Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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11

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY Part I: The role of echocardiography in predicting outcome after CRT

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients who remain symptomatic despite optimal medical therapy (New York Heart Association functional class II-III and ambulatory class IV) with a wide QRS complex (≥130 ms) and reduced left ventricular ejection fraction (LVEF) ≤35%. The benefits of CRT, however, may differ according to the QRS complex duration and morphology. In **chapter 2**, the effect of baseline QRS duration and morphology on LV reverse remodeling and LVEF improvement after CRT was investigated. Patients with a baseline QRS ≥150 ms demonstrated more LV reverse remodeling (mean reduction in LV end-systolic volume (LVESV) of 34.3 ml vs. 14.8 ml; P<0.001) and a greater LVEF improvement (mean increase 6.8% vs. 5.2%; P<0.001), compared to those with QRS <150 ms. Similarly, CRT recipients with left bundle branch block (LBBB) at baseline, evidenced more LV reverse remodeling (P<0.001) and LVEF improvement (P<0.001) than those with non-LBBB QRS morphology. LBBB QRS morphology and increasing QRS duration therefore translated into a greater degree of LV reverse remodeling and systolic function improvement than non-LBBB morphology and a lesser QRS duration, which is supportive of contemporary guidelines for CRT placement.

In **chapter 3**, different CRT response definitions were compared. An LV volumetric response to CRT is conventionally defined as a ≥15% reduction in LVESV at 6 months post-CRT. An improvement in global longitudinal strain (GLS) on speckle tracking echocardiography may also be seen in response to CRT. A CRT volumetric response and an improvement in LV GLS are not always seen in the same patient, and the prognostic impact of seeing: i) an improvement in GLS or a reduction in LVESV or ii) an improvement in GLS and a reduction in LVESV, was subsequently investigated. CRT recipients with an improvement in LV GLS and a reduction in LVESV, had significantly lower all-cause mortality compared to those who had either: i) an improvement in LV GLS or a reduction in LVESV, but not both and ii) no improvement in either LV GLS and no reduction in LVESV (P<0.001). This reflects the fact that these two parameters (LV GLS and LVESV) represent different mechanisms, and supports the use of LV GLS as a meaningful parameter in defining CRT response, in addition to the more commonly used definition which is based on a reduction in LVESV.

Chapter 4 examines the role of LV mechanical dispersion (LVMD) in the long-term outcome of CRT recipients. LVMD is a novel, echocardiographic parameter which quantifies mechanical heterogeneity of the LV, and is defined as the standard deviation of the time from the onset of the QRS complex on the triggered ECG to the peak longitudinal myocardial strain (measured with speckle tracking echocardiography) in a 17-segment model of the LV. LVMD has been associated with ventricular arrhythmias in a number of cardiac diseases. Risk stratification of patients after CRT implantation remains a clinical challenge, and LVMD was calculated in a

cohort of heart failure CRT recipients post-implant. They were divided into groups according to the median LVMD at 6 months after CRT implantation. Those with less LVMD (≤84 ms) experienced fewer ventricular arrhythmias and lower all-cause mortality than those with LVMD >84 ms, and a greater LVMD was independently associated with a higher mortality risk (hazard ratio (HR) 1.002; confidence interval (CI) 1.000-1.005; P=0.037) and more frequent ventricular arrhythmias (HR 1.003; CI 1.000-1.005; P=0.026).

CRT restores mechanical efficiency to the failing LV by resynchronization of contraction. In **chapter 5**, global, LV myocardial work efficiency was measured with a recently introduced, non-invasive technique, synthesizing data from speckle tracking strain echocardiography and sphygmomanometric blood pressure recordings. Patients with class I indications for CRT were dichotomized according to the baseline, mean global LV myocardial work efficiency before CRT implantation. Those recipients with less efficient myocardial energetics at baseline (global, LV myocardial work efficiency <75%), experienced lower mortality rates than those with more efficient left ventricles (log-rank test, P=0.029). On multivariable analysis, global LV myocardial work efficiency <75% was associated with a decreased risk of all-cause mortality (HR 0.48; 95% CI 0.25-0.92; P=0.027). Global, LV myocardial work efficiency at baseline therefore holds promise to risk-stratify heart failure patients before CRT implantation, and may help to refine selection criteria in those who already have class I indications for CRT implantation.

Functional mitral regurgitation (FMR) is a common complication of heart failure, which worsens prognosis, but is also amenable to improvement with CRT. In **chapter 6**, the prognostic impact of FMR evolution in CRT patients was evaluated. Moderate or severe FMR at baseline, which remained unchanged at 6 months after the institution of CRT, was independently associated with long-term mortality (HR 1.77; 95% CI 1.41-2.22; P<0.001). The prognostic implication of moderate or severe FMR, which did not improve with CRT at 6 months, was independent of LV volumetric response to CRT, indicating that FMR evolution is not merely a reflection of the LV volumetric change, but contributes uniquely to long-term survival. **Chapter 7** focuses on the impact of atrial fibrillation (AF) on FMR improvement after CRT. FMR improved in 45.6% of CRT recipients with sinus rhythm (SR) before implantation, compared to 30.7% with AF (P=0.011). Despite a similar degree of LV reverse remodeling at 6 months post-CRT, patients with SR at baseline had smaller left atrial volumes (63.0±26.5 ml vs. 103.1±41.0 ml; P<0.001) and mitral annular diameters (42.3±5.6 mm vs. 46.1±5.8 mm; P<0.001) in comparison to those with AF. This suggests an inhibitory effect of AF on left atrial and mitral annular reverse remodeling, leading to less FMR improvement after CRT.

SUMMARY Part II: Imaging approaches to risk-stratification of cardiac disease

Chapter 8 provides a brief review of the role of multimodality imaging in the risk-stratification of sudden cardiac death (SCD). Since SCD is the cause of up to one-fifth of global deaths, and often occurs in individuals who have not previously been diagnosed with cardiac disease, primary prevention remains a challenge. The most effective strategy for primary and secondary

prevention of SCD is insertion of an implantable, cardioverter-defibrillator (ICD). Currently, the decision to implant an ICD is predicated mainly on an LVEF ≤35%; however, this approach is known to lack sensitivity and specificity. Multimodality imaging has shown incremental value over LVEF to identify patients who stand to benefit from ICD implantation, e.g. speckle tracking strain echocardiography, late gadolinium contrast enhanced (LGE) cardiac magnetic resonance (CMR) imaging and radionuclide imaging (e.g. iodine-123 metaiodobenzylguanidine uptake).

The role of cardiac imaging techniques in the risk-stratification of genetic, dilated cardiomyopathy (DCM) is extensively reviewed in **chapter 9**. Mutation carriers for genetic DCM are often asymptomatic until cardiac disease manifests with heart failure, arrhythmias or SCD. Risk-stratification of such individuals encompasses both early diagnosis and the phenotyping of established disease. Various imaging modalities are able to demonstrate early functional and structural abnormalities in genetic DCM mutation carriers, e.g. tissue Doppler imaging, speckle tracking strain echocardiography, integrated backscatter echocardiography, CMR LGE and phosphorous-31 magnetic resonance spectroscopy. Functional, cellular abnormalities can be probed with nuclear techniques, e.g. myocardial perfusion by means of single-photon emission computed tomography. In the case of established disease, echocardiography-based methods and CMR have demonstrated incremental benefit to LVEF for effective risk-stratification.

Chapter 10 investigates the use of GLS speckle tracking echocardiography in the early diagnosis of genetic DCM patients. Three groups were compared: i) genotype-positive, phenotype-positive (GPFP) patients, with a pathogenic mutation and an LVEF <55%, ii) genotype-positive, phenotype-negative (GPFN) individuals, with a pathogenic mutation and an LVEF ≥55% and iii) genotype-negative, phenotype-negative (GNFN) controls. Decreased LV GLS distinguished GPFN individuals from normal controls (P<0.001), in contradistinction to LVEF. Such early diagnosis of cardiac involvement in genetic DCM mutation carriers may permit the timely institution of therapy to delay or prevent disease progression.

CONCLUSIONS AND FUTURE PERSPECTIVES

Characterization and risk-stratification of CRT candidates remain a clinical challenge. Reducing the percentage of CRT non-responders, as well as optimizing management of recipients of CRT, continue to be priorities in cardiology practice. Novel cardiac imaging parameters are expected to play a pivotal role in refining the characterization of heart failure patients who are considered for CRT, as well as in the risk-stratification of those who have already received such therapy. The EuroCRT study will prospectively evaluate various cardiac imaging markers (including LVMD and global, LV myocardial work efficiency) for their prognostic value.[1]

The effect of FMR treatment on outcome, is currently under scrutiny. The recently published Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR)[2] and Cardiovascular Outcomes Assessment of the MitraClip Percuta-

neous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT)[3] studies investigated the impact of transcatheter mitral valve repair on outcome in heart failure patients with FMR. Both these trials, however, included patients with and without CRT. The COAPT trial demonstrated a lower rate of hospitalization for heart failure and lower all-cause mortality in the device treatment group (HR 0.53; 95% CI 0.40-0.70; P<0.001), while the MITRA-FR trial failed to show a decrease in the composite primary outcome of all-cause mortality and heart failure hospitalization (odds ratio 1.16; 95% CI 0.73-1.84; P=0.53). Clearly, more data are required to resolve the question of prognostic benefit in the treatment of FMR. AF rhythm control (especially by means of catheter ablation) is a potential therapeutic target to improve FMR in CRT recipients with AF at baseline, and warrants further study.

Although the diagnostic role of multimodality cardiac imaging is well defined for genetic DCM, further research will inform on its ability to predict long-term outcome (e.g. the development of symptoms, decrease in LVEF, ventricular arrhythmias and mortality) in asymptomatic mutation carriers. Additionally, the utility of imaging in effectively guiding the early institution of therapy (e.g. angiotensin converting enzyme (ACE)-inhibitors or ICDs) which may delay or prevent disease progression in genetic DCM mutation carriers, remains to be explored. Adequately defining the role of multimodality cardiac imaging in both the prediction of long-term outcome and the guidance of early therapy, will require prospective studies. Since long-term follow-up in uncommon cardiomyopathies in prospective, multicenter studies will no doubt be challenging, employing imaging biomarkers as therapeutic targets in themselves, may prove especially useful.

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