For patients with end-stage heart failure, heart transplantation (HTX) is the ultimate therapy. Knowledge of pre- and post-operative medical treatment and management resulted in improved graft survival and patient outcome. For tissue and coronary staging after HTX, the reference standards are invasive procedures like coronary angiography, whereas tissue staging is carried out by potentially hazardous myocardial biopsies. Additionally, these procedures expose patients to a substantial radiation dose, and the hazard of nephro-toxic contrast agents. To circumvent these shortcomings, a non-invasive imaging approach would be a helpful tool saving health costs and improve patient’s quality of life. Cardiovascular magnetic resonance (CMR) is the reference standard imaging modality for evaluation of ventricular morphology, volumes and mass due to excellent image quality as compared to other modalities. The ability of CMR to characterize ventricular morphology, systolic and diastolic function, inflammation, fibrosis and infarction makes it an excellent candidate for post HTX staging.

CMR techniques like T2 assessment have shown good correlation to biopsy proven heart transplant rejection although the reproducibility of T2 measures as well as limited access have likely hampered the adoption of CMR into routine post HTX clinical care. Improvements in CMR hardware combined with appropriate pulse sequences for T2 quantification make routine ascertainment of T2 relaxation more feasible and improve inter-center reproducibility. Early and late gadolinium enhancement may also prove useful in diagnosing transplant rejection just as it has in the diagnosis of myocarditis. Studies are needed evaluating promising CMR correlates of rejection such as diastolic function, gadolinium enhancement and other contrast agents. Future studies should focus on combining multiple CMR measures into a transplant rejection scoring system to improve the sensitivity in detecting heart transplant rejection and possibly reduce, if not eliminate, the need for endo-myocardial biopsy.

Key words: end-stage heart failure, heart transplantation, coronary angiography, myocardial biopsy, cardiovascular mangetic resonance imaging

MRI-Untersuchung des Herzens bei herztransplantierten Patienten


CMR-Techniken wie die T2-Untersuchung haben eine gute Korrelation mit biopsiatisch gesicherter Herztransplantatabstoßung gezeigt, auch wenn die Reproduzierbarkeit der T2-Messungen sowie der eingeschränkte Zugang zu diesem Verfahren die Einführung des CMR in die routinemäßige klinische Betreuung von Patienten nach HTX wahrscheinlich behindert haben. Verbesserungen in der CMR-Hardware zusammen mit geeigneten Pulsssequenzen für T2-Quantifizierung erleichtern die routinemäßige Überprüfung der T2-Relaxierung und verbessern die Reproduzierbarkeit zwischen den Zentren. Frühe und späte Gadolinium-Anreicherung kann sich in der Diagnose einer Trans-
Cardiac Magnetic Resonance Imaging in Heart Transplant Patients

For patients with end-stage heart failure, heart transplantation (HTX) is the ultimate therapy. Worldwide, nearly four thousand patients receive HTX per year [1]. Knowledge of pre- and post-operative medical treatment and management, as well as improvement in surgical techniques have increased tremendously in the last two decades, resulting in improved graft survival and patient outcome [1].

The causes of deaths in patients after HTX can be divided into acute and chronic processes. Acutely, these patients die of infections (33%), transplant failure (18%) or acute organ rejections (12%). Chronically, they pass away because of transplant vasculopathy (30%), tumors (22%), infections (10%) or myocardial fibrosis (10%) [1]. For staging of HTX coronary arteries, the reference standards are invasive procedures like coronary angiography, intravascular ultrasound (IVUS) whereas tissue staging is carried out by myocardial biopsies. Unfortunately, these routine annual HTX assessments expose patients to a substantial radiation dose, the hazard of nephro-toxic contrast agents and nonetheless potentially life threatening myocardial biopsies [2].

To circumvent these shortcomings in staging HTX patients, a non-invasive approach with advanced tissue characterisation would be a helpful tool [3] to save health costs and improve patient’s quality of life.

Cardiovascular magnetic resonance (CMR) is the reference standard imaging modality for evaluation of ventricular morphology, volumes and mass due to excellent image quality as compared to echocardiography and nuclear modalities [4-6]. CMR can also be employed to measure functional parameters like ventricular diastolic properties, regional myocardial tissue strain and rotation [7]. Additionally, due to inherent different tissue contrast patterns, CMR also has proven utility in detecting myocardial inflammation in disease states such as myocardial infarction [8], viral myocarditis [9], dilated cardiomyopathy [10], as well as heart transplant rejection in both animal [11] and human [12] models.

The ability of CMR to characterize ventricular morphology, systolic function, diastolic function, myocardial inflammation, fibrosis and infarction makes it an excellent candidate to non-invasively diagnose and screen for acute heart transplant rejection. The correlation between biopsy proven rejection and echocardiographically determined ventricular morphology is specific in severe cases of acute cellular rejection but is too insensitive to be used as a screening tool [13]. It has been postulated that the superior spatial resolution of CMR may lead to improved sensitivity in diagnosing rejection on the basis of changes to ventricular morphology [6]. Myocardial wall thickness has been shown to increase in both animal [14,15] and human [16] CMR trials of transplant rejection. Several animal studies showed that increased wall thickness during acute rejection was correlated to ex-vivo total myocardial water content [17]. However, wall thickness was not capable of accurately identifying the severity of a rejection episode. Changes in ventricular morphology and systolic function as measured by CMR are associated with rejection [18]. Despite the excellent spatial resolution of CMR, these variables are probably of insufficient sensitivity to detect the early and milder forms of rejection that are of clinical interest.

Diastolic dysfunction is one of the earliest measurable features of heart transplant rejection [19]. The reduction in compliance preceded any evidence of systolic dysfunction. Despite these provocative results, there have been no human studies assessing CMR measures of diastology in transplant rejection to date. Measuring diastolic function using strain rate imaging with CMR may improve sensitivity in diagnosing rejection, however work in this area would need to differentiate changes in diastolic properties due to rejection and those due to the fibrotic and hypertrophic remodeling that accompanies heart transplantation even in the absence of rejection [19].

Apart from the ability of CMR to assess cardiac function and morphology, the non-invasive tissue characterisation due to different T1 and T2 tissue properties is even more attractive. Myocardial T2 signal intensity (SI) is influenced by myocardial water content and can clinically detect myocardial inflammation associated with myocarditis [8], Tako-Tsubo cardiomyopa-
thy [9], and acute myocardial infarction [20]. The ability of T2 SI to detect heart transplant rejection has been inconsistent in the literature [21]. But potentially, this technique suggests that the relationship between T2 relaxation and rejection is highly sensitive for any cases of advanced rejection. Improvements in T2 imaging in the current era such as higher field strengths, fast turbo-spin sequences, and improved blood and fat suppression techniques will likely strengthen the association between T2 relaxation times and transplant rejection [22].

In addition, T1 weighted CMR images are also influenced by myocardial water content, although to a lesser extent when compared to T2 weighted images. Similarly to the T2 studies, non-contrast agent enhanced T1 signal intensity has shown an inconsistent correlation with rejection in animal models of heart transplantation [23]. But the relationship between T1 relaxation and transplant rejection has been even less well studied than that of T2 relaxation. The superior sensitivity to water content of T2 weighted imaging makes it a better choice for imaging myocardial inflammation, and likely accounts for the paucity of trials investigating T1 relaxation and rejection.

Gadolinium based contrast agents are by far the most common contrast agents used in clinical CMR imaging. Intravenous gadolinium increases signal intensity on T1 weighted images acquired early after contrast administration, in proportion to the degree of tissue perfusion and is thought to reflect the hyperemia seen in inflamed tissue. Increase in signal intensity early after contrast injection (early enhancement) has shown utility in the diagnosis of other disorders of myocardial inflammation such as myocarditis. In two human trials of transplant rejection, post contrast signal intensity tended to increase with the degree of rejection although it could not consistently identify the full spectrum of abnormal endomyocardial biopsies diagnostic of rejection [21].

Gadolinium can also be used in CMR to detect areas of myocardial scar or myocardial fibrosis. The rate at which gadolinium is cleared from the myocardium is slower in areas with fibrosis compared to healthy myocardium. T1 weighted images taken several minutes (‘late’) after contrast injection will show higher concentrations of gadolinium in areas of myocardial fibrosis making these areas appear bright. Late gadolinium enhancement (LGE) has correlated well to pathologic assessment of myocardial fibrosis in ischemic [24] and non-ischemic [25] myocardial injury. A recent study of LGE patterns in heart transplant patients found that 50% of patients had a nonischemic LGE pattern similar to that seen in diseases of myocardial inflammation such as myocarditis. No study to date has looked at presence, degree, or location of LGE patterns in acute human heart transplant rejection.

Iron oxide contrast agents have been used in clinical and experimental MR since the 1980s predominantly in the field oncology [27]. More recently, these agents have been shown to be safe [28] and useful for contrast MR angiography. Iron oxide contrast agents contain superparamagnetic particles with an iron oxide crystal core wrapped in an outer coating (i.e. dextran) which shorten both T1 and T2/T2* relaxation [29]. Over time, iron oxide particles are taken up by macrophages which shortens their T2/T2* properties. Thus, accumulation of macrophages, which contain iron oxide, in inflamed tissue can be visualized as a signal loss on T2 weighted images. CMR with iron oxide particles is a novel and potentially powerful method to evaluate inflammation in the heart. T1 imaging early post iron oxide contrast injection can identify increased vascular permeability, while delayed T2 imaging gives information into in-vivo macrophage accumulation. Human trials of transplant rejection and iron oxide contrast agents are needed.

Several CMR variables have shown good correlation to biopsy proven heart transplant rejection, the strongest of which is quantitative T2 assessment. Criticism regarding the reproducibility of T2 measures [30] as well as limited access to CMR has likely hampered the adoption of CMR into routine post transplant clinical care. Improvements in CMR hardware combined with appropriate pulse sequences for T2 quantification make routine ascertainment of T2 relaxation more feasible and improve inter-center reproducibility over traditional T2 results based on signal intensity. Early enhancement may also prove useful in diagnosing transplant rejection just as it has in the diagnosis of myocarditis. Studies are needed evaluating promising CMR correlates of rejection such as diastolic function, late gadolinium enhancement, and paramagnetic iron oxide contrast agents. Future studies should focus on combining multiple CMR measures into a transplant rejection scoring system to improve the sensitivity in detecting heart transplant rejection and possibly reduce, if not eliminate, the need for endo-myocardial biopsy.

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