Cardiac complications of COVID-19 vaccination: now we know more

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The proliferation of good quality observational studies on the potential adverse effects of COVID-19 vaccination has greatly increased our knowledge on myocarditis and pericarditis, and also, more recently, on arterial hypertension. According to some recent studies, the incidence of a significant increase in blood pressure after COVID-19 vaccination is about 3.2% (95% CI: 1.62–6.21). The incidence of serious hypertensive emergencies or stage III hypertension has been reported as 0.6%. It is well known that the ‘spike protein’ of the Sars-CoV-2 virus, the synthesis of which is induced by vaccines, binds to ACE2 receptors, inducing their migration towards the inside of the cell. This would result in a lack of ACE2 activity on cell surfaces and therefore a relative deficiency of angiotensin1-7 with a relative excess of angiotensin II, which could explain, at least in part, the blood pressure increases. Regarding myo-pericarditis, there is evidence that the advantages of COVID-19 vaccination over non-vaccination remain preponderant in terms of prevented hospitalizations and serious complications of COVID-19, compared with the risk of developing myocarditis. In the age group most at risk of COVID-19 vaccine myocarditis (12–29 years), for every 100 000 vaccinated, compared to about four more cases of myocarditis we have 56 fewer hospitalizations, 13.8 admissions to intensive care and 0.6 fewer deaths. Several studies have shown that post vaccine myocarditis/pericarditis are generally short-lasting phenomena with favourable clinically course.

Introduction

According to data from the World Health Organization (https://covid19.who.int/), as of 20 May 2022 confirmed cases of COVID-19 were 522 million worldwide (of which over 17 million in Italy), associated with a total number of deaths of over 6 million (165 738 in Italy). Also worldwide, on the same date over 12 billion total doses of the vaccine were administered, of which over 136 million in Italy. In Italy, 48 million individuals have undergone a complete vaccination.

Currently, five different vaccines are authorized in Italy: (i) Pfizer-BioNtech ‘Comirnaty’; (ii) ‘Spikevax’ by Moderna; (iii) ‘Vaxzevria’ by AstraZeneca; (iv) ‘Janssen’ by Johnson & Johnson; (v) ‘Nuvaxovid’ by Novavax. Obviously, this is not the place to discuss the enormous benefits that COVID-19 vaccination is bringing to public health through the prevention of the most fearful complications of Sars-CoV-2 infection.

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From a cardiovascular standpoint, it is important to remember that in the summer of 2021, approximately six months after the authorization of the two mRNA vaccines by Pfizer and Moderna, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) reported cases of myocarditis and pericarditis as potential, albeit rare, side effects of vaccination (FDA: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-june-25-2021; EMA: https://www.ema.europa.eu/en/news/covid-19-vaccines-update-ongoing-evaluation-myocarditis-pericarditis).

Both regulatory bodies concluded that the advantages of vaccination remain paramount over the risk of myocarditis and pericarditis, a risk that should in any case be monitored. The Italian Society of Cardiology (SIC) recently published in the Italian Journal of Cardiology an ‘Expert Opinion’ on myocarditis and pericarditis associated with vaccination against COVID-19. Another possible undesirable effect recently associated with vaccination against COVID-19 seems to be the arterial hypertension, also reported so far as a relatively rare and probably transient effect.

COVID vaccination and arterial hypertension

In a Research Letter published in Hypertension, Meylan et al. described for the first time a series of nine patients, eight of whom with arterial hypertension well controlled by treatment, who were vaccinated with Pfizer (Comirnaty) or Moderna (Spikevax). In the hours or days after vaccination, blood pressure increased variably from individual to individual, up to levels of 220 mmHg for systolic, and up to 115 mmHg for diastolic. Subsequently, results were published for 287 subjects who underwent anti-COVID-19 vaccination, in whom blood pressure was measured between 15 minutes before and 15 minutes after vaccination. Vaccination was associated with an increase in blood pressure differential of more than 40 mmHg in 29% of subjects.

Obviously, these results do not exclude the possibility that the reported increase in blood pressure may be attributable to emotional factors related to vaccination. We then conducted a survey of healthcare workers vaccinated with Pfizer vaccine. These subjects monitored blood pressure at home before and after vaccination. We predefined an increase in systolic blood pressure of 10 mmHg or greater between 5 days prior to vaccination and 5 days following vaccination as clinically significant. Overall, we analysed 113 subjects with a mean age of 43 years (73% women) with a history of arterial hypertension in 18% of cases. A significant increase in systolic blood pressure was observed in six subjects (5.3%). In four subjects, it was necessary to modify the antihypertensive therapy upwards. Two subjects showed a similar increase in blood pressure values even after the second dose of vaccine. It is interesting to note that subjects who had a previous SARS-CoV-2 virus infection experienced a higher incidence of elevated blood pressure values (23% vs. 3%, \( P = 0.002 \)).

Interesting results are emerging, albeit with all the necessary precautions, from the analysis of large administrative databases. Karla Lehmann analysed EMA’s EudraVigilance database. As is known, this is a database that collects all reports, transmitted anonymously, of adverse events in association with anti-COVID vaccinations. It is therefore not a clinical trial. It is not possible to identify individual patients, and it is not possible to evaluate all the potential factors that could interfere with the association between vaccination and hypertension. An acute increase in blood pressure values (‘hypertensive crisis’) was however present in 6130 reports, equal to 2.9% of all Pfizer vaccine administrations, with as many as 29 deaths (0.47%) among the subjects for whom the hypertensive crisis was reported. Unfortunately, the blood pressure values measured before and after vaccination were not known, but it is believed that the reporting of ‘hypertensive crisis’ only concerned subjects with a real and considerable increase in blood pressure. This was followed by reports of ‘tachycardia’ (\( n = 5788 \) with 0.7% deaths) and arrhythmias (\( n = 1809 \) with 4.1% deaths). There were also 1719 cases of cardiac arrest following Pfizer vaccination (0.8% of all doses) and among these subjects death occurred in 92% of cases (1575 subjects).

Meta-analysis of observational studies

We recently completed a meta-analysis of observational studies, published in peer-reviewed journals by 22 February 2022 and without language limitations, which reported a clinically important increase in blood pressure as a potentially adverse event of the anti-COVID vaccine. Studies were selected through MEDLINE, Scopus, Web of Science, and CINHAL, using the keywords ‘SARS-CoV-2’, ‘COVID-19’, ‘2019-ncov’, ‘coronavirus’, ‘blood pressure’, ‘hypertension’, and ‘adverse events’. Six studies entered the final analysis, for a total of 357387 subjects and 13444 cases of increased blood pressure associated with vaccination. After the exclusion of the two ‘outliers’ studies in both directions, the incidence of a significant increase in blood pressure after vaccination was 3.2% (95% confidence interval: 1.62-6.21). The results are shown in Figure 1. In particular, the incidence of hypertensive emergencies or stage III hypertension was 0.6%. How to explain the hypothesis of increased blood pressure in association with anti-COVID vaccination? The data obtained so far should be read as ‘hypothesis generating’ and certainly not as ‘certainties’. The main points to clarify are the following:

1. We need studies conducted on large case series that include a standard measurement of blood pressure in the days immediately before and after vaccination.
2. We need to understand what the average duration of the pressure increase is. From several anecdotal data published so far, the duration of the pressure rise would seem limited to a few days, or a few weeks at most.
It should be understood what might be the most appropriate therapeutic approach in these patients. In theory, an angiotensin II blocking drug could represent a rational choice.

Possible basic mechanisms

Pathophysiology can help us understand the ‘vaccine hypertension’ phenomenon. As is known, the ACE2 receptors, located mainly in the lungs, vessels, intestines, heart, and testes, detach the amino acid phenylalanine from angiotensin II (composed of eight amino acids), thus giving rise to angiotensin 1-7, composed of seven amino acids (Figure 2).

Angiotensin1-7 exerts important effects completely opposite to those of angiotensin II, i.e. it induces vasodilation, inhibition of inflammation and inhibition of thrombosis. The structural and functional integrity of ACE2 receptors is therefore extremely important for vital functions. Now, it is known that the ‘spike protein’ of the Sars-CoV-2 virus, the synthesis of which is induced by vaccines, in addition to generating an immune response by the immune system, binds with the ACE2 receptors, inducing their migration (internalization) towards the interior of the cell (Figure 3). In fact, it is the same process that occurs in the course of Sars-Cov-2 infection, with the difference that only the ‘spike protein’ enters here, while in the course of infection the entire virion enters the cells, which then replicates and spreads to other cells. In any case, it follows a lack of ACE2 activity on cell surfaces, and therefore a relative deficiency of angiotensin1-7 with a relative excess of angiotensin II.

This excess of angiotensin II, unbalanced by angiotensin1-7, could be responsible, at least in part, not only for the blood pressure increases, but also for any thrombotic and inflammatory phenomena secondary to vaccination, as well as the infection itself with Sar-CoV-2.

Vaccination against COVID and myocarditis –pericarditis

As previously discussed, refer to the Expert Opinion of the SIC, by Sinagra et al., for many insights on this matter. The first reports that appeared in the literature on myocarditis/pericarditis as possible undesirable effects of the anti-COVID vaccination, had shown the rarity and substantial benignity of the phenomenon.

Patients generally present with chest pain, usually occurring a few days after inoculation of the second dose of mRNA vaccine, ST elevation, increased levels of serum troponin, protein C-reactive, and atrial natriuretic peptide. The ejection fraction is <50% in a very small fraction of patients. In those subjected to MRI, it is possible to find ‘late gadolinium enhancement’ and edema. We have very few data on myocardial biopsy, which usually shows some inflammatory infiltrate with T cells and macrophages, eosinophils, and rare plasma cells, but in several cases the biopsy was normal. Resolution is usually complete and spontaneous within a few days. Only in subjects with persistent symptoms are non-steroidal anti-inflammatory drugs, colchicine, and/or steroids indicated. Obviously, circulatory support

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\begin{array}{c|c|c|c|c|c}
\text{Study} & \text{Events} & \text{Total} & \text{Rate per 100} & \text{Estimate} & 95\%-\text{CI} \\
\hline
\text{Bouhanick et al.} & 1776 & 91761 & & 1.94 & [1.85; 2.03] \\
\text{Bouhanick et al.} & 5197 & 21909 & & 23.72 & [23.16; 24.29] \\
\text{Kaur et al.} & 283 & 30523 & & 0.93 & [0.82; 1.04] \\
\text{Lehmann et al.} & 6130 & 212053 & & 2.89 & [2.82; 2.96] \\
\text{Tran et al.} & 52 & 1028 & & 5.06 & [3.80; 6.58] \\
\text{Angeli et al.} & 6 & 113 & & 5.31 & [1.97; 11.20] \\
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\text{Overall} & 13444 & 357387 & & 3.91 & [1.25; 11.56] \\
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The vaccine is inoculated

The vaccine enter into the cell and induces the synthesis of ‘spike proteins’.

The ‘spike proteins’ produced for effect of vaccine migrate on the cell surface and induce the synthesis of antibodies.

The ‘spike proteins’ enters the circulation and bind to ACE₂ receptors. This causes internalization of ACE₂ receptors with consequent less degradation of angiotensin II into angiotensin₁₋₇.

The anti-spike antibodies produced by the immune system after vaccination are ready to efficiently bind the spike-protein of the Sars-Cov-2 virus in case of future infection.

**Figure 2** Role of ACE₂ receptors in the context of the renin-angiotensin system.

**Figure 3** Effect of ‘spike’ viral proteins, whose synthesis is induced by mRNA or DNA platform vaccines, on ACE₂ receptors.
measures are indicated in case of significant worsening of contractile function.

**Epidemiology**

Israeli colleagues have created an efficient system for monitoring the effects of COVID vaccination, notably the Comirnati (Pfizer) vaccine. About 884,000 vaccinated subjects (cases) were compared with about 884,000 unvaccinated subjects (controls) homogeneous by age, sex, socio-economic status, etc.). In addition, about 173,000 COVID positive subjects (cases) were compared with about 173,000 negative subjects (controls). All were followed up for about 21 days of follow-up both after the first and second dose of vaccine (total 42 days). The underlying question was the following: assuming that the anti-COVID vaccination is actually directly responsible for cases of myocarditis and pericarditis, how many more cases of myocarditis and pericarditis occur among vaccinated than unvaccinated subjects, as well as among COVID positive vs. COVID negative subjects? As seen in Figure 4, there were only three more cases of myocarditis (and one case of pericarditis) over 100,000 subjects among vaccinated versus non-vaccinated subjects. The overall incidence of myocarditis (awarded by cardiologists according to standard criteria) was 2.1 per 100,000 (4.2 in males; 0.2 in females). In particular, it was equal to 5.5 cases per 100,000 between the ages of 16 and 29 and 1.1 cases per 100,000 aged 30 and over. The maximum peak number of myocarditis cases was 10.7 cases per 100,000 among males aged 16–29 years. Among these 54 cases of myocarditis, only one patient presented cardiogenic shock and another patient, already suffering from pre-existing heart disease, died of unknown causes after discharge. An initial, reversible reduction in ejection fraction was noted in 29% of 54 patients.

Another analysis of Israeli data examined 54 cases of myocarditis out of 2.5 million subjects followed for 42 days overall. The overall incidence of myocarditis was 0.61/100,000/21 days among males aged 16–29 years. Overall, the incidence of myocarditis was higher after the second dose (0.61/100,000/21 days) compared with the first dose (0.51/100,000/21 days). Among these 54 cases of myocarditis, only one patient presented cardiogenic shock and another patient, already suffering from pre-existing heart disease, died of unknown causes after discharge. An initial, reversible reduction in ejection fraction was noted in 29% of 54 patients.

Other analyses by Israeli colleagues showed that myocarditis excess was concentrated essentially in the first 5–7 days after the second dose of vaccine, and in younger subjects. In particular, the highest incidence (between 7 and 15 cases out of 100,000) was found in males between the ages of 16 and 39.

Other studies performed in different parts of the world have substantially confirmed these data. The VAERS database (Vaccine Adverse Event Reporting System) should be mentioned, which collected, in the USA, reports on 354,100,845 total vaccinations in subjects aged >12 years of age vaccinated with Pfizer-BioNTech or mRNA-1273 Moderna. There were 1626 adjudicated cases...
of myocarditis (0.8 per 100,000) according to ‘Centre for Disease Control’ criteria. Under 20 years of age, the highest incidence of myocarditis per million doses seems to cluster between 16 and 17 years of age, then tending to decrease not only in older ages (>17 years), but even in younger (<16 years). Considering separately the different types of vaccine, the peak incidence of myocarditis cases occurred in the ages between 15 and 17 years for the Pfizer vaccine, and 18-23 years for the Modern vaccine. There are also important European studies. For example, 23,122,522 subjects vaccinated with Pfizer (BNT162b2), mRNA-1273 (Moderna), and AZD1222 (Astra-Zeneca) in Denmark, Sweden, Norway, and Finland were followed for 28 days of overall follow-up (after first and second dose). As many as 4,308,454 unvaccinated subjects represented the control group. There were 1,077 total cases of myocarditis. This study also confirmed a slight excess incidence of myocarditis among vaccinated vs. unvaccinated (4.7 excess events out of 100,000 vaccinations with Pfizer vaccine, and 9.28 excess events with Moderna vaccine). It is clear that this slight excess must be balanced against the enormous benefits of the vaccine in terms of preventing the serious complications of COVID.

In our ward, we admitted seven patients with myocarditis associated with COVID vaccination in the period between 1 July 2021 and 1 June 2022. There were six patients with an average age of 23 years, six males and one female. None of these patients required circulatory support measures.

Meta-analysis

A very recent meta-analysis published in Lancet Respiratory Medicine, which examined 22 studies for a total of 405,272,721 vaccine doses, showed three main findings:

1. The incidence of myocarditis/pericarditis tends to be lower with COVID vaccines compared to non-COVID vaccines (1.6 vs. 5.6 cases/100,000; P = n.s.).
2. A significantly higher incidence of myocarditis/pericarditis with mRNA vaccines than with non-mRNA vaccines (2.26 vs. 0.79 cases/100,000; P = 0.001).
3. A progressively higher incidence of myocarditis with decreasing age.

Conclusions

The benefits of vaccination over non-vaccination in terms of prevented hospitalizations and serious COVID-19 complications remain undisputable. In the age group, most at risk of vaccine myocarditis (12-29 years), for every 100,000 vaccinated, compared to about four more cases of myocarditis we have 56 fewer hospitalizations, 13.8 fewer admissions to intensive care and 0.6 fewer deaths. We must not forget to compare different groups of subjects (vaccinated against unvaccinated, COVID against non-COVID) before drawing conclusions on the possible association between COVID vaccination and myocarditis. The rate of myocarditis in non-COVID and unvaccinated subjects is not zero, but is approximately 0.33 cases per million per day (98 cases per 296,377,727 person-days), compared with 0.78 cases per million for day in vaccinated subjects (117 cases per 149,786,065 person-days). This equates to a 2.35-fold increase in the risk of myocarditis in association with vaccination (Rate Ratio 2.45 (1.10-5, 02)), but with a rate of myocarditis in the comparison group (unvaccinated) not equal to zero. According to the ‘Centre for Disease Control’, an excess of observed cases, compared with those predicted on the basis of the historical trend of myocarditis (unvaccinated subjects), is observed only up to the age of 29 in females, and 49 years in the male sex (https://cdc.gov/vaccines). To simplify the concept, it is not certain that the finding of a myocarditis in a subject affected by COVID, or that he has just been vaccinated, represents the sure demonstration that myocarditis is caused by COVID or vaccination. These figures bring to mind a famous cartoon of two British statisticians meeting: One asks the other: ‘How do you do?’ And the other replies without delay: ‘Compared to whom?’

Acknowledgements

Work supported, in part, by the Fondazione Umbra Cuore e Ipertensione-ONLUS, Perugia, Italy.

Conflict of interest: None declared.

References

1. Sinagra G, Porcari A, Merlo M et al. Update 2022 dell’Expert opinion della società Italiana di cardiologia su miocarditi, pericarditi e vaccini contro il COVID-19. G Ital Cardiol 2022; 23:1-6.
2. Angeli F, Reboldi G, Trapp M, Santilli G, Zappa M, Verdecchia P. Blood pressure increase following COVID-19 vaccination: a systematic overview and meta-analysis. J Cardiovasc Dev Dis 2022; 9:1-9.
3. Angeli F, Reboldi G, Trapp M, Verdecchia P. Ipertensione dopo vaccinazione anti-COVID. G Ital Cardiol 2021; 22:1-5.
4. Meylan S, Livio F, Foerster M et al. Stage III hypertension in patients after mRNA-based SARS-CoV-2 vaccination. Hypertension 2021; 77: e56-e57.
5. Sanidas E, Anastasiou T, Papadopoulo D, Vellion M, Mantzourani M. Short term blood pressure alterations in recently COVID-19 vaccinated patients. Eur J Intern Med 2022; 96: 115-116.
6. Zappa M, Verdecchia P, Spanevello A, Visco D, Angeli F. Blood pressure increase after Pfizer/BioNTech SARS-CoV-2 vaccine. J Expert Opin 2022; 19: 111-113.
7. Lehmann K. Suspected cardiovascular side effects of two Covid-19 vaccines. J Biol Today’s World 2021; 10:1-6.
8. Bozkurt B, Kamat I, Hotek PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation 2021; 144: 471-484.
9. Diaz GA, Parsons GT, Gerring SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA 2021; 326: 1210-1212.
10. Barda N, Dagan N, Ben-Shlomo Y et al. Safety of the BNT162B2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021; 385: 1078-1090.
11. Wittberg B, Barda N, Hoss S et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med 2021; 385: 2132-2139.
12. Mevorach D, Anis E, Cedar N et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 2021;385:2140-2149.

13. Oster ME, Shay DK, Su JR et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA* 2022;327:331-340.

14. Karlstad O, Hovi P, Husby A et al. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. *JAMA Cardiol* 2022;7:600-612.

15. Ling RR, Ramanathan K, Tan FL et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *Lancet Respir Med* 2022;10:679-688.

16. Writing C, Gluckman TJ, Bhave NM et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American college of cardiology solution set oversight committee. *J Am Coll Cardiol* 2022;79:1717-1756.