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CMR findings in patients referred for suspected myocarditis following mRNA-based COVID vaccination compared with pre-COVID myocarditis referrals: A single-centre observational study

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ABSTRACT

Background: Vaccination is considered the key to overcome the COVID pandemic. For the first time mRNA-based vaccinations are used in humans. Case series suggested an increased risk of myocarditis after vaccination. This study sought to describe CMR findings in patients with suspected mRNA-vaccine associated myocarditis.

Methods: A total of 33 consecutive patients referred for CMR work-up of suspected myocarditis associated with mRNA-based vaccination were included. A historical cohort of 135 consecutive patients referred for suspected myocarditis in the pre-COVID era served as control group. All patients underwent multi-parametric CMR including CINE and late gadolinium enhancement (LGE) imaging as well as parametric T1/T2 mapping of the left ventricular myocardium.

Results: Patients referred for suspected vaccination-related myocarditis were more often female (55 % vs 32 %, p = 0.015) and demonstrated smaller LV dimensions as well as a better LV function compared to patients of the control group. CMR revealed a lower prevalence of non-ischemic LGE in patients with suspected vaccination-myocarditis (6 % vs 22 %, p = 0.04). However, among patients without LGE we observed a higher prevalence of an abnormal T1/T2 mapping result in patients with suspected vaccination-myocarditis compared to the control group (45 % vs 18 %, p = 0.010).

Conclusion: In this small single-centre study, compared to myocarditis referrals in the pre-COVID era, patients currently referred for CMR work-up of suspected mRNA-vaccination-associated myocarditis demonstrated lower prevalence of LGE but higher prevalence of abnormal T1/T2 mapping. These hypothesis-generating observations may point towards a rather subtle myocardial damage and support the routine use of T1/T2 mapping in this indication.

1. Introduction

Vaccination is considered the key to overcome the COVID-19 pandemic, which has been impacting on the world for >2 years now. In these times, mRNA-based vaccines have been widely used in humans and have been proven highly effective [1]. However, recent reports suggested an increased risk of myocarditis after vaccination with mRNA-based vaccines potentially holding-off patients from (booster) vaccinations [2–4]. Since in the future mRNA-based therapies will most likely not be limited to vaccinations but may also become the basis for other therapies (e.g. cancer), the rare but potentially devastating side effect of myocarditis needs to be thoroughly investigated.

Based on increasing scientific evidence regarding cardiac magnetic resonance imaging (CMR) in the setting of inflammatory cardiomyopathies [5], CMR has emerged as the first-line diagnostic tool (ESC class I, level C recommendation) in the assessment of suspected myocarditis [6]. While its diagnostic and prognostic value in suspected viral myocarditis is well-established [7,8], the role of CMR in the work-up of patients with suspected mRNA-vaccine associated myocarditis ('vaccination-myocarditis') remains currently unknown. In the present study, we sought to evaluate clinical characteristics and CMR findings of patients with suspected vaccination-myocarditis and compared them to patients with suspected vaccination-unrelated myocarditis in the pre-COVID/vaccination era.

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Table 1
General characteristics and CMR results of the study population.

	Suspected COVID vaccination-myocarditis referrals (n = 33)	Suspected pre-COVID myocarditis referrals (n = 135)	P value
Demographics			
Age, Median (Q1-Q3)	34 (25–47)	36 (27–50)	0.81
Male, n (%)	15 (45 %)	92 (68 %)	**0.015**
LV morphology and function			
LVEF, %	66 ± 5	62 ± 10	**0.03**
Reduced LVEF (<50 %)	2 (6 %)	12 (9 %)	0.60
LVEDV, ml	127 ± 30	152 ± 45	**0.003**
LVEDD, mm	47 ± 5	50 ± 6	**0.003**
IVS, mm	8 ± 2	10 ± 2	**<0.001**
Myocardial tissue characterization			
Late gadolinium enhancement	2 (6 %)	30 (22 %)	**0.04**
LGE localisation, n (% of LGE+)			
- inferior/lateral	2 (100 %)	28 (93 %)	1.00
- anterior/septal	0	7 (23 %)	
- epicardial	1 (50 %)	9 (30 %)	0.53
- midwall	1 (50 %)	21 (70 %)	
Parametric mapping (global LV)			
T1 native, ms	991 ± 48	999 ± 49	0.41
- Pts with abnormal T1 (>1025 ms), n (%)	8 (24 %)	22 (16 %)	0.28
T1 post contrast, ms	495 ± 39	518 ± 63	0.05
- Pts with abnormal T2 (<455 ms), n (%)	6 (18 %)	12 (9 %)	0.12
ECV, %	27 ± 4	28 ± 6	0.28
- Pts with abnormal ECV (>33 %), n (%)	3 (9 %)	17 (13 %)	0.57
T2 native, ms	47 ± 2	49 ± 4	**0.034**
- Pts with abnormal T2 (>54 ms), n (%)	0	13 (10 %)	–
Abnormal mapping (T1, T2 or ECV)	15 (45 %)	36 (27 %)	**0.035**
Abnormal mapping without LGE	15 (45 %)	24 (18 %)	**0.010**

ECV, extracellular volume; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; IVS, interventricular septum; LGE, late gadolinium.
enhancement; LV, left ventricular.

2. Methods

2.1. Study population

All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments. The study protocol was approved by the local ethics committee. Between January 2021 and December 2021 consecutive all-comer patients referred for CMR work-up of suspected myocarditis following mRNA-vaccination against SARS-CoV2 were included. A historical cohort of consecutive all-comer patients who were referred for CMR work-up of suspected myocarditis in the pre-COVID era served as control group.

2.2. Cardiovascular MR imaging

All patients underwent standardized state-of-the-art multi-parametric CMR for work-up of myocarditis as previously described [9] and in line with current recommendations [10]. Briefly, CMR was performed ECG-gated in breath-hold using a 1.5-T MAGNETOM Aera (Siemens Healthcare, Erlangen, Germany). Cine-SSFPs and late gadolinium enhancement (LGE) short-axis images were prescribed every 10 mm (slice thickness 6 mm) from base to apex. LGE images were acquired on average 5–10 min after contrast administration using a segmented inversion recovery gradient echo sequence, constantly adjusting inversion time to null normal myocardium. The contrast dose (gadoteridol) was 0.15 mmol/kg. Short-axis T2 mapping was performed in three short-axis slices (basal, midventricular, apical) before the administration of contrast agent using an ECG-triggered T2-prepared single-shot balanced SSFP sequence with multiple T2 preparation times. A modified look-locker inversion recovery sequence (MOLLI) was used for T1 mapping, which was performed in three short-axis slices (basal, midventricular, apical) before and 20 min after administration of gadoteridol contrast. The myocardial extracellular volume (ECV) was calculated using the following formulas [11]:

$$\Delta R1_{myo} = 1/T1_{myo\text{-}post\text{-}contrast} - 1/T1_{myo\text{-}pre\text{-}contrast}$$

$$\Delta R1_{blood} = 1/T1_{blood\text{-}post\text{-}contrast} - 1/T1_{blood\text{-}pre\text{-}contrast}$$

$$ECV = (1 - \text{hematocrit}) \times (\Delta R1_{myo}/\ \Delta R1_{blood})$$

Table 2
Time interval from symptom onset to CMR exam in patients with suspected vaccination-myocarditis.

Time interval	# of patients
< 1 month	14 (42 %)
1 to 3 months	9 (27 %)
> 3 months	5 (15 %)
unknown	5 (15 %)

2.3. Statistical analysis

Variables are presented as mean ± standard deviation (SD), median (Q1-Q3) or absolute numbers (%). Data analysis was carried out using GraphPad Prism. Continuous variables were compared using student's *t*-test or Mann-Whitney-*U* test, as appropriate. The Fisher's exact test was used for categorical variables. A two-tailed p-value <0.05 was considered significant.

3. Results

In total, 33 patients undergoing CMR for suspected myocarditis following mRNA-based vaccination against SARS-CoV2, as well as 135 patients who underwent CMR for suspected myocarditis in the pre-COVID era (control group) were included. Patients in both groups were of similar age (34 [25–47] vs 36 [27–50], p = 0.81),. However, patients with suspected vaccination-myocarditis were more often female (55 %) whereas patients with suspected vaccination-unrelated myocarditis were more often male (68 %), Table 1. In most patients with suspected vaccination-myocarditis CMR was performed within 3 months after symptom onset (Table 2). CMR work-up of suspected myocarditis revealed significant differences between the two populations both with regard to left ventricular morphology and function, as well as with regard to multi-parametric myocardial tissue characterization:

Patients with suspected vaccination-myocarditis had better LV function, smaller LV size and thinner interventricular septal wall compared to the control group (Table 1). CMR tissue characterization using late gadolinium enhancement imaging revealed a significantly lower prevalence of non-ischemic LGE in patients with suspected vaccination-myocarditis compared to patients with suspected vaccination-unrelated myocarditis (6 % vs 22 %, p = 0.04). Advanced myocardial tissue characterization using parametric mapping techniques demonstrated no significant overall difference regarding surrogates of myocardial fibrosis, but slightly higher T2 values among the historical control group of patients with suspected myocarditis

Table 3
Detailed mapping results of LGE-negative patients with abnormal mapping.

	Suspected COVID vaccination-myocarditis referrals (n = 15)	Suspected pre-COVID myocarditis referrals (n = 24)	P value
T1 native, ms	1010 ± 56	1047 ± 60	0.11
T1 post contrast, ms	486 ± 50	514 ± 118	0.12
ECV, %	28 ± 5	35 ± 9	**0.020**
T2 native, ms	47 ± 3	52 ± 7	0.36

ECV, extracellular volume; LGE, late gadolinium enhancement.

(Table 1). Notably, the prevalence of a pathological CMR mapping result (either T1, T2 or ECV abnormal) was higher in patients with suspected vaccination-myocarditis compared to the control group, particularly in the subgroup of patients without LGE (45 % vs 18 %, p = 0.010). In this subgroup of LGE-/Mapping+ patients, those with suspected vaccination-myocarditis demonstrated rather milder mapping abnormalities compared to LGE-/Mapping+ myocarditis referrals in the pre-COVID era, although this was only statistically significant for ECV (Table 3).

4. Discussion

The main finding of this study is that compared to patients with suspected myocarditis in the pre-mRNA-vaccination era, patients currently referred for CMR work-up of suspected mRNA-vaccination-associated myocarditis demonstrated a lower prevalence of LGE, but had a higher prevalence of abnormal parametric T1/T2 mapping (see Fig. 1). This observation may suggest a rather subtle extent of mRNA-associated myocardial damage in vaccination-myocarditis and supports the routine use of parametric T1/T2 mapping in this indication.

Considering the high volume of current and future mRNA-based vaccinations and other mRNA-based therapies, as well as the rare but well-known risk of myocarditis as a potential side effect, it is of utmost importance to establish efficient diagnostic work-up strategies in this clinical setting. During the last two decades, CMR has mainly taken over from endomyocardial biopsy as the first-line modality for the diagnostic and prognostic stratification of patients with suspected myocarditis [7,8,12]. Particularly with regard to its non-invasiveness it seems obvious that CMR may become the diagnostic tool of choice also in patients with suspected mRNA-therapy-associated myocarditis. However, there is currently insufficient data regarding the diagnostic and prognostic role of CMR in this indication. Comparing patients currently referred for work-up of suspected vaccination-myocarditis with a historical cohort referred for suspected myocarditis before the COVID/mRNA-vaccination era, we observed that patients with suspected vaccination-myocarditis had a lower prevalence of focal myocardial fibrosis/LGE. However, we found a higher prevalence of abnormal parametric mapping (T1, T2, and ECV) in the absence of LGE among patients with suspected mRNA-vaccination-associated myocarditis. In the absence of LGE, we observed a trend towards milder mapping abnormalities in patients with suspected vaccination-myocarditis compared to pre-COVID myocarditis referrals. Taken together, these observations may provide a first hint that myocardial damage following mRNA-therapy-induced myocarditis is more diffuse and subtle compared to other forms of myocarditis such as viral myocarditis. Notably, in our study, we did not observe any severe case of mRNA-vaccination-associated myocardial damage (e.g. a patient with extensive LGE or at least moderately impaired LV function). While there is by now a large body of evidence for the excellent prognostic value of CMR in patients with suspected myocarditis in general [7,13,14], more data is currently needed to investigate whether this also holds true in the setting of suspected mRNA-vaccination-associated myocarditis.

4.1. Limitations

There are some limitations of the present study: First, this was a small single-centre study, thus, our observations should be interpreted as hypothesis-generating and are sought to stimulate further research in this field. Due to the current awareness for vaccination-associated myocarditis on both the patients' and physicians' side, referral bias is likely in this study. Nevertheless, the high rate of pathological CMR results in patients referred for suspected vaccination-myocarditis indicates appropriate pre-selection despite potential influences of referral bias. Second, CMR was considered the non-invasive reference standard to assess myocardial damage and no routine endomyocardial biopsy was

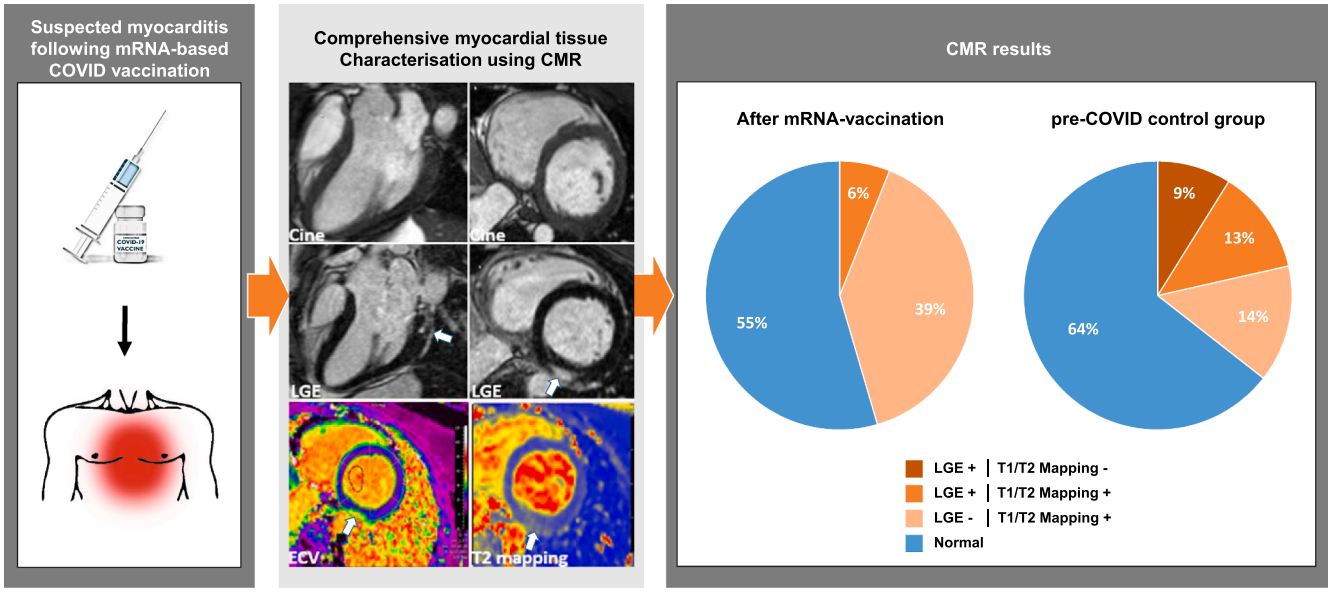

Fig. 1. CMR findings in patients referred for suspected myocarditis following mRNA-based COVID vaccination compared with pre-COVID myocarditis referrals. Comprehensive CMR work-up of consecutive patients with suspected myocarditis including late gadolinium enhancement (LGE) and parametric T1/T2 mapping techniques revealed a lower prevalence of LGE in patients with suspected vaccination-associated myocarditis. However, we observed a higher prevalence of pathological mapping in these patients. The middle panel demonstrates an exemplary patient with posterolateral LGE as well as pathological mapping results.

performed, which would have been inappropriate in most of the included patients considering the benign clinical course. Finally, there was no clinical follow-up data available yet to assess the prognostic value of CMR, which however, will be subject of future studies.

5. Conclusions

In this small single-centre study, patients currently referred for CMR work-up of suspected mRNA-vaccination-associated myocarditis demonstrated a lower prevalence of LGE compared to patients with pre-COVID myocarditis referrals. However, we observed a higher prevalence of pathological parametric T1/T2 mapping in patients with suspected mRNA-vaccination-associated myocarditis. These observations may provide a first hint for a rather subtle myocardial damage in mRNA-vaccination-induced myocarditis that can be identified by comprehensive CMR including T1/T2 mapping. More studies in larger, matched cohorts are needed to further investigate the hypothesis-generating observations from the present study.

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.

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References

[1] S.J. Thomas, E.D. Moreira Jr., N. Kitchin, et al., Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months, N. Engl. J. Med. 385 (19) (2021) 1761–1773.
[2] B. Bozkurt, I. Kamat, P.J. Hotez, Myocarditis With COVID-19 mRNA Vaccines, Circulation 144 (6) (2021) 471–484.
[3] M.E. Oster, D.K. Shay, J.R. Su, et al., Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021, JAMA 327 (4) (2022) 331–340.
[4] G. Witberg, N. Barda, S. Hoss, et al., Myocarditis after Covid-19 Vaccination in a Large Health Care Organization, N. Engl. J. Med. 385 (23) (2021) 2132–2139.
[5] C. Tschope, E. Ammirati, B. Bozkurt, et al., Myocarditis and inflammatory cardiomyopathy: current evidence and future directions, Nat. Rev. Cardiol. 18 (3) (2021) 169–193.
[6] T.A. McDonagh, M. Metra, M. Adamo, et al., 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur. Heart J. 42 (36) (2021) 3599–3726.
[7] S. Greulich, A. Seitz, K.A.L. Muller, et al., Predictors of Mortality in Patients With Biopsy-Proven Viral Myocarditis: 10-Year Outcome Data, J Am Heart Assoc. 9 (16) (2020) e015351.
[8] H. Mahrholdt, C. Goedecke, A. Wagner, et al., Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology, Circulation 109 (10) (2004) 1250–1258.
[9] S. Greulich, V.M. Ferreira, E. Dall'Armellina, et al., Myocardial Inflammation-Are We There Yet? Curr Cardiovasc Imaging Rep. 8 (3) (2015) 6.
[10] C.M. Kramer, J. Barkhausen, C. Bucciarelli-Ducci, et al., Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update, J. Cardiovasc. Magn. Reson. 22 (1) (2020) 17.
[11] M. Ugander, A.J. Oki, L.Y. Hsu, et al., Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology, Eur. Heart J. 33 (10) (2012) 1268–1278.
[12] C. Grani, C. Eichhorn, L. Biere, et al., Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis, J. Am. Coll. Cardiol. 70 (16) (2017) 1964–1976.
[13] P. Thavendiranathan, L. Zhang, A. Zafar, et al., Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor-Associated Myocarditis, J. Am. Coll. Cardiol. 77 (12) (2021) 1503–1516.
[14] C. Eichhorn, S. Greulich, C. Bucciarelli-Ducci, et al., Multiparametric Cardiovascular Magnetic Resonance Approach in Diagnosing, Monitoring, and Prognostication of Myocarditis, JACC Cardiovasc Imaging (2021).