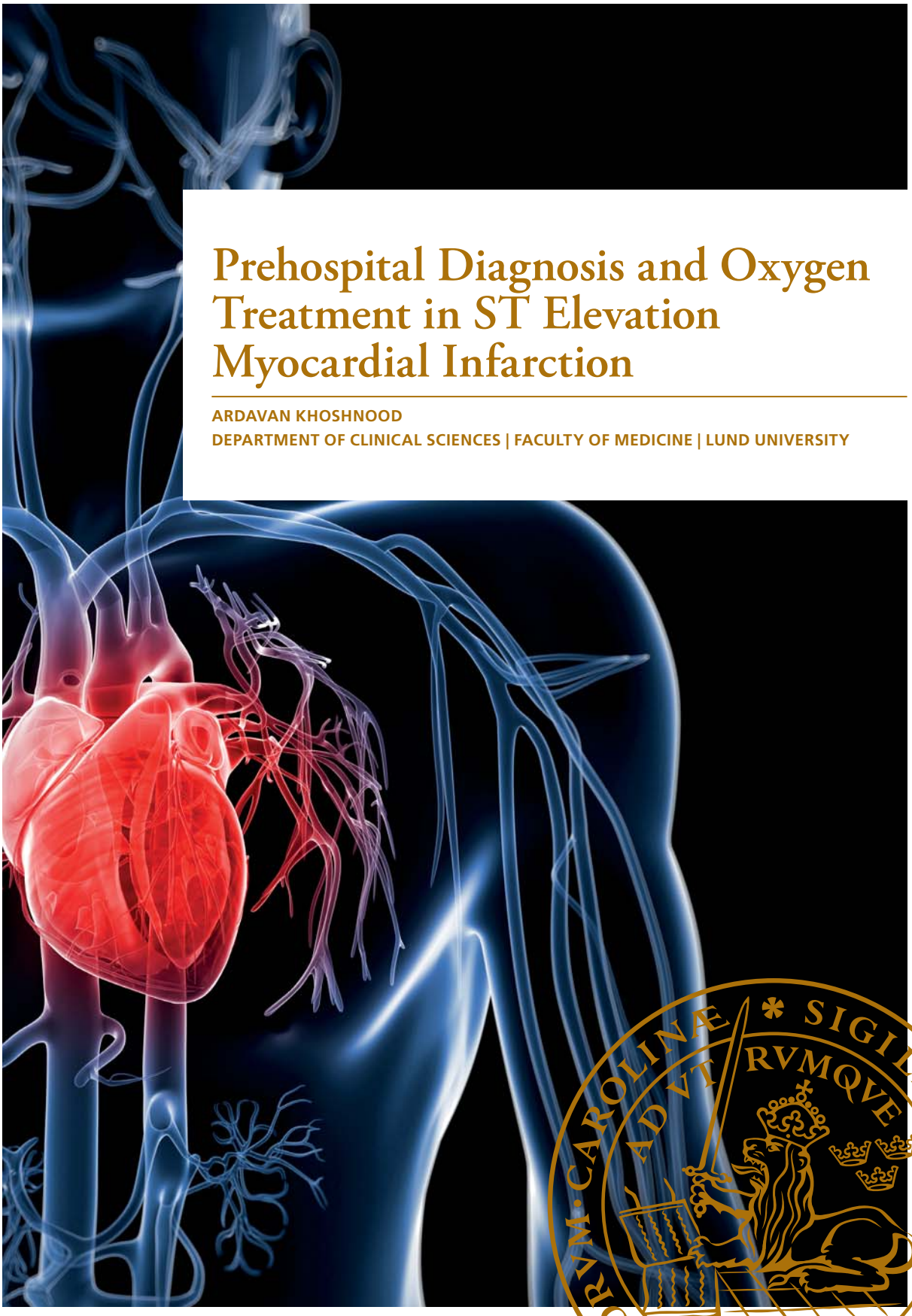


# Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

ARDAVAN KHOSHNOOD
DEPARTMENT OF CLINICAL SCIENCES | FACULTY OF MEDICINE | LUND UNIVERSITY

Printed by Media-Tryck, Lund 2017 NORDIC ECOLABEL, 3041 0903

LUND UNIVERSITY
Faculty of Medicine

Department of Clinical Sciences
Lund University

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2017:136
ISBN 978-91-7619-519-2
ISSN 1652-8220

# Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

Ardavan Khoshnood
MD, MSc, BSc

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Belfragesalen, BMC, on Friday, 3rd November 2017 at 13:00.

*Faculty opponent*
Professor Erika Frischknecht Christensen
Department of Clinical Medicine, Pre-hospital and Emergency Research, Aalborg University, Denmark; Department of Anaesthesiology, Aalborg University Hospital, Denmark

| Organization | Document name |
|---|---|
| LUND UNIVERSITY | Doctoral Dissertation |
| Department of Clinical Sciences, Emergency and Internal Medicine, Lund Faculty of Medicine | Date of issue<br>November 3, 2017 |
| Author(s)<br>Ardavan Khoshnood | Sponsoring organization<br>- |


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.

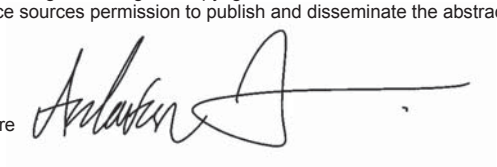


Key words: Acute Coronary Syndrome, Artificial Neural Network, Cardiology, Emergency Medicine, Oxygen Therapy, ST Elevation Myocardial Infarction.

Classification system and/or index terms (if any)

| Supplementary bibliographical information | | Language<br>English |
|---|---|---|
| ISSN and key title 1652-8220 | | ISBN 978-91-7619-519-2 |
| Recipient's notes | Number of pages 82 | Price |
| | Security classification | |




Signature  Date 2017-09-25

# Prehospital Diagnosis and Oxygen Treatment in ST Elevation Myocardial Infarction

Ardavan Khoshnood
MD, MSc, BSc


LUND
UNIVERSITY

*Supervisor*
Professor Ulf Ekelund
Department of Clinical Sciences, Lund University
Emergency and Internal Medicine, Skåne University Hospital
Lund, Sweden

Coverphoto by Eraxion, *X Ray silhouette high lighting the human heart in red*, iStock



Department of Clinical Sciences, Faculty of Medicine, Lund University
Department of Emergency and Internal Medicine, Skåne University Hospital
Lund, Sweden

Lund University, Faculty of Medicine Doctoral Dissertation Series 2017:136
ISBN 978-91-7619-519-2
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University, Lund 2017

*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

All published articles are printed with permission from the publishers.

# 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 |

# List of Figures, References


| | |
|---|---|
| Figure 1 | Image by Henry Vandyke Carter as illustrated in Gray's Anatomy authored by Henry Gray. |
| Figure 2 | Image adapted from Anatomy & Physiology, Connexions Web site: http://cnx.org/content/col11496/1.6/ |
| Figure 3 | Image by Henry Vandyke Carter as illustrated in Gray's Anatomy authored by Henry Gray. |
| Figure 4 | Image by the United States Department of Health and Human Services: https://www.nhlbi.nih.gov/health/health-topics/topics/hbc/ |
| Figure 5 | Image by Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". Wikiversity Journal of Medicine 1 (2): 10. doi:10.15347/wjm/2014.010. ISSN 2002-4436. |
| Figure 6 | Image adapted from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". Wikiversity Journal of Medicine 1 (2): 10. doi:10.15347/wjm/2014.010. ISSN 2002-4436. |
| Figure 7 | Illustration By en:User:Cburnett [GFDL (http://www.gnu.org/copyleft/fdl.html) or CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0/)], via Wikimedia Commons. |
| Figure 8 | Figure by Currie et al. (2013), Understanding MRI: basic MR physics for physicians, Postgraduate Medical Journal, 89 (1050), 209-223. |
| Figure 9 | Illustration by SensorWiki.org. http://sensorwiki.org/doku.php/sensors/ultrasound |
| Figure 10 | Figure by Khoshnood et al. (2015), The Effects of Oxygen Therapy on Myocardial Salvage in ST Elevation Myocardial Infarction Treated with Acute Percutaneous Coronary Intervention: The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) Study, Cardiology, 132 (1), 16-21. |
| Figure 11 | Image by Carlsson et al. (2009), Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography, JACC: Cardiovascular Imaging, 2 (5), 569-576. |
| Figure 12 | Formula by the author of this dissertation. |

Figure 13 Illustration by Lebeau et al. (2012), Assessment of left ventricular ejection fraction using the wall motion score index in cardiac magnetic resonance imaging, Archives of Cardiovascular Diseases, 105 (2), 91-98.

Figure 14 Figure by Forberg et al. (2012), 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, 20 (1), 8.

Figure 15 Figure by Forberg et al. (2012), 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, 20 (8).

Figure 16 Figure by the author of this dissertation

Figure 17 Figure by Khoshnood et al. (2016), Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: the randomized SOCCER trial, European Journal of Emergency Medicine. Epub ahead of print.

Figure 18 Figure by Khoshnood et al. (2017), Effects of oxygen therapy on wall motion score index in patients with ST Elevation Myocardial Infarction – The randomized SOCCER trial, Echocardiography, 34(8):1130-1137.

Figure 19 Figure by Khoshnood et al. (2017), Effects of oxygen therapy on wall motion score index in patients with ST Elevation Myocardial Infarction – The randomized SOCCER trial, Echocardiography, 34(8):1130-1137.

# List of Tables, References

| | |
|---|---|
| Table 1 | Table by the author of this dissertation. |
| Table 2 | Table by Forberg et al. (2012), 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, 20 (1), 8. |
| Table 3 | Table by Khoshnood et al. (2017), Effects of oxygen therapy on wall motion score index in patients with ST Elevation Myocardial Infarction – The randomized SOCCER trial, Echocardiography, 34(8):1130-1137. |

# 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]

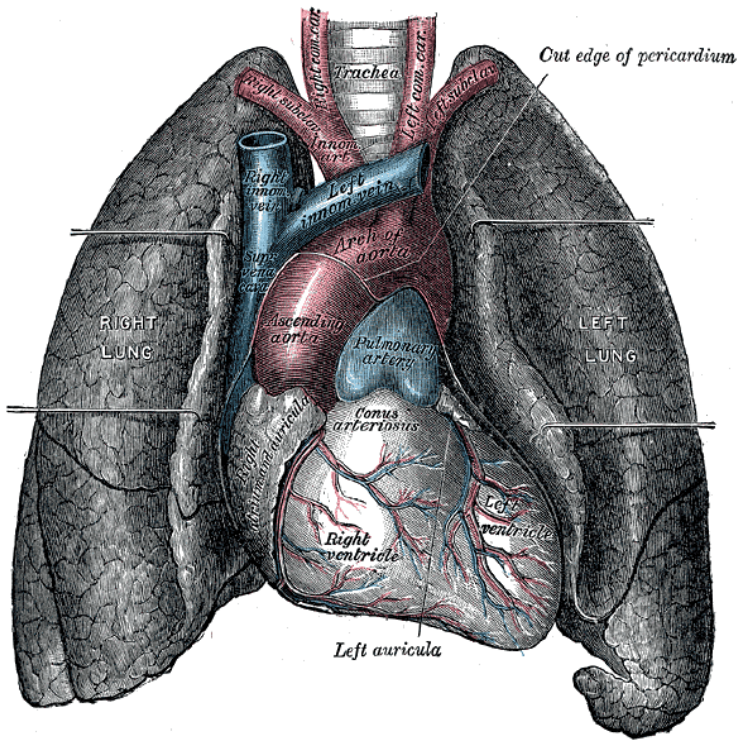



***Figure 1*** *Image of the heart and its surrounding anatomy.*

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]

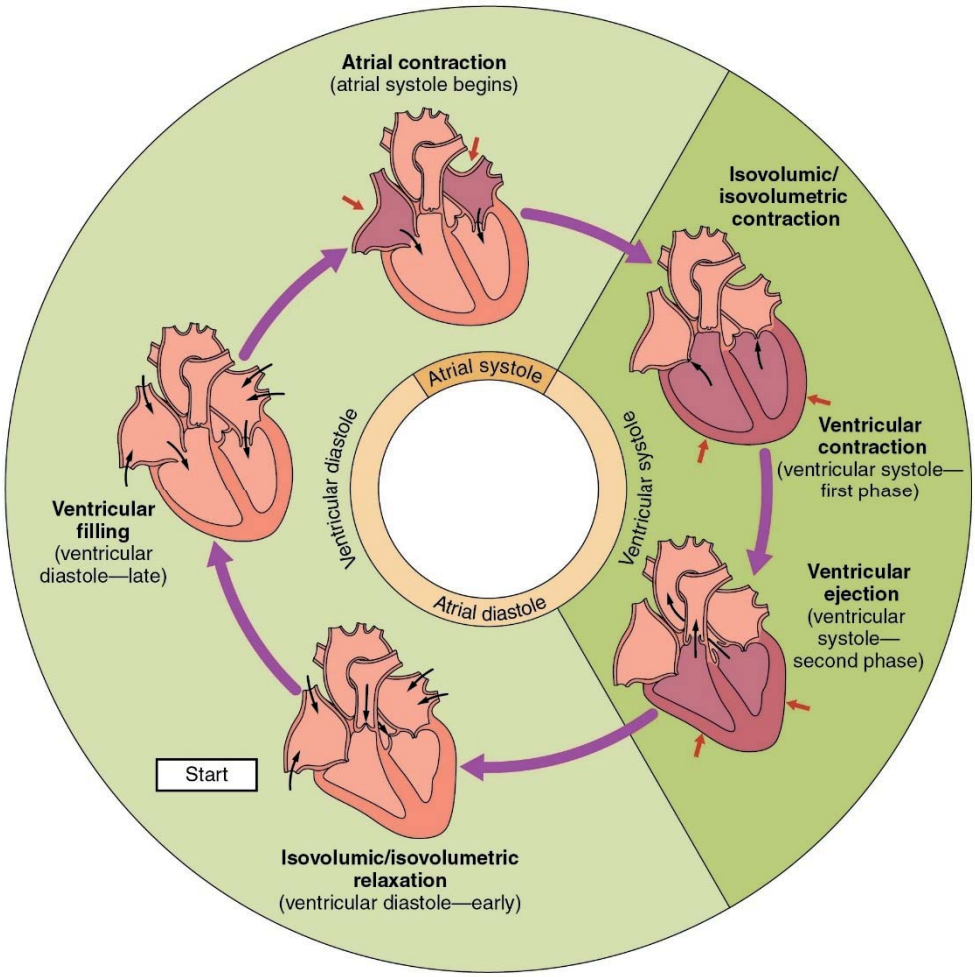



***Figure 2*** *The cardiac cycle.*

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]

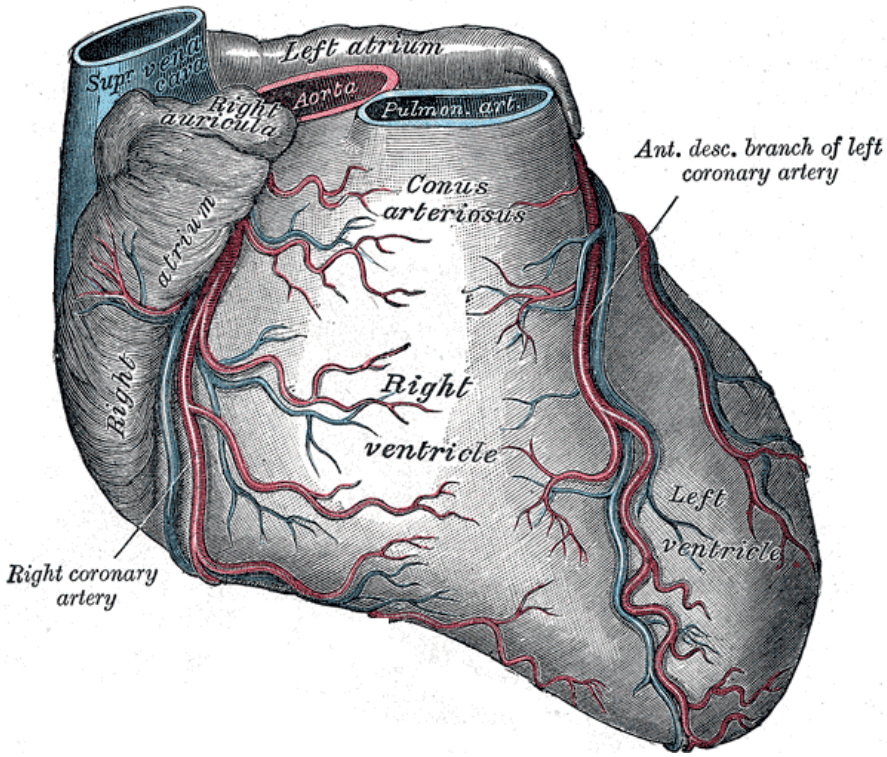



***Figure 3*** *Image of the heart and its vessels.*

# 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]

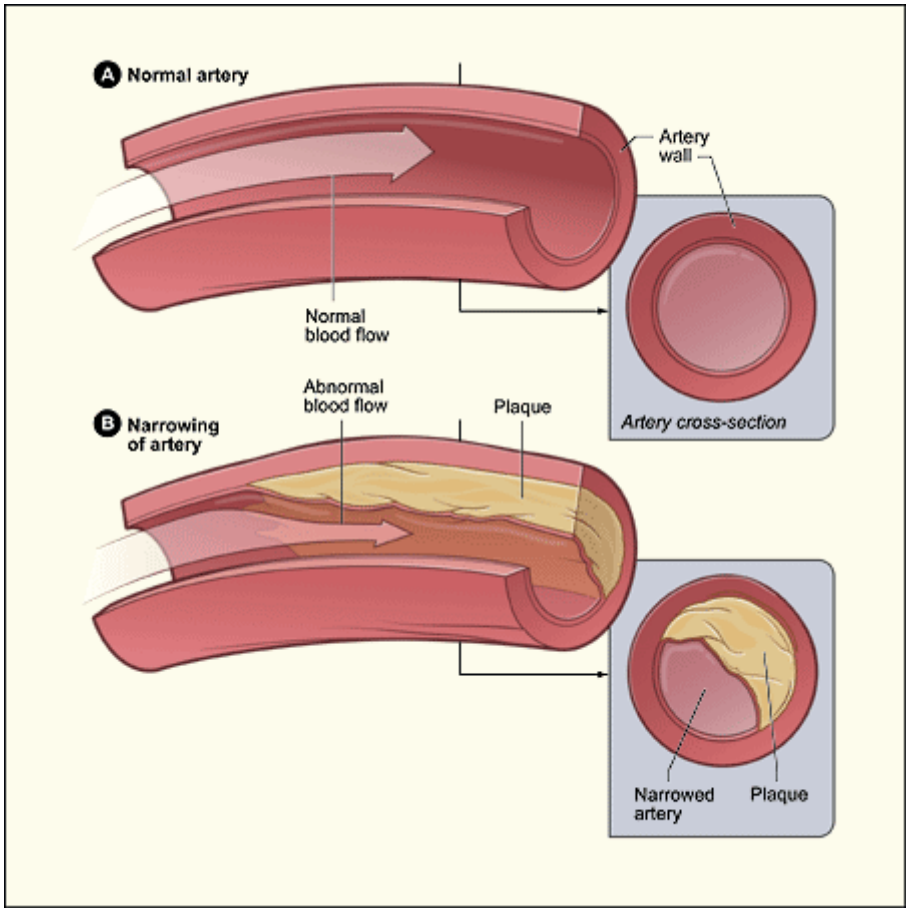



***Figure 4*** *Image of a normal artery (A) and a narrowed artery because of atherosclerosis (B).*

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]

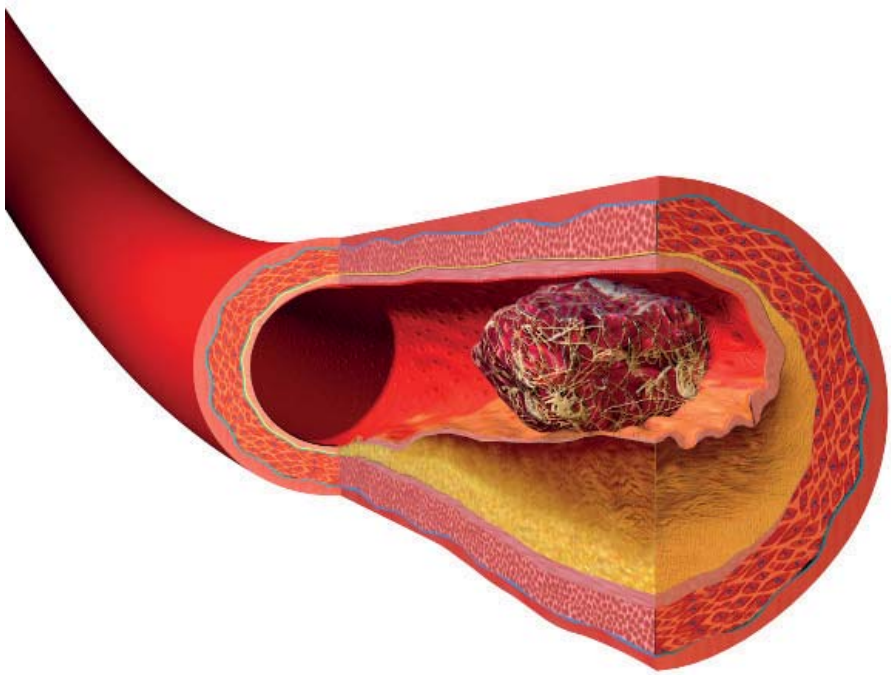


***Figure 5*** *Formation of a thrombosis in an atherosclerotic artery.*

### 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 $\geq 0.1$ mV in all leads expect for the $V_2$ and $V_3$ precordial leads in which the elevation must be $\geq 0.2$ mV, $\geq 0.25$ mV and $\geq 0.15$ mV for men $\geq 40$ 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]

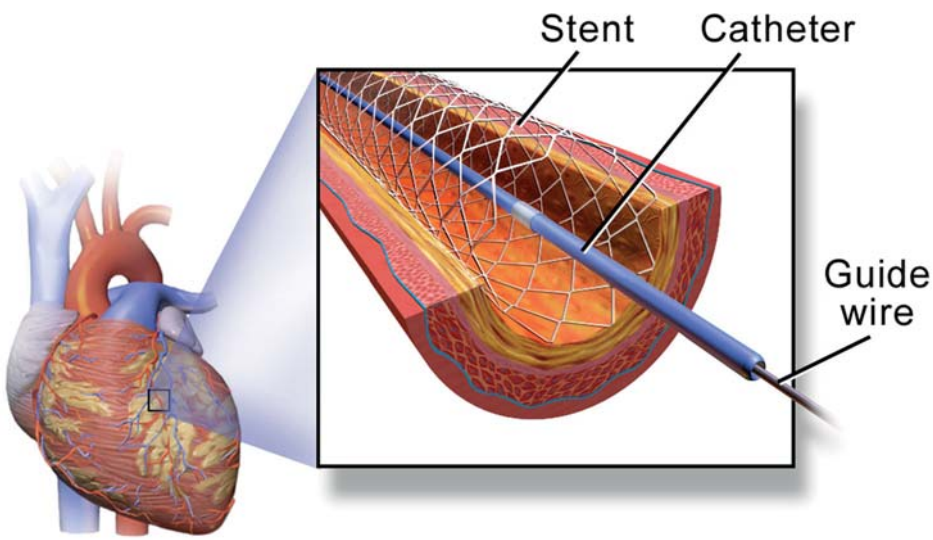



***Figure 6*** *Percutaneous Coronary Intervention (PCI).*

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]

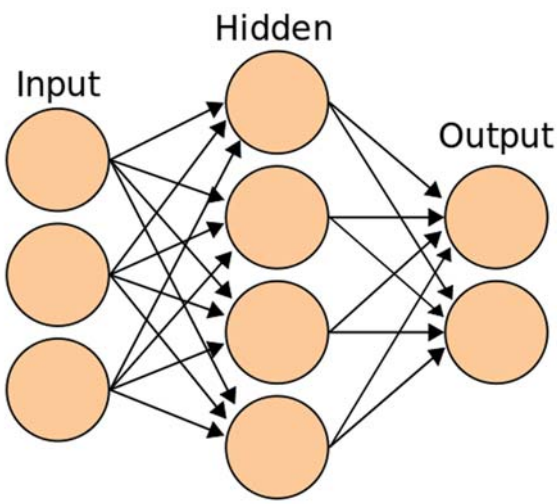



***Figure** 7 Basic illustration of an Artificial Neural Network.*

# 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]

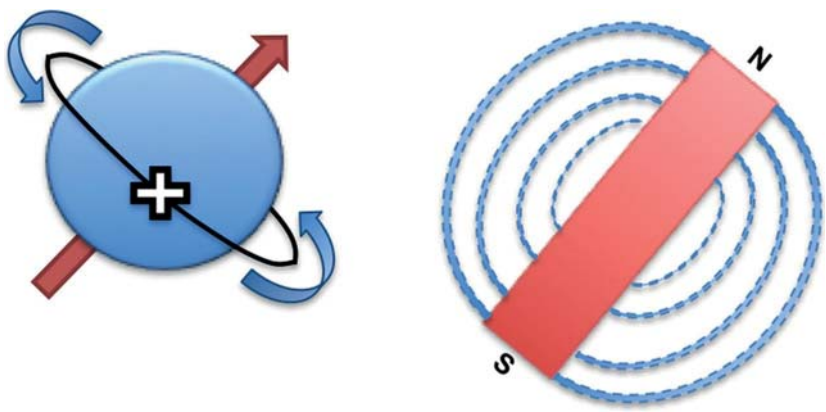



***Figure 8*** *The protons are spinning around their own axis, generating a magnetic field.*

# 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]

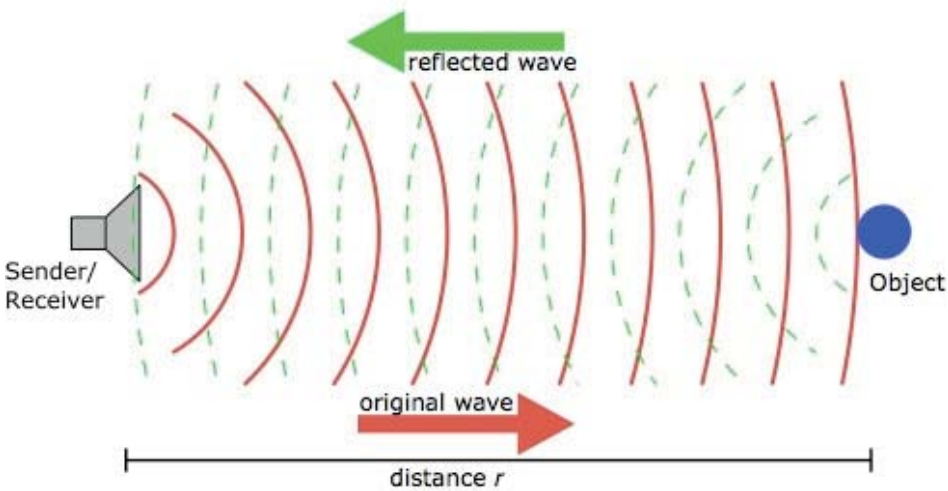



***Figure 9*** *Basic principles of how image is produced in an echocardiography.*

# 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*).

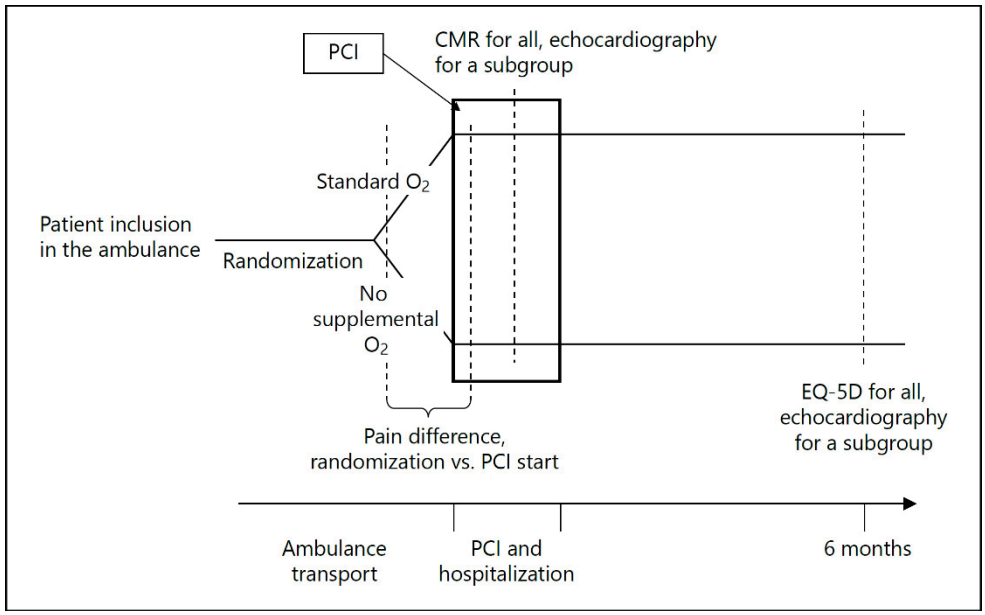



***Figure 10*** *Study design for the SOCCER study.*

*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]

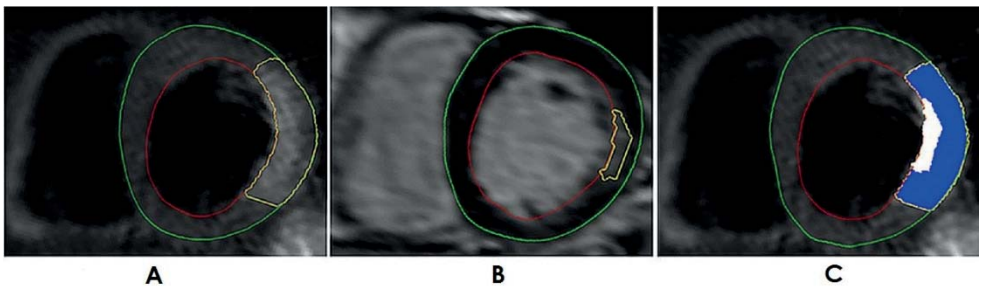



***Figure 11*** *Image A outlines the MaR (yellow). In image B, the IS is traced (yellow), and image C shows the salvaged myocardium (blue).*

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]

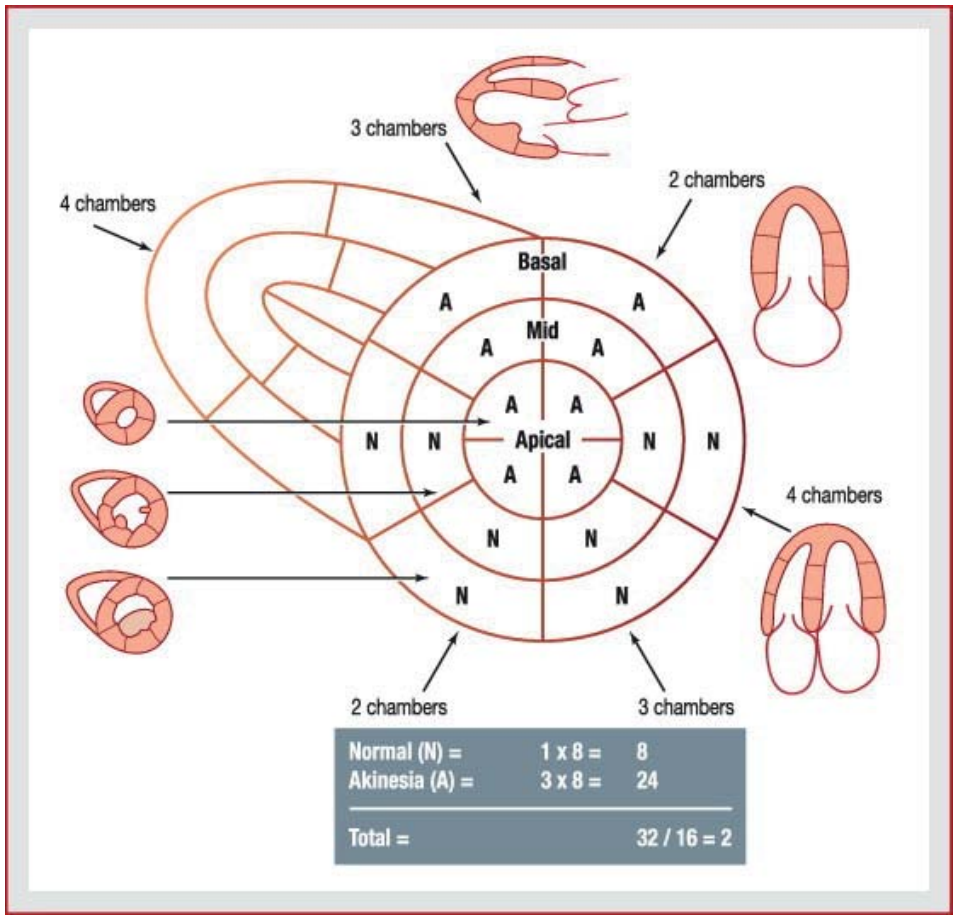



***Figure 13*** *WMSI calculation. In this example, the patient has eight normal segments and eight akinetic segments, giving a WMSI of 2.*

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.

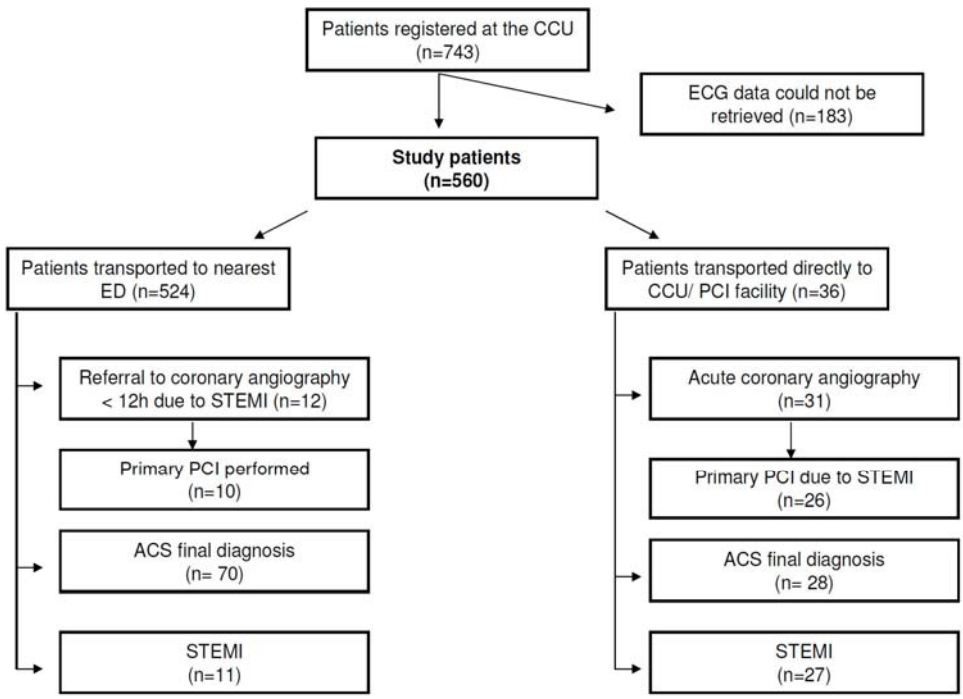



***Figure 14*** *Study profile.*

### 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).

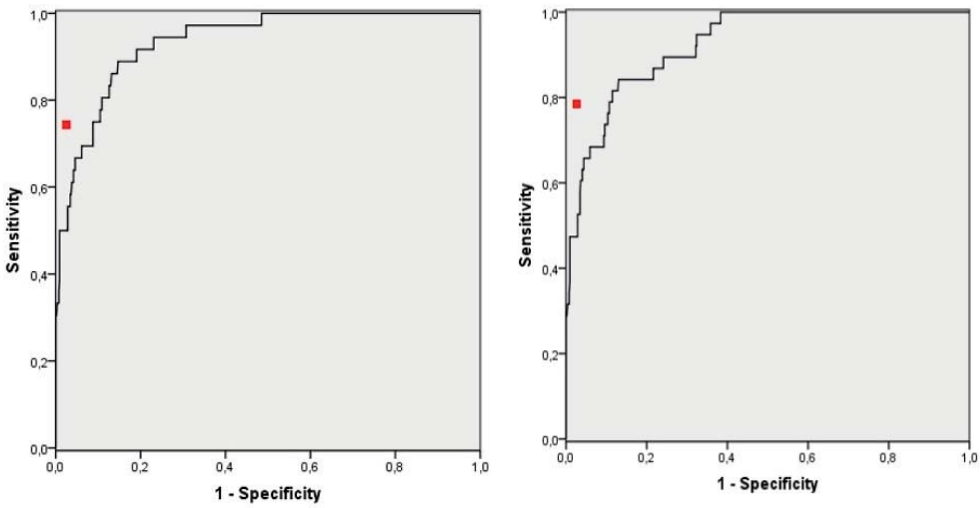



***Figure 15*** *The AUROC for the ANN to detect STEMI (right) and the AUROC for the ANNs ability to predict the need of an acute PCI (left). The red dots indicate the performance of the CCU physician in predicting STEMI and the need of acute PCI respectively.*

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.

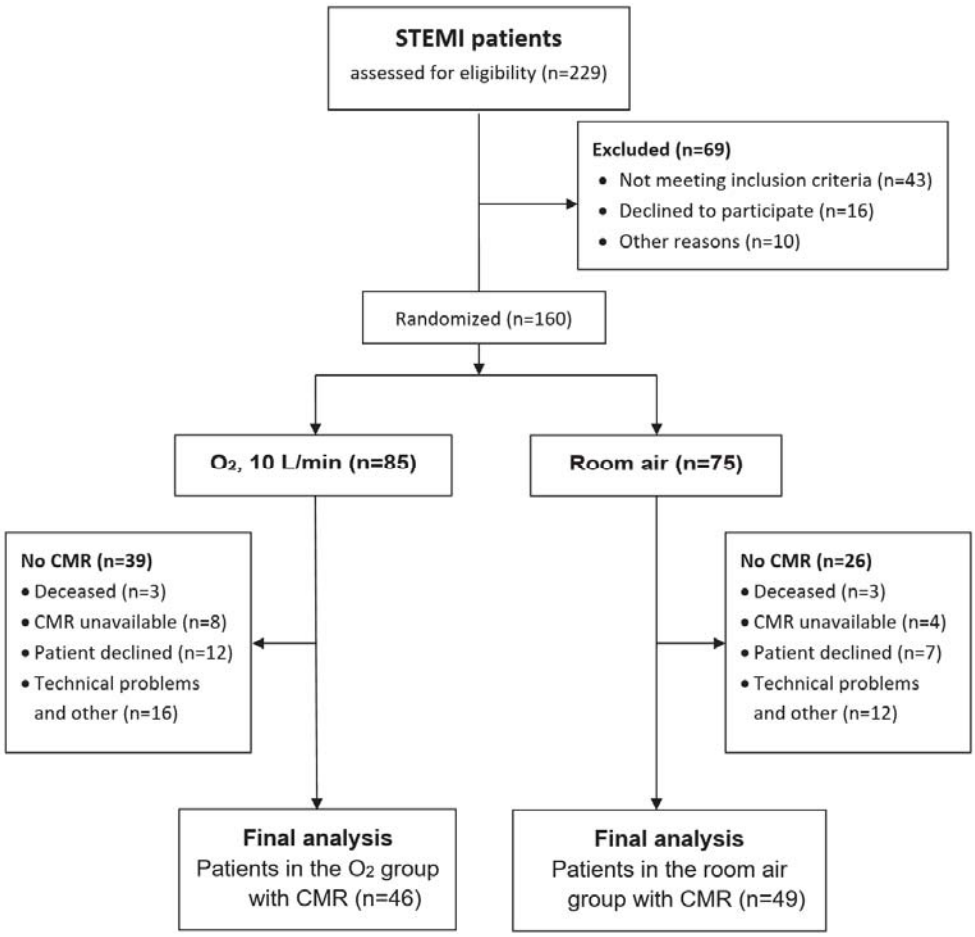
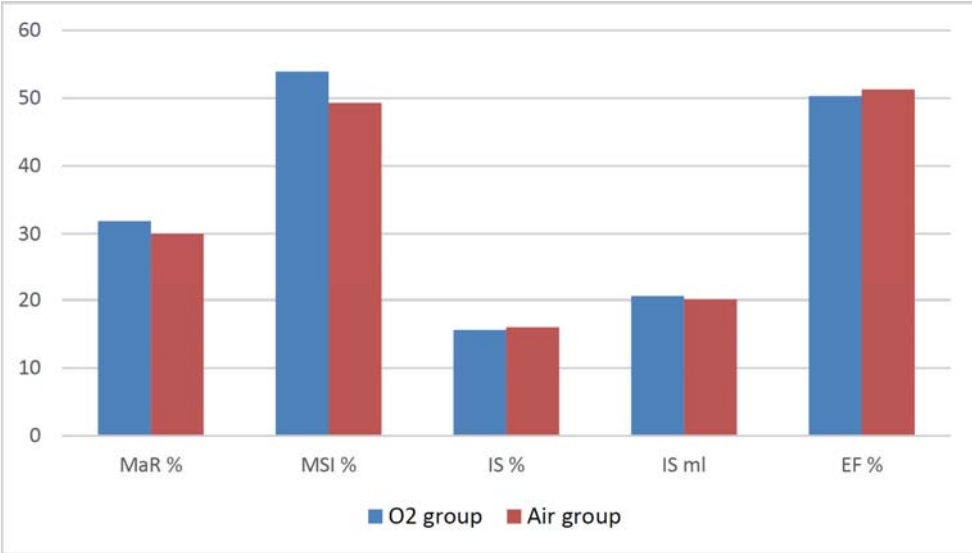



***Figure 16*** *Study profile.*

### 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%; $P = 0.02$).

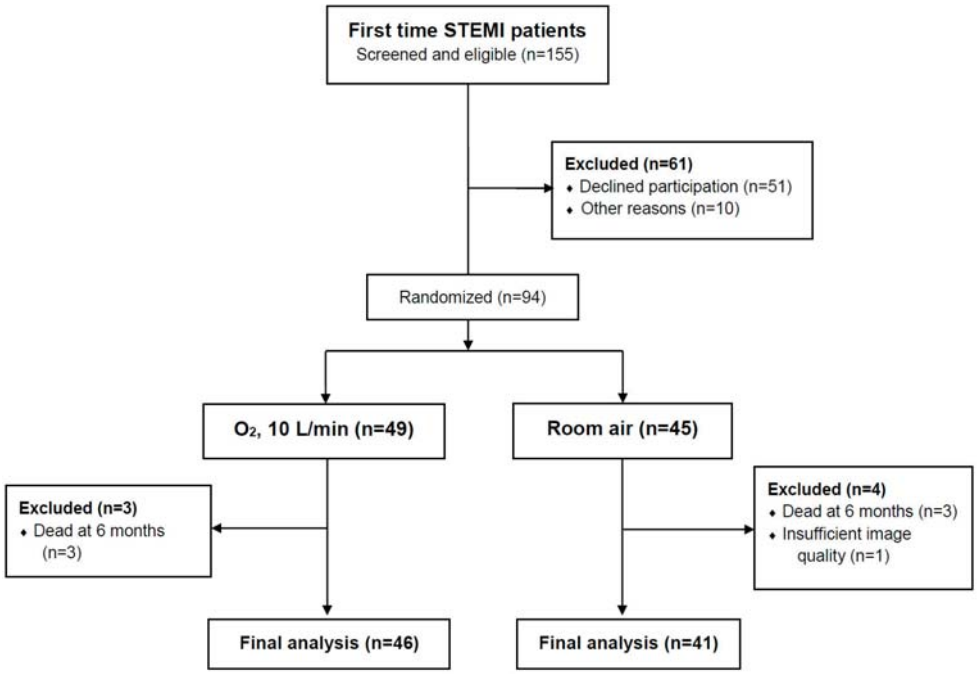
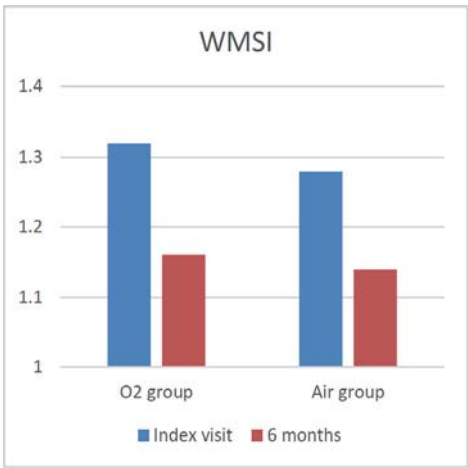
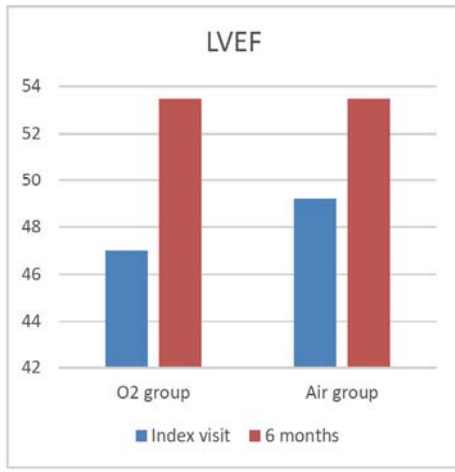



***Figure 18*** *Study profile.*

### 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


[1] Lee TH, Rouan GW, Weisberg MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *American Journal of Cardiology.* 1987;60(4):219-224.

[2] Pedersen SH, Galatius S, Hansen PR, et al. Field triage reduces treatment delay and improves long-term clinical outcome in patients with acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Journal of the American College of Cardiology.* 2009;54(24):2296-2302.

[3] International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 5: Acute Coronary Syndromes. *Resuscitation.* 2005;67(2-3):249-269.

[4] Pollack CV, Diercks DB, Roe MT, et al. 2004 American College of Cardiology/American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction: implications for emergency department practice. *Annals of Emergency Medicine.* 2005;45(4):363-376.

[5] Chew DP, Aroney CN, Aylward PE, et al. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006. *Heart, Lung and Circulation.* 2011;20(8):487-502.

[6] Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal.* 2011;32(23):2999-3054.

[7] O'Gara PT, Kushner FG, Ascheim DD, et al. American College of Emergency Physicians. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2013;61(4):e78-e140.

[8] Noble A, Johnson R, Thomas A, et al. *The Cardiovascular System: Systems of the Body Series.* China: Elsevier; 2010.

[9] Ellis H. The anatomy of the heart. *Anaesthesia & Intensive Care Medicine.* 2006;7(9):305-307.

[10] Klabunde R. *Cardiovascular physiology concepts.* China: Lippincott Williams & Wilkins; 2011.

[11] Hall JE. *Guyton and Hall textbook of medical physiology.* Philadelphia: Elsevier Health Sciences; 2015.

[12] Moss RL, Fitzsimons DP. Frank-Starling Relationship Long on Importance, Short on Mechanism. *Circulation Research.* 2002;90(1):11-13.

[13] Whitaker RH. Anatomy of the heart. *Medicine.* 2014;42(8):406-408.

[14] Ramanathan T, Skinner H. Coronary blood flow. *Continuing Education in Anaesthesia, Critical Care & Pain.* 2005;5(2):61-64.

[15] Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *British Heart Journal.* 1985;53(4):363.

[16] Mokhtari A, Borna C, Gilje P, et al. A 1-h combination algorithm allows fast rule-out and rule-in of major adverse cardiac events. *Journal of the American College of Cardiology.* 2016;67(13):1531-1540.

[17] Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-2035.

[18] Heusch G, Gersh BJ. The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *European Heart Journal.* 2017;38(11):774–784.

[19] Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation.* 2005;111(25):3481-3488.

[20] Santos-Gallego CG, Picatoste B, Badimón JJ. Pathophysiology of acute coronary syndrome. *Current Atherosclerosis Reports.* 2014;16(4):1-9.

[21] Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *New England Journal of Medicine.* 1998;338(23):1650-1656.

[22] Nemetz PN, Roger VL, Ransom JE, et al. Recent trends in the prevalence of coronary disease: a population-based autopsy study of nonnatural deaths. *Archives of Internal Medicine.* 2008;168(3):264-270.

[23] Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation.* 1995;92(5):1355-1374.

[24] Sakakura K, Nakano M, Otsuka F, et al. Pathophysiology of atherosclerosis plaque progression. *Heart, Lung and Circulation.* 2013;22(6):399-411.

[25] Stary HC, Chandler AB, Glagov S, et al. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 1994;14(5):840-856.

[26] Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *New England Journal of Medicine.* 2013;368(21):2004-2013.

[27] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *New England Journal of Medicine.* 2005;352(16):1685-1695.

[28] Ho-Tin-Noé B, Demers M, Wagner DD. How platelets safeguard vascular integrity. *Journal of Thrombosis and Haemostasis.* 2011;9(s1):56-65.

[29] Müller F, Renné T. Platelet polyphosphates: the nexus of primary and secondary hemostasis. *Scandinavian Journal of Clinical and Laboratory Investigation.* 2011;71(2):82-86.

[30] Cimmino G, Golino P. Platelet biology and receptor pathways. *Journal of Cardiovascular Translational Research.* 2013;6(3):299-309.

[31] Davies MJ. The pathophysiology of acute coronary syndromes. *Heart.* 2000;83(3):361-366.

[32] Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European Heart Journal.* 2016;37(3):267-315.

[33] Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2014;64(24):e139-e228.

[34] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2013;31(4):485-510.

[35] Advanced Life Support Group. *Acute Medical Emergencies: the Practical Approach.* 2 ed. London: BMJ Books; 2004.

[36] International Liaison Committee on Resuscitation. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 4: Advanced Life support. *Resuscitation.* 2005;67(2-3):213-247.

[37] Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology.* 2007;50(7):e1-e157.

[38] McCulloch WS, Pitts W. A logical calculus of the ideas immanent in nervous activity. *Bulletin of Mathematical Biophysics.* 1943;5(4):115-133.

[39] Hebb DO. *The Organization of Behavior: A Neuropsychological Theory.* New York: John Wiley & Sons, Inc.; 1949.

[40] Rosenblatt F. The perceptron: A probabilistic model for information storage and organization in the brain. *Psychological Review.* 1958;65(6):386-408.

[41] Baxt WG, Shofer FS, Sites FD, et al. A neural computational aid to the diagnosis of acute myocardial infarction. *Annals of Emergency Medicine.* 2002;39(4):366-373.

[42] Baxt WG, Shofer FS, Sites FD, et al. A neural network aid for the early diagnosis of cardiac ischemia in patients presenting to the emergency department with chest pain. *Annals of Emergency Medicine.* 2002;40(6):575-583.

[43] Harrison RF, Kennedy RL. Artificial neural network models for prediction of acute coronary syndromes using clinical data from the time of presentation. *Annals of Emergency Medicine.* 2005;46(5):431-439.

[44] Hedén B, Öhlin H, Rittner R, et al. Acute myocardial infarction detected in the 12-lead ECG by artificial neural networks. *Circulation.* 1997;96(6):1798-1802.

[45] Adams ST, Leveson SH. Clinical prediction rules. *British Medical Journal.* 2012;344:d8312.

[46] Bishop CM. *Neural networks for pattern recognition.* Oxford: Clarendon Press; 1995.

[47] Tu JV. Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes. *Journal of Clinical Epidemiology.* 1996;49(11):1225-1231.

[48] Ai T, Morelli JN, Hu X, et al. A historical overview of magnetic resonance imaging, focusing on technological innovations. *Investigative Radiology.* 2012;47(12):725-741.

[49] Damadian R. Tumor detection by nuclear magnetic resonance. *Science.* 1971;171(3976):1151-1153.

[50] Lauterbur PC. Image formation by induced local interactions: examples employing nuclear magnetic resonance. *Nature.* 1973;242:190-191.

[51] Mansfield P, Grannell PK. NMR 'diffraction' in solids? *Journal of Physics C: Solid State Physics.* 1973;6(22):L422-L426.

[52] Nobelprize.org. The Nobel Prize in Physiology or Medicine 2003. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2003/. Accessed 23 September, 2016.

[53] Pooley RA. Fundamental Physics of MR Imaging 1. *Radiographics.* 2005;25(4):1087-1099.

[54] Hanson LG. Is quantum mechanics necessary for understanding magnetic resonance? *Concepts in Magnetic Resonance Part A.* 2008;32(5):329-340.

[55] Pennell DJ. Cardiovascular magnetic resonance. *Circulation.* 2010;121(5):692-705.

[56] Singh S, Goyal A. The Origin of Echocardiography: A Tribute to Inge Edler. *Texas Heart Institute Journal.* 2007;34(4):431-438.

[57] Roelandt J. Seeing the invisible: a short history of cardiac ultrasound. *European Heart Journal: Cardiovascular Imaging.* 2000;1(1):8-11.

[58] Feigenbaum H. Evolution of echocardiography. *Circulation.* 1996;93(7):1321-1327.

[59] Wild JJ, Crawford HD, Reid JM. Visualization of the excised human heart by means of reflected ultrasound or echography: Preliminary report. *American Heart Journal.* 1957;54(6):903-906.

[60] Wild J, Reid J. Diagnostic use of ultrasound. *British Journal of Physical Medicine: Including its Application to Industry.* 1956;19(11):248.

[61] Keidel W. Uber eine methode zur Registrierung der Volumanderungen des Herzens am Menschen. *Z Kreislaufforsch.* 1950;39:257-261.

[62] Edler I, Lindström K. The history of echocardiography. *Ultrasound in Medicine & Biology.* 2004;30(12):1565-1644.

[63] Lee D, Solomon SD. Introduction to Imaging: The Normal Examination. In: Solomon SD, ed. *Essential Echocardiography: A Practical Guide With DVD*. New Jersey: Humana Press; 2007:19-34.

[64] Solomon SD. Echocardiographic Instrumentation and Principles of Doppler Echocardiography. In: Solomon SD, ed. *Essential Echocardiography: A Practical Guide With DVD*. New Jersey: Humana Press; 2007:3-18.

[65] Priestley J. *Experiments and observations on different kinds of air.* Vol 2. London: St. Paul's Church-Yard; 1775.

[66] Birch S. On Oxygen as a Therapeutic Agent. *British Medical Journal.* 1859;1(156):1033-1035.

[67] Steele C. Severe angina pectoris relieved by oxygen inhalations. *British Medical Journal.* 1900;2(2083):1568-1568.

[68] Levy RL, Barach AL. The therapeutic use of oxygen in coronary thrombosis. *Journal of the American Medical Association.* 1930;94(18):1363-1365.

[69] Boland EW. Oxygen in high concentrations for relief of pain: In coronary thrombosis and severe angina pectoris. *Journal of the American Medical Association.* 1940;114(16):1512-1514.

[70] Rizer R. Oxygen in the Treatment of Coronary Occlusion: Preliminary Report. *Minnesota Medicine.* 1929;12:506-507.

[71] Barach AL. The therapeutic use of oxygen in heart disease. *Annals of Internal Medicine.* 1931;5(4):428-440.

[72] Boothby W. Oxygen administration; the value of high concentration of oxygen for therapy. Paper presented at: Proc. Staff Meet., Mayo Clin1938.

[73] Russek HI, Regan FF, Naegele CF. One hundred per cent oxygen in the treatment of acute myocardial infarction and severe angina pectoris. *Journal of the American Medical Association.* 1950;144(5):373-375.

[74] Wijesinghe M, Shirtcliffe P, Perrin K, et al. An audit of the effect of oxygen prescription charts on clinical practice. *Postgraduate Medical Journal.* 2010;86(1012):89-93.

[75] Kbar FA, Campbell IA. Oxygen therapy in hospitalized patients: the impact of local guidelines. *Journal of Evaluation in Clinical Practice.* 2006;12(1):31-36.

[76] Burls A, Emparanza JI, Quinn T, et al. Oxygen use in acute myocardial infarction: an online survey of health professionals' practice and beliefs. *Emergency Medicine Journal.* 2010;27(4):283-286.

[77] Garg P, Lagan J. Oxygen Therapy in Cardiology: Local prescribing experience at a large regional cardiac centre. *The Internet Journal of Cardiology.* 2010;9(2):1-4.

[78] Neill WA. Effects of arterial hypoxemia and hyperoxia on oxygen availability for myocardial metabolism: patients with and without coronary heart disease. *American Journal of Cardiology.* 1969;24(2):166-171.

[79] Eckenhoff J, Hafkenschiel J, Landmesser C. The coronary circulation in the dog. *American Journal of Physiology--Legacy Content.* 1947;148(3):582-596.

[80] Sobol BJ, Wanlass SA, Joseph EB, et al. Alteration of coronary blood flow in the dog by inhalation of 100 per cent oxygen. *Circulation Research.* 1962;11(5):797-802.

[81] Bak Z, Sjöberg F, Rousseau A, et al. Human cardiovascular dose–response to supplemental oxygen. *Acta Physiologica.* 2007;191(1):15-24.

[82] Milone SD, Newton GE, Parker JD. Hemodynamic and biochemical effects of 100% oxygen breathing in humans. *Canadian Journal of Physiology and Pharmacology.* 1999;77(2):124-130.

[83] Waring WS, Thomson AJ, Adwani SH, et al. Cardiovascular effects of acute oxygen administration in healthy adults. *Journal of Cardiovascular Pharmacology.* 2003;42(2):245-250.

[84] Rousseau A, Bak Z, Janerot-Sjöberg B, et al. Acute hyperoxaemia-induced effects on regional blood flow, oxygen consumption and central circulation in man. *Acta Physiologica Scandinavica.* 2005;183(3):231-240.

[85] Bergofsky EH, Bertun P. Response of regional circulations to hyperoxia. *Journal of Applied Physiology.* 1966;21(2):567-572.

[86] Kenmure A, Murdoch W, Hutton I, et al. Hemodynamic effects of oxygen at 1 and 2 Ata pressure in healthy subjects. *Journal of Applied Physiology.* 1972;32(2):223-226.

[87] Thomson AJ, Drummond GB, Waring WS, et al. Effects of short-term isocapnic hyperoxia and hypoxia on cardiovascular function. *Journal of Applied Physiology.* 2006;101(3):809-816.

[88] Whitehorn W, Edelmann A, Hitchcock FA. The cardiovascular responses to the breathing of 100 per cent oxygen at normal barometric pressure. *American Journal of Physiology--Legacy Content.* 1946;146(1):61-65.

[89] Mak S, Azevedo ER, Liu PP, et al. Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. *CHEST Journal.* 2001;120(2):467-473.

[90] Bodetoft S, Carlsson M, Arheden H, et al. Effects of oxygen inhalation on cardiac output, coronary blood flow and oxygen delivery in healthy individuals, assessed with MRI. *European Journal of Emergency Medicine.* 2011;18(1):25-30.

[91] Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *American Heart Journal.* 2009;158(3):371-377.

[92] Helmerhorst HJ, Roos-Blom M-J, van Westerloo DJ, et al. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies. *Critical Care Medicine.* 2015;43(7):1508-1519.

[93] Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. *Current Opinion in Critical Care.* 2007;13(1):73-78.

[94] Eggers G, Paley H, Leonard J, et al. Hemodynamic responses to oxygen breathing in man. *Journal of Applied Physiology.* 1962;17(1):75-79.

[95] Shibata S, Iwasaki K-i, Ogawa Y, et al. Cardiovascular neuroregulation during acute exposure to 40, 70, and 100% oxygen at sea level. *Aviation, Space, and Environmental Medicine.* 2005;76(12):1105-1110.

[96] Rubanyi G, Vanhoutte P. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *American Journal of Physiology-Heart and Circulatory Physiology.* 1986;250(5):H822-H827.

[97] Gustafsson U, Sjöberg F. Serotonin–One Possible Link between Oxygen Metabolism and the Regulation of Blood Flow in the Brain? *International Journal of Microcirculation.* 1996;16(3):143-146.

[98] Messina EJ, Sun D, Koller A, et al. Increases in oxygen tension evoke arteriolar constriction by inhibiting endothelial prostaglandin synthesis. *Microvascular Research.* 1994;48(2):151-160.

[99] Kaneda T, Ku K, Inoue T, et al. Postischemic reperfusion injury can be attenuated by oxygen tension control. *Japanese Circulation Journal.* 2001;65(3):213-218.

[100] Gore A, Muralidhar M, Espey MG, et al. Hyperoxia sensing: from molecular mechanisms to significance in disease. *Journal of Immunotoxicology.* 2010;7(4):239-254.

[101] Haque WA, Boehmer J, Clemson BS, et al. Hemodynamic effects of supplemental oxygen administration in congestive heart failure. *Journal of the American College of Cardiology.* 1996;27(2):353-357.

[102] Saadjian A, Paganelli F, Levy S. Hemodynamic response to oxygen administration in chronic heart failure: role of chemoreflexes. *Journal of Cardiovascular Pharmacology.* 1999;33(1):144-150.

[103] Daly WJ, Behnke RH. Hemodynamic consequences of oxygen breathing in left ventricular failure. *Circulation.* 1963;27(2):252-256.

[104] O'Neill WW, Martin JL, Dixon SR, et al. Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT): a prospective, randomized trial of intracoronary hyperoxemic reperfusion after percutaneous coronary intervention. *Journal of the American College of Cardiology.* 2007;50(5):397-405.

[105] Bourassa MG, Campeau L, Bois MA, et al. The effects of inhalation of 100 per cent oxygen on myocardial lactate metabolism in coronary heart disease. *American Journal of Cardiology.* 1969;24(2):172-177.

[106] Dixon SR, Bartorelli AL, Marcovitz PA, et al. Initial experience with hyperoxemic reperfusion after primary angioplasty for acute myocardial infarction: results of a pilot study utilizing intracoronary aqueous oxygen therapy. *Journal of the American College of Cardiology.* 2002;39(3):387-392.

[107] Foster GL, Casten GG, Reeves T. The effects of oxygen breathing in patients with acute myocardial infarction. *Cardiovascular Research.* 1969;3(2):179-189.

[108] Ganz W, Donoso R, Marcus H, et al. Coronary hemodynamics and myocardial oxygen metabolism during oxygen breathing in patients with and without coronary artery disease. *Circulation.* 1972;45(4):763-768.

[109] Horvat M, Yoshida S, Prakash R, et al. Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency. *Circulation.* 1972;45(4):837-844.

[110] Kenmure A, Murdoch W, Beattie A, et al. Circulatory and metabolic effects of oxygen in myocardial infarction. *British Medical Journal* 1968;4(5627):360-364.

[111] McNulty PH, King N, Scott S, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *American Journal of Physiology-Heart and Circulatory Physiology.* 2005;288(3):H1057-H1062.

[112] McNulty PH, Robertson BJ, Tulli MA, et al. Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. *Journal of Applied Physiology.* 2007;102(5):2040-2045.

[113] Rawles J, Kenmure A. Controlled trial of oxygen in uncomplicated myocardial infarction. *British Medical Journal.* 1976;1(6018):1121-1123.

[114] Stone GW, Martin JL, de Boer M-J, et al. Effect of supersaturated oxygen delivery on infarct size after percutaneous coronary intervention in acute myocardial infarction. *Circulation: Cardiovascular Interventions.* 2009;2(5):366-375.

[115] Ukholkina GB, Kostyanov IY, Kuchkina NV, et al. Oxygen Therapy in Combination with Endovascular Reperfusion during the First Hours of Acute Myocardial Infarction: Clinical and Laboratory Findings. *International Journal of Interventional Cardioangiology.* 2005(9):45-51.

[116] Warda HM, Bax JJ, Bosch JG, et al. Effect of intracoronary aqueous oxygen on left ventricular remodeling after anterior wall ST-elevation acute myocardial infarction. *American Journal of Cardiology.* 2005;96(1):22-24.

[117] Lancaster R, McNicol M. Oxygen therapy in myocardial infarction. *Postgraduate Medical Journal.* 1967;43(505):706.

[118] Nehme Z, Stub D, Bernard S, et al. Effect of supplemental oxygen exposure on myocardial injury in ST-elevation myocardial infarction. *Heart.* 2016;102(6):444-451.

[119] Ranchord AM, Argyle R, Beynon R, et al. High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: a pilot randomized controlled trial. *American Heart Journal.* 2012;163(2):168-175.

[120] Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment elevation myocardial infarction. *Circulation.* 2015;131(24):2143–2150.

[121] Wilson A, Channer K. Hypoxaemia and supplemental oxygen therapy in the first 24 hours after myocardial infarction: the role of pulse oximetry. *Journal of the Royal College of Physicians of London.* 1997;31(6):657-661.

[122] Maroko PR, Radvany P, Braunwald E, et al. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation.* 1975;52(3):360-368.

[123] Kelly RF, Hursey TL, Parrillo JE, et al. Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion. *American Heart Journal* 1995;130(5):957-965.

[124] Guensch DP, Fischer K, Shie N, et al. Hyperoxia Exacerbates Myocardial Ischemia in the Presence of Acute Coronary Artery Stenosis in Swine. *Circulation: Cardiovascular Interventions.* 2015;8(10):e002928.

[125] Beasley R, Aldington S, Weatherall M, et al. Oxygen therapy in myocardial infarction: an historical perspective. *Journal of the Royal Society of Medicine.* 2007;100(3):130-133.

[126] Burls A, Cabello JB, Emparanza JI, et al. Oxygen therapy for acute myocardial infarction: a systematic review and meta-analysis. *Emergency Medicine Journal.* 2011;28(11):917-923.

[127] Cabello JB, Burls A, Emparanza JI, et al. Oxygen therapy for acute myocardial infarction. *The Cochrane Library.* 2016.

[128] Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. *Journal of the American College of Cardiology.* 2010;56(13):1013-1016.

[129] Nicholson C. A systematic review of the effectiveness of oxygen in reducing acute myocardial ischaemia. *Journal of Clinical Nursing.* 2004;13(8):996-1007.

[130] Shuvy M, Atar D, Steg PG, et al. Oxygen therapy in acute coronary syndrome: are the benefits worth the risk? *European Heart Journal.* 2013;34(22):1630-1635.

[131] Sepehrvand N, Ezekowitz JA. Oxygen Therapy in Patients With Acute Heart Failure. *JACC: Heart Failure.* 2016;4(10):783-790.

[132] Kones R. Oxygen therapy for acute myocardial infarction—then and now. A century of uncertainty. *American Journal of Cardiology.* 2011;124(11):1000-1005.

[133] Wijesinghe M, Perrin K, Ranchord A, et al. Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart.* 2009;95(3):198-202.

[134] Atar D. Should oxygen be given in myocardial infarction? *British Medical Journal.* 2010;340:c3287.

[135] Richard Conti C. Oxygen therapy–use and abuse in acute myocardial infarction Patients. *Clinical Cardiology.* 2009;32(9):480-481.

[136] Nedeljkovic ZS, Jacobs AK. $O_2$ for STEMI: Still Up in the Air. *Circulation.* 2015;131(24):2101-2103.

[137] Saltzman H. Efficacy of oxygen enriched gas mixtures in the treatment of acute myocardial infarction. *Circulation.* 1975;52(3):357-359.

[138] Shuvy M, Lotan C. Oxygen therapy in myocardial infarction? Still waiting for an answer. *Cardiology.* 2015;132(1):68-70.

[139] Hofmann R, James SK, Jernberg T, et al. Oxygen Therapy in Suspected Acute Myocardial Infarction. *New England Journal of Medicine.* 2017; Epub ahead of print.

[140] Olsson SE, Ohlsson M, Öhlin H, et al. Decision support for the initial triage of patients with acute coronary syndromes. *Clinical Physiology and Functional Imaging.* 2006;26(3):151-156.

[141] Swedish coronary angiography and angioplasty register. SCAAR. http://www.ucr.uu.se/swedeheart/start-scaar.

[142] MedCore. En maske leverer 24% - 90% oksygen. 2013; http://www.medcore.se/wp-content/uploads/OxyMask.pdf. Accessed 21 September, 2016.

[143] Swedeheart. 2016; http://www.ucr.uu.se/swedeheart/. Accessed 21 September, 2016.

[144] Skane.se. Melior. http://vardgivare.skane.se/it/it-stod-och-tjanster-a-o/melior/. Accessed 21 September, 2016.

[145] Carlsson M, Ubachs JF, Hedström E, et al. Myocardium at risk after acute infarction in humans on cardiac magnetic resonance: quantitative assessment during follow-up and validation with single-photon emission computed tomography. *JACC: Cardiovascular Imaging.* 2009;2(5):569-576.

[146] Lønborg J, Vejlstrup N, Kelbæk H, et al. Final infarct size measured by cardiovascular magnetic resonance in patients with ST elevation myocardial infarction predicts long-term clinical outcome: an observational study. *European Heart Journal: Cardiovascular Imaging.* 2012;14(4):387–395.

[147] Wu E, Ortiz JT, Tejedor P, et al. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart.* 2008;94(6):730-736.

[148] Bulluck H, Hammond-Haley M, Weinmann S, et al. Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies: Insights From Randomized Controlled Trials. *JACC: Cardiovascular Imaging.* 2017;10(3):230-240.

[149] Heiberg E, Sjögren J, Ugander M, et al. Design and validation of Segment-freely available software for cardiovascular image analysis. *BMC Medical Imaging.* 2010;10(1):1.

[150] Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation.* 1999;100(19):1992-2002.

[151] Doltra A, Hoyem Amundsen B, Gebker R, et al. Emerging concepts for myocardial late gadolinium enhancement MRI. *Current Cardiology Reviews.* 2013;9(3):185-190.

[152] Sörensson P, Heiberg E, Saleh N, et al. Assessment of myocardium at risk with contrast enhanced steady-state free precession cine cardiovascular magnetic resonance compared to single-photon emission computed tomography. *Journal of Cardiovascular Magnetic Resonance.* 2010;12(25).

[153] Heiberg E, Ugander M, Engblom H, et al. Automated quantification of myocardial infarction from MR images by accounting for partial volume effects: animal, phantom, and human study. *Radiology.* 2008;246(2):581-588.

[154] Engblom H, Tufvesson J, Jablonowski R, et al. A new automatic algorithm for quantification of myocardial infarction imaged by late gadolinium enhancement cardiovascular magnetic resonance: experimental validation and comparison to expert delineations in multi-center, multi-vendor patient data. *Journal of Cardiovascular Magnetic Resonance.* 2016;18(27).

[155] Jablonowski R, Engblom H, Kanski M, et al. Contrast-enhanced CMR overestimates early myocardial infarct size: mechanistic insights using ECV measurements on day 1 and day 7. *JACC: Cardiovascular Imaging.* 2015;8(12):1379-1389.

[156] Jablonowski R, Engblom H, Kanski M, et al. The Authors Reply. *JACC: Cardiovascular Imaging.* 2016;9(8):1016-1017.

[157] Saremi F. Cardiac MR Imaging in Acute Coronary Syndrome: Application and Image Interpretation. *Radiology.* 2016;282(1):17-32.

[158] Aletras AH, Tilak GS, Natanzon A, et al. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation.* 2006;113(15):1865-1870.

[159] Kellman P, Aletras AH, Mancini C, et al. T2-prepared SSFP improves diagnostic confidence in edema imaging in acute myocardial infarction compared to turbo spin echo. *Magnetic Resonance in Medicine.* 2007;57(5):891-897.

[160] Ubachs JF, Sörensson P, Engblom H, et al. Myocardium at risk by magnetic resonance imaging: head-to-head comparison of T2-weighted imaging and contrast-enhanced steady-state free precession. *European Heart Journal: Cardiovascular Imaging.* 2012;13(12):1008-1015.

[161] Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: Patient-level analysis from 10 randomized trials. *Journal of the American College of Cardiology.* 2016;67(14):1674-1683.

[162] Dastidar AG, Rodrigues JC, Baritussio A, et al. MRI in the assessment of ischaemic heart disease. *Heart.* 2016;102(3):239-252.

[163] Roes SD, Kelle S, Kaandorp TA, et al. Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction. *American Journal of Cardiology.* 2007;100(6):930-936.

[164] Hombach V, Merkle N, Bernhard P, et al. Prognostic significance of cardiac magnetic resonance imaging: Update 2010. *Cardiology Journal.* 2010;17(6):549-557.

[165] Eitel I, Desch S, de Waha S, et al. Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Heart.* 2011;97(24):2038-2045.

[166] Hendriks T, Hartman MH, Vlaar PJ, et al. Predictors of left ventricular remodeling after ST-elevation myocardial infarction. *The International Journal of Cardiovascular Imaging.*33(9):1415-1423.

[167] Eitel I, Desch S, Fuernau G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Journal of the American College of Cardiology.* 2010;55(22):2470-2479.

[168] Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation.* 1992;86(1):81-90.

[169] Engblom H, Heiberg E, Erlinge D, et al. Sample size in clinical cardioprotection trials using myocardial salvage index, infarct size, or biochemical markers as endpoint. *Journal of the American Heart Association.* 2016;5(3):e002708.

[170] Stiermaier T, Eitel I, de Waha S, et al. Myocardial salvage after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction presenting early versus late after symptom onset. *The International Journal of Cardiovascular Imaging.* 2017; Epub ahead of print.

[171] Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *Journal of the American College of Cardiology.* 2009;54(23):2145-2153.

[172] Busk M, Kaltoft A, Nielsen SS, et al. Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs. 12–72 h. *European Heart Journal.* 2009;30(11):1322-1330.

[173] Wahr DW, Wang YS, Schiller NB. Left ventricular volumes determined by two-dimensional echocardiography in a normal adult population. *Journal of the American College of Cardiology.* 1983;1(3):863-868.

[174] Quiñones MA, Waggoner AD, Reduto L, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation.* 1981;64(4):744-753.

[175] Rumberger JA, Behrenbeck T, Bell MR, et al. Determination of ventricular ejection fraction: a comparison of available imaging methods. Paper presented at: Mayo Clinic Proceedings 1997.

[176] Lang RM, Bierig M, Devereux RB, et al. Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography. *Journal of the American Society of Echocardiography.*18(12):1440-1463.

[177] White HD, Norris R, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987;76(1):44-51.

[178] Galasko G, Basu S, Lahiri A, et al. A prospective comparison of echocardiographic wall motion score index and radionuclide ejection fraction in predicting outcome following acute myocardial infarction. *Heart.* 2001;86(3):271-276.

[179] Møller JE, Hillis GS, Oh JK, et al. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. *American Heart Journal* 2006;151(2):419-425.

[180] Kjøller E, Køber L, Jørgensen S, et al. Long-term prognostic importance of hyperkinesia following acute myocardial infarction. *American Journal of Cardiology.* 1999;83(5):655-659.

[181] Jaarsma W, Visser CA, Van MJE, et al. Prognostic implications of regional hyperkinesia and remote asynergy of noninfarcted myocardium. *American Journal of Cardiology.* 1986;58(6):394-398.

[182] Piérard LA, Lancellotti P. Risk stratification after myocardial infarction: toward novel quantitative assessment of left ventricular mechanics? *Journal of the American College of Cardiology.* 2010;56(22):1823-1825.

[183] Broderick TM, Bourdillon PD, Ryan T, et al. Comparison of regional and global left ventricular function by serial echocardiograms after reperfusion in acute myocardial infarction. *Journal of the American Society of Echocardiography.* 1989;2(5):315-323.

[184] Lancellotti P, Hoffer EP, Piérard LA. Detection and clinical usefulness of a biphasic response during exercise echocardiography early after myocardial infarction. *Journal of the American College of Cardiology.* 2003;41(7):1142-1147.

[185] Pièard L, Albert A, Chapelle J-P, et al. Relative prognostic value of clinical, biochemical, echocardiographic and haemodynamic variables in predicting in-hospital and one-year cardiac mortality after acute myocardial infarction. *European Heart Journal.* 1989;10(1):24-31.

[186] Maioli M, Bellandi F, Leoncini M, et al. Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAx-AMI Trial). *Journal of the American College of Cardiology.* 2007;49(14):1517-1524.

[187] Liistro F, Grotti S, Angioli P, et al. Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circulation: Cardiovascular Interventions.* 2009;2(5):376-383.

[188] Carluccio E, Tommasi S, Bentivoglio M, et al. Usefulness of the severity and extent of wall motion abnormalities as prognostic markers of an adverse outcome after a first myocardial infarction treated with thrombolytic therapy. *American Journal of Cardiology.* 2000;85(4):411-415.

[189] Jurado-Román A, Agudo-Quílez P, Rubio-Alonso B, et al. Superiority of wall motion score index over left ventricle ejection fraction in predicting cardiovascular events after an acute myocardial infarction. *European Heart Journal: Acute Cardiovascular Care.* 2016; Epub ahead of print.

[190] Atar D, Arheden H, Berdeaux A, et al. Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. *European Heart Journal.* 2014;36(2):112-119.

[191] Erlinge D, Götberg M, Lang I, et al. Rapid endovascular catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction: the CHILL-MI trial: a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct to percutaneous coronary intervention for the treatment of acute myocardial infarction. *Journal of the American College of Cardiology.* 2014;63(18):1857-1865.

[192] Götberg M, Olivecrona GK, Koul S, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circulation: Cardiovascular Interventions.* 2010;3(5):400-407.

[193] Stub D, Smith K, Bernard S, et al. A randomized controlled trial of oxygen therapy in acute myocardial infarction Air Verses Oxygen In myocarDial infarction study (AVOID Study). *American Heart Journal.* 2012;163(3):339-345. e331.

[194] Hofmann R, James SK, Svensson L, et al. DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial. *American Heart Journal* 2014;167(3):322-328.

[195] Sejersten M, Sillesen M, Hansen PR, et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial

infarction to primary percutaneous coronary intervention. *American Journal of Cardiology.* 2008;101(7):941-946.

[196] Clark EN, Sejersten M, Clemmensen P, et al. Automated electrocardiogram interpretation programs versus cardiologists' triage decision making based on teletransmitted data in patients with suspected acute coronary syndrome. *American Journal of Cardiology.* 2010;106(12):1696-1702.

[197] Ashfield R, Gavey C. Severe acute myocardial infarction treated with hyperbaric oxygen. Report on forty patients. *Postgraduate Medical Journal.* 1969;45(528):648-654.

[198] Madias JE, Madias NE, Hood WB. Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. *Circulation.* 1976;53(3):411-417.

[199] Stavitsky Y, Shandling AH, Ellestad MH, et al. Hyperbaric oxygen and thrombolysis in myocardial infarction: the 'HOT MI'randomized multicenter study. *Cardiology.* 1998;90(2):131-136.

[200] Anderson JL, Morrow DA. Acute myocardial infarction. *New England Journal of Medicine.* 2017;376(21):2053-2064.

[201] Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *The Lancet.* 2017;389(10065):197-210.

[202] Nordlund D, Klug G, Heiberg E, et al. Multi-vendor, multicentre comparison of contrast-enhanced SSFP and T2-STIR CMR for determining myocardium at risk in ST-elevation myocardial infarction. *European Heart Journal: Cardiovascular Imaging.* 2016;17(7):744-753.

[203] Ross AM, Gibbons RJ, Stone GW, et al. A Randomized, Double-Blinded, Placebo-Controlled Multicenter Trial of Adenosine as an Adjunct to Reperfusion in the Treatment of Acute Myocardial Infarction (AMISTAD-II). *Journal of the American College of Cardiology.* 2005;45(11):1775-1780.

[204] Nikolaou NI, Arntz H-R, Bellou A, et al. European Resuscitation Council guidelines for resuscitation 2015 section 8. initial management of acute coronary syndromes. *Resuscitation.* 2015;95:264-277.

[205] Heden B, Ohlin H, Rittner R, et al. Acute myocardial infarction detected in the 12-lead ECG by artificial neural networks. *Circulation.* 1997;96(6):1798-1802.

[206] Berikol GB, Yildiz O, Özcan İT. Diagnosis of acute coronary syndrome with a support vector machine. *Journal of Medical Systems.* 2016;40(4):1-8.

[207] Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *Journal of American Medical Association.* 2016;316(15):1583-1589.

[208] Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology.* 2008;59:565-590.

[209] Fitterman N. Why Oxygen Is Not Necessary for All STEMIs. *JAMA Internal Medicine.* 2017;177(2):267-268.

*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.