Introduction

The incidence of heart failure is increasing (1). Some of these patients present with acute heart failure syndrome (AHFS) and an unclear underlying etiology (2). About 60% of these patients do have coronary artery disease (CAD) (3), so coronary angiography and potentially revascularization are indicated in most cases. However, in about 40% of cases, the etiology of heart failure remains unclear even after coronary angiography, as coronary artery disease was ruled out or its extent could not explain the obvious myocardial dysfunction. Appropriate treatment decisions require clarification of the underlying disease. For the clinical work-up of these patients cardiovascular magnetic resonance (CMR) imaging has shown to be of particular benefit (4). CMR not only depicts cardiac size and function but also tissue composition and can thereby reveal the underlying cause of heart failure in a considerable number of patients.

Suggested CMR protocol

In clinical routine echocardiography is and will remain the basic tool for cardiac imaging in the acute setting. Many of the patients discussed here have already undergone echocardiography. Some information about cardiac size, global and regional myocardial function usually is available given a sufficient acoustic window was present. Still, more information is necessary to clarify the etiology of heart failure. The referral for CMR is therefore warranted. Based on the long-term experience in our center the following protocol is suggested. The society of cardiovascular magnetic resonance has published similar suggestions in 2008 (5).

(I) Scout/localizer images
(II) Steady state free precession cine imaging in 3 long axes
(III) Steady state free precession cine imaging in short axes
(IV) T2-weighted imaging in 3 long axes and as many short axes as possible
(V) First pass rest perfusion in 3 long axes
(VI) Late gadolinium enhancement in 3 long axes and multiple short axes

This scan will take, depending on the numbers of repetitions necessary and the amount of contrast given, between 20 and 40 minutes.

Abstract: In a subgroup of patients with acute heart failure coronary artery disease can be excluded. To explain symptoms and optimize therapy cardiac magnetic resonance (CMR) imaging can contribute to elucidate the underlying pathology in non-ischemic heart disease. A diagnostic algorithm for the work-up of these patients using CMR is suggested. The review discusses various modules of a dedicated CMR protocol. It explains diagnostic markers and challenges of CMR imaging in non-ischemic heart disease. Based on these suggestions the literature in the field is reviewed.

Key Words: Coronary artery disease (CAD); cardiovascular magnetic resonance (CMR); imaging; diagnostic algorithm
Cine imaging

Cine imaging basically reproduces echo information regarding cardiac cavity size and wall motion. Steady state free precession cine loops acquired during breath hold represent the current state of the art. There are options available to shorten acquisition time or increase coverage with a certain trade-off in image quality or resolution. In general temporal resolution is poorer than in echocardiography, but image contrast, endocardial contour detection and reproducibility is much better. CMR is the gold standard for left ventricular mass. So far routine CMR approaches to assess diastolic function are limited to time-consuming volume over time curves.

T2-weighted edema imaging

Acute ischemic or inflammatory myocardial injury results in transient myocardial edema. There is an ongoing debate about the pathophysiological details behind edema evolvement and the best CMR sequence to detect it (6). Nevertheless most CMR users agree that edema is an early phenomenon in acute myocardial injury (7). CMR detects edema in acute infarction, acute myocarditis and Takotsubo cardiomyopathy as well as those sarcoidosis patients that are admitted with an acute event like ventricular arrhythmias. In acute infarction the edema is typically larger than the scar and most often transmural. Inflammatory edema can be patchy and smaller and can located in epicardial locations corresponding to late gadolinium enhancement lesions. If black blood fast spin echo images are acquired it can sometimes be difficult to differentiate edema (bright signal within the myocardial wall) from slow flow (bright signal within the ventricular lumen). Cine loops in the same location should be inspected for comparison. In uncertain cases an additional orthogonal slice should be acquired to confirm an area of questionable increased signal intensity as true edema.

Perfusion imaging

Perfusion imaging is not essential in this setting. As contrast agent has to be administered anyway this can be used for early imaging after contrast. Resting perfusion is clinically useful, if embolic infarction is the suspected underlying mechanism for heart failure. This might be the case even if coronary angiography was considered normal, as small, occluded peripheral branches may have been overlooked. For this reason perfusion images should be acquired in long axis orientation to cover the LV apex. Resting perfusion detects acute infarction as a perfusion defect even after successful revascularization if CMR is done within a few days after the event. If there is no clinical rationale for perfusion imaging in this scenario angiography may be an alternative to be done at this point.

Late gadolinium enhancement imaging

LGE imaging is the key to reveal a certain myocardial disease beyond mere wall motion abnormalities. It reveals the amount of viable myocardium with potential for functional improvement (8). From our experience it is essential to invest great effort for optimal choice and adjustment of the inversion time to suppress normal myocardium (9). Additional orthogonal slices should be acquired to confirm or rule out any questionable lesions. Comparison with cine images in the same position and slice thickness may help to confirm whether a questionable lesion actually has an intramyocardial position or is extramyocardial (e.g., lumen, pericardial fat or fluid). Fat also appears hyperintense on LGE images and can be identified by dedicated fat suppression methods (10) and its hyperintense signal on corresponding cine and pre-contrast T1-weighted spin echo images. Basically the position within the wall differentiates the etiology of LGE lesions: While the classical myocardial infarction of coronary etiology is subendocardial or transmural within a single coronary territory, non-ischemic lesions cover the intramural or epicardial portion of the myocardial wall and may be scattered across various coronary territories (11). Meawton et al. reviewed CMR assessment of diffuse myocardial fibrosis (12). However, not all patients with acute heart failure but normal coronaries do have late gadolinium enhancement lesions.

Diagnostic algorithm

Certain phenotypic patterns suggest various underlying pathologies. In Figure 1 we suggest an algorithm for a systematic work-up of patients with heart failure despite normal coronaries.

Normal LV size and regional wall motion abnormality

Regional wall motion abnormality in a patient with acute heart disease points to coronary heart disease. Even if coronary angiography was normal, embolic infarction can explain regional hypokinesia, focal edema and scar. Either a
A small distal coronary side branch had been thrombotically occluded without leaving a stump as an angiographic hint, or the occluded vessel was spontaneously recanalized before angiography was done. Paradoxical thromboembolism across a patent foramen ovale can result in myocardial infarction (Figure 2) (4,13). A acute small non-revascularized infarction will be visible as perfusion defect on resting perfusion images (Figure 2A). If CMR suggests embolic infarction a transesophageal echocardiography is indicated to search for the source of embolism.

Takotsubo cardiomyopathy presents as apical ballooning typically in postmenopausal women after a stressful event including cerebral injury (14). Apical edema may be present. The key element for diagnosis is the exclusion of apical infarction scar despite the prominent wall motion abnormality. It is important to confirm normalized wall motion within weeks during follow-up.

Normal LV size and no or mild wall motion abnormality

In patients with normal-sized left ventricle and no or subtle wall motion abnormalities myocarditis or sarcoidosis is a potential diagnosis. In young male patients with viral myocarditis CMR often detects focal myocardial edema either regional similar to a posterolateral infarction or in multifocal spotty pattern in the epicardial portion of the lateral wall (15). It is important to scan these patients early as edema disappears 2-3 weeks after the initial presentation. Typically these patchy spots of edema correspond to focal myocardial fibrosis on late gadolinium enhancement images. The LGE lesions typically persist but tend to slowly shrink over time.

In sarcoidosis some of the patients feature LGE lesions. Patel et al. reported five different patterns of LGE in sarcoidosis (16). In our experience we typically see pattern

Figure 1 Diagnostic algorithm for patients with acute heart failure but normal coronaries using CMR
Figure 2 A 42-year-old female was admitted with chest pain. Troponin was positive, ECG indicated inferolateral ST-elevation. Instant coronary angiography was normal, but an apical wall motion abnormality was noted. CMR was done the next day. A: Resting perfusion in 4-chamber-view shows an apical area of hypointense signal indicating a perfusion defect. B: Late gadolinium enhancement in the same orientation reveals a bright transmural apical area indicating scar with a large hypointense core. This dark core does not represent viable myocardium but microvascular obstruction in the case of non-revascularized infarction of embolic origin. A patent foramen ovale was found as the most likely route of embolism

D according to Patel et al., i.e. bright epicardial rims with certain focal transmural spots (Figure 3). Occasionally a patchy myocarditis-like-pattern E (according to Patel et al.) might occur. Pathology reports indicate fibrotic lesions in epicardial and intramural locations (17,18). In patients presenting with an acute event (e.g., ventricular tachycardia, acute chest pain) focal edema may be detectable in areas corresponding to LGE lesions (Figure 3) (19,20). This pattern remains typical even if sarcoidosis presents with a dilated left ventricle (21).

LV hypertrophy

All forms of heart failure with left ventricular hypertrophy (LVH) tend to feature preserved systolic LV function and impaired diastolic function. Left atrial size is a long-term marker of diastolic dysfunction and can easily be quantified by CMR (22,23). There is no easy way to measure diastolic function by CMR beyond that due its limited temporal resolution. Some groups have calculated diastolic peak filling rates based on time-volume-curves across the cardiac cycle (24,25). Others have added septal tissue velocity measurements to characterize diastolic dysfunction (26).

Hypertrophic cardiomyopathy

The phenotype of hypertrophic cardiomyopathy (HCM) comprises several subtypes (27). In most cases the hypertrophy is most obvious in the septum and rather asymmetric than symmetric. Obstruction of the left ventricular outflow tract may or may not be part of the disease. Late gadolinium enhancement is present in roughly 60% of cases based on the 3 largest observational trials to date (28-30).

Hypertension

The most frequent reason for LV hypertrophy is long-lasting arterial hypertension. Typically it results in symmetric hypertrophy both in the septal and the lateral wall. Intramural LGE has been found in 13 out of 26 (50%) hypertensive patients with marked myocardial hypertrophy on CMR (31).
Amyloidosis

In some patients with unclear LVH (Figure 4A) it appears impossible to suppress the myocardium in LGE images despite various attempts with different inversion times (Figure 4B) (32,33). Cardiac amyloidosis with extensive rapid myocardial uptake of the myocardium might explain this phenomenon. A preserved systolic LV function, dilated atria, pericardial and pleural effusions support the diagnosis, even if unspecific on their own. If amyloidosis is suspected before CMR, LGE imaging should be started earlier than usual (i.e. within minutes after contrast administration) (34). Hypointense myocardium on T2-weighted STIR images and increased early contrast uptake might further support the diagnosis of cardiac amyloidosis (35).

Aortic stenosis

Cine imaging in the 3-chamber-view easily reveals aortic valve thickening and high-velocity transvalvular flow as a bright jet. A set of orthogonal cine images across the valve reliably allows the planimetry of the aortic valve orifice area (36). In patients with aortic stenosis focal lesions of late gadolinium enhancement have been found that are associated with a worse prognosis (37,38). Whether this phenomenon is really independent from LV hypertrophy, is not yet totally resolved.

Fabry disease

X-chromosomal Anderson-Fabry disease features reduced galactosidase-activity resulting in glycogen storage in various tissues including the myocardium. Of note, even female patients can be affected (39). Interestingly the posterolateral wall appears to be a preferred location for tissue changes detected by LGE images (40). Once LGE lesions are present they seem to not to be influenced by enzyme replacement therapy (41).

Dilated left ventricle

Dilated cardiomyopathy

The left ventricle and most often even the left atrium are dilated. The walls are thin. If the right ventricle is also dilated, this is a marker for an adverse prognosis (42). About a third of dilated cardiomyopathy (DCM) patients feature a midwall late gadolinium enhancement, associated with a worse outcome (43,44). It is unclear why some of the
patients do show LGE and some do not or whether those with LGE have a post-inflammatory origin.

If a transmural or other LGE pattern occurs, consider sarcoidosis (21) or embolic infarction. Myocardial biopsy is recommended in cases of new-onset heart failure with normal-sized or dilated left ventricle and hemodynamic compromise or in those with new-onset heart failure and ventricular arrhythmias or heart block and failure to improve within one to two weeks (45).

Non-compaction cardiomyopathy
Some heart failure patients with dilated ventricles feature prominent apical and lateral trabeculations with a thin compact myocardial layer. Arrest of intrauterine myocardial development is one explanation for non-compaction cardiomyopathy. There is a wide morphologic spectrum with overlap into apparently normal hearts, DCM and HCM (46). Petersen et al. suggested diagnostic criteria for CMR in long axis images (47). Dawson et al. published reference values for wall thickness of compact and non-compact myocardium across all segments in short axis (48), while Jacquier et al. quantified the extent of trabeculations in short axis images (49). LGE might be present in a minority of patients (50,51).

Dilated and dysfunctional right ventricle
Arrhythmogenic right ventricular cardiomyopathy
A dilated RV with reduced RVEF and regional akinesia or dyskinesia are indicative for arrhythmogenic right ventricular cardiomyopathy (ARVC). A diagnosis is not based on CMR alone, but on a combination of imaging, history, ECG etc. (52). The left ventricle can be involved. Typically the patients do not present with heart failure but with ventricular arrhythmias. A severe tricuspid regurgitation is not a typical feature of ARVC.

Other reasons for right heart failure
A dilated pulmonary artery, tricuspid regurgitation, enlarged right atrium and focal late gadolinium enhancement in the right ventricular insertion points are markers for pulmonary arterial hypertension. In case of unclear enlargement of the right cardiac cavities an intracardiac shunt should be excluded via flow measurements across the aortic and pulmonary valve to verify a normal Qp/Qs ratio. If pulmonary arterial hypertension can be ruled out, a primary tricuspid valve problem can occasionally explain enlarged right cardiac cavities. In patients with congenital heart disease a history of previous surgery is most often known.
Discussion

Once coronary artery disease had been ruled out in a patient with heart failure modern cardiologic reasoning does not come to an end but excitement begins.

CMR can contribute to elucidate the underlying mechanism for patients with acute heart failure but normal coronaries. The manuscript explains how this might work in daily routine. Assomull et al. described a series of 60 consecutive patients that presented with chest pain, positive troponin but normal coronaries. CMR including cine, T2-weighted and late gadolinium enhancement imaging could clarify the underlying disease in 65% of the patients (4). Late gadolinium enhancement is the key tool of the CMR armory in this setting but not the only one (53). Mather et al. published a very instructive case collection to illustrate the diagnostic potential of CMR in the patient population discussed here (54). It is important to investigate patients as soon as they are clinically stable, as temporary markers like myocardial edema or perfusion defects might no longer be detectable during later follow-up (4,55,56). To underscore the potential of CMR White et al. investigated the findings in 82 patients after resuscitation due to sudden cardiac death or sustained ventricular tachycardia (57). CMR found myocardial disease in 74% and thereby more than one in a control group without CMR (51%). In general it is considered pivotal in acute heart failure patients to elucidate how much myocardium is still viable and therefore has potential for improvement (8). CMR is ready for this task.

Of course a patient with enlarged ventricle, reduced systolic function and heart failure will most likely have CAD. Within the context of this discussion we assume that CAD has already been ruled out. Several authors have suggested to differentiate ischemic and non-ischemic heart failure simply by LGE CMR (11,58-60). If typical subendocardial infarction scars are present, the patient presumably has CAD, if no scars or intramural fibrosis is present, non-ischemic heart disease might be the reason for heart failure. It should be very clear to the reader that the exclusion of myocardial scar does not rule out coronary artery disease (61). Even severe three-vessel-disease can be present without any scar due to collateral blood supply. Assomull et al. conceded this option as a mere theoretical but unlikely scenario (62). The clinician should also evaluate whether a certain LGE lesion really explains the extent of functional impairment or whether it may represent “bystander disease” if the remodeling is out of proportion (62).

Conclusions

In patients acutely admitted with heart failure and normal coronaries CMR can contribute to elucidate the underlying mechanism. A diagnostic algorithm is suggested to differentiate various pathologic conditions. CMR should therefore considered to be part of the regular work-up for these patients (1).

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