Evaluating Treatment and Diagnostics in Cardiac Intervention

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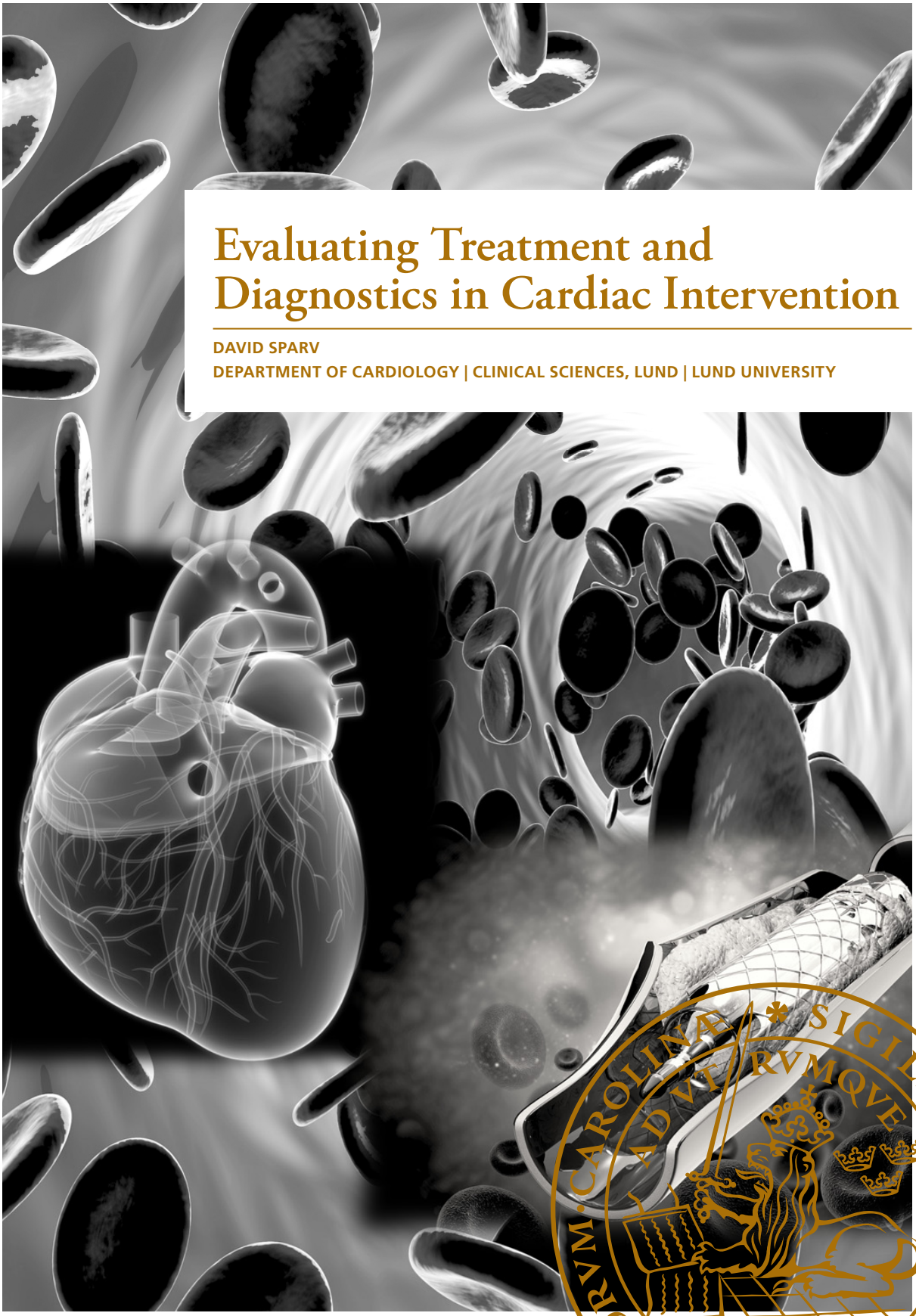

Evaluating Treatment and Diagnostics in Cardiac Intervention

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Abstract
Introduction: Cardiovascular disease is a major challenge of global health. The modern treatment of coronary artery disease (CAD) is based on the development of novel cardiac interventions. In 1977, the first percutaneous coronary intervention (PCI) was performed, initiating the era of percutaneous revascularization. The field of cardiac intervention evolves rapidly, and the need to continuosly evalute existing and new methods is thus prominent. The rationale of the present thesis was to investigate the use of different treatments and diagnostic methods in cardiac intervention, with an incentive to improve patient outcome. **Aims:** The aims of the thesis were (i) to investigate the analgesic effect of supplemental oxygen therapy during PCI, (ii) to study the long-term effects of oxygen therapy on mortality, (iii) investigate the effects of targeted temperature management (TTM) in transcatheter aortic valve replacement (TAVR) and (iv) to evaluate the effects of an increased dose of intravenous adenosine in Fractional Flow Reserve (FFR). **Methods:** In paper I, we sought to determine the analgesic effect of oxygen during PCI in a placebo-controlled, randomized clinical trial. In paper II, using a registry-based, randomized clinical trial design, we conducted the prospective, multicentre DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial (DETO2X-AMI) to evaluate the effect of oxygen on mortality. Paper III was a prespecified subgroup study of the DETO2X-AMI trial where we aimed to assess the analgesic effect of oxygen in a cohort of patients with acute coronary syndrome treated with PCI. In paper IV, the objective was to determine safety, feasibility and hemodynamic effects of transnasal evaporative cooling during TAVR. A secondary objective was to investigate a possible neuroprotective effect of cooling with neurological biomarkers. Paper V aimed to study a possible diagnostic improvement by increased dose of intravenous adenosine in FFR. Secondary objectives were to study hemodynamic effects and patient discomfort. **Results:** Routine use of supplemental oxygen in patients with normal arterial oxygen saturation did not relieve pain and did not alter the use of opiates and sedatives during PCI. In addition, supplemental oxygen in patients with suspected myocardial infarction with normal arterial oxygen saturation did not reduce one-year all-cause mortality, rehospitalisation with myocardial infarction or infarct size measured with biomarkers. Targeted temperature management induced by transnasal evaporative cooling was well tolerated without adverse side effects and may improve hemodynamic stability during TAVR, but was not associated with either a beneficial or detrimental neurological effect. Increased dose of intravenous adenosine in FFR measurements did not affect FFR-values significantly, but was associated with a significant increase of patient discomfort. **Conclusions:** Three main conclusions were drawn: (i) Routine use of supplemental oxygen in normoxemic patients with stable angina and acute coronary syndrome is not recommended, but if hypoxemia occurs, it must be detected and treated immediately. (ii) TTM during TAVR is safe and without adverse side effects, and may be considered in order to improve hemodynamic stability. (iii) High dose adenosine in the assessment of FFR is not associated with an improved accuracy but with increased patient discomfort, and is thus not recommended.

Key words: cardiac intervention, coronary artery disease, supplemental oxygen, transcatheter aortic valve replacement, targeted temperature management, fractional flow reserve, adenosine

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"Science is organized knowledge. Wisdom is organized life"

Immanuel Kant (1724-1804)

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MADE IN SWEDEN

To my dear wife and amazing children

Contents

List of publications

I. Zughaft (Sparv) D, Bhiladvala P, Van Dijkman A, Harnek J, Madsen Hardig B, Bjork J, Ekelund U, Erlinge D. The analgesic effect of oxygen during percutaneous coronary intervention (the OXYPAIN trial). Acute Card Care. 2013 Sep; 15(3): 63-8. Doi: 10.3109/17482941.2013.822083.

II. Hofmann R, James S, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D…Svensson, L. for the DETO2X-SWEDEHEART investigators. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med. 2017 Sep 28; 377(13): 1240-1249. Doi: 10.1056/NEJMoa1706222

III. Sparv D, Hofmann R, Gunnarsson A, James S…Erlinge D. The Analgesic effect of Oxygen in Suspected Acute Myocardial Infarction – a substudy of the DETO2X-AMI trial. 2018. *Submitted*

IV. Zughaft (Sparv) D, Hyllén S, Harnek J, Nozohoor S, Bjursten H, Gotberg, M. Safety, Feasibility, and Hemodynamic Effects of Mild Hypothermia in Transcatheter Aortic Valve Replacement (the TAVR-CHILL trial). Ther Hypothermia Temp Manag. 2015 Dec; 5(4): 209-16. Doi: 10.1089/ther.2015.0011.

V. Sparv D, Gotberg M, Harnek J, Persson T, Madsen Hardig B, Erlinge D. Assessment of increasing intravenous adenosine dose in fractional flow reserve. BMC Cardiovasc Disord. 2017 Feb 14; 17(1): 60. Doi: 10.1186/s12872-016-0463-4.

In addition to the articles above, the author published seven other articles in international, peer-reviewed journals. Please note that the author changed last name in 2016 from “Zughaft” to “Sparv”, hence the differences of first author in the list of papers. All papers are attached in the appendix with due permission from each publisher.

Abbreviations

ACS	Acute coronary syndrome
AS	Aortic stenosis
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBF	Coronary blood flow
CMR	Cardiac magnetic resonance imaging
CO	Cardiac output
CVD	Cardiovascular disease
ECG	Electrocardiography
FFR	Fractional flow reserve
LDL	Low-density lipoprotein
MACE	Major adverse cardiac event
MAP	Mean arterial pressure
MI	Myocardial infarction
NSE	Neuron-specific enolase
NSTEMI	Non-ST-elevation myocardial infarction
OMT	Optimal medical therapy
PCI	Percutaneous coronary intervention
PO_2	Partial oxygen pressure
RVP	Rapid ventricular pacing
SaO_2	Arterial oxygen saturation
SAVR	Surgical aortic valve replacement
SCAD	Stable coronary artery disease
$SctO_2$	Cerebral oxygen tissue saturation
$ScvO_2$	Central venous oxygen saturation
SMC	Smooth muscle cell
STEMI	ST-elevation myocardial infarction
SVR	Systemic vascular resistance
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TAVR	Transcatheter aortic valve replacement
THV	Transcatheter heart valve
TTM	Targeted temperature management
VAS	Visual analogue scale

Introduction

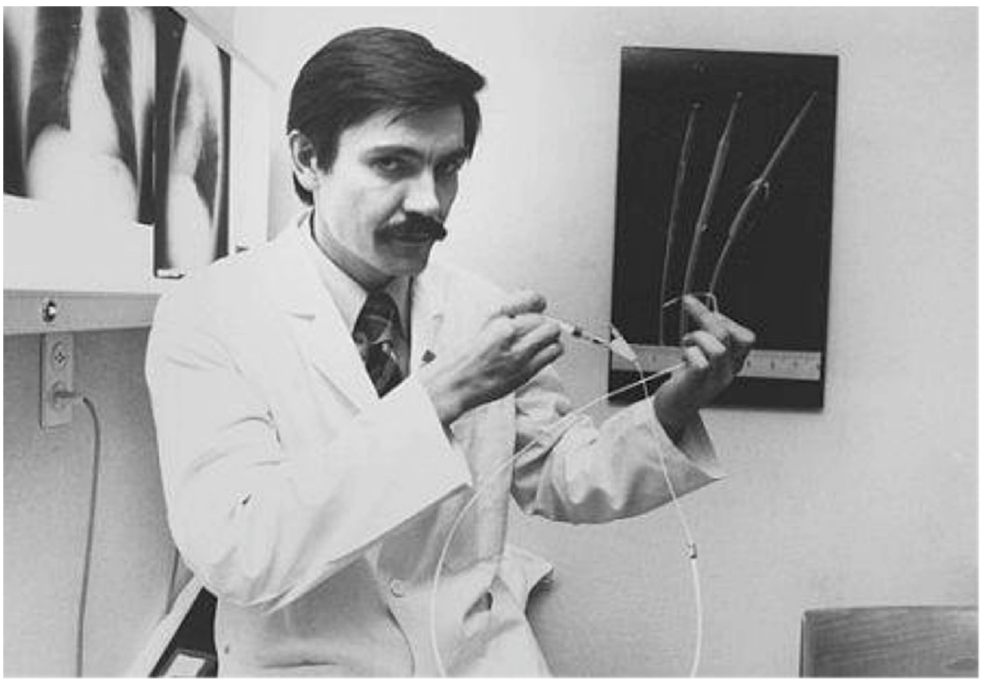
History and development

Cardiovascular disease and cardiac intervention

Cardiovascular disease (CVD) is one of the major challenges of global health.[1] Even though major progress in treatment and diagnostics have been made, coronary artery disease (CAD) remains the leading cause of death globally.[1] Myocardial infarction, MI, represents the most acute presentation of CAD, recognized as a clinical diagnosis in the early 20th century.[2] Prior to modern treatment, MI was a much-feared condition, associated with considerable mortality (approximately 40%).[3] Treatment options were scarce and mainly symptomatic, for example pain management and extensive bed rest.[4] The first important steps toward modern treatment included continuous electrocardiography (ECG) monitoring in dedicated coronary care units, which reduced mortality considerably,[5] and the development of different techniques for revascularization. In the 1960s, the first coronary artery bypass grafting (CABG) was performed.[6] In 1976, the first case of successful fibrinolysis was reported[7], opening a new course of pharmacological therapy, including aspirin, $P2Y_{12}$ receptor antagonists, statins, beta-blockers and angiotensin-converting-enzyme inhibitors, which further improved outcome.[8-10]

However, the modern treatment of CAD is closely correlated to the development of cardiac interventions.[11,12] Ever since the German physicist Wilhelm Conrad Roentgen discovered a previously unknown, highly penetrating ray that he named "X-ray" in 1885, the strive to master treatment and diagnostics by imaging and catheter-based interventions has been persistent among clinicians worldwide.[13] In 1929, Werner Forssmann, searching for an access route to inject drugs, performed the first vessel catheterization. Dr Forssmann managed to advance a urethral catheter via his own antecubital vein up to the heart during local anaesthesia.[14] Further steps followed, including percutaneous access by catheter replacement of the needle,[15] the first selective coronary angiography[16], and in 1964, the birth of interventional radiology when Charles Dotter successfully dilated a stenosis in the left femoral artery of an 82-year-old woman.[17] Simultaneously, technical devices

such as guide wires and catheters dedicated for invasive procedures were developed by, among others, Melvin Judkins and Kurt Amplatz.[18,19] By these procedural and technical achievements, a new paradigm of cardiac interventions begun in September 16th, 1977, when Andreas R. Grüntzig performed the first percutaneous transluminal coronary angioplasty, later renamed percutaneous coronary intervention (PCI).[20]



Dr Andreas Grüntzig, one of the pioneers of cardiac interventions. Reproduced by permission according to the GNU Free Documentation License, version 1.2.

The initial technique involved balloon angioplasty only, which conveyed complications such as dissections and neointimal proliferations of smooth muscle cells (SMC), resulting in high rates of restenosis.[21] This led to the development of self-expanding bare metal stents[22], that decreased the complication rates in de novo coronary lesions by approximately 30%.[23] Furthermore, in 2003, the first generation stents coated with anti-proliferative drugs were made commercially available, which further decreased the incidence of clinical restenosis.[24,25] Alongside this technical development, several randomized controlled trials (RCT) compared PCI to thrombolytic therapy in the treatment of acute MI, and since the results consistently pointed towards better results for PCI, primary PCI became the golden standard.[26-28]

Even though convincing evidence for PCI in the treatment of acute MI was consolidated already twenty years ago, the use of PCI versus optimal medical therapy (OMT) in stable coronary artery disease (SCAD) has been debated. In a study by Boden et al (2007),[29] PCI failed to reduce the risk of death, recurrent MI or other major adverse cardiac events (MACE). A discussion about patient and lesion selection emerged, and the need to identify coronary stenosis inducing ischemia on a per-vessel basis, became urgent.[30,31] Early in the era of PCI, the importance of quantifying hemodynamic impact of a coronary lesion was considered. Thus, the concept to measure coronary blood flow by a pressure-derived index called fractional flow reserve (FFR) emerged in the early 1990s.[32] The long-term results of FFR-guided PCI in SCAD was promising already prior to the trial of Boden,[33] and was confirmed by the FAME trial[30] where the use of FFR in patients with multivessel disease resulted in a significant reduction of MACE at one year as compared to angiography alone. In the following trial in 2012, FAME2, FFR plus OMT were compared to OMT alone in patients with stable angina, which resulted in a reduction of repeated revascularization in the FFR cohort.[34] Today, the use of FFR in SCAD carries a strong guideline recommendation (Class I, level of evidence A).[35]

In parallel with the evolvement of cardiac interventions for CAD, a similar technique for treatment of aortic stenosis (AS) emerged, named transcatheter aortic valve replacement (TAVR), also called transcatheter aortic valve intervention (TAVI).[36] Even though surgical treatment by standard aortic valve replacement (SAVR) was associated with favourable results, for 20-30% of the population, mainly elderly with considerable co-morbidity, SAVR was contra-indicated.[37] Therefore, the technique of balloon aortic valvuloplasty (BAV) was developed in 1986 by Cribier and colleagues.[38] In similar to the early phase of PCI, complications of BAV occurred in the shape of restenosis.[39] Following extensive research in the late 1990s, the first bioprosthetic transcatheter heart valve (THV) was implanted in 2002.[40] In 2007, THV was CE marked and following the PARTNER trial in 2010, TAVR as compared to standard pharmacological treatment was associated with a significant lower mortality, a finding that initiated the era of percutaneous cardiac intervention in valvular heart disease.[41]

Supplemental oxygen therapy

Supplemental oxygen (O_2) has been a cornerstone in the treatment of ischemic heart disease for more than 100 years.[42] The element of oxygen was discovered by the Swedish chemist Carl Wilhelm Scheele,[43] but was first published by Joseph Priestley in 1775.[44] Continuous oxygen inhalation for medical purposes was introduced in the treatment of pneumonia by Dr Albert Novatus Blodgett in

1890.[45] Inspired by the beneficial respiratory effects, Steele et al provided supplemental oxygen to patients with angina pectoris and reported a relieve of symptoms.[42] These findings resulted in the practice to routinely administer oxygen to patients with suspected CAD, regardless level of arterial oxygen saturation.[42,46] Oxygen was thus considered favourable in the management of ischemic pain following MI, and administered in concentrations around 80-100% via oxygen tents and the first face masks.[47,48] The evidence were mainly empirical from small case-series, based on the assumption that in the case of impaired oxygen supply in the myocardium, hyperoxygenated blood would increase oxygen content by collateral circulation to the ischemic tissue.[49,50] This theory has prevailed ever since, suggesting supplemental oxygen to by an increased oxygenation of the myocardium decrease size of infarction, reduce the risk of arrhythmias and hence, mortality.[51] This assumption was further supported by animal models,[52,53] studies of hyperbaric oxygen[54,55] and non-randomized trials conducted prior to the era of myocardial revascularization.[56,57]

However, already in 1950, Russek et al found that inhalation of 100% oxygen in patients with normal arterial oxygen saturation (SaO_2) aggravated and prolonged the electrocardiographic (ECG) changes of ischemia, and did not relieve pain.[58] Furthermore, during the 1960s and 70s, data emerged about potential hemodynamic consequences of hyperoxemia such as a decrease in stroke volume and cardiac output (CO) and an increase of systemic vascular resistance (SVR).[59,60] Rawles and Kenmure published data in 1976 from the first RCT of oxygen in acute MI, showing a significantly larger infarct size and a non-significant increase of mortality in the group receiving oxygen.[61] But, these results were not followed by a change in practice or guidelines despite additional studies showing hemodynamic side effects such as exacerbation of reperfusion injury in MI[62,63] and reduction of coronary blood flow (CBF).[64]

In 2010, the Cochrane institute performed a systematic review and meta-analysis of the role of oxygen in myocardial infarction.[65] The rationale of the review was the sparsely underpinned evidence base of oxygen in MI, emphasizing the lack of evidence of beneficial as well as detrimental effects in patients with normal SaO_2. In the review, three studies (n=387) were included, and even though the pooled risk ratio implied benefit for ambient air over oxygen in terms of death, the mortality rate was too low to draw further conclusions, and the authors urged the need for a sufficiently powered RCT. In 2013, the review was repeated with one additional trial (n=430) with similar results.[66] In 2015, Stub et al published the results of the Air Versus Oxygen In ST-Segment-Elevation Myocardial Infarction (AVOID) trial,[67] a RCT comparing oxygen versus air (n=441) in a STEMI population. The results demonstrated a larger myocardial injury in the oxygen group, assessed by biomarkers, and significantly larger infarct size at 6 months by cardiac magnetic resonance imaging (CMR). In a third review by Cochrane,

incorporating the evidence from two new trials (n=1173), the results on mortality and pain management were still inconclusive, and no further beneficial effect for oxygen emerged.[68] Thus, the need for further research remains.

Rationale of thesis

The author of the present thesis started working in the cardiac intensive care unit and the coronary catheterization laboratory in 2001, in the transition period from thrombolytic therapy to primary PCI. Working in this highly dynamic environment over the perhaps most innovative and creative years of cardiac intervention, triggered several ideas of potential improvements. First, the routine use of oxygen in AMI was categorical argued by older colleagues to relieve pain, alleviate nausea, improve coronary blood flow and thus, patient outcome. This mainly empirical notion inspired to challenge and to study the effects of supplemental oxygen. Secondly, in 2008, the first TAVR in Sweden was performed in Lund. Even though the first results were promising, peri- and postoperative complications were quite common, and initiated the hypothesis that by a small exploratory study investigate if hypothermia would be beneficial in TAVR. Thirdly, the swift evolution of coronary physiology and the common practice to increase adenosine doses to achieve maximal hyperemia, despite quite severe patient discomfort, triggered the idea to investigate different doses of adenosine when measuring FFR.

Thus, the rationale of the present thesis was to evaluate and challenge the use of different treatments and diagnostic methods in cardiac intervention, with an incentive to improve patient outcome.

Epidemiology

Coronary artery disease

In the 2016 Global Burden of Disease study,[1] CVD remains the leading cause of death (17.6 million in 2016) and is the number one cause of disability-adjusted life years worldwide.[1] In addition, CAD is the primary cause of global years of life lost.[1] The total death rate of CAD was 9.48 million in 2016, a rise by close to 20% from 1980 to 2016. However, substantial improvement in primary prevention has been made, demonstrated by a decrease in the global, age-standardized incidence of acute MI in all ages during 1990-2010, from 222.7 to 195.3 per 100 000 in

males and from 136.3 to 115.0 in females, however with large regional variability.[69]

Despite an increasing awareness of risk factors, progress in treatment and the advancements of cardiac rehabilitation, the long-term mortality of MI is still considerable.[1] In Sweden, one of the worlds most advanced healthcare systems, CAD is still the leading cause of death. In 2016, 25 700 patients suffered an acute MI, which represents approximately an all-age incidence of 500 per 100 000 inhabitants in males and 250 per 100 000 in females.[70] Furthermore, as demonstrated by the Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[71], the in-hospital, as well as the 30 day-mortality levelled off below 10%, and the one-year mortality seems to have stabilized around 15% (Figure 1).[72]

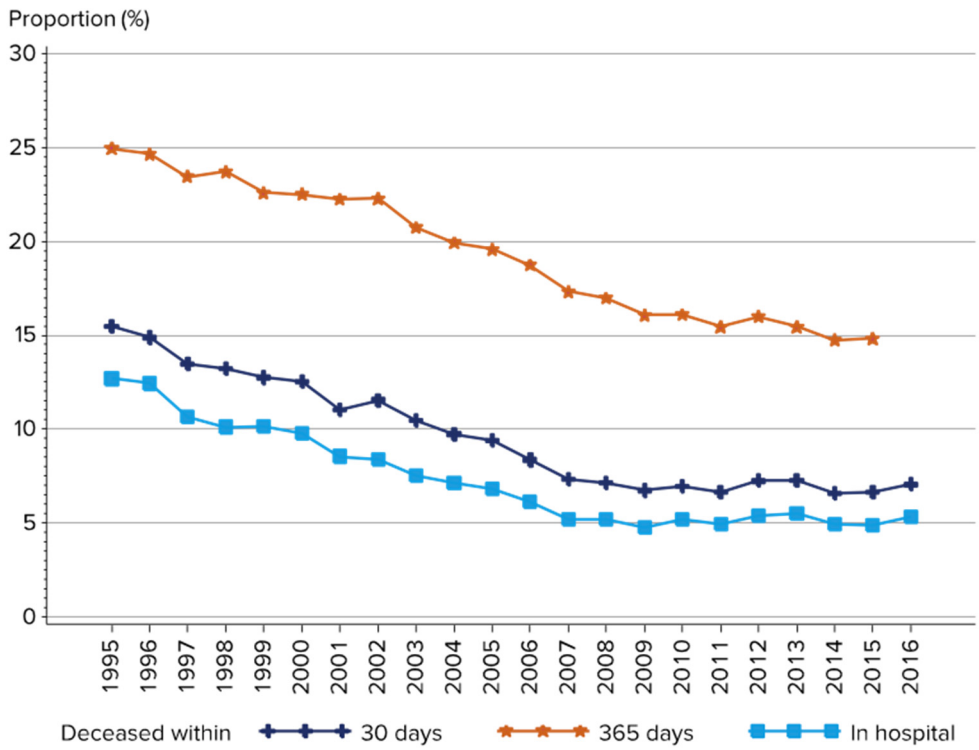


Figure 1. Mortality trends in Swedish MI patients, all ages, 1995-2016. Reproduced with permission from SWEDEHEART (T.Jernberg).

Valvular heart disease

The knowledge on the outcome of having chronic valvular heart disease is limited mainly by some uncertainty regarding the natural history among asymptomatic patients.[73] Also, the prevalence and the type of valvular disease are reflective of the demographic structure of the population and socioeconomic development. In the high-income countries with an increased share of elderly, defined as 65 years and above,[74] degenerative valvular disease is the most common with a prevalence around 2.5% (2.2%-2.7%, 95% CI).[75] In the low- and middle-income countries, rheumatic valve disease is still a common valvular disease with a prevalence between 1 and 7 cases per 1000 subjects.[76]

In the Euro Heart Survey on valvular heart disease from 2006, the most common single-valve diseases were aortic stenosis (AS) and mitral regurgitation (MR), together accounting for ≥ 75% of the total distribution.[37] The prevalence of AS is approximately 0.4% in the overall population, and increases rapidly after the age of 65 from ≤ 0.2% [75] to around 9.8% in the population ≥ 80 years[77] (Figure 2). Aortic stenosis is a severe disease with considerable mortality, untreated around 50% in the first two years after symptom onset.[78] Furthermore, the prevalence of aortic stenosis will most probably increase due to an aging population, in a French study estimated to rise from approximately 160 000 to 330 000 over a 50-year perspective.[79]

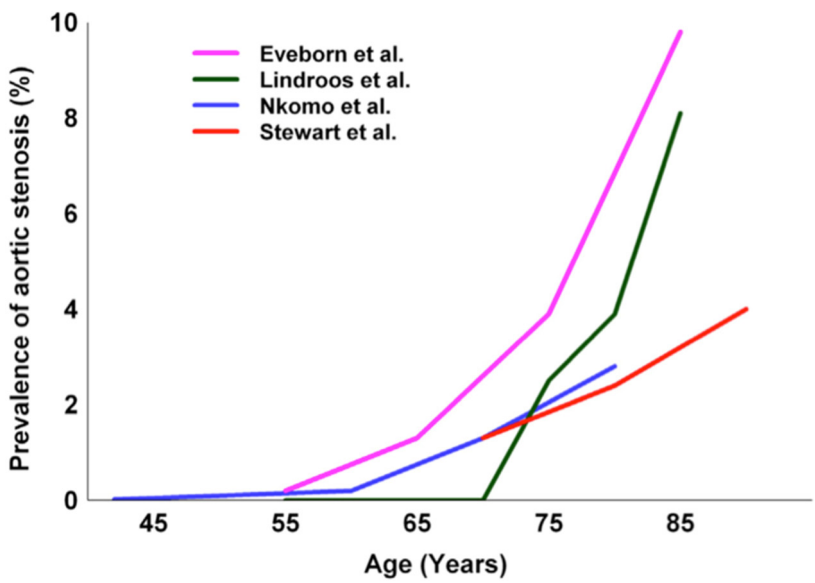


Figure 2. The prevalence of aortic stenosis according to age in four populationbased studies; Eveborn et al[77], Lindroos et al[80], Nkomo et al[75] and Stewart et al.[81] Reproduced with permission from Elsevier.

Definitions

Coronary artery disease

The definition of coronary artery disease includes stable angina pectoris and acute coronary syndrome (ACS).[35] In the definition of ACS, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) are included.[82] This present thesis focuses on both stable coronary disease and ACS in the studies of supplemental oxygen therapy and invasive coronary diagnostics. Thus, myocardial infarction will be included, defined according to the Third Universal Definition of Myocardial Infarction[82] by a characteristic rise and/or fall of cardiac biomarkers together with at least one of the following criteria: Symptoms of ischemia, significant ECG-changes including ST-segment T wave (ST-T) or new left bundle branch block, pathological Q waves, imaging evidence of loss of viable myocardium/abnormal wall motion and presence of intracoronary thrombus in coronary angiography or by autopsy.[82] Furthermore, MI is divided in five different categories. In the present thesis, only type 1 will be discussed, which indicates the event of an atherosclerotic plaque rupture resulting in a thrombus in the coronary arteries and subsequently myocyte necrosis by insufficient coronary blood flow.[82]

This thesis also discusses ischemic pain in the context of supplemental oxygen therapy. Ischemic pain is defined in NSTEMI patients as an intermittent or continuous retrosternal sensation of pressure or heaviness, ordinarily radiating to the left arm, neck and/or jaw.[83] In STEMI, ischemic pain is defined by the same cardinal symptoms together with a persistent presentation.[84] For NSTEMI as well as STEMI, additional symptoms such as shortness of breath, nausea, fatigue, palpitations and syncope may occur. Atypical symptoms may include abdominal pain.[83,84]

Fractional flow reserve, investigated in paper V, is a pressure-derived index, defined as the ratio of maximal blood flow in a stenotic artery to normal maximal flow.[30,85] FFR is measured by a pressure guidewire that is advanced distally of a coronary lesion. The ratio of the pressure measured by the guidewire and the aortic pressure measured by the guiding catheter is calculated during maximal hyperemia, usually induced by an infusion of adenosine. A FFR value of $\leq$0.80 is considered significant with a diagnostic accuracy of approximately 90%.[30,86]

Aortic stenosis

Valvular heart disease represents a spectrum of different conditions such as mitral stenosis, mitral regurgitation, aortic regurgitation and aortic stenosis.[73] This thesis focuses only on aortic stenosis. The definition of aortic stenosis is a degenerative process involving calcification of the native leaflets, that over time causes an impairment of leaflet mobility with outflow obstruction.[87] Aortic stenosis is categorized by the severity of the obstruction, measured by echocardiography,[88] by which the presence of a stenosis and the degree of calcification is assessed. Furthermore, valve area, flow rate, mean pressure gradient, ventricular function, size, wall thickness and functional status must be considered. By this definition, the ESC Guidelines of the management of valvular heart disease[88], states four different categories:

- Normal-flow, low gradient AS with preserved ejection fraction (EF) (valve area <1cm^2, mean gradient <40 mmHg, ejection fraction ≥ 50%, stroke volume index (Svi) >35 mL/m^2).
- Low-flow, low gradient AS with preserved ejection fraction (valve area <1 cm2, mean gradient <40 mmHg, ejection fraction >_50%, SVi <_35 mL/m2). This category could imply a severe AS, but additional diagnostics will be required.
- Low-flow, low-gradient AS with reduced ejection fraction (valve area <1 cm2, mean gradient <40 mmHg, ejection fraction <50%, SVi <_35 mL/m2).
- High-gradient AS (valve area <1cm2, mean gradient >40 mmHg). Severe AS is probable irrespective ejection fraction and flow rate.

Finally, targeted temperature management (TTM), as an adjunctive therapy in paper IV, was previously defined as induced mild or moderate systemic hypothermia, measured by body core temperature.[89] Mild hypothermia was defined as 34°C and moderate hypothermia as 30°C.[89] In paper IV, we only investigated the effects of mild hypothermia. Following updated guidelines that were published after the finalization of paper IV, the terminology was altered in the light of new evidence to the current term TTM, defined as temperature control between 32°C to 36°C.[90]

Patophysiology

Coronary artery disease

Together with age, gender and heredity, the development of CAD and MI is associated with mainly modifiable risk factors.[35] As demonstrated already in the Framingham heart study,[91] hypertension and hypercholesterolemia is associated with CAD. Furthermore, in the INTERHEART study[92] from 2004; Yusuf et al investigated the generalizability of known risk factors in a global context. Including data of >15000 MI patients from 52 countries, the following risk factors were found to account for most of the risk of MI: Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruit, vegetables and alcohol, and level of physical activity.[92] Coronary artery disease may present in a stable or acute setting. The most common aetiology of CAD is coronary atherosclerosis either with or without the formation of luminal thrombus and vasospasm.[93] While atherosclerosis is associated to stable coronary disease, coronary thrombi are the most important part of the pathogenesis in ACS.[94]

Atherosclerosis is a lipid accumulation and inflammatory disease that first and foremost arises in medium and large arteries in pre-disposed sites in the presence of endothelial low shear stress.[95,96] The atherosclerotic process is a complex array of different mechanisms that begins early in life and develops gradually.[94] In the presence of hypercholesterolemia, low-density-lipoproteins (LDL) infiltrate and accumulate in the intima of the arterial wall, with a concomitant inflammatory response.[97] This response includes oxidation and modification of lipids that in turn, stimulates endothelial cells to express adhesion molecules. Furthermore, cytokines are released and monocytes enter the intima and subsequently differentiate into macrophages.[98] The macrophages incorporate modified lipids even further, and turn into foam cells that are the major element of the fatty streaks (Figure 3).[98] From this first manifestation, the thickening of the intima continues by accumulation of oxidative lipids inside the cell as well as in extracellular pools, forming the intermediate atherosclerotic plaque.[99] From this stage, some lesions transforms further into fibroatheromas. The fibroatheroma consist of an inner necrotic core with lipids, macrophages and other debris, covered by a layer of smooth muscle cells in a collagen matrix.[99]

A thin cap fibroatheroma constitutes a vulnerable plaque, at risk for rupture that consequently is the main cause of ACS.[94] Plaque rupture is a complex process driven by inflammatory reactions, where macrophages in the cap release matrix metalloproteinase that gradually together with shear stress wears the cap down. When the cap eventually ruptures, the content of the necrotic core is exposed to

the circulating blood, hence initiating the coagulation cascade by platelet activation. By reactions in different platelet receptors and granules, together with fibrinogen, a coronary thrombus is formed and thus, a potential ACS event.[94,97,100]

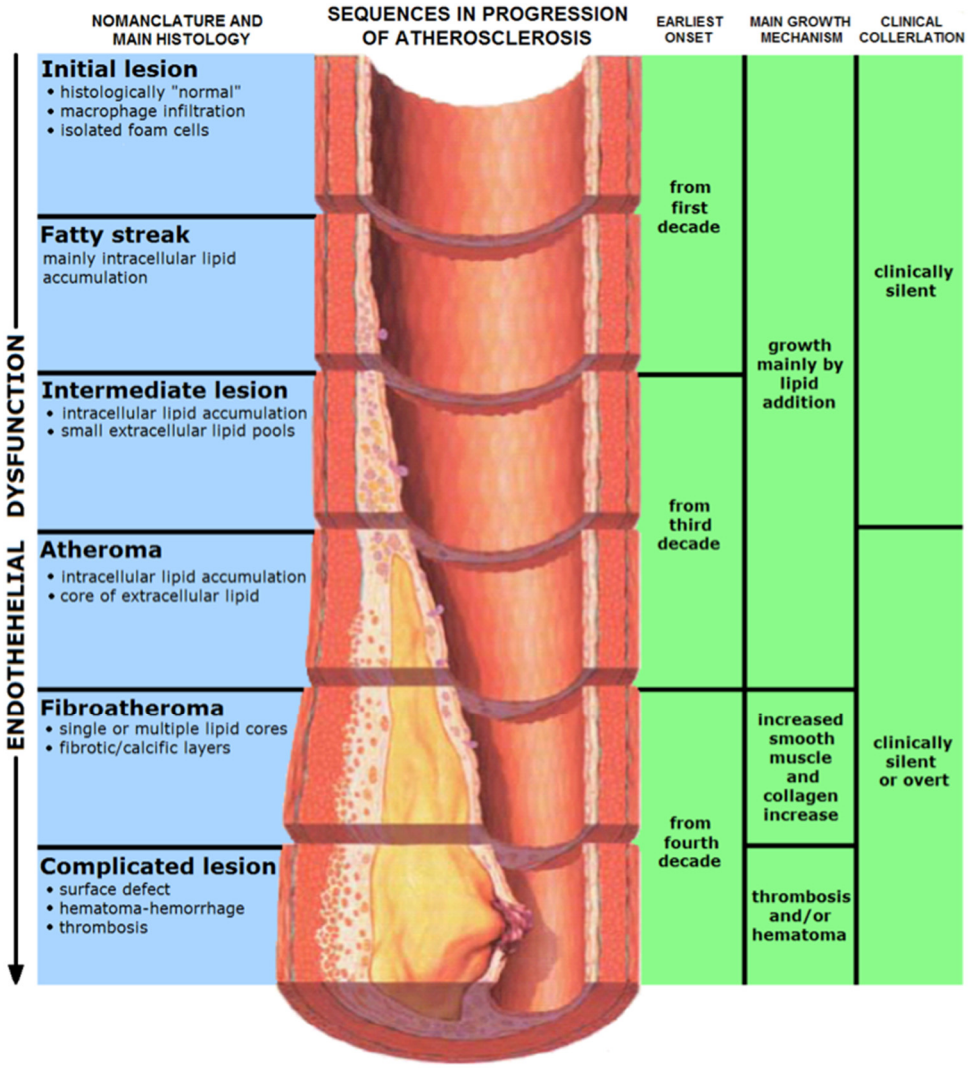


Figure 3 The progression of atherosclerosis. Reproduced by permission according to the GNU Free Documentation License, version 1.2.

Aortic stenosis

In the high-income countries, aortic stenosis is first and foremost a calcific degenerative valvular heart disease. Calcific aortic valve disease represents a range of mechanisms from cell modifications in the leaflets into the severe aortic stenosis with left ventricular outflow obstruction.[87] The progression of AS is dependent of clinical, genetic and anatomical risk factors, where the most common abnormality is the congenital bicuspid aortic valve.[101] The bicuspid valvular stenosis develops by the same processes as for tricuspid aortic stenosis, but presumably due to more unfavourable hemodynamic, earlier as compared to the tricuspid disease.[102]

The aortic valve is constructed by highly differentiated cells and layers of extracellular matrix organized in dynamic tissue structures with high durability.[103] The first signs of calcific aortic valve disease are macroscopic calcification and focal thickening of the leaflets, which is defined as aortic valve sclerosis.[87] Prior to this visual manifestation, the calcification has proceeded for some time within the leaflets, mainly initiated by accumulation and oxidation of lipids.[104] Over time, the calcification progress and includes formation of calcium nodules, where often bone cell phenotypes (by expression of osteoblasts) and new blood vessels (angiogenesis) are present.[105] The orifice of the aortic valve is normally around 3 cm^2, and when the calcification and thickening of the leaflets develops further, a narrowing of the orifice causes an obstruction of left ventricular outflow, measured by a gradient.[101] The valve structure, as mentioned, is highly dynamic and responsive to changes, but when about 50% of the orifice is impaired and a pressure overload occurs, a compensatory mechanism of left ventricular hypertrophy arises.[106] When the calcification implies restriction of cusp movement and a raised transaortic peak instantaneous velocity (V_{max}) >2.5 m/s, the disease proceed from sclerosis to stenosis, in epidemiological studies with the rate of approximately 0.1 cm^2/ year, although with a high degree of variability.[107]

A severe aortic stenosis with significantly narrowed orifice could remain asymptomatic for several years with a concomitant risk of death <1%/year.[108] However, following the increasing filling pressures, development of diastolic dysfunction and over time, insufficient oxygenation of the myocardium, the typical symptoms of shortness of breath, syncope or angina pectoris arises (Figure 4).[78] In symptomatic patients, the risk of death increases dramatically with a median survival of around 5 years with effort angina and only 1-2 years in patients with symptoms of heart failure.[78,108] In the end-stage of aortic stenosis, the opening of the cusps are heavily obstructed by large nodules of calcium on the leaflets, hence resulting in a major left ventricular outflow obstruction.[87]

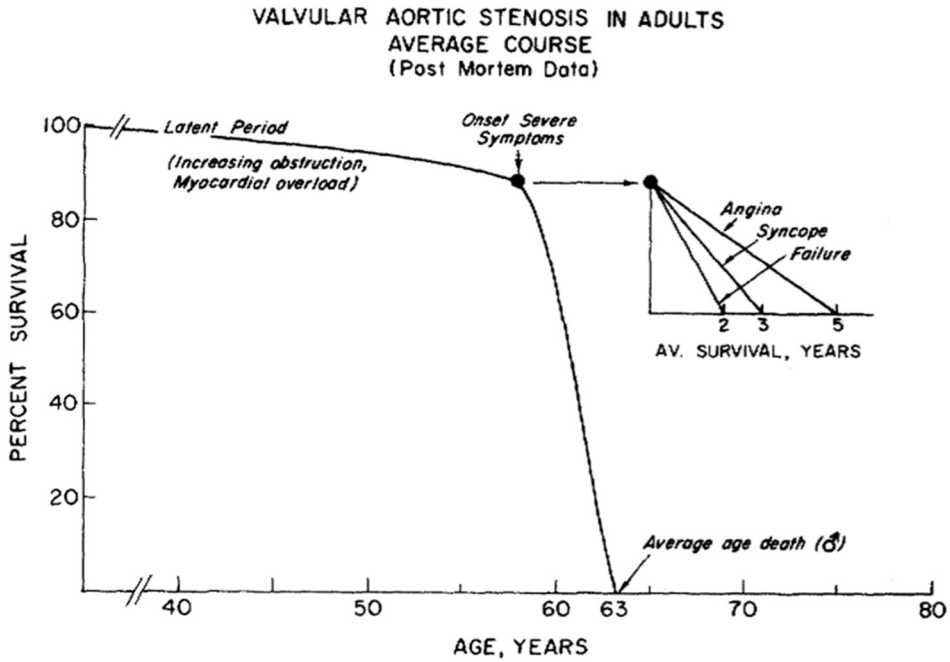


Figure 4. The average course of survival in valvular aortic stenosis in adults over the latent period and after onset of severe symptoms by Ross et al.[78] Reproduced with permission from Rightslink, Wolters Kluwer, 4223500093528.

Treatment and diagnostics in cardiac intervention

Supplemental oxygen therapy

Myocardial ischemia is caused by an imbalance of oxygen supply and demand, often due to obstruction of CBF by a stenosis or plaque rupture in the epicardial coronary arteries.[82] The mismatch of oxygen supply and demand leads to ischemic symptoms, myocardial injury, development of arrhythmias and in the final stages, myocardial necrosis.[109] Since ischemia represents an insufficient oxygenation of the myocardium, it may seem reasonable to provide ischemic patients with supplemental oxygen.[4] In hypoxemia, defined as a partial arterial oxygen pressure (PO_2) <60 mmHg or an arterial oxygen saturation <90%, the role of oxygen is indisputable.[110] But, when oxygen content is raised above normal, referred to as hyperoxemia, the effect may become hazardous.[51]

Hence, the rationale for supplemental oxygen is to improve oxygenation of the myocardium.[68] In the arterial blood, only about 2% of oxygen is dissolved in plasma, which represents approximately 3 ml/L.[111] The remaining 98% is bound to the haemoglobin molecule in the erythrocytes, each able to carry four oxygen molecules. The relationship between the partial pressure of oxygen and saturation of haemoglobin in the blood (oxyhaemoglobin, HbO_2) is plotted in the oxygen-haemoglobin dissociation curve (Figure 5). As visualized by the slope of the curve, the amount of oxygen carried by the red blood cells increases rapidly to about 50-60 mmHg, and then becomes quite flat. [111] Hence, in patients with normal oxygen saturation, the potential increase of oxygen content in arterial blood by supplemental oxygen is limited and effects on a cellular level uncertain.[46,112]

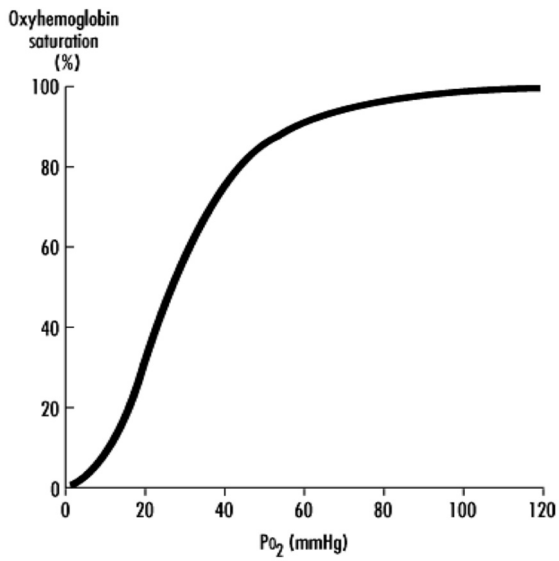


Figure 5. The oxygen-haemoglobine dissociation curve. Reproduced by permission according to the GNU Free Documentation License, version 1.2.

Vasoactive properties of hyperoxygenated blood have been recognized for many years, described as vasoconstriction of retinal blood vessels[113] and reports of a decrease in cerebral[114] and renal blood flow.[115] In studies of the cardiac hemodynamic system, an increase of blood pressure and systemic vascular resistance (SVR) has been reported and in addition, a reduction of stroke volume and cardiac output (CO).[50,59,60,116]. Furthermore, in a systematic review of six studies (n=67), hyperoxemia significantly decreased coronary blood flow.[112] In one of the reviewed studies,[64] inhalation of 100% oxygen during cardiac catheterization resulted in a decrease of CBF by approximately 30% (Figure 6).

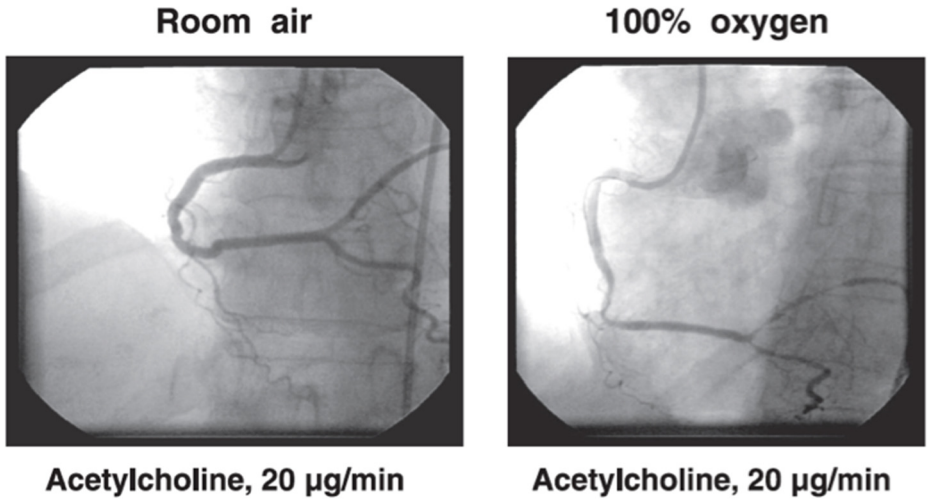


Figure 6. Right coronary angiogram during intracoronary infusion of 20 µg/min ACh and breathing of ambient air (left) and 100% oxygen (right).[64] Reproduced by permission of the American Physiological Society.

The hemodynamic effects is considered related to vasoconstriction in the cardiac vasculature.[117] Different underlying mechanisms have been proposed: Increased production of reactive oxygen species (ROS) decreasing the bioavailability of nitric oxide leading to subsequent vasoconstriction,[118-120] direct vasoconstriction caused by closure of ATP-sensitive K^+–channels,[121] direct effects on L-type $Ca2^+$-channels,[122] an increased production of the vasoconstrictor metabolite 20-HETE,[123] and an increased engagement of the Angiotensin I-II system.[124]

Ischemic pain

Ischemic pain represents a visceral pain sensation mediated by chemosensitive nociceptors in the heart muscle.[125] In the presence of myocardial ischemia, a number of chemical mediators including serotonin, thromboxane A2, bradykinin and reactive oxygen species are released, which stimulates a production of prostaglandins through a cyclooxygenase pathway.[126] The chemical response stimulates nociceptors, mainly located in the epicardium, which results in a depolarization of the cardiac visceral spinal afferent fibers. The cell bodies of the fibers are located in the dorsal root ganglia, primarily in the T2-T6 segments, where the innervation enters the central nervous system.[127] Even though extensive research have been utilized in order to understand the complex neural pathways involved, the complete mechanisms are yet to be determined.[128]

Furthermore, pain is a complex outcome to measure, mainly due to the high degree of subjectivity, but also because of a lack of objective methods to quantify individual pain experience. However, there are a considerable number of tools available for self-reported estimation of pain, divided into unidimensional, multidimensional and behavioural scales.[129] One of the most commonly used is the visual analogue scale (VAS), initially developed for measurement of chronic pain,[130,131] and in further studies validated also in quantification of acute pain.[132,133]

Fractional flow reserve

Fractional flow reserve was developed as one of the first methods to measure hemodynamic significance of coronary lesions by pressure.[31] Pijls et al[134] developed the technique from previous research in coronary physiology[135] and applied Ohm´s law to describe that if coronary resistance is close to constant, coronary flow and pressure is closely related.[134] Under the influence of maximal arterial vasodilatation, hyperemia, the resistance is stable and close to constant and FFR could hence predict coronary flow and lesion severity.[134] Thus, maximal hyperemia is a prerequisite for the diagnostic accuracy of FFR.[86,136,137]. Different pharmaceutical agents have been used to induce hyperemia, where papaverin and adenosine are the most validated.[134,138] The purine nucleoside adenosine is a potent vasodilator with short duration time, why the effect sometimes is unpredictable.[139] The standard dose is 140μg/kg/min, administered by an intravenous infusion,[140,141] but higher doses are sometimes used in clinical practice. In addition, optimal dosages have been studied, but mainly in the fashion of intracoronary injections.[142-145] Thus, the effects of increasing dose of intravenous adenosine are yet to be determined.

Transcatheter aortic valve replacement

Percutaneous techniques are rapidly increasing in the treatment of valvular heart disease, and in the light of new evidence, the European guidelines were recently updated. In the treatment of aortic stenosis, TAVR now holds a class 1B recommendation in patients who are at “increased surgical risk” (page 2755).[88] In the elderly, high-risk population that up until now been treated by TAVR, certain peri- and postoperative complications have been reported. During the procedure, hemodynamic instability following rapid ventricular pacing (RVP), BAV or valve insertion is not uncommon.[146,147] In addition, paravalvular leak[148] and conduction system disorders with a subsequent need of permanent pacemaker implantation are also prevalent.[149] Also, the TAVR procedures have been afflicted by cerebral embolic events with an incidence ranging from 1-10%. The rationale of cerebral

embolization is believed to include RVP, manipulation of guide wires in the aortic arch and in addition, manipulation and insertion of the valve prothesis.[150,151] Different strategies have been developed in order to avoid cerebral injury, e.g. filters placed in the carotid arteries[152], but with conflicting results. One possibility could be to use hypothermia to protect the brain, a method commonly used for cardiac transplantation and aortic surgery. Hypothermia, achieved by TTM has been associated with an improved neurological outcome following cardiac arrest,[89,153] and even though optimal target temperature remains uncertain,[154], it is recommended by international guidelines.[90] Furthermore, TTM has been shown to decrease infarct size in acute MI[155,156] and to improve hemodynamic stability in cardiogenic shock.[157-159] However, to our knowledge, the effects of TTM in TAVR to improve hemodynamic stability and reduce cerebral injury have previously not been reported.

Aims

The general aim of the present thesis was to investigate and evaluate the rationale of different treatments and diagnostic methods in cardiac intervention, with an incentive to improve patient outcome.

I. To investigate the potential analgesic effect of supplemental oxygen therapy during percutaneous coronary intervention and to study the peak value of the cardiac biomarker troponin T as a marker of myocardial injury in a randomized, double-blinded, placebo-controlled clinical trial.

II. To study the long-term effect of oxygen therapy on mortality in patients with suspected acute myocardial infarction in a multicenter, prospective, registry-based randomized clinical trial (RRCT), using the SWEDEHEART registry.

III. To investigate the potential analgesic effect of supplemental oxygen therapy in suspected acute myocardial infarction in a substudy of the DETO2X-AMI trial of patients undergoing treatment with percutaneous coronary intervention.

IV. To investigate safety, feasibility and hemodynamic effects of targeted temperature management in transcatheter aortic valve replacement in an exploratory, randomized clinical trial with a hypothesis-generating design.

V. To evaluate the effects of an increased dose of intravenous adenosine in fractional flow reserve in a prospective, non-randomized clinical trial with an open-label design.

Methods

This is a summary of the material and methods used in the thesis. The complete details are to be found in each individual paper.

Supplemental oxygen treatment (Paper I-III)

Study design

In paper I, we sought to determine the analgesic effect of oxygen during PCI. A RCT with a double blind, placebo-controlled design was performed at the Skane University Hospital in Lund and Malmö. In paper II, using a registry-based, randomized clinical trial (RRCT) design, we conducted the prospective, multicentre DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial (DETO2X-AMI). Paper III was a prespecified substudy of the DETO2X-AMI trial where we aimed to assess the analgesic effect of oxygen in a cohort of patients treated with PCI at eight Swedish heart centres.

Patient population

In paper I, patients with SCAD or ACS, age >18 years with angiographic significant stenosis eligible for PCI, an oxygen saturation ≥95% and a written informed consent were eligible for inclusion. Exclusion criteria were patients presenting with STEMI, hypoxemia defined as an oxygen saturation of <95%, confusion and/or inability to comprehend the study information. In paper II, trial participants were required to be ≥30 years and to have symptoms suggestive of myocardial infarction (defined as chest pain or shortness of breath) for less than 6 hours, an oxygen saturation of ≥90%, and either ECG changes indicating ischemia[82] or elevated cardiac troponin T. Patients with on-going oxygen therapy and those who presented with a cardiac arrest or had a cardiac arrest between presentation and enrolment were excluded. In paper III, all patients with suspected AMI included in the main trial (paper II) at the participating hospitals were

considered eligible if PCI was carried out within the time frame of the main study intervention.

Procedure and data collection

Paper I: Following randomization, the patients received oxygen or air by a nasal cannula at a flow rate of 3 L/minute to mimic clinical practice. The oxygen saturation was measured continuously. The patients were unaware whether oxygen or air were administered and if ischemic pain arised, opiates were given according to clinical practice. After PCI, patients were asked by an investigator blinded to treatment to score peak level of chest pain during PCI by VAS where 0 was translated to 'no pain' and 10 to 'worst conceivable pain'. The cardiac injury biomarker troponin T was measured before and one day after the procedure.

Paper II: After abbreviated informed consent was obtained, patients were randomly assigned to receive either oxygen therapy (at 6 L/minute for 6 to 12 hours delivered through an open face mask) or ambient air. Oxygen saturation was documented at the beginning and at the end of the treatment period. If it was deemed clinically necessary, particularly in cases of hypoxemia (defined as an oxygen saturation <90%), supplemental oxygen outside the protocol was provided. The data was collected from the SWEDEHEART registry and the Swedish National Population Registry.

Paper III: All patients followed the protocol of paper II. Oxygen saturation was measured continuously during PCI. Five minutes after removal of the guiding catheter from the arterial sheath, the patients were asked to estimate the peak level of chest pain during the time span of the intervention, defined as the period from insertion to removal of the arterial sheath. The VAS was used to estimate the level of pain. Furthermore, the total amount of opiates and sedative agents administered during the intervention were reported.

Statistical analysis

The results are presented as means and standard deviations for normally-distributed data. Non-normal distributed data are presented as medians and interquartile range (IQR). A two-tailed p-value of less than 0.05 was considered significant and 95% confidence intervals were used.

Paper I: In the sample size calculations, we assumed that a 30% reduction in pain was clinically meaningful. Based on previous VAS data from our coronary catheterisation laboratory, a sample size of 150 in each group resulted in 80% power. The Mann-Whitney test was used to compare the oxygen and air groups.

Paper II: The sample size was calculated from published data[160,161] and analyses from SWEDEHEART for the years 2005 through 2010. The 1-year total mortality among patients with myocardial infarction was estimated to be 14.4%. A clinically relevant effect of supplemental oxygen was defined as a 20% lower relative risk of death from any cause within 1 year. With a power of 90%, this would require a total of 2856 patients per group. To control for patients crossing over or not completing the trial, the planned sample size was increased to 3300 patients per group. The analysis of death from any cause within 365 days after randomization is presented as time-to-event curves. Hazard ratios were calculated with the use of a Cox proportional-hazards model, with adjustment for age in years and sex.

Paper III: Based on previous VAS data, an estimated sample size of 150 in each group resulted in 80% power to detect a relative difference of 15% between the study groups. Since we also included STEMI patients who we presumed have more severe pain and thus more variation in VAS score, we decided to increase the sample size to 250 in each arm. The Mann-Whitney test was used to compare VAS score in the groups of supplemental oxygen and ambient air. Categorical variables were analysed using the Chi-square or Fischer´s exact test as appropriate.

Transcatheter aortic valve replacement (Paper IV)

Study design

In paper IV, the objective was to determine safety and feasibility of transnasal evaporative cooling during TAVR and to investigate the hemodynamic response in TAVR-patients during TTM. A secondary objective was to investigate neurological effects as indicated by neurological biomarkers. The study was performed as a RCT with a hypothesis-generating design, conducted as a single-centre trial at Skane University Hospital, Lund, Sweden, from January 2013 to January 2014.

Patient population

Patients scheduled for TAVR were considered eligible for inclusion if the following criteria were fulfilled: age ≥18 years with severe aortic stenosis (indication for TAVR according to multidisciplinary conference), life expectancy >1 year and signed informed consent before randomisation. Exclusion criteria were previous cerebral vascular insult (CVI), malignant hyperthermia, previous

surgery in the epipharynx area, confusion and/or inability to comprehend the study information.

Procedure and data collection

All procedures were carried out under general anaesthesia. TAVR was performed using the Edwards SAPIEN XT™ valve prosthesis. Vasoactive and inotropic drugs were used to maintain hemodynamic stability with a target mean arterial pressure (MAP) of ≥80mm Hg. Transnasal evaporative cooling (Figure 7) was initiated following endotracheal intubation, defined as the baseline point in the protocol and was maintained until the target tympanic temperature of 34°C was reached. At completion of the procedure, defined as puncture site closure, the rewarming process was initiated at a maximum rate of 0.5°C/h by external heating. During rewarming, general anaesthesia was continued until a urinary bladder temperature of 36°C was reached.

Figure 7. The Rhinochill™ transnasal, evaporative cooling system. Nasal cannula (left) and base unit (right). Reproduced with permission from the Braincool corporation.

Statistical analysis

The sample size was estimated based on a previous explorative study of hypothermia at the Skane University Hospital, Sweden, where 10 patients in each arm were included.[155] For the hemodynamic variables, an area under curve (AUC) analysis was performed. The comparison between the groups was analysed by the Mann-Whitney test. The rise/fall of neuron-specific enolase and S100-B for the entire study population was analyzed by Wilcoxon matched-pairs signed rank test.

Fractional flow reserve (Paper V)

Study design

Paper V was a prospective, non-randomized, single-centre trial. The objective of the trial was to study the effects of an increased dose of intravenous adenosine in FFR. Secondary objectives were to study hemodynamic effects and patient discomfort.

Patient population

The inclusion criteria were age ≥18 years, borderline-significant coronary stenosis (indication for FFR according to ESC Guidelines[35]) and signed informed consent prior to enrolment. Exclusion criteria were allergy to adenosine or contrast media, baseline MAP <60 mmHg, baseline heart rate <50, pharmacological treated asthma, chronic obstructive pulmonary disease equivalent to GOLD classification III and IV,[162] confusion or inability to comprehend the study information.

Procedure and data collection

Following coronary angiography and intracoronary administration of 200 µg Nitroglycerin, a 0.014-inch pressure guide wire was advanced into the coronary artery, calibrated and subsequently advanced distal of the lesion. The infusion of intravenous adenosine was started at a weight-adjusted rate equivalent to standard dose 140 µg/kg/min and terminated when a two minute measurement (±5 s) was completed. Adenosine was administered through a peripheral intravenous line. Prior to the second measurement, a recovery time was mandatory (minimum five minutes). After recovery, the second measurement was performed with similar FFR technique and an intravenous adenosine infusion of 220 µg/kg/min. The FFR-value was considered significant if ≤0.80. The FFR results of standard dose were used for clinical decision of revascularization. Consumption of caffeine was defined as a minimum of 200 ml filter coffee consumed ≤6 h prior to FFR.

Statistical analysis

Based on standard deviations of FFR-measurements in previous studies[142,143], a sample size of 72 would have a 90% power to detect a 15% difference of FFR with a significance level of 0.05%. In order to compensate for data loss due to a

presumed inability to tolerate high doses of adenosine, the a priori number of patients we intended to include was 85. The correlation of adenosine doses was calculated by Wilcoxon matched-pairs signed rank test and a linear regression model. The agreement was graphically displayed in a Bland-Altman plot. In addition, for the continuous hemodynamic measurements of MAP and heart rate, an AUC analysis was performed.

Ethical considerations

All studies were conducted according to the Declaration of Helsinki[163]. Paper I, IV and V obtained an ethical approval from the Ethical Review Board of Lund and paper II and III from the Ethical Review Board of Gothenburg, for paper III as an amendment to the study in paper II. For paper II, an additional approval from the Swedish Medical Products Agency (MPA) was obtained.

For paper I, IV and V, a written informed consent was mandatory prior to enrolment. In paper II, a principle of abbreviated informed consent was applied, meaning that a verbal informed consent was obtained prior to intervention, and a written confirmation within 24 hours. In paper III, according to the amendment status approved by the Ethical Review Board, no additional consent was required.

Research in acute medical conditions poses a challenge for ethical considerations.[164] The informed consent process is vital, and according to the Declaration of Helsinki[163], aims, methods, sources of funding and risk-benefit analysis should be thoroughly presented to the patient. This information should preferably be discussed in a calm environment with time for questions and reflection. Obviously this is very difficult to achieve in a study concerning AMI patients. Therefore, different options have been developed for studies in the acute setting; abbreviated consent and delayed consent. Since the delayed consent, obtained retrospectively after the study intervention, is not allowed in Sweden, the remaining option for paper II was an abbreviated consent, described as of above. Even though this is common practice, well accepted and approved by the Ethical Review Board and MPA, in paper II, 403 patients (6.1%) provided a verbal acceptance but, of miscellaneous reasons, not followed by a written confirmation. This constitutes an ethical issue to consider in relation to patient selection and for future research.

Results

Paper I

305 patients were included, 154 allocated to oxygen and 151 to air. 5 patients (1.6%), all from the air group, developed hypoxemia and were not included in the analysis. For the remaining 300 patients, there was no significant difference in peak level of chest pain estimated by VAS (Oxygen: 2.0, [0 – 4] versus Air 2.0, [0 – 5] (median, [IQR 25–75%]), p=0.12. The median difference in VAS score was 0, [0 – 1] (median, [95% CI]) (Figure 8).

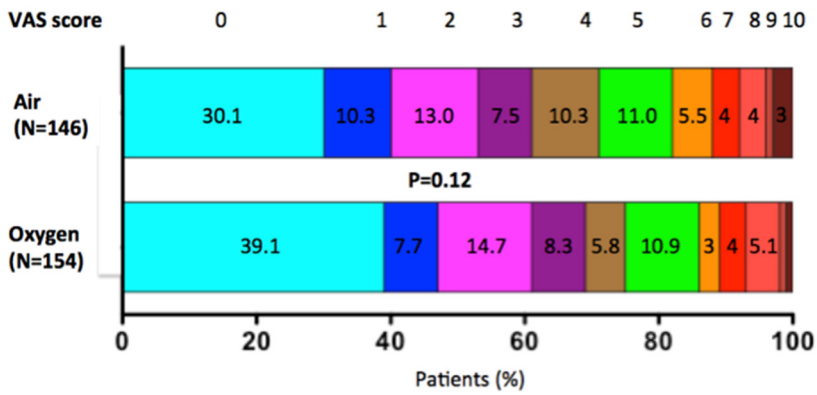


Figure 8. Maximum pain estimation by VAS. Values are presented in percentage of patients per level of VAS (0-10).

The peak value of troponin T after PCI was 38 [11-352] in the oxygen group and 61 [16 – 241] in the air group, p=0.46 (Figure 9). In the oxygen group, 14 patients (9.1%) received opiates versus 17 (11.6%) in the air group. The quantity of opiates administered was 0.44 ± 0.11 mg versus 0.46 ± 0.13 (mean ± SD). No significant difference was found between the groups.

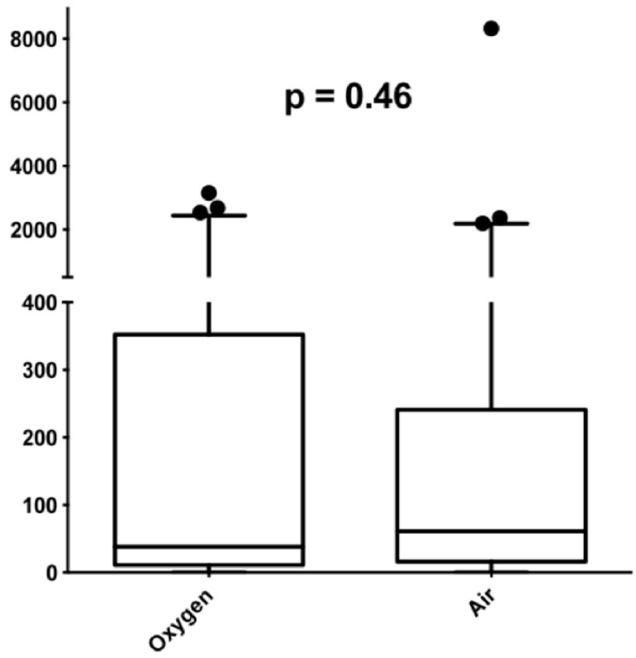


Figure 9. Peak value of troponin T after PCI.

Paper II

Between April 13, 2013, and December 30, 2015, a total of 6629 patients with suspected AMI were enrolled and included in the intention-to-treat analysis (Figure 10).

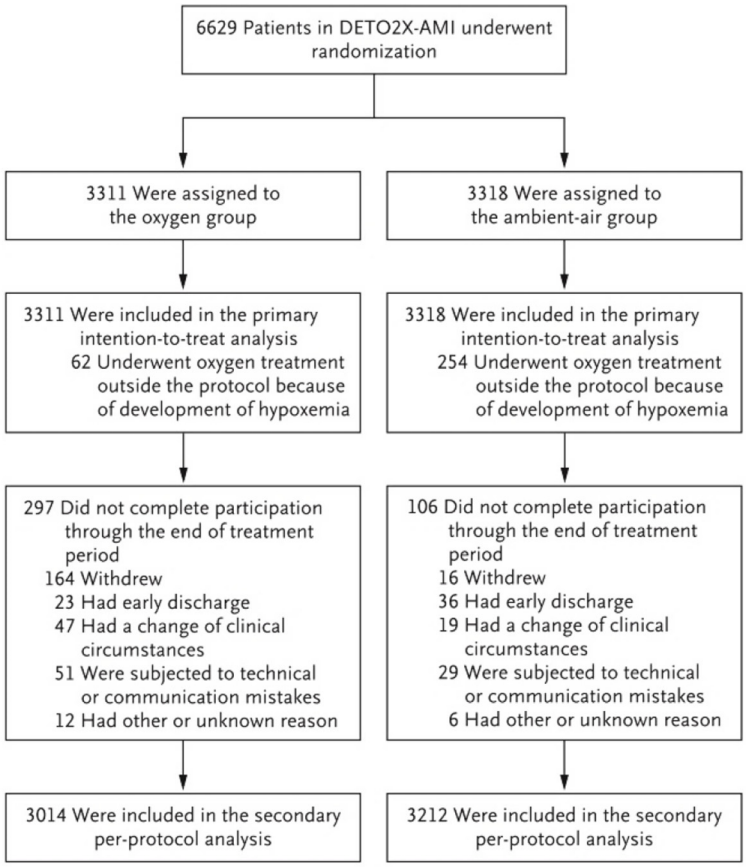


Figure 10. Enrolment, randomization and analysis.[165] Reproduced with permission from Hofmann et al, copyright Massachusetts Medical Society.

There was no significant difference in baseline characteristics, clinical presentation or final diagnoses between the groups.

Procedural data, as well as medications and in-hospital complications were similar, except development of hypoxemia and use of inotropic agents that were more common in the ambient air group (Table 1).

Table 1 . Data on procedures, medications and in-hospital complications.[165]

	Oxygen group (N=3,311)	Ambient Air (N=3,318)	P Value
Trial procedural data			
Duration of oxygen therapy hours, median (IQR)	11.6 (6.0-12.0)	—	
Received oxygen due to the development of hypoxemia	62 (1.9)	254 (7.7)	<0.001
Oxygen saturation at end of treatment period — %, median (IQR)	99 (97-100)	97 (95-98)	<0.001
Procedures — no. (%)			
Coronary angiography	2,797 (84.5)	2,836 (85.5)	0.26
PCI	2,183 (65.9)	2,246 (67.7)	0.13
CABG	96 (2.9)	110 (3.3)	0.51
Hospital stay — days, median (range)	3.0 (0-68)	3.0 (0-95)	0.87
Medication — no. (%)			
Intravenous diuretics	309 (9.3)	322 (9.7)	0.58
Intravenous inotropes	46 (1.4)	70 (2.1)	0.02
Intravenous nitroglycerin	252 (7.6)	221 (6.7)	0.14
Aspirin	2,758 (83.3)	2,803 (84.5)	0.16
P2Y12 Receptor Inhibitors	2,445 (73.8)	2,463 (74.2)	0.62
Beta-blockers	2,702 (81.6)	2,752 (82.9)	0.13
Statins	2,782 (84.0)	2,765 (83.3)	0.46
ACE-inhibitors or AT II-blockers	2,586 (78.1)	2,557 (77.1)	0.32
Calcium-blockers	519 (15.7)	547 (16.5)	0.36
Diuretics	607 (18.3)	615 (18.5)	0.82
Complications — no. (%)			
Reinfarction	17 (0.5)	15 (0.5)	0.72
New-onset atrial fibrillation	94 (2.8)	103 (3.1)	0.53
Atrioventricular-block, type II or III	46 (1.4)	58 (1.7)	0.24
Cardiogenic shock	32 (1.0)	37 (1.1)	0.54
Cardiac arrest	79 (2.4)	63 (1.9)	0.17
Death	53 (1.6)	44 (1.3)	0.35

The primary endpoint of death from any cause within 1 year after randomization occurred in 5.0% of patients (166 of 3311) assigned to oxygen and in 5.1% of patients (168 of 3318) assigned to ambient air (adjusted hazard ratio, 0.97; 95% CI 0.79 to 1.21; p = 0.80).

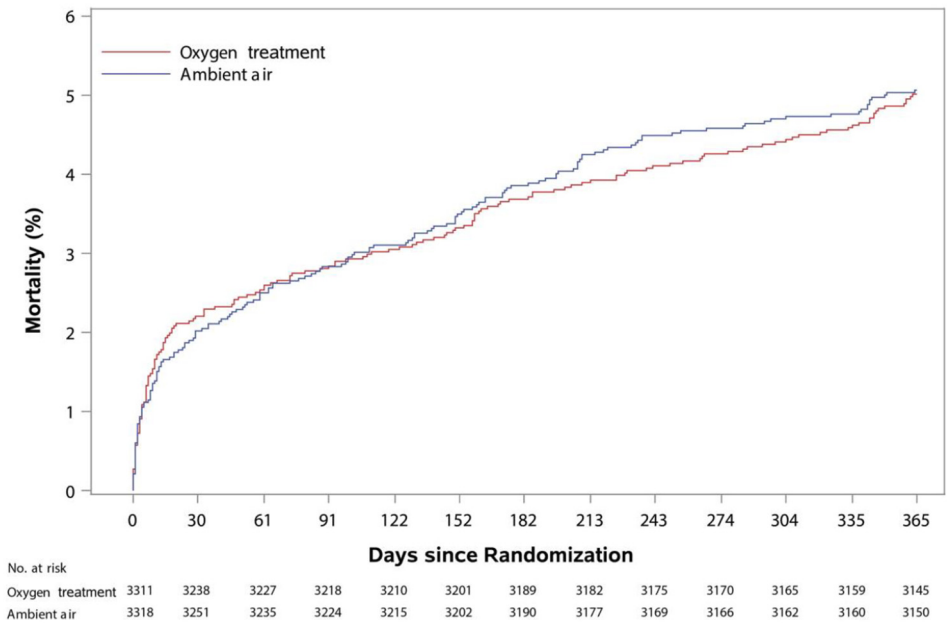


Figure 11. Kaplan-Meier curves for the cumulative probability of death from any-cause up to 365 days following randomization to oxygen treatment or ambient air.[165] Reproduced with permission from Hofmann et al, Copyright Massachusetts Medical Society.

There was no significant difference between the two groups for the secondary endpoints of rehospitalisation with myocardial infarction or the composite of death and rehospitalisation with AMI at 30 days or during the one-year follow-up period. In the prespecified subgroup analyses, no further differences were found.

Paper III

From the main cohort of paper II, 624 patients (9.4%) were enrolled, 330 allocated to oxygen treatment and 294 to ambient air. In the ambient air group, two patients were excluded from the analysis due to missing data. Five patients in the oxygen group and 21 in the air group received additional oxygen due to development of

hypoxemia. Thirteen additional patients did not complete the study intervention of miscellaneous reasons.

There was no significant difference in peak level of pain measured by VAS between the groups (Oxygen: 4.0 [1.0 – 6.0] vs. Air: 3.0 [0.6 – 6.0], (median, [IQR 25–75%]), p=0.37. Subgroup analyses were performed in the groups of STEMI, NSTEMI, males and females. There were no differences in any of the subgroup analyses (Table 2).

Table 2 . Peak level of pain estimated by the Visual-Analouge scale and the use of opiates and sedatives.

	Patients (n)	Oxygen group	Ambient Air group	P value
Peak level of pain estimated by VAS				
Main study (median, IQR)	622	4 (1.0-6.0)	3 (0.6-6.0)	0.37
STEMI (median, IQR)	465	4 (1.0-6.0)	4 (1.0-6.7)	0.97
NSTEMI (median, IQR)	115	3.5 (1.6-6.0)	2 (0.0-5.0)	0.11
Males (median, IQR)	456	3.5 (1.0-6.0)	2.8 (0.6-6.6)	0.35
Females (median, IQR)	157	4.5 (1.0-6.5)	4 (1.0-6.0)	0.75
Use of opiates and sedatives				
Median use of opiates (IQR) — mg	225	0.0 (0.0-3.0)	0.0 (0.0-3.0)	0.31
Median use of sedatives (IQR) — mg	621	2.5 (0.0-2.5)	2.5 (0.0-2.5)	0.74

Among all patients, 225 (36.1%) received opiates. The median dosage (mg) did not differ between the groups (Oxygen: 0.0 [0.0 – 3.0] vs. Air: 0.0 [0.0 – 3.0], p=0.31). Six hundred and twenty-one patients (99.8%) received sedatives. There was no difference in dosage (mg) between the groups (Oxygen: 2.5 [0.0 – 2.5] vs. Air: 2.5 [0.0 – 2.5], p=0.74).

Paper IV

Twenty-two patients scheduled for TAVR were included. One patient was converted to open-heart surgery and another suffered a femoral complication before the study intervention was initiated, both thus excluded from the analysis. The remaining 20 patients were allocated to hypothermia (n = 10) or control (n = 10).

Targeted temperature management

All patients in the hypothermia group reached target tympanic temperature (34 °C) prior to RVP. The mean time from initiation of hypothermia to target temperature was 27 ± 9 minutes. Target tympanic and urinary bladder temperature were

reached at valve implantation, and were significantly lower in the hypothermia group throughout the procedure (Figure 12). The total time of anaesthesia, defined as time from intubation to extubation, was 412 ± 113 minutes in the hypothermia group and 166 ± 162 minutes in the control group (p= 0.014).

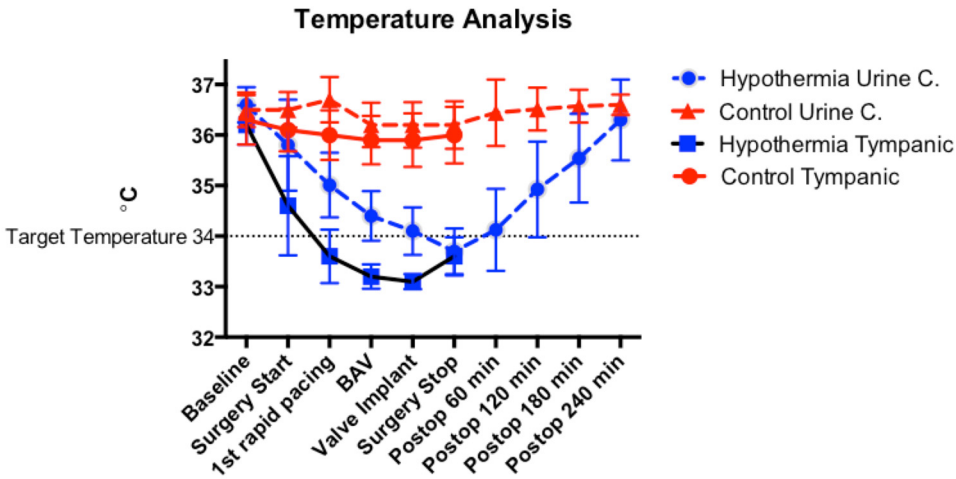


Figure 12. Hypothermia was induced directly following endotracheal intubation, defined as baseline in the protocol. Target tympanic temperature was 34°C and hypothermia was maintained throughout the procedure until valve implantation was performed. The dotted line indicates target temperature. The mean time from induction of hypothermia to target temperature was 27 ± 9 minutes.

There were no serious complications related to the transnasal evaporative cooling. No deaths occurred during the 6-month follow-up period. One transitory ischemic attack and one haemorrhagic stroke were reported in the hypothermia group, and one thromboembolic stroke occurred in the control group. All cerebral events occurred more than 4 months after TAVR. No myocardial infarction, device failure, or major bleeding was reported.

Hemodynamic data

The hemodynamic variables were similar at baseline. Following cooling, the mean systolic blood pressure was higher in the hypothermia group compared to the normothermia group at the start of surgery (137 ± 32 vs. 106 ± 12 mmHg). Mean arterial pressure was also higher at this time point (89 ± 20 vs. 71 ± 13 mmHg). At BAV, systolic pressure was higher in the hypothermia group (144 ± 17 vs. 118 ± 15 mmHg), as was MAP (90 ± 17 vs. 73 ± 14 mmHg). There were no differences in the assessed hemodynamic parameters at valve implantation or by the end of the procedure (Figure 13).

Norepinephrine was used in 19 of 20 patients and dobutamine in 11 of 20 patients (4/10 in hypothermia and 7/10 in control). The dose of norepinephrine utilized to maintain a MAP ≥80mmHg was lower in the hypothermia group throughout the procedure (Figure 13).

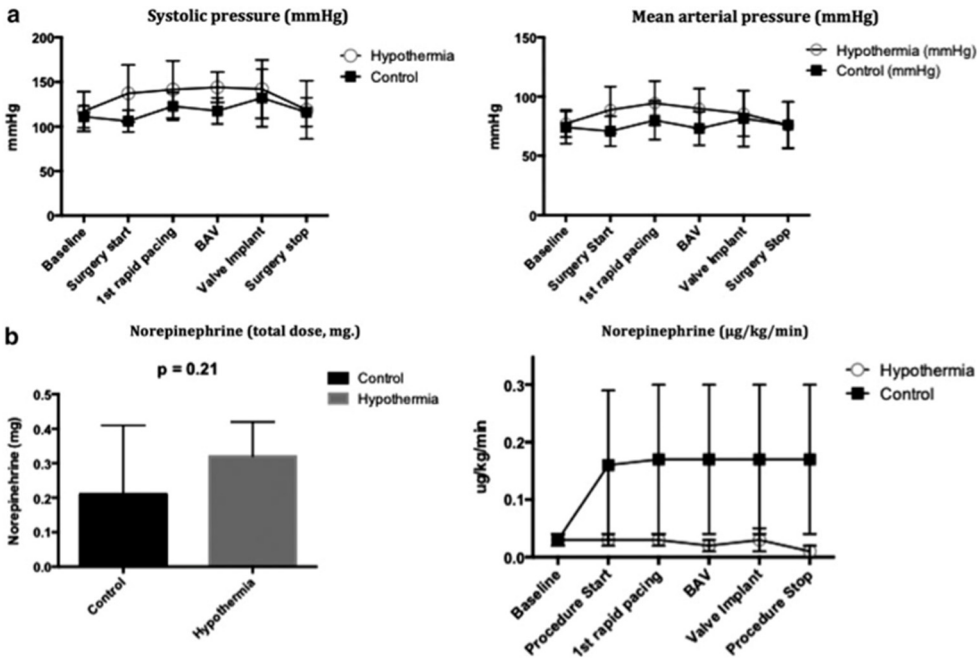


Figure 13. (a) The figures demonstrate the trends of higher systolic and mean arterial pressure in the group of hypothermia. There was a significant increase of systolic and mean arterial pressure at the start of surgery and during BAV. **(b)** Norepinephrine doses in terms of total dose (mg) and doses at the different time points of the procedure.

Biochemical markers

The biomarker neuron-specific enolase (NSE) was measured at baseline and after 24 and 72 hours. There was no significant difference between the groups. For the entire study population, there was a significant increase at 24 hours compared to baseline (16.0 [15.0–23.3] vs. 20.0 [19.8–28.5], (median, [IQR 25–75%]), p=0.02. For S-100B, there were no significant differences.

Paper V

In paper V, 87 patients were included. Ten patients (11%) developed atrioventricular block during administration of standard dose adenosine and were excluded from the second measurement and further analysis. Another two patients declined to participate in the second measurement due to severe discomfort from adenosine administration. In the remaining 75 patients, two complete FFR measurements of the same coronary lesion using the two different doses were performed. In 28% of the cases, FFR was ≤0.80 after the first measurement and PCI was performed after the study protocol was completed. Procedural success was 100%. There was no significant difference in the matched-pairs comparison of intravenous adenosine infusion of 140 µg/kg/min versus 220 µg/kg/min (0.85 [0.79–0.90] vs. 0.85 [0.79–0.89], p=0.41). (Figure 14). High dose adenosine showed a linear correlation to standard dose (r = 0.86, slope = 0.89) (Figure 15).

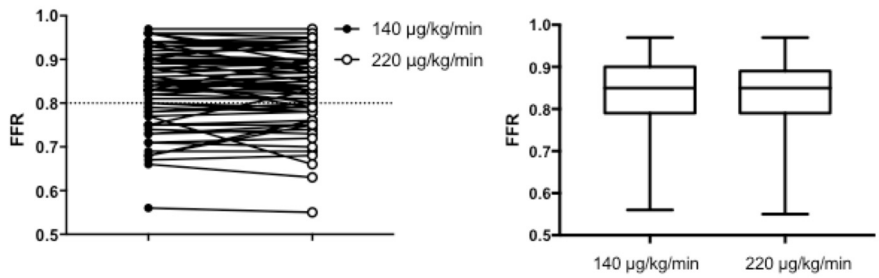


Figure 14. Wilcoxon matched-pairs signed rank test: There was no significant difference in the matched-pairs comparision of intravenous adenosine infusion of 140 µg/kg/min versus 220 µg/kg/min (0.85 [0.79–0.90] vs 0.85 [0.79–0.89], p=0.41)

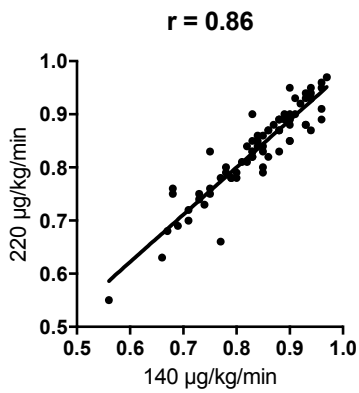


Figure 15. Unadjusted linear regression model: High dose adenosine showed a linear correlation to standard dose (r = 0.86, slope = 0.89).

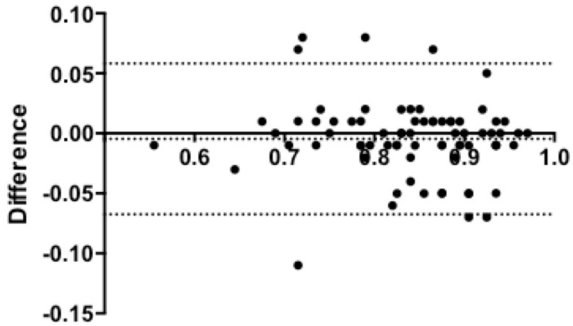


Figure 16. In a Bland-Altman analysis, average of the differences was -0.005 ± 0.03 (mean bias ± SD) [−0.07 to 0.06], [95% CI]

In a Bland-Altman analysis, average of the differences were -0.005 ± 0.03 (mean bias ± SD) [-0.07 to 0.06], [95% CI] (Figure 16). In four patients (5.3%), the higher dose of adenosine caused a change in agreement due to decreasing FFR below the treatment threshold of 0.80 (i) 0.85–0.79, (ii) 0.81–0.78, (iii) 0.81–0.79 and (iv) 0.81–0.79. The higher dose did not decrease FFR below 0.75 in any of the 75 cases.

There was no difference in MAP or heart rate between the different adenosine doses. The occurrence of atrioventricular block and bradyarrhytmias was 5.3%. Patient maximal discomfort during adenosine administration, measured by VAS, was significantly higher in the dosage of 220 μg/kg/min (8.0 [5.0–9.0]) versus standard dose (5.0 [2.0–7.0]), p <0.001.

A subgroup analysis was performed in the 43 patients (57%) of the study population who reported caffeine consumption ≤6h prior to FFR. In a paired comparison of caffeine consumers in the study population, FFR was significantly higher in the group receiving standard dose versus high dose adenosine (0.89 [0.83–0.93] vs. 0.87 [0.81– 0.91], p <0.001). In the control group, this difference was reversed to significantly lower FFR in standard dose compared to high dose (0.82 [0.75–0.85] vs. 0.83 [0.77–0.89], p=0.02) (Figure 17).

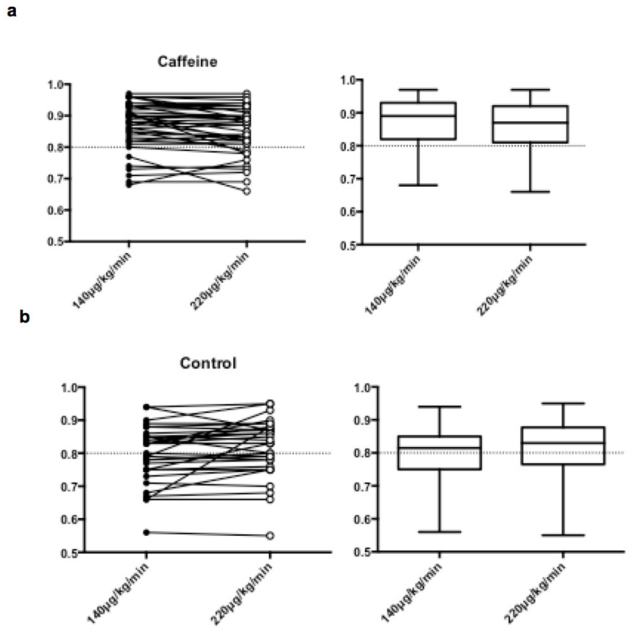


Figure 17. (a) In a paired comparision of caffeine consumption, FFR was significantly higher in the group receiving standard dose versus high dose (0.89 [0.83–0.93 vs 0.87 [0.81–0.91], p <0.001). **b** In the control group, this difference was reversed to significantly lower FFR in standard dose compared to high dose (0.82 [0.75–0.85] vs 0.83 [0.77–0.89], p=0.02).

Discussion

Supplemental oxygen treatment (Paper I-III)

Major findings

In paper I-III, the clinical implications of supplemental oxygen were studied. In paper I, supplemental oxygen during PCI in patients with stable angina and ACS was not associated with a significant analgesic effect, measured by VAS. In addition, there was no difference in myocardial injury measured by troponin T. In paper II, the primary endpoint was all-cause mortality within one year in the intention-to-treat population with suspected AMI. We could not demonstrate any benefit of routine oxygen supplementation concerning mortality, rehospitalisation with AMI, or myocardial injury assessed by troponin T. The results were consistent in all prespecified subgroups. In paper III, a substudy of paper II, we assessed the analgesic effect of oxygen in patients with suspected AMI and normal oxygen saturation treated by PCI. There was no significant difference in peak level of pain between the groups of oxygen and ambient-air. Furthermore, there was no difference in the use of opiates or sedatives between the groups.

Supplemental oxygen and clinical outcomes

Supplemental oxygen has been an essential part in the treatment of CAD for more than 100 years,[42] and by the wide indications, one of the most utilized pharmaceuticals in acute medicine.[166] Despite a considerable lack of evidence for normoxemic patients, the belief in supplemental oxygen has been strong and persistent also in the era of revascularization.[51] In a survey investigating the opinion of healthcare professionals about oxygen treatment in AMI, 98% routinely used oxygen regardless level of arterial oxygen saturation, 55% considered oxygen to decrease mortality and approximately 35% stated that oxygen decreased ischemic pain.[167] This reflects the perception of oxygen in clinical practice, and illustrates the difficulty in changing a prevailing paradigm. On the other hand, it could be argued that even though oxygen is not beneficial in terms of improved outcome, it is harmless and may provide relive by a placebo effect.[168] However, as demonstrated in several publications, oxygen is a potent vasoactive substance and hyperoxemia may be associated with potentially harmful effects that possibly

could increase ischemia.[117] In the recent AVOID trial (n=441),[67] infarct size measured by creatine kinase and MRI was significantly larger in the oxygen group. In DETO2X-AMI (paper II), we conducted the, by far, largest trial (n=6629) of supplemental oxygen in suspected AMI and could not demonstrate any beneficial or detrimental effects. The discrepancy between the findings of these two trials could partly be explained by the substantial difference in sample size (n=441 vs. n=6629). Furthermore, in the AVOID trial, only STEMI patients enrolled by the ambulance service were included in the analysis, while we enrolled patients with suspected AMI regardless prehospital presentation. Also, different levels of arterial oxygen saturation and oxygen concentration were used for enrolment. In the AVOID trial, a SaO_2 of 94% was used and oxygen administered by a flow rate of 8L/minute by a closed facemask. In the DETO2X-AMI trial, we enrolled patients with a SaO_2 of 90%, and provided oxygen by an open facemask of 6 L/minute. It is reasonable to assume that patients in the AVOID trial received a higher concentration of oxygen, which might be one possible explanation for the different results. However, the mechanisms of myocardial ischemia are complex, and in another recent RCT of supplemental oxygen in AMI, (The Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion trial, SOCCER),[169] the same enrolment principles and levels of oxygenation were used as in the AVOID trial, but no difference was found in infarct size measured by MRI. Thus, it is important to further investigate the different physiological and biochemical components of ischemia.[46]

In the recently updated ESC guidelines for AMI presenting with ST-segment elevation,[84] routine use of supplemental oxygen is not recommended for patients with a SaO_2 ≥90% (class III, level of evidence B) due to the possible harmful effects of hyperoxemia. In hypoxemia, defined as a partial arterial oxygen pressure of <60 mmHg or an arterial oxygen saturation of <90%, supplemental oxygen is recommended (class 1, level of evidence C). In addition, the ACCF/AHA guidelines[170] states that oxygen is appropriate in patients with a SaO_2 <90%, and recommend that oxygen is used with caution due to the vasoactive properties. Hence, our results are consistent with current international guidelines and we find it reasonable to limit the use of oxygen in AMI to hypoxemic patients with a SaO2 ≤ 90% only.

Supplemental oxygen and relief of ischemic chest pain

Oxygen has been used to relieve ischemic symptoms for more than 100 years, which was the very first indication of oxygen therapy in suspected AMI.[42] The theory behind the use of oxygen as an analgesic agent is that supplemental oxygen is considered to improve oxygenation of the ischemic heart muscle and by this, diminish the effects of the chemical and mechanical response to ischemia.[128,171,172] Even though early studies suggested supplemental oxygen to relieve ischemic

chest pain,[42,47,48] more recent findings imply that in contrast, inadvertent hyperoxemia is associated with vasoconstrictive effects that may worsen myocardial ischemia. This could result in a more severe pain experience and partially explain why supplemental oxygen, in contrast to common belief, could increase ischemic pain.[172]

Several studies have investigated the analgesic effect of oxygen, either by proxy variables,[61,173] or by direct measurements.[67] In paper I and III, we performed a direct measurement of peak level of pain by VAS, and did not find any difference between the groups. In the ESC guidelines of STEMI,[84] the authors emphasize the importance of pain relief. Pain is associated with an increased sympathetic activity with a subsequent vasoconstriction and increased workload for the heart, and thus important to manage. In the guidelines, titrated intravenous opiates and sedatives in anxious patients are recommended for pain relief (class IIa, level of evidence C), but due to a lack of evidence, oxygen is not included. Hence, our present results are in agreement with current clinical guidelines,[84] and strengthen even further the recommendation that it is safe to withhold oxygen from patients with suspected AMI and normal oxygen saturation, and that supplemental oxygen is not associated with an analgesic effect in these study populations. In addition, the findings are consistent for stable angina, unstable angina, NSTEMI and STEMI. Even though we did not perform a pooled analysis of the results, we consider it reasonable and in accordance with current evidence and guidelines to limit the use of oxygen in all patients during PCI to hypoxemic patients with a SaO2 $\leq$ 90%, irrespective of the level of pain.

Limitations

There are some limitations that should be noted. In paper I, we used a placebo-controlled design where the patients received oxygen or air via a nasal cannula. Due to logistic difficulties in the ambulance service with no access to pressurized air, enrolment of patients was not possible in the prehospital setting. Therefore, STEMI-patients were excluded; a limitation that poses a selection bias of the patients that probably experience most pain. Furthermore, in paper I, we provided the patients with supplemental oxygen at a flow rate of 3L/minute by a nasal cannula, and only during the time frame of the PCI. In addition, according to the inclusion criteria, a SaO_2 of 95% was required for enrolment, a discrepancy towards paper II and III that accepted a SaO_2 of 90% or higher, and utilized oxygen by a flow rate of 6L/minute for 6-12 hours. It is reasonable to assume that the level of oxygenation would differ between the studies, and impact the comparability. However, when we designed paper I, current guidelines[174] recommended an oxygen level of 95% for oxygen supplementation (class I, level of evidence C) and in our local practice, 3L/minute were used for relieve of

ischemic pain during PCI. Also, no trials have been able to determine optimal dosage, level of oxygenation or treatment duration for supplemental oxygen. This reflects a lack of evidence and emphasizes the importance of integrating new evidence into clinical practice.

Another limitation for paper I as well as for paper III is the difficulty of pain estimation. Pain is a complex outcome to measure due to the high degree of subjectivity and a lack of objective methods to quantify individual pain experience. Some of the tools available for self-reported estimation of pain; unidimensional, multidimensional and behavioural scales,[129] have different advantages and disadvantages. In the acute setting, unidimensional scales, for example the numerical rating scale, verbal rating scale and VAS are swift and uncomplicated to use, and, in addition, easy to comprehend for the patient.[129] Yet, multidimensional scales, for example the short-form McGill Pain Questionnaire (SF-MPQ)[175] and the Treatment Outcomes of Pain Survey (TOPS)[176], offers a more comprehensive depiction of pain estimation and treatment in regards to cultural, psychological and socio-economic factors.[177,178] Even though a detailed description of individual pain experience would be desirable in order to customize treatment and evaluation, unidimensional scales have demonstrated high validity and reliability in measurement of acute pain intensity.[132,133,179] Nevertheless, pain estimation by any tool might be affected by interviewer bias where the research staff might influence the response of the subject. Therefore, in both studies, we used a standardized procedure with firm instructions for the interviewers, that to some extent should adjust for this.

Furthermore, in paper II and III, an open-label design was used. Due to difficulties of providing patients with placebo (pressurized air) in the prehospital part of the study, we decided to use this design, which might have an impact of, for example, estimation of pain. Also, data collection was not centrally adjudicated due to the RRCT design where we gathered data from the SWEDEHEART registry and from the Swedish National Population Registry. However, the primary endpoint of all-cause death would not require adjudication in Sweden due to the registry-based inclusion based on unique personal identity numbers, and any other uncertainty should be equally distributed between the study groups. Also, the SWEDEHEART registry is monitored on a regular basis and the historic accuracy and data safety is high.[71,72] Finally, in the design phase of paper II, historical data and other sources suggested a one-year mortality of 14.4%, which in our results turned out significantly lower. This poses a limitation that has to be considered in the perspective of the study population. In the historical SWEDEHEART data, all patients were diagnosed with AMI while our cohort consisted to 24.4% of other diagnoses. In addition, we excluded hypoxemic patients and patients with cognitive impairment, a group with presumed higher risk of events. We cannot therefore completely rule out a small beneficial or detrimental effect of oxygen.

However, by the superimposable time-to-event curves and the consistency throughout the analysis in the pre-specified subgroups, we consider this potential deviation unlikely. In future studies, it could be considered to increase power by a larger sample size, adjustment in study design to a cluster-randomized controlled trial or by using a more event-driven endpoint.

Transcatheter aortic valve replacement (Paper IV)

In paper IV, safety, feasibility and hemodynamic effects of TTM (mild hypothermia) in TAVR were investigated. Target temperature was reached in all patients in the hypothermia group within 27 ± 9 minutes and no adverse effects of the transnasal evaporative cooling were observed. In addition, some possibly favourable hemodynamic effects were noted.

Over the last decade, TAVR has matured as an interventional technique.[36] Due to major improvements of devices and clinical experience, the procedures of today are simpler and safer. In addition, from the initial indication of inoperable patients, the indication has now expanded to include high- and intermediate risk patients.[88] Hence, in order to maintain good long-term results, patient selection and risk stratification will be important to minimize peri- and postoperative complications.[36] During TAVR, hemodynamic impairment under the influence of RVP is not uncommon.[146,147] The technique of RVP during balloon inflation and valve implantation has been a pre-requisite for a safe and precise valve positioning, and was initially developed to minimize the risk of valve embolization.[180] Rapid ventricular pacing involves a pacemaker-induced tachycardia ranging from 180-220 beats/minute that effectively diminish the systolic ejection of the left ventricle and results in a substantial decrease of perfusion pressure. Thus, cardiac movement and blood flow across the valve are kept to a minimum until the valve is safely implanted and RVP is terminated. Once sinus rhythm is restored, a subsequent hyperemia is not uncommon, which could be considered a reperfusion of systemic blood flow.[181] In the design of paper IV, we hypothesized that protective hypothermia, induced prior to the first hemodynamic insult would be beneficial in terms of hemodynamic stability during TAVR. In our observations, we did notice trends of higher systolic and mean arterial pressure, and also less need of vasoactive substances. Even though this was a small exploratory study, not sufficiently powered to determine clinical endpoints, similar positive effects of hypothermia have been demonstrated previously. Moriyama et al[157] studied the effects of hypothermia in eight patients with cardiogenic shock after open heart surgery and found a significant decrease of tissue oxygen consumption. In a similar study, Yahagi et al[158] demonstrated

hemodynamic improvement by increased cardiac index and SvO_2 during hypothermia. These small, non-randomized studies suggest a potential role of hypothermia to improve hemodynamic stability by decreased peripheral oxygen consumption. Furthermore, when paper IV was designed, the hemodynamic turbulence during TAVR was considered to constitute a potential risk of cerebral complications.[150] In previous studies, the occurrence of cerebral embolic particles during TAVR ranges from 70-100% measured by transcranial Doppler.[182-184] In addition, neurological biomarkers such as NSE and S-100B have been known to increase following TAVR.[150] Although a vast majority of the cerebral embolic events remain subclinical, the correlation between silent brain infarcts and long-term outcome is not fully known,[185,186] and may be correlated to long-term cognitive impairment.[187] Different cerebral-protective strategies have been studied e.g. filters placed in the carotid arteries,[152] but the results have been conflicting. Moderate hypothermia has been used for many years in cardiac and aortic surgery in order to protect the brain from ischemia.[188,189] In paper IV, we aimed to study if hypothermia would be beneficial also in TAVR, measured by neurological biomarkers. We could not see any difference between the groups, but when we pooled all patients, there was a significant rise of NSE at 24 hours as compared to baseline, in agreement with previous findings.[150,190]

Limitations

Paper IV was a small, exploratory feasibility-study with a hypothesis-generating design. Thus, this trial was not intended to, or sufficiently powered to detect differences in clinical endpoints between the groups. Also, there were some differences in patient characteristics that may influence the results. In the control group, atrial fibrillation and transapical approach were more common, which may influence the hemodynamic stability during TAVR. Furthermore, the effect of hypothermia is closely correlated to body core temperature, which we did not measure in this trial. Tympanic temperature, in combination with urinary bladder temperature, is considered reliable, but some deviation from a true core value is probable. Nevertheless, several publications have demonstrated tympanic measurements to be sufficient.[191,192] Since all subjects reached target tympanic and urinary bladder temperature before valve implantation, we find it reasonable to consider the cooling effect adequate.

In regards to the hemodynamic variables, we did not measure cardiac output, cardiac index, or pulmonary artery pressure. The absolute values and variations in arterial pressure, ScvO2, and SctO2 were taken into consideration when evaluating the hemodynamic state. These parameters do not replace extended invasive analysis, but are validated methods of estimating tissue oxygen consumption and, by extension, hemodynamic stability.[158] Finally, we only used NSE and S100-B to

evaluate neurological effects of TTM during TAVR. The limited data supporting the use of the biomarkers in this setting is associated with some uncertainty. First, even though NSE is widely used as an indicator in comatose patients, it is also a tumour biomarker and the sensitivity and specificity may not be accurate for this kind of analysis. For future trials, novel neuro-biomarkers would be of interest, for example Tau proteins.[193] Secondly, potential cognitive and mental effects of cerebral events needs to be assessed by different methods of functional testing during long-term follow up, and not only by biochemical markers.[194]

Fractional flow reserve (Paper V)

In paper V, we evaluated the effects of an increased dose adenosine in FFR compared to standard dose. No significant differences in FFR-values were found. There was no difference in hemodynamic variables, but patient discomfort was significantly higher during administration of high dose adenosine. Atrioventricular block occurred in ten patients (11.0%) during the administration of standard dose, and in another four patients (5.3%) during high dose.

One of the key elements in the development of FFR was to establish a clinical cut-off value for detection of inducible ischemia.[31] In the initial work of De Bruyne and colleagues,[195] a comparison was made towards exercise treadmill testing, and based on the findings pre- and post PCI, a cut-off of 0.75 was suggested with an overall diagnostic accuracy of approximately 80%. When other diagnostic methods were acknowledged for comparison, e.g. stress echocardiography and myocardial perfusion imaging,[85] a decreased specificity in the interval 0.76-0.80 was identified, defined as the FFR grey zone.[196] Therefore, a cut-off value of 0.80 was suggested by Pijls et al[197] with an approximated ability to exclude ischemia in 90% of the cases. By accepting this value, that was subsequently implemented by the FAME trial[31] and used henceforth,[196] the risk of false positive findings increased further, but on the other hand, the potential number of ischemic lesions not treated, decreased. Nevertheless, values in the grey zone 0.76-0.80, still poses a challenge in daily practice, which further stress the importance of reliable measurements where maximal hyperemia constitutes a pre-requisite. Adenosine is the most validated hyperemic agent, used in major trials and during the initial validation at a dose of 140 μg/kg/min administered by an intravenous infusion.[198,199] The hyperemic properties of adenosine includes an interaction with A_{2A} receptors that mediates a smooth muscle relaxation and vasodilatation.[200] In paper V, we compared 140 μg/kg/min versus 220 μg/kg/min in 75 patients and found no significant difference in FFR. The physiological response of different intravenous adenosine doses has been investigated before in a smaller study,[201] and

our results confirm that previous findings are reproducible in a larger, clinical patient population. In addition, in only four patients, the higher dose decreased FFR below 0.80 and in no case below 0.75. Thus, all changes remained in the borderline region, implying that an increased dose adenosine is not associated with improved accuracy in this population, irrespective of whether cut-off values 0.80 or 0.75 are used.

As a secondary endpoint, we investigated the systemic effects of adenosine in terms of hemodynamic characteristics and patient discomfort. Adenosine regulates the autonomic innervation by inhibition of the A_1 receptors, and by that, mediates a negative chronotropic and dromotropic effect in the conduction system.[202] A concern in administration of adenosine, foremost in high dose regime, is that patients will develop adenosine-induced systemic hypotension and bradyarrhytmias. Even though usually not persistent, hemodynamic impairment involves discomfort, which may be a reason why adenosine is prematurely terminated during FFR, which makes the hyperemic effect uncertain.[196] In our results, there was no difference in the occurrence of hypotension and bradyarrhytmias between standard dose and high dose. However, peak level of patient discomfort, measured by VAS, was significantly higher during high dose administration, manifested by shortness of breath and severe heat sensation. Since our results did not reveal any impact on hemodynamic parameters, we suggest that symptoms during adenosine administration are not solely related to a systemic response or coronary hemodynamic changes, but rather via a direct effect on, for example, pulmonary C-fibers as demonstrated in a previous study.[203]

An exploratory endpoint was to observe the effect of caffeine as a well-known adenosine antagonist. Caffeine, a derived methylxanthine acting as a competitive inhibitor of adenosine receptors, is considered a relative contraindication to adenosine perfusion diagnostics.[204] In this study, caffeine consumption was not randomized or controlled, but we found trends coherent with previous findings. Matsumoto et al[205] investigated the effect of intravenous adenosine doses of 140, 175 and 210 μg/kg/min and found that caffeine attenuates hyperemia during FFR and that doses up to 210 μg/kg/min do not fully compensate this antagonism. In a paired comparison of caffeine consumers in paper V, FFR was significantly higher in standard dose versus high dose adenosine, which implies that caffeine attenuated the hyperemic properties of adenosine. However, as discussed in limitations, the results should be interpreted with caution.

Limitations

First, this was a non-randomized trial, at risk for bias and confounding associated with weaker study designs.[206] Even though the higher dose was always administered after the lower dose in order to mimic clinical practice, a crossover design might have yielded different results. However, this is the way adenosine is used in clinical practice, and no one would consider starting with the higher dose in all patients. In terms of adenosine administration, we used a peripheral intravenous line, which compared to a central vein might have a slightly delayed systemic effect. However, we did flush the adenosine infusion together with an infusion of saline, a clinical method to increase bioavailability and making the possible delay negligible. Also, in the era of transradial approach, a peripheral route for adenosine is desirable, and previous findings have demonstrated comparable results.[199,207] Furthermore, the dose and timing of caffeine consumption were not randomized or controlled which makes the results uncertain. This was, however, an exploratory secondary endpoint and needs to be further addressed in a randomized, controlled trial. Finally, this was a clinical study investigating a common issue in daily practice, and thus not sufficiently powered to determine outcome.

Conclusions

This thesis evaluated the clinical implications of supplemental oxygen in patients with stable angina and ACS for symptom management and clinical outcomes, the safety and feasibility of targeted temperature management during transcatheter aortic valve replacement and assessed the effects of increasing adenosine dose in fractional flow reserve. The following conclusions were drawn:

- Routine use of supplemental oxygen in patients with normal arterial oxygen saturation does not relieve pain and does not alter the use of opiates and sedatives during percutaneous coronary intervention. The results are consistent in stable angina, unstable angina, NSTEMI and STEMI.
- Routine use of supplemental oxygen in patients with suspected myocardial infarction with normal arterial oxygen saturation does not reduce one-year all-cause mortality, rehospitalisation with myocardial infarction or infarct size measured by biomarkers.
- Routine use of supplemental oxygen in normoxemic patients with stable angina and acute coronary syndrome is thus not recommended, but if hypoxemia occurs, it must be detected and treated immediately.
- Targeted temperature management induced by transnasal evaporative cooling is well tolerated without adverse side effects and may improve hemodynamic stability during transcatheter aortic valve replacement.
- Increased dose of intravenous adenosine in fractional flow reserve measurements do not affect FFR-values but is associated with a significant increase of patient discomfort. Our findings do not support high dose adenosine in the assessment of fractional flow reserve.

The rationale of the present thesis was to challenge the use of different treatments and diagnostic methods in cardiac intervention, with an incentive to improve patient outcome. In paper I-III, the use of supplemental oxygen in normoxemic patients were challenged, resulting in a recommendation to limit the use of oxygen to hypoxemic patients only. In paper IV, the use of targeted temperature management in TAVR was evaluated, resulting in a conclusion that hypothermia during TAVR is well tolerated and may improve hemodynamic stability during the

procedure. In paper V, the use of increased dose adenosine during FFR was challenged and we found no advantage of the increased dosage. In contrast, high dose adenosine was associated with increased patient discomfort, and is therefore not recommended.

Summary in Swedish (populärvetenskaplig sammanfattning)

Hjärt- och kärlsjukdomar utgör den vanligaste dödsorsaken globalt och orsakar för tidig död, funktionsnedsättning och nedsatt livskvalitet. I denna avhandling studerades tre olika behandlingsmetoder vid kranskärlssjukdom och vid sjukdom i hjärtats klaffar.

Kranskärlssjukdom är ett samlingsbegrepp för olika former av kärlkramp och hjärtinfarkt. En av de mest etablerade och utbredda behandlingsmetoderna vid kranskärlssjukdom är tillförsel av syrgas. När syrebrist uppstår, vilket innebär att syremättnaden i blodet understiger 90 %, finns god evidens och tydliga behandlingsriktlinjer. Hos patienter med normal syremättnad, (90 % och därutöver), är kunskapsläget mer oklart. Befintlig evidens härstammar från mindre studier som genomfördes innan moderna behandlingsmetoder infördes. Vid en hjärtinfarkt uppstår syrebrist i hjärtmuskeln på grund av ett nedsatt blodflöde. Hypotesen bakom att använda syrgas är att ökad syretillförsel tros motverka denna syrebrist, och därmed begränsa skadeverkningar. I tillägg finns empirisk erfarenhet av att syrgas minskar smärta och illamående i samband med syrebrist i hjärtmuskeln.

Dock har experimentella studier visat att en förhöjd syremättnad i blodet, hyperoxemi, är förenat med potentiellt skadliga effekter på grund av kärlsammandragning, vasokonstriktion. När en vasokonstriktion sker, finns belägg för att blodflödet reduceras och att fria syreradikaler frisätts, något som skapar obalans och risk för skadliga effekter i kroppen. Studier har visat att hyperoxemi kan vara förenat med en sämre prognos vid hjärtinfarkt, men resultaten har inte varit konklusiva. Då det dessutom inte finns vetenskapligt underbyggda rekommendationer om vilken koncentration av syrgas som ska användas, hur länge den ska administreras och hur effekten ska utvärderas, är det följaktligen viktigt att studera syrgasens effekter vid kranskärlssjukdom.

I delarbete I studerades den potentiellt smärtstillande effekten av syrgas i samband med ballongvidgning, PCI. I denna studie inkluderades patienter med

företrädelsevis stabil kranskärlssjukdom, och effekten uppmättes dels genom användning av en självskattningsskala (VAS), och dels genom användning av smärtstillande läkemedel. I studien analyserades även hjärtskademarkören troponin T i syfte att bedöma eventuell hjärtskada. En viktig aspekt var också att studera om syrebrist, hypoxemi, var vanligt förekommande. I studien inkluderades 305 patienter, varav 5 patienter exkluderades på grund av syrebrist. De resterande 300 patienterna fördelades slumpmässigt mellan tillförsel av syrgas och luft, som administrerades via en näsgrimma med ett flöde av 3 liter/minut. I resultaten kunde ingen skillnad i smärtupplevelse noteras, mängden smärtstillande läkemedel var likartad mellan grupperna och ingen skillnad i troponin T kunde uppmätas. Syrebrist var ovanligt.

I delarbete II genomfördes en registerbaserad studie i hela landet där 6629 patienter med misstänkt hjärtinfarkt inkluderades och 35 sjukhus deltog. Genom det nationella kvalitetsregistret SWEDEHEART och Folkbokföringsregistret/ Dödsorsaksregistret inhämtades data. I denna studie studerades dödligheten efter ett år mellan en grupp som erhöll syrgas och en kontrollgrupp. Dessutom studerades frekvensen av återinläggning på sjukhus med hjärtinfarkt inom ett år och påverkan på hjärtskademarkören troponin T. Dödligheten efter ett år var 5.0% i syrgasgruppen och 5.1% i kontrollgruppen, därmed kunde ingen signifikant skillnad ses. Även återinläggning med hjärtinfarkt och nivåer av troponin T skiljde sig inte åt mellan de båda grupperna. I denna studie kunde alltså inga gynnsamma eller skadliga effekter av syrgas påvisas.

Delarbete III var en understudie till delarbete II, där den smärtstillande effekten av syrgas studerades hos patienter med normal syresättning och misstänkt hjärtinfarkt där ballongvidgning genomfördes under studieinterventionen. Precis som i delarbete I uppskattades smärtupplevelsen med en skala, och mängden smärtstillande läkemedel noterades. Inte heller i denna studie kunde vi se någon skillnad i smärtupplevelse eller i mängd smärtstillande läkemedel mellan grupperna. Sammantaget konstateras att hos patienter med normal syresättning och misstänkt hjärtinfarkt kan någon gynnsam effekt av syrgas inte styrkas genom dessa tre arbeten, och heller inte någon smärtstillande effekt. Resultaten innebär en rekommendation att vid kranskärlssjukdom använda syre vid syrebrist, men inte rutinmässigt vid normal syresättning.

I delarbete IV studerades en relativt ny behandlingsmetod av klaffsjukdomen aortastenos. Denna förträngning av klaffen mellan vänster kammare och kroppspulsådern (aorta) är en allvarlig sjukdom där standardbehandling inneburit öppen hjärtkirurgi. Även om resultaten har varit goda har inte alla patienter kunnat behandlas på ett säkert sätt. Därför utvecklades en teknik för inläggning av aortaklaff med så kallad perkutan teknik, vilket förkortas TAVR. Resultaten har varit goda, men även vissa komplikationer har varit relativt vanligt förekommande

såväl under som efter operationen i form av låg puls och blodtryck, och även risk för hjärnblödning (stroke). Kylbehandling (hypotermi) har påvisat gynnsamma effekter i samband med hjärt- och aortakirurgi, och dessutom förbättrad prognos efterföljande hjärtstopp. I denna experimentella studie studerades effekterna av mild kylbehandling i samband med TAVR. I studien inkluderades 20 patienter som lottades till kylbehandling eller standardbehandling. Metoden som användes för att inducera hypotermi, transnasal kylbehandling, visade sig vara säker, effektiv och utan allvarliga biverkningar. Det fanns inga skillnader i neurologiska effekter som uppmättes med biomarkörer, men däremot trendmässigt positiva tecken avseende puls och blodtryck.

I delarbete V studerades en diagnostisk metod vid kranskärlssjukdom, FFR, där tryckfallet över en misstänkt förträngning i kranskärlet registreras vid maximalt blodflöde. Metoden är en av de mest använda i diagnostisering av kranskärlsförträngningar, och kräver maximalt blodflöde vilket induceras genom ett läkemedel vid namn adenosin. Detta läkemedel skapar ett högt blodflöde genom vidgning av blodkärlen, men genom påverkan av andra receptorer finns även risk för en låg hjärtfrekvens och obehag för patienten. I valideringsstudier användes en standard dos för att skapa generaliserbara resultat. I klinisk användning har en praxis utvecklats att vid osäkra resultat öka adenosindosen, något som kan befaras ge ökat obehag och risk för låg hjärtfrekvens och sänkt blodtryck. I delarbete V jämfördes standard dos och högdos hos 75 patienter med gränssignifikanta kranskärlsförträngningar. I resultaten kunde ingen skillnad ses mellan standard dos och högdos adenosin avseende FFR-värde. Dessutom upplevde patienterna ett signifikant ökat obehag med den höga dosen. Våra resultat styrker fynd från tidigare genomförda studier där en hög dos adenosin inte kan rekommenderas vid FFR.

Sammanfattningsvis har tre vanligt förekommande behandlingsmetoder vid kranskärlssjukdom och klaffsjukdom studerats i denna avhandling. Genom en ökad kunskap av olika effekter och påverkan avseende sjuklighet, dödlighet och välbefinnande, har avhandlingen resulterat i ett något förbättrat kunskapsläge inom behandling och diagnostisering av hjärtsjukdom.

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