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Multimodality imaging for myocardial injury in acute myocardial infarction and the assessment of valvular heart disease

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10

Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven

SUMMARY

SUMMARY Part I: Cardiovascular magnetic resonance-derived left ventricular strain after acute myocardial infarction

In **Part I** the role of left ventricular (LV) strain with feature-tracking cardiovascular magnetic resonance (CMR) to evaluate myocardial injury and cardioprotective effects of early intravenous metoprolol were explored in the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) clinical trial. In **Chapter 2** an overall improvement of global circumferential (GCS) and longitudinal (GLS) strain between 1-week and 6-month follow-up after the acute anterior ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) was demonstrated (change in GCS and GLS 3.2%, P<0.001 for both). This was paralleled by an increase in left ventricular ejection fraction (LVEF) and a reduction in late gadolinium enhancement (LGE)-assessed infarct size over 6 months after STEMI, and is in line with previous findings from speckle-tracking echocardiography.[1] Moreover, early administration of intravenous metoprolol was associated with more preserved LV GCS and GLS at 1 week after myocardial infarction (GCS: -13.9±3.8% versus -12.6±3.9%, respectively; P=0.013; GLS: -11.9±2.8% versus -10.9±3.2%, respectively; P=0.032). On the other hand, the differences in global LV strain indices at 6 months after STEMI did not reach the level of statistical significance. However, when dividing the overall cohort of patients in quartiles of GCS and GLS, there were significantly lower number of patients receiving early intravenous metoprolol in the first GCS and GLS quartile (i.e., the worst LV systolic function), both at 1 week and at 6 months after STEMI. These results strengthen the evidence to support the use of early intravenous metoprolol in STEMI patients without contraindications to beta-blockers undergoing primary PCI.

In **Chapter 3** the evolution of the LV circumferential strain has been studied separately for the infarct and the remote zone myocardium. Since the METOCARD-CNIC trial included a homogeneous population of anterior STEMI patients with a culprit lesion in the left anterior descending coronary artery (LAD), the infarct zone was defined as the LAD perfusion territory while the rest of the LV myocardium was defined as the remote zone.[2-4] In the overall population the infarct zone strain significantly improved from 1 week to 6 months after STEMI (from -8.6% to -14.5%; P<0.001), while no significant changes in the remote zone strain were observed (from -19.5% to -19.2%; P=0.466). Similar results were observed among different subgroups of patients – the infarct zone strain improved in patients who did and did not receive

early intravenous metoprolol in addition to the standard STEMI therapy, in patients with and without microvascular obstruction (MVO), intramyocardial hemorrhage (IMH), and in patients who developed adverse LV remodeling at 6 months after STEMI (defined as ≥20% increase in LV end-diastolic volume). This demonstrates a preserved healing capacity of the infarcted myocardium even in the presence of adverse CMR findings (e.g., MVO or IMH). On the other hand, no significant dynamics in the remote zone circumferential strain were observed among the analyzed subgroups, apart from patients who developed adverse LV remodeling. Among them the remote zone strain worsened between 1 week and 6 months after STEMI (P=0.036), indicating that possible maladaptive processes like excessive inflammation/fibrosis of the remote myocardium[5] may become manifest as an impaired circumferential strain. Moreover, regional strain analysis demonstrated that patients receiving early intravenous metoprolol had more preserved infarct zone circumferential strain compared to the control group, both at 1 week and at 6 months after STEMI (P=0.038 and P=0.033; respectively). This is a very important finding, especially in the view that the differences in global strain between both treatment arms at 6 months were nonsignificant,[6] underscoring the long-lasting cardioprotective effects of early intravenous metoprolol. Interestingly, no significant differences in the remote zone circumferential strain were found between both groups of patients, implying that the beneficial cardioprotective effects were largely confined to the infarct zone myocardium.

Chapter 4 focuses on the long-term 5-year follow-up data of patients included in the METOCARD-CNIC trial. In contrast to the previously published results,[7] a significant reduction in major adverse cardiac events (MACE; a prespecified clinical endpoint, comprised of death, rehospitalization for heart failure, reinfarction and malignant ventricular arrhythmias) among patients receiving early intravenous metoprolol was demonstrated (HR: 0.500, 95% CI: 0.277-0.903; P=0.022). Impaired LV GCS and GLS strain were significantly associated with increased occurrence of MACE (GCS: HR:1.208, 95%CI:1.076-1.356, P=0.001; GLS: HR:1.362, 95%CI:1.180-1.573, P<0.001). On multivariable analysis, LV GLS provided incremental prognostic value over LGE and LVEF for the occurrence of MACE (LGE+LVEF chi-square=12.865, LGE+LVEF+GLS chi-square=18.459; P=0.012). Patients with more impaired GLS (above median value ≥-11.5%) who received early intravenous metoprolol were 64% less likely to experience MACE than their counterparts with same degree of GLS impairment (HR:0.356, 95%CI:0.129-0.979; P=0.045). These results show that early intravenous metoprolol had a long-term beneficial clinical effect, particularly in patients who were at a greater risk for the adverse events due to severely impaired LV systolic function.

SUMMARY Part II: Multimodality cardiac imaging in valvular heart disease

Multimodality cardiac imaging plays a central role in the management of patients with valvular heart disease (VHD). In **Chapter 5** the role of imaging to assess patients with VHD and coexisting heart failure was explored. Two common scenarios were discussed, i.e. secondary mitral regurgitation (MR) and low-flow low-gradient severe aortic stenosis (AS) with reduced LVEF. The challenges to determine the severity of secondary MR and to decide upon the optimal treatment option (medical therapy versus surgical or percutaneous intervention) with standard transthoracic echocardiography derive from the fact that the evaluation of MR severity is heavily influenced by the LV loading conditions, systemic blood pressure, the non-circular shape of regurgitant jet orifice and by temporal variation of MR during cardiac cycle. 3-dimensional (3D) echocardiography with direct planimetric measurement of vena contracta and regurgitant volume estimation with phase-contrast CMR may overcome some of these difficulties. Among patients with AS, reduced LVEF and contractile reserve, dobutamine stress echocardiography is the primary diagnostic method to differentiate between true severe and pseudo-severe AS. On the other hand, among patients with discrepant measures of AS severity and no contractile reserve, the assessment of aortic valve calcification burden with cardiac computed tomography (CT) may help to estimate the severity of AS. Furthermore, the role of multimodality imaging to select the optimal intervention in patients with secondary MR (surgical repair, replacement or percutaneous edge-to-edge repair) and AS (surgical versus transcatheter aortic valve replacement) were discussed.

In **Chapter 6** the advantages and limitations of different cardiac imaging techniques for patient selection, procedural planning and follow-up after transcatheter aortic valve replacement (TAVR) were explored. Compared to 2-dimensional methods 3D techniques like 3D transesophageal echocardiography (TEE), multidetector row computed tomography (MDCT) and CMR have proven to more accurately determine the aortic annulus size, the most important parameter for the choice of TAVR prosthesis size. The use of 3D methods has translated into lower incidence of significant paravalvular regurgitation after TAVR. The detailed vascular anatomy assessment (vessel size, tortuosity, degree of calcification and plaque burden) of the thoracoabdominal aorta and iliofemoral arteries using MDCT allows planning of the optimal TAVR access route (transfemoral, transaortic or transapical). While most of the centers currently perform TAVR under fluoroscopic guidance, periprocedural TEE as well as transthoracic echocardiography can be of an added value for early assessment of procedural complications (e.g., paravalvular and valvular regurgitation, aortic an-

nulus rupture, coronary ostium occlusion, prosthesis malpositioning or dislodgement), reduced radiation exposure and lower use of nephrotoxic contrast. After TAVR, transthoracic echocardiography remains the first-choice imaging technique to evaluate the procedural results, the durability of the prosthesis, and the changes in LV dimensions and function. However, recent studies using MDCT, which showed an increased incidence of hypo-attenuated leaflet thickening with reduced leaflet motion of TAVR prostheses (an early marker of prosthetic valve thrombosis), raised a question whether MDCT should be systematically included in the surveillance of TAVR patients.[8-10]

In **Chapter 7** novel automated 3D TEE imaging software was shown to allow reliable assessment of the aortic annulus dimensions in patients with severe AS undergoing TAVR. Compared to MDCT, 3D TEE measurements slightly underestimated the aortic annulus dimensions, which is in line with previously published literature.[11-13] The agreement between 3D TEE and MDCT for the measurement of the aortic annulus dimensions was superior among patients with low aortic valve calcification burden compared to the patients with high calcification burden. Importantly, 3D TEE measurements based on automatic software analysis and MDCT led to the same prosthesis size selection in the majority (88%) of the patients. However, the agreement between 3D TEE and MDCT on the prosthesis size selection was better among patients with low versus high aortic valve calcification burden (agreement in 95% versus 81% of patients; respectively) and in the majority of patients the 3D TEE measurements suggested smaller prosthesis size compared to MDCT. 3D TEE thus represents a valuable alternative to MDCT in patients with AS undergoing TAVR when the latter is contraindicated (impaired renal function) and might be particularly attractive in patients with less calcified aortic valves.

Chapter 8 focuses on the role of CMR to assess myocardial fibrosis in severe VHD. In patients with AS the presence of LGE, a marker of focal replacement fibrosis, and increased values of native T1 or extracellular volume (ECV), markers of diffuse interstitial myocardial fibrosis, have been associated with worse symptoms, worse LV systolic and diastolic function and higher levels of serum cardiac biomarkers. The presence of LGE was associated with an increase in all-cause mortality among patients with high grade AS, which has been recently confirmed in a large multi-center observational study.[14] Furthermore, all-cause mortality rates rose progressively across patients with normal indexed ECV without LGE (no myocardial fibrosis), patients with increased indexed ECV without LGE (diffuse interstitial myocardial fibrosis) and patients with LGE (focal replacement myocardial fibrosis), implying adverse

outcome with more advanced stages of myocardial fibrosis assessed with CMR. Similarly, LV circumferential strain with CMR tagging was significantly associated with all-cause mortality in severe AS patients undergoing surgical and transcatheter aortic valve replacement. The data on myocardial fibrosis in aortic regurgitation and MR is less extensive, however studies have shown an inverse correlation between the amount of myocardial fibrosis and measures of systolic and diastolic function, functional capacity and long-term survival after valve surgery.

In **Chapter 9** the role of myocardial fibrosis was further discussed with the emerging data on patients with mitral valve prolapse (MVP). Focal replacement fibrosis of the papillary muscles and of the inferolateral LV wall, detected with LGE, has been characterized as a unique feature of MVP, that has neither been observed in primary MR of other etiologies nor has been associated with the severity of MR. On the other hand, the diffuse interstitial fibrosis detected with ECV was shown to be a marker of the severity of MR unrelated to the mechanism. Focal replacement fibrosis has been proposed as a substrate for the electrical instability of the adjacent myocardium and represents a hallmark of the so-called arrhythmogenic MVP, which describes patients with MVP who have an increased risk for malignant ventricular arrythmias and sudden cardiac death.[15]

CONCLUSIONS AND FUTURE PERSPECTIVES

The assessment of LV strain as a functional surrogate of myocardial injury in acute myocardial infarction with feature-tracking CMR is feasible, both as a global and regional functional parameter. LV strain can provide important insights into the healing processes in the myocardium. In particular, LV GLS assessed early after PCI can provide important prognostic information above conventional CMR parameters like LVEF and LGE in the risk stratification of STEMI patients. Paralleled with the advances of the primary PCI and long-term medical therapy after STEMI, novel therapies aiming at reducing the acute ischemia-reperfusion injury are pursued. Early intravenous beta blockade was the first cardioprotective medical therapy that showed prognostic benefit in a randomized clinical trial and was adopted by the current European Society of Cardiology guidelines as a class IIa recommendation for hemodynamically stable STEMI patients undergoing primary PCI.[16] However, large-number data from observational studies and patient registries are required to confirm the same findings in the real-life situation. Importantly, LV strain

assessment with feature-tracking CMR can serve as a powerful complementary tool to evaluate the benefits of novel cardioprotective therapies.

Multimodality cardiac imaging plays a central role in the management of patients with VHD (Figure 1). Transthoracic echocardiography, TEE, cardiac CT and CMR help in the assessment of the etiology of VHD, valve anatomy, mechanism and severity of dysfunction and co-existing VHD. 3D techniques provide important advantages over standard 2-dimensional imaging. Furthermore, imaging provides crucial insights into ventricular remodeling and dysfunction, the most important adverse consequences of VHD. Parameters like chamber volumes and ejection fraction are the key to decide the eligibility and optimal timing for valve intervention, as recommended by the current guidelines.[17,18] However, novel risk markers, such as myocardial fibrosis with CMR and strain imaging with echocardiography and CMR may redefine our future treatment strategies. Clinical trials comparing early valve intervention versus standard care in patients with asymptomatic severe AS and primary MR, who do not meet current guidelines criteria for surgery but present with LV myocardial fibrosis, are recruiting patients.[19,20] Advanced imaging helps in discovering high-risk features of adverse outcome, e.g. increased risk of life-threatening ventricular arrhythmias in MVP patients with papillary muscles or lateral LV wall fibrosis, detected with LGE-CMR. Future clinical trials need to investigate whether implantable cardioverter defibrillator in these patients would lead to favorable outcomes. Wide implementation of TAVR established multimodality imaging, in particular cardiac CT, a key for procedural planning. With emerging transcatheter mitral and tricuspid valve therapies, CT and other 3D imaging techniques will have even greater impact on procedural planning. 3D TEE is fundamental to guide percutaneous edge-to-edge mitral valve repair and novel transcatheter therapies. Fusion imaging, i.e., side-by-side registration of data rendered by more than 1 non-invasive imaging modality (CT or CMR with real-time fluoroscopy and TEE) may increase the smoothness of structural interventions by combining anatomic, morphological, and functional information. Finally, cardiac imaging is essential to evaluate the long-term results of valve interventions to detect possible complications and to compare the efficacy of novel therapies with the gold standards in order to improve patients outcome.

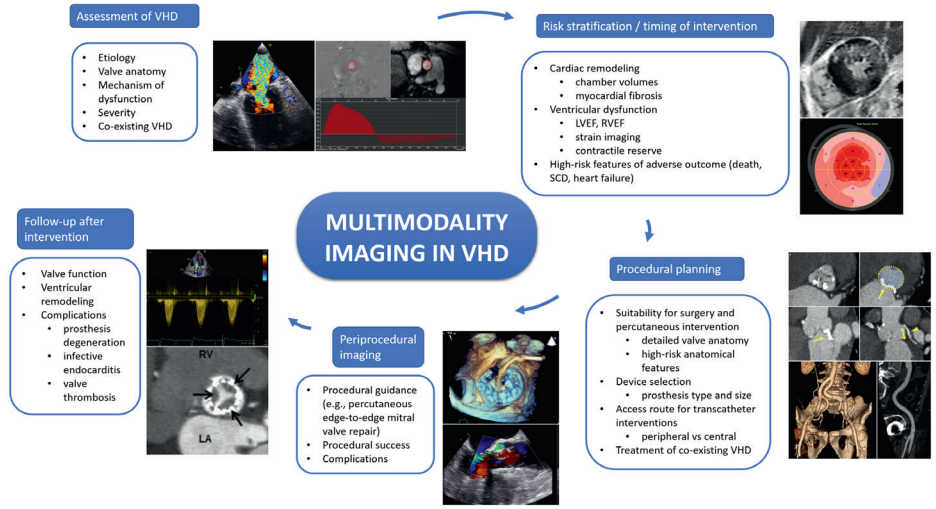

Figure 1: Multimodality cardiac imaging in valvular heart disease. LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; VHD = valvular heart disease.

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