Original Article

The Midterm Effects of COVID-19 on the Heart of a Healthy Population: A Cardiac MRI Study

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ABSTRACT

Background: Multiple investigations have reported cardiac involvement in the early and late phases of COVID-19 infection. It is associated with notable morbidity and mortality. Early detection of cardiac involvement may render timely intervention, reducing residual myocardial injuries. We evaluated cardiac magnetic resonance imaging (MRI)-derived functional and inflammatory findings 3 to 6 months after acute COVID-19 infection in a healthy population recovered from the disease and compared them with normal controls.

Methods: Twenty cases with a definite history of respiratory COVID-19 infection, in the preceding 3 to 6 months and 28 age- and sex-matched healthy subjects were assessed. The non-contrast cardiac MRI findings of the 2 groups were compared. Moreover, pulmonary parenchymal involvement in the acute phase and its correlation with cardiac MRI findings were evaluated. Data analysis was performed with SPSS, version 22, and a *P* value of less than 0.05 was considered significant.

Results: Twenty subjects (mean ± SD of age = 35.30 ± 5.27 y; 55% female) with a definite history of COVID-19 infection and 28 healthy controls (mean ± SD of age = 31.07 ± 4.35 y; 50% female) were included. Biventricular ejection fraction, biventricular global longitudinal strain, right ventricular global circumferential strain, and right ventricular global radial strain were significantly different between the 2 groups. Six patients (30%) in the COVID-19 group exhibited regional myocardial edema. No significant linear correlations existed between the severity of pulmonary involvement and cardiac MRI parameters.

Conclusions: In the midterm follow-up of healthy patients after COVID-19 infection, a significant reduction was observed in myocardial strain and function, independent of the severity of lung disease. ***(Iranian Heart Journal 2024; 25(1): 19-26)***

KEYWORDS: COVID-19, Cardiac function, Cardiac MRI

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After the grueling COVID-19 pandemic and the introduction of treatment and prevention protocols against the disease, there is still debate concerning complications, especially long-term after recovery. [1, 2] One of the potential complications that have been emphasized both acutely and chronically following COVID-19 is cardiovascular disorders and primarily myocardial dysfunction. [3-7] Due to the high concentration of the specific receptor of the COVID-19 virus in myocardial tissue, the likelihood of myocardial damage and progressive cardiovascular disorders, such as heart failure, is suggested. [8, 9] Cardiac defects caused by COVID-19 may be due to the direct invasion of the virus through the pointed receptors or indirectly because of the activation of inflammatory cascades and induced hypoxia. [10, 11] Regardless of the cause of such events, COVID-19 is associated with significant morbidity and mortality in patients without a history of cardiovascular disease or potential risk factors. [12]

The resultant cardiac damage can be efficiently tracked using conventional cardiac assessment methods, including 2D speckle-tracking echocardiography and cardiac magnetic resonance imaging (CMR). [13]

Assessment of global and segmental myocardial strains utilizing conventional and novel imaging techniques can provide an opportunity for the early detection of subclinical myocardial dysfunction compared with usual cardiac functional indices. [14-16] Nevertheless, there are still several questions regarding changes in myocardial function following COVID-19. For instance, it is unknown whether these disorders will persist months after recovery from the disease and whether their endurance correlates with the severity of the initial illness.

Objectives

In the present study, we investigated the functional and strain values of the myocardium 3 to 6 months after recovery from respiratory COVID-19 disease utilizing CMR in patients without a history of cardiac disorder or any cardiac risk factors.

METHODS

Study Population

The present study was conducted on 20 patients with a definite history of COVID-19 infection in the preceding 3 to 6 months and 28 age-, sex-, and body mass index-matched healthy subjects without such a history. The non-contrast CMR findings of the 2 groups were compared. The study population signed informed consent, and the institutional ethics committee approved the study (ethical approval code: IR.RHC.REC.1399.062).

The healthy subjects were selected from our archive of normal CMR cases gathered before the pandemic. After comprehensive physical examinations and lab data evaluations, including lipid profiles, fasting blood sugar measurements, thyroid function tests, renal function tests, and serum electrolyte assessments, the healthy subjects underwent a non-contrast CMR examination.

None of our studied cases in both groups had a previous history of cardiac diseases (coronary or noncoronary) in themselves or their family, known systemic disorders with cardiac involvement, and cardiovascular risk markers, including smoking, hypertension, diabetes mellitus, and dyslipidemia.

All the COVID-19 group members had a history of suspicious clinical symptoms, followed by a positive reverse transcription-polymerase chain reaction test, and underwent chest computed tomography (CT) scanning within the acute phase of the disease on day 3 or 4 after symptoms onset.

The CMR Protocol

CMR data were obtained utilizing an 8-element phased-array receiver surface coil (Siemens Avanto, Erlangen, Germany). The cvi42 (Circle Cardiovascular Imaging,

Calgary, Alberta, Canada) application, version 5.6.2, was utilized to obtain functional and deformation parameters.

ECG-gated cine functional sequences were applied to acquire images in multiple long- and short-axis planes at the end of expiration in a breath-hold (slice thickness = 8 mm, field of view = 300 mm, imaging matrix = 156 × 192, and repetition time/echo time =31/1.2 ms). Short-tau inversion recovery (STIR) images were acquired by applying a slice thickness of 9 mm, a field of view of 420 mm, an echo time of 47 milliseconds, a repetition time of 640 milliseconds, and an inversion time of 170 milliseconds.

CMR analysis

For the calculation of biventricular systolic function, end-diastolic and end-systolic points were determined. The endocardial borders were drawn in the entire ventricular length in both phases in short-axis images.

The endocardial and epicardial borders were traced manually at end-diastole in 2-, 3-, and 4-chamber views and in all short-axis stacks. Then, the borders were propagated to the entire cardiac cycle to calculate 3D biventricular global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS).

A STIR sequence was utilized to reveal myocardial inflammation. It is a fat suppression technique demonstrating the edematous areas as high signal intensity regions. Myocardial edema was defined by the STIR sequence as a ratio of myocardial-to-skeletal muscle signal intensity of more than 1.9. [17]

An expert cardiologist with 6 years of experience in CMR interpretation blinded to the patients' data interpreted all the CMR findings.

The Chest CT Scanning Protocol

A Siemens SOMATOM scope 16-slice multidetector scanner was utilized, and a low-dose institutional non-contrast pulmonary CT protocol was performed. Image acquisition parameters were as follows: a tube voltage of 120 KVp, a tube current of 70 to 80 mAs, and a slice thickness of 3 mm at a 10 mm slice interval. A 1.5 mm high-resolution algorithm was used to reconstruct the lung window. The mean CT dose index volume was 4.1 mGy (range = 3–6.3 mGy). An expert radiologist blinded to the patients' data interpreted all the CT images in both lungs (width = 1500 HU and level = −600 HU) and mediastinal (width = 350 HU and level = 50 HU) windows.

Pulmonary Involvement Scoring on Chest CT

The involvement of each lobe by defined COVID-19 patterns according to different available consensuses was recorded. [18, 19] A total severity score (TSS) was calculated as follows: each of the 5 pulmonary lobes was evaluated separately to assess the percentage of lobar involvement and classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%), with a corresponding score of 0, 1, 2, 3, or 4. TSS was calculated by summing the scores (range = 0–20). TSS ≥ 8 was considered severe involvement, according to previous studies. [18] An expert radiologist with 10 years of experience in chest CT interpretation blinded to the patients' data evaluated the images.

Statistical Analysis

Descriptive results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized as frequencies (percentages) for categorical variables. Between-group comparisons for qualitative variables were performed using the χ^2 or Fisher exact test, and continuous variables were compared using the *t* or Mann-Whitney *U* test. The Spearman test was applied to investigate the presence of a

linear correlation between TSS and CMR parameters. A *P* value ≤ 0.05 was considered statistically significant. The SPSS software, version 22.0, (IBM, United States) was used for data analysis.

RESULTS

Participants' Characteristics

Twenty subjects (mean ± SD of age = 35.30 ± 5.27 y; 55% female) with a definite history of COVID-19 infection in the preceding 3 to 6 months and 28 healthy controls (mean ± SD of age = 31.07 ± 4.35 y; 50% female) were included in the present investigation. There were no significant differences between the groups in terms of age and sex (*P* = 0.2 and *P* = 0.7, respectively). Table 1 demonstrates the study population's demographics and chest CT and CMR findings.

CMR Results

The following CMR parameters were significantly different between the 2 study groups: biventricular ejection fraction (EF), biventricular GLS, right ventricular (RV) GCS, and RV GRS (Fig. 1, A-G).

Six patients (30%) in the COVID-19 group exhibited regional myocardial edema (Fig. 1, H).

Chest CT Results

The mean ± SD of TSS in the study population was 3.67 ± 3.43. No significant linear correlations existed between the calculated TSS of pulmonary disease and CMR parameters. Furthermore, no significant differences in CMR values were observed between patients with TSS ≥ 8 and those with TSS < 8 (all *P*s > 0.05) (Table 2).

Table 1: Demographics and Baseline CMR Parameters of the Study Population

Variable	Positive COVID-19 History Frequency (n)* (%)	Negative COVID-19 History Frequency (n)* (%)	*P* value
Sex (female)	11 (55)	14 (50)	0.7
Variables	Mean±SD	Mean±SD	
Age, y	35.30±5.27	31.07±4.35	0.2
BMI, kg/m^2	25.95±1.93	24.75±1.70	0.1
LVEF%	55±4.5	58±1.7	0.006
RVEF%	52±4.9	56±1.2	0.002
LVGLS%	15.95±3.08	18.07±1.35	0.008
LVGCS%	18.89±2.32	18.69±2.18	0.7
LVGRS%	39.63±7.57	39.83±7.78	0.9
RVGLS%	26.66±4.62	23.58±4.48	0.02
RVGCS%	10.85±4.21	17.68±1.79	<0.001
RVGRS%	17.17±6.66	31.05±7.75	<0.001

*n: number; CMR: cardiac magnetic resonance imaging; LV: left ventricle; BMI: body mass index; EF: ejection fraction; RV: right ventricle; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain

Table 2: Comparison of Demographics and CMR Parameters Between the TSS* Groups

Variable	TSS<8 (n=14) Frequency (n) (%)	TSS≥8 (n=4) Frequency (n) (%)	*P* value
Sex (female)	7 (50)	2 (50)	1
Regional edema	5 (35.7)	1 (25)	1
Variable	Median (IQR)	Median (IQR)	
Age, y	41.5 (12)	40.50 (18)	0.8
LVEF%	54.75 (6)	54.75 (3)	0.7
RVEF%	52.5 (8)	50 (7)	0.3
LVGLS%	16.76 (3.3)	14.46 (2.7)	0.1

LVGCS%	19.17 (4.57)	17.82 (3.90)	0.5
LVGRS%	42.86 (13)	37.63 (13)	0.3
RVGLS%	26.14 (5.77)	26.43 (3.44)	0.1
RVGCS%	11.90 (5.54)	9.42 (9.02)	0.2
RVGRS%	18.63 (8)	14.26 (15)	0.4

* CMR: cardiac magnetic resonance imaging; TSS: total severity score; n: number; LV: left ventricle; EF: ejection fraction; RV: right ventricle; GLS: global longitudinal strain; GCS: global circumferential strain; GRS: global radial strain

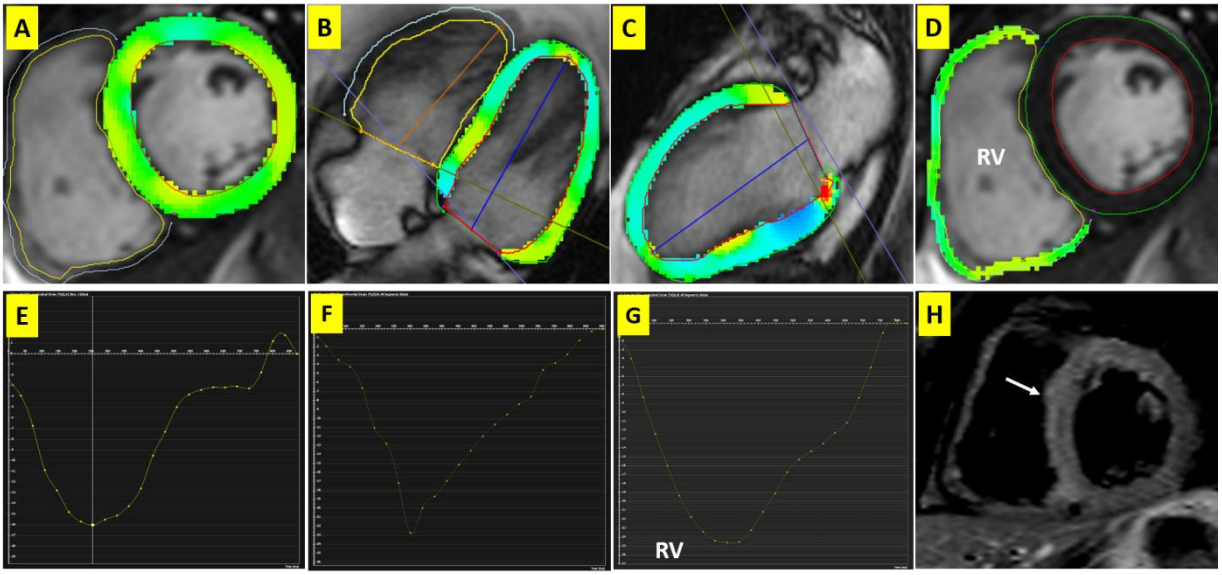

Figure 1: The images present cardiac magnetic resonance imaging in a patient 5 months after COVID-19 infection. A-D: The images illustrate biventricular strain measurements in short-axis views (A and D) and long-axis views (B and C). E-G: The images present curves for left ventricular global longitudinal and circumferential strain values (E and F) and the right ventricular global longitudinal strain value (G). H: The short tau inversion recovery sequence in the short-axis view reveals subepicardial septal hyper signal stripe, consistent with regional left ventricular myocardial edema (arrow).

RV: right ventricle

DISCUSSION

COVID-19 complications, especially long-term after recovery from the disease, are still under active research. Myocardial dysfunction and inflammation are reported as potential adverse events during the acute and chronic phases following COVID-19. [20] The present prospective study compared CMR findings between patients with recent COVID-19 respiratory infection and healthy controls. None of the subjects had a history of cardiac disorders or conventional cardiac risk profiles.

Our principal findings are as follows:

1) Biventricular EF was significantly reduced in the COVID-19 group compared with the healthy controls.

2) Compared with the control group, the strain values of left ventricular (LV) GLS, RVGCS, and RVGRS were significantly reduced, while RVGLS was significantly increased in the COVID-19 group.

3) No association was found between ventricular function and strain values vs TSS.

4) Persistent myocardial edema was detected in one-third of the patients.

Our results showed that otherwise healthy patients with a history of COVID-19 infection had evidence of reduced EF compared with healthy controls. Our patient group was a highly selected population without any risk factors or history of cardiac disease. Therefore, it can be assumed that changes in myocardial function and strains are related to

the direct viral involvement of the myocardium vs the host immune response. Various studies based on imaging techniques have shown such changes in both myocardial structure and function. Recently, a meta-analysis using CMR on a large group of post–COVID-19 nonathletes and athletes conducted by Kato et al [21] showed impairment of both LVEF and RVEF, especially in nonathletes. In our patients, the clinical signs and symptoms of the disease had improved entirely at the time of patient evaluation 3 to 6 months after index infection. At the same time, we demonstrated a significant decline in ventricular systolic function and strains. In a study by Carlessi et al [22] on 156 patients who recovered from COVID-19, RV (17.9%) and LV (13.4%) systolic dysfunction were the most frequent findings. Additionally, Carlessi and colleagues evaluated the presence of late gadolinium enhancement (LGE) and demonstrated an inverse correlation between the presence of LGE and ventricular dysfunction.

Myocardial strain is a sensitive parameter capable of demonstrating early myocardial dysfunction in numerous cardiac pathologies. [23, 24] We showed a significant decline in RV strain parameters, including RVGCS and RVGRS. However, the amount of RVGLS was high compared with that in the control group. We surmised that it was probably related to a compensatory increase in myocardial shortening in the longitudinal direction. In a study by Ulloa et al [25] on 57 post–COVID-19 patients and 20 healthy volunteers, GCS and GRS values were significantly reduced during a short interval of 8 weeks. Still, afterward, these changes were reversed. Concerning LV function, the only significantly different parameter was LVGLS. Likewise, Ramadan et al [26] indicated reduced LVGLS in 30% of patients in CMR and diastolic dysfunction in 40% of echocardiographic studies about 3 to 6 months after recovery.

We compared the association between CMR parameters and the severity of pulmonary involvement on the baseline CT of COVID-19 patients. There was no relationship between the severity of the initial involvement of COVID-19 disease and the presence of cardiac dysfunction.

Previous studies have shown that the myocardium could be involved through direct viral attack or indirectly via the persistence of immune response, systemic inflammation, and dysregulation of the renin-angiotensin system. Myocardial injury could affect patients without a history of cardiac disease in about one-quarter of patients and is associated with higher mortality and long-term complications. Similarly, we demonstrated that in midterm follow-up, a third of our COVID patients had evidence of persistent myocardial edema. [27] Therefore, cardiac morbidity can occur in patients independent of the severity of the initial involvement in the months following recovery from COVID-19. However, it is crucial to study the consequences for such patients in longer-term follow-up studies.

There were several limitations in our work. Firstly, our small sample size was small due to the small number of patients with COVID-19 without any underlying disease, low patient cooperation, and lack of multicenter evaluation. Secondly, this research was designed as a case-control investigation. We suppose that a mixed cohort study design would be more suitable to compare the CMR findings of healthy subjects before and after the COVID-19 pandemic. Unfortunately, the follow-up data of our healthy subjects were not available. Thirdly, we did not perform LGE sequences and mapping techniques in our study, which can reveal more findings in follow-up studies. Finally, we suppose that a longer follow-up time is required to obtain more robust results.

In conclusion, a significant decline in myocardial strain and ventricular function among COVID-19 patients was found during midterm follow-up, even in the absence of previous cardiac dysfunction. One-third of our patients revealed persistent myocardial edema. The occurrence of cardiac structural and functional changes was utterly independent of the severity of the lung disease in our COVID-19 patients.

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