Chapter 6

Summary and Future Perspectives
SUMMARY

Myocardial perfusion abnormalities occur in a variety of cardiac disease states, including coronary artery disease, and both primary and secondary cardiomyopathies. The assessment of perfusion in these pathological conditions yields important diagnostic and prognostic information and allows for monitoring the effect of therapeutic interventions. Positron emission tomography (PET) using a flow tracer, such as oxygen-15-labeled water (H\textsubscript{2}15O), can noninvasively measure myocardial blood flow (MBF) in absolute terms. Furthermore, this particular tracer provides the possibility of estimating the volume of distribution of water in myocardial tissue, which correlates with the extent of fibrosis. In this thesis, clinical studies in patients with heart failure are described in order to extend the knowledge of the interactions between perfusion, fibrosis, and function and to assess the effects of therapy.

In chapter 1, the validation process of H\textsubscript{2}15O as a PET perfusion tracer is described. In addition, outcome of clinical studies in cardiac (patho)physiology are discussed. Furthermore, the clinical value of the perfusable tissue index (PTI) as an index of myocardial fibrosis and a marker of myocardial viability was evaluated. Pooling of viability studies revealed that dysfunctional, but viable, myocardium was characterized by a significantly higher PTI value than non-viable tissue. This finding supports the hypothesis that scar tissue in not able to rapidly exchange water and a reduction in PTI reflects the extent of myocardial scarring. A cut-off value of 0.7 yielded the best diagnostic accuracy in the distinction between viable and non-viable tissue in three out of four examined studies. It should be mentioned, however, that these results were based on studies from a limited number of centers in a small number patients. More studies are warranted to gain further insight into the clinical value of PTI.

In chapter 2.1, the effects of cardiac resynchronization (CRT) therapy on MBF in fourteen patients with either ischemic or idiopathic dilated cardiomyopathy and intraventricular conduction delay are reported. Hyperemic perfusion was impaired in these heart failure patients, regardless of aetiology, although in ischemic cardiomyopathy the extent of impairment was more pronounced. In addition, MBF at rest displayed marked heterogeneity with a reduction in perfusion in the interventricular septum compared with the lateral free wall. During cardiac resynchronization by means of biventricular pacing, these regional differences were completely abolished. Moreover, in a subset of patients, predominantly affected by idiopathic dilated
cardiomyopathy, global hyperemic MBF increased significantly. This phenomenon was related to a reduction in estimated wall stress induced by CRT.

Subsequently, in chapter 2.2, an overview is given of the currently available literature regarding the metabolic effects of CRT and the assessment of cardiac mechanical dyssynchrony. As also described chapter 2.1, regional differences in perfusion, glucose metabolism, and oxygen consumption between interventricular and lateral free walls are normalized by CRT. These observations are compatible with the hypothesis that CRT rebalances the loading conditions of the dyssynchronous failing heart. In contrast to positive inotropic agents, improved cardiac function is not achieved at the expense of increased oxygen consumption. Indeed, myocardial efficiency is increased. Furthermore, studies have demonstrated that electrical intraventricular conduction delay is at best a moderate marker of actual mechanical dyssynchrony. The latter observation is a possible explanation for the fact that approximately 20-30% of eligible patients do not respond to this form of therapy. Identifying patients who are most likely to respond by assessing mechanical dyssynchrony rather than electrical conduction delay is therefore important.

Various echocardiographic markers have been validated to determine mechanical dyssynchrony, including M-mode, two and three dimensional echocardiography, and tissue Doppler imaging. The most accurate manner to assess the pattern of mechanical activation of the heart can be derived with high temporal and spatial resolution MRI tissue tagging. This method, however, is limited by its limited availability, elaborate postprocessing, and relatively high costs.

In chapter 3.1, the potential of noninvasive quantification of myocardial fibrosis using the water perfusable tissue index (PTI) was explored in patients with idiopathic dilated cardiomyopathy. This primary cardiomyopathy is characterized by the presence of interstitial fibrosis and a reduction in PTI in this patient group was hypothesized. Fifteen symptomatic idiopathic dilated cardiomyopathy patients were compared with 11 healthy volunteers and PTI was indeed reduced in the patient group. In addition, the reduction in PTI was highly variable, both at a regional level and between patients. There was, however, no correlation between the reduction in PTI and left ventricular ejection fraction measured with echocardiography. This study suggests that PTI can be used to non-invasively assess interstitial fibrosis, which may be useful for investigating the relation between the extent of fibrosis and prognosis, and for monitoring therapeutic interventions in future studies. It must be noted, however, that histological validation studies remain imperative to fully elucidate the value of PTI in this patient group.
In chapter 3.2, the interrelationships between myocardial perfusion, fibrosis (PTI), and contractile function were investigated on a regional level in patients with idiopathic dilated cardiomyopathy through the combination of PET and MRI tissue tagging. Sixteen patients and 6 healthy controls were studied. In line with previous studies, hyperemic MBF, PTI, and contractile function were all impaired in patients with cardiomyopathy and MBF at baseline was comparable between patients and controls. In patients, both resting and hyperemic MBF as well as PTI were related to systolic function, whereas PTI and MBF did not show agreement. The reduction in hyperemic perfusion was directly related to the estimate in left ventricular end-diastolic wall stress. These data suggest that, next to endothelial dysfunction, hyperemic perfusion is impaired due to extravascular compression of the microvascular vessels. The latter may in turn induce periods of myocardial ischemia and exacerbate systolic dysfunction.

In chapter 4.1, PTI measurements were performed in patients with hypertrophic cardiomyopathy. In these patients delayed contrast enhancement (DCE) visualized with MRI is a common finding in the hypertrophied interventricular septum. The pathophysiologic basis of this observation remains unclear as currently histologic comparison is lacking. Nevertheless, it is generally assumed that DCE-MRI represents myocardial fibrosis. Therefore the study described in chapter 6 was conducted to compare PTI and DCE-MRI in 21 patients with hypertrophic cardiomyopathy. Twelve patients with chronic myocardial infarction and 6 healthy volunteers served as control groups. In healthy volunteers no DCE was present and PTI was within the normal range. In patients with a previous myocardial infarction, PTI was reduced in proportion to the extent of DCE, indicating scar tissue. In patients with hypertrophic cardiomyopathy, however, an opposite pattern was observed, i.e. an increase in DCE was accompanied by an increase in PTI. These observations indicated that DCE in hypertrophic cardiomyopathy may not solely represent myocardial fibrosis and other pathological changes are, at least in part, responsible for DCE in these patients.

In chapter 4.2, additional MRI tissue tagging was performed in a subset of 14 of the patients with hypertrophic cardiomyopathy described in the previous chapter. It is well established that regional MBF at baseline is not homogeneous in hypertrophic cardiomyopathy. The determinants of resting perfusion, however, are not well defined. The results indicated that not regional heterogeneity in systolic function determined by MRI tissue tagging, but the extent of DCE-MRI correlated with resting MBF.
Finally in chapter 5, in 20 patients with chronic ischaemic left ventricular dysfunction, PTI and DCE-MRI were compared. As hypothesized and already observed in chapter 6, a reduction in PTI was correlated with the extent of DCE. PTI, however, underestimated infarct size relative to DCE-MRI estimated infarct size. The mechanisms responsible for this discrepancy warrants further investigations. Furthermore, a cut-off value of 0.89 for PTI yielded the highest diagnostic accuracy when DCE-MRI was taken as a reference for detection of myocardial viability. This value is distinctly higher than the value found in previous studies as mentioned in chapter 1. Again, follow-up studies after revascularization procedures are needed to define the optimum cut-off value. MBF in perfusable tissue was shown to be a poor marker of viability and confirms the hypothesis that chronic hypoperfusion is not likely the leading cause of contractile dysfunction in chronic ischaemic heart disease.

**FUTURE PERSPECTIVES**

Quantification of myocardial perfusion using PET has proven to provide valuable insight into the (patho)physiology of the human heart. Nevertheless there are some important issues that warrant further investigation and development. First, almost without exception, perfusion deficits first occur in the subendocardium. Current PET scanners are generally not equipped to distinguish between subendocardial and subepicardial MBF, except for some limited experience in extreme left ventricular hypertrophy. Corrections for cardiac and respiratory motion and improvement in spatial resolution with 3D PET scanners in the near future will hopefully facilitate transmural quantification of metabolism and perfusion. Initial experiences in this field are in fact promising. Second, given the fact that there is close coupling between metabolism and function, it is of paramount importance to combine metabolic with functional imaging techniques. In the present thesis, for this purpose, studies were performed that combined MRI or echocardiography with PET. Alignment between imaging techniques was performed by consensus in region of interest definition using anatomical landmarks. Although this generally yields reliable results in matching between myocardial territories, image fusion in the postprocessing phase may give more accurate results and should be further explored. Moreover, new developments in dual-imaging-techniques, such as PET/CT, allow for almost perfect alignment and, in contrast to separate imaging techniques, metabolic and anatomical imaging can be performed within a timeframe of a few minutes assuring almost identical hemodynamic conditions. The first reports on cardiac applications of PET/CT indeed look promising. Even more exciting are the first prototypes of combined PET/MRI scanners, which allow for simultaneous imaging acquisition without the
additional radiation burden that accompanies a CT-acquisition. This latter technique, however, is only just glooming at the horizon and still far removed from clinical applications. Finally, at present, perfusion PET is predominantly used as a research tool. The increasing number of PET scanners and on-site cyclotrons worldwide in addition to a reduction in postprocessing time will increase the availability of perfusion imaging with PET, which may result in better access for diagnostic purposes. This could be especially beneficiary for patients with e.g. obesity, where conventional imaging techniques such as SPECT and echocardiography are limited with respect to their capacity of detecting ischemic heart disease due to lack of attenuation correction and poor ultrasound window, respectively. Larger prospective trials are needed to assess diagnostic accuracy of perfusion PET for detecting ischemic heart disease.