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The Effects of Oxygen Therapy on Myocardial Salvage in ST Elevation Myocardial Infarction Treated with Acute Percutaneous Coronary Intervention: The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) Study

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Abstract

Objectives: Despite a lack of scientific evidence, oxygen has long been a part of standard treatment for patients with acute myocardial infarction (AMI). However, several studies suggest that oxygen therapy may have negative cardiovascular effects. We here describe a randomized controlled trial, i.e. Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER), aiming to evaluate the effect of oxygen therapy on myocardial salvage and infarct size in patients with ST elevation myocardial infarction (STEMI) treated with a primary percutaneous coronary intervention (PCI).

Methods: One hundred normoxic STEMI patients accepted for a primary PCI are randomized in the ambulance to either standard oxygen therapy or no supplemental oxygen. All patients undergo cardiovascular magnetic resonance imaging (CMR) 2–6 days after the primary PCI, and a subgroup of 50 patients undergo an extended echocardiography during admission and at 6 months. All patients are followed for 6 months for hospital admission for heart failure and subjective perception of health. The primary endpoint is the myocardial salvage index on CMR.

Discussion: Even though oxygen therapy is a part of standard care, oxygen may not be beneficial for patients with AMI and is possibly even harmful. The results of the present and concurrent oxygen trials may change international treatment guidelines for patients with AMI or ischemia.

Key Words
Oxygen therapy · Acute myocardial infarction · Cardiovascular magnetic resonance imaging · Emergency medicine · Cardiology

Background

Oxygen (O_2) is a cornerstone in the emergency treatment of all serious medical conditions, including acute myocardial infarction (AMI). Although recent guidelines [1,2,3,4,5,6] stress the lack of evidence for routine oxygen administration to patients with AMI, standard emergency care concepts like MedicALS [7] and other international guidelines [8,9,10,11] prescribe immediate administration of 10-15 liters O_2/min, including to the majority of patients who are normoxic. The underlying assumption is that inhalation of additional O_2 increases or ascertains O_2 delivery to the ischemic myocardium. However, in recent years, small case series and nonrandomized studies have suggested that O_2 may have negative cardiovascular effects [12,13,14]. In both healthy subjects and patients with heart failure, hyperoxia has been noted to increase blood pressure and systemic vascular resistance and decrease the cardiac output (CO) [12,13,14]. Furthermore, during O_2treatment in patients with coronary artery disease, a decreased coronary blood flow has been observed [15]. In patients with AMI, both increased and decreased levels of myocardial ischemia have been reported [16]. In general, however, the methods used in these studies have been less precise, indirect, or invasive. Also, the levels of O_2 in blood have rarely been measured but have been estimated via indirect techniques [12,13,14]. Although O_2 is a part of standard treatment, the acute cardiovascular effects of O_2 in AMI patients are unclear, and it is unknown whether O_2 therapy is beneficial or detrimental to AMI patients [16,17,18,19]. Recent reviews stress the need for solid clinical trials [16,17,18,19,20].

In a recent limited pilot trial in patients with first-time ST elevation myocardial infarction (STEMI) [21], there was no significant difference in 30-day mortality or infarct size (IS) using troponin between high-dose oxygen therapy (6 liters/min) and titrated oxygen treatment to a 93-96% blood oxygen saturation. At least 2 additional studies have evaluated the effects of O_2 therapy in AMI patients. The Air Versus Oxygen In myocarDial Infarction Study (AVOID) [22] in Australia examined IS using peak troponin in STEMI patients randomized to O_2 therapy or room air, and the ongoing Swedish DETermination of the role of OXygen in Acute Myocardial Infarction (DETO2X-AMI) [23] trial studies 1-year mortality in patients with suspected AMI randomized to O_2 therapy or room air.

We have previously studied the effects of graded O_2 inhalation in healthy subjects using cardiac magnetic resonance imaging (CMR) [24]. At 15 liters O_2/min, the PaO_2 increased to 51.0 kPa,

the left ventricular (LV) perfusion decreased by 23%, and the CO decreased by 10%. Because of the fall in LV perfusion and CO, the systemic and coronary O_2 delivery fell by 4 and 11% at 8 liters O_2/min in spite of the increased blood oxygen content. If the effects are similar in AMI patients, O_2 treatment in these patients may not be beneficial.

In the present paper, we describe the design of a randomized controlled trial (Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion; SOCCER) in STEMI patients treated with a primary percutaneous coronary intervention (PCI). CMR and echocardiography are used to evaluate the effects of O_2 on myocardial salvage, IS and cardiac function. SOCCER is being conducted at Skåne University Hospital in Malmö and Lund in southern Sweden and has been approved by the regional ethics committee in Lund (May 3, 2011, Dnr 2011/258) and by the Swedish Medical Products Agency (EudraCT No. 2011-001452-11).

Methods

Study Setting

Region Skåne is the southernmost region of Sweden and has a population of 1.2 million. Skåne University Hospital has two 24-hour general emergency departments with a yearly patient census close to 150,000. All ambulances in Skåne are staffed with at least one specialist nurse and all are equipped with modern medical technology, including mobile 12-lead ECG equipment, monitoring, and wireless ECG transmission.

Since the year 2000, the vast majority of STEMI patients undergo a primary PCI and are transported directly to the PCI laboratory, bypassing the emergency department. To guide these transport decisions, the ECG is transmitted from the ambulance to the coronary care unit, where the physician on call interprets the ECG and decides the patient's disposition. The ambulance guidelines in Region Skåne state that 10 liters O_2/min is standard therapy for STEMI patients.

Study Design

The SOCCER study is an investigator-initiated, dual-center, single-blind, parallel-group, randomized controlled trial without commercial funding. One hundred normoxic (blood O_2 saturation ≥94%) STEMI patients accepted for a primary PCI are randomized 1:1 in the ambulance to standard O_2 therapy (10 liters/min) or no supplemental O_2 to be given until the end of the primary PCI.

The study protocol is outlined in figure 1. All patients undergo CMR on days 2-6 after the PCI to determine the myocardium at risk (MaR, i.e. the ischemic area before the PCI), the IS, and the myocardial salvage index (MSI) calculated as (1 - IS/MaR) × 100%. A subgroup of 50 patients undergo an extended echocardiography early during their hospital stay and at 6 months to assess remodeling by quantification of LV volumes and LV ejection fraction (LVEF) as well as the wall motion score index (WMSI). A study physician follows all patients for 6 months for readmission to in-hospital care and development of heart failure. At 6 months, the EQ-5D questionnaire is used to grade patients' subjective level of health [25]. At the index visit and at 6 months, a blood sample for N-terminal pro brain natriuretic peptide is collected.

Study Endpoints

The study endpoints are described in table 1. The primary endpoint is MSI on CMR, and the main secondary endpoints are IS and MaR on CMR, and WMSI on echocardiography.

Patient Inclusion and Informed Consent

The inclusion and exclusion criteria are shown in table 2. In the ambulance, the patient is briefly informed of this study by the specialist nurse and then verbally accepts or declines inclusion. Patients who request more information in order to make their decision are excluded from this study; discussion in the ambulance about the risks and benefits of participation would delay transportation and is considered unethical. At the hospital ward, within 72 h after the PCI, the patient receives verbal and written information about this study by the local study physician and consents to participation in writing. The patient is also informed of their right to withdraw from this study at any time without having to provide a reason.

Randomization

Patients are randomized 1:1 to O_2 or room air in blocks of 6 with the use of a web application (http://www.randomization.com/). Each block of 6 randomizations is distributed in a pack of sealed envelopes to the ambulances. After verbal informed consent and patient inclusion in the ambulance, an envelope with the study group allocation is opened by the ambulance nurse.

Study Intervention

As determined by randomization, patients receive either 10 liters/min O_2 or room air from study inclusion to the end of the PCI. All patients have an Oxymask™ [26] fitted, but in the air group the tubing from the mask is not connected to the oxygen outlet. The patients are not informed

of their group allocation and are kept blinded as long possible. The Oxymask™ was chosen because it causes a negligible increase in dead space and no CO_2retention. In every other aspect, patients receive standard care. If the blood O_2 saturation drops below 94%, this is noted and O_2 therapy is initiated according to standard care (10 liters/min). After termination of the PCI, standard care is given at the coronary care unit by personnel blinded to the patient's group allocation. Patients may or may not receive additional oxygen at the coronary care unit.

Data Collection

After inclusion and randomization, the ambulance nurse and the personnel in the PCI laboratory note the patient management on case report forms which are submitted to the study coordinators and then registered electronically in the study database. Data entered by the prehospital personnel into the case report forms include blood pressure, heart rate, blood oxygen saturation, chest pain intensity using a visual analog scale (1-10), ECG rhythm (sinus or not), and times and dosages of administered opiates and/or β-blockers.

All other in-hospital data regarding management and outcomes including adverse events, laboratory results, and ECG are retrieved from the computerized patient records of Region Skåne (Melior; Siemens, Germany) and from the SWEDEHEART quality registries RIKS-HIA [27] and SCAAR [28].

The 6-month follow-up data registered from patient interviews, including current medications and the medical history since the index visit, is complemented and verified by probing the electronic medical record system in the entire Region Skåne (Melior) as well as the national inpatient registry of the Swedish Board of Health and Welfare.

Data Safety Management

Data handling is conducted according to local requirements and in accordance with ICH GCP guidelines (paragraph 5.5). In this study, there is no interim analysis or safety committee. The included patients are few, and from a safety perspective it seems very unlikely that large differences between the study groups will be observed.

Number of Patients and Statistics

All analyses are performed on an intention-to-treat basis by researchers blinded to the group allocation. A secondary analysis on a per-protocol basis is also performed. Missing data result

in exclusion of the patient in the analysis at hand. All data are gathered and statistically analyzed using Microsoft Excel and IBM SPSS Statistics V22.

Data from the 2 treatment groups are primarily compared using a 2-sided Mann-Whitney test. The null hypothesis is that there is no difference between the 2 treatment groups. $p < 0.05$ is considered statistically significant.

CMR. Assuming an MSI of 60 ± 20% [29,30,31,32] in the O_2 group (standard treatment), a total sample size of 100 allows detection of an MSI difference of 15% points between groups with a power >90% (actual power 96%) at a 5% risk of an α error.
Echocardiography Subgroup. Assuming a WMSI of 1.6 ± 0.2 [33] in the O_2 group after the PCI, a total sample size of 50 allows detection of a WMSI difference of 0.2 between groups with a power >90% (actual power 93%) at a 5% risk of an α error. The same 50 patients undergo a second echocardiography after 6 months to detect a difference in WMSI of 0.2 with a power >90% (actual power 93%) at a 5% risk of an α error.

Cardiac Magnetic Resonance Imaging

All patients undergo CMR on days 2-6 to assess the primary endpoint MSI [34]. A Philips 1.5T Achieva is used at Skåne University Hospital in Lund, and a Siemens 1.5T Avanto is used in Malmö. Imaging is performed using the 3 standard long-axis images (2-chamber, 4-chamber, and LV outflow tract views) and a stack of short-axis images covering the entire left ventricle during breath holds. MaR is visualized using T2-weighted triple inversion recovery imaging [29] (Philips Achieva) or T2-prepared steady-state free precession (SSFP) [35] (Siemens Avanto) as well as contrast-enhanced SSFP short-axis images 5 min after 0.2 mmol/kg intravenous administration of the contrast agent gadoteric acid (Gd-DOTA). The T2-weighted technique for MaR was originally described by Aletras et al. [36] and was validated for quantification of MaR in AMI patients up to 1 week after STEMI by Carlsson et al. [29]. Contrast-enhanced SSFP for MaR was described and validated by Sörensson et al. [37] and Ubachs et al. [38].

IS is quantified with late gadolinium-enhanced CMR approximately 15 min after Gd-DOTA administration [39]. For assessment of cardiac function, the SSFP cine images acquired after contrast administration are used.

CMR Image Analysis

All quantitative assessments (below) are performed on the short-axis images. The analysis of ventricular dimensions, MaR, and IS is performed using the postprocessing software Segment v.1.9 R3084 (http://segment.heiberg.se) [40]. The observers for MaR and IS are blinded to all clinical data. The endocardial and epicardial borders are manually traced in end diastole and end systole of the contrast-enhanced SSFP cine images and in the T2-weighted and late gadolinium-enhanced-images. End-diastolic and end-systolic volumes, ejection fractions, and stroke volumes are quantified by summation of the endocardial volumes in the short-axis imaging stack. For MaR the myocardium with an increased signal intensity is delineated in T2-weighted and contrast-enhanced SSFP images, as previously described [37,38]. The MaR is expressed as a percentage of the LV myocardium. The IS in late gadolinium-enhanced images is quantified using a previously described and validated automatic infarct quantification method taking partial volume effects in the periphery of the infarction into account [41]. Manual adjustments are made if the computer algorithm is clearly wrong. Microvascular obstruction is defined as hypointense regions in the core of the infarction with a signal intensity less than the threshold for infarction and is included in the infarct. MaR and IS are expressed as a percentage of the LV myocardium and MSI is quantified as (1 - IS/MaR) × 100%.

Echocardiography

A subgroup of 50 patients are subjected to an extended echocardiographic investigation on days 2-3 after the PCI and at 6 months in order to assess LVEF and WMSI. WMSI is calculated to semiquantitate the extent of regional wall motion abnormalities and equals the sum of wall motion scores (1-4, where 1 is normal and 2-4 represents gradually decreased contractility) in 16 myocardial segments divided by the number of segments assessed. A normally contracting LV has a WMSI of 1, and the index increases as wall motion abnormalities become more severe. The WMSI reflects IS and regional and total contractility during and after AMI [42] and also the subsequent myocardial remodeling [33,42]. WMSI is superior to LVEF as a predictor for prognosis in STEMI patients and predicts both mortality and rehospitalization for heart failure [43]. A change in WMSI over time can be used to assess the therapeutic success of an acute PCI [33].

Feasibility and Study Progress

The feasibility of the proposed study is supported by previous studies with emergency inclusion of STEMI patients in Lund [44], by our own results from studies with cardiac CMR [24,29], and by the successful inclusion so far (November 16, 2014) of 85 patients.

Strengths and Limitations

SOCCER is a blinded randomized controlled trial, and the results will therefore probably have good validity. Both the AVOID [22] and the DETO2X [23] trials are open studies in which placebo and/or nocebo effects are likely. The main endpoints of the SOCCER trial (MSI, IS and MaR on CMR, and WMSI on echocardiography) are established, well validated, and based on state-of-the-art imaging. Much of the study data are retrieved from preexisting quality registries (RIKS-HIA and SCAAR), and in that sense SOCCER lends from the new family of randomized registry trials [45].

Limitations include that SOCCER is a comparatively small trial including only STEMI patients. The results are thus not necessarily generalizable to patients with NSTEMI, unstable angina, or suspected acute coronary syndrome. Further, the size of the trial precludes reliable conclusions on the effects of oxygen therapy on morbidity and mortality. On the other hand, the used endpoints (amount of salvaged and infarcted myocardium) are strongly correlated with prognosis [34,43] and should therefore be highly relevant for an emergency decision to treat the patient with oxygen.

Discussion

The SOCCER trial addresses a significant knowledge gap in the routine care of AMI patients. Every year, millions of AMI patients are treated with oxygen all around the world. Based on previous observations [12,13,14,16,17,18,19,24], it may well be that O_2 therapy does not benefit these patients, and perhaps even harms them. The results of SOCCER and concurrent oxygen trials may thus change international treatment guidelines for patients with AMI or ischemia. Indeed, the results may be of interest in the management of all emergency patients where oxygen treatment is considered.

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