General discussion and future perspectives
In the last decades, early mortality rates after acute myocardial infarction (AMI) have decreased significantly. This is mainly due to early restoration of the epicardial blood flow by percutaneous coronary intervention (PCI). However, a proportion of patients shows signs of a hampered restoration of the myocardial microvascular circulation, also known as the no-reflow phenomenon, leading to a diminished myocardial salvage, larger infarct sizes, a worse residual LV function and increased morbidity and long-term mortality. Although multiple non-invasive cardiac imaging techniques such as myocardial contrast echocardiography and cardiovascular magnetic resonance imaging (CMR) are available for evaluating no-reflow after AMI, earlier research already showed that this is best studied by CMR late gadolinium enhancement (LGE) imaging and described as microvascular obstruction (MVO). It has long been assumed that this MVO, depicted as a lack of Gadolinium-contrast wash-in within a contrast-enhanced infarcted area, is a result of embolization of thrombotic debris, swollen intraluminal endothelial protrusions and plugging by activated inflammatory cells, erythrocytes, platelets and fibrin thrombi, leading to obstructed microvasculature.

NOVEL INSIGHTS IN THE ORIGIN AND CHARACTERISTICS OF REPERFUSION INJURY

Porcine models of coronary occlusion and reperfusion have given new insights in the development of MVO by providing a link between CMR and histopathological findings of myocardium after a reperfused myocardial infarction. Histopathological examination of the porcine myocardial samples showed that the infarct core - that contained MVO on LGE images - contains extensive necrosis with extravasation of erythrocytes due to destruction of the local vasculature and hence, no ‘true’ microvascular obstruction. In the surrounding area, which matched with the Gadolinium-enhanced area on LGE images, granulation tissue with infiltration by leukocytes was seen. In this area, morphological intact microvessels containing microthrombi were seen, without extravasation of erythrocytes. Although further studies on this subject are needed, the results suggest that the currently defined areas of microvascular obstruction contain extensive destruction of the microvasculature as well, while the ‘genuine’ microvascular obstruction may be found in the surrounding Gadolinium-enhanced area.

While the exact histopathological substrate of MVO in humans after reperfused AMI is not yet fully understood, its exact effects on different CMR parameters remains to be discussed as well. While we almost did not find any MVO without signs of intramyocardial hemorrhage on CMR STIR images and vice versa, other studies described the separate presence of intramyocardial haemorrhage in relation to MVO.
EVALUATING NEW DIAGNOSTIC AND THERAPEUTIC STRATEGIES AFTER ACUTE MYOCARDIAL INFARCTION USING CMR

With the emergence of more quantitative CMR measures for tissue characterization such as T1 mapping, the effects of reperfusion injury on local T1 values have joined this discussion as well. As haemorrhage consists of accumulated erythrocytes within the infarcted myocardial core, local magnetic properties change due to the accumulation of haemoglobin breakdown products such as deoxyhemoglobin and methemoglobin. (14;15) This has initially been shown in brain ischemia and haemorrhage studies, but exploratory CMR studies after AMI confirm that local T1, T2 and T2* values change after AMI. (16;17) The measurement of local T1, T2 and T2* values are currently under investigation for their potential in depicting myocardial injury and predicting future events. However, some studies postulate that the local edema and inflammation increase local T1 values, (17) while others state that paramagnetic effects from local intramyocardial haemorrhage decrease local T1 and T2* values. (16;18). We assessed targeted local T1 and T2* values of different myocardial infarct zones and found that reperfusion injury changes both local T1 and T2* parameters. (19) Additionally, the results suggested that T1 values need to be interpreted in the context of T2* values, cine and STIR images if reperfusion injury and edema are simultaneously present. The findings confirm again that the infarcted myocardium should not be approached as a homogeneously afflicted myocardial zone, but that it likely consists of tissue with different gradations of injury, ranging from edema formation up to infarction with tissue destruction and the formation of haemorrhage. These differences result in local changes in various CMR parameters. However, as long as the exact histological correlate of these CMR findings remains to be discussed, we advocate the use of more fitting nomenclature by referring to the severely injured, Gadolinium-devoid infarct core as ‘microvascular injury’ (MVI), since this term better reflects the diverse findings in different infarct areas.

While T1, T2 and T2* value measurements may provide us with new methods for assessing myocardial injury severity and may help us identify patients at increased risk for adverse cardiac events, these measurements will not be helpful in the early detection and thus, prevention of microvascular injury. In order to devise new treatment strategies for reperfusion injury, new biomarkers need to be found for early prediction of the formation of MVI. Recent studies have already assessed whether intracoronary pressure-flow measurements can predict the development of MVI. For example, pressure-flow derived hyperemic microvascular resistance (HMR) measured immediately after PCI shows predictive value for the development of MVI. (20) However, whether these findings are predictive of worse functional outcome and more clinical adverse events needs to be established. CMR provides solid parameters for the detection of present MVI and can
be useful as a surrogate endpoint for new techniques in the prediction and prevention of reperfusion injury development after AMI.

The aforementioned increase in long-term morbidity and mortality due to maladaptive remodeling of the left ventricle and the development of congestive heart failure or ventricular arrhythmias after reperfusion has led to the search for new treatment strategies to minimize reperfusion damage and adverse remodeling. The HEBE trial assessed whether paracrine effects from locally infused autologous stem cells can help attenuate the adverse remodeling and decrease the number of adverse events. Patients were randomized to either mononuclear bone marrow-derived cells, mononuclear peripheral blood-derived cells, or standard therapy (without placebo infusion). Intracoronary cell delivery was performed between 3 and 8 days after AMI. The trial, which has been published earlier, did not show any differences between the treatment groups for the main endpoints on a short term follow-up (clinical events or differences in global or regional myocardial function at 4 months follow-up). It was postulated that the possible paracrine and neo-angiogenic effects of cell therapy may improve the myocardium in more subtle manners, such as improving myocardial perfusion or by attenuating ongoing adverse left ventricular (LV) remodeling on long-term follow-up in either the myocardial core or the adjacent border. Unfortunately, no additional effects from cell therapy on perfusion restoration were found. Assessment of the long-term effects of cell therapy showed that patients treated with bone marrow-derived cells had slightly less adverse LV remodeling after 2 years.

As certain subsets of inflammatory cells from the monocyte population show an association with adverse outcome in regional myocardial function and perfusion, the exact role of the inflammatory system on myocardial restoration after AMI needs further investigation. Modulation of immune system pathways may lead to new targets for attenuating myocardial injury, but possible unintentional side effects should be evaluated as well. Although cell therapy may induce adverse side effects such as induction of tissue heterogeneity and abnormal intercellular electrical coupling, no association was found with either an increase or decrease in ventricular arrhythmias on short-term follow-up.

Adversely, patients treated with peripheral blood-derived cells suffered from significantly more major adverse cardiovascular events in patients treated with bone marrow-derived cells. This increase in event rate in patients treated with cell therapy suggests that not all effects of cell therapy—be it beneficiary or adverse—are yet known.

With regard to whether tissue heterogeneity after AMI may be associated with ventricular arrhythmias, we evaluated whether dividing the Gadolinium-enhanced area in a dense core area and a surrounding ‘penumbra’ could predict the occurrence of ventricular arrhythmias on 24-hour ECG registration at 1 month. It was found that larger proportions of penumbra within the enhanced area were associated with an increased risk of developing VTs. Although further research is needed, further stratification of
the contents of the Gadolinium-enhanced area may provide us with new tools for risk stratification.

FUTURE PERSPECTIVES

New diagnostic tools are necessary to detect reperfusion injury as soon as possible, in order to reduce the additional damage to the myocardium as much as possible. Current CMR techniques provide solid and robust biomarkers for reperfusion injury, such as MVI on LGE imaging, which can be used as a surrogate for adverse outcome and worse prognosis. As we now know that MVI does not only incorporate microvascular obstruction, but a haemorrhagic component as well, studies on adjunct therapies to attenuate the myocardial haemorrhage may alter the outcome in revascularized AMI-patients. The incorporation of novel CMR techniques such as T1, T2 and T2* measurements allows us not only to further investigate the composition of the infarcted tissue, but may also provide us with additional tools for assessing the risk of adverse cardiac events, such as the development of congestive heart failure or the occurrence of sudden cardiac death. Further research in the CMR-measured composition of the infarcted myocardium may allow us to further identify patients with potential benefit of prophylactic ICD implantation, or to identify patients in need of more stringent follow-up of cardiac function. The further development of these CMR parameters and their combined use may provide us with a completely new set of tools to identify the patients at risk of future adverse events.
REFERENCES


