Párraga R, Real C, García-Lunar I, Pizarro G, Sánchez-González J, Diaz-Munoz R, González-Calvo E, Fernandez-Alvira JM, Martínez-Gómez J, Fernández-Jiménez R*. Absence of Myocardial Involvement After SARS-CoV-2 Vaccination in Asymptomatic Adolescents. ***J Cardiovasc Transl Res***. 2024 Jun;17(3):554-557. doi: 10.1007/s12265-023-10455-w. Epub 2023 Dec 19. PMID: 38112908.

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Absence of myocardial involvement after SARS-CoV-2 vaccination in asymptomatic adolescents

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Short title: Cardiac involvement after SARS-CoV-2 vaccination

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Abbreviations
CMR: Cardiovascular Magnetic Resonance
EnIGMA: Early ImaGing Markers of unhealthy lifestyles in Adolescents
MOLLI: Modified Look-Locker Inversion recovery
SSFP: Standard Segmented cine steady-state Free-Precession
T2-GraSE: T2 gradient-spin-echo

Key words: adolescents, SARS-CoV-2, myocarditis, cardiovascular magnetic resonance.

Text word count: 818 words

TEXT

Introduction

Myocardial inflammation is a rare but serious complication after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vaccination.[1] Most prior studies focused on symptomatic cases of clinically-suspected myocarditis.[2] However, myocardial inflammation after SARS-CoV-2 vaccination, particularly in asymptomatic young individuals, has not been addressed. This study used state-of-the-art cardiac magnetic resonance (CMR) imaging to assess the presence of subclinical myocardial involvement in asymptomatic adolescents according to their SARS-CoV-2 status.

Methods

The Early ImaginG Markers of unhealthy lifestyles in Adolescents (EnIGMA) cross-sectional study enrolled adolescents aged 15 to 18 years from 7 public secondary schools in the Madrid region. [3] The study protocol was approved by the research ethics committee of the *Instituto de Salud Carlos III* (identifier CEI PI 63_2020).

CMR examinations were conducted between March and October 2021 using a Philips 3-Tesla Elition X whole-body scanner (Philips Healthcare, Best, The Netherlands), as previously described. [3]

On the day of the CMR examination, a rapid qualitative IgG/IgM SARS-CoV-2 antibody test was performed on capillary blood sample and participants were asked to provide the dates of confirmed previous SARS-CoV-2 infection and vaccinations. Participants were then categorized according to SARS-CoV2 status as naïve (non-infected and unvaccinated), infected (unvaccinated), and vaccinated (independently of past infection status).

One-way ANOVA and multivariable linear regression analysis were used for crude and adjusted between-group comparisons of continuous variables, respectively. Statistical analyses were performed with Stata software package version 16 (StataCorp, College Station, Texas).

Results

CMR imaging examinations were performed on 120 adolescents with a mean age of 16.0±0.4 years (51% girls) who provided complete SARS-CoV-2 status information (**Figure 1A)**. According to SARS-CoV-2 status, adolescents were categorized as naïve (n=74), infected (n=23), or vaccinated (n=23). Median number of days from vaccination to CMR examination was 26 (first quartile, 8 days; third quartile 46 days; range 0 to 72 days).

Global myocardial T2 relaxation time was similar in the three groups (44.1 ± 2.2 ms, 44.1 ± 1.8 ms, and 44.7 ± 2.6 in naïve, infected, and vaccinated participants, respectively; p = 0.487), and there were no significant differences in any of the analyzed myocardial segments. Global native T1 relaxation time was slightly higher in the vaccinated group (1249±35 ms) than in naïve and infected adolescents (1231±30 ms and 1227±29 ms, respectively; p = 0.035; **Figure 1B**). This difference remained statistically significant and of similar magnitude after multivariate linear regression analysis. In the by-segment analysis, statistically significant differences were only found in the anterior, anteroseptal, and anterolateral myocardial segments.

Discussion

This cross-sectional study conducted in asymptomatic adolescents found no evidence of subclinical myocardial involvement after SARS-CoV-2 vaccination, as assessed by state-

of-the-art non-contrast CMR imaging.[4] Previous studies focused on symptomatic cases of myocarditis after SARS-CoV-2 vaccination in large populations, in which CMR was performed in fewer than 50% of suspected cases.[2] In contrast, the present study is, to our knowledge, the first to assess subclinical myocardial inflammation after vaccination using CMR in asymptomatic adolescents.

While the incidence of myocarditis after SARS-CoV-2 vaccination is even lower than that reported after infection,[1] the highest post-vaccination rates have been reported in adolescence or early adulthood, particularly after vaccination with mRNA vaccines.[2] Recently updated Lake-Louise criteria for the diagnosis of myocarditis highlight the importance of using CMR-based T1 and T2 relaxation times to characterize myocardial tissue properties and detect myocardial inflammation.[4].

We detected slightly higher T1 relaxation times (~20ms) in SARS-CoV-2–vaccinated adolescents than in previously infected or naive individuals. This difference remained statistically significant after adjusting for variables that can affect T1 values: age, sex, heart rate, body-mass-index, and physical activity.[3] Nevertheless, the observed differences appear to be clinically irrelevant, for the following reasons. First, the differences are within the 95% confidence interval for the limits of agreement in reported reproducibility analyses.[3] Second, larger differences have been reported between sexes, and between athletes and sedentary individuals, in otherwise healthy populations. Third, differences in native T1 relaxation time between pediatric patients with acute myocarditis and healthy controls are much higher (~100 ms).[5] Forth, we observed no statistically significant between-group differences in the inferolateral wall, the most affected myocardial segment in myocarditis.[4] Finally, myocarditis episodes have reported to be more frequent during the first week after vaccine inoculation;[2] however, we did not detect higher myocardial T1 or T2 values in the first days after vaccination in our study

population (data not shown). Added to this, we detected no between-group differences in edema-sensitive T2-mapping or LV wall motion abnormalities, supporting the absence of subclinical myocardial inflammation in vaccinated adolescents in the present study.

Because of its cross-sectional nature, the present study demonstrates associations but not causation. The imaging protocol did not include gadolinium-based intravenous contrast administration, and therefore we could not assess myocardial extracellular volume or late gadolinium enhancement. The sample size was small relative to the estimated incidence of clinical myocarditis after SARS-CoV-2 exposure.

In conclusion, this observational study found no evidence of subclinical myocardial involvement after SARS-CoV-2 vaccination in asymptomatic adolescents.

Figure 1.

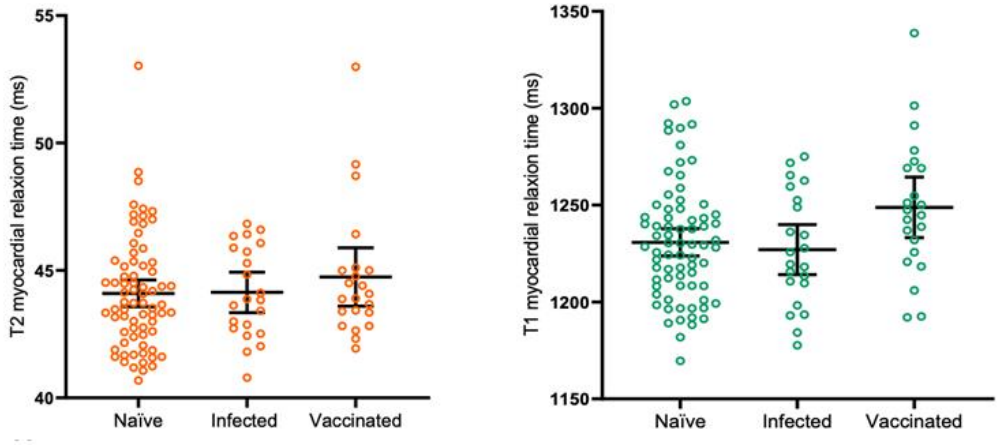
Panel A. Participant characteristics, overall and stratified by SARS-CoV-2 exposure. Data are presented as mean (SD) for continuous variables and frequency (%) for categorical variables. p-values for the comparison of non-adjusted between-group differences are derived from one-way ANOVA test for continuous variables and chi-square test for categorical variables. BMI categories were defined according to age- and sex-adjusted body mass index percentiles (P) based on Centers for Disease Control reference values: normal weight (<P85), overweight (P85-P95), and obese (>P95). BMI was calculated as weight (kg) divided by height squared (m^2). For indexed values, body surface area (m^2) was determined using the Du Bois formula. BMI, body mass index; LV EDV, left ventricular end-diastolic volume; LV ESV, left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; RV EDV, right ventricular end-diastolic volume; RV ESV, right ventricular end-systolic volume; RVEF, right ventricular ejection fraction

Panel B. Dot plots representing myocardial T2 (left) and native T1 (right) relaxation times in naïve (non-infected and unvaccinated), infected (unvaccinated), and vaccinated (independently of past infection status) asymptomatic adolescents. The central bar represents the mean, and the whiskers represent the 95% confidence interval of the mean.

A

	Total	Naive	Infected	Vaccinated	
	N = 120	n = 74	n = 23	n = 23	p value
Girls	61 (50.8%)	41 (55.4%)	8 (34.8%)	12 (52.2%)	0.22
Age, years	16.0 (0.4)	15.9 (0.3)	16.0 (0.6)	16.4 (0.4)	<0.01
Body mass index, kg/m^2	21.4 (3.2)	21.3 (3.3)	21.4 (2.7)	21.7 (3.7)	0.86
Categorized body mass index					0.97
Normal weight	104 (86.7)	65 (87.8)	19 (82.6)	20 (87.0)	
Overweight	12 (10.0)	7 (9.5)	3 (13.0)	2 (8.7)	
Obese	4 (3.3)	2 (2.7)	1 (4.4)	1 (4.3)	
Body surface area, m^2	1.70 (0.16)	1.69 (0.17)	1.73 (0.18)	1.68 (0.13)	0.52
LV EDV, ml/m^2	84.9 (12.1)	83.7 (11.7)	88.6 (13.6)	85.1 (11.4)	0.24
LV ESV, ml/m^2	31.9 (6.4)	31.2 (6.3)	33.2 (6.7)	33.0 (6.4)	0.29
LVEF, %	62.5 (4.1)	62.9 (4.2)	62.6 (4.1)	61.4 (3.9)	0.33
RV EDV, ml/m^2	92.7 (15.0)	91.2 (14.1)	98.6 (17.2)	91.5 (14.8)	0.11
RV ESV, ml/m^2	41.0 (9.4)	40.0 (8.3)	43.5 (11.2)	41.6 (10.4)	0.28
RVEF, %	56.2 (4.7)	56.4 (4.3)	56.4 (5.5)	55.1 (5.1)	0.46
Heart rate, bpm	69 (11)	68 (10)	69 (12)	69 (14)	0.90

B



Acknowledgments

The authors are indebted to adolescents who participated in the study. Simon Bartlett (CNIC) provided English editing. This work was presented as moderated poster at the European Society of Cardiology Congress (Barcelona, August 2022).

Patient Consent Statement: The authors confirm that participant consent forms have been obtained for this article. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975.

Funding: The EnIGMA (Early ImaGing Markers of unhealthy lifestyles in Adolescents) study was funded by the Instituto de Salud Carlos III (ISCIII) through the project "PI19/01704" and co-funded by the European Union. CR is granted by the Fundacion Interhospitalaria para la Investigación Cardiovascular. J.M-G is a recipient of grant FPU21/04891 (*Ayudas para la formación de profesorado universitario*, FPU-2021) from the Ministerio de Educación, Cultura y Deporte. The CNIC is supported by the ISCIII, the *Ministerio de Ciencia e Innovación* (MCIN) and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIN/AEI/10.13039/501100011033).

Disclosures: Javier Sánchez-González is a Philips Healthcare employee. The rest of the authors declare no conflicts of interest.

Author's contributions

Rocio Parraga performed recruitment of participants and consent process, made substantial contributions to the interpretation of data, and drafted the initial manuscript.

Carlos Real made substantial contribution to the design of the data collection tools, coordinated recruitment of participants and consent process, and made substantial contributions to the interpretation of data.

Inés García-Lunar and Gonzalo Pizarro performed imaging analyses and made substantial contributions to the interpretation of data.

Javier Sánchez-González designed the imaging protocol and made substantial contributions to the interpretation of data.

Raquel Diaz-Munoz assisted with recruitment of participants and consent process, made substantial contributions to the acquisition of imaging and anthropometric data, and performed capillary blood tests.

Ernesto Gonzalez-Calvo assisted with recruitment of participants and consent process, made substantial contributions to the acquisition of imaging data and and performed analyses of quality assessment for acquired images.

Juan Miguel Fernandez-Alvira and Jesus Martinez-Gomez conducted statistical analyses.

Rodrigo Fernandez-Jimenez conceptualized, designed and coordinated the overall study.

All authors revised the manuscript critically for relevant intellectual content, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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