Theragnostic Options for Microvascular Obstruction in STEMI

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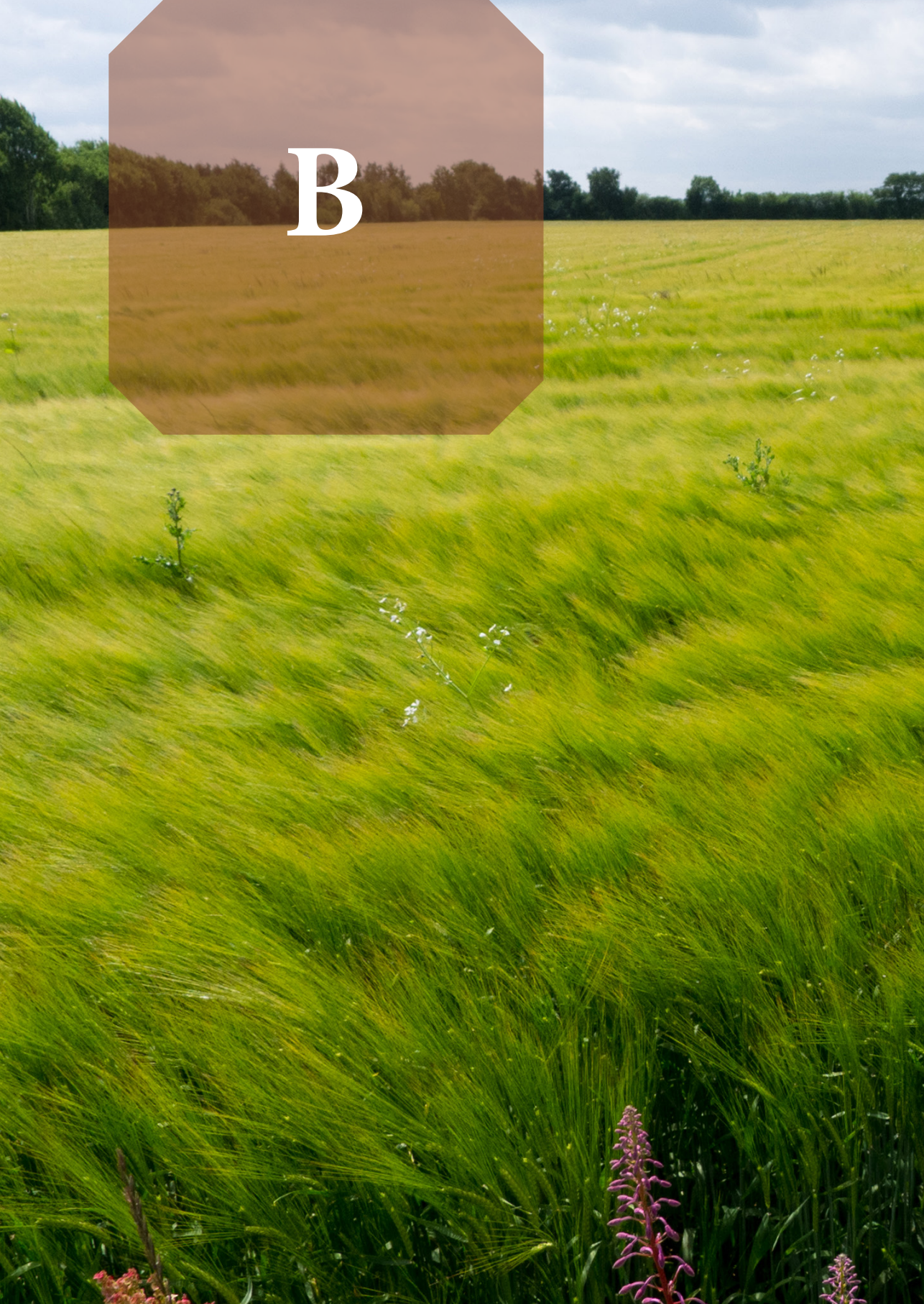
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Appendix B: English Summary

Advances in health care and advanced therapeutic options in the field of ST segment elevated acute myocardial infarction (STEMI) have drastically reduced mortality. The introduction of primary percutaneous coronary intervention (PCI) as treatment option for STEMI is a major scientific achievement. While being readily available in many countries, the ancient adage 'time is muscle' still holds. Patients will not be in the catheterization laboratory fast enough for PCI to have a complete therapeutic effect. Immediately following occlusion of the artery, intracellular ischemic changes occur triggering a cascade ultimately leading to cellular apoptosis. The two contributors are called lethal reperfusion injury and microvascular obstruction (MVO). Reperfusion injury occurs due to a combination of myocardial edema, endothelial swelling, vasospasm, inflammatory responses and distal thrombus embolization. MVO on the other hand occurs mostly due to wire and balloon manipulation of the occlusion, although it is very likely that there is overlap between these two pathways. The aim of the research bundled in this thesis was to evaluate possible new therapeutic options targeting reperfusion injury and MVO. First, chapter one consists of a general introduction and outline of this thesis.

Of course, being able to determine what patient benefits most from additional therapy is very important. This will not only save money, as novel therapies are often very expensive, but prevents additional side-effects from occurring and (thus) improves patient compliance. The first part discusses possibilities to improve this situation, starting with the second chapter, where a novel non-invasive imaging technique was developed and tested on a population of STEMI patients, in order to determine whether it is possible to predict what patients are more likely to benefit from additional therapy. This technique was called the FLASH (Fluoroscopy Assisted Scoring of Myocardial Hypoperfusion). It consists of the ratio between multiple flow/velocity measurements using frame counts on a coronary angiographic image. Obviously, invasive measurements, e.g. performed during the initial procedure,

are the golden standard when it comes to determining coronary flow. But this requires additional equipment and expertise, which might not always be available. FLASH was found to be able to predict patient mortality in a large population of STEMI patients.

In chapter three an effort was made to predict the long term consequences of STEMI, by using 3D ultrasound to measure myocardial strain. After myocardial infarction, part of the muscle that dies is replaced by connective tissue. The overall function and shape of the heart therefore change, something that can either be good (reverse remodelling) or bad (adverse remodelling). Currently, most clinics use 2D ultrasound to visualize the left ventricle after myocardial infarction, in order to determine infarct size and myocardial function. Furthermore, using ultrasound, it is possible to visually determine the amount of strain, or effort, the myocardium is under when it contracts. In this thesis, it is shown that the 3D obtained global longitudinal strain is predictive of adverse remodelling in patients, while the 3D global circumferential strain at baseline is predictive of the occurrence of reverse remodelling. Determining what patients are most likely to suffer, or benefit, from these phenomena, is critical for long term patient treatment.

The second part starts in the fourth chapter with a review of the multiple pathways by which reperfusion injury has been targeted by novel therapeutic strategies, such as adenosine and glucose-insulin administration. Of these, recent preclinical trials regarding glucagon-like-peptide-1 receptor stimulation show some promising potential.

One of these GLP1- receptor agonists is called exenatide, which offers a novel therapeutic strategy for reperfusion injury which was researched in human STEMI patients. The results are outlined in chapter five. The infarct size caused by a STEMI occurs due to direct cell death from a lack of oxygen, but is partially dependent on the occurrence of microvascular obstruction. Animal studies have shown that the infarct size can be reduced by administering exenatide, a glucagon like peptide 1 receptor agonist, something confirmed in an initial human trial. While in our study no direct effect was visible on infarct size, it is possible that a dose related effect may have played an important part.

The third part starts with the sixth chapter which focusses on a literature review of another therapeutic field targeting microvascular obstruction, utilizing the combination of ultrasound and microbubbles (or Ultrasound Contrast Agents (UCA)); a technique that is called sonothrombolysis. This therapy utilizes a combination of ultrasound and microbubbles to specifically target and treat localized arterial thrombi. All previously published clinical trials are discussed summarizing currently known data about human trials regarding ischemic cerebrovascular attacks and myocardial infarction. Ideally, treatment of a patient starts as soon as possible after a diagnosis has been made. With STEMI, this usually means administration of pharmaceutical agents in the ambulance and immediate (or with as short of a delay as possible) transport to the catheterization laboratory. Earlier, preclinical studies and early human trials have demonstrated that sonothrombolysis can be a means of treating arterial clots. This is accomplished by a process called cavitation, where UCA are agitated by high intensity ultrasound. When an ultrasound wave hits a microbubble, the sheer force of impact from the sound wave causes UCA to deform (stable cavitation); if the intensity of the ultrasound is high enough, the UCA actually explodes (inertial cavitation). This causes intense stress on the surrounding tissues.

Chapter seven consists of an experiment using an in vitro arteriole mimicking flow model, designed to determine the physical kinetic properties of inertial cavitation. Venous clots were injected into a blood filled flow system, occluding the microvasculature, which was mimicked by means of a small nylon mesh. By changing the ultrasound parameters, as well as adding different combinations of pharmaceutical agents, an optimal therapeutic effect was found.

The final chapter (eight) applied these latest ultrasound settings in a human pilot study, abbreviated as ROMIUS. This study was designed to apply the latest knowledge about ultrasound kinetics in patients with STEMI, in order to determine the therapeutic effect on long term myocardial recovery. Patients admitted to the hospital were randomized to either sham ultrasound without UCA infusion, or ultrasound therapy (sonolysis) with administration of UCA. Unfortunately, this study was prematurely cancelled due to safety concerns; application of ultrasound in patients caused, in contrast with earlier human trials, severe coronary vasoconstriction. Long term side-effects fortunately did not occur, but additional research is necessary in order to fine tune this therapy before widespread use can be considered.