Myocardial injury in patients with acute ischemic stroke detected by cardiovascular magnetic resonance imaging

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A B S T R A C T

Background: Patients with acute ischemic stroke (AIS) are at high risk of adverse cardiovascular events. Until now, the burden of myocardial injury derived from cardiovascular magnetic resonance imaging (CMR) has not been established in this population.
Methods: Patients with AIS underwent CMR at 3 Tesla within 120 h after the index stroke as part of a prospective, single-center study. Patients with persistent atrial fibrillation were excluded. Morphology and function of both cardiac chambers and atria were assessed applying SSFP cine. Myocardial tissue differentiation was based on native and contrast-enhanced imaging including late gadolinium enhancement (LGE) after 0.15 mmol/kg gadobutrol for focal fibrosis and parametric T2- and T1-mapping for diffuse findings. To detect myocardial deformation global longitudinal (GLS), circumferential (GCS) and radial (GRS) strain was measured applying feature tracking. Cardiac troponin was measured using a high-sensitivity assay (99th percentile upper reference limit 14 ng/L). T2 mapping values were compared with 20 healthy volunteers.
Results: CMR with contrast media was successfully performed in 92 of 115 patients (mean age 74 years, 40% female, known myocardial infarction 6%). Focal myocardial fibrosis (LGE) was detected in 31 of 92 patients (34%) of whom 23/31 (74%) showed an ischemic pattern. Patients with LGE were more likely to have diabetes, prior myocardial infarction, prior ischemic stroke, and to have elevated troponin levels compared to those without. Presence of LGE was accompanied by diffuse fibrosis (increased T1 native values) even in remote cardiac areas as well as reduced global radial, circumferential and longitudinal strain values. In 14/31 (45%) of all patients with LGE increased T2-mapping values were detectable.
Conclusions: More than one-third of patients with AIS have evidence of focal myocardial fibrosis on CMR. Nearly half of these changes may have acute or subacute onset. These findings are accompanied by diffuse myocardial changes and reduced myocardial deformation. Further studies, ideally with serial CMR measurements during follow-up, are required to establish the impact of these findings on long-term prognosis after AIS.

1. Introduction

Both ischemic stroke and heart failure are known to be major causes of morbidity and mortality. Patients with ischemic stroke are at an approximately 3-fold increased risk for incident heart failure at one year after the event compared with matched individuals from the general population [1]. Vice versa, individuals with heart failure have a high risk of incident ischemic stroke even without atrial fibrillation and with a preserved ejection fraction [2].

A severe cardiac adverse event including myocardial infarction, heart failure or arrhythmia occurs in 10–25% of patients with acute ischemic stroke (AIS) during the early post-stroke phase [3]. The term "stroke-heart syndrome" has been recently proposed to summarize this spectrum of post-stroke cardiac dysfunction and injury [3]. The

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presumed pathophysiology of stroke-heart syndrome is diverse. It has been discussed that neurohumoral factors and inflammatory cytokines may lead to demand ischemia or inflammatory-mediated damages [1]. Recognizing the etiology of stroke-related cardiac dysfunction is important as cardiac involvement is associated with poor functional prognosis, and increased mortality and major adverse cardiovascular events [1,4]. However, early cardiac involvement after stroke is potentially overlooked and underdiagnosed, e.g. due to stroke-related symptoms. Usually, laboratory values, ECG and transthoracic or transesophageal echocardiography are used to identify an involvement of the heart [5,6]. Echocardiography helps to define probable stroke causes such as thrombi or persistent foramen ovale as well as the quantification of the left ventricular function including wall motion abnormalities. Beyond the precise assessment of volume and function, Cardiovascular Magnetic Resonance (CMR) has the unique ability to differentiate myocardial tissue injury including the detection and localization of edema, as well as focal scars and diffuse fibrosis. Previous studies applying CMR after AIS have focused mainly on the detection of cardiac sources of embolism or cardiomyopathies [7,8,9]. Currently, prospective studies applying quantitative myocardial tissue differentiation using CMR in patients early after AIS are missing.

In this study, we aimed to prospectively evaluate the burden of clinical and subclinical myocardial fibrosis and associated CMR findings in patients with AIS by applying multiparametric CMR.

2. Methods

2.1. Study population

Participants were prospective enrolled in the CORONA-IS (CardiOmyocyte injuRy follOwing Acute Ischemic Stroke) study. The primary aim of CORONA-IS is to identify pathomechanisms of stroke-associated myocardial injury (NCT03892226) [10]. In brief, patients with AIS confirmed by cerebral MRI underwent CMR during acute in-hospital stay. Per protocol, we aimed at scheduling CMR between 72 and 120 h after stroke onset because this time-window was shown to provide the best yield of edema detection in patients with MI [11]. Stroke imaging pattern was classified as lacunar or non-lacunar. All patients underwent cerebral MRI to confirm diagnosis of ischemic stroke. Patients with impaired kidney function (eGFR < 30 ml/min/ 1,73 m^2), recent cardiac intervention, persistent atrial fibrillation with tachycardia, with contraindications for CMR or patients unable to undergo CMR examination were excluded. All patients that gave informed consent and finally underwent CMR from January 2019 until September 2020 were analyzed. This included a pilot phase between January and April 2019. Twenty healthy volunteers underwent CMR without contrast media application on the same scanner.

All patients underwent routine clinical procedures, including demographics and medical history, medication, and information about the current stroke (time of symptom onset, time of hospital admission and AIS treatment) as recently published [10]. Stroke severity was measured according to the National Institutes of Health Stroke Scale (NIHSS, ranging from 0 to 42 with higher numbers indicating higher stroke severity). Modified Rankin Scale (mRS, ranging from 0 to 6 with 0 indicating no disability and 6 indicating death) was used to determine the functional status. Mortality at 1 year was recorded. Routine diagnostic procedures such as blood pressure measurements and 12-lead ECG were performed during the stay at the Stroke Unit. Cardiac troponin was measured upon hospital admission (assay: hs troponin T, Roche Elecsys, Gen 5; 99th percentile upper reference limit = 14 ng/l; 10% coefficients of variation precision = 13 ng/l; limit of detection = 5 ng/l).

The study design was approved by the local ethics committee (EA4/ 123/18) and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all study participants.

2.2. CMR protocol

According to a predefined CMR protocol, we applied CMR on a 3 T Scanner, Magnetom Prisma^{fit} (Siemens Healthineers, Erlangen, Germany) [10]. Cine imaging was performed applying a steady-state free precession (SSFP) sequence to determine the global cardiac performance. We acquired the following long axis (LAX) views covering the left ventricle (LV): four (4ch), three (3ch) and two (2ch) chamber views (ch) and one for the right ventricle (RV); imaging parameters: TR 45.78 ms, TE 1.43 ms, Flip angle (FA) 80°, Slice thickness 6.0 mm) as well as a short axes stack (SAX), after contrast media application, to cover the left and right ventricle (imaging parameters: TR 44.80 ms, TE 1.4 ms, Flip angle (FA) 58°, Slice thickness 7.0 mm, no gap). For myocardial tissue differentiation, parametric T1- and T2-mapping and focal fibrosis imaging (Late Gadolinium Enhancement, LGE) were applied.

Focal fibrosis imaging by LGE was performed in the same slice position as the cine imaging in 4ch, 3ch, 2ch and SAX using a phase sensitive inversion recovery sequence (PSIR). Imaging parameters: (TR 750.0 ms, TE 1.55 ms, FA 20°, Slice thickness 7.0 mm) as well as full coverage of the LV in a short axis package (imaging parameters: TR 1002.4 ms, TE 1.24 ms, FA 55°, slice thickness 8.0 mm). TI was adapted to suppress the myocardium.

T2- and T1-mapping was performed in basal, medial and apical slices as described recently [12,13]. Calculations were carried out for each segment and for each slice. Motion-corrected T2 mapping was based on a fast low angle shot (FLASH) gradient echo sequence in 4ch and three SAX views at the basal, medial and apical levels. T2 maps were based on images with T2 preparation times of 0/30/55 ms, and slice thickness of 6.0 mm, TR 251.49 ms and TE 1.32 ms.

Motion-corrected T1 mapping based on the Modified Look-Locker Inversion Recovery (MOLLI) technique using a 3–3-5 pattern was performed before and 15 min after contrast media (0.15 mmol/kg body weight Gadobutrol, Gadovist®, Bayer Healthcare, Berlin, Germany) application in 4ch and three SAX views for basal, medial and apical slices (imaging parameters: TR = 281.64 ms (4ch) and 332.67 ms (SAX), TE = 1.12 ms, slice thickness 6.0 mm, GRAPPA acceleration factor 2).

2.3. Findings of interest and data analysis

Image analysis was performed using cvi42 version 5.11.4 (Circle Cardiovascular Imaging cvi Inc., Calgary, Canada). The reader was blinded to clinical details.

The primary finding of interest was the presence of focal myocardial fibrosis on LGE. LGE pattern was considered ischemic if focal fibrosis was located subendocardially or transmurally matching a coronary distribution and as non-ischemic if located midmyocardial or sub-epicardial. We defined an embolic pattern as narrow, transmural often wedge-shaped LGE lesions [14]. Moreover, we performed a subgroup analysis excluding patients with known MI. The visual evaluation of the LGE images was performed by two independent, experienced readers (SCMR Level III), the presence, number and location of focal scars was analyzed.

SAX cine images were used to determine left ventricular (LV) volumes, mass and function by drawing endo- and epicardial contours (papillary muscles as part of the mass) at the end of the systolic and diastolic phases [15]. 4ch and 2ch cine images were used to determine atrial area, volumes and function [16]. Wall motion abnormalities (WMA) were described as regional hypokinesia, akinesia or dyskinesia.

Both the values of T2 and T1 maps were quantified as previously reported. The qualitative survey implied the exclusion of segments in case of artifacts (e.g., caused by susceptibility effects or unintended thoracic motion) or wrong motion correction as described recently [12,13]. To avoid the influence of focal myocardial tissue injury (LGE), segments with focal fibrosis were excluded from the mapping analyses.

Global longitudinal strain (GLS) was assessed in three LAX views: 4ch, 3ch, and 2ch. Global radial and circumferential strain was assessed

in short axis stack (LV full coverage). Endo- and epicardial contours were manually drawn in the end-diastolic phase, defined as the phase with the largest LV volume. Trabeculae, papillary muscles, pericardium, and epicardial fat were consequently excluded from contouring [17]. Quantitative mapping analysis was done following the American Heart Association (AHA) segment model [18].

2.4. Statistical analysis

To compare patients with and without focal myocardial fibrosis and other groups we used a Mann–Whitney *U* test, *T*-test or Student's *t*-test where appropriate. Normal distribution was analyzed graphically and with the Kolmogorov-Smirnov test. All results are shown as mean ± standard deviation and/or median with interquartile range (IQR). The statistical analysis was performed using IBM® SPSS® Statistics 25 (IBM Corp., USA). A p value < 0.05 was considered to indicate a statistically significant difference. Correlation analyses were performed using the Spearman rank correlation coefficients. For intra- and interobserver reproducibility, images were analyzed twice by blinded readers.

3. Results

A total of 115 patients with AIS gave informed consent, 98 (85%) patients underwent CMR, and contrast media was applied in 92/98 (94%) patients. Seventeen patients had to be excluded due to arrhythmias and poor clinical condition. Six patients did not receive contrast media due to severely reduced kidney function (eGFR < 30 ml/min/1,73 m^2) or refusal of contrast media application. Median time from first symptoms of AIS to CMR was 81 h (IQR 71 h-97 h). Overall stroke severity was mild-to-moderate (range 0–25, IQR 1–5, 16.5% with NIHSS > 5 and 4.4% with NIHSS > 10) and the majority of patients had non-lacunar stroke. Baseline characteristics and main findings of patients who underwent contrast-enhanced CMR are given in Table 1 and Fig. 1.

3.1. Focal myocardial changes

In patients who received contrast media, there was focal fibrosis in 31/92 (34%) of whom 23/31 (74%) had an ischemic LGE pattern (Figs. 1A, 2A and 2B). After exclusion of patients with known MI (n = 6), there was evidence of ischemic type of LGE pattern in 18/86 (21%) of all patients and in 18/27 (67%) patients with focal changes. Non/ischemic type of fibrosis was present in 10/86 (12%) of the whole cohort and in 10/27 (37%) patients with focal changes. As shown in Table 1, patients with focal fibrosis were more likely to have a history of diabetes, prior ischemic stroke, prior MI, and higher baseline hs-cTnT levels compared to those without. Other baseline characteristics did not differ significantly.

Mortality at 1 year (3.3 % versus 16.1%) was higher in patients with focal fibrosis than in those without. This remained not statistically significant after adjusting for age, sex, troponin levels, diabetes, history of stroke and history of myocardial infarction (adjusted OR 3.7, 95% CI 0.56–25.4).

3.2. Quantification of ventricular volumes and function including myocardial deformation

Patients with focal fibrosis were more likely to have WMA than those without. Of 31 patients with LGE, 17 patients (55%) had focal fibrosis and 14 patients did not (45%). In one patient, WMA were suggestive for Takotsubo cardiomyopathy without focal fibrosis (Fig. 3). No significant differences were found between patients with and without focal fibrosis in LV and RV volume. LV function as well as GLS, GRS and GCS were significantly lower in patients with focal myocardial injury. For details see Table 2.

Table 1

Baseline characteristics of patients who underwent contrast-enhanced CMR.

Baseline characteristics	All patients (n = 92)	LGE neg. (n = 61)	LGE pos. (n = 31)	P value
Age (years), mean ± SD	74 ± 11	74 ± 11	74 ± 10	0.719
Sex (male), n (%)	55 (59.8)	34 (55.7)	21 (67.7)	0.276
Heart rate (beats per minute), mean ± SD	77 ± 15	76 ± 13	79 ± 18	0.333
Systolic blood pressure (mmHg), mean ± SD	143 ± 23	143 ± 22	143 ± 25	0.932
Systolic blood pressure (mmHg), mean ± SD	77 ± 14	76 ± 14	79 ± 15	0.260
Prior myocardial infarction, n (%)	6 (6.5)	1 (1.6)	5 (16.1)	**0.008**
Hypertension, n (%)	69 (75.0)	44 (72.1)	25 (80.6)	0.373
Diabetes mellitus, n (%)	14 (15.2)	4 (6.6)	10 (32.3)	**0.001**
Prior ischemic stroke, n (%)	19 (20.7)	9 (14.8)	10 (32.3)	**0.050**
Known malignancy, n (%)	15 (16.3)	9 (14.8)	6 (19.4)	0.572
Hs-cTnT upon admission (ng/l), median (IQR)	13 (7–21)	11 (7–18)	18 (12–28)	**0.003**
Hs-cTnT above upper reference limit (>14 ng/l), n (%)	41 (44.6)	23 (37.7)	18 (58.1)	0.063
Time from stroke onset to admission (hours), median (IQR)	4 (2–16)	4 (2–14)	5 (1–22)	0.490
Time from stroke onset to CMR (hours), median (IQR)	81 (71–97)	81 (71–96)	86 (70–98)	0.880
NIHSS on admission, median (IQR)	2 (1–5)	3 (1–5)	2 (1–4)	0.443
Acute lacunar infarction on cerebral MRI, n (%)	25 (27.2)	19 (31.1)	6 (19.4)	0.229
Wahlund score on cerebral MRI, median (IQR)	7 (3–12)	7 (3–13)	8 (5–12)	0.562
Thrombolytic treatment, n (%)	32 (34.8)	21 (34.4)	11 (35.5)	0.920
mRS on admission, median (IQR)	2 (2–3)	3 (2–3)	2 (1–3)	0.100
mRS on admission > 1, n (%)	72 (78.3)	50 (82.0)	22 (71.0)	0.227

Data are shown as mean values ± standard deviation (SD) according to the AHA-segment model. Significant differences (p < 0.05) are highlighted in bold. LGE = late gadolinium enhancement. HR = heart rate, BP = blood pressure, IHD = ischemic heart disease, MI = myocardial infarct, NIHSS = National Institute of Health Stroke Scale. Hs-cTnT – high-sensitivity cardiac troponin T, WMA = wall motion abnormalities, IQR interquartile range, OR odds ratio, mRS = Modified Rankin Scale.

3.3. Atrial volume and function

The size of the left and right atrium size and left atrium function did not differ within the comparative groups with and without focal fibrosis, however left atrial function was often reduced below normal values in the whole cohort, although there was no difference according to LGE status [16]. For details see Table 2.

3.4. Diffuse myocardial changes – Parametric mapping

The basal, medial and apical slices were analyzed. To avoid an influence of focal fibrosis LGE positive segments were excluded. Reliability was high for both inter- and intra-observer evaluations (r = 0.93 and 0.94, ICC = 0.82 and 0.92).

3.5. T1 Native mapping

Basal, medial and apical T1 maps were evaluated. Due to artifacts 188/1472 (13%) segments had to be excluded. We found significant differences in T1 native times between LGE-positive and LGE-negative patients. Patients with focal fibrosis had higher T1 mapping values also in regions without focal findings (basal: p = 0.020; medial: p < 0.001, apical: p = 0.028). For details see supplementary file 1.
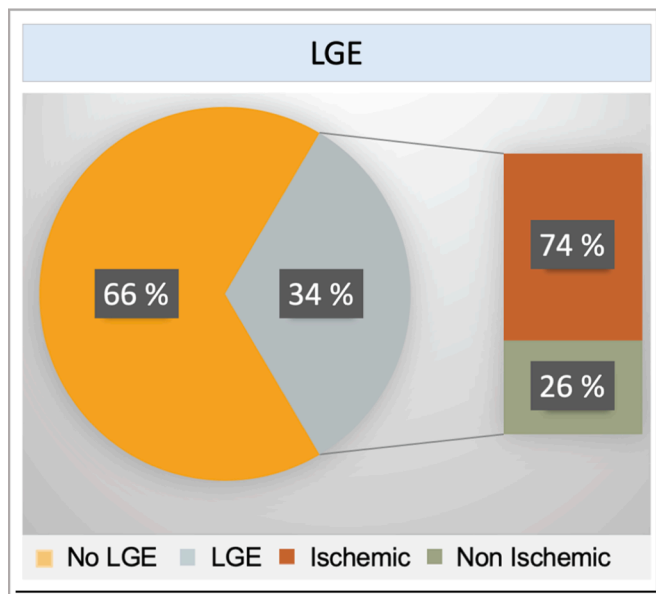
Fig. 1. Frequency of late gadolinium enhancement and ischemic vs non-ischemic pattern in patients with acute ischemic stroke.

3.6. T2-Mapping

Basal, medial and apical T2 maps were evaluated. Due to artifacts, 92/1456 (6%) segments had to be excluded. Increased T2-mapping values were detectable in 14/31 (45%) of all patients with LGE. There were 2 patients with embolic LGE pattern, 3 patients with non-ischemic LGE pattern and 9 patients with ischemic pattern without known history of MI. The whole group of LGE positive patients showed significantly higher T2 times compared with the healthy volunteers. (LGE + vs healthy T2 mapping: basal 40 ± 3 ms vs 37 ± 1 ms, $p = 0.002$, medial 40 ± 3 vs 38 ± 1 ms; $p < 0.001$, apical 42 ± 4 ms vs 40 ± 1 ms $p = 0.024$). The highest T2 values (62 ms) were detectable in a patient with takotsubo pattern without presence of LGE. (Fig. 3).

Neither T1 nor T2 mapping revealed differences within ischemic- and non-ischemic LGE pattern (supplementary file 1).

4. Discussion

In our study, we were able to show that it is possible to perform CMR scans in the early phase after an acute stroke with mild-to moderate stroke severity. Our main findings were: First, more than one-third of AIS patients had focal myocardial fibrosis. Two-thirds of focal fibroses had an ischemic pattern, mostly without any previous history of myocardial infarction. Second, patients with focal fibrosis had a high burden of concomitant myocardial injury such as diffuse myocardial processes. Reduced myocardial deformation capability was often detectable in the entire cohort, and significantly more often in patients with focal fibrosis. Third, focal changes were accompanied by increased T2 values as evidence of an acute or subacute onset in nearly half of cases and even in remote areas. Left atrial function was often impaired in both groups compared to normal values. To the best of our knowledge, this is the first prospective study providing detailed myocardial tissue-characterization using multiparametric CMR in patients with AIS.

4.1. Focal and diffuse myocardial findings

In our study we could demonstrate that in patients with AIS, focal
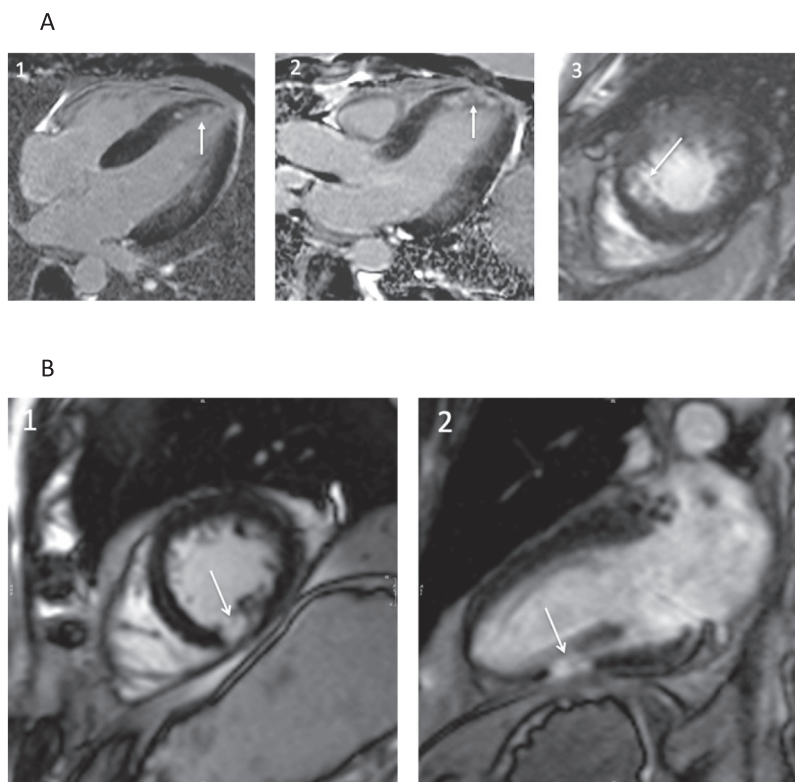
IHD = ischemic heart disease, LGE = late gadolinium enhancement, ch = chamber

Fig. 2. 2A. 82-year-old patient with unknown IHD and ischemic LGE pattern – septal infarct (*arrows*). Late gadolinium enhancement in long axis 4ch view (1), long axis 3ch view (2) and short axis (3). 2B. 70-year-old patient without known heart disease and ischemic LGE-pattern suspected of an embolic cause within the inferior wall (arrows). LGE in short axis (1) and two chamber view (2).
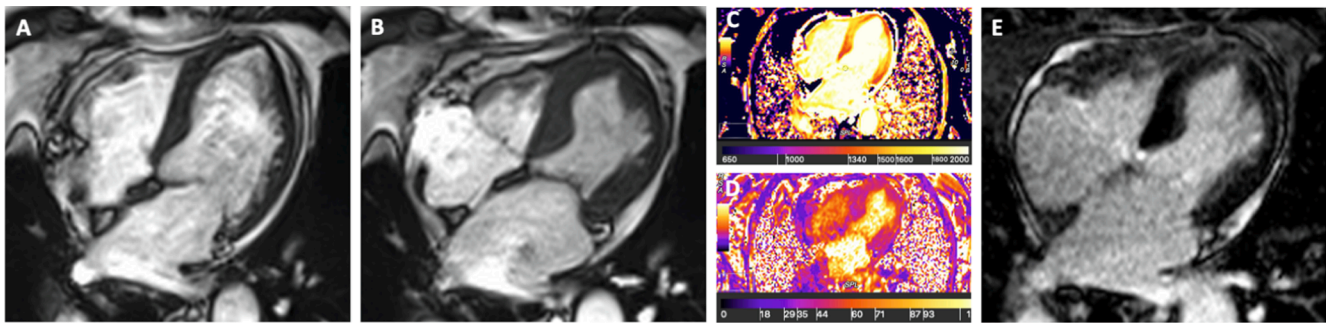
Fig. 3. 85-year-old patient with a takotsubo cardiomyopathy phenotype and strongly elevated troponin values. No history of cardiac diseases. A large wall-motion abnormality within medial and apical segments could be visualized in the cine images. LGE was without any focal fibrosis. A. 4ch view cine diastole, B. 4ch view cine systole, C. corresponding T1 native map, D. corresponding T2 map, E. 4ch view LGE.

Table 2
Basic CMR parameters and diffuse myocardial changes in patients with and without presence of LGE.

	Entire population	Presence	of LGE	*P* value
	(n = 92)	No (n = 61)	Yes (n = 31)	
CMR parameter				
LVEF *(% ± SD)*	62 ± 11	65 ± 8	57 ± 13	**0.021**
LVEDV-I *(ml/m ± SD)*	72 ± 22	70 ± 18	76 ± 27	0.342
LVSV-I *(ml/m² ± SD)*	40 ± 8	41 ± 8	39 ± 6	0.185
RV EF *(% ± SD)*	51 ± 5	51 ± 5	51 ± 5	0.580
RVEDV-I *(ml/m² ± SD)*	75 ± 15	75 ± 14	75 ± 17	0.776
RVSV-I *(ml/m² ± SD)*	38 ± 8	38 ± 8	36 ± 6	0.232
Left atrium *(cm² ± SD)*	22 ± 5	21 ± 4	23 ± 5	0.081
Left atrium *(ml/m² ± SD)*	42 ± 20	40 ± 20	46 ± 21	0.305
Left atrium EF *(%± SD)*	47 ± 16	49 ± 15	43 ± 19	0.423
Reduced LA EF n (%)	48 (52)	30 (49)	17 (55)	0.402
Right atrium *(cm² ± SD)*	22 ± 5	22 ± 5	23 ± 5	0.157
GLS *(% ± SD)*	−15.8 ± 6	−16.9 ± 6	−13.4 ± 5	**<0.001**
GRS *(% ± SD)*	29.1 ± 9	31.9 ± 9	22.6 ± 9	**<0.001**
GCS *(% ± SD)*	−17.3 ± 1	−18.4 ± 3	−14.4 ± 4	**<0.001**
WMA, n (%)	20 (22)	3 (5)	17 (55)	**<0.001**

Data are shown as mean values ± standard deviation (SD) according to the AHA-segment model. Significant differences (p < 0.05) are highlighted in bold. LVEF = left ventricular ejection fraction, LVEDV-I = left ventricular enddiastolic volume index, LVSV-I = left ventricular stroke volume index, RVEF = right ventricular ejection fraction, RVEDV-I = right ventricular enddiastolic volume index, RVSV-I = right ventricular stroke volume index, WMA = wall motion abnormalities, GLS = global longitudinal strain, GRS = global radial strain, GCS = global circumferential strain.

myocardial injury with ischemic LGE pattern is common, even in patients without documented prior IHD.

That might be interpreted as subclinical myocardial injury and remodeling in patients with AIS as most of the patients had not history of cardiac events. In our study, focal fibrosis was more often detectable in patients with history of diabetes, prior stroke, and prior MI. Diabetes is a known risk factor for silent MI and the history of stroke could be considered as a marker of more advanced (cerebro)vascular disease but may also lead to premorbid changes in physiological heart and brain axis [19,20]. As expected patients with known MI were more likely to have focal fibrosis. However, in a subgroup analysis excluding patients with known MI, we observed similar proportion of patients with focal changes as well as ischemic and non-ischemic fibrotic changes.

Until now, the role of CMR in the evaluation of acute IHD after AIS is yet to be established. A previous study reported an ischemic pattern of fibrosis in approximately 15% of AIS patients [8]. Presence of an

ischemic LGE pattern in AIS was linked to presence of a coronary culprit lesion on coronary angiography in a small case series [21]. In our cohort, even 22% of patients without previous MI known showed an ischemic pattern of LGE. Since AIS patients are often elderly, it is possible that they have concomitant, but asymptomatic cardiac disease and AIS can be the first manifestation of IHD. On the other hand, it was shown that coronary culprit lesions are significantly less frequent in AIS patients compared to patients with NSTE-ACS despite similar baseline troponin levels. Moreover, about 50% of AIS patients with troponin elevation show no angiographic evidence of IHD [22,23]. Therefore, non-ischemic causes of post-stroke myocardial injury have been discussed [1,20,24]. In our study, one third of patients with focal fibrosis had a non-ischemic pattern.

It is known, that the usage of CMR techniques like T1, T2 mapping and T2 weighted sequences enables the differentiation between acute and chronic myocardial infarction. In our study, patients with focal fibrosis had evidence of an altered myocardial structure in regions without focal fibrosis as shown by increased native T1 and T2 mapping values. In our cohort, focal changes were accompanied by increased T2 mapping values even in remote areas, and nearly half of patients with focal fibrosis had evidence of an acute or subacute onset. This suggests that there may be a certain percentage of unrecognized myocardial infarction (UMI) prior to AIS. Since patients had no CMR before AIS, it is difficult to distinguish stroke-related changes from premorbid UMI. It is known, that UMI have similar prognostic implication than classical myocardial infarction [21]. Since UMI is prognostic relevant, it may have an additional prognostic impact in AIS to detect UMI [25]. The high proportion of diffuse myocardial changes like diffuse fibrosis, inflammation and impaired myocardial deformation suggests that part of the alterations are stroke-related. It has been discussed that AIS but also subarachnoid hemorrhage may initiate a cascade of different types myocardial injury due to catecholamine surge and increased systemic inflammation [1,3,20].

4.2. Morphology and function - ventricles

Left ventricular dysfunction (LVD) is known to be an important cause of cardioembolic stroke [26]. LVD, even mild, is independently associated with an increased risk of ischemic stroke [27,28]. The mechanisms underlying the association between LVD and stroke, and vice versa, are not clear. In our cohort, the size of the ventricle was in the normal range, however the average LV EF was preserved also in patients with focal scar or fibrosis.

It is known that myocardial segments might show severe WMA even in the absence of focal scar. One example is the Takotsubo syndrome (TTS), which is a non-ischemic acute transient cardiomyopathy characterized by a typical pattern of reversible WMA and detection of myocardial edema and/or inflammation, mostly without a focal scar [29]. TTS has been described in approximately 0.5–1.2% of AIS patients,

and stroke is a common trigger for TTS [3,21,24]. Our population confirms the frequency of TTS secondary to AIS, although an interestingly high number displayed WMA without focal scar which may represent focal variants of TTS. Patients with TTS presented also the highest T2 values regarding both groups with and without LGE present.

4.3. Morphology and function - atria

Approximately 25–30% of ischemic strokes have an unknown cause [30]. Recent studies showed that not only atrial fibrillation but other supraventricular arrhythmias such as atrial ectopy, multiple atrial premature contractions or atrial tachycardias seem to be significantly correlated with an increased left atrial volume index and decrease of atrial function, which could predict future stroke events [31,32,33,34]. It was demonstrated, that the LA volume index and systolic function may be useful to identify AIS patients with high likelihood of AF detection [35,36,37,38,39,40]. In our study, persistent AF was an exclusion criterion, still in both groups LAEF was lower in comparison to normal values measured in healthy volunteers as published recently from our group [16]. Our results suggest that decrease of its systolic function per se tended to be associated with ischemic stroke independent from the predominant rhythm.

4.4. Myocardial deformation

Quantification of myocardial deformation applying myocardial strain is of growing interest in CMR. It allows quantitative measurement of myocardial deformations offering additional information beyond ejection fraction and enables early detection of subclinical myocardial dysfunction in patients with ischemic and non-ischemic heart disease even in the presence of a preserved ejection fraction and without wall motion abnormalities [41,42,43]. In our cohort, all three strain values (GLS, GRS and GCS) were significantly associated with the presence of focal fibrosis. The long-term consequences of impaired strain in patients with ischemic stroke have yet to be studied. Given the high incidence of heart failure after stroke [1,4,40] our findings underline the potential impact of an advanced cardiovascular assessment after AIS to detect subclinical myocardial injury and deformation. Furthermore, it is increasingly recognized that GLS, GRS and GCS offer the opportunity to detect cardiac dysfunction even in patients with normal EF. [37,38,39].

4.5. Clinical implications

Even if CMR is usually superior in comparison to echocardiography for detecting LV-thrombi, an individualized approach of selecting the appropriate imaging modality to search for cardiac sources of embolism is needed [44,45]. However, our study highlights the potential role of CMR to identify patients with UMI. In fact, the results of CMR may influence further diagnostics and treatment. In patients with ischemic pattern of LGE suspicious of acute event, invasive evaluation for possible coronary heart disease and more intense lipid-lowering therapy can be recommended. In patients with unknown primary or secondary cardiomyopathies further diagnostics, including family screening and appropriate medication is warranted.

While increasing healthcare costs have to be taken in account, one could expect that an early detection of MI may have a positive long-term impact. Interestingly, Ge et al could show the cost-effectiveness of CMR in patients obstructive coronary artery disease if used prior to invasive cardiac angiography [46]. Patients with a UMI in CMR have a similar risk for death compared to patients with recognized myocardial infarction (RMI) [21]. Compared with RMI patients, those with UMI are less likely to receive guideline-directed medical therapies [21], which highlights the need for timely detection of UMI in risk populations like patients with AIS.

5. Limitations

First, it was not possible to perform CMR with contrast media application in all patients. Second, patients with known ischemic heart disease were included in the study. When we designed the study, we decided not to exclude patients with known ischemic heart disease, because the prevalence of post-stroke cardiac changes is higher among patients with known heart disease [3,20]. Patients with known heart disease seem to be more vulnerable to stroke-related changes. This is in line with the 'stress test' hypothesis of stroke-related cardiac injury [3,20]. Either the severity of the stroke ('stress') or the vulnerability of the cardiac substrate influence the severity of cardiac injury ('stress response'). Therefore, we decided not to a priori exclude this population. Third, some patients were excluded due to arrhythmias or contraindications for CMR or due to severely impaired kidney function. In addition, there was no information regarding exsiccosis and acute infection which could have an influence on CMR findings. Moreover, patients had to provide informed consent which led to inclusion of patients with mild-to moderate stroke severity. This means that severely affected stroke patients with larger brain lesions were underrepresented in our cohort. Taking these limitations into account, the prevalence of focal fibrosis in AIS may be even higher than observed in our study. Finally, none of the included patients had a CMR before AIS. Therefore, it is difficult to distinguish whether the observations are stroke-related or represent unrecognized subclinical MI that occurred before the stroke. The patients did not receive CMR follow-up. Further studies are needed to prove if CMR is useful for further therapeutic decision making in AIS patients. Larger cohorts with longer follow-up periods are needed to determine the impact of CMR findings on cardiac outcomes after stroke.

6. Conclusions

In our study, we could demonstrate that it is possible to perform early CMR scans in AIS patients with mild- to moderate stroke severity and to identify cardiac involvement. A relevant proportion of patients without known prior myocardial infarction showed focal myocardial fibrosis, mainly with an ischemic pattern. Increased T2 mapping values may be evidence of an acute or subacute onset. Focal fibrosis was accompanied by concomitant diffuse myocardial tissue changes, and reduced myocardial deformation. Further follow-up studies, ideally with serial CMR measurements during follow-up, are required to establish the impact of these findings on long-term prognosis after AIS.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.

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