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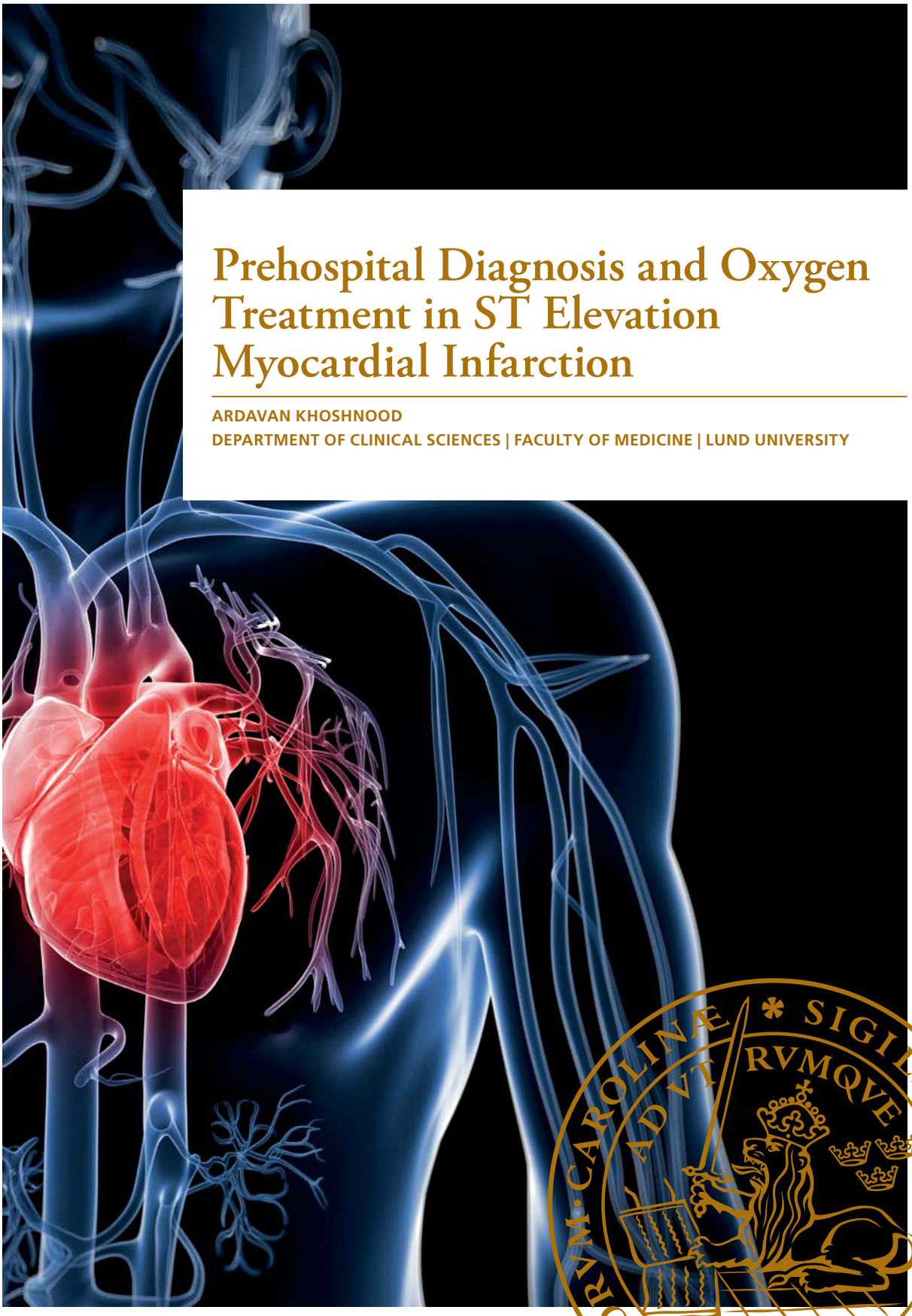

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Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

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Title and subtitle

Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

Abstract

Introduction

Paper I: An Artificial Neural Network (ANN) was constructed to identify ST Elevation Myocardial Infarction (STEMI) and predict the need for Percutaneous Coronary Intervention (PCI).

Paper II, III and IV: Studies suggest that O_2 therapy may be harmful in STEMI patients. We therefore conducted the SOCCER study to evaluate the effects of O_2 therapy in STEMI patients.

Methods

Paper I: 560 ambulance ECGs sent to the Cardiac Care Unit (CCU), was together with the CCU physicians interpretation and decision of conducting an acute PCI or not collected, and compared with the interpretation and PCI decision of the ANN.

Paper II, III, IV: Normoxic (≥94%) STEMI patients accepted for acute PCI were in the ambulance randomized to standard care with 10 L/min O_2 or room air. A subset of the patients underwent echocardiography for determination of the Left Ventricular Ejection Fraction (LVEF) and the Wall Motion Score Index (WMSI). All patients had a Cardiac Magnetic Resonance Imaging (CMRI) to evaluate Myocardial area at Risk (MaR), Infarct Size (IS) and Myocardial Salvage Index (MSI).

Results

Paper I: The area under the ANN's receiver operating characteristics curve for STEMI detection as well as predicting the need of acute PCI were very good.

Paper II, III, IV: No significant differences could be shown in discussing MaR, MSI or IS between the O_2 group (n=46) and the air group (n=49). Neither could any differences be shown for LVEF and WMSI at the index visit as well after six months between the O_2 group (n=46) and the air group (n=41)

Conclusions

Paper I: The results indicate that the number of ECGs sent to the CCU could be reduced with 2/3 as the ANN would safely identify ECGs not being STEMI.

Paper II, III, IV: The results suggest that it is safe to withhold O_2 therapy in normoxic, stable STEMI patients.

Key words: Acute Coronary Syndrome, Artificial Neural Network, Cardiology, Emergency Medicine, Oxygen Therapy, ST Elevation Myocardial Infarction.

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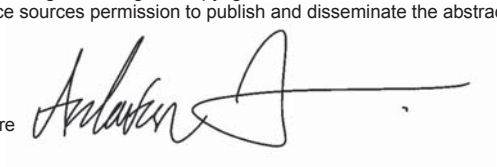
Signature  Date 2017-09-25

Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

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To my mother and father.
For their sacrifices, guidance and love…

Content

List of Publications

This dissertation is based on the following papers, which in the text will be referred to by their Roman numerals:

Paper I:

Forberg L J, **Khoshnood A**, Green M, Ohlsson M, Björk J, Jovinge S, Edenbrandt L, Ekelund U. *An artificial neural network to safely reduce the number of ambulance ECGs transmitted for physician assessment in a system with prehospital detection of ST elevation myocardial infarction*. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine 2012;20(8). DOI: 0.1186/1757-7241-20-8

Paper II:

Khoshnood A, Carlsson M, Akbarzadeh M, Bhiladvala P, Roijer A, Bodetoft S, Höglund P, Zughaft D, Todorova L, Erlinge D, Ekelund U. *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 2015;132(1):16-21. DOI: 10.1159/000398786

Paper III:

Khoshnood A, Carlsson M, Akbarzadeh M, Bhiladvala P, Roijer A, Nordlund D, Höglund P, Zughaft D, Todorova L, Mokhtari A, Arheden H, Erlinge D, Ekelund U. *Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: The randomized SOCCER trial*. European Journal of Emergency Medicine 2016. Epub ahead of print. DOI: 10.1097/MEJ.0000000000000431

Paper IV:

Khoshnood A, Akbarzadeh M, Roijer A, Meurling C, Carlsson M, Bhiladvala P, Höglund P, Zughaft D, Todorova L, Mokhtari A, Erlinge D, Ekelund U. *Effects of oxygen therapy on wall motion score index in patients with ST elevation myocardial infarction – Results from the randomized controlled SOCCER trial*. Echocardiography 2017;34(8):1130-1137. DOI: 10.1111/echo.13599

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Abbreviations

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ANN	Artificial Neural Network
AUROC	Area Under the Receiver-Operating-Characteristic Curve
AV-node	Atrioventricular Node
BP	Blood Pressure
CA	Circumflex Artery
CAD	Coronary Artery Disease
CCU	Coronary Care Unit
CK	Creatine Kinase
CMRI	Cardiac Magnetic Resonance Imaging
CO	Cardiac output
CRF	Case Report Forms
cTn	Cardiac Troponin
ECG	Electrocardiograph
ED	Emergency Department
EF	Ejection Fraction
HR	Heart Rate
ICU	Intensive Care Unit
IS	Infarct Size
LCA	Left Coronary Artery
LGE	Late Gadolinium Enhancement
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MaR	Myocardial area at Risk
MI	Myocardial Infarction
Min	Minute(s)

MRI	Magnetic Resonance Imaging
MSI	Myocardial Salvage Index
NPV	Negative Predictive Value
NSTEMI	Non-ST Elevation Myocardial Infarction
O_2	Oxygen
PCI	Percutaneous Coronary Intervention
PPV	Positive Predictive Value
RCA	Right Coronary Artery
RCT	Randomized Controlled Trial
SA-node	Sinoatrial Node
SCAAR	Swedish Coronary Angiography and Angioplasty Register
Sens	Sensitivity
SOCCER study	Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion Study
Spec	Specificity
STEMI	ST Elevation Myocardial Infarction
SV	Stroke Volume
SVR	Systemic Vascular Resistance
TnI	Troponin I
TnT	Troponin T
UA	Unstable Angina
WMSI	Wall Motion Score Index

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Populärvetenskaplig sammanfattning

Hjärtinfarkt är ett allvarligt tillstånd som är vanligt bland befolkningen, och bröstsmärta är dess vanligaste symptom. Snabb diagnos och behandling är av stor vikt för att minimera skadorna som uppstår på hjärtat.

Majoriteten av de patienter som drabbas av bröstsmärtor kontaktar ambulansen som efter att ha träffat patienten, tar ett EKG och skickar detta via dator vidare till närmaste hjärtintensivavdelning (HIA) för tolkning. Skulle EKG visa tecken på stor hjärtinfarkt (så kallad STEMI) dirigeras ambulansen med patienten direkt till HIA för behandling. Den viktigaste behandlingen vid en STEMI är en ballongvidgning av det kärl i hjärtat som är tilltäppt, så kallad akut PCI.

Dagligen får HIA vid Skånes Universitetssjukhus i Lund flertalet ambulans-EKG skickade till sig, vilket är tidskrävande för HIA-läkarna som måste tolka dessa, och vilket dessutom kan bidra till tidsspill för ambulansen som måste invänta svar från HIA.

Vi byggde därför ett datorprogram som kallas artificiellt neuralt nätverk (ANN) som tränades i att detektera EKG som tyder på STEMI. Under drygt 6 månader samlade vi in 560 ambulans-EKG, och HIA-läkarens bedömning av varje EKG jämfördes därefter med vårt ANNs tolkning. Vårt ANN var då betydligt bättre på att identifiera EKG med tecken på STEMI (bättre sensitivitet) än HIA-läkaren, men identifierade även något fler utan STEMI (sämre specificitet). Ett i systemet inbyggt ANN som ”förtolkar” alla ambulans-EKG före översändning till HIA skulle därmed kunna minska antalet EKG skickade till HIA med hela 2/3, utan risk för missade STEMI-fall.

I behandlingen av akut hjärtinfarkt har syrgas varit en självklarhet de senaste 100 åren. Användandet av syrgas vid hjärtinfarkt har dock på senare tid blivit omdiskuterad, och experimentella studier har visat att det till och med skulle kunna vara dåligt för patienter med normal syresättning i blodet att få extra syrgas. Teorin är att denna över-syresättning dels bidrar till att kärlen i kroppen drar ihop sig och således ger upphov till att mindre blod strömmar till vävnaderna, samt dels att denna över-syresättning bidrar till en ökad produktion av så kallade fria radikaler som kan vara skadlig för kroppens vävnader.

Några tidigare studier som tittat på effekten av syrgas på patienter med dels misstänkt och dels konstaterat hjärtinfarkt, har visat icke konklusiva resultat, varför

vi fortfarande inte vet huruvida extra syrgas till patienter med konstaterat hjärtinfarkt som också har en normal syresättning är farligt eller inte.

För att kunna utvärdera syrgaseffekten hos dessa patienter, genomförde vi två studier där vi med magnetkamera (MR) och ultraljud undersökte hjärtat på STEMI-patienter som fick respektive inte fick behandling med syrgas.

I studien där MR användes ingick 95 STEMI-patienter. Under transporten till akut PCI fick 46 av patienterna 10 liter/min syrgas, medan 49 fick enbart vanlig luft. Efter några dagar undersöktes deras hjärta med MR för att utvärdera hur stor skada hjärtat fått efter infarkten. Våra resultat visade inga skillnader mellan de två grupperna, vilket tyder på att det varken är till nytta eller skada för STEMI-patienter att behandlas med syrgas.

I studien med ultraljud undersökte vi 87 STEMI-patienter, varav 46 fick syrgas medan 41 fick vanlig luft under transporten till akut PCI. Patienterna undersöktes sedan efter några dagar, och igen efter 6 månader, med ultraljud för att utvärdera hjärtats funktion. Inte heller i denna studie fanns det någon skillnad mellan de två grupperna.

Sammantaget tyder alltså våra studier på att syrgasbehandling vid STEMI hos patienter med normal syresättning varken är till nytta eller till skada för patienten. Om ytterligare studier visar detsamma kan ambulanspersonalen i framtiden utan risk avstå från syrgasbehandling till patienter med hjärtinfarkt.

Foreword

The path to this thesis has been long, challenging and inspiring. Not infrequently, it felt as though I was the star of a movie about Murphy's Law. But really, what is a path to PhD, if you are not to cross the *infer*no and the *purgatorio* so that you at last can come through to the *paradiso*? Yes indeed, the most familiar work of Dante, *Divina Comedia*, can truly be cited in my case.

To be less dramatic, and perhaps also closer to the truth, the reality is that ever since I began my journey in the fascinating world of research and science, even the difficulties and the obstacles have been charming.

This thesis you have before you, may have my name on the cover, but its existence would have been impossible if it was not for the help, encouragement and inspiration from people for which I have the outmost respect, love and admiration.

I am, first and foremost, indebted to my main supervisor, **Ulf Ekelund**. Ever since 2004, when I, as a medical student, joined Ulf and his research team, he has been a valued and appreciated mentor and a highly esteemed friend. Ulf is not only an excellent physician, but he is also a distinguished researcher, from whom I have learned a great deal. The humbleness of Ulf, his endless and tireless support for his colleagues, and the fact that he is always available for discussion, makes him an invaluable individual. Ulf, from the deepest depths of my heart, down to the last strains of my myocardium, I thank you for all your support and your precious and irreplaceable friendship. It has been a true honor to work with you.

My deepest gratitude also to my co-supervisors **Marcus Carlsson** and **Jakob Lundager-Forberg**. Marcus has not only always been helpful and supportive, but he also introduced me to the world of abbreviations: CMR, MRI, MaR, IS, MSI… Thank you for always being so helpful Marcus. Jakob, I have known since 2004. Over the years, he has been a close and great friend, whom I highly appreciate and respect. As a young medical student, Jakob taught me so much about emergency medicine. Jakob, your friendship means a lot.

Another valued colleague and friend, and a great physician and researcher, is **Arash Mokhtari**. Thank you for always being so supportive and always being ready for scientific discussions. I have learnt a great deal from you.

I am also grateful to our research nurse, **Mahin Akbarzadeh**, for her hard work in every step of my different projects. Thank you for all the help and all the work you have done.

The writing of this thesis would have been impossible if it was not for the **co-authors** of the included articles. Thank you for all your efforts. A special thanks to the **Echocardiography team** in Lund, the **MRI team** in Lund and Malmö, the **Cardiac Care Unit** in Lund and Malmö, the **PCI laboratory** in Lund and Malmö as well as the **Ambulance unit** in Skåne, especially Lund and Malmö.

Another outstanding physician with whom I have had the honor to work, to learn from, and to call myself his student, is **Eric Dryver**. Ever since 2004, when I first met Eric, I have dreamt of becoming him. His humbleness and his never-ending support for friends and colleagues makes Eric a true role model. My dear Eric, I am highly privileged and honored to have you as my friend and teacher.

To my **friends** and **colleagues**, not least my dear **Nicolina Carlsson**, I wish to express my gratitude for their feedback, input and support, and for always being there for me and showing that loyalty is still alive and kicking.

A warm thank you also to **Maria Ohlsson Andersson**, the head of the Department of Emergency Medicine and Internal Medicine at the Skåne University Hospital, for always being so supportive. Also, a special thanks to **Ulrika Pahlm**, the head of the Department of Emergency Medicine at Skåne University Hospital Lund. Without your help and support, this thesis would have been impossible. Thank you, Ulrika!

Last, but certainly not least, I am for always indebted to my family. Without their wholehearted and tireless support, help and motivation, I would not be where I am today.

My late grandfather, **Jahangir**, was probably my greatest fan and never stopped motivating me. “Respect him, he is a doctor!”, Jahangir always used to say whenever the family demanded that I help with the chores at home. Dear Baba, you are deeply missed.

Navid, my dear uncle, have always been supportive and helpful in every event of my life. Your support has been invaluable.

My brothers; **Arvin**, **Ashkan** and **Abtin**. Oh boy, how often have I not threatened you guys to someday write a book about you? Well… Here we are! But this time I will be nice. The truth is really that I will never be able to thank you enough for always being there for me. The positive aspect of having three younger brothers is not only that you will became a great fighter, but you have also one hell of a backup when one is needed.

And finally, how can I express all my love and gratitude for my parents, **Nahid** and **Masoud**? There are no words that can show my love and gratitude for you, so I

sought help from our beloved Hafez who wrote: “Even when my bones decompose and rot, my soul will hold that love in reverence”.

Although many have been involved in helping to create this thesis, I am solely responsible for all shortcomings.

A Word of Gratitude

As a young physician and researcher, I am indebted to colleagues from earlier generations. I am indebted to these brave women and men who struggled for the best of humanity. It would be highly disturbing for me not to express my deep gratitude to these colleagues. Two of them, being great role models for me both in my personal life and in my career as a physician, are Dr. Farrokhro Parsa and Dr. Mohammad Reza Ameli-Tehrani.

Dr. Farrokhro Parsa, a physician, became the minister of education in 1968, in Iran, as the first women in the history of the country to hold a cabinet position. Her work for education and women rights in Iran, was invaluable.

Dr. Mohammad Reza Ameli-Tehrani, an anesthesiologist, became the minister of education in 1979. Before that, Dr. Ameli-Tehrani had been active both as Minister of Information in the Iranian government and as a lecturer in the field of anesthesiology at the Tehran University.

After the Islamic revolution in Iran 1979, both Dr. Parsa and Dr. Ameli-Tehrani were arrested, and convicted in the Islamic revolutionary court to be a “corruptor on earth” and for “conducting a war against god”. They were given the death penalty.

Dr. Ameli-Tehrani was executed by a firing squad on May 8, 1979. Dr. Parsa was executed by a firing squad on May 8, 1980.

There are no incurable diseases — only the lack of will.
There are no worthless herbs — only the lack of knowledge.

Ibn Sina[1]

[1] Ibn Sina (980-1037), known as Avicenna in the western world, was a known Iranian physician and philosopher. In 1025, he compiled an encyclopedia of medicine consisting of five books, known as the "Canon of Medicine". The Canon is still considered as one of the authorities in the history of medicine.

Chapter 1: Introduction

1.1 Background and Objectives

ST Elevation Myocardial Infarction is a life-threatening condition where diagnosis, treatment and time to reperfusion is of vital importance. This creates a large responsibility for the health care and not least the prehospital care of these patients.

Most STEMI patients arrive the ED with an ambulance after first contacting the emergency services. The ambulance personnel, after arrival, register the patients' vital parameters and then usually initiate treatment with O_2, as an ECG is taken.

To reduce the time to acute PCI for reperfusion, the prehospital ECG is electronically transmitted to the closest CCU for interpretation by a physician. She will then decide whether the patient has a STEMI and therefore should be transported to the PCI laboratory for reperfusion, or that the patient does not have a STEMI and should be transported to the ED instead.[1,2] Every day, numerous ECGs are transmitted to the CCU for interpretation, why this task is highly time consuming for the CCU clinicians

To minimize the numbers of ECGs transmitted to the CCU, an ANN could be of interest. In **Paper I**, we studied if an ANN could identify prehospital ECGs with low probability of STEMI, and thereby possibly decrease the number of ECGs transmitted to the CCU.

For more than a century, O_2 therapy has been an evident and important treatment in STEMI patients. O_2 therapy is therefore prehospitally initiated according to guidelines for patients with chest pain and STEMI.[3,4] There are, however, several publications questioning the use of O_2 therapy in normoxic STEMI patients.[5-7] In **Paper II**, **III** and **IV**, we aimed to study the effects of O_2 therapy in normoxic STEMI patients.

1.2 Overview of the Cardiac Anatomy and Physiology

The cardiovascular system consists of the heart and the blood vessels. The heart is responsible for pumping blood to the body and thereby provide the body's organs and tissues with O_2 and nutrients, as well as receiving waste and CO_2 from the same organs and tissues.

The heart is a muscle lying in the middle of the thorax behind the sternum, surrounded by the lungs (Figure 1). It is wrapped in the pericardium, a two-folded sack consisting of the parietal pericardium and the visceral pericardium. The parietal pericardium is the outer layer of the pericardium which attaches the heart to the diaphragm and the sternum. The visceral pericardium is the inner part of the pericardium lying on the surface of the heart. Between the two layers of pericardium there is a small amount of fluid making it easy for the heart to move and pump.[8]

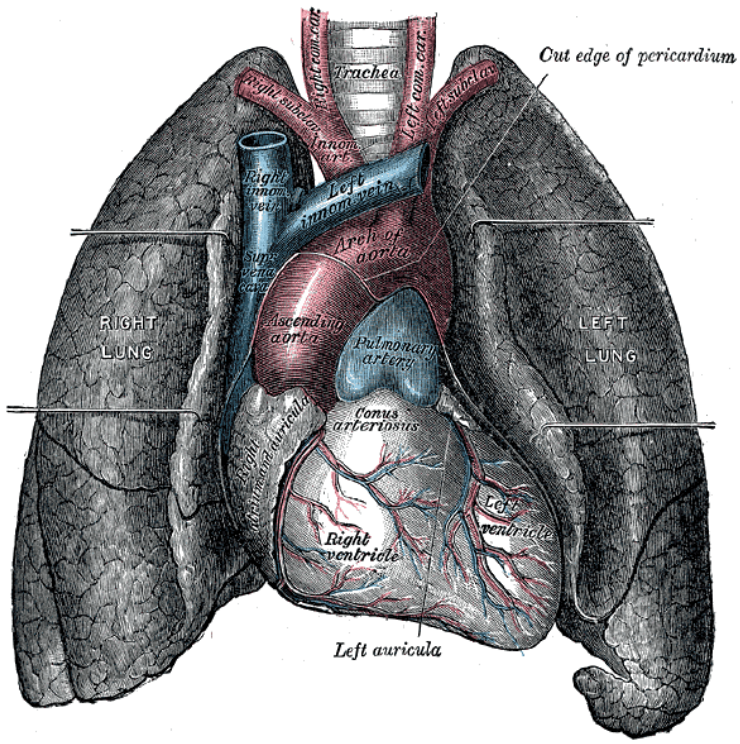


Figure 1 *Image of the heart and its surrounding anatomy.*

The heart is composed of myocardium which encircles four cavities; the right and the left atrium, as well as the right and the left ventricle. The blood returns from the rest of the body to the right atrium via the superior and inferior vena cava. Also, the heart itself has a system of drainage via the coronary sinus. Unlike the other heart veins, however, the anterior cardiac veins do not drain into the coronary sinus, but directly into the right atrium.

The right atrium is separated from the right ventricle by the tricuspid valve where the blood travels through. When the heart contracts, the blood is ejected from the right ventricle through the pulmonary valve into the two pulmonary arteries and to the lungs where the blood is oxygenated and CO_2 delivered to the alveoli for expiration. The blood then travels through the four pulmonary veins to the left atrium and through the mitral valve into the left ventricle where the blood is pumped through the aortic valve to the aorta and the rest of the body.[8,9]

The phase where the ventricles of the heart contract to eject blood is termed systole. Diastole is the phase in which the ventricles are filled with blood. Both systole and diastole are a part of what is called the cardiac cycle which also includes (1) isovolumetric contraction at the beginning of the systole, and (2) isovolumetric relaxation at the beginning of diastole (Figure 2).[10,11]

Contraction of the heart is strictly controlled by its own electrical conduction system which consists of the SA-node, AV-node, the HIS bundle, the right and the left bundles as well as the purkinje fibers. The electrical impulse is generated in the pacemaker cells of the SA-node and then propagated to the muscles of the right and the left atrium and then to the AV-node where the impulse is briefly halted so that the atriums can fully contract. The impulse then spreads through the HIS bundle to its right and left branches and out to the purkinje fibers which initiate the contraction of the ventricular muscle.[8,9] The heart is also supplied by parasympathetic and sympathetic nerves. The former inhibits the HR through the tenth cranial nerve, vagus, while the later increase the HR through cervical and thoracic sympathetic ganglia.[9]

With each contraction, the heart pumps approximately 70 ml of blood into the aorta. This is called the SV. When multiplying the SV with the HR, the CO is calculated. The CO is defined as the amount of blood pumped into the aorta each minute. The most important factor determining the CO is the amount of blood returning to the heart, the venous return, which in turn is determined by the function of the peripheral circulation. Thus, the venous return decides the SV and the CO. This is known as the Frank-Starling law which states that the venous return decides the SV by stretching the walls of the ventricle. As more blood returns to the heart the wall is stretched more, which in turn will make the ventricle contract with more force, thus more blood will be pumped out.[11,12]

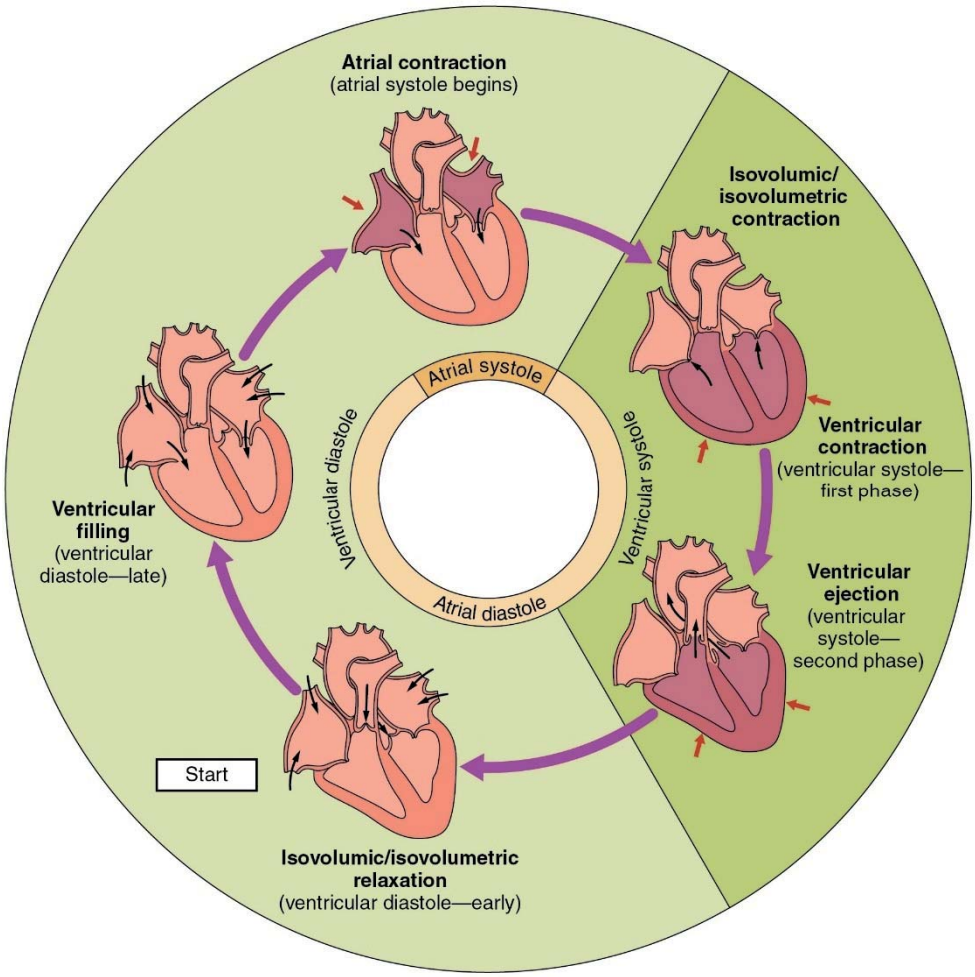


Figure 2 *The cardiac cycle.*

Several arteries supply the myocardium with blood (Figure 3). The RCA descends from the aortic root and travels anteriorly to enter the so-called AV groove and have branches into the right atrium, the SA-node, the AV-node as well as the right marginal artery and the posterior interventricular artery. The main responsibility of the RCA is to supply the right ventricle. The LCA also arises from the aortic root and mainly supply the left part of the myocardium. The LCA travels anteriorly in the left anterior AV groove and divides into the CA and the anterior interventricular artery. It is important to point out that the RCA in only 60% of the cases supply the SA-node while the LCA has this responsibility in the rest 40%. In 90% of the people it is the RCA that gives rise to the posterior interventricular artery which supplies the AV-node. The CA is responsible in the remaining 10%.[9,13]

Because of the high ventricular pressure as the ventricles contract during systole, the coronary vessels in the subendocardium (i.e. the myocardium closest to the ventricular cavities) are compressed, which decreases blood perfusion in this tissue. During diastole, however, when the ventricular pressure is low, blood will flow freely through the arteries and supply the entire myocardium.[14]

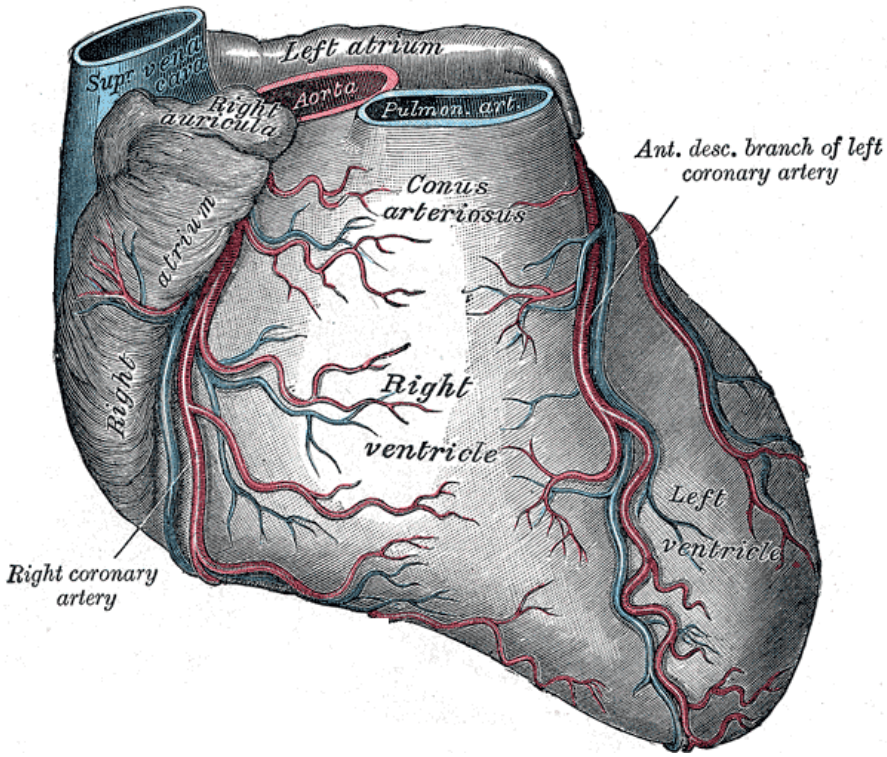


Figure 3 *Image of the heart and its vessels.*

1.3 Acute Coronary Syndrome

1.3.1 Definition

ACS is defined as an acute manifestation of CAD, and is divided in AMI and UA.[15,16]

The third universal definition of myocardial infarction[17] define AMI as a clinical diagnosis with evidence of myocardial necrosis. AMI can also be divided according to ECG findings, in either STEMI or NSTEMI.

STEMI, which is the objective of this dissertation, is the result of a complete or partial occlusion of a coronary artery giving rise to myocardial ischemia on the base of termination of O_2 supply to the myocardium. The occlusion is due to a rupture or erosion in a plaque thus creating a thrombosis which occlude or narrows the artery.[18]

1.3.2 Pathophysiology

1.3.2.1 Atherosclerosis

Atherosclerosis is a condition affecting the arterial walls, and is the most common cause of ACS.[19] The process of atherosclerosis in the coronary artery begins already in adolescence and progress through the years with a pace depending on several factors (Figure 4).[20-22]

The American Heart Association divides the atherosclerotic lesions in the coronary artery in six types.[23] Type I is microscopically characterized by an increased number of macrophages and macrophage foam cells contributing to a thickening of the intima.[24,25] In the Type II lesion, the macrophage foam cells are distributed into the coronary arteries smooth muscle cells contributing to a so called “fatty streak”.[25] As the thickening of the intima continues and becomes pathological, lipid droplets can also be found extracellularly, which is the main characteristic of a Type III lesion. In the next step, Type IV lesion, an atheroma is built.[23,25] The atheroma is usually characterized by a necrotic core covered by a fibrous cap which is made up by smooth muscle cells.[26] When fibrous connective tissue is formed in the atheroma, the lesion is called a Type V lesion. A Type VI lesion is present when the atheroma is complicated by a fissure, hematoma, or thrombus.[23]

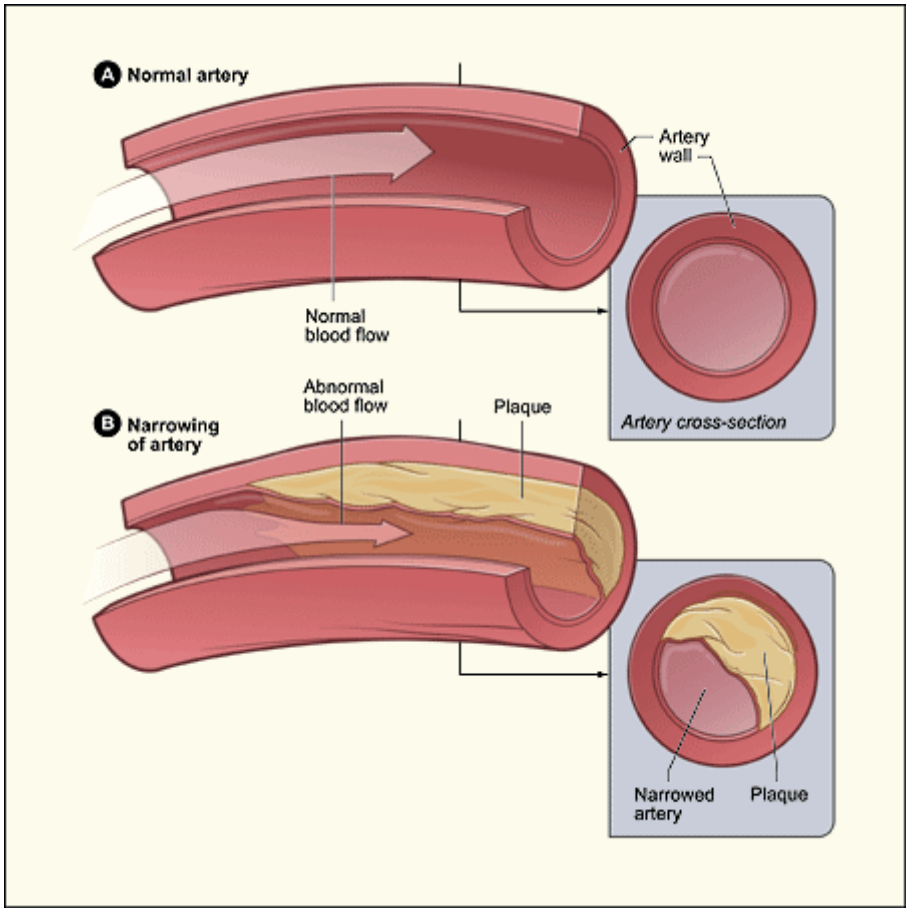


Figure 4 *Image of a normal artery (A) and a narrowed artery because of atherosclerosis (B).*

ACS is mostly caused by a thrombus narrowing or occluding a coronary artery. The thrombus in turn is usually caused by a plaque erosion or rupture. Because of this, both Type IV and Type V lesions are the most important and relevant clinical lesions.[23,24] Any injury to the fibrous cap, like an erosion or plaque rupture, will activate pro-thrombotic proteins and factors which form a thrombus in the coronary artery, causing myocardial ischemia.[26,27]

1.3.2.2 Thrombosis

Hemostasis depends on the thrombocytes which acutely stop the bleeding in a vessel through developing a thrombotic plug, a process called primary hemostasis.[28] Secondary hemostasis is the process in which the coagulation starts and fibrin is produced.[29]

As a vascular injury take place, for example after a plaque rupture or erosion of the atheroma, several pro-thrombotic proteins like collagen and von Willebrand factor are exposed. This initiates the primary hemostasis which consist of thrombocyte adhesion, activation and aggregation.[30] The result is the formation of a thrombosis narrowing or occluding the coronary artery. In a plaque erosion, the thrombus usually adhere to the surface of the plaque, in contrast to a plaque rupture in which the thrombosis is formed inside the plaque itself and extends into the vessel (Figure 5).[31]

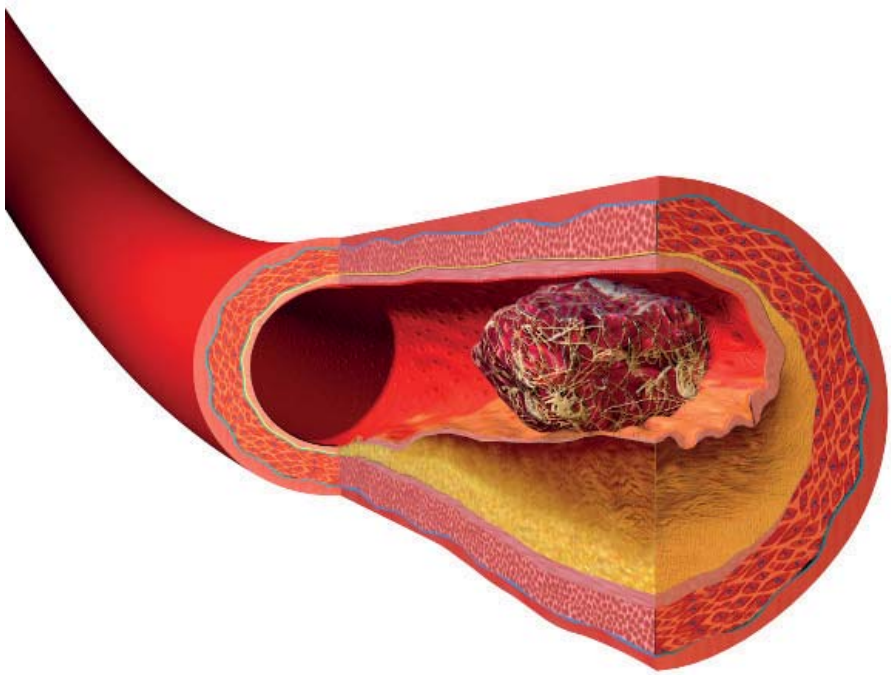


Figure 5 *Formation of a thrombosis in an atherosclerotic artery.*

1.3.3 Diagnosis

The diagnosis of ACS is ternary; patient history, ECG and blood tests for cTn. These three, are the most important tools for diagnosing AMI.[17] In patients with symptoms of myocardial ischemia and a STEMI on the ECG, cardiac troponins have no role since the patient is usually rushed to the coronary angiography laboratory for an acute PCI.

According to the Third Universal Definition of Myocardial Infarction[17], in order to diagnose STEMI, there must be an ST elevation in two contiguous leads in the ECG with an elevation of ≥ 0.1 mV in all leads expect for the V_2 and V_3 precordial leads in which the elevation must be ≥ 0.2 mV, ≥ 0.25 mV and ≥ 0.15 mV for men ≥ 40 years, men < 40 years and women respectively. The measurement of the elevation is done at the J point, which is the junction between the end of the QRS-complex and the beginning of the ST segment.

1.3.4 Treatment

The treatment of ACS is highly depended on whether the patient presents with STEMI, NSTEMI or UA. Treatment for NSTEMI and UA are quite similar in the acute phase, but differ from STEMI in which acute PCI is the most important treatment (Figure 6).[32-34]

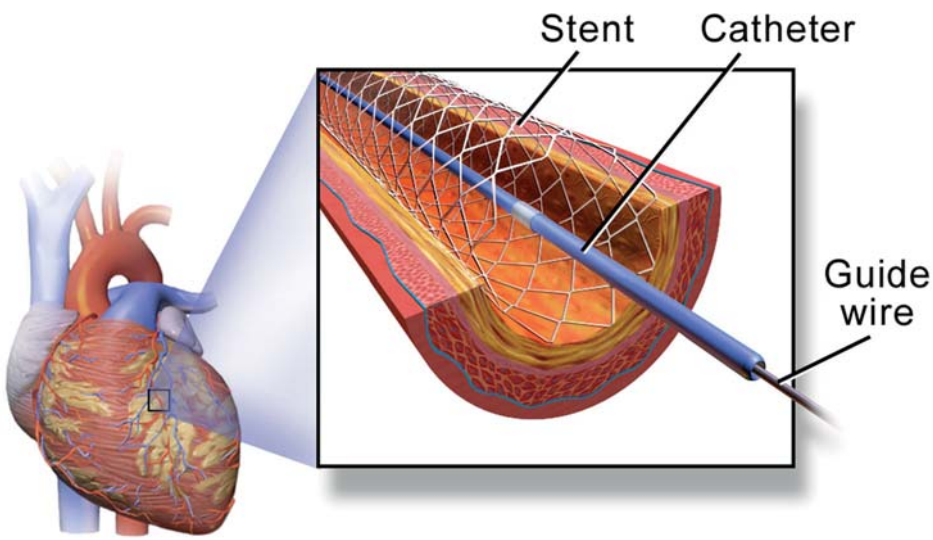


Figure 6 *Percutaneous Coronary Intervention (PCI).*

According to international guidelines[32,34] all STEMI patients should in the acute phase be treated with pharmacological dual antiplatelet therapy and as soon as possible have a PCI. Additional treatment should be based on the patients' symptoms.

Immediate administration of O_2 to patients with ACS or suspected ACS, irrespective of blood O_2 saturation, has for a long time been a cornerstone in the treatment of these patients as stated in different international guidelines.[3,4,35-37]

1.4 Artificial Neural Network

1.4.1 Historical Perspective

The birth of ANN can be traced to 1943 and an article published in Bulletin of Mathematical Biophysics, in which McGulloch and Pitts showed that neural networks could quite simple function logically.[38] Six years later in 1949, the psychologist Donald Hebb published a theory in which he further discussed and developed the ANN in what is known as the Hebbian theory.[39]

In the late 1950s, the psychologist Frank Rosenblatt, created a model for pattern recognition, thus further evolving the Neural Network.[40] Rosenblatt developed the ANN as we know it today.

1.4.2 The Structure and Function of the Artificial Neural Network

Previous studies have showed that an ANN can be used to diagnose ACS.[41-43] An ANN is a computational model of neurons which among other things can make decisions, as data are registered and results are specified. The analysis of the data fed to the ANN is conducted at the activation node. This node recognizes patterns, which is also what is important when the physician interprets an ECG.[44]

As data is inserted to the ANN (input), they are sent through so called synapses to the activation node in which the data is calculated, and the results presented (output) (Figure 7).[45-47]

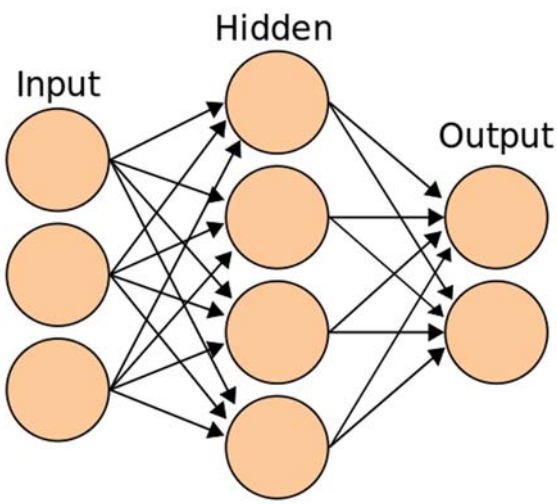


***Figure** 7 Basic illustration of an Artificial Neural Network.*

1.5 Cardiac Magnetic Resonance Imaging

1.5.1 Historical Perspective

MRI was first introduced for clinical use in 1980[48], and has since become widely used in the health care system because of its non-invasive nature and its lack of hazardous radiation. The first images taken on humans by MRI was of the Thorax in July 1977 by Dr. Raymond Damadian.[48] Beside Damadian[49], scientists like Lauterbur[50] and Mansfield[51] also made great contributions in the MRI field. In fact, both Dr. Lauterbur and Sir Mansfield received the Noble prize in physiology or medicine in 2003 "for their discoveries concerning magnetic resonance imaging"[52] leaving Damadian out, thereby giving rise to an infected debate lasting until today.

1.5.2 Basics of Magnetic Resonance Imaging

The human body is up to 70% consisted of water. The central element in MRI is the hydrogen protons in the human body.[53] These protons which poses a positive charge, create an electromagnetic field as they spin around their own axis, and when located in another magnetic field, the proton spins will be polarized and magnetization created (Figure 8). As a radio frequency pulse is released by the MRI machine, the pulses will be directed to the part of the body examined, a phase called excitation.[54] The next phase, relaxation, occurs after the end of the radio frequency pulse, and is divided into two parts; T1- and T2-relaxation. The relaxation phase returns the magnetization to its normal state.[54,55]

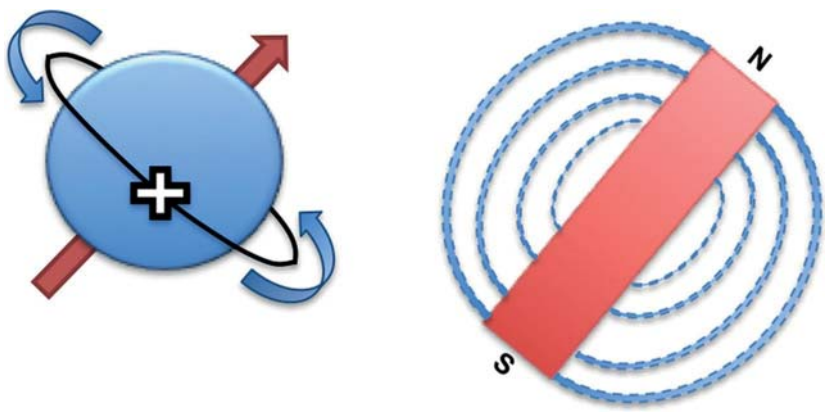


Figure 8 *The protons are spinning around their own axis, generating a magnetic field.*

1.6 Echocardiography

1.6.1 Historical Perspective

In 1937 Sergei Sokolov received the first patent for an ultrasonic device, followed by Floyd Firestone in 1942.[56] It was, however, the Czechoslovakian-Austrian Dr. Karl Dussik who first used ultrasound for medical diagnosis.[57] The World War II came like a blessing for ultrasound technology, as research and investments in this field increased because of the use of naval sonar.[58] Even though many researchers continued to work with this technology and made important contributions[59-61], it was the Swedish Cardiologist Inge Edler and the electrical engineer Hellmuth Hertz, both at Lund University, who introduced echocardiography as we know it today.[58,62]

1.6.2 Basics of Echocardiography

Echocardiography has become one of the most used tools to examine the heart. The good image quality and its non-invasiveness has probably been factors contributing to its popularity and use. The base of echocardiography are high-frequency sounds, i.e. ultrasounds, which travel from the transducer to tissues and structures in the body and bounce back to the transducer which then shows the image on the monitor (Figure 9).[63,64]

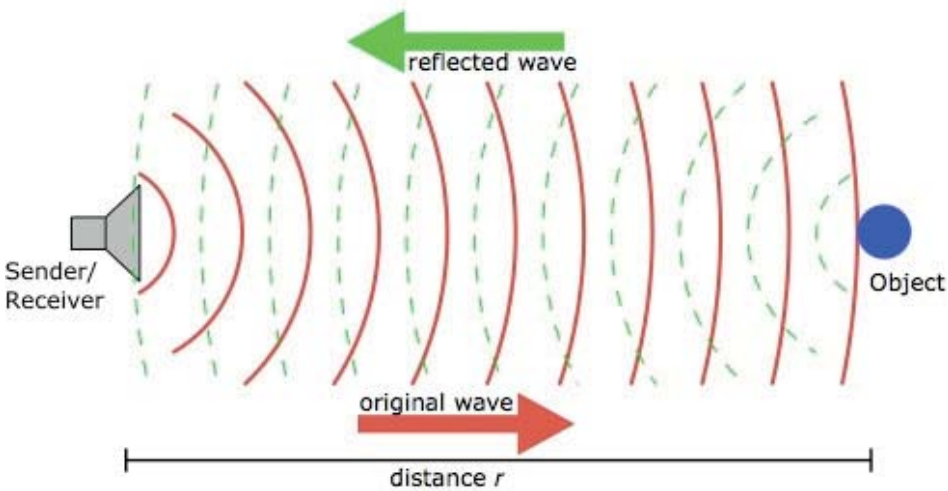


Figure 9 *Basic principles of how image is produced in an echocardiography.*

1.7 Oxygen Therapy

1.7.1 Historical Perspective

The British Joseph Priestley, among others a chemist and a political theorist, is deemed to have discovered O_2. In 1775 he described the burning of a candle thanks to the O_2 in the air. He stated that O_2 could be used as a medicine, at the same time warning for possible toxic effects.[65] In 1859, Birch[66] noted that even though O_2 therapy has positive effects, it must be used with caution and that more clinical trials are needed. As far as known, the first written discussion on the role of O_2 therapy in patients with chest pain/ACS was presented by Dr. Charles Steele[67] in 1900 in a letter where he described how O_2 therapy relieved angina in a single patient of his.

Through the decades more studies were published on the role of O_2 therapy in patients with chest pain/ACS, which showed positive effects on both the circulation and in relieving the pain.[68-72] Russek et al.[73] in 1950, however, in contrast to the studies above, showed that administration of 100% O_2 to five patients with angina pectoris had no effect on the ECG or chest pain. The authors, nevertheless, recommended that O_2 therapy should be initiated not only when it is indicated, but also when the physician merely suspect its use might be of importance.

Studies of the positive and negative effects of O_2 therapy in patients with ACS continued through the 1960s and 1970s. Most of the results, however, remained inconclusive. However, because of the belief that O_2 is an innocent medicine without harm, medical personnel have been using O_2 therapy loosely and mostly without prescription from a physician.[74-77]

1.7.2 The Cardiovascular Physiology of Oxygen Therapy

Several studies have shown that O_2 administration to healthy individuals have negative cardiovascular effects. An early study from 1969 on 10 healthy individuals with hyperoxemia showed that the venous blood O_2 saturation rise, but that the coronary blood flow decrease.[78] The same results were also found in research on canines.[79,80]

Continued studies have shown that hyperoxemia causes arterial vasoconstriction both in the coronary and peripheral circulation, a diminished SV and CO, decreased left ventricular perfusion, an increase in LV end-diastolic pressure as well as an increase in the SVR.[81-91] Both the vasoconstriction as well as the increased SVR is believed to cause impaired blood flow to organs and thereby perhaps contributing to organ injuries.[83,92,93]

Regarding the effect of oxygen in decreasing CO, it is mostly believed that the peripheral vasoconstriction is the main cause[81]; the vasoconstriction gives rise to an increased SVR thus contributing to a diminished SV and thereby CO.[83,94] Another theory, however, is that the CO decreases because of a diminished HR as the parasympathetic nervous system are stimulated.[82,95] In a study on 16 healthy subjects receiving graded O_2 administration, LV perfusion and CO decreased by 23% respective 10%.[90] In another study on nine healthy individuals with hyperoxemia[81], the authors showed that the CO decreased because of a decrease in SV, without affecting the HR. The authors concluded that since the HR was not affected, it is more likely that the diminished CO and SV is the results of the peripheral vasoconstriction and the increase in SVR, rather than a stimulation of the parasympathetic nervous system. The vasoconstriction is believed to be mediated either by an increase in vasoconstrictors like free oxygen radicals[96,97], or a decrease in vasodilators like prostaglandin E2[98]. Rousseau et al.[84] conclude that these factors contribute to a vasoconstriction raising the BP, which in turn activates the baroreceptors which decrease the HR and thereby also the CO. In another study the authors showed that O_2 therapy increased the sensitivity of baroreceptors, supporting this theory.[83]

It has also been stated that hyperoxemia increase free oxygen radicals which have been proposed to facilitate injuries to the heart or promoting arrhythmias by impaired endothelial function, cell injury and microvascular damage.[83,91,92,99,100]

1.7.3 Oxygen Therapy in Myocardial Infarction

O_2 therapy has been shown to alter hemodynamics not only in healthy individuals, but also in patients with cardiac failure.[101-103] In discussing AMI, however, the results are conflicting. A large number of clinical studies in humans[104-121] and animals[122-124], reviews and reports[125-133] as well as editorials[134-138] have been written on the matter which still remains unclear.

Most of these studies have been conducted with weak methods, and no strong and reliable conclusions can be made. A Cochrane report from 2013[127] stated that there is no evidence to support the routine use of O_2 therapy in patients with AMI. One of the problems, the authors pointed out, was the lack of RCTs.

1.7.3.1 Randomized Controlled Trials

There are only six RCTs focusing on O_2 therapy in patients with AMI (Table 1).[113,115,119-121,139]

The first RCT in patients with AMI was performed in 1976 by Rawles and Kenmure[113] where they, after exclusion, included 157 patients with confirmed AMI

and randomized them to either O_2 therapy or air for 24 hours. There were 12 in-hospital deaths; three in the air group and nine in the O_2 group. This difference in mortality, however, was not significant. The IS, however, was larger in patients treated with O_2 when measured by serum aspartate aminotransferase (99.9 IU/ml versus 80.7 IU/ml; P = <0.05).

It would take two decades before the next RCT. In 1997, Wilson and Channer[121] conducted an open-label RCT with 50 AMI patients, of which half received O_2 therapy for 24 hours. Because of exclusions, only 42 patients were analyzed. All patients were monitored for arrhythmias and ST segment changes. Since there was no difference between the two groups in the incidence of arrhythmias and ST segment changes, the authors believed that it is unnecessary to treat all AMI patients with supplemental O_2. Their recommendation was to use pulse oximetry to guide O_2 therapy.

In 2005, Ukholkina et al.[115] included 137 patients in an open-label prospective randomized study. Patients were randomized to an "O_2 group" where they received 30-40% O_2 therapy, and a "control group" where the patients breathed room air. Inhalation of O_2 prior to and after PCI reduced the area of necrosis in both anterior (8.61%±1.5 versus 13.23%±1.7; P = <0.02) and posterior AMI (4.37%±1.2 versus 7.76%±0.9; P = <0.015). The authors conclude that O_2 therapy decreased IS and improved central hemodynamics.

Ranchord et al.[119] performed a RCT in which 136 first-time STEMI-patients were randomized to either high flow O_2 (6 L/min) or titrated O_2 (O_2-saturation goal of 93-96%). All patients were treated for 6 hours. There was no significant difference in IS as measured by TnT between the high flow and the titrated O_2 group (2.2 ng/mL versus 2.9 ng/mL; 95% CI -1.5-0.2; P = 0.12). IS was also measured with CMRI in almost half of the patients in week 4-6 after the inclusion. There was no significant difference between the high flow O_2 group or the titrated O_2 group in IS expressed as absolute mass or percent of LV mass (difference −0.8 g; 95% CI −7.6 to 6.1; P = 0.82 and −0.6%; 95% CI −5.6 to 4.5; P = 0.83, respectively).

In 2015, Stub et al.[118] randomized 441 patients with STEMI to either O_2 therapy or no supplemental O_2. The main objectives were to study IS as measured by TnI and CK, as well as by CMRI six months after inclusion. No significant difference was observed in mean peak TnI between the O_2 and the no supplemental O_2 group (57.4 versus 48.0 μg/L; 95% CI 0.92–1.56; P = 0.18). There was, however, a significantly larger increase in mean peak CK in the O_2 group (1948 versus 1543 U/L; 95% CI 1.04–1.52; P = 0.01). Of those included, 139 patients (65 in the O_2 group and 74 in the no supplemental O_2 group) underwent a CMRI after six months. The absolute IS mass was larger in the O_2 than in the no supplemental O_2 group (20.3 g versus 13.1 g; P = 0.04), but there was no difference in IS expressed as percent of LV mass.

A published post-hoc analysis of this study showed a significant link between an increase in TnT and O_2 therapy.[118]

The most recent study was published by Hofmann et al.[139] in 2017. This was a Swedish registry-based randomized trial conducted between April 2013 and December 2015, with a main objective to evaluate the effects of oxygen treatment on one-year all-cause mortality in patients with suspected AMI and normoxemia at inclusion. A total of 6629 patients were enrolled of which 3311 were randomized to the O_2 group and 3318 to the ambient-air group. The mortality was 5% in the O_2 group and 5.1% in the ambient-air group ($P = 0.80$). There were no significant differences in morbidity, which was the secondary outcome. Even though the study proved to be underpowered, its results, based on the large study population included, strongly supports that O_2 therapy is neither beneficial nor detrimental in normoxic patients with suspected AMI.

Table 1 *Oxygen therapy in myocardial infarction - Randomized Controlled Trials.*

Author (Year)	Method	Inclusion	Final analysis cohort	Results
Rawles et al. (1976)[113]	Double blind RCT.	Suspected AMI.	n = 157; 77 patients received O_2 (6 L/min). 80 patients received compressed air (6 L/min).	Increased IS in the O_2 group as measured by AST.
Wilson et al. (1997)[121]	Open-label RCT.	Confirmed AMI.	n = 42; 22 patients received O_2 (4 L/min). 20 patients received air.	No differences between the groups in the incidence of arrhythmias and ST segment changes.
Ukholkina et al. (2005)[115]	Open-label RCT.	Confirmed AMI.	n = 137; 58 patients received 3-6 L/min O_2 (28 received O_2 30 min prior to and for 3h after revascularization. 30 received O_2 only for 3h after revascularization). 79 patients breathed normal air.	Area of necrosis, peri-infarction area and the rate of arrhythmias were significantly lower in the O_2 group.
Ranchord et al. (2012)[119]	Open-label RCT.	First time STEMI or LBBB.	N = 136; 68 received O_2 therapy (6 L/min). 68 received titrated O_2 to achieve an O_2-saturation of between 93-96%.	No significant differences between the two groups in IS as measured by TnT and CMRI.
Stub et al. (2015)[120]	Open-label RCT.	STEMI.	N = 441; 218 received O_2 therapy (8 L/min). 223 breathed normal air.	Significant increase in mean peak CK, the rate of recurrent MI, arrhythmias and IS in the O_2 group.
Hofmann et al. (2017)[139]	Open-label RCT.	Suspected AMI.	n = 6629; 3311 randomized to O_2 therapy (6 L/min), 3318 to ambient air.	No significant differences in one-year mortality and morbidity.

AST = Aspartate Aminotransferase; LBBB = Left Bundle Branch Block.

Chapter 2: Material and Methods

2.1 Study Setting

The SOCCER study was conducted at the Skåne University Hospital in Lund and Malmö, whereas the ANN study was conducted in only Lund. Both hospitals have a 24/7 ED and the combined census is more than 150 000 patients annually. The hospitals have also a comprehensive CCU with at least one physician present at all times. There are also several state-of-the-art PCI laboratories, with at least one interventionist always on call. Both cities have state-of-the-art ambulances equipped with modern technology including wireless ECG transmission. All ambulances are also staffed with at least one specialist nurse.

The absolute majority of patients with STEMI are identified in the ambulance and directly transported to the PCI laboratory bypassing the ED. All patients with chest pain contacting the emergency telephone number and having an ambulance dispatched, will have their ECG transmitted to the nearest CCU where the physician on call, after analyzing the ECG, will direct the ambulance either to the PCI laboratory (in case of STEMI) or to the ED. According to the current guidelines in Skåne for the ambulances, all STEMI patients are to be treated with 10 liters O_2/min.

2.1.1 Paper I

2.1.1.1 Study Design

This prospective study was approved by the Regional Ethical Review Board in Lund (Dnr. 2005/137) and was conducted between August 30, 2005 and February 18, 2006.

2.1.1.2 Data Collection

All ECGs transmitted to the CCU during the study period was interpreted by the CCU physician on call, who at the same time documented on CRFs whether the patient had a STEMI or left bundle branch block (as a STEMI equivalent), and whether the patient was directly transported to the PCI laboratory or not. Every day the CRFs were collected and electronically registered.

2.1.1.3 Artificial Neural Network

The ANN had previously been trained to interpret ECGs by feeding it with 3000 ECGs from 1306 unique patients of which 552 had STEMI.[140]

The ECGs transmitted to the CCU in *Paper I* was all interpreted by the ANN. Results from the ANN was then compared with the CCU physician´s real-time ECG interpretation and his decision on whether to perform an acute PCI or not. All the collected ECGs were also interpreted by two senior physicians experienced in ECG interpretation, and their results were deemed as the reference standard.

The ANN interpretation was also compared with the results of the coronary angiography and PCI, and these data were collected from the SCAAR[141] which includes information on all coronary angiographies and PCIs performed in Lund (and Sweden).

2.1.1.4 Study Endpoints

The endpoints were two; to study if the ANN can (1) identify patients without STEMI, and (2) determine if the patient needs a PCI or not.

2.1.1.5 Statistical Analysis

The *t* test was used to compare continuous variables, while the chi square test or the Fischer exact test were for comparing categorical variables. The predictive ability of the ANN was analyzed using the AUROC.

2.1.2 Paper II, III and IV

2.1.2.1 Study Design

The study was an investigator-initiated, single blind, parallel group, randomized controlled trial with no commercial funding (Figure 10). Both the Regional Ethical Review Board in Lund (Dnr. 2011/258) as well as the Swedish Medical Products Agency (EudraCT No. 2011-001452-11) approved the study which was conducted between January 23, 2012 and August 5, 2015.

After inclusion and admission, the patients underwent an extended echocardiography both at the index visit and after six months (*Paper IV*). Between days 2-6 the patients also underwent a CMRI (*Paper III*).

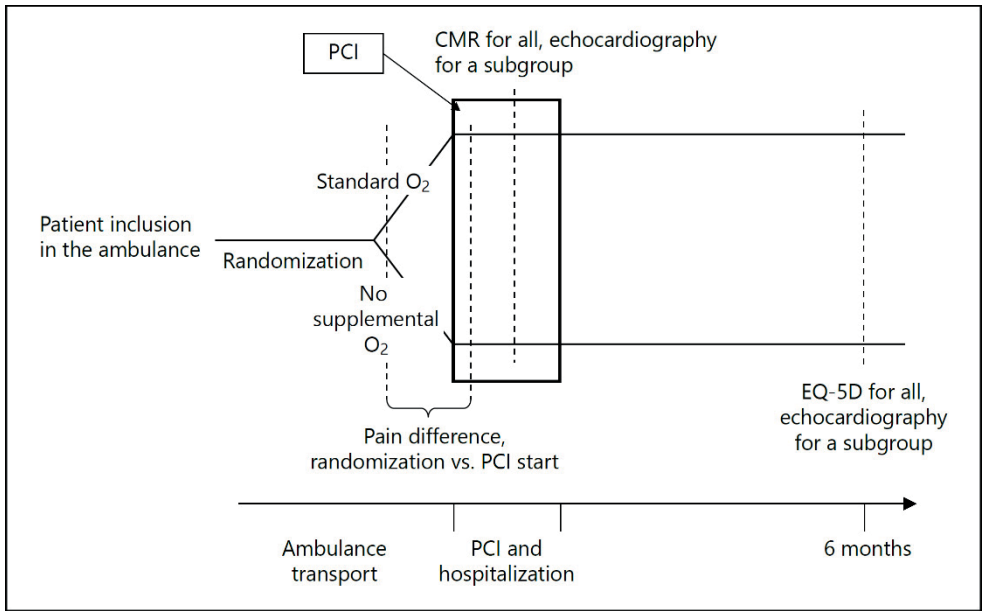


Figure 10 *Study design for the SOCCER study.*

2.1.2.2 Inclusion and exclusion

Normoxic (blood O_2 saturation ≥ 94%) STEMI patients accepted for PCI with symptom duration < 6 h were included. Previous AMI, inability to decide to participate, severe claustrophobia and implanted magnetic material in the body were exclusion criteria.

Patients eligible for inclusion were after verbal consent in the ambulance randomized 1:1 to either administration of 10 liter O_2/min or no supplemental O_2 until the end of the PCI. Independent of their study allocation, all included patients received an OxyMask™.[142] The patients were thus blinded to their study group allocations.

After the PCI, all patients were treated according to standard CCU protocol. Within 72 hours after the PCI, a physician met the patient to receive an informed consent in writing.

2.1.2.3 Data Collection

The ambulance nurses and the personnel in the PCI laboratory noted all patient data including vital parameters and given medications on CRFs, which later were registered electronically in a database. In-hospital data including blood sample results, PCI results and adverse events were retrieved from the Swedish nationwide online cardiac registry, SWEDEHEART[143]. Other data of interest, e.g. for the six

months follow-up, were retrieved from Melior[144], the electronic medical record system used in Skåne.

2.1.2.4 Cardiac Magnetic Resonance Imaging

In *paper III* we study the effect of O_2 therapy on IS, MaR and MSI as measured by CMRI. Several studies have established that CMRI is the gold standard method for evaluating IS, MaR and MSI (Figure 11).[145-148]

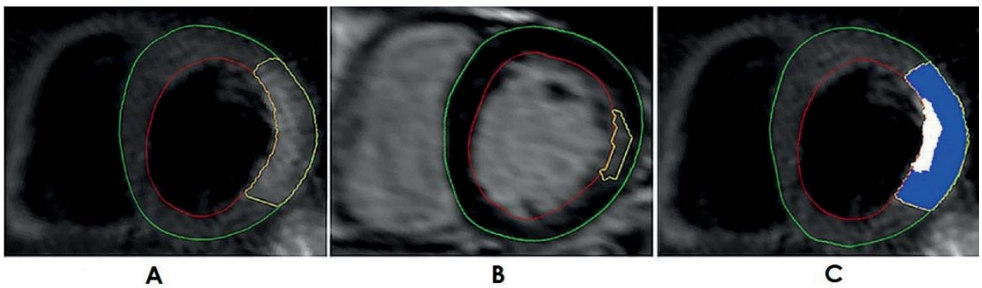


Figure 11 *Image A outlines the MaR (yellow). In image B, the IS is traced (yellow), and image C shows the salvaged myocardium (blue).*

The patients undergoing CMRI in Lund (Philips 1.5T Achieva or Siemens 1.5T Aera) or Malmö (Siemens 1.5T Avanto) had their images taken in the standard three long-axis images as well as a stack of short axis images. All images were analyzed using the software Segment, v.1.9 R3084 (http://segment.heiberg.se).[149] The physicians assessing the images were blinded to the patients' study group allocation.

All images were assessed in the short-axis images after intravenous administration of gadoteric acid which is a gadolinium-based contrast agent. Since gadolinium is an extracellular agent, LGE has been shown to be a very useful tool in assessing AMI.[150,151] Details of how the images are analyzed and quantified is beyond the scope of the present thesis, and relevant details have been published previously.[152,153] Different CMRI methodologies affect infarct quantification, and in the present thesis we used a validated method with semi-automatic algorithm[154] showing no bias in comparison to histochemical staining 7 days after AMI[155,156].

2.1.2.4.1 Myocardial area at Risk

MaR is defined as the size of the ischemic section before the PCI[157], is expressed as a percentage of the LV myocardium and can be visualized by a T2-weighted technique (Philips Achieva) first described in 2006[158]. The technique was later validated for measuring MaR in patients with STEMI up to one week after their diagnosis.[145] Another technique in which MaR can be quantified is through a T2-prepared steady-state free precession (Siemens Avanto) as well as contrast-

enhanced steady-state free precession short-axis images.[159] The latter was described and validated by researchers in Lund.[152,160]

2.1.2.4.2 Infarct Size

IS, expressed as percentage of the LV myocardium, is the final ischemic injury to the heart after the PCI, and is associated with both mortality and cardiovascular morbidity.[161,162] It is measured and quantified with CMRI 15 minutes after the administration of the contrast agent gadoteric acid.[150] Quantification of IS is made using an automatic infarct quantification method described and validated by Heiberg et al.[153] The use of CMRI to quantify IS is of great prognostic value for all-cause mortality and future cardiovascular events.[147,157,163-165] To assess LV remodeling is of importance since it is highly related to morbidity and mortality.[166]

2.1.2.4.3 Myocardial Salvage Index

MSI was the primary endpoint for the SOCCER study as discussed in *papers II and III*. It is defined as the area of the myocardium affected by the ischemia but salvaged from permanent injury by the PCI. MSI is quantified as (1 – IS/MaR) x 100.

MSI was chosen as the primary endpoint mainly for two reasons: (1) a recent prospective study by Eitel et al.[167] concluded that MSI as measured by CMRI to a higher degree predicted prognosis like mortality and major adverse cardiac events than IS measurement, at least partly because final IS depends on many factors[168], and (2) by measuring MSI instead of IS, sample size can be smaller. Engblom et al.[169] showed that sample size can be reduced between 46% - 65% without losing statistical power.

The use of MSI as the studies primary endpoint was also the reason for why STEMI patients with symptoms > 6 h were excluded from the study. Previous publications state that myocardial salvage as well as MSI may to some degree decrease as the time to reperfusion from symptom onset is delayed.[170-172]

2.1.2.5 Echocardiography

In *paper IV* we studied the effect of O_2 therapy on LVEF and WMSI as measured by echocardiography. As a part of standard management, all STEMI patients undergo an echocardiography in the first days after PCI. In the SOCCER study, a subgroup of patients, the first 50 included, were subjected to an extended echocardiography both at admission and once again at six months. All patients underwent echocardiography with Philips 133 ultrasound system, and the physicians performing the echocardiography and assessing the images were all blinded for the patients group allocation.

2.1.2.5.1 Left Ventricular Ejection Fraction

An echocardiography is used to assess cardiac function and LVEF is one of the important measures. Defined as the fraction of blood pumped out from the LV with each beat, the LVEF was calculated in 2-chamber and 4-chamber view according to the Simpson´s biplane disk methodic (the modified Sipmson´s rule).[173-175] In order to calculate the LVEF, both the end diastolic volume (EDV) and the end systolic volume (ESV) are estimated (Figure 12).[176] LVEF was chosen as a SOCCER endpoint since it has prognostic value in patients with AMI both regarding mortality and morbidity.[106,177-179] However, LVEF measurements are highly dependent on the physician assessing the images and the method used.[179-182]

$$\mathrm{LVEF} = \frac{(\mathrm{EDV} - \mathrm{ESV})}{\mathrm{EDV}}$$

Figure 12 *The formula used to calculate the LVEF.*

2.1.2.5.2 Wall Motion Score Index

Another method to assess the LV systolic function superior to LVEF, is to use WMSI.[106,183-185] Sixteen segments of the myocardium are assessed with echocardiography and given a score between 1 to 5, where 1 is normal wall movement and 2-5 describes diminished wall movement as decreased contractility. The WMSI is calculated by summing up the scores of the segments and then dividing the result with the number of segments assessed (Figure 13).

WMSI was one of our endpoints since it is of high value both in the acute and chronic phases of an AMI in assessing IS, myocardial contractility, myocardial remodeling and prognosis like morbidity and mortality.[178,179,186-188] WMSI has also been shown to be superior to LVEF with respect to prognosis after an AMI including cardiovascular events.[189]

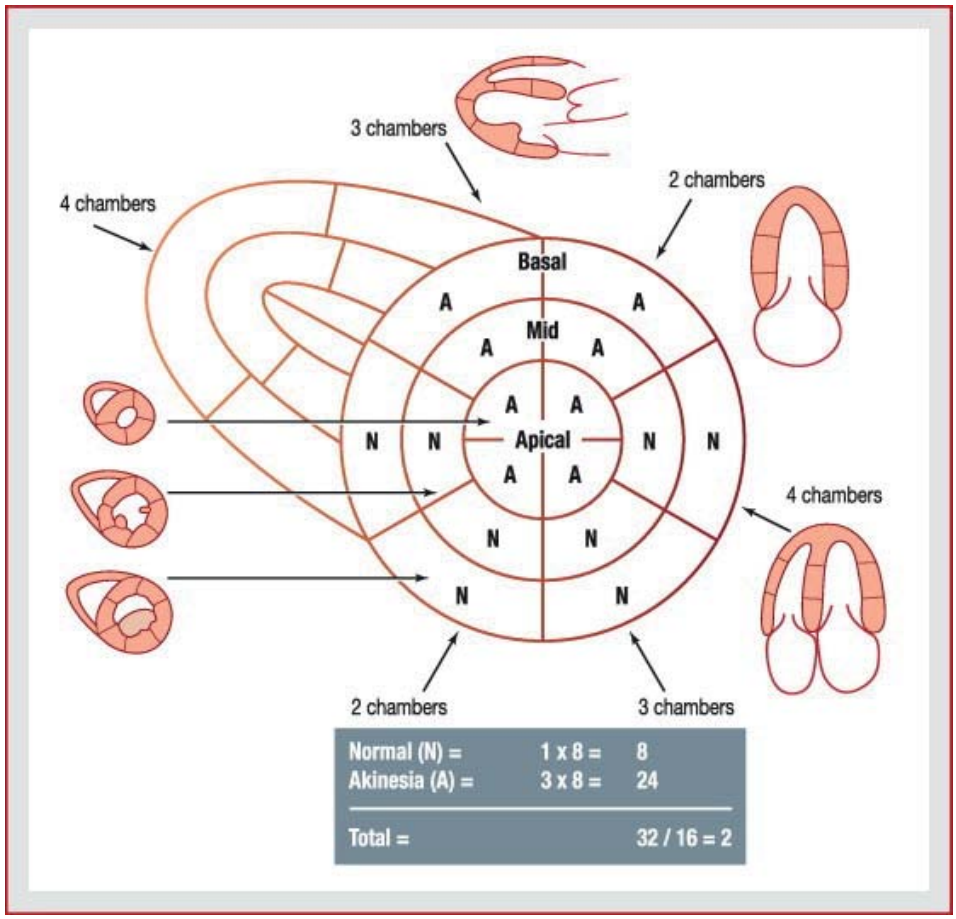


Figure 13 *WMSI calculation. In this example, the patient has eight normal segments and eight akinetic segments, giving a WMSI of 2.*

2.1.2.6 Study Endpoints

Endpoints for the SOCCER study can be divided into primary and secondary. The primary endpoint was MSI as measured by CMRI. Secondary endpoints included IS and MaR on CMRI, subjectively perceived health at six months as well as LVEF and WMSI as measured by echocardiography.

2.1.2.7 Statistical Analysis

The null hypothesis in all studies was that there is no difference between patients randomized to O_2 therapy versus air. A 2-sided Mann-Whitney test was used to compare the two groups in which $P < 0.05$ was considered statistically significant.

In *Paper III*, we made the following sample size calculation: If MSI is assumed to be 60 ± 20%[145,190-192] in the O_2 group, 100 included patients will allow us to detect an MSI difference of 15% points between the two treatment groups with an actual power of 96% at a 5% risk of an α error.

In *Paper IV*, we made the following sample size calculation: If we assume a WMSI of 1.6 ± 0.2[187] in the O_2 group, 50 included patients will allow us to detect a WMSI difference of 0.2 between the two treatment groups with an actual power of 93% at a 5% risk of an α error. The same calculation applies for the same patients undergoing a second echocardiography six months after inclusion.

Chapter 3: Results

3.1 Paper I

3.1.1 Study Profile

Of 743 ECGs transmitted to the CCU, 560 could be further analyzed (Figure 14). Of these 560 patients, 36 were deemed by the CCU physician to have a STEMI and was therefore directly transported to the PCI laboratory. The rest were transported to the nearest ED.

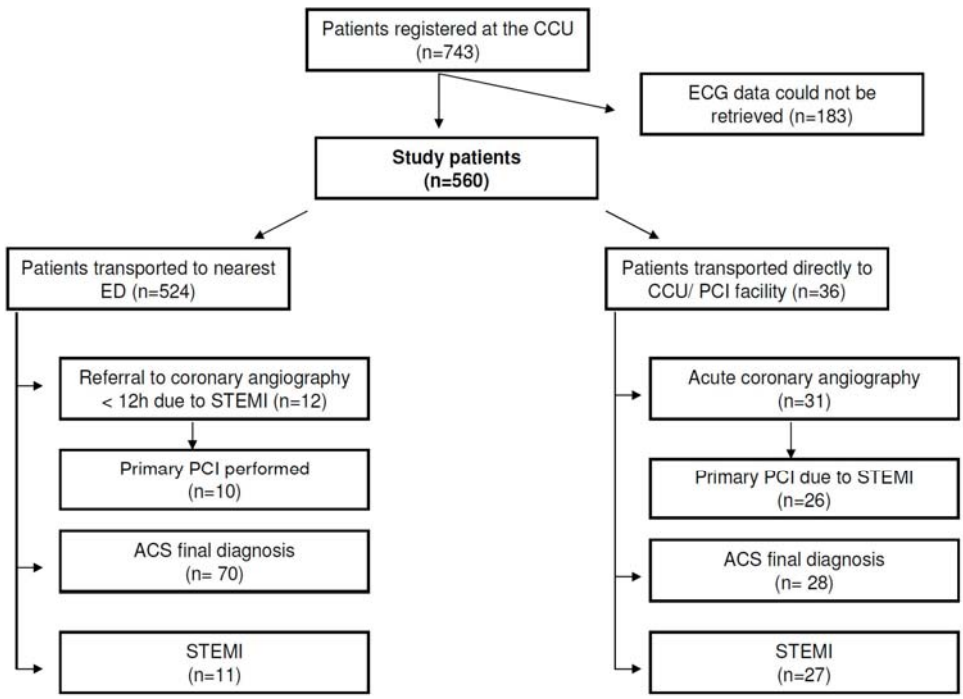


Figure 14 *Study profile.*

3.1.2 Predictive Ability of the Artificial Neural Network

The AUROC for the ANN to detect STEMI was 0.93 (95% CI 0.89 – 0.96), and the AUROC for the ANNs ability to predict the need of an acute PCI was 0.94 (95% CI 0.90 – 0.97) (Figure 15).

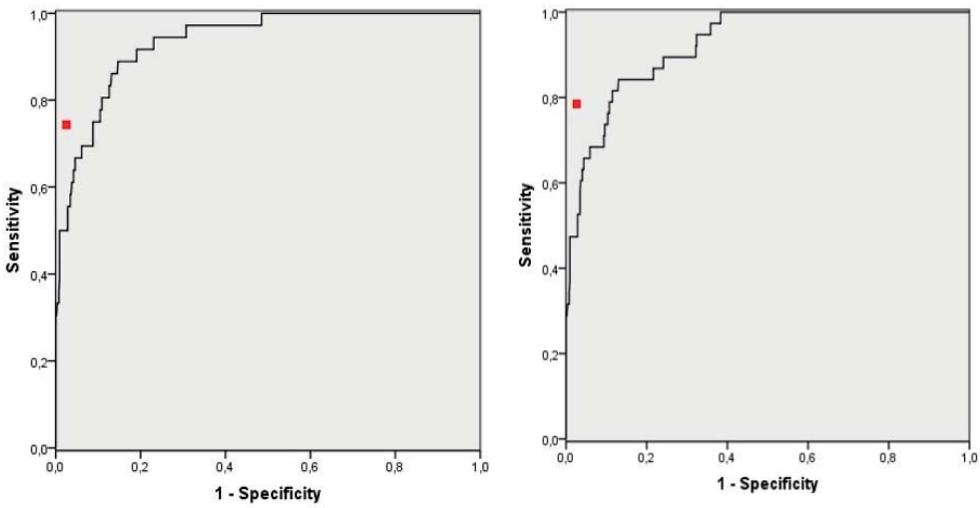


Figure 15 *The AUROC for the ANN to detect STEMI (right) and the AUROC for the ANNs ability to predict the need of an acute PCI (left). The red dots indicate the performance of the CCU physician in predicting STEMI and the need of acute PCI respectively.*

The predictive performances of the ANN and the CCU physician is presented in Table 2. The ANN had a superior sensitivity compared to the CCU physician in predicting STEMI (0.95 vs 0.74) and the need for an acute PCI (0.97 vs 0.78). However, the specificity was much lower for the ANN than the CCU physician in predicting STEMI (0.68 vs 0.98) and the need for an acute PCI (0.68 vs 0.98).

Table 2 *Predictive performances of the ANN and the CCU physician.*

	Sens	Spec	PPV	NPV
Predicting STEMI				
ANN	0.95 (0.82–0.99)	0.68 (0.63–0.73)	0.18 (0.13–0.23)	0.99 (0.98–1.00)
CCU physician	0.74 (0.57–0.87)	0.98 (0.97–0.99)	0.76 (0.59–0.088)	0.98 (0.97–1.00)
ANN and CCU physician*	0.74 (0.57–0.87)	0.99 (0.98–1.0)	0.80 (0.63–0.92)	0.98 (0.97–0.99)
Predicting need of acute PCI				
ANN	0.97 (0.85–1.0)	0.68 (0.63–0.72)	0.17 (0.12–0.23)	1.0 (0.98–1.00)
CCU physician	0.78 (0.61–0.90)	0.98 (0.97–0.99)	0.76 (0.59–0.89)	0.98 (0.97–0.99)
ANN and CCU physician*	0.78 (0.61–0.90)	0.99 (0.98–1.0)	0.80 (0.63–0.92)	0.98 (0.97–0.99)

*Theoretical diagnostic performances if only ECGs in which the ANN predicted STEMI were to be transmitted to the CCU physician.

3.2 Paper II

O_2 therapy has for the last century been an important part of the treatment of chest pain and ACS, regardless of the patients' blood oxygen saturation, and has been repeatedly recommended by international guidelines.[3,4,36,37]

The theory behind the above recommendations is that supplemental O_2 to patients with ACS, will increase the delivery of O_2 to the ischemic myocardium, thus diminishing the IS and the risk for arrhythmias. However, in the last years, several studies have suggested that O_2 therapy may have negative cardiovascular effects such as increasing blood pressure, decreasing CO and coronary blood flow and increasing systematic vascular resistance.[83,84,90,101,111] These adverse findings of O_2 therapy have been seen in healthy individuals, patients with heart failure as well as patients with CAD.[83,84,90,101,111]

In discussing patients with AMI, Ranchord et al.[119] recently showed no significant difference in IS measured by cTn nor 30-day mortality in first-time STEMI patients receiving 6 l/min O_2 or titrated O_2 to reach a blood oxygen saturation of 93-96%. They did not find any significant difference either when IS was measured by CMRI in a subset of the included patients. Ongoing studies evaluating O_2 therapy in AMI patients are the AVOID study in Australia[193], the DETO2X-AMI study in Sweden[194] and our SOCCER study, the study design of which is presented in this paper.

Our literature study shows that the cardiovascular effects of O_2 therapy in AMI patients are still unclear and that the results from different studies are unclear and inconclusive. Often these studies have also had major as well as minor methodological issues which may have affected the results of the studies. In light of these findings, we have initiated the SOCCER study in order to evaluate the effect of O_2 therapy in normoxic STEMI patients. The effect of O_2 therapy will be evaluated with the help of CMRI and echocardiography in order to determine IS, MaR, MSI as well as WMSI.

3.3 Paper III

3.3.1 Study Profile

Of 229 patients assessed for eligibility, 160 was randomized to either the O_2 group or the air group. After excluding patients not undergoing CMRI, 45 patients were finally analyzed in the O_2 group and 49 patients in the air group (Figure 16). Pre-hospital and intra-hospital patient characteristics of the two groups were similar.

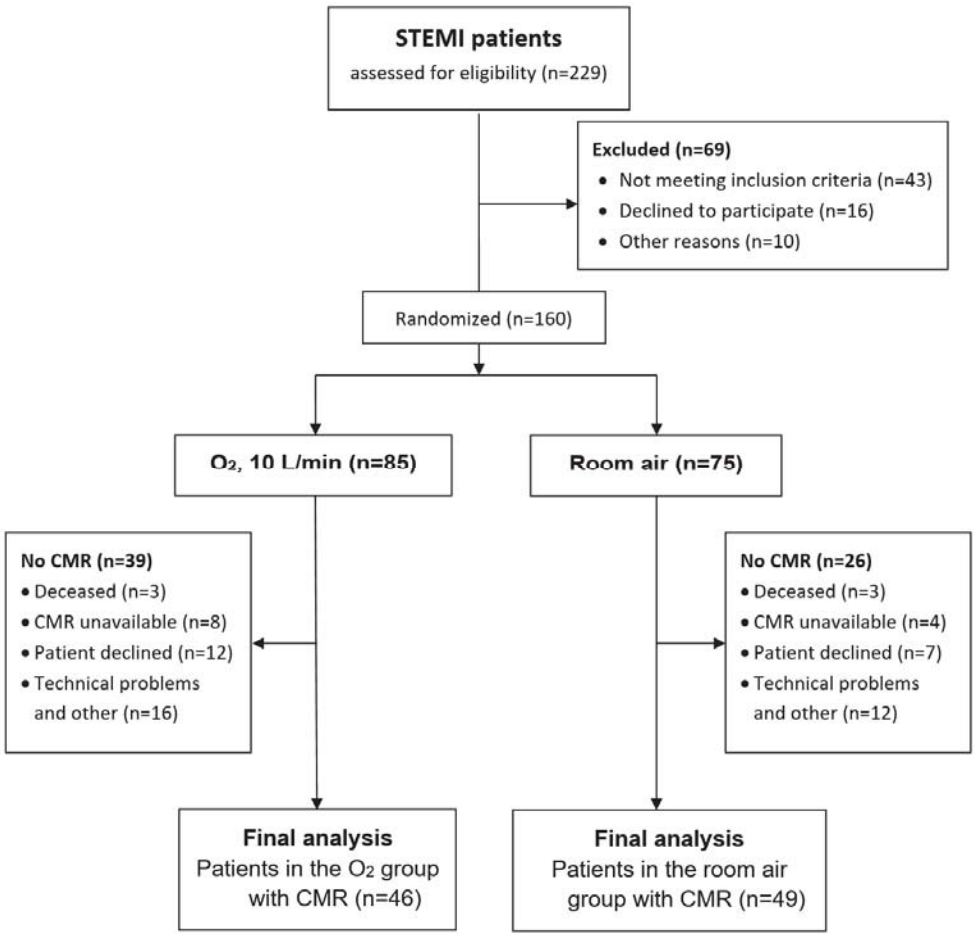
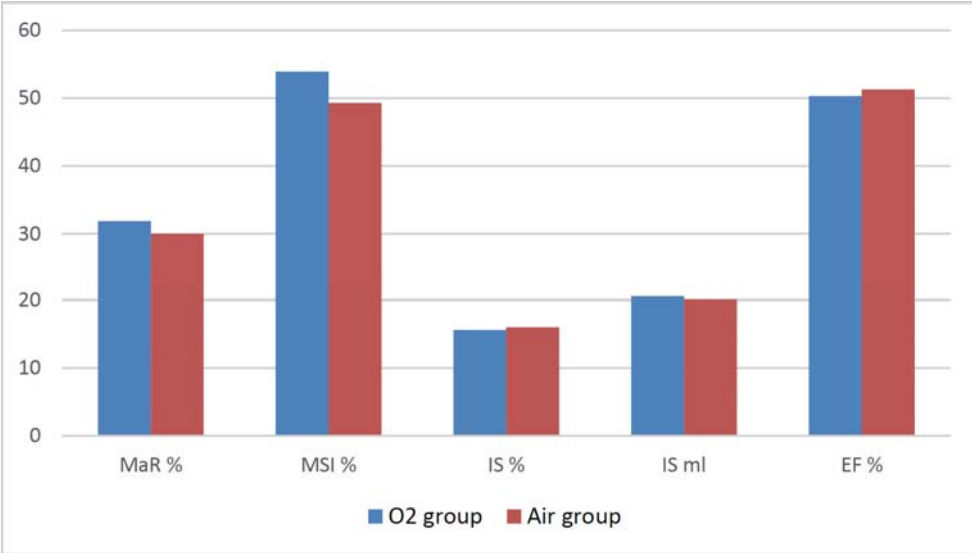


Figure 16 *Study profile.*

3.3.2 Cardiac Magnetic Resonance Imaging

There were no significant differences between the O_2 group and the air group regarding MSI (53.9% vs 49.3%; 95% CI for difference: -5.4 – 14.6%), MaR (31.9% ± 10.0% vs 30.0% ± 11.8%; 95% CI -2.6 – 6.3) and IS (15.6% ± 10.4% vs 16.0% ± 11.0%; 95% CI -4.7 – 4.1) (Figure 17).

In a post-hoc analysis, we found that with the MSI results presented above, the actual power to detect a MSI difference of 15% points between the groups was 86% at a 5% risk for an α error.



CMR results mean (SD)	O_2 group (n=46)	Air group (n=49)	95% Confidence Interval for difference
MaR % of LV	31.9 (10.0)	30.0 (11.8)	-2.6 – 6.3
MSI %	53.9 (25.1)	49.3 (24.0)	-5.4 – 14.6
IS % of LV	15.6 (10.4)	16.0 (11.0)	-4.7 – 4.1
IS ml	20.6 (15.6)	20.1 (15.9)	-5.9 – 6.9
EF %	50.2 (9.1)	51.3 (11.5)	-5.4 – 3.1

Figure 17 *Effects of O_2 therapy versus room air in STEMI patients as measured by CMRI.*

3.4 Paper IV

3.4.1 Study profile

Of 155 patients assessed as eligible, 94 was randomized to either the O_2 group or the air group. After excluding patients not undergoing echocardiography both at index visit and after six months, the final analysis consisted of 46 patients in the O_2 group and 41 patients in the air group (Figure 18). Pre-hospital and intra-hospital patient characteristics for the two groups were in general similar. However, the patients in the O_2 group had significantly more often multivessel disease than in the air group (50% vs 26.8%; $P = 0.02$).

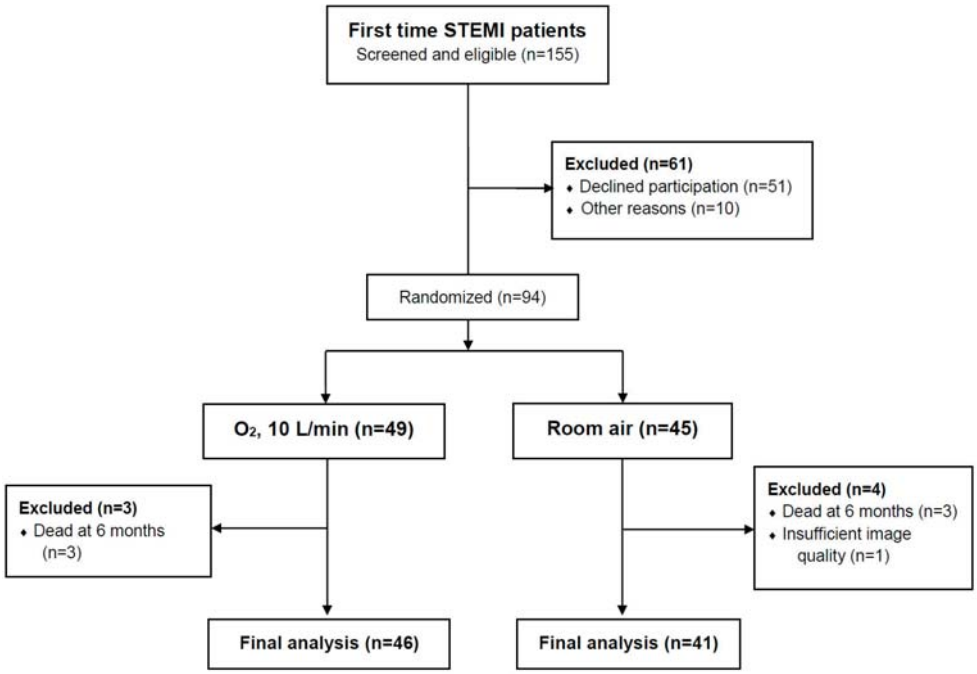
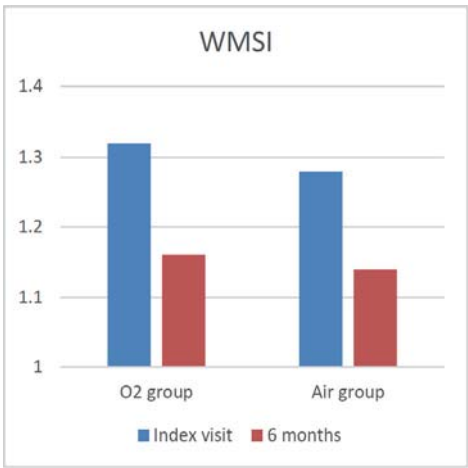
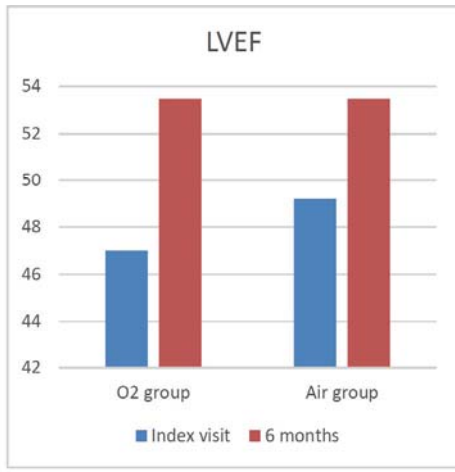


Figure 18 *Study profile.*

3.4.2 Echocardiography

At the index visit, there were no significant differences between the O_2 and air groups in LVEF (47.0 ± 8.5% vs 49.2 ± 8.1%) and WMSI (1.32 ± 0.27 vs 1.28 ± 0.28). Nor were there differences at six months between the O_2 and the air group in LVEF (53.5 ± 5.8% vs 53.5 ± 6.9%) and WMSI (1.16 ± 0.25 vs 1.14 ± 0.24) (Figure 19).





Echocardiography results (mean (SD))	**O_2 group (n=46)**	**Air group (n=41)**	**95% Confidence Interval for difference**	**P-value**
WMSI, index visit	1.32 (0.27)	1.28 (0.28)	-0.1 – 0.2	0.342
WMSI, 6 months	1.16 (0.25)	1.14 (0.24)	-0.1 – 0.1	0.816
LVEF %, index visit	47.0 (8.49)	49.2 (8.06)	-5.8 – 1.3	0.159
LVEF %, 6 months	53.5 (5.82)	53.5 (6.86)	-2.7 – 2.8	0.948

Figure 19 *Effects of O_2 therapy versus room air in STEMI patients as measured by echocardiography at the index visit and at six months.*

3.4.3 Six months Follow-up

At the six months follow-up, the only significant difference between the study groups was that patients in the O_2 group received beta-blockers to a higher degree (97.8% vs 73.2%; $P = 0.001$). Using the subjective health grading tool EQ-5D, the overall health for both groups were similar with no significant differences (Table 3).

Table 3 *Six months follow-up characteristics.*

Characteristics	O_2 group (n=46)	Air group (n=41)	P-value
Patient alive, n (%)	46 (100%)	41 (100%)	-
Readmission for heart failure, n (%)	1 (2.2%)	1 (2.4%)	0.920
Drugs prescribed, n (%)			
ACEi	35 (76.1%)	31 (75.6%)	0.959
Anticoagulant	2 (4.3%)	4 (9.8%)	0.323
ARBs	8 (17.4%)	4 (9.8%)	0.305
Aspirin	43 (93.5%)	38 (92.7%)	0.884
Betablocker	45 (97.8%)	30 (73.2%)	*0.001*
CCB	5 (10.9%)	6 (14.6%)	0.600
Diuretics	4 (8.7%)	7 (17.1%)	0.208
Nitrates	1 (2.2%)	3 (7.3%)	0.245
Other antithrombotic drugs	42 (91.3%)	33 (80.5%)	0.229
Other lipid-lowering medications	1 (2.2%)	2 (4.9%)	0.479
Statins	45 (97.8%)	39 (95.1%)	0.493
EQ-5D, n (%)			
Mobility, > Level 1	7 (15.2%)	8 (19.5%)	0.552
Personal care, > Level 1	1 (2.2%)	3 (7.2%)	0.242
Usual activities, > Level 1	4 (8.7%)	9 (21.9%)	0.057
Pain/Discomfort, > Level 1	13 (28.3%)	12 (29.3%)	0.839
Anxiety/Depression, > Level 1	15 (32.6%)	13 (31.7%)	0.924
Health state, % (SD)	79.1 (17.9)	82.9 (13.1)	0.813

ACEi = Angiotensin Converting Enzyme Inhibitor; ARBs = Angiotensin II Receptor Blockers; CCB = Calcium Channel Blockers.

Chapter 4: Discussion

The aim of this thesis was twofold. One aim was to evaluate how effectively an ANN can diagnose STEMI in ECGs transmitted from the ambulance and predict the need of acute PCI in comparison with the CCU physician. Another aim was to evaluate the effect of O_2 therapy in uncomplicated STEMI patients by determining MaR, IS and MSI measured by CMRI, as well as LVEF and WMSI measured by echocardiography. The main findings of the thesis can be summarized as follows:

Paper I: The ANN had a very good ability to both predict STEMI and the need of acute PCI. The ANN has thus the ability to reduce the number of ECGs transmitted from the ambulance to the CCU.

Paper II: O_2 therapy has been a cornerstone in the treatment of ACS for the last century. There is, however, no consensus in the literature on the positive or negative effects of O_2 therapy is these patients, and randomized controlled studies are therefore needed.

Paper III: There were no significant differences in MaR, IS and MSI between STEMI patients randomized to O_2 or air. This suggests that it is neither beneficial nor harmful to treat normoxic STEMI patients with O_2, and supports that O_2 can safely be withheld.

Paper IV: There were no significant differences in LVEF and WMSI between the O_2 group and the air group at the index visit or at six months. These results further support the conclusion that it is safe withhold O_2-therapy in normoxic STEMI patients.

4.1 Paper I

The large ANN AUROC for both predicting STEMI and the need for an acute PCI, indicates that the number of transmitted ECGs to the CCU can be safely decreased with the use of an ANN. The sensitivity of the ANN was much better than the CCU physician in both predicting STEMI and the need for acute PCI. However, the much lower specificity of the ANN compared with the CCU physician indicates that the ANN cannot be used alone to interpret the transmitted ECGs. The low specificity and PPV makes it vital for a physician to interpret the ECG and make the final decision in order to avoid a large number of patients being unnecessarily sent to the PCI laboratory. The low PPV of the ANN is probably partly related to our low prevalence of STEMI (7%) among the transmitted ECGs, which is lower than in other studies.[195,196]

At least today, only a physician can assess the ECG, pain history and symptoms together for the final decision. There are more diagnoses than AMI that can give a STEMI-like ECG pattern, for example aortic dissection. However, an ANN could be of value as a decision support system for the CCU physician.

Since the ANN was so effective in excluding STEMI (high NPV), it would be possible to create a system in which only ECGs deemed as STEMI by the ANN would be interpreted by the CCU physician. In this way, not only would the number of ECGs transmitted to the CCU decrease with no risk of missing STEMI cases, but the ambulance transport would also be faster with less waiting time for the CCU physician to interpret the ECG.

4.2 Paper II, III and IV

For more than 100 years, O_2 therapy have been a cornerstone in the treatment of AMI. However, our knowledge of the effects of O_2 therapy in patients with AMI including STEMI is incomplete as studies show inconclusive results. Although some studies[104,122,123,197-199] have shown that O_2 therapy may have positive effects on the circulation, new studies indicate that O_2 therapy may have negative cardiovascular effects[83,84,90,120].

AMI is one the most common causes of death in the world with millions of people succumbing to this life-threatening condition every year.[200,201] Since the use of O_2 supplementation is still widespread and common in the management of normoxic patients with AMI, and there is a risk that this supplemental O_2 therapy can be harmful, randomized controlled trials in this matter is important and highly needed. We therefore initiated the SOCCER study, in which we evaluate the effects of O_2

therapy in STEMI patients by CMRI (*Paper III*) and Echocardiography (*Paper IV*), which may contribute to increased knowledge regarding O_2 therapy in AMI patients.

Paper III evaluated the effect of O_2 therapy on MaR, IS and MSI using CMRI, which is the gold standard method to evaluate these measures.[145-147] MSI[167] was chosen as the primary endpoint of the study.

There were no significant differences between the O_2 and air groups in MaR, MSI and IS. Regarding IS, there was no difference both when IS was expressed as absolute volume and as a fraction of the LV mass. This indicates that supplemental O_2 during the ambulance transport does not affect the efficacy of acute PCI in STEMI patients.

Ranchord et al.[119] also found no significant effect of O_2 therapy on the cardiovascular system. The AVOID study,[120] however, showed a small negative effect of O_2 therapy in terms of an increased IS expressed in grams, but there was no significant effect when the IS was expressed as percentage of the LV mass. In comparison to the SOCCER study, both of these studies had some important methodological limitations; Ranchord et al.[119] focused solely in inpatients not taking the pre-hospital treatment, among them supplemental O_2, in consideration. Also the fact that 30 of the 136 patients analyzed by Ranchord et al.[119] received thrombolysis rather than PCI, may have contributed to a skewness in the results. The AVOID study[120] was an open-label study, thus both the patient and the rater was unblinded. Another limitation in the study, was that the CMRI was only performed in patients being well enough and willing to travel to the CMRI site. This limitation may be a source of serious selection and reporting bias.

Our study was the first to evaluate the effects of O_2 therapy with state-of-the-art CMR measurements of MaR and MSI,[150,152,153,160,202] and our results of no acute cardiovascular effects might therefore be viewed as relatively trustable.

In *Paper IV*, we evaluated the effect of O_2 therapy on LVEF and WMSI both at the index visit and at six months after inclusion. This was the first study to evaluate both short-term and medium-term effects of O_2 therapy in STEMI patients. LVEF as well as WMSI were chosen since they both provide important information on both LV function as well as mortality and morbidity.[106,178,179,183-185,188] However, WMSI has been shown to be superior to LVEF to assess LV function.[106,183-185]

There were no significant differences between the O_2 and air groups in WMSI and LVEF at the index visit or at six months. Also, at six months there were no significant difference between the two groups in subjective health status as measured by the EQ-5D. These results confirm and extend our previous results that supplemental O_2 does not affect the efficacy of acute PCI in STEMI patients. The six months follow-up data are important since IS in the acute phase may not correlate with long term outcome.[203]

The combined results from Papers III and IV support that it is safe to withhold supplemental O_2 therapy in normoxic, STEMI patients. We found neither benefit nor harm from O_2 therapy in these patients. Our studies thereby provide a solid evidence base for the current European Resuscitation Council Guidelines stating that O_2 therapy should be initiated in ACS patients only when the patient presents with hypoxia, dyspnea or symptoms of heart failure.[204]

The SOCCER study, however, was not powered to detect differences in clinical events like mortality and morbidity. The Swedish DETO2X-AMI study, however, which included 6629 patients with suspected AMI, showed no significant difference in 1-year mortality in patients randomized to O_2 therapy compared to room air.[139]

4.3 Future Implications

4.3.1 Paper I

Since ANN both in our study as well in other studies has shown to be superior to physicians to predict AMI and ACS,[205,206] ANNs could and should be evaluated with a focus on ACS diagnosis and not merely STEMI. One interesting question is whether troponin blood samples already in the ambulance could enhance the ability of the ANN to rule-in or rule-out ACS.

4.3.2 Paper II, III and IV

More randomized trials are needed to fully understand the effects of O_2 therapy in AMI and ACS patients, i.e. patients with acute myocardial ischemia. These studies should include a large number of patients with complicated as well as uncomplicated AMI and ACS, and should analyze the subgroups STEMI, NSTEMI and UA. Some focus should also be dedicated to clinical events like mortality and morbidity which lacked in the SOCCER study.

Future studies on O_2 therapy should also focus on the role of supplemental O_2 in other patients and settings, e.g. in ischemic stroke and in ICU patients. A recent study on 434 Italian ICU patients showed that patients randomized to conservative O_2 therapy (arterial O_2 saturation of 94-98%) had significantly lower mortality, liver failure and bacteremia than those receiving standard O_2 therapy (O_2 saturation 97-100%).[207]

Other areas that could be the focus of future research are the question of placebo effects[208] of O_2 therapy, and the question of cost of O_2 therapy. Until June 15, 2017

there was not a single paper in PubMed (search phrase (oxygen therapy[Title]) AND placebo[Title/Abstract]) which discussed possible placebo effects of oxygen therapy in patients with chest pain, ACS or AMI. While a placebo effect of O_2 therapy on MaR, IS, MSI, LVEF and WMSI seems unlikely, there may well be a placebo effect on the patient's overall well-being. In discussing the issue of cost and cost-effectiveness, Fitterman[209] stated in a commentary in JAMA Internal Medicine, that O_2 therapy in STEMI patients in only the USA, may cost as much as 100 million dollars annually, thus showing the importance of studies on the matter of O_2 therapy in STEMI patients.

Chapter 5: Limitations

5.1 Paper I

Only one ambulance district and one hospital was studied. The performance of the ANN may thus not be generalizable to other districts and hospitals.

One-hundred-eighty-three ECGs could not be collected because of technical and other problems. These problems were randomly distributed and unrelated to patient characteristics, so we believe that the risk of ECGs altering the results is low.

Because of the lack of follow-up of patients not deemed to have a STEMI by the CCU physician, and thus transported to the ED, there is a risk that both the CCU and ED physicians missed a STEMI. This risk is, however, very low since the ED physician assessed the patient in person and had access to both the prehospital and the ED ECGs.

5.2 Papers II, III and IV

The SOCCER study was relatively small, only conducted at two hospitals, and only included stable STEMI patients. The results may thus not be applicable to other hospitals and settings, and also not to other forms of ACS like NSTEMI and UA.

The mean time of receiving O_2 therapy was close to 90 minutes. A longer O_2 therapy time may have altered the results. However, the time of the dose of the O_2 therapy was the same as in routine care.

Although the SOCCER study was blinded to the patients, the ambulance personal as well as the CCU staff were not blinded to the study allocation. The treatment of the patients may therefore have been influenced to some extent, but our combined management data for the patient groups suggest that this was not the case.

One serious limitation in *Paper III* is the large number of patients not undergoing CMR. We cannot exclude that this was a source of bias, but we consider the risk of this as small. Most of the patients not undergoing CMR were prevented from this by technical/logistical issues, unrelated to patient characteristics.

Chapter 6: Conclusions

6.1. Paper I

The large AUROC indicates that the ANN has a great ability to identify STEMI and recommend acute PCI in ECGs transmitted from chest pain patients in the ambulance. The ANN can thus contribute to a faster diagnosis and triage of STEMI patients in need of acute PCI, and if built into the electronic system, may safely reduce the number of ECGs transmitted to the CCU physician.

6.2 Papers II, III and IV

Paper II. The effects of O_2 therapy in AMI patients are unclear, and the results from the literature are partly conflicting. Based on the current knowledge, we designed the SOCCER study which is described in this paper. The results of the SOCCER study are presented in *Paper III* and *IV*.

Paper III. We found no effects of O_2 therapy on MaR, MSI and IS as measured by CMR in STEMI patients undergoing acute PCI.

Paper IV. There were also no effect of O_2 therapy on WMSI and LVEF as measured by CMR in STEMI patients.

Taken together, these results firmly support the safety of withholding O_2 therapy in normoxic STEMI patients.

Chapter 7: References

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The doctor`s aim is to do good,
even to our enemies,
so much more to our friends…

Zakaria Razi[2]

[2] Zakaria Razi (854-925/935), also called Rhazes in the western world, was a known Iranian physician, alchemist and philosopher. He discovered alcohol, and is known to have been the first to describe several medical conditions. Razi was also the first to discuss the theory of acquired immunity.

Paper I

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An artificial neural network to safely reduce the number of ambulance ECGs transmitted for physician assessment in a system with prehospital detection of ST elevation myocardial infarction

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Abstract

Background: Pre-hospital electrocardiogram (ECG) transmission to an expert for interpretation and triage reduces time to acute percutaneous coronary intervention (PCI) in patients with ST elevation Myocardial Infarction (STEMI). In order to detect all STEMI patients, the ECG should be transmitted in all cases of suspected acute cardiac ischemia. The aim of this study was to examine the ability of an artificial neural network (ANN) to safely reduce the number of ECGs transmitted by identifying patients without STEMI and patients not needing acute PCI.

Methods: Five hundred and sixty ambulance ECGs transmitted to the coronary care unit (CCU) in routine care were prospectively collected. The ECG interpretation by the ANN was compared with the diagnosis (STEMI or not) and the need for an acute PCI (or not) as determined from the Swedish coronary angiography and angioplasty register. The CCU physician's real time ECG interpretation (STEMI or not) and triage decision (acute PCI or not) were registered for comparison.

Results: The ANN sensitivity, specificity, positive and negative predictive values for STEMI was 95%, 68%, 18% and 99%, respectively, and for a need of acute PCI it was 97%, 68%, 17% and 100%. The area under the ANN's receiver operating characteristics curve for STEMI detection was 0.93 (95% CI 0.89-0.96) and for predicting the need of acute PCI 0.94 (95% CI 0.90-0.97). If ECGs where the ANN did not identify a STEMI or a need of acute PCI were theoretically to be withheld from transmission, the number of ECGs sent to the CCU could have been reduced by 64% without missing any case with STEMI or a need of immediate PCI.

Conclusions: Our ANN had an excellent ability to predict STEMI and the need of acute PCI in ambulance ECGs, and has a potential to safely reduce the number of ECG transmitted to the CCU by almost two thirds.

Background

Reducing time to reperfusion treatment for patients with ST-segment elevation myocardial infarction (STEMI) improves patient outcomes [1-3], and every delay to primary percutaneous coronary intervention (PCI) increases long term mortality [4]. The recording of a pre-hospital 12-lead ECG in chest pain patients reduces time to PCI [5] and is an established tool to accelerate correct and timely management [6].

In order not to miss any STEMI cases, it is recommended that all ambulance-transported patients with symptoms suggesting acute coronary syndrome (ACS) have an ECG transmitted to the coronary care unit (CCU) physician on call. However, this extends the ambulance transport time in patients without STEMI [5], and could, if many ECGs are transmitted,

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overburden the CCU physician. A system where ECGs with a very low probability of STEMI are not transmitted would be highly useful.

Decision support tools based on artificial neural networks (ANNs) has been shown to improve junior doctors' detection of STEMI [7], to be superior to commercially available interpretation programs [8] and to be at least as good as experienced physicians to predict ACS [9] and myocardial infarction (MI) [8,10]. However, ANNs to predict STEMI have not yet been prospectively validated and compared with the real-time interpretation of CCU physicians in routine care. To our knowledge, ANNs predicting the need of acute PCI have not been presented.

The aim of this study was to examine the ability of an ANN to identify ambulance ECGs with a very low probability of STEMI and need of acute PCI, and to safely reduce the number ECGs transmitted to the CCU physician.

Methods

Study Population

Skåne University Hospital at Lund is a 900 bed institution with a primary catchment area of some 300 000 inhabitants, an ambulance district of about 300 000 inhabitants, and in-house PCI and coronary bypass surgery available 24 hours/day. When pre-hospital personnel suspect an ACS, a 12-lead ECG is recorded in the ambulance and electronically transmitted to the Lund CCU. The CCU physician evaluates the ECG for STEMI and decides whether or not to directly transport the patient to the PCI facility at Lund. Otherwise, the patient is transported to the nearest ED.

The CCU physician has instant access to the Region Skåne database of previously recorded ECGs and to the computerized patient records at Skåne University Hospital. The CCU physician may also in some cases call the ambulance personnel and hear a brief patient history. During the study, if the CCU physician was briefly unavailable, an experienced CCU nurse read the ECG, made the triage decision and had the decision approved by the CCU physician shortly after. Thrombolysis for STEMI was rarely, if ever, performed.

Data collection

Between 30 August 2005 and 18 February 2006, ambulance ECGs were registered 24/7 by the CCU physicians on call at Skåne University Hospital at Lund. For each ECG the physician documented, in real-time on special forms, the identification (Y/N) of ST changes or left bundle branch block indicating a STEMI in the received ECG, as well as the decision (Y/N) to let the ambulance transport the patient directly to primary PCI. All patients deemed to have a STEMI were thus not transported directly to the PCI facility (e.g. due to terminal illness), and some patients without STEMI were transported to the PCI facility due to a suspected need of acute PCI for other causes. During the study period, a significant ST elevation was defined as an ST elevation in at least two adjacent leads ≥ 2 mm in V1-V3 and ≥ 1 mm in all other leads. The ambulance ECG was saved in the Lund ECG database.

Using the statistical software ClickView (ClickTech, Sweden), clinical data for each patient was extracted from the computerized patient records at Skåne University Hospital (Melior™, Siemens). Coronary angiography data was retrieved from the Swedish coronary angiography and angioplasty register (SCAAR) [11].

The study was approved by the regional ethics committee at Lund.

Electrocardiography

The 12-lead ECGs in the study were recorded using computerized ECG recorders from Ortivus AB (Danderyd, Sweden) in the ambulances and Siemens-Elema AB (Solna, Sweden) in the ED. The ED ECGs (training set, see below) were traditional 12-lead ECGs with distal placement of the limb leads whereas the ambulance ECGs (testing set) had proximal placement of the limb leads ("the Lund system") [12]. This changes the waveforms slightly, but these changes have been considered clinically acceptable [12].

For the ANN, the following 13 measures were extracted from each lead: Q, R, and S amplitudes; QRS area; QRS duration; positive and negative T amplitudes; along with amplitudes of six different positions from the ST segment. In total 12 × 13 = 156 variables were created and further reduced down to 20 by principal component analysis. Reducing the number of variables used in the model in this way is warranted since there is a high degree of correlation between the measurements extracted from the 12-lead ECG. The remaining 20 variables were then normalized into Z-scores before they were used as inputs to our neural network ensemble.

Artificial neural network ensembles

Several artificial neural networks were combined into an ensemble by bagging. The final ensemble consisted of 25 individually trained neural networks, which has been found to be sufficient in numerical studies. The ensemble prediction was calculated by averaging the outputs of its individual members. Each network consisted of a fully connected feed-forward multilayer perceptron with one hidden layer featuring 15 nodes. The networks were trained using a cross-entropy error function with an added weight elimination term that has the ability to improve generalization by controlling the complexity of the network via a tunable constant. The value of this

constant, along with the number of hidden nodes, was selected through a cross-validation run on the training set. For a more general introduction to artificial neural networks see Bishop [13]. All neural networks computations were performed using in-house software.

The neural network was trained on 3000 ECGs (training set) from patients attending the ED at Skåne University hospital between 1990 and 1997 [7]. The ECGs indicating ST elevation Myocardial Infarction (STEMI) were identified by two experienced cardiologists. The ANN was only trained to detect STEMI ECG changes and not trained on coronary angiogram findings. In the present study however, the ability of the ANN to predict significant coronary artery disease on angiography was also tested (Results).

For calculation of specificity and predictive values for the ANN, the sensitivity for detecting STEMI was set to 95%. This somewhat arbitrary level was chosen in order to achieve comparable performance as with ED evaluation, where some 2-5% of the ACS patients are erroneously discharged from the ED [14,15], which implies a sensitivity of at least 95%.

Expert consensus ECG interpretations

Two physicians highly experienced in ECG reading (UE and SJ) acted as the ECG reference standard and separately classified all 560 ECGs into: 1) ST changes/left bundle branch block as in STEMI or 2) Not STEMI. In addition to using the above mentioned ECG criteria for STEMI, these physicians also considered the configuration of the ST segment as in the clinical routine interpretation of ECGs. To somewhat mimic the situation of the CCU physician, patient records from the ambulance were available to the expert ECG interpreters. The experts made the same primary classification in 493 of the 560 ECGs. For the discrepant cases, a consensus classification was made.

Definitions of outcomes

In this study, a STEMI was defined as a discharge diagnosis of ACS together with an ECG with ST changes/left bundle branch block as in STEMI according to the two ECG experts. The final discharge diagnose (ACS or not) was recorded from the discharge record (which included ICD10 codes) made by the ward physician and reviewed for quality by the responsible specialist ward physician, or, for patients not admitted to in-hospital care, by the responsible ED physician. The diagnostic criteria for ACS (acute myocardial infarction; AMI, or unstable angina pectoris; UA) were those recommended by the European Society of Cardiology/American College of cardiology [16] using Troponin T as the critical biomarker with a cut-off at 0.05 μg/l.

AMI was diagnosed in patients with at least one troponin T ≥ 0.05 μg/l with rising or falling on serial testing, who also had typical ischemic symptoms and/or significant ischemic ECG changes (pathological Q-wave, ST elevation, ST depression or T-wave inversion). UA was diagnosed in patients with typical ischemic symptoms with or without ischemic ECG changes and with or without slightly elevated (below AMI decision level) troponin T levels.

The need of an acute PCI was in this study defined as the patient undergoing an acute coronary angiography within 12 h after the pre-hospital ECG, with a balloon angioplasty performed due to a culprit lesion or significant coronary disease.

Statistical analysis

Continuous variables are expressed as mean ± SD and were compared by the independent samples *t* test. Analysis for categorical variables was performed using chi-square test or Fisher exact test where appropriate. The area under the receiver-operating-characteristic curve (AUROC) was used as an overall measure of the predictive ability of the ANN. Statistical analyses were performed using SPSS 16.0.1 (SPSS Inc, Chicago, U.S.). Exact confidence intervals were calculated for sensitivity and specificity using the Clopper-Pearson method.

Ethical approval

The Regional Ethics Committee at Lund approved the study.

Results

Transmitted ECGs and patient characteristics

Of the registered 743 ECGs, 560 ECGs were successfully retrieved from the local electronic ECG database and were included in the final analysis (Figure 1). Patient characteristics are given in table 1. There were no significant differences in age or ACS prevalence between the cases with missing (n = 183) and retrieved ECGs. Of the 560 ECGs, 118 were evaluated at the CCU by a specialist in cardiology, 184 by a specialist in internal medicine, 227 by a resident, and 31 initially by a CCU nurse.

Predictive performances of the ANN and the CCU physician

The predictive performances of the ANN as compared to the CCU physician are given in Table 2. If the sensitivity of the ANN was set to the same level as the CCU physician (0.74) the specificity of the ANN for STEMI and a need of acute PCI was 0.90 (95% CI 87-93%) and 0.90 (95% CI 87-93%), respectively. The AUROC of the ANN was 0.93 (95% CI 0.89-0.96; Figure 2) for the ability to detect STEMI, and 0.94 (95% CI 0.90-0.97; Figure 3) for predicting the need of acute PCI.

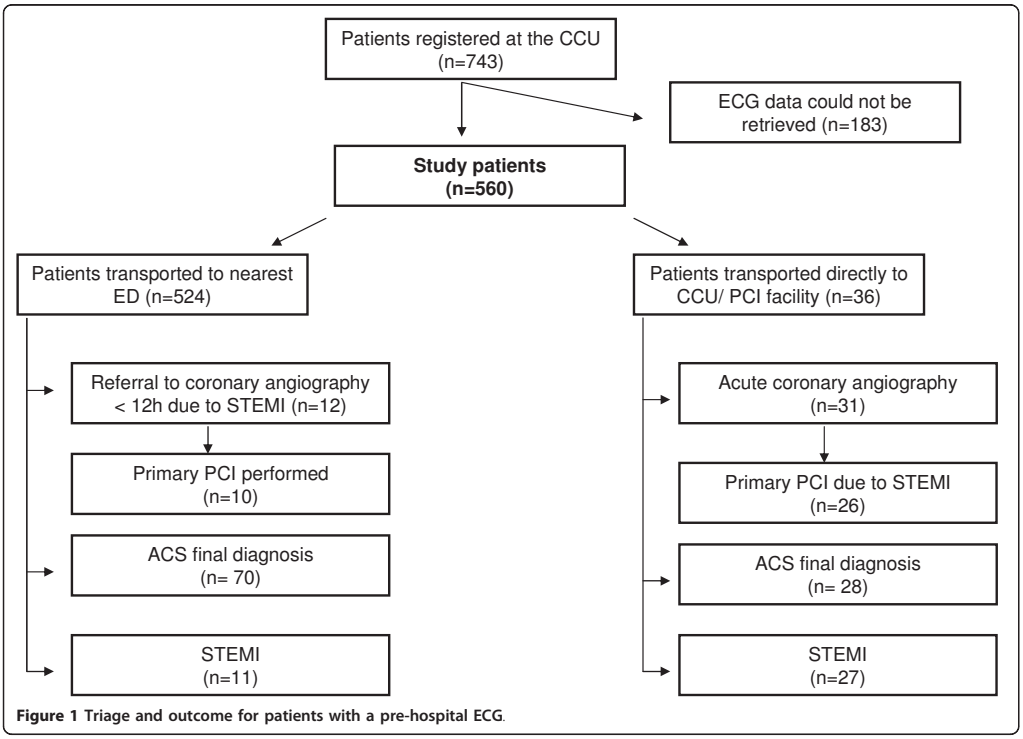

Figure 1 Triage and outcome for patients with a pre-hospital ECG.

When the ANN was set to 95% (95% CI 82-99%) sensitivity for STEMI, it had 97% (95% CI 85-100%) sensitivity for the need for acute PCI.

Patients with STEMI or a need of acute PCI not identified by the ANN

With the STEMI sensitivity set to 95%, the ANN missed two patients with STEMI. None of these patients had ECGs that were classified as STEMI by the CCU physician, and none underwent an acute PCI.

With this ANN setting, the ANN missed one patient without STEMI who needed an acute PCI. This patient was also missed by the CCU physician, i.e. the patient was triaged to the ED. Due to progressing ECG changes the patient underwent an acute PCI 3 h and 48 min after the prehospital ECG recording.

Patients identified correctly only by the ANN

Eight patients with STEMI were correctly identified by the ANN, but not classified as STEMI by the CCU physician.

In eight patients with a need of acute PCI, the CCU physician neither referred the patient to an acute PCI nor classified the patients as having a STEMI. Only one of these patients had a STEMI according to the

Table 1 Patient characteristics, n = 560.

Age, years ± SEM	70.1 ± 0.6
Women	249 (45%)
Patients admitted to in-hospital care	417 (74%)
Length of stay of admitted patients, days ± SD	4.5 ± 6.2
ACS as final diagnosis	98 (18%)
STEMI	38 (7%)
Acute coronary angiography within 12 hours due to suspicion of STEMI	43 (8%)
Primary PCI within 12 h from pre-hospital ECG	36 (6%)

Table 2 Predictive performances of the CCU physician and the ANN.

	Sens	Spec	PPV	NPV
Predicting STEMI				
ANN	0,95 (0,82-0,99)	0,68 (0,63-0,73)	0,18 (0,13-0,23)	0,99 (0,98-1,00)
CCU physician	0,74 (0,57-0,87)	0,98 (0,97-0,99)	0,76 (0,59-0,088)	0,98 (0,97-1,00)
ANN and CCU physician*	0,74 (0,57-0,87)	0,99 (0,98-1,0)	0,80 (0,63-0,92)	0,98 (0,97-0,99)
Predicting need of acute PCI				
ANN	0,97 (0,85-1,0)	0,68 (0,63-0,72)	0,17 (0,12-0,23)	1,0 (0,98-1,00)
CCU physician	0,78 (0,61-0,90)	0,98 (0,97-0,99)	0,76 (0,59-0,89)	0,98 (0,97-0,99)
ANN and CCU physician*	0,78 (0,61-0,90)	0,99 (0,98-1,0)	0,80 (0,63-0,92)	0,98 (0,97-0,99)

Sens; sensitivity, Spec; specificity, PPV; positive predictive value, NPV; negative predictive value *Theoretical diagnostic performances if only ECGs in which the ANN predicted STEMI were to be transmitted to the CCU physician.

definition in this study, but, interestingly, seven of these patients were identified by the ANN.

Effects of ANN screening before ECG transmission to the CCU

If ambulance ECGs where the ANN did not identify a STEMI or a need of acute PCI were theoretically to be withheld from transmission, the number of ECGs evaluated in the CCU could have been reduced from 560 to 204 (by 64%) without missing any case with STEMI or a need of immediate PCI. The serially combined predictive performance of the ANN and the CCU physician is shown in Table 2.

Discussion

In this study, we present an ANN with the ability to predict STEMI and a true need for acute PCI in prehospital chest pain patients. The large ANN AUROCs (0.93

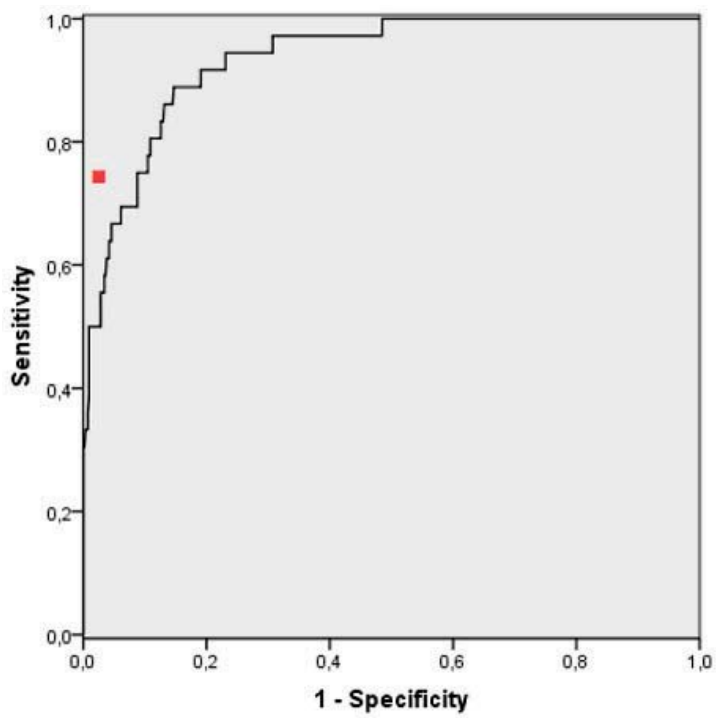

Figure 2 Receiver operating characteristics curve for ANN prediction of STEMI in 560 ambulance patients with symptoms suggesting ACS. AUROC = 0,93 (95% CI 0,89-0,96). The red dot indicates the performance of the CCU physician in predicting STEMI.

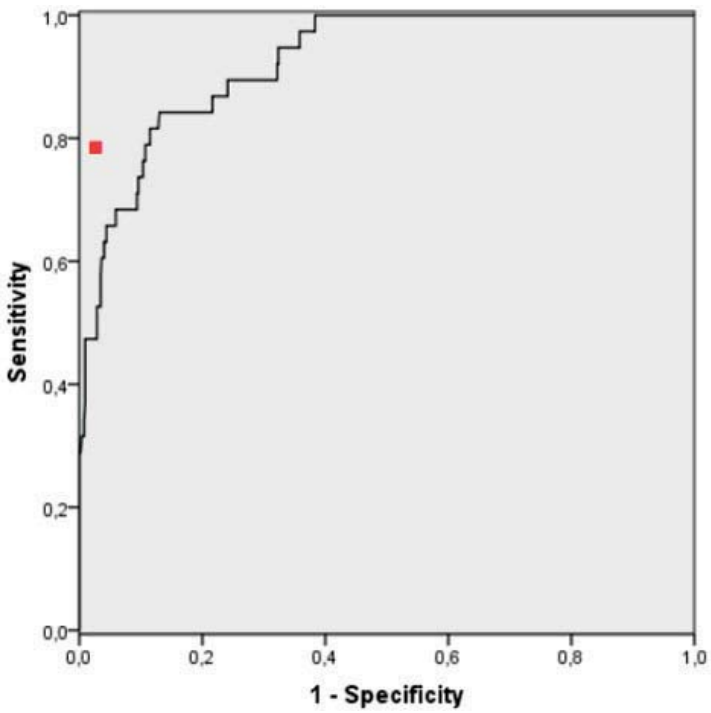

Figure 3 Receiver operating characteristic curve for ANN prediction of the need of acute PCI within 12 hours in 560 patients with symptoms suggesting ACS. AUROC = 0,94 (95% CI 0,90-0,97). The red dot indicates the performance of the CCU physician in predicting the need of acute PCI.

and 0.94 for detecting STEMI and need of acute PCI) imply an excellent predictive ability, which could potentially be used to safely reduce the number of ambulance ECGs sent to the CCU by almost two thirds. To our knowledge, the present study is the first to demonstrate a decision support tool that can predict the presence of a culprit lesion or significant coronary artery disease.

At a STEMI sensitivity of 95%, the sensitivity of our ANN for a need of acute PCI was as high as 97% which was clearly better than the 74% sensitivity of the CCU physician. Among eight patients with a need of acute PCI missed by the CCU physician, the ANN correctly identified seven. However, the specificity of the ANN was only 68%, and the positive predictive value (PPV) in our population only 18%.

Should the ANN be implemented in a prehospital ECG system, a final ECG interpretation and triage decision by a physician is therefore clearly needed to avoid unnecessary catheterization laboratory activation. Pain history and symptoms suggesting other causes (e.g. aortic dissection) of chest pain, co-morbidities and CCU bed/PCI availability are usually important information for the final triage decision, and a high specificity in the triage decision is also needed because coronary angiographies carry a risk of complications. The low PPV of the ANN was of course also related to the STEMI prevalence of only 7%, which is lower than reported by Sejersten et al. (28%) [5] and Clark et al. (34%) [17]. This indicates a very low threshold among the ambulance personnel to transmit an ECG. The STEMI prevalence in our material was in fact comparable to the estimated real prevalence in the prehospital setting [18].

In Table 2, the serially combined predictive performance of the ANN and the CCU physician is shown. These data are based on a system where the decisions of the CCU physician are not influenced by the ANN. As output, our ANN generates a likelihood of STEMI/need of acute PCI. Should this information be available to the CCU physician, we believe it is likely that the serially combined performance would improve towards the

higher sensitivity of the ANN. If so, the ANN would enable the physician to miss fewer patients with STEMI and a need of acute PCI. In this way, eight of the 36 patients (22%) in need of acute PCI that was not detected by the CCU physician could theoretically have had the time to reperfusion reduced if the ANN results were available to the CCU physician. The true effects of our ANN in such a system remain to be established.

Methods to safely reduce the number of ECGs transmitted to the CCU could include ECG interpretation by 1) the ambulance personnel, 2) computer programs with rule-based interpretation or 3) ANN computer programs. Studies indicate that ambulance paramedics can reliably interpret the ECG [19], but this requires additional training for all personnel. Also, the number of false negative cases in routine care has to our knowledge not been reported. Studies of rule-based ECG interpretation programs in routine care have shown a sensitivity and specificity for STEMI of 78% and 91-94% [17] respectively, thus missing about 1 in 5 STEMI cases. When our ANN was set to 95% sensitivity it did not miss any STEMI case that was detected by the CCU physician.

When setting the ANN to the sensitivity of the CCU physician, the ANN specificity for STEMI was lower (0.91 vs 0.98). In this prospective routine care study, and at the sensitivity of the CCU physician, we could thus not confirm the reported superior STEMI prediction by an ANN compared to physicians in retrospective ECGs [8]. There might be at least two reasons for this. First, the CCU physician had access to previous ECGs, medical records and a brief clinical history, which should have improved specificity when predicting STEMI. Evaluating also previous ECGs have been shown to improve physicians' specificity for STEMI and to reduce CCU admissions [20]. Feeding also a previous ECG to the ANN, if technically feasible, could be a way of improving the ANN's specificity. In a previous study, the ability of an ANN to predict AMI was significantly improved when a previous ECG was supplied together with the new ECG [21]. The benefit of previous ECGs should even be larger when predicting STEMI than when predicting AMI, since ECG changes are less specific in the average AMI case. Secondly, the ANN was not trained on prehospital ECGs. In addition to the slightly different ECG appearance with the prehospital lead placement, the performance of our ANN could be reduced by the sometimes poorer technical quality of the prehospital ECG compared to the in-hospital ECGs in the training set.

The clearly higher specificity than sensitivity of the CCU physicians in routine care in this and other studies [5,17] may seem surprising, but should be viewed in the context of a constant bed shortage in the CCU and high catheterization laboratory utilization, which forces the physicians to focus on specificity more than sensitivity. The reasoning is that the patient can always be secondarily transferred from the ED to the CCU of to acute PCI.

Among the present ambulance patients, 98 (18%) had ACS as the final discharge diagnosis. ANNs have been shown to be superior to experienced cardiologists to predict both MI and ACS [8]. In the prehospital setting, an ANN could therefore not only be used to predict STEMI and a need of PCI, but also ACS. This could potentially improve the pre-hospital triage of chest pain patients and contribute to a more timely ACS treatment, perhaps especially if cardiac biomarkers in the ambulance were also analyzed [22].

Clinical implications

If the high diagnostic performance of our ANN is confirmed in other cohorts, we believe that it could be used to reduce the number of ambulance ECG's transmitted for expert interpretation in patients with symptoms suggesting ACS. The ANN interpretation will be available instantly, and if STEMI is not detected, transport to the nearest ED could be initiated without delay. It is even possible that a fast and easy ANN interpretation would increase the number of prehospital ECGs registered, and increase the number of STEMI patients identified already in the ambulance. If the ANN suggests a STEMI or a need of acute PCI, the ECG should be transmitted to a cardiologist for interpretation and a final triage decision. If introduced, there is of course a risk that ECG interpretation skills could decrease among EMS staff. However, future ANNs could perhaps explain their interpretations and instead help educate the EMS staff [23].

Limitations

The ANN was evaluated in only one pre-hospital district, and the predictive performance of the ANN and the potential reduction in the ECGs sent to the CCU are therefore not necessarily generalizable to other districts. This ANN should not be clinically applied outside our district before validation in new cohorts.

We were unable to retrieve 183 ECGs due to 1) technical problems when trying to save the ECG, 2) ECG could not be saved because the patient was not a Swedish citizen or not reliably identified, or 3) the CCU nurse did not save the ECG to the database. The ACS prevalence was not significantly different among patients with and without saved ECGs, and it is unlikely that missing these ECGs had any significant effect on the results.

No follow-up of patients discharged from the ED was performed in this study. Some patients with STEMI and

a need of PCI might therefore have been missed both by the CCU physician and the ED physician, and discharged home from the ED. Although we cannot completely exclude this possibility, we consider it highly unlikely since the ED physician had access to both the prehospital and the ED ECG.

Conclusions

In the present study, we demonstrate for the first time an ANN with an ability to predict a true need for an acute PCI. The AUROC was large indicating an excellent overall predictive performance. Set to a high sensitivity, the ANN could be used to identify patients with a very low likelihood of a STEMI or a need of acute PCI, where the ECG does not need to be sent to the CCU physician for assessment. Using the ANN in this way could potentially reduce the number of ECG transmitted to the CCU by almost two thirds without missing any patient needing an acute PCI.

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Authors' contributions

JLF participated in the design of the study, data acquisition, data analysis, and wrote the manuscript. AK collected and analysed data. MG and MO constructed the ANN model. JB participated in the statistical analysis. SJ made the expert ECG interpretations. LE participated in the design of the study. UE participated in the conception and design of the study, expert ECG interpretation, managed the project and wrote the manuscript. All authors have contributed with critical revisions of the manuscript and have read and approved the final version.

Competing interests

The authors declare that they have no competing interests.

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Paper II

Original Research – Clinical Trial Design

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

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.

Background

Oxygen (O_2) is a cornerstone in the emergency treatment of all serious medical conditions, including acute myocardial infarction (AMI). Although recent guidelines [1–6] stress the lack of evidence for routine oxygen administration to patients with AMI, standard emergency care concepts like MedicALS [7] and other international guidelines [8–11] prescribe immediate administration of

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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 [12–14]. 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) [12–14]. Furthermore, during O_2 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 O_2 in blood have rarely been measured but have been estimated via indirect techniques [12–14]. 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 [16–19]. Recent reviews stress the need for solid clinical trials [16–20].

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 $(1 - IS/MaR) \times 100\%$. 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.

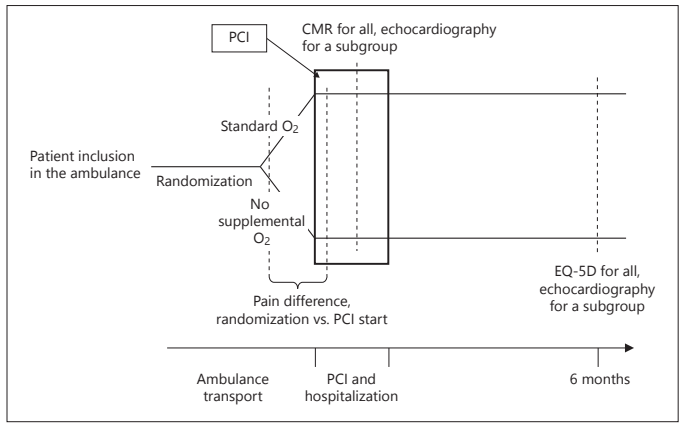

Fig. 1. Study design.

Table 1. Endpoints

Primary endpoint
– MSI on CMR
Secondary endpoints
– IS on CMR
– MaR on CMR
– Ejection fraction on CMR
– Microvascular obstruction on CMR
– Pain difference (visual analog scale) at randomization vs. at PCI balloon inflation start
– Doses of opioids (substance and mg) and β-blockers (substance and mg) given before and during the PCI
– SaO_2 change from inclusion to PCI start
– IS as measured in hospital with the area under the tropinin T curve (first 24 h)
– ST-segment elevation resolution
– TIMI flow during PCI
– Use of heart failure medications (e.g. β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, digoxin, and sinus node inhibitors) at 6 months
– Subjectively perceived health (EQ-5D) at 6 months
Secondary endpoints for the echocardiography subgroup
– WMSI on echocardiography
– Assessment of remodeling by quantification of LV volumes, LVEF, and WMSI at index hospitalization to 6 months

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
– STEMI patients transported via ambulance and accepted for primary PCI at Skåne University Hospital in Lund or Malmö	– Previous AMI – Inability to make the decision to participate; dementia and the like
– Symptom duration less than 6 h	– For CMR: significant claustrophobia, prostheses or other magnetic material inside the body
– Normal blood oxygen saturation (≥94%) measured with a pulse oximeter	
– Informed consent	

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_2 retention. 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% [29–32] 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 $(1 - IS/MaR) \times 100\%$.

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

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 [12–14, 16–19, 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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Paper III

Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: the randomized SOCCER trial

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Objective **Recent studies suggest that administration of O_2 in patients with acute myocardial infarction may have negative effects. With the use of cardiac MRI (CMR), we evaluated the effects of supplemental O_2 in patients with ST elevation myocardial infarction (STEMI) accepted for acute percutaneous coronary intervention (PCI).**

Materials and methods **This study was a randomized-controlled trial conducted at two university hospitals in Sweden. Normoxic STEMI patients were randomized in the ambulance to either supplemental O_2 (10 l/min) or room air until the conclusion of the PCI. CMR was performed 2–6 days after the inclusion. The primary endpoint was the myocardial salvage index assessed by CMR. The secondary endpoints included infarct size and myocardium at risk.**

Results **At inclusion, the O_2 ($n = 46$) and air ($n = 49$) patient groups had similar patient characteristics. There were no significant differences in myocardial salvage index [53.9 ± 25.1 vs. 49.3 ± 24.0%; 95% confidence interval (CI): − 5.4 to 14.6], myocardium at risk (31.9 ± 10.0% of the left ventricle in the O_2 group vs. 30.0 ± 11.8% in the air group; 95% CI: − 2.6 to 6.3), or infarct size (15.6 ± 10.4% of the left ventricle vs. 16.0 ± 11.0%; 95% CI: − 4.7 to 4.1).**

Conclusion **In STEMI patients undergoing acute PCI, we found no effect of high-flow oxygen compared with room air on the size of ischemia before PCI, myocardial salvage, or the resulting infarct size. These results support the safety of withholding supplemental oxygen in normoxic STEMI patients.** ***European Journal of Emergency Medicine*** **00:000–000**

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Keywords: acute myocardial infarction, cardiology, cardiovascular MRI, emergency medicine, oxygen therapy

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Introduction

For many years, oxygen (O_2) has been central in the treatment of patients with acute myocardial infarction (AMI). The common assumption is that supplemental O_2 increases O_2 delivery to the ischemic myocardium, hence limiting or reducing ischemia and the risk of arrhythmias [1]. However, studies suggest that supplemental O_2 may have negative cardiovascular effects, such as increasing blood pressure and systemic vascular resistance, as well as increasing infarct size (IS) in patients with AMI [2]. In a study on healthy individuals using cardiac MRI (CMR), 15 l O_2/min reduced left ventricular (LV) perfusion and cardiac output by 23 and 10%, respectively [3].

Recently, two clinical trials have studied the effects of supplemental O_2 on IS in patients with reperfused ST elevation myocardial infarction (STEMI). Ranchord *et al.* [4] found that high-flow versus titrated O_2 had no effect on IS assessed by troponin T (TnT). In the AVOID trial [5], high-flow O_2 versus room air increased IS as measured with creatine kinase, but not when analyzed with troponin I. In a subgroup of patients at 6 months, IS assessed with CMR was larger in the O_2 group when measured in absolute volume, but not when expressed as a percentage of the LV. The effects of O_2 treatment in patients with AMI are thus still unclear.

In the present study, we describe the results of the Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) trial. We used CMR to evaluate the effects of supplemental O_2 on myocardial salvage index (MSI), myocardium at risk (MaR), and IS

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in STEMI patients treated with acute percutaneous coronary intervention (PCI). MSI was chosen as the primary endpoint as the prognosis of patients with STEMI is closely related to the amount of myocardial salvage [6].

Materials and methods

The SOCCER study was carried out at the Skåne University Hospitals in Lund and Malmö in southern Sweden. The study was an investigator-initiated, single-blind, parallel-group, randomized-controlled trial with no commercial funding. The trial was approved by the regional Ethical Review Board in Lund (Dnr 2011/258) and the Swedish Medical Products Agency (EudraCT No. 2011-001452-11; ClinicalTrials.gov Identifier: NCT01423929). This study is reported in accordance with the CONSORT statement [7].

The study design and methods of the SOCCER trial have been published previously [8], and are only briefly described below.

Patient inclusion and management

Patients with STEMI, symptom duration less than 6 h, and normal O_2 saturation (defined as $\geq 94\%$), who were accepted for acute PCI at the Skåne University Hospitals in Lund or Malmö, were included after verbal consent in the ambulance. The patients included were randomized 1 : 1 to administration of either standard O_2 therapy (10 l/min; 'O_2 group') or no supplemental O_2 ('air group') by an open design OxyMask [9] until the end of the PCI. For randomization details, please see reference [8]. All patients thus had an OxyMask fitted, but in the air group, the tubing from the mask was not connected to the oxygen outlet. The patients were not informed of their group allocation and were kept blinded as far as possible. The OxyMask was chosen because it causes a negligible increase in dead space and no CO_2 retention.

Exclusion criteria were previous AMI and patient inability to make a decision to participate, for example dementia. Within 72 h after the PCI, the patient was approached by a study physician and provided informed consent in writing. At this point, patients with severe claustrophobia or implanted magnetic material were excluded.

In every aspect apart from the study intervention, patients received standard care in the ambulance. The patient's blood O_2 saturation was measured continuously from inclusion until the end of the PCI. If it decreased below 94% in the ambulance or in the PCI lab, O_2 therapy was initiated according to standard care (10 l/min). After termination of the PCI and the study intervention, standard care was provided at the cardiac care unit by personnel blinded to the patient's group allocation. According to the standard cardiac care unit protocol, supplemental O_2 was only administered to patients with O_2 saturation of up to 90%.

At days 2–6 after the PCI, all patients underwent CMR to determine MaR (the ischemic region before the PCI) IS, and MSI calculated as $(1 - \text{IS/MaR}) \times 100\%$.

Data collection

The ambulance and PCI laboratory personnel noted the patient management on case report forms later registered electronically in the study database. All other in-hospital data on management and outcomes including adverse events, laboratory results, and ECG were retrieved from the computerized patient records of Region Skåne (Melior; Siemens, Erlangen, Germany) and from the SWEDEHEART quality registries RIKS-HIA and SCAAR [10].

Cardiac MRI

The patients included underwent CMR in either Malmö (Siemens 1.5T Avanto, Erlangen, Germany) or Lund (Philips 1.5T Achieva, Best, Netherlands or Siemens 1.5T Aera, Erlangen, Germany), in the standard three long-axis images (two-chamber, four-chamber, and LV outflow tract views), and a stack of short axis images covering the entire LV during breath-holds. The imaging details and the process of quantifying MaR and IS are described elsewhere [8,11,12]. Infarct quantification by CMR is affected by the methodology used [13]. In this study, we used a validated semi-automatic algorithm [12] that has been shown to have no significant bias compared with histochemical staining 1 week after infarction [14, 15]. The analysis of the images was carried out using the postprocessing software Segment, v.1.9 R3084 [16] by a physician blinded to all clinical data, including the patient's study group allocation. A similarly blinded senior physician (M.C.; specialist clinical physiologist) reviewed all image assessments for quality before the statistical analyses and had the final word.

Statistical analysis

The primary endpoint was MSI on CMR and the main secondary endpoints were MaR and IS on CMR. All analyses were carried out on an intention-to-treat basis by researchers blinded to the group allocation. Missing data resulted in exclusion of the patient in the analysis at hand. For continuous variables, mean and SD are described, and for differences in CMR results between the study groups, 95% confidence intervals are given. The groups were compared with respect to our endpoints using two-sided Mann–Whitney tests, with a P less than 0.05 considered as statistically significant. All data were analyzed using Microsoft Excel; Redmond, Washington, USA and IBM SPSS Statistics, V22; Armonk, New York, USA.

We planned to include 100 patients, with 50 undergoing CMR in each study group. Assuming an MSI of $60 \pm 20\%$ [17–20] in the O_2 group (i.e. with the current standard treatment), a total sample size of 100 would enable the

detection of an MSI difference of 15% points between groups with a power of more than 90% (actual power 96%) at a 5% risk of an α error.

Results

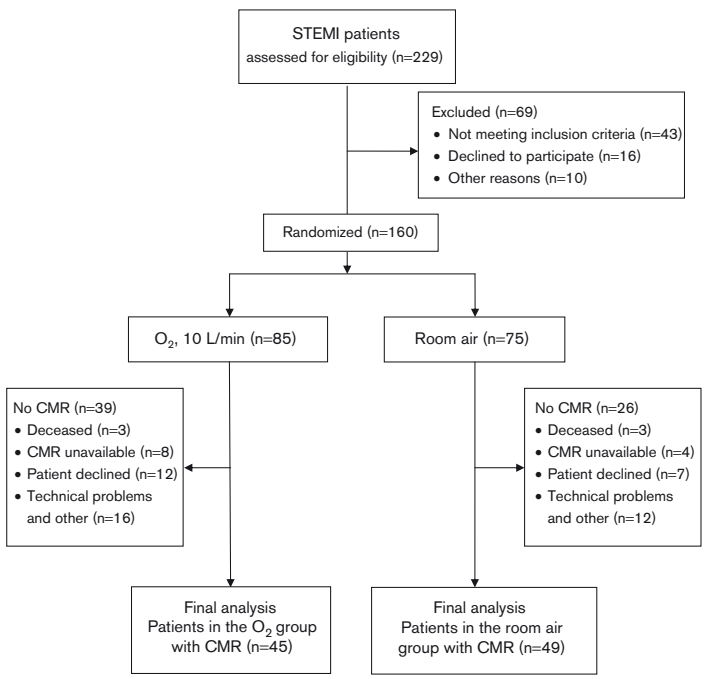
The SOCCER study was carried out between 23 January 2012 and 5 August 2015. Figure 1 shows the study profile. A total of 229 patients were screened for participation and 69 were excluded. Of the remaining 160 patients, 85 were randomized to the O_2 group, where 46 patients had CMR, and 75 were randomized to the air group, where 49 had CMR. Patient and procedural characteristics as well as blood test results for the 160 randomized patients are shown in the online appendices (Supplemental digital content 1, *http://links.lww.com/EJEM/A142*). In general, the two study groups were similar.

Characteristics for the 95 patients included in the final analysis are presented in Table 1. Although not statistically significant, more patients in the air group had previous hypertension or diabetes, with consequent differences in medications. Blood test results are presented in Table 2. There was no significant difference between the groups in pro-BNP or in peak TnT levels after the PCI.

All 95 patients underwent PCI and Table 3 summarizes the procedural characteristics. Again, the two groups were similar, including the culprit lesion with the left anterior descending artery dominating. Overall, there were few complications in both study groups. At the PCI laboratory, no patients developed cardiac tamponade or hemodynamic, neurological, or other complications. No patient had intrahospital cardiogenic chock, rescue PCI, kidney failure, cardiac tamponade, neurological complications, or other forms of severe complications.

Figure 2 shows the CMR findings. MSI was not significantly different in the O_2 and room air groups (53.9 vs. 49.3%; 95% confidence interval for difference: −5.4 to 14.6%), nor were there significant differences between the O_2 and air groups in MaR, IS, or LV ejection fraction. On the basis of the MSI findings in the present study, the actual power to detect an MSI difference of 15% points between the O_2 and air groups was 86% at a 5% risk of an α error.

Fig. 1



Patient flow diagram. CMR, cardiac MRI; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

Table 1 Patient characteristics

Characteristics	O_2 group ($n=46$)	Air group ($n=49$)	*P*-value
Demographics			
Male sex [*n* (%)]	29 (63.0)	34 (69.4)	NS
Age (year) [mean (SD)]	63.7 (13.1)	65.5 (11.5)	NS
BMI [mean (SD)]	26.1 (3.4)	27.0 (4.2)	NS
Current smoker [*n* (%)]	15 (32.6)	16 (32.7)	NS
Past smoker [*n* (%)]	16 (34.8)	17 (34.7)	NS
Medical history [*n* (%)]			
Diabetes	3 (6.5)	9 (18.4)	NS
Hypertension	11 (24.0)	21 (43.0)	NS
Previous stroke/TIA	0 (0)	3 (6.1)	NS
Previous medication [*n* (%)]			
ACEi	8 (17.4)	5 (10.2)	NS
Anticoagulant	1 (2.2)	0 (0)	NS
ARBs	2 (4.3)	2 (4.1)	NS
Aspirin	6 (13.0)	3 (6.1)	NS
β-blocker	0 (0)	7 (14.3)	NS
CCB	1 (2.2)	7 (14.3)	NS
Diuretics	1 (2.2)	7 (14.3)	NS
Oral antidiabetic medication	2 (4.3)	5 (10.2)	NS
Insulin	1 (2.2)	2 (4.1)	NS
Nitrates	1 (2.2)	1 (2.2)	NS
Statins	2 (4.3)	5 (10.2)	NS
Process times (min) [mean (SD)]			
Symptom to ambulance arrival	110.9 (112.6)	98.2 (87.8)	NS
Symptom to PCI	175.9 (121.6)	161.3 (93.1)	NS
Patient's home to PCI	39.4 (11.2)	37.4 (10.4)	NS
Duration of study intervention (O_2 or room air)			
Time (min) [mean (SD)]	85.6 (27.7)	85.4 (25.8)	NS
Intervention not for entire duration [*n* (%)]	3 (6.5)[a]	5 (10.2)[b]	NS
Findings at inclusion			
Heart rate (BPM) [mean (SD)]	84.2 (17.3)	82.7 (18.2)	NS
Systolic BP (mmHg) [mean (SD)]	154.0 (29.6)	153.7 (29.1)	NS
Diastolic BP (mmHg) [mean (SD)]	94.7 (17.0)	91.4 (20.0)	NS
Blood oxygen saturation [mean (SD)]	98.0 (1.7)	97.7 (1.6)	NS
Findings at arrival to the PCI laboratory			
Heart rate (BPM) [mean (SD)]	74 (13.1)	75 (18.9)	NS
Systolic BP (mmHg) [mean (SD)]	142.3 (22.2)	140.4 (23.8)	NS
Diastolic BP (mmHg) [mean (SD)]	85.3 (15.3)	84.8 (14.6)	NS
Cardiogenic shock [*n* (%)]	0 (0)	1 (2.0)	NS
Blood oxygen saturation (%) [mean (SD)]	99.2 (1.1)	97.0 (1.9)	0.00

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; BP, blood pressure; BPM, beats per minute; CCB, calcium channel blockers; CCU, cardiac care unit; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.
[a]In two cases, the study group allocation was unclear to the PCI personnel and in one case, the O_2 therapy was ended in the PCI lab because of the patient's chronic obstructive pulmonary disease.
[b]All patients received O_2 in the PCI laboratory because blood O_2 saturation decreased < 94%.

Table 2 Blood analyses

Blood tests	Mean (SD) O_2 group ($n=46$)	Mean (SD) Air group ($n=49$)	*P*-value
At arrival to the PCI laboratory			
Creatinine (μmol/l)	72.9 (15.6)	82.0 (19.7)	0.02
CRP (mg/l)	10.6 (19.6)	9.0 (19.1)	NS
Hb (g/l)	131.4 (11.3)	134.7 (14.0)	NS
Glucose (mmol/l)	7.6 (2.2)	8.1 (2.5)	NS
Pro-BNP (ng/l)[a]	404.6 (635.4)	405.3 (772.1)	NS
After the PCI			
Peak troponin T (ng/l)	3638 (3118)	3345 (3524)	NS

CRP, c-reactive protein; Hb, hemoglobin; PCI, percutaneous coronary intervention.
[a]Pro-BNP reported as < 50 ng/l was interpreted as 25 ng/l.

Table 3 Procedural and postprocedural characteristics, and complications

Characteristics	*n* (%) O_2 group ($n=46$)	*n* (%) Air group ($n=49$)	*P*-value
Killip class at arrival to the PCI laboratory			
Class I	45 (97.8)	48 (98.0)	NS
Class II	1 (2.2)	1 (2.0)	NS
Drugs given			
IV/SC anticoagulant	1 (2.2)	9 (18.4)	0.01
IV β-blocker	3 (6.5)	5 (10.2)	NS
IV diuretics	3 (6.5)	6 (12.2)	NS
IV inotropes	0 (0)	1 (2.0)	NS
IV nitrate	3 (6.5)	2 (4.1)	NS
Culprit lesion			
Left anterior descending artery	23 (50.0)	23 (46.9)	NS
Left circumflex artery	4 (8.7)	3 (6.1)	NS
Right coronary artery	18 (39.1)	20 (40.8)	NS
Other	1 (2.2)	3 (6.1)	NS
Coronary disease			
Single vessel	25 (54.3)	29 (59.2)	NS
Multivessel	20 (43.4)	17 (34.7)	NS
Left main coronary artery	1 (2.2)	3 (6.1)	NS
Procedures			
Thrombectomy	11 (24.0)	13 (26.5)	NS
CABG	2 (4.4)[a]	2 (4.0)[a]	NS
Complications at PCI laboratory			
Arrhythmia	1 (2.2)	0 (0)	NS
Intrahospital complications			
Atrial fibrillation/flutter	2 (4.3)	4 (8.2)	NS
Heart failure	5 (10.9)	8 (16.3)	NS
Reinfarction	1 (2.2)	0 (0)	NS
Cardiac arrest	1 (2.2)	3 (6.1)	NS

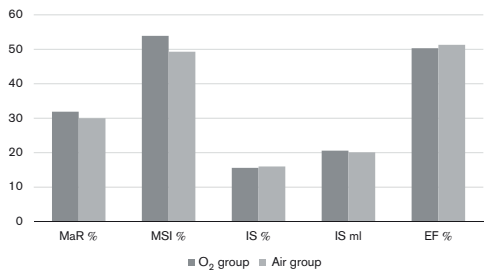
CABG, coronary artery bypass grafting; IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous.
[a]One during admission and one after discharge.

Discussion

In this trial on the effects of high-flow oxygen versus room air in STEMI patients undergoing PCI, we found no differences in MaR before PCI, MSI, or the resulting IS. The effects of O_2 therapy were analyzed using CMR, which is the gold-standard method to evaluate MaR, MSI, and IS [17,21,22].

Our study is the first to analyze the effects of O_2 therapy on MaR and MSI in acute reperfused myocardial infarction. We chose MSI as the primary endpoint as the prognosis in reperfused STEMI patients is related to the amount of myocardial salvage [6] and as the MSI outcome measure enables determination of treatment efficacy with lower patient numbers than with infarct size [23]. MSI analysis encompasses the combination of IS and MaR, and both these CMR measures have been validated previously [11,12,24–26] and used in multicenter cardioprotection trials [18,19]. Our finding of no

Fig. 2



CMR results mean (SD)	O_2 group (n=46)	Air group (n=49)	95% Confidence Interval for difference
MaR % of LV	31.9 (10.0)	30.0 (11.8)	–2.6 – 6.3
MSI %	53.9 (25.1)	49.3 (24.0)	–5.4 – 14.6
IS % of LV	15.6 (10.4)	16.0 (11.0)	–4.7 – 4.1
IS ml	20.6 (15.6)	20.1(15.9)	–5.9 – 6.9
EF %	50.2 (9.1)	51.3 (11.5)	–5.4 – 3.1

Effects of O_2 therapy versus room air in STEMI patients undergoing acute PCI. Results of CMR. CMR, cardiac MRI; EF, ejection fraction; IS, infarct size; MaR, myocardium at risk; MSI, myocardial salvage index; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

difference in MSI between the O_2 and air groups indicates that supplemental O_2 did not affect the efficacy of the PCI reperfusion.

Previous studies indicate that hyperoxia have the potential to increase myocardial ischemia in acute coronary disease, probably by coronary vasoconstriction and increased systemic vascular resistance [2,3]. Several mechanisms for this have been suggested, for example generation of superoxide anion, which decreases the activity of endothelium-derived vasodilator NO [27], and/or an increased formation of vasoconstrictor endothelin [28]. In the present study, however, we found no evidence for an effect of high-flow O_2 therapy on myocardial ischemia, MaR, in STEMI patients.

There is a close relationship between IS and prognosis in AMI patients [21,22,29,30], and CMR is the in-vivo reference standard for the assessment of IS [26]. In accordance with the lack of effect on MaR and MSI in this study, there was no significant difference in IS between the O_2 and air groups, either in absolute volume or as a fraction of LV mass. In addition, we observed no difference in LV function; the EF was similar in the two study groups. Our data thereby confirm and extend the results of Ranchord *et al.* [4], who compared high-flow (6 l/min) with titrated oxygen (to an O_2 saturation of 93–96%) in reperfused STEMI patients. In their study, no significant difference was observed in IS measured with TnT or when determined with CMR at 4–6 weeks after PCI. In contrast, some evidence of a negative effect of supplemental O_2 on IS was reported from the AVOID trial [5,31]. In this trial, 8 l O_2/min versus room air increased IS as measured with creatine kinase, but not with TnI. CMR at 6 months performed in one-quarter of the patients showed a larger IS in grams in the O_2 group, but no difference in IS when expressed as percentage of the LV. A post-hoc analysis showed an association between O_2 exposure in the first 12 h after inclusion and a significant increase in both creatine kinase and TnI release [31]. The reason for the differences in the results compared with the present observations is unclear, but might include the unblinded design, the longer oxygen exposure, and the timing of the CMR in the AVOID trial. All these results, however, taken together, indicate that supplemental O_2 does not decrease IS in STEMI patients, either in the short or in the long term.

The SOCCER study was powered to detect a clinically significant difference in MSI between the study groups, but not a difference in clinical events. Even though MSI and IS are well correlated with both mortality and morbidity [6,29,30,32], further research is needed to establish the effects of supplemental O_2 on the prognosis of AMI patients. Data on the long-term effects on clinical events, including 1-year mortality, will hopefully be provided by the DETO2X-AMI trial [33].

In the absence of data on clinical events, the results of the present and recent trials suggest that it might be safe to withhold supplemental O_2 in normoxic, stable STEMI patients. Empirical evidence is thus now accumulating in support of current recommendations [34] that patients with suspected acute coronary syndrome should only receive supplemental O_2 if presenting with hypoxia, dyspnea, or signs of heart failure.

Study limitations

This study included patients at two hospitals only, and the results are therefore not necessarily applicable to all STEMI patients, especially as we studied a relatively low-risk STEMI-population with mostly Killip class 1 and few in-hospital adverse events. In general, however, our patients and the overall management were quite similar to those in other studies [17–20], with the exception that our patients were somewhat younger and more often women. Further, we studied only STEMI patients, and our results may not be applicable to patients with suspected or established non-STEMI or unstable angina.

Patients received O_2 only for some 86 min from the ambulance arrival to the end of the PCI. It is possible that longer exposure may have yielded different results, but the IS results of a study with O_2 therapy during 6 h [4] were similar to ours.

The ambulance and PCI lab personnel were aware of the patient's group allocation, which could have influenced patient treatment. However, our management data (Table 3 and Supplemental digital content 1, *http://links.lww.com/EJEM/A142*) may suggest that such an influence

was small. The researchers analyzing the data and reviewing the CMR images were blinded to all clinical data, and in contrast to previous studies, our patients were blinded to the study intervention.

A considerable number of the included patients did not undergo CMR (Fig. 1), which introduces a risk of bias. The size of this bias may, however, be limited as most of the patient loss was because of technical or logistical problems and as the characteristics of the lost patient were similar to those of the patients undergoing CMR.

Conclusion

In normoxic STEMI patients undergoing acute PCI, we found no effect of high-flow oxygen compared with room air on the size of ischemia before PCI, myocardial salvage, and the resulting infarct size. Our results support the safety of withholding supplemental oxygen in normoxic and stable STEMI patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Supplementary online-only material

Online data supplement 1. Patient characteristics at randomization.

Characteristics	O_2 group (n=85)	Air group (n=75)	P-value
Demographics			
Male gender, n (%)	54 (63.5)	51(68.0)	ns
Mean age, year (SD)	64.4 (12.3)	67.6 (12.0)	ns
Mean body mass index (SD)	26.3 (3.4)	26.5 (4.3)	ns
Current smoker n (%)	30 (35.3)	24 (32.0)	ns
Past smoker, n (%)	24 (28.2)	30 (40.0)	ns
Medical history, n (%)			
Diabetes	11 (12.9)	12 (16.0)	ns
Hypertension	27 (31.8)	32 (42.7)	ns
Previous stroke/TIA	0 (0)	5 (6.7)	*0.01*
Prior medication, n (%)			
ACEi	15 (17.6)	9 (12.0)	ns
Anticoagulant	2 (2.4)	1 (1.3)	ns
Antidiabetic medication, oral	9 (10.6)	6 (8.0)	ns
ARBs	2 (2.4)	5 (6.7)	ns
Aspirin	9 (10.6)	11 (14.7)	ns
Betablocker	5 (5.9)	15 (20.0)	*0.05*
CCB	4 (4.7)	8 (10.7)	ns
Diuretics	3 (3.5)	11 (14.7)	ns
Insulin	3 (3.5)	4 (5.3)	ns
Nitrates	0 (0)	3 (4.0)	ns
Statins	5 (5.9)	8 (10.7)	ns
Duration of study intervention (O_2 or room air)			
Mean time, min (SD)	89.4 (37.0)	92.7 (38.8)	ns
Findings at inclusion			
Mean heart rate, BPM (SD)	85.4 (18.5)	85.4 (17.0)	ns
Mean systolic BP, mm Hg (SD)	148.0 (32.5)	153.4 (29.0)	ns
Mean diastolic BP, mm Hg (SD)	91.0 (17.8)	91.8 (21.7)	ns
Mean blood oxygen saturation, % (SD)	98.0 (1.7)	97.7 (1.8)	ns
Findings at arrival to the PCI laboratory			
Mean heart rate, BPM (SD)	75.2 (15.1)	74.9 (17.1)	ns
Mean systolic BP, mm Hg (SD)	143.2 (24.1)	141.7 (26.1)	ns
Mean diastolic BP, mm Hg (SD)	83.9 (15.8)	82.9 (15.4)	ns
Cardiogenic shock, n (%)	1 (1.2)	2 (2.7)	ns
Mean blood oxygen saturation, % (SD)	99.0 (1.4)	97.2 (2.0)	*0.00*

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.

Online data supplement 2. Blood analyses for all randomized patients.

Blood test	**O_2 group (n=85)**	**Air group (n=75)**	**P-value**
At arrival to the PCI laboratory			
Mean Creatinine, µmol/L (SD)	77.8 (19.0)	88.7 (38.4)	*0.05*
Mean CRP, mg/L (SD)	9.1 (17.6)	12.3 (29.2)	ns
Mean Hb, g/L (SD)	133.4 (13.9)	133.0 (15.3)	ns
Mean Glucose, mmol/L (SD)	8.0 (2.5)	8.1 (3.7)	ns
Mean Pro-BNP, ng/L (SD)*	342.7 (542.6)	461.1 (960.6)	ns
After the PCI			
Peak Troponin T, ng/L (SD)	2930.2 (2953.2)	3103.9 (3387.8)	ns

CRP, c-reactive protein; Hb, hemoglobin; O_2, oxygen; PCI, percutaneous coronary intervention.
* Pro-BNP reported as <50 ng/L was interpreted as 25 ng/L.

Online data supplement 3. Procedural and post-procedural characteristics and complications for all randomized patients.

Characteristics	O_2 group (n=85)	Air group (n=75)	P-value
Killip class at arrival to the PCI laboratory, n (%)			
Class I	81 (95.3)	73 (97.3)	ns
Class II	4 (4.7)	2 (2.7)	ns
Drugs given, n (%)			
IV/SC Anticoagulant	13 (15.3)	16 (21.3)	ns
IV Betablocker	4 (4.7)	6 (8.0)	ns
IV Diuretics	8 (9.4)	11 (14.7)	ns
IV Inotropes	3 (3.5)	4 (5.3)	ns
IV Nitrate	6 (7.1)	6 (8.0)	ns
Culprit lesion, n (%)			
Left Anterior Descending artery	44 (51.8)	33 (44.0)	ns
Left Circumflex Artery	6 (7.1)	6 (8.0)	ns
Right Coronary Artery	29 (34.1)	28 (37.3)	ns
Other	6 (7.1)	8 (10.7)	ns
Coronary disease, n (%)			
Single vessel	39 (45.9)	41 (54.7)	ns
Multivessel	39 (45.9)	27 (36.0)	ns
Left main coronary artery	3 (3.5)	4 (5.3)	ns
Other[1]	4 (4.7)	3 (4.0)	ns
Procedure, n (%)			
Thrombectomy	17 (20.0)	15 (20.0)	ns
CABG	4 (4.7)[2]	3 (4.0)[3]	ns
Complications in the PCI Laboratory, n (%)[4]			
Arrythmia	1 (1.2)	0 (0)	ns
Intra-hospital complications, n (%)[5]			
Atrial fibrillation/flutter	4 (4.7)	8 (10.7)	ns
Heart failure	12 (14.1)	15 (20.0)	ns
Reinfarction	1 (1.2)	0 (0)	ns
Cardiac arrest	4 (4.7)	4 (5.3)	ns
Cardiogenic chock	2 (2.4)	1 (1.3)	ns
Cardiac tamponade	1 (1.2)	0 (0)	ns

CABG, coronary artery bypass grafting; IV, intravenous; O_2, oxygen; PCI, percutaneous coronary intervention; SC, subcutaneous.
1 Other indicates normal/atheromatous vessels.
2 Three during admission and one after discharge.
3 Two during admission and one after discharge.
4 No patients suffered from cardiac tamponade, or hemodynamic, neurological or other complications.
5 No patients had rescue PCI, acute kidney failure, neurological complications or other form of severe complications.

Paper IV

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WILEY Echocardiography

Effects of oxygen therapy on wall-motion score index in patients with ST elevation myocardial infarction—the randomized SOCCER trial

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Background: Although oxygen (O_2) is routinely used in patients with acute myocardial infarction (AMI), it may have negative effects. In this substudy of the SOCCER trial, we aimed to evaluate the effects of O_2-treatment on myocardial function in patients with ST elevation myocardial infarction (STEMI).

Methods: Normoxic (≥94%) STEMI patients were randomized in the ambulance to either supplemental O_2 or room air until the end of the percutaneous coronary intervention (PCI). The patients underwent echocardiography on day 2–3 after the PCI and once again after 6 months. The study endpoints were wall-motion score index (WMSI) and left ventricular ejection fraction (LVEF).

Results: Forty-six patients in the O_2 group and 41 in the air group were included in the analysis. The index echocardiography showed no significant differences between the groups in WMSI (1.32±0.27 for O_2 group vs 1.28±0.28 for air group) or LVEF (47.0±8.5% vs 49.2±8.1%). Nor were there differences at 6 months in WMSI (1.16±0.25 vs 1.14±0.24) or LVEF (53.5±5.8% vs 53.5±6.9%).

Conclusion: The present findings indicate no harm or benefit of supplemental O_2 on myocardial function in STEMI patients. Our results support that it is safe to withhold supplemental O_2 in normoxic STEMI patients.

KEYWORDS
cardiology, echocardiography, emergency medicine, oxygen therapy, ST elevation myocardial infarction

1 | INTRODUCTION

Oxygen (O_2) therapy has long been central in the management of patients with acute myocardial infarction (AMI) and is recommended by international guidelines.[1–3] There is however no evidence supporting the indiscriminate use of O_2 in the treatment of AMI. On the contrary, studies indicate that O_2 therapy may have negative cardiovascular effects such as increased peripheral resistance and mean arterial pressure, as well as a decreased heart rate and cardiac output.[4–6]

Three important studies on the effects of O_2 therapy in ST elevation myocardial infarction (STEMI) patients have recently been published. Ranchord et al.[7] randomized STEMI patients to 6 L O_2/min vs titrated O_2 and found no difference in infarct size (IS) measured with troponin T and, in half of the patients, with cardiac magnetic resonance imaging (CMR) at 6 months. In the AVOID trial,[8] O_2 therapy vs room air increased IS measured with creatine kinase, but not with troponin I. On CMR at

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

6 months in 1/3 of the patients, oxygen increased IS in grams but not as a percentage of the LV. In our recent SOCCER trial,[9] CMR at the index visit showed no effect of O_2 therapy on myocardial salvage index (MSI), myocardium at risk (MaR), or IS. Although these studies suggest no major benefit or harm of O_2 therapy in STEMI patients, the effects on myocardial function and patient outcomes have not yet been reported.[10–13]

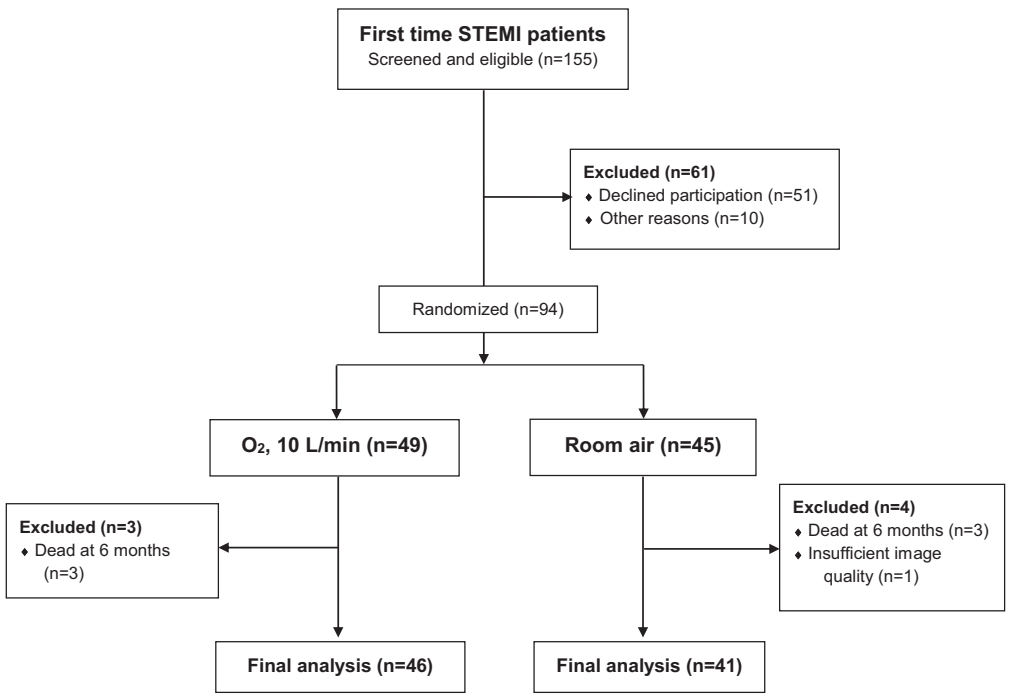
In the present SOCCER substudy, we evaluated the effects of O_2 therapy vs room air on myocardial function in STEMI patients by analyzing wall-motion score index (WMSI) and left ventricular ejection fraction (LVEF) with echocardiography, as well as N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, at the index visit and at 6 months.

2 | METHODS

The SOCCER trial's design and method have been published elsewhere.[9,14] The study was a single-blinded randomized controlled trial with no commercial funding, conducted between January 23, 2012 and August 5, 2015 at the Skåne University Hospitals in Lund and Malmö, Region Skåne, Sweden. Both the Regional Ethical Review Board and the Swedish Medical Products Agency approved the trial (EudraCT No 2011-001452-11). The present prespecified SOCCER substudy is reported in accordance with the CONSORT statement.[15]

2.1 | Patient inclusion and study design

Normoxic patients (blood O_2 saturation ≥94% on room air) with a first time STEMI accepted for acute percutaneous coronary intervention (PCI), and with symptom duration of less than 6 h, were included in the ambulance after verbal consent. Patients with a previous AMI or inability to make a decision to participate were excluded. Included patients were randomized 1:1 to the administration of either 10 L O_2/min in accordance with the prehospital guidelines of Region Skåne ("O_2 group"), or room air ("air group") from randomization until the end of



O_2, Oxygen; STEMI, ST Elevation Myocardial Infarction.

FIGURE 1 Patient flow diagram for the present study. A total of 87 patients underwent echocardiography both at the index visit and at 6 months

the PCI, and all patients received an open design OxyMask (MedCore, Stockholm, Sweden). In the patients randomized to room air, the OxyMask was not connected to the oxygen outlet. All patients were blinded to their group allocation, but the paramedics and the personnel in the PCI laboratory were not. A written informed consent was obtained by a study physician at the hospital within 72 h after the PCI.

The first 87 patients included in the main SOCCER study underwent an extended echocardiography on day 2–3 of their hospital admission after the PCI, and once again 6 months after the index STEMI, as described below.

All included patients were followed up at 6 months after admission, where the occurrence of reinfarction, current medication and admissions for heart failure were recorded. At the follow-up, the patients completed an E -5 uestionnaire.[16] The E -5 is a well-established tool to grade the subjective level of health and has been validated in post-AMI patients.[17,18] Blood samples for NT-ProBNP were obtained both at the arrival to PCI laboratory and at 6 months.

2.2 | Patient management

Apart from the study intervention, the patients received standard care in the ambulance and were treated with aspirin, ticagrelor, heparin, β-blockers, and morphine as needed. In the patient group receiving room air, the study intervention was terminated if blood O_2 saturation dropped below 94% after inclusion until the termination of the PCI, and O_2 therapy was initiated with 10 L/min.

After conclusion of the PCI, the patients received standard care at the cardiac intensive care unit (CICU) by personnel blinded to the patient's group allocation. According to CICU guidelines, only patients with a blood O_2 saturation below 90% received O_2 treatment.

2.3 | Data collection

Patient management, including drugs administered, and vital parameters were recorded by the ambulance nurse and the nurses in the

TABLE 1 Patient characteristics

Characteristics	O_2 group (n=46)	Air group (n=41)	*P*-value
emographics			
Male gender, n (%)	29 (63.0)	29 (70.7)	.450
Mean age, yr (S)	62.5 (12.1)	65.5 (11.6)	.154
Mean body mass index (S)	26.5 (3.1)	26.3 (4.3)	.663
Current smoker n (%)	18 (39.1)	14 (34.1)	.786
Past smoker, n (%)	15 (32.6)	15 (36.6)	.699
Medical history, n (%)			
iabetes	5 (10.9)	8 (19.5)	.262
Hypertension	15 (32.6)	14 (34.1)	.992
Previous stroke/TIA	0 (0)	2 (4.9)	.132
Prior medication, n (%)			
ACEi	8 (17.4)	5 (12.2)	.863
Anticoagulant	0 (0)	1 (2.4)	.289
ARBs	2 (4.3)	1 (2.4)	.718
Aspirin	6 (13.0)	4 (9.8)	.633
β-blocker	4 (8.7)	6 (14.6)	.244
CCB	3 (6.5)	4 (9.8)	.342
iuretics	0 (0)	6 (14.6)	*.010*
Oral antidiabetic medication	4 (8.7)	6 (14.6)	.389
Insulin	1 (2.2)	1 (2.4)	.935
Nitrates	0 (0)	2 (4.9)	.132
Statins	3 (6.5)	4 (9.8)	.405
Findings at inclusion			
Mean heart rate, BPM (S)	89.6 (16.5)	85.8 (16.8)	.373
Mean systolic BP, mm Hg (S)	150.4 (33.5)	151.7 (31.8)	.703
Mean diastolic BP, mm Hg (S)	92.5 (18.0)	87.5 (17.7)	.147
Mean blood oxygen saturation, % (SD)	98.0 (1.5)	97.6 (1.7)	.331

Values in italic indicate statistical significance. ACEi=angiotensin-converting enzyme inhibitor; ARBs angiotensin II receptor blockers BP blood pressure BPM beats per minute CCB calcium channel blockers CRP C-reactive protein Hb hemoglobin O_2 oxygen PCI percutaneous coronary intervention TIA transient ischemic attack.

PCI laboratory on case report forms and later registered electronically in the study database. All other data, including data for heart failure admissions and treatments up to 6 months, were retrieved from Region Skåne's computerized patient records (Melior; Siemens, ermany) and from the Swedish nationwide online cardiac registry SWE EHEART.[19]

2.4 | Echocardiography

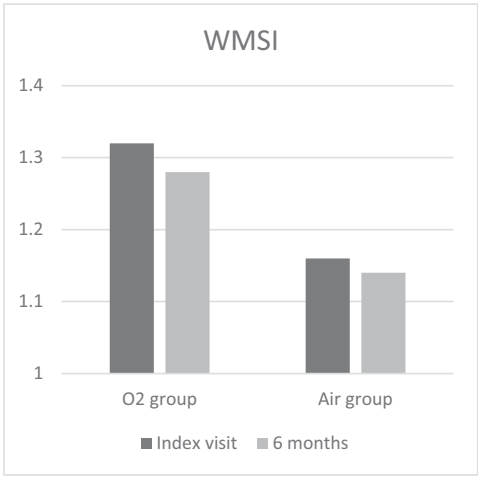
Patients underwent an extended echocardiography using a Philips 133 ultrasound system with assessment of LVEF and WMSI at day 2–3 after the acute PCI, and again during the 6-month follow-up. LVEF was calculated according to Simpson's biplane disk methodic apical four- and four-chamber view.

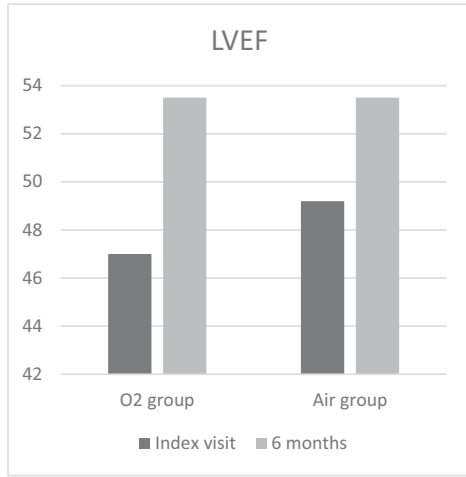
To calculate WMSI, wall motion was assessed in 16 myocardial segments as 1–5, where 1 is normal and 2–5 represents decreased contractility. WMSI was then derived as the sum of all segment scores divided by the number of segments visualized. The senior cardiologists performing and interpreting the echocardiographic examination were blinded to the patient's group allocation. WMSI is a good predictor of mortality or readmission for heart failure[20] and reflects IS, regional and total contractility, and may be used both in the acute phase and after an AMI, for example, to assess myocardial remodeling.[21,22] Conse uently, WMSI can also be used to assess the success of an acute PCI.[22]

TABLE 2 Findings in the percutaneous coronary intervention (PCI) laboratory and interventions

Characteristics	O_2 group (n=46)	Air group (n=41)	*P*-value
uration of study intervention (O_2 or room air)			
Time, min (S)	87.0 (32.1)	85.4 (24.0)	.938
Intervention not for entire duration, n (%)	4 (8.7)[a]	7 (17.1)[b]	.243
Findings at arrival to the PCI laboratory			
Mean Heart rate, BPM (S)	74.3 (12.2)	75.1 (18.3)	.289
Mean systolic BP, mm Hg (S)	146.5 (24.7)	137.8 (24.0)	.130
Mean diastolic BP, mm Hg (S)	85.6 (15.4)	82.4 (14.4)	.206
Cardiogenic shock, n (%)	0 (0)	1 (2.4)	.289
Mean blood oxygen saturation, % (SD)	99.2 (1.1)	97.0 (1.8)	*.000*
Creatinine, μmol/L (S)	77.8 (19.8)	81.8 (20.0)	.392
CRP, mg/L (S)	9.8 (18.6)	11.1 (25.7)	.362
Hb, g/L (S)	134.7 (12.8)	133.3 (15.9)	.863
illip class at arrival to the PCI laboratory, n (%)			
Class I	46 (100)	40 (97.6)	.289
Class II	0 (0)	1 (2.4)	.289
Culprit lesion, n (%)			
Left anterior descending artery	22 (47.8)	17 (41.5)	.554
Circumflex artery	6 (13.0)	2 (4.9)	.191
Right coronary artery	14 (30.4)	19 (46.3)	.129
Other	4 (8.7)	3 (7.3)	.815
Coronary disease, n (%)			
Single vessel	19 (41.3)	28 (68.3)	*.012*
Multivessel	23 (50.0)	11 (26.8)	*.028*
Left main coronary artery	1 (2.2)	2 (4.9)	.493
Normal vessel/atherosclerosis	3 (6.5)	0 (0)	.098
Procedure in addition to PCI, n (%)			
Trombectomy	12 (26.1)	6 (14.6)	.191
CAB	2 (4.4)[c]	3 (7.3)[d]	.555

CAB coronary artery bypass grafting O_2 oxygen. Values in italic indicate statistical significance.
[a]These four patients received O_2 in the ambulance, but none of them received O_2 during the PCI.
[b]During the PCI, the blood oxygen saturation declined (≤90%) why O_2 was administrated.
[c]One during admission, and one after discharge.
[d]Two during admission, and one after discharge.





Echocardiography results (mean (SD))	O_2 group (n=46)	Air group (n=41)	95% Confidence Interval for difference	P-value
WMSI, index visit	1.32 (0.27)	1.28 (0.28)	-0.1 – 0.2	0.342
WMSI, 6 months	1.16 (0.25)	1.14 (0.24)	-0.1 – 0.1	0.816
LVEF %, index visit	47.0 (8.49)	49.2 (8.06)	-5.8 – 1.3	0.159
LVEF %, 6 months	53.5 (5.82)	53.5 (6.86)	-2.7 – 2.8	0.948

FIGURE 2 Effects of O_2 therapy vs room air in ST elevation myocardial infarction (STEMI) patients undergoing acute percutaneous coronary intervention (PCI). Results of echocardiography at the index visit and at 6 months

2.5 | Statistical analysis

The study groups were compared with respect to our endpoints using two-sided Mann–Whitney *U* tests with *P*.05 considered statistically significant. The null hypothesis was that there was no difference between the groups. All data were analyzed using Microsoft Excel and IBM SPSS Statistics V22, Armonk, N, USA. The results are described with means and standard deviations, and 95% confidence intervals (CI) are shown for the differences in echocardiography results.

A post hoc analysis, based on the findings and the number of analyzed patients, showed an actual power >80% to detect an LVEF difference of 5 percentage points or a WMSI difference of 0.17 between the O_2 and air groups at a 5% risk of an alpha error.

3 | RESULTS

The patient flow is presented in Figure 1. The final analysis included 46 patients in the O_2 group and 41 patients in the air group who underwent echocardiography at the index visit and at 6 months. Characteristics for these patients are described in Tables 1 and 2. In general, the patients in the two study groups were similar, but those in the O_2 group more often had multivessel disease.

WMSI and LVEF results are presented in Figure 2. Both at admission and at 6 months, WMSI and LVEF were not significantly different in the two study groups. Also, there were no significant differences in the changes over 6 months in LVEF (P.110) or WMSI (*P*.543) between the groups.

Effects of the study intervention on NT-proBNP levels are described in Table 3. There were no significant differences in mean levels between the groups at the PCI or at 6 months, nor in the change from the index visit up to 6 months.

Additional observations at 6 months are described in Table 4. No patients died. Readmissions for heart failure were very few and similar in the groups, as were the pharmacological treatment for heart failure and other cardiovascular diseases. However, more patients in the O_2 group received β-blockers than in the air group (97.8% vs 73.2%; P.001). Based on the E -5 results, many patients in both study groups had problems with anxiety/depression as well as pain/

TABLE 3 Mean N-terminal pro-brain natriuretic peptide (NT-proBNP) levels

Blood test	O_2 group (n=46)	Air group (n=41)	*P*-value
At arrival to the PCI laboratory			
NT-proBNP, ng/L (S)[a]	257.0 (307.8)	474.0 (921.9)	.062
At 6 months			
NT-proBNP, ng/L (S)[a]	515.0 (965.1)	357.4 (300.0)	.880
Change from index NT-proBNP, ng/L (S)[a]	258.0 (911.1)	−116.6 (947.8)	.139

PCI percutaneous coronary Intervention.
[a]Pro-BNP 50 ng/L were interpreted as 25 ng/L.

discomfort, but there was no difference in overall health; 80% for the O_2 group vs 78% for the room air group.

4 | DISCUSSION

In this study, we evaluated the effects of O_2 therapy on myocardial function in STEMI patients undergoing PCI. We found no difference in WMSI, LVEF, or NT-proBNP levels at the index visit or at 6 months after admission.

To the best of our knowledge, our study is the first to analyze the short- and medium-term effects of O_2 therapy on myocardial function in AMI patients. It is well established that LV function after AMI provides important prognostic information, both regarding morbidity and mortality.[20,23] Previous studies[7–9] have suggested no major effect of oxygen treatment on IS, but it is well known that that IS does not correlate entirely with long-term patient outcome (eg.,[24]).Using echocardiography, we assessed both WMSI and LVEF. Compared to WMSI, LVEF is highly dependent on the method used and may be less precise when assessing myocardial damage.[20,25–27] WMSI has been shown to be superior to LVEF both in assessing LV function[28–31] and in predicting morbidity and mortality.[20,23,32]

Our findings of no significant differences in LVEF and WMSI at the index visit indicate that O_2 therapy has no major effect on LV function in the first days after the PCI. These results confirm and extend our previous observations with CMR that supplemental O_2 therapy has no short-term effect on LVEF.[9] The lack of effect on both LVEF and WMSI in the present study also supports that there is no major effect of O_2 treatment on IS or on the ischemic area before the PCI (myocardium at risk).[9]

Similarly, the presence of no significant differences in both WMSI and LVEF at 6 months between the study groups indicates that O_2 therapy has no medium-term effect on myocardial function in

TABLE 4 Follow-up at 6 months for the included patients

Characteristics	O_2 group (n=46)	Air group (n=41)	*P*-value
Patient alive, n (%)	46 (100%)	41 (100%)	–
Readmission for heart failure, n (%)	1 (2.2%)	1 (2.4%)	.920
Drugs prescribed, n (%)			
ACEi	35 (76.1%)	31 (75.6%)	.959
Anticoagulant	2 (4.3%)	4 (9.8%)	.323
ARBs	8 (17.4%)	4 (9.8%)	.305
Aspirin	43 (93.5%)	38 (92.7%)	.884
β-blocker	45 (97.8%)	30 (73.2%)	*.001*
CCB	5 (10.9%)	6 (14.6%)	.600
iuretics	4 (8.7%)	7 (17.1%)	.208
Nitrates	1 (2.2%)	3 (7.3%)	.245
Other antithrombotic drugs	42 (91.3%)	33 (80.5%)	.229
Other lipid-lowering medications	1 (2.2%)	2 (4.9%)	.479
Statins	45 (97.8%)	39 (95.1%)	.493
EQ-5D, n (%)			
Mobility, >Level 1	7 (15.2%)	8 (19.5%)	.552
Personal care, >Level 1	1 (2.2%)	3 (7.2%)	.242
Usual activities, >Level 1	4 (8.7%)	9 (21.9%)	.057
Pain/discomfort, >Level 1	13 (28.3%)	12 (29.3%)	.839
Anxiety/depression, >Level 1	15 (32.6%)	13 (31.7%)	.924
Health state, % (SD)	79.1 (17.9)	82.9 (13.1)	.813

Values in italic indicate statistical significance. ACEi=angiotensin-converting enzyme inhibitor; ARBs angiotensin II receptor blockers CCB calcium channel blockers O_2 oxygen.

STEMI patients. This conclusion is also compatible with the results of Ranchord et al.,[7] who found no effect of O_2 therapy on IS in STEMI patients undergoing CMR at 6 months after the PCI.

There is a clear association between increases in NT-proBNP after STEMI on one hand, and both larger IS and diminished LVEF as a sign of LV dysfunction[33–38] on the other. In a recent study,[36] NT-proBNP levels at 1 year after STEMI was significantly correlated with IS and LV function evaluated by CMR. NT-proBNP also correlates well with mortality.[39–42] In light of our WMSI and LVEF findings, the lacking effect of O_2 therapy on NT-proBNP levels in both the acute phase and at 6 months was therefore not surprising. In the STEMI patients in the present study, mortality and readmissions for heart failure at the 6-month follow-up were almost nonexistent in both study groups. There was also no difference in subjective health status assessed by E -5 . Taken together with our NT-proBNP data, these results further support the notion that there are no clinically significant effects of O_2 therapy in STEMI patients on IS or myocardial function in the medium term.

The present investigation included too few patients to allow meaningful conclusions regarding the effects of oxygen treatment on clinical events in STEMI patients. It is our hope that such data will be provided by the large ETO2 -AMI trial.[43]

4.1 | Study limitations

This trial only included stable, low-risk STEMI patients from two university hospitals and the results may not be applicable to all STEMI patients, although the characteristics and the management of our patients seemed to be similar to those in other studies.[44–49] As this trial included only STEMI patients, the results might not be generalizable to patients with others forms of acute coronary syndrome.

The average duration of the O_2 administration from inclusion to the end of the PCI was close to 90 min. Even though our results are compatible with observations in studies with longer O_2 administration,[7] we cannot exclude that a longer O_2 exposure would have given different results. However, our O_2 administration reflected the standard care in the participating ambulances and hospitals and may also be representative of routine care at other centers.

Both the paramedics and the PCI nurses were aware of the patient's group allocation. This may of course have influenced patient management, but data in the main SOCCER study[9] suggest that such an influence was small or absent. The physicians analyzing the echocardiography images and the clinical data were not informed whether the patient received oxygen or room air, and in contrast to other studies,[7,8] the patients were blinded to the study intervention.

5 | CONCLUSION

Compared to room air, O_2 therapy in STEMI patients undergoing PCI had no significant effect on myocardial function as measured with WMSI, LVEF, or NT-proBNP at the index visit or at 6 months. This study provides further evidence to support the safety of withholding O_2 therapy in normoxic STEMI patients before and during the PCI. Larger studies are needed to analyze the effects of oxygen therapy on clinical events in AMI patients.

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