General introduction and outline of the thesis

Chapter 1
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Introduction
The introduction of microbubbles and the technical development in ultrasound facilitates the qualitative and quantitative assessment of the myocardial infarct size as well as microvascular perfusion using myocardial contrast echocardiography (MCE) and can therefore potentially help the clinician in choosing the optimal treatment strategy during and after an acute coronary syndrome. Both ultrasound frequency and intensity play important roles in microbubble behavior, resulting in three different behavioral mechanisms. This is why the term mechanical index or “MI” was created, which is defined as the peak negative pressure divided by the square root of the frequency. Under influence of low acoustic pressure, the microbubble oscillates linearly resulting in backscatter enhancement. When the MI increases, the behavior of microbubbles starts to change to a non-linear oscillation, which results in the emission of harmonics. A MI above roughly 0.7 typically results in microbubble disruption. However, this threshold may vary depending on microbubble shell composition. The microbubble properties during low and high acoustic pressures are used for diagnostic purposes in perfusion imaging.

Diagnostic contrast ultrasound
The first applications of microbubbles in the field of diagnostic cardiac ultrasound for left-sided cardiac contrast enhancement was the evaluation of wall motion, volumes and assessment of intracardiac structures. Real-time assessment implies the use of low MI imaging, since high MI imaging results in the local destruction of microbubbles, thereby creating artifacts in the image. Several studies demonstrated an enhanced delineation of the endocardial border using contrast enhanced ultrasound compared to ultrasound without the use of contrast agents, both in rest and during stress echocardiography. When compared to reference standards, including cardiac magnetic resonance imaging (MRI) and radionuclide ventriculography, measurement of left ventricular volumes and ejection fraction using contrast enhanced ultrasound demonstrated a better agreement and a reduction in intra- and interobserver variability. Nowadays, the use of contrast echocardiography to improve left ventricular segmental opacification is widely used and recommended when non-contrast echocardiography is inconclusive.

The development of new ultrasound techniques also led to new diagnostic opportunities with contrast ultrasound. Destruction of microbubbles at a high MI during a continuous infusion of microbubbles is followed by the replenishment of microbubbles in the microvasculature. Low MI, non-destructive imaging techniques like power pulse inversion enables the visualization of this replenishment curve. The principle of power pulse inversion is based on the transmission of several ultrasound pulses with alternating polarity. This permits cancellation of any tissue signals, which exhibit primarily fundamental linear responses at a low MI, and enhancement
of microbubbles due to their non-linear responses at this same low MI. Hence, one visualizes a subtracted background image of microbubble replenishment in the myocardium, which facilitates the quantitative and qualitative assessment of perfusion defects in patients with coronary artery disease. (10)

**Therapeutic contrast ultrasound**

In the course of years, attention has shifted from diagnostic to potential therapeutic applications of contrast ultrasound. Local application of ultrasound results in several biophysical effects, such as non-linear responses (harmonics and ultraharmonics), stable and inertial cavitation, and even local increase in temperature. (11, 12)

In the early nineties it was already demonstrated that high frequency, low intensity ultrasound was able to enhance fibrinolysis. Nevertheless, this implied an invasive therapy which was not readily available in daily clinical practice. With the introduction of microbubbles, the threshold for these biophysical effects to take place was lowered. This resulted in the possibility to enhance fibrinolysis using diagnostic ultrasound machines during infusion of microbubbles. A number of studies have been conducted with these ultrasound settings to evaluate their effect on thrombolysis. In combination with a thrombolytic agent; e.g. tissue-plasminogen activator (t-PA), it was observed that thrombolysis was accelerated compared to treatment of thrombus with t-PA alone. (13) The optimal ultrasound settings in this therapeutic setting still remain a matter of debate. Nevertheless, the two main factors contributing to its therapeutic results are the mechanical index and the pulse duration.

During *in vivo* pig studies it was also demonstrated that therapeutic application of contrast ultrasound not only improved recanalization rates but also resulted in amelioration of microvascular flow even in the absence of recanalization of the culprit vessel.

**Aims and outlines of the thesis**

The set-up of this thesis was not only to realise translational research with contrast ultrasound in the field of cardiology, but to expand its field of application to a multidisciplinary level combining expertise of several medical disciplines (cardiology, anaesthesiology and vascular surgery).

The aim of the work presented in this thesis was to evaluate possible new diagnostic applications of contrast ultrasound, as well as an evaluation of translational research regarding therapeutic applications of contrast ultrasound.

For this purpose, the thesis has been divided in three parts. The first part is focussing on the diagnostic application of contrast ultrasound in the field of cardiology and anaesthesiology. The second and third part of this thesis will encompass the translational research performed in the cardiovascular field of therapeutic application of contrast ultrasound. With the focus of
the second part on \textit{in vivo} studies performed and the third part evaluating its possible clinical application.

\textit{Part 1: Novel diagnostic application of myocardial contrast echocardiography}

\textbf{Chapter 2} reviews the diagnostic application of contrast ultrasound for the quantitative assessment of myocardial perfusion. The introduction of this new diagnostic tool creates the possibility to perform bed-side imaging during interventions and is an introduction to the next chapter. In \textbf{chapter 3} the effect of general anaesthesia on myocardial perfusion in healthy subjects is assessed by quantitative measurement of myocardial perfusion using diagnostic contrast ultrasound.

\textit{Part 2: Therapeutic contrast ultrasound in arterial thrombosis: pig models}

In \textbf{chapter 4} two pig models are examined, a normal and an atherosclerotic model, in which ST elevation myocardial infarction were obtained by creating coronary thrombosis. The effect of diagnostic contrast ultrasound was evaluated on both microvascular flow and epicardial recanalization. \textbf{Chapter 5} concerns the set-up of a new pig model in which acute peripheral arterial occlusions are created and the treatment with contrast ultrasound and prevention of severe allergic reactions are evaluated. The same model and settings are used in \textbf{chapter 6} which focuses on the results of contrast ultrasound on top of standard thrombolytic therapy in acute peripheral arterial occlusions.

\textit{Part 3: Therapeutic (contrast) ultrasound in coronary artery disease: clinical studies}

Part 3 commences with the rationale and design of the sonolysis study in \textbf{chapter 7}. This is worldwide the first clinical study in acute STEMI patients evaluating the effect of contrast ultrasound on top of fibrinolytics on epicardial recanalization. \textbf{Chapter 8} evaluates the first results of the sonolysis study and recommendations regarding future studies. \textbf{Chapter 9} is a critical appraisal of the current literature with respect to therapeutic application of contrast ultrasound. It focuses on the biomechanical effects on a macrovascular and microvascular level in acute coronary syndromes, the optimal settings and the results thus far. Although, high-intensity ultrasound has proven its potential effect on thrombus dissolution it has never been further investigated due to its invasive aspect. Recent new technical developments made it possible to apply high-intensity ultrasound in a non-invasive manner. Pre-clinical research demonstrated a potential coronary neovascularization in the ischemic area treated with high intensity ultrasound, which could result in relief of symptoms and lower ischemic burden in patients with refractory angina. In \textbf{chapter 10} the effect of this new shockwave therapy in patients with ischemic heart disease is evaluated.
References
