



LUND UNIVERSITY

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.

Khoshnood, Ardavan; Carlsson, Marcus; Akbarzadeh, Mahin; Bhiladvala, Pallonji; Roijer, Anders; Bodetoft, Stefan; Höglund, Peter; Sparv, David; Todorova, Lizbet; Erlinge, David; Ekelund, Ulf

Published in:
Cardiology

DOI:
[10.1159/000398786](https://doi.org/10.1159/000398786)

2015

Document Version:
Peer reviewed version (aka post-print)

[Link to publication](#)

Citation for published version (APA):

Khoshnood, A., Carlsson, M., Akbarzadeh, M., Bhiladvala, P., Roijer, A., Bodetoft, S., Höglund, P., Sparv, D., Todorova, L., Erlinge, D., & Ekelund, U. (2015). 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. *Cardiology*, 132(1), 16-21.
<https://doi.org/10.1159/000398786>

Total number of authors:
11

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

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

Ardavan Khoshnood^a Marcus Carlsson^b Mahin Akbarzadeh^a Pallonji Bhiladvala^f Anders Roijer^c Stefan Bodetoft^a Peter Höglund^d David Zughaft^c Lizbet Todorova^e David Erlinge^c Ulf Ekelund^a

Sections of ^a Emergency Medicine and ^b Clinical Physiology, Clinical Sciences Lund, Lund University, and ^c Department of Cardiology, Skåne University Hospital, ^d Region Skåne Research and Development Centre, and ^e Region Skåne Prehospital Unit, Lund, and ^f Department of Cardiology, Skåne University Hospital, Malmö , Sweden

Contact information:

Dr. Ardavan Khoshnood
Akutmottagningen, EA10, SUS Lund
SE-221 85 Lund (Sweden)
E-Mail ardavan.khoshnood@med.lu.se

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 (O₂) 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 O₂/min, including to the majority of patients who are normoxic. The underlying assumption is that inhalation of additional O₂ increases or ascertains O₂ delivery to the ischemic myocardium. However, in recent years, small case series and nonrandomized studies have suggested that O₂ 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 O₂ treatment 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 O₂ in blood have rarely been measured but have been estimated via indirect techniques [12,13,14]. Although O₂ is a part of standard treatment, the acute cardiovascular effects of O₂ in AMI patients are unclear, and it is unknown whether O₂ 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 O₂ 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 O₂ 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 O₂ therapy or room air.

We have previously studied the effects of graded O₂ inhalation in healthy subjects using cardiac magnetic resonance imaging (CMR) [24]. At 15 liters O₂/min, the PaO₂ 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 O₂ delivery fell by 4 and 11% at 8 liters O₂/min in spite of the increased blood oxygen content. If the effects are similar in AMI patients, O₂ 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 O₂ 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 O₂/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 O₂ saturation $\geq 94\%$) STEMI patients accepted for a primary PCI are randomized 1:1 in the ambulance to standard O₂ therapy (10 liters/min) or no supplemental O₂ 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 $(1 - \text{IS}/\text{MaR}) \times 100\%$. 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 O₂ 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 O₂ 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 CO₂ retention. In every other aspect, patients receive standard care. If the blood O₂ saturation drops below 94%, this is noted and O₂ 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 $60 \pm 20\%$ [29,30,31,32] in the O₂ 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 O₂ 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 $(1 - \text{IS}/\text{MaR}) \times 100\%$.

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

SOCER is a blinded randomized controlled trial, and the results will therefore probably have good validity. Both the AVOID [22] and the DETOX [23] trials are open studies in which placebo and/or nocebo effects are likely. The main endpoints of the SOCER 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 SOCER lends from the new family of randomized registry trials [45].

Limitations include that SOCER 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 SOCER 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 O₂ therapy does not benefit these patients, and perhaps even harms them. The results of SOCER 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.

References

1. Chew DP, Aroney CN, Aylward PE, Kelly A-M, White HD: 2011 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand guidelines for the management of acute coronary syndromes (ACS) 2006. *Clin Trials* 2011;4:6.
2. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology; Bassand J-P, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, Ohman EM, Wallentin L: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28:1598-1660.
3. Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
4. Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC); Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F: ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-2619.
5. O'Connor RE, Brady W, Brooks SC, Diercks D, Egan J, Ghaemmaghami C, Menon V, O'Neil BJ, Travers AH, Yannopoulos D: Acute coronary syndromes - 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 10. *Circulation* 2010;122:S787-S817.
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-e140.
7. Group ALS: Acute Medical Emergencies: the Practical Approach, ed 2. London, BMJ Books, 2004.

8. International Liaison Committee on Resuscitation: 2005 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. 5. Acute coronary syndromes. *Resuscitation* 2005;67:249-269.
9. International Liaison Committee on Resuscitation: 2005 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. 4. Advanced life support. *Resuscitation* 2005;67:213-247.
10. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Chavey WE, Fesmire FM, Hochman JS, Levin TN, Lincoff M, Peterson ED, Theroux P, Wenger NK, Wright S, Smith SC, Jacobs AK, Adams CD, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons - endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1-e157.
11. Pollack CV Jr, Diercks DB, Roe MT, Peterson ED: 2004 American College of Cardiology/American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction: implications for emergency department practice. *Ann Emerg Med* 2005;45:363-376.
12. Waring WS, Thomson AJ, Adwani SH, Rosseel AJ, Potter JF, Webb DJ, Maxwell SR: Cardiovascular effects of acute oxygen administration in healthy adults. *J Cardiovasc Pharmacol* 2003;42:245-250.
13. Rousseau A, Bak Z, Janerot-Sjoberg B, Sjoberg F: Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man. *Acta Physiol Scand* 2005;183:231-240.
14. Haque WA, Boehmer J, Clemson BS, Leuenberger UA, Silber DH, Sinoway LI: Hemodynamic effects of supplemental oxygen administration in congestive heart failure. *J Am Coll Cardiol* 1996;27:353-357.

15. McNulty PH, King N, Scott S, Hartman G, McCann J, Kozak M, Chambers CE, Demers LM, Sinoway LI: Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol* 2005;288:H1057-H1062.
16. Nicholson C: A systematic review of the effectiveness of oxygen in reducing acute myocardial ischaemia. *J Clin Nurs* 2004;13:996-1007.
17. Beasley R, Aldington S, Weatherall M, Robinson G, McHaffie D: Oxygen therapy in myocardial infarction: an historical perspective. *J R Soc Med* 2007;100:130-133.
18. Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T: Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev* 2010;6:CD007160.
19. Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Weatherall M, Beasley R: Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009;95:198-202.
20. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Beasley R: Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009;158:371-377.
21. Ranchord AM, Argyle R, Beynon R, Perrin K, Sharma V, Weatherall M, Simmonds M, Heatlie G, Brooks N, Beasley R: High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: a pilot randomized controlled trial. *Am Heart J* 2012;163:168-175.
22. Stub D, Smith K, Bernard S, Bray JE, Stephenson M, Cameron P, Meredith I, Kaye DM: A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Versus Oxygen In myocarDial infarction study (AVOID study). *Am Heart J* 2012;163:339-345.
23. Hofmann R, James SK, Svensson L, Witt N, Frick M, Lindahl B, Östlund O, Ekelund U, Erlinge D, Herlitz J, Jernberg T: Determination of the role of oxygen in suspected acute myocardial infarction trial. *Am Heart J* 2014;167:322-328.
24. Bodetoft S, Carlsson M, Arheden H, Ekelund U: Effects of oxygen inhalation on cardiac output, coronary blood flow and oxygen delivery in healthy individuals. *Eur J Emerg Med* 2010;18:25-30.
25. EuroQol Group: EQ-5D - a standardised instrument for use as a measure of health outcome. 2014. <http://www.euroqol.org/home.html>.
26. MedCore: Oxymask product information. Kista, MedCore, 2014.
27. Swedeheart: Riks-hia. 2014. <http://www.ucr.uu.se/rikshia/>.

28. Swedeheart: Scaar. 2014.<http://www.ucr.uu.se/scaar/>.
29. Carlsson M, Ubachs JF, Hedstrom E, Heiberg E, Jovinge S, Arheden H: Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. *JACC Cardiovasc Imaging* 2009;2:569-576.
30. Atar D, Arheden H, Berdeaux A, Bonnet J-L, Carlsson M, Clemmensen P, Cuvier V, Danchin N, Dubois-Randé J-L, Engblom H: Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. *Eur Heart J* 2015;36:112-119.
31. Erlinge D, Götberg M, Lang I, Holzer M, Noc M, Clemmensen P, Jensen U, Metzler B, James S, Bötter HE: Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction: the CHILL-MI trial - a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *J Am Coll Cardiol* 2014;63:1857-1865.
32. Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, van der Pals J, Algotsson L, Arheden H, Erlinge D: A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Interv* 2010;3:400-407.
33. Liistro F, Grotti S, Angioli P, Falsini G, Ducci K, Baldassarre S, Sabini A, Brandini R, Capati E, Bolognese L: Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv* 2009;2:376-383.
34. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, Thiele H: Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol* 2010;55:2470-2479.
35. Kellman P, Aletras AH, Mancini C, McVeigh ER, Arai AE: T2-prepared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. *Magn Reson Med* 2007;57:891-897.
36. Aletras AH, Tilak GS, Natanzon A, Hsu L-Y, Gonzalez FM, Hoyt RF, Arai AE: Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging histopathological and

displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation* 2006;113:1865-1870.

37. Sörensson P, Heiberg E, Saleh N, Bouvier F, Caidahl K, Tornvall P, Rydén L, Pernow J, Arheden H: Research assessment of myocardium at risk with contrast enhanced steady-state free precession cine cardiovascular magnetic resonance compared to single-photon emission computed tomography. *J Cardiovasc Magn Reson* 2010;12:25.
38. Ubachs JF, Sörensson P, Engblom H, Carlsson M, Jovinge S, Pernow J, Arheden H: Myocardium at risk by magnetic resonance imaging: head-to-head comparison of T2-weighted imaging and contrast-enhanced steady-state free precession. *Eur Heart J Cardiovasc Imaging* 2012;13:1008-1015.
39. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen E-L, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM: Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;100:1992-2002.
40. Heiberg E, Sjögren J, Ugander M, Carlsson M, Engblom H, Arheden H: Design and validation of segment-freely available software for cardiovascular image analysis. *BMC Med Imaging* 2010;10:1.
41. Heiberg E, Ugander M, Engblom H, Gotberg M, Olivecrona GK, Erlinge D, Arheden H: Automated quantification of myocardial infarction from MR images by accounting for partial volume effects: animal, phantom, and human study. *Radiology* 2008;246:581-588.
42. Maioli M, Bellandi F, Leoncini M, Toso A, Dabizzi RP: Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAX-AMI trial). *J Am Coll Cardiol* 2007;49:1517-1524.
43. Moller JE, Hillis GS, Oh JK, Reeder GS, Gersh BJ, Pellikka PA: Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. *Am Heart J* 2006;151:419-425.
44. Götberg M, Olivecrona GK, Koul S, Carlsson M, Engblom H, Ugander M, van der Pals J, Algotsson L, Arheden H, Erlinge D: A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Interv* 2010;3:400-407.
45. Lauer MS, D'Agostino RB Sr: The randomized registry trial - the next disruptive technology in clinical research? *N Engl J Med* 2013;369:1579-1581.