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Original article

INCREASE IN CORONARY SINUS RHYTHM IN UNIVERSITY STUDENTS AS POTENTIAL CORRELATE OF COVID-19 INFECTIONS

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ABSTRACT

The COVID-19 pandemic has significantly disrupted human life demonstrating also a substantial impact on cardiac diseases. In particular, some researchers have reported an increased incidence of cardiac arrhythmias in patients with COVID-19, emphasizing the need for further investigations. Accordingly, this study aimed to evaluate the prevalence of cardiac arrhythmias in university students before and after COVID-19, in order to better understand if this risk increased over time. Cross-sectional study conducted on students attending the University of Palermo from 2015 to 2024. For each subject demographic data, patient medical history information and information relating to vaccination against Sars-CoV-2 were recorded. Moreover, each visit was associated with the execution of a 12-lead ECG performed at rest in order to assess for alterations of the electrical heart rhythm. During the study period 1,217 patients were visited, including 401 (33%) males and 815 (67%) females. The median age at the visit was 20.40 years. Overall, we observed a statistically significant increase in the risk of coronary sinus rhythm and respiratory arrhythmia in subjects with a previous diagnosis of COVID-19 (OR=5.0, 95% CI=1.6-16.0 and OR=3.4, 95% CI= 2.4-4.8, respectively). This study is especially compelling as it focuses on an increased risk of respiratory arrhythmia and coronary sinus rhythm in young healthy subjects after the COVID-19 pandemics. If our results should be confirmed by other more extensive studies they could be relevant to clinicians since they should be aware of cardiac arrhythmias as one of the complications attributable to COVID-19 emergence.

1. Introduction

The COVID-19 pandemic has significantly disrupted human life having a deep impact on health systems, economies, social interactions, and education worldwide, and leading to widespread illness, economic hardship, social isolation, and educational challenges. In particular, in the health sector, COVID-19 had a substantial impact on cardiac diseases, with evidences suggesting an increased risk of cardiovascular complications, including myocardial injury, arrhythmias, and thrombotic events, particularly among individuals with pre-existing cardiovascular conditions [1].

More recently, some studies have reported an increased incidence of cardiac arrhythmias in patients with COVID-19, emphasizing the need for further investigation to better understand the nature and clinical implications of this correlation [2].

Proposed mechanisms for explaining a possible relationship between COVID-19 and cardiac arrhythmias include the systemic inflammatory response that may alter cardiac electrical conductivity, endothelial dysfunction associated with angiotensin-converting enzyme 2 (ACE2)

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activation, and the possible formation of thrombi that could impact cardiac function [2].

The SARS-CoV-2 virus, responsible for COVID-19 disease, was initially recognized for its marked affinity for cells of the respiratory tract via the ACE2 receptor, the main entry receptor of the virus. In addition, several studies have also highlighted the presence of this marker in cardiac cells, suggesting a direct involvement of the cardiovascular system [3].

The Sars-Cov-2 virus is able to enter the cells that express the ACE2 receptor and it has been shown that the cardiac cells are more abundant in these receptors than lung cells. The S1 subunit of the outer spike proteins of the virus attaches to the ACE2 receptor, facilitating the attachment of the virus to the host cell. Inside the cell, this virus replicates via several molecular mechanisms, such as the NF-κB pathway [4] which once activated affects the transcription of a subunit of transient outward potassium current (Ito), affecting the action potential of the cardiac cell membrane, with subsequent arrhythmogenic effects [5].

The virus can also induce death of cardiomyocytes, with mild fibrosis and hypertrophy, inducing arrhythmias [6].

The respiratory alterations that appear in the COVID-19 infection, in particular hypoxemia, exposes the myocardium to hypoxia. Due to the fact that cardiac cells' ion channels are ATP-mediated, hypoxia affects the passage of ions, with subsequent modifications of the action potential and repolarisation, promoting arrhythmias. For instance, this phenomenon modifies the structure of the fast-activated delayed rectified potassium channel (IKr), thus extending the ventricular repolarization, together with the elevation of the late sodium current [7].

On the contrary, the interference with the Ca2+-activated K+ (SK) channels can cause a shortening of the repolarisation, also increasing the chance of arrhythmias [8,9]. In addition, after the virus invades the host cells, it downregulates the expression of ACE2 receptors in the heart, which leads to a pro-inflammatory environment, and thus to the complications of the disease, in particular cardiac arrhythmias [10]. Cardiac complications associated with COVID-19 include myocarditis, pericarditis, and acute heart failure. Additionally, there is a growing interest in cardiac arrhythmias as a potential consequence of SARS-CoV-2 infection.

On the other hand, it should also be considered that some pharmacological agents, used in a first moment for the treatment of the SARS-CoV-2 virus infection, such as hydroxychloroquine, chloroquine, or azithromycin, can lead to QT interval prolongation, thus to arrhythmias [11].

Therefore, it is crucial to consider the complexity of the relationship between the virus and the cardiovascular system, as multiple factors may contribute to cardiac manifestations in the context of COVID-19. A detailed analysis of available scientific data is essential to accurately delineate the real world correlation between SARS-CoV-2 infection and cardiac arrhythmias, in order to develop targeted diagnostic and therapeutic strategies. According to the previous considerations, this study aimed to evaluate the prevalence of cardiac arrhythmias in university students before and after COVID-19, in order to better understand if this risk increased over time.

2. Material and methods

This is an observational cross-sectional study carried out on a random sample of 1,217 students attending the University of Palermo from 2015 to 2024.

All of the students were examined at the University Hospital "P. Giaccone" of Palermo (Italy) during the occupational health visits that were carried out according to the national Italian law [12].

For each subject the following data have been recorded: demographic data (sex, and date of birth), patient medical history information (date of visit, any previous cardiovascular pathology, thyroid pathologies, and other relevant clinical conditions), and information relating to vaccination against Sars-CoV-2 (whether vaccinated or not, number of doses).

Moreover, each visit was associated with the execution of a 12-lead ECG performed with a Schiller Cardiovit CS-200 electrocardiograph, at rest in order to assess for alterations of the electrical heart rhythm. The ECG was evaluated by two different occupational medical physicians in order to increase accuracy of the diagnosis.

All patients provided signed informed consent to the performed clinical examinations and the study was approved by the local Ethical Committee of the University Hospital "P. Giaccone" (n. protocol 8/2024).

Statistical analysis

Demographic, clinical, and medical history information, including any diagnoses, were collected for each patient and were analyzed in order to assess their contribute in increasing the risk of arrhythmias.

Qualitative variables are summarized as absolute and relative frequencies. Quantitative variables are reported as mean (standard deviation, SD) if normally distributed or, otherwise, as median (25th – 75th percentile, interquartile range IQR). The chi-square test or the Fisher exact tests if appropriate were used to assess significant differences between investigated qualitative variables in the pre- (2015-2019) and post-COVID (2020-2024) periods. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for each risk factor.

Analyses were performed using R Software analysis [13]. A p-value less than 0.05 was considered statistically significant.

3. Results

As reported in Table 1, during the study period from 2015 to 2024, 1,217 patients were visited, including 401 (33%) males and 815 (67%) females. The median age at the visit was 20.40 years, with a higher prevalence of subjects in the age groups ≤19 and ≥21 years, accounting for 38.7% and 30.4%, respectively.

Regarding year or subject recruitment, the majority of students were observed in the 2015-2016 (24.1%) and 2023-2024 (29.9%), although there are no significant differences in the total number of observed students between the pre (54.1%) and post-COVID (45.9%). The average heart rate was found to be 75 beats per minute (bpm).

A large majority of the participants were vaccinated against SARS-CoV-2 with 3 doses (75.3%) and about one out of four stated to have had COVID-19. Considering only the post-Covid-19 period, 269 (48.1%) stated to have had diagnosed a previous COVID-19 infection.

Considering demographic differences in the pre and post covid period we observed no difference in terms of sex (M/F ratio 0.51 vs. 0.46, p=0.34) and a statistically significantly difference of 3 months of age in students examined in the post-COVID period (p<0.001).

Table 1. General characteristics of the patients seen at the occupational medicine office (Italy, 2015-2024).

Total, N		1,217
Gender, N (%)		
	- Males	402 (33.0%)
	- Females	815 (67.0%)
Age at the visit, median (IQR)		20.4 (19.6-22.7)
Age Groups		
	≤19	472 (38.7%)
	20	258 (21.1%)
	21	116 (9.5%)
	≥22	371 (30.4%)
Year of subject recruitment, N (%)		
	- 2015-2016	294 (24.1%)
	- 2017-2018	156 (12.8%)
	- 2019-2020	70 (5.7%)
	- 2021-2022	194 (15.9%)
	- 2023-2024	365 (29.9%)
Period of visit, N (%)		
	- Precovid	658 (54.1%)
	- Postcovid	559 (45.9%)
Heart rate, mean (SD)		75 (13.1)
Number of SARS-CoV-2 vaccine doses (only in subjects examined after 2020)		
	- 0	17 (3.0%)
	- 1	10 (1.8%)
	- 2	101 (18.1%)
	- 3	421 (75.3%)
	- 4	10 (1.8%)
Previous COVID-19 disease (only in subjects examined after 2020)		
	- Yes	269 (48.1%)
	- No	290 (51.9%)

In table 2 we compared the prevalence of several pathologies in the pre and post covid period. We found a statistically significant increase in the prevalence of respiratory arrhythmia ($p<0.05$), and coronary sinus rhythm ($p<0.05$). Otherwise, we observed a statistically significant decrease in the prevalence of the disorders of interventricular conduction ($p<0.05$).

Table 2. Comparison between prevalence of diseases in the pre and post COVID-19 period.

	Pre Covid-19 N (%)	Post Covid-19 N (%)	p-value
Cardiovascular pathology	4 (0.6%)	3 (0.53%)	NS
Thyroid pathologies	7 (1.06%)	10 (1.78%)	NS
Asthma/respiratory pathologies	35 (5.31%)	33 (5.90%)	NS
Tachycardia	24 (3.64%)	31 (5.54%)	NS
Bradycardia	61 (9.27%)	41 (7.33)	NS
Extrasystole	9 (1.36%)	6 (1.07%)	NS
Block/Hemiblock	12 (1.82%)	20 (3.57%)	NS
Coronary sinus rhythm	2 (0.30%)	10 (1.78%)	<0.05
Respiratory arrhythmia	43 (6.53%)	118 (21.10%)	<0.05

Finally, in table 3, we observed a statistically significant increase in the risk of coronary sinus rhythm and respiratory arrhytmia in subjects with a previous diagnosis of COVID-19 (OR=5, 95% CI=1.6-16.0 and OR=3.4, 95% CI= 2.4-4.8, respectively).

	COVID-19 positive N/Tot (%)	COVID-19 negative N/Tot (%)	OR (95% CI)	p-value
Coronary sinus rhythm	7/269 (2.6%)	5/948 (0.5%)	5.0 (1.6-16.0)	0.002
Respiratory arrhythmia	71/269 (23.4%)	90/948 (9.5%)	3.4 (2.4-4.8)	<0.001

Table 3. Risk of coronary sinus rhythm and respiratory arrhythmia according to a previous COVID-19 diagnosis.

4. Discussion

Certainly, there are still many unknowns regarding the impact of COVID-19 epidemics on the human health not only due to the direct effects of the virus but also because of other associated phenomena that could have contributed to increase some risks.

Our study, in particular, gets ideas from the initial observation of an increased number of cases of coronary sinus rhythm in the post-COVID-19 period and, considering a large number of students who were examined also in the pre-COVID-19 period, confirms that this increase was not merely random, thus, suggesting the presence of patterns that deviate from what would be expected by chance alone. Specifically, our observations indicate that individuals with a history of COVID-19 diagnosis may experience a more than 5-fold increase in the risk of coronary sinus rhythm and a roughly 3-fold increase in respiratory arrhythmia.

However our findings are not isolated and there are some other studies in literature, as well, that highlighted a strong correlation between COVID-19 and the development of cardiac arrhythmias [11]. In this sense, a study

carried out in elderly African patients in 2021 suggests a higher incidence of COVID-19 complications, such as cardiac arrhythmias, especially in obese patients or in patients with comorbidities. These patients had a greater chance of developing complications probably due to their comorbidities, altered lifestyle and dietary habits [14]. However, this explanation could be not valid for our sample since we assessed young students who were mainly healthy and with low prevalence of other chronic diseases.

More similarly to what we found, a recent observational study showed that there was an association between COVID-19 and electrocardiographic modifications in patients who previously had no cardiovascular disease [15]. However, also in this study the patients were mainly elderly patients, and those who suffered complications were older by a few years than the group compared to those who did not suffer the complications. Our results seem to suggest that, regardless of the health condition of the subjects, the prevalence of coronary sinus rhythm increased after the COVID-19 period. It should be stressed that we do not have evidence that this increase could be due to SARS-CoV-2 infection, SARS-CoV-2 vaccination or other risks factors increased after the SARS-CoV-2 emergence as physical inactivity, altered mental health, reduced access to healthcare, other treatments improperly used with cardiotoxicity (e.g. idroxychlorochine). However, more recently, some authors documented that there is strong evidence about the safety of the Pfizer-BioNTech BNT162b2, Moderna mRNA-1273 and AstraZeneca ChAdOx1 vaccines regarding their arrhythmogenic effect A transient and not clinically significant risk of developing arrhythmias was found in the first 28 days after the second dose of an Moderna mRNA-1273 vaccine [16].

There are some limitations of our study that should be acknowledged because they could affect its validity. Firstly, our study is a cross-sectional study which, by its characteristics, cannot assess the chronological relationship between exposure to some risk factors and the coronary sinus rhythm that occurred in our patients. Secondly, there could be multiple unstudied risk or not properly measured factors that could have contributed to the development of these arrhythmias. Regarding this matter, further studies should be conducted to evaluate these other risk factors and the causal relationship between each of these factors and the cardiac problems that we observed. Thirdly, the relatively small sample size of this study could have incurred a lower statistical power also considering that coronary sinus rhythm is a quite rare event and only twelve cases were included in our study. This it is also the reason for which we could not implement a multivariable statistical analysis in order to rule out the possible role of main confounding factors.

Despite these possible limitations, this study is especially compelling as it focuses on a sample of young healthy subjects and if our results should be confirmed by other more extensive studies they could be relevant to clinicians since they should be aware of cardiac arrhythmias as one of the complications attributable to COVID-19 emergence. Moreover, a thorough monitorization and special follow-up care of these subjects should be given in order to assess the possible clinical evolution of these arrhythmias and their eventual long-term complications.

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Data Availability Statement

Conflicts of interests: no conflict of interest

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