svar på om syrgas är bra eller dåligt för patienter utan syrebrist med hjärtinfarkt. Det behövs stora studier med flera tusen deltagare för att man ska kunna säkerställa om det är nyttigt eller skadligt att ge syrgas till dessa patienter. Fram tills den dagen är kommen bör man vara restriktiv med att ge syrgas till patienter som inte lider av syrebrist.

Abstract

Background: Routine oxygen therapy has for a long time been used as part of the standard treatment for myocardial infarction (MI), despite a lack of randomized controlled trials (RCT) to support the use. A recent Cochrane review on oxygen treatment for normoxic MI patients found no evidence supporting the use, rather the trend pointed towards possible harm for oxygen. The SOCCER-study (Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion) is an ongoing RCT to address this question.

Objective: The aim of this study was to compare infarct size as measured by wall motion score index (WMSI) on transthoracic echocardiography (TTE) for the first patients included in SOCCER with ST-elevation myocardial infarction (STEMI) receiving high flow oxygen treatment versus room air.

Method: A randomized controlled trial was undertaken including 15 normoxic patients with first time STEMI accepted for immediate percutaneous coronary intervention (PCI). Patients were randomized in the ambulance to receive either 10 L O_2/min or room air during the transport to and during the PCI. On day 2-4, TTE was performed and assessed for the primary outcome WMSI. Secondary outcomes included peak level Troponin T (TnT) and area under the curve (AUC) of TnT during 24 hours.

Results: There was 1 (of 8) deaths for oxygen and 1 (of 7) deaths for room air. There was no significant difference in WMSI between the groups: Median WMSI for oxygen vs room air (8 vs 6 patients) was 1.16 vs 1.28, p=0.87. Nor were there any significant difference in peak TnT and TnT_{AUC} for oxygen vs room air (8 vs 7) patients. Median peak TnT 1700 vs 4125 ng/L, p=0,054, and TnT_{AUC} was 931 vs 2272 ng/L/h, p=0,072 respectively.)

Conclusion: This interim analysis of the SOCCER study found no difference in infarct size as measured by WMSI or TnT between high flow oxygen and room air to patients with first time STEMI undergoing PCI. However the small number of patients in the analysis might have prevented us from detecting any difference. Large studies are urgently required to address the effects of oxygen to MI patients. Until then physicians should use care when administering oxygen to normoxic patients.

Background

The logical assumption that supplemental oxygen treatment in normoxic patients with myocardial infarction (MI) secures the availability and delivery of O_2 to the ischaemic myocardium has long been an accepted thesis. However, the evidence to support this is of low quality and lacks statistical significance. In fact, the only existing quality evidence points towards harmful effects of supplemental oxygen treatment for MI.[1]

More than a century has passed since the first article suggesting that oxygen administered to patients with angina pectoris could relieve pain was published. Since then supplemental oxygen has been part of most international treatment guidelines for MI.[2] At present the recommendation in many international guidelines is to administer oxygen even if the blood O_2 saturation is adequate.[3,4] However, recently updated guidelines are more cautious.[5] Current Swedish guidelines from Lund[6] also recommend the use of O_2 to patients with ST Elevation Myocardial Infarction(STEMI) but the Swedish Council on Health Technology Assessment (SBU) have identified this as an area where more research is required.[7]

The first indication that oxygen therapy actually might be harmful came from Russek and colleagues in 1950 who showed that patients receiving oxygen therapy had a significant increase in the duration and severity of ECG changes and that it did not affect the onset or duration of anginal pain.[8]

In 1976 Madias and colleagues suggested that oxygen administered during a myocardial infarction might reduce the ischemic injury, based on precordial ST segment mapping. This article represents the major clinical evidence that support the use of oxygen.[9] However the study lacks a number of critical features such as randomization and blinding.[2]

The first randomized, double-blinded and controlled trial was published in 1976 by Rawles and Kenmure, comparing the use of oxygen at a rate of 6 l/min to room air in uncomplicated MI. The relative risk of death was 2.9 (95% CI 0.81-10.3; P=0.08) in the oxygen group, but the study was underpowered.[10]

Two more recent randomized controlled trials are: Wilson, 1997 and Ukholkina, 2005.[11,12] These studies together with Rawles' study are part of a Cochrane collaboration review from 2010.[1] The same authors, Burls et al, performed a meta-analysis with the results from the three articles but did not reach statistical significance, however the trend pointed toward potential harm when high flow oxygen was given to normoxic patients with uncomplicated MI.[13]

The most recent study was published in 2012 by Ranchord and colleagues. The authors

compared high flow oxygen with titrated oxygen for STEMI and found no evidence that either treatment was beneficial or harmful.[14]

The hyperoxia that high flow oxygen therapy leads to causes a reduction in coronary blood flow in both healthy subjects[15,16] and patients with ischemic heart disease[16-18] and patients congestive heart failure (CHF).[19] Further, oxygen treatment reduces cardiac output in both healthy individuals[15] and in patients with CHF.[19]

Objective

In this study we tested the hypothesis that there is a difference in infarct size as measured by cardiac Wall Motion Score Index (WMSI) after receiving high flow oxygen (10 l/min) vs no supplemental oxygen in the ambulance in normoxic patients undergoing acute PCI for STEMI.

Method

Trial

This study was a prospective, randomized, controlled, single blinded, non-commercial trial undertaken at the University Hospital of Skåne which consists of two tertiary hospital centers, Lund and Malmö in the Region Skåne, Sweden. The study involved the ambulance centrals at both Lund and Malmö, the coronary angiography center at the hospital in Lund and the echocardiography centers at both hospitals, and was coordinated via the center for emergency medicine in Lund. The study was approved by the Regional Ethics Review Board, Skåne, and the Swedish Medical Products Agency (Läkemedelsverket). The study was funded by the Swedish Heart-Lung Foundation, The Lærdal Foundation, ALF-funds at Lund University, and donation funds at the University Hospital of Skåne. All participants gave written informed consent. Ethical approval was obtained for the use of a shortened oral information and consent at the time of inclusion by an ambulance specialist nurse, followed by more detailed oral and written information and formal written consent to a doctor within the first 72 hours of the participants in-hospital stay after the percutaneous coronary intervention (PCI). This study was a subgroup analysis of the 15 first participants included in the larger study Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER, Study ID/no/EudraCT No 2011-001452-11).

Population

Subjects were eligible for inclusion if they had an ST-elevation myocardial infarction (STEMI) in the ambulance and were accepted for immediate angiography and PCI at the center at Lund. Any suspect ECG pathology in the ambulance is examined by a cardiologist via the LifeNet® (Medtronic Physio-Control, Remond, WA) system for wireless transmission of ECG's from the ambulance to the cardiac intensive care unit (ICU) at the hospital, and thus, only patients with ST-elevations confirmed by a cardiologist are accepted for immediate PCI. Additional inclusion criteria were duration of chest pain less than 6 h at the time of ambulance arrival and blood oxygen saturation (SaO_2) ≥94 % measured by pulse oximeter. Exclusion criteria were previous MI and claustrophobia or other contraindications against magnetic resonance imaging (MRI), such as magnetic prostheses or items in the body. Furthermore, patients were excluded if a MI was not confirmed by an elevation of plasma-Troponin T (TnT).

Design

Subjects were included in the ambulance following short oral information by the ambulance nurse and randomized (blocked randomization, 1:1 ratio with 6 participants per block) by opening a sealed envelope to either receive oxygen via an Oxymask® (MedCore AB, Kista, Sweden) with a flow of 10 L O_2/min or to just be fitted with the Oxymask® connected to the oxygen outlet valve, but not receive any supplemental oxygen. The patients were not informed as to what treatment they were allocated to. The large holes in the Oxymask® allow the patient to breathe room air freely, without obstruction or increase in dead space. The patient received the allocated study intervention for the duration of the transport to, and during, the PCI. The ambulance staff continuously monitored the SaO_2 during transport as in routine care, and if at any time this fell below 92 % in a participant allocated to receive room air, the nurse would start supplying oxygen at 10 L/min, note the event, and continue to treat the patient as in routine care (which dictates 10 L O_2/min to all patients with suspected acute MI). After the PCI, the Oxymask® was removed and the patients received standard medical care at the cardiac ICU and cardiology ward for the rest of their in-hospital stay.

Recommended standard oxygen therapy at the cardiac ICU in Lund is to administer 4 L O_2/min for the first 8 h, however this is not always adhered to.

Patients residing in the Malmö area were transferred to the Malmö hospital center when deemed stable by the attending cardiologist.

Ultrasound imaging protocol

The participants underwent transthoracic echocardiography (TTE) on day 2-4 of their in-hospital stay. The TTE was performed by trained echocardiographers or cardiologists, and WMSI was later assessed by a cardiologist blinded to the treatment allocation. WMSI was measured using the following algorithm: The left ventricle is divided into 16 segments. Wall motion score for each of the visualized segments was then assessed by using a 5 graded scale, 1= Normal, 2= Hypokinesis, 3= Akinesis, 4= Dyskinesis, 5=Aneurysmal. The total score collected was then divided by the number of evaluated segments. Any segments that were not visualized were excluded. A heart with normal contractility thus has a WMSI of 1.

$$\text{WMSI} = \frac{\text{Sum of individual segment score}}{\text{Number of evaluated segments}}$$

Outcome variables

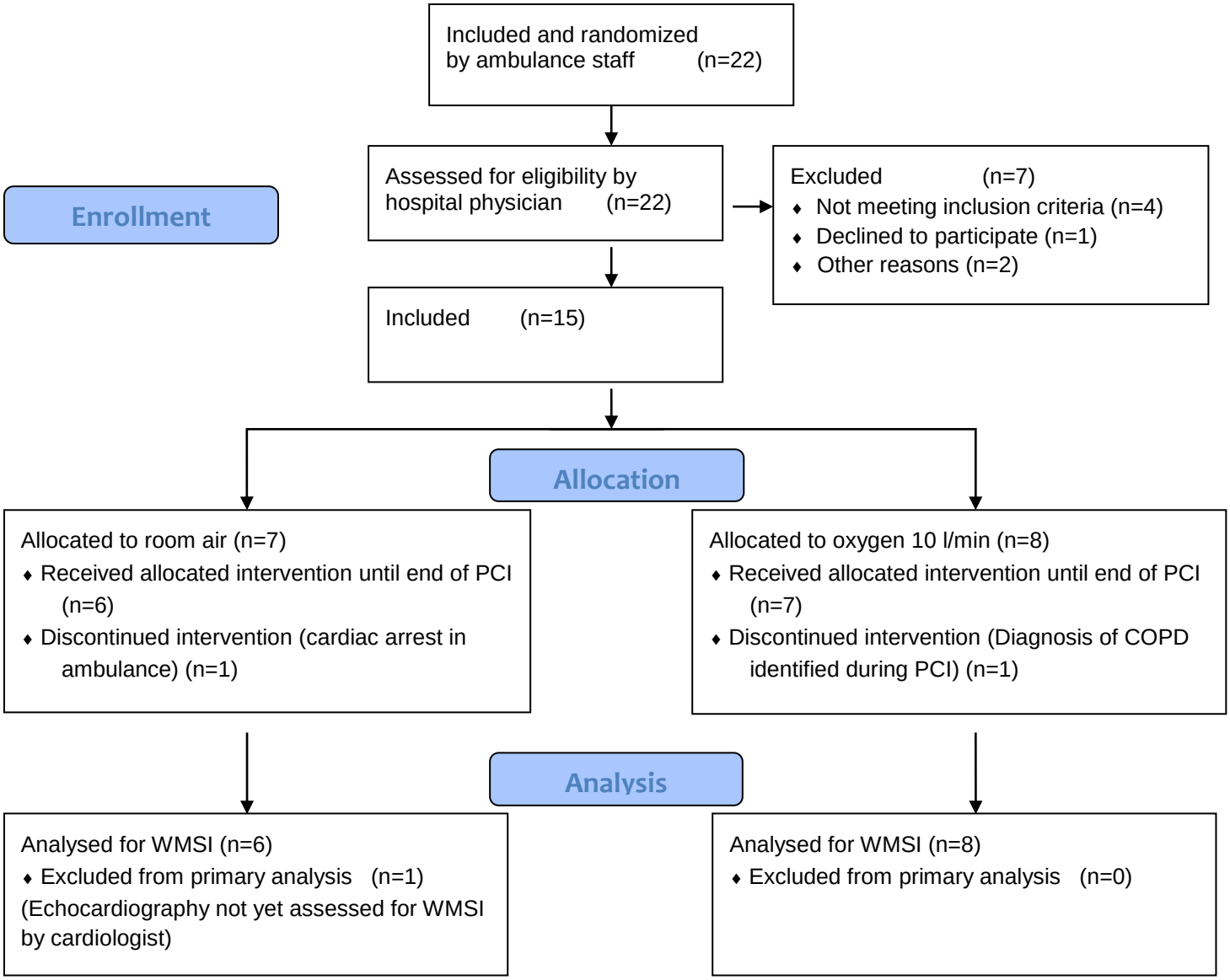
The main outcome variable of our subgroup analysis was infarct size assessed as WMSI[20] on day 2-4 after infarction. Secondary outcome measures were infarct size as measured by peak level[21] and area under curve (AUC)[22] of cardiac troponin T (TnT; Cobas® e601 high sensitive analyser, functional sensitivity of 13 ng/L, Roche Diagnostics, Basel, Switzerland) during the first 24 h after inclusion, subjective ratings of chest pain from 1 to 10 on a visual analog scale (VAS) immediately before PCI and administered doses of morphine and beta blockers during the ambulance transport.

Peak level TnT was defined as the highest level measured within 24 h. The AUC of cTnT (TnT_{AUC}) was calculated using the trapezoidal rule. The time points for measurements were not standardized, nor were the number of measurements. Where a measurement was present after 24 h, a virtual point at 24 h was calculated by interpolation. The calculated AUC for 24 h was then divided by 24 to give units in ng/L. If the last time point for measured TnT was at less than 24 h, the AUC was calculated over the time points present and then divided by the appropriate time interval. The TnT_{AUC} thus represents the mean AUC per hour.[23]

Statistical analysis

Because of the low number of participants in the analysis and thus inability to make assumptions of normality, Mann-Whitney U tests for independent, non-parametric samples was used to compare the median values of the continuous outcome variables. IBM SPSS Statistics v.20 (IBM Corporation, Armonk, NY) was used to do the analyses. The null hypothesis was that there was no difference between the treatment arms, and the alternative hypothesis that there was a difference (two-tailed tests).

Figure 1. Study flow Diagram



	All patients (n=15)	Oxygen group (n=8)	Room air group (n=7)
Male sex, n (%)	10 (66,7)	5 (65,2)	5 (71,4)
Age (y), median (range)	73 (42-86)	68,5 (56-86)	73 (42-80)
BMI ($kg \cdot m^{-2}$), mean (SD)	27,2 (±3,9)	26,3 (±4,6)	28,3 (±2,9)
Hypertension, n (%)	5 (33,3)	2 (25,0)	3 (42,9)
Diabetes, n (%)	5 (33,3)	2 (25,0)	3 (42,9)
Hyperlipidemia, n (%)	3 (20,0)	1 (12,5)	2 (28,6)
Past smoker, n (%)	5 (33,3)	3 (37,5)	2 (28,6)
Current smoker, n (%)	4 (26,7)	2 (25,0)	2 (28,6)
COPD, n (%)	2 (13,3)	1 (12,5)	1 (14,3)
Medications at inclusion			
Statins, n (%)	4 (26,7)	1 (12,5)	3 (42,9)
ASA, n (%)	4 (26,7)	2 (25,0)	2 (26,8)
Beta-blockers, n (%)	1 (6,7)	0	1 (14,3)
ACE-inhibitors/ARB, n (%)	2 (13,3)	1 (12,5)	1 (14,3)
CCB, n (%)	2 (13,3)	0	2 (28,6)
Culprit occlusion			
LAD, n (%)	5 (33,3)	2 (25,0)	3 (42,9)
RCA, n (%)	7 (46,7)	4 (50,0)	3 (42,9)
LCX, n (%)	2 (13,3)	1 (12,5)	1 (14,3)
Unknown, n (%)	1 (6,7)	1 (12,5)	0

Table 1. Patient characteristics and culprit occlusion. BMI: Body Mass Index. COPD: Chronic Obstructive Pulmonary Disease. ASA: Acetylsalicylic Acid. ACE: Angiotensin converting enzyme. ARB: Angiotensin II receptor blockers. CCB: Calcium channel blockers. LAD: Left Anterior Descending. RCA: Right Coronary Artery. LCX: Left Circumflex

Results

Between January 23rd and April 30th 2012, 22 patients were included after oral consent and randomized by the ambulance staff. Fourteen patients were included in the final analysis of WMSI, 8 in the oxygen group and 6 in the room air group. See figure 1. The allocated intervention was discontinued in 2 patients. In one patient, the allocated O_2 was discontinued during PCI by the attending cardiologist due to chronic obstructive pulmonary disease (COPD) and in one patient room air was discontinued in the ambulance at arrival to the hospital due to cardiac arrest. The patient with cardiac arrest survived, but was excluded from our final analysis of WMSI due to an echocardiography not yet assessed by cardiologist. Reasons for exclusion by the hospital physician were: no myocardial infarction identified by coronary angiography or release of TnT (3), previous MI identified (1), patient declined to participate (1), patient admitted to a non-study hospital post PCI (1) and patient inclusion not reported to investigators by ambulance staff (1).

Characteristics for the patients included in the final analysis are listed in table 1. One 80 year old patient in the room air group with advanced diabetes and renal failure died in the

hospital 5 days after inclusion due to terminal congestive heart failure. One 86 year old patient in the oxygen group died of unknown cause 52 days post infarction.

Subjective pain ratings (VAS) immediately before PCI were available for 12 patients (7 in the oxygen group and 5 in the room air group). Median VAS score in the oxygen vs the room air group was 3.0 (mean 3.0, 95%CI 0.8-5.2) vs 5.0 (mean 3.8, 95%CI 0-7.7, p=0.61), however median administered doses of morphine for these 12 patients was 6.0 mg (mean 6.0 mg, 95%CI 3.6-8.4) vs 5.0 mg (mean 5.2 mg, 95%CI 0-12.1), p=0.73). No patients were given beta-blockers.

The locations of the culprit occlusions identified on coronary angiography can be seen in table 1. One patient in the O_2 group had no clear culprit occlusion, probably due to a dissolved thrombus. One patient in the room air group had a chronic total occlusion of LAD, which was impenetrable and thus not reperfused.

TnT measurements were analyzed for 15 patients (8 oxygen vs 7 room air). Mean (range) number of measurements available for each patient was 3.5 (2-5). Median peak TnT in the oxygen group vs the room air group was 1700 ng/L (mean 1829 ng/L, 95% CI 844-2816) vs 4125 ng/L (mean 4422 ng/L, 95% CI 1333-7511, p=0,054). Median TnT_{AUC} in the oxygen group vs the room air group was 931 ng/L (mean 1351 ng/L, 95% CI 449-2253) vs 2272 ng/L (mean 3483 ng/L, 95% CI 681-6285, p=0,072).

Mean (range) number of segments visualized on TTE was 15.2 (13-16). Median WMSI on TTE day 2-4 post PCI for the oxygen group vs the room air group (8 vs 6 patients) was 1.16 (mean 1.27, 95% CI 0.97-1.57) and 1.28 (mean 1.45, 95% CI 0.87-2.03, p=0.87) respectively.

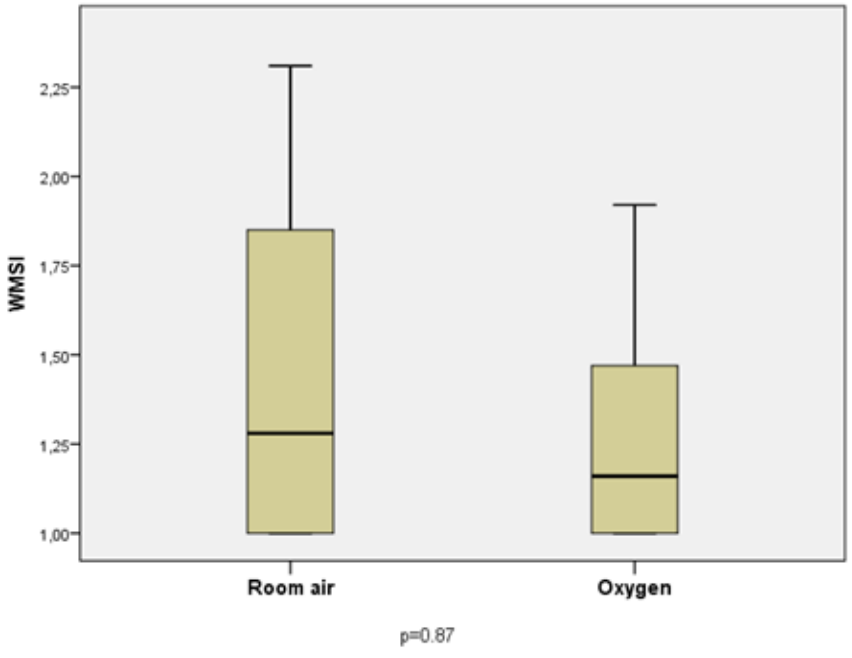


Figure 2. WMSI for 14 patients.

Discussion

Key findings

SOCCER is a randomized controlled single-blinded trial comparing high flow oxygen vs room air to normoxic patients presenting with first time STEMI and accepted for immediate PCI, with the intervention administered during the ambulance transport and PCI. In the first included 14 patients, we found no significant difference in infarct size (WMSI) between the group that received 10 L O_2/min and the group receiving room air. Further, there was no statistically significant difference in peak TnT or TnT_{AUC} between the groups, and there was no difference in subjective pain ratings at start of PCI or administered doses of opioids during transport.

Possible mechanisms and explanations

Supplemental oxygen treatment in normoxic patients induces hyperoxia, 8 L O_2/min has been shown to result in a blood partial pressure of O_2 of about 35 kPa, and increase the blood oxygen content from 180 ml/l to 193 ml/l in healthy subjects.[15] This hyperoxia decreases coronary blood flow in healthy subjects as well as in patients with ischemic heart disease and patients with CHF.[15-19] Studies on coronary and systemic vascular resistance during hyperoxia, suggest that this is due to increased coronary vasoconstriction.[16,17,24]

Thus, as a result of the relatively small increase in blood oxygen content and a relatively larger decrease in coronary blood flow, the coronary O_2 delivery actually decreases.[15] This effect may in part explain why a trend towards possible harm for oxygen [1] has been seen.

The mechanism behind the hyperoxia-induced vasoconstriction has been investigated by several research groups. Iscoe and Fisher (2005) suggested that the vasoconstriction might be due to hyperoxia-induced hypocapnia,[25] but Thomson et al. (2006) showed that the hyperoxia-induced systemic vasoconstriction remained during isocapnic conditions.[24] In addition, in healthy humans hyperoxia probably does not lead to hypocapnia.[15] Hyperoxia has been shown to accelerate systemic formation of reactive oxygen species (ROS).[26] Several studies suggest that this increased generation of ROS in the arterial lumen mediates the increased vascular resistance via oxidative quenching of endothelium-derived Nitric Oxide (NO).[27,28] This hypothesis has been further confirmed by studies showing that administration of vitamin C prevents hyperoxia-induced vasoconstriction in forearm circulation of healthy subjects,[29] and coronary circulation of patients with ischemic heart disease.[18]

We found no benefit or harm for oxygen treatment to MI patients which is most likely explained by the low number of participants in the analysis as seen in the wide CI's. However, if we for a moment assume that these results remain in a larger population and represent a "true" finding, this might be explained by that a beneficial effect of increased blood oxygen tension is being cancelled by the coronary vasoconstriction limiting the availability of this hyper-oxygenated blood to cardiomyocytes. Alternatively, a beneficial effect of increased oxygen availability during the ischemic phase might be cancelled by a detrimental effect of increased oxidative reperfusion damage after removal of the occlusion.

During a coronary occlusion the area of myocardium surrounding the absolute ischemic zone is being partly perfused by small collateral arteries from adjacent main coronary arteries. These small collaterals are maximally dilated due to metabolic stimuli from the ischemic myocytes. The question remains to be solved whether these collaterals are sensitive to hyperoxic vasoconstriction, which thus might influence the effect of hyperoxia in coronary occlusion.

Comparison with other studies

In this study we used WMSI on TTE as primary outcome. The reason we used WMSI when left ventricular ejection fraction (LVEF) is easier to measure is because WMSI is better correlated to the actual ventricular function than LVEF as the LVEF can be kept at an adequate level due to regional hyperkinesis even when the ventricle is heavily damaged.[30] Furthermore WMSI better predicts all-cause mortality and hospitalization for CHF after MI, and LVEF does not provide additional prognostic information.[30]

There are three randomized controlled trials of normobaric oxygen therapy to MI published prior to ours; Rawles et al. (1976), Ukholkina et al. (2005),and Ranchord et al. (2012). Another clinical trial is in progress (Air Versus Oxygen In myocarDial infarction, AVOID).[31]

Rawles and Kenmure performed the first randomized controlled double-blinded trial on oxygen to patients with uncomplicated MI in 1976. They analyzed data of patients randomized to either 6 L O_2/min (n=80) or 6 L compressed air/min (n=77) during 24 hours after presentation for arrhythmias, administered morphine, aspartate aminotransferase, and in-hospital mortality. The only significant results they found were higher levels of aspartate aminotransferase and higher incidence of sinus tachycardia in the oxygen group. There were 9

deaths in the oxygen group versus 3 deaths in the air group, but this did not reach statistical significance. Ironically, more than 35 years ago, the authors conclude that oxygen treatment does not appear to be of any benefit to non-hypoxic patients with uncomplicated MI.[10] The study, however, was undertaken before the era of thrombolysis or reperfusion, and the results might not be valid in today's medicine

Ukholkina et al. included 137 patients with uncomplicated Q-wave MI randomized to receive oxygen or room air. The oxygen arm had two subgroups: 28 patients received 3-6 L/min for 30 min prior to PCI and during 3 h after, and 30 patients received the same dose of oxygen for 3 hours post PCI only. One (1) patient died in the oxygen group on the first day, and none in the room air group. The main outcome measure was the size of necrotic area estimated from the number of q-waves on a 48 lead ECG in a subset of 31 patients in the oxygen group. These results showed a potential benefit for the oxygen group but no information on how the comparison was done was provided.[32] This was a crude approximation of infarct size subject to bias as the randomization was unblinded; the person attaching the leads and interpreting the ECG might have been aware of the group allocation. Since the risk of bias is significant, no conclusions can be drawn from the study and the study is considered to be of low quality.[1]

In the most recently published study, Ranchord et al compared high flow oxygen versus titrated oxygen for patients with STEMI. They included a total of 136 patients in their analysis, 68 patients in the high-flow group received 6 L/min and the other 68 patients received titrated oxygen to achieve SaO2 of 93-96%. The high flow or titrated oxygen was given for a total of 6 h after presentation to the emergency room. There was 1 death in the high flow group and 2 deaths in the titrated group. They found no significant results when comparing TnT or infarct mass and percent infarct mass on MRI. When they performed a meta-analysis with data from Rawles[10] and Ukholkina[32] they found an odds ratio for mortality of high flow oxygen of 2.2(95% CI 0.8-6.0).[14] The study design had a number of weaknesses as the authors themselves point out. Patients received oxygen for an average of 60 minutes in the ambulance before they were assessed for inclusion which could affect the results. They excluded patients with COPD, cardiogenic shock and with previous MI which resulted in a low-risk population with limited generalizability. Not all patients received PCI, some received thrombolysis. As the authors point out, a better way to design a protocol would be where the patients are allocated in the ambulance prior to any supplemental oxygen is given.

To summarize the results of these trials are partly conflicting and inconclusive. However, one conclusion to be drawn is that oxygen has not yet been shown to be beneficial.

There are also ongoing investigations regarding the use of hyperbaric oxygen therapy (HBO) to patients with MI. It is possible that the effects and outcomes of HBO vary greatly from normobaric oxygen treatment due to altered physiological conditions in the setting of high pressure. However, as equipment required for this type of treatment is not readily available at most hospitals, and is not likely to become routinely used in the near future, we have chosen to not investigate into this area.

Oxygen therapy in ischemic stroke

In regards to the uncertainty and controversy on the subject of oxygen treatment to MI we wanted to look into another field of research where the pathophysiological setting is similar: ischemic stroke. The same logical statement as in MI can be used for ischemic stroke; a high blood oxygen content might reduce ischemic damage. We performed a search on the PubMed database for articles about ischemic stroke and oxygen treatment to investigate if any conclusive evidence could be found. Three RCT:s on human subjects with ischemic stroke treated with normobaric oxygen were found..[33-35]

Rønning and Guldvog (1999) from Norway randomized patients according to their date of birth to either oxygen treatment with 3L/min for 24 h after inclusion or to room air. 292 patients were randomized to oxygen and 258 to room air. There was significant higher 1-year mortality for oxygen in patients with mild and medium stroke according to the Scandinavian stroke scale. There was also a conflicting trend towards benefit from oxygen for the group with severe stroke.[33]

Singhal et al. (2005) included 16 patients, 9 in the oxygen treatment group (45 L/min) and 7 that did not receive treatment unless they fell below 95% in saturation in which case they got 3 L/min. Both groups' stroke scale improved during the study intervention, and there was a trend towards larger improvement in the oxygen group with a peak 24 h after study intervention (reaching statistical significance), but after 1 week the difference disappeared.

Lesion volumes on MRI at 4 h showed a significant difference between the groups in favor of oxygen. At later time points there was no significance.[34]

Padma et al. (2010) performed a pilot study in India where 40 patients who did not receive trombolysis were randomized to either 10 L O_2/min or to room air unless they fell below 95% in saturation. If so, patients were given 2 L O_2/min. The only significant result was a lower (more favorable) stroke assessment score according to the National Institutes of Health Stroke Scale (NIHSS) for the room air group. There was also a trend towards smaller lesions on MRI after 3 months in the oxygen group.[35]

In conclusion, there are conflicting data and the question of routine normobaric oxygen treatment to ischemic stroke has yet to be resolved. It seems however that the larger studies indicate that caution is required before supplying oxygen to ischemic stroke patients.

Limitations of the present study

Our initial intention with this study was to include 20 patients, 10 in each arm. Although we knew that our study would be underpowered, a goal of 10 patients in each arm would allow us to include all the patients we needed in the allocated time. However as the study progressed we soon noticed that the inclusion rate was inadequate for our target number. This was probably due to miscalculation from our side as to the real incidence of first time STEMI in our study area, inclusion problems at the ambulance stations and because one hospital intended to participate withdrew prior to the start of the study.

In this report we included a total of 15 patients, 8 in the oxygen arm and 7 in the room air arm. This small material severely restricts us from drawing any conclusions from our material. This can also be seen in the wide 95% confidence intervals. In addition, the TnT sampling was not standardized by the investigators, and thus the number of and time intervals between measurements varied greatly which makes these outcomes unreliable.

In the larger trial SOCCER of which our study was a sub analysis the primary outcome was Myocardial Salvage Index (MSI) on MRI day 4-6. Because of the inability to distinguish between any old infarction from a new infarction when calculating infarct mass on MRI, an exclusion criterion for previous MI was added (however the same reasoning applies to WMSI on TTE). Because of this restriction our results can not easily be extrapolated to all patients with STEMI, previous MI or not.

In the initial SOCCER protocol one additional hospital was supposed to participate in the study and it was described as a multicenter study. Due to administrative difficulties, this hospital withdrew from participation before the start of the study. All PCIs were performed in Lund. In conclusion, all PCIs were performed at a single center and the medical care post PCI, including MRI, at two centers. Thus, the study is considered a single center study which limits the generalization to hospitals with a similar structure in organization and medical custom.

Because all ambulances participating in the trial does not carry compressed air flasks, compressed air could not be administered to patients allocated to this arm. To compensate for this in regards to blinding, both groups were fitted with an Oxymask® with the tube connected to an oxygen outlet valve in the ambulance or to an O_2 flask in an attempt to blind the patients as to what treatment they received. However, there is always the possibility of the patients noticing the lack or presence of flow in the Oxymask® which could make them aware of which arm they are in and thus make them unblinded. We do not believe that this flaw in blinding process has a significant impact on the primary objective outcomes. However we cannot rule out the risk of bias for the subjective outcome pain on VAS. Further, there is a significant risk of bias in administered doses of morphine, as the ambulance staff were not blinded.

After the patients had undergone PCI they were transferred to a cardiac ICU in either Lund or Malmö. The regime for oxygen therapy at these centers was not controlled or documented by the investigators but followed local guidelines. We cannot rule out that the administered doses of oxygen might have varied significantly between the study groups or, more likely, that the possible oxygen therapy during the first hours post PCI might reduce the difference in outcome between the groups.

There were some ethical questions of special consideration in this study. First, the patients were included after agreeing to a short text read out to them by the ambulance specialist nurse. According to the WMA declaration of Helsinki, before patients are asked for consent they "...must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail...".[36] This is not fully achievable in the setting of an ambulance with a patient suffering of pain and stress. Neither is the next part of the declaration... "After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot

be expressed in writing, the non-written consent must be formally documented and witnessed."[36] An ambulance specialist nurse is in our opinion qualified to inform the patient of the trial to the extent they can in the ambulance, but no written consent is collected in the ambulance which is a problem since the trial intervention starts in the ambulance. The patients were instead approached by a physician within 72 h from intervention start, and given both oral and written information as well as asked for their written, now informed, consent. Ethical approval for this exception to the declaration of Helsinki was sought and obtained at the regional Ethics Review Board in Lund as well as the Swedish Medical Products Agency.

Clinical and research implications

The reason for the lack of proper previous studies is twofold. The first reason is the vast number of patients required to reach statistically significant differences in mortality and morbidity which are the clinically most interesting outcomes. The studies so far have focused on secondary outcomes that to different degrees correlate with mortality or morbidity. In a recently published study on the subject, Ranchord et al. performed a power calculation for the number of patients required to reach statistical significance in mortality. The total number of patients required was approximately 7600 with a power of 90% at an α of 5% to determine a 1.5 fold difference with a predicted mortality of 4% for patients with uncomplicated STEMI.[14] As they point out, this is well within the capacity of the international community or even large multicenter studies from single countries. The second problem and perhaps the largest reason for the lack of studies is that none of the large multinational pharmaceutical companies have any interest in funding these kind of studies since they see no possible way of making profit. This problem is not only relevant for the field which we study but for the scientific world as a whole as Angell pointed out in a recent article in JAMA.[37]

Conclusion

There are many unsolved problems with studies involving supplemental oxygen treatment, perhaps the largest problems being the difficulty to include a sufficient amount of patients to measure mortality and morbidity and the lack of interest from pharmaceutical companies.
In this study of STEMI patients we found no statistically significant difference in infarct size, measured by WMSI and TnT, between patients given high flow oxygen or room air. We hope that the SOCCER study, when completed, will give a good indication towards the clinical effect of oxygen.

However, until the international community can arrange an adequately powered study to determine whether oxygen is beneficial or detrimental for patients with AMI, present literature suggest that caution should be used when administering O_2 to normoxic patients.

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