Review

Arrhythmias after Covid-19 vaccination: have we left all stones unturned?

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Abstract: SARS-CoV-2 vaccination offered the opportunity to get out of the pandemic and thereby worldwide health, social, and economic disasters. However, in addition to efficacy, safety is an important issue for any vaccine. The mRNA-based vaccine platform is considered to be safe but side effects are being reported more frequently as more and more people around the world become treated. Myo-pericarditis is the major, but not the only cardiovascular complication of this vaccine, hence it is important not to underestimate other side effects. We report a case series of patients affected by cardiac arrhythmias post mRNA vaccine from our clinical practice and the literature. Reviewing the official vigilance database emerged that heart rhythm disorders after Covid vaccination are not uncommon and deserve more clinical and scientific attention. Since Covid vaccine is the only vaccination to have been related to this side effect questions arose about whether these vaccines could affect heart conduction. Although the risk-benefit is clearly in favor of vaccination heart rhythm disorders are not a negligible issue and there are red flags in the literature about the risk of post-vaccination malignant arrhythmias in some predisposed patients. In light of these findings, we investigated the potential molecular pathways for the Covid vaccine to impact on cardiac electrophysiology and cause heart rhythm disorders.

Keywords: SARS-CoV-2 vaccine side effect; vaccines and Heart rhythm disorders; Spike Protein and cardiac arrhythmias; ACE system and heart conduction; Angiotensin II and cardiac arrhythmias

1. Introduction

SARS-CoV-2 vaccination has significantly reduced disease-related hospitalizations and mortality saving the healthcare and the economic system from an imminent crash. However, in addition to efficacy, safety is an important issue for any vaccine. Since all COVID-19 vaccines are new drugs, it is essential to monitor their adverse events post-approval. Some questions regarding the safety of COVID-19 vaccines have been raised due to sparse reports of severe systemic reactions after vaccination. The vaccines based on the mRNA vaccine platform are considered safer and are spreading all over the world, nonetheless side-effects are being reported. Myocarditis and pericarditis are the most commonly highlighted (1,2) but there is a side effect which in our view has not yet been thoroughly investigated, namely heart rhythm disorders. We detected post vaccine arrhythmias in several patients in our clinical practice and further investigated the issue. A review of case reports and clinical studies on the topic, and an analysis of the data from official vigilance databases of the mRNA vaccine was performed. We found that heart rhythm disorders are more common than myo-pericarditis, the "most famous" vaccine side effect, and deserve more clinical and scientific attention. Moreover,

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unlike myocarditis, none of the other vaccines were described in case reports or other publications to have this side effect.

Since less than 10% of the arrhythmias are symptomatic (3,4), epidemiological comparison of the incidence of heart rhythm disorders in patients pre and post Covid vaccination is not achievable from the available data, but the disturbance of heart rhythm is not a minor issue and, considering some red flags reported in the literature, it is very important to properly investigate the topic. In light of these findings, we hypothesize on the mechanism of the impact of the mRNA Covid vaccine on cardiac electrophysiology and heart rhythm disorders.

2. Data from the literature and vigilance databases

We experienced several patients complaining palpitations or worsening of palpitations and arrhythmic events after mRNA Covid vaccination in our clinical practice. The review of the literature for post vaccine heart rhythm disorders yielded several cases of heart rhythm disorders after mRNA covid vaccination (5-11) (Table 1). Interestingly the Covid vaccine was the only that was been found to be related to this side effect.

Actually, the analysis of the vigilance database showed that one of the most frequent symptoms described after SARS-CoV-2 vaccination are palpitations (11,12). Tachycardia or increased heart rate can be a physiological or stress-related response after vaccination, also called Immunization stress-related response (ISRR) (13,14). This component in a patient that has recently undergone a new vaccine administration might have played an important role and has to be taken into account, yet there are some important red flags related to vaccine-induced arrhythmias that we cannot overlook.

Table 1. Case reports regarding cardiac arrhythmias after Covid vaccination.

Authors	Title	Year	N. of cases	Centre/Nation	Type of vaccine	Type of arrhythmia
Aiba T et al. (5)	"Frequent Premature Ventricular Contraction and Non-Sustained Ventricular Tachycardia After the SARS-CoV-2 Vaccination in Patient with Implantable Cardioverter Defibrillator Due to Acquired Long-QT Syndrome"	June 2021	1	Japan	Pfizer-BioNTech	Premature ventricular contraction and non-sustained polymorphic ventricular tachycardia
Abrich and Olshansky (6)	"Torsades de pointes following vaccination for COVID-19"	June 2022	1	USA	Pfizer-BioNTech	Torsades de pointes-ventricular fibrillation
Beccarino et al. (7)	"Covid-19 vaccination associated right ventricular outflow tract ventricular tachycardia in a structurally normal heart"	March 2022	1	USA	Pfizer-BioNTech	Sustained unstable ventricular tachycardia
Slater et al.(8)	"VT storm in long QT resulting from COVID-19 vaccine allergy treated with epinephrine"	Nov 2021	1	Canada	Moderna	Ventricular tachycardia storm in long QT
M. Teresa Marco García et al. (9)	"Tachycardia as an undescribed adverse effect to the Comirnaty© vaccine (BNT162b2 Pfizer-BioNTech Covid-19 vaccine): Description of 3 cases	May 2022	3	Spain	Pfizer-BioNTech	Ventricular Tachycardia and extrasystoles in physicians

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	with a history of SARS-CoV-2 disease"					
Hoffer Etienne et al. (10)	"Transient but recurrent complete heart block in a patient after COVID-19 vaccination - A case report."	April 2022	1	Belgium	Pfizer-BioNTech	Transient but recurrent complete heart block
Kyung Hee Lim and Jong-Sung Park (31)	COVID-19 Vaccination-Induced Ventricular Fibrillation in an Afebrile Patient With Brugada Syndrome	April 2022	1	Korea	Pfizer-BioNTech	Ventricular fibrillation

In August 2021 Lehmann et al. focused on the anonymously reported adverse events of vaccinated healthy individuals in publicly available databases or reports as well as data retrieved from web reports of EudraVigilance of the European Medicines Agency (EMA) and the safety report from the German PEI" (9). Findings highlighted alarming cases of thrombotic/embolic events related to Vaxzevria (Astra Zeneca) but also some cardiac complication related to Comirnaty (Pfizer mRNA vaccine) where the cardiac arrhythmias ranked second after hypertensive crisis: "because of their frequency and importance, they should exert a signaling function and need to be better communicated" (15).

Patone M. et al. reported an increased risk of cardiac arrhythmia at 1–7 days following a second dose of mRNA-1273 (Moderna) (16). Norazida Ab Rahman et al. in an analysis of a population-based study covering over 20 million vaccinated individuals in Malaysia reported the risk of post vaccination hospitalization for predefined diagnoses among patient vaccinated with BNT162b2, CoronaVac, and ChAdOx1 vaccines. This self-controlled case-series study found a significant association between COVID-19 vaccination and cardiac arrhythmia, "although no study has found an association between arrhythmia and COVID-19 vaccines, our findings suggest that arrhythmia following vaccination in our population is an adverse event of special interest (AESI) of concern" (17). Chupong Ittiwut et al. highlighted that the presence of proarrhythmic genetic mutation increase the risk of life-threatening arrhythmias in post Covid vaccine patients. In particular SCN5A variants could be associated with sudden death within 7 days of COVID-19 vaccination, regardless of vaccine type, number of vaccine dose, and presence of underlying diseases or postvaccine fever. Because of these observations the authors exhorted to closely monitoring individuals who harbor variants in SCN5A, and possibly in other genes that predispose to cardiac arrhythmias or cardiomyopathies, for 7 days after the administration of COVID-19 vaccines, regardless of preexisting underlying diseases and the presence of vaccination-associated fever. (18).

These data add to other ambiguous red flags previously reported in the literature like the study from Sun CLF et al. that reported the trends of calls for sudden cardiac arrest (defined as electrical malfunction) increased in the vaccination period in the younger population (19), and from Maffetone et al. regarding the anomalous number of sudden death in athlete "post-COVID-19 and/or vaccination worldwide" with a 500% increase only in the FIFA member (20).

The analysis of the recent data of the UK Yellow Card Scheme until June 29, 2022, the mRNA Pfizer/BioNTech vaccine analysis print confirmed that palpitations (6174, 3,6%) is one on the most frequent reported adverse event, with a frequency comparable with rash (6745) (21). Furthermore, 3610 (2%) cases of rate and rhythm disorders were reported. Myocarditis, the "star" of the vaccine related complication, had 777 (0,45%) reports, and including pericarditis the number of reports went up to 1310 (0,77%), that is far lower in comparison to the heart rhythm disorder. Looking at the entire population Myocarditis was reported in 3 per 100000 patient and heart rhythm disorders in 14,4 per 100000 after pfizer vaccine (21). The trend from COVID-19 Moderna Vaccine Analysis Print is not much different (22). Ajmera KM et al analyzed the Vaccine Adverse Event Reporting System (VAERS) data in the USA and reported a suspect incidence of atrial fibirllation: more than 2000 AF post-COVID-19 vaccination (23). These data brought Ayeesha Kattubadi et al to investigate the topic and

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their pharmacovigilance analysis also confirmed the correlation between the Pfizer COVID vaccine and atrial fibrillation (24).

To ascertain the relationship between vaccination and arrhythmic events, Naruepat Sangpornsuk et al studied the occurrence of arrhythmia in patients with cardiac implantable electronic device before and after a SARS-CoV-2 vaccination and reported that the incidence of arrhythmia was significantly increased after the SARS-CoV-2 vaccination with a 73% increase in the incidence rate of sopraventricular arrhythmias and a 316% increase in the incidence ratio of ventricular arrhythmias (25).

Myocarditis is a described side effect of the vaccination and was also reported in the context of other vaccines, like influenca vaccine, but heart rhythm disorders were never associated with vaccination other than the Covid vaccine (26). Influenza vaccination represents an ideal control for the ongoing COVID-19 vaccination due to the fact that, on the one hand, seasonal influenza-viruses share with coronaviruses substantial similarities regarding symptomatology, infectivity, pathogenecity, letality, and transmission and, on the other hand, a large proportion of the adult populations in the EU and US is vaccinated against influenza every season. Therefore, Diego Montano estimated the absolute and relative risks of serious adverse reactions associated with the COVID-19 vaccines reports in comparison to influenza vaccines drawing on data from the VAERS and EudraVigilance databases (27). "The rationale behind the comparison of adverse reaction risks between COVID-19 and influenza vaccines allow to assess the potential risk profile of the new vaccines. Thus, COVID-19 vaccines and influenza vaccines were compared on the common metric of the probability of observing serious adverse reactions following vaccination". A higher risk of reporting serious adverse reactions was observed for the COVID-19 vaccines in comparison to the influenza vaccines from the European and United States pharmacovigilance systems and the cardiac arrhythmias were between the adverse reaction with the largest relative risk (RR 99% CI of 83.10 [43.59–158.41]) (27). Ao Shi et al in a recent meta-analysis explored the incidence of arrhythmia after COVID-19 vaccination and compared it with the incidence of arrhythmia after non–COVID-19 vaccination. The overall incidence of arrhythmia from 36 studies (1,528,459,662 vaccine doses) was 291.8 (95% CI 111.6-762.7) cases per million doses. The incidence of arrhythmia was significantly higher after COVID-19 vaccination (2263.4 cases per million doses) than after non–COVID-19 vaccination (9.9 cases per million doses). Compared with COVID-19 vaccines, the influenza, pertussis, human papillomavirus, and acellular pertussis vaccines were associated with a significantly lower incidence of arrhythmia. The incidence of tachyarrhythmia was significantly higher after COVID-19 vaccination (4367.5 cases per million doses) than after non–COVID-19 vaccination (25.8 cases per million doses). Arrhythmia was also more frequent after the third dose of COVID-19 vaccine (19,064.3 cases per million doses) than after the first dose (3450.9 cases per million doses) or second dose (2262.5 cases per million doses) (28).

A possible interference of COVID-19 vaccination on cardiac ion channel was suspected as a result of some clinical case report. There has been described mRNACovid vaccination unmasking type 1 Brugada ECG pattern not related to body temperature and concern that vaccination may induce life-threatening ventricular arrhythmias in patients with Brugada syndrome (29-30). Kyung Hee Lim et al described a case of 43-year-old man with no history of spontaneous type 1 Brugada ECG pattern, no history of faintness or syncope, or familial history of sudden cardiac death, presented with cardiac arrest 2 days after the second coronavirus disease 2019 (COVID-19) vaccination with an mRNA vaccine. Electrocardiograms showed ventricular fibrillation and type 1 Brugada pattern ST segment elevation. The patient reported having no symptoms, including febrile sensation. There were no known underlying cardiac diseases to explain such electrocardiographic abnormalities. ST segment elevation completely disappeared in two weeks. Although there were no genetic mutations or personal or family history typical of Brugada syndrome, flecainide administration induced type 1 Brugada pattern ST segment elevation. "This case suggests that COVID-19 vaccination may induce cardiac ion channel dysfunction and cause life threatening ventricular arrhythmias in specific patients with Brugada syndrome" (31). These observations are in line with the result from the study of Chupong Ittiwut et al, in which SCN5A, a variant associated with Brugada Syndrome, was related to a major risk of life-threatening arrhythmias.

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In a recent systematic review and metanalyses focused on the risks of cardiac arrhythmia associated with COVID-19 Vaccination, Mohammed H. Abutaleb et all highlighted that mRNA vaccines were associated with a higher risk of arrhythmia compared to vector-based vaccines, in the same study inactivated vaccines showed the lowest IR of arrhythmia (32). "Studies have reported that various cardiac arrhythmias complicate COVID-19 vaccination, although the incidence of cardiac arrest is low. Myocardial inflammation, cytokine storm, autonomic dysfunction, and ion channel dysfunction appear to be associated with the occurrence of COVID-19 vaccination-induced cardiac arrhythmias however, the exact pathophysiologic mechanisms responsible remain unknown" (33-34)

The question remains if the mRNA Covid vaccine has a pathophysiologic impact on heart electrophysiology that could explain an effect on heart rhythm.

3. The molecular pathway behind the heart electrophysiology alteration

The most relevant cardiovascular side effect of the vaccines is considered to be the myocarditis (35-36). Actually, vaccine induced myo-pericarditis are the major players of vaccine cardiovascular complications and also the heart rhythm disorder is considered a consequence of vaccine induced myocarditis by many experts (35-38). The myocardial inflammation causing heart rhythm disorders has solid and strong literature, however signs of inflammation were not detected in the cases reported and we want to highlight other molecular pathways that could be involved in the pathophysiology of the vaccine-induced cardiac arrhythmia.

The target of the Covid vaccine is the spike protein which is the protein interfering with the Angiotensin-converting enzyme 2 (ACE2) receptor representing the door of entry of the virus during the infection. ACE2 is not only a receptor, but also an important catalytic site and its activity represents a pillar for the balance of the Renin-Angiotensin system (RAS), one of the most important systems for cardiovascular homeostasis preservation. Indeed, the RAS depends on the tissue angiotensin system (ACEs) that is the product of a balance between Angiotensin II (AT II), derived by the enzymatic activity of ACE from Angiotensinogen, and Angiotensin 1/7 and 1/9, derived by the activity of ACE2 from AT II. AT II has pro-hypertensive, prothrombotic, pro-inflammatory and pro-fibrotic properties and Angiotensin 1-7 anti-hypertensive, anti-thrombotic anti-inflammatory and anti-fibrotic pathways. Thus, ACE2 has a fundamental role in local and systemic hemodynamics, lower blood pressure, promote vasodilation and has antioxidant and antiproliferative effects, promoting the production of Angiotensin 1-7 from AT II. ACE2 is highly expressed in the heart, more than other organs such as lungs or kidneys, and is secreted into the plasma (39-41). It was demonstrated that spike protein of SARS-CoV-2 competes with AT II for ACE2 in terms of internalization, and the binding blocks ACE2 activity and expression (41) favoring inflammation, thrombosis and endothelial damage due to AT II accumulation (42-44). The alteration of ACE is considered the pathophysiological key of the Covid related cardiovascular complication (42-46)

Vaccine induced spike protein has high affinity for ACE2 and can promote ACE2 internalization and degradation, bringing ACE imbalance like in Covid infection. This could explain some described "Covid like" side effect, an effect that Angeli et al. called "the spike effect" (47). But what is the role of ACE on heart electrophysiology?

ACE is also a strong regulator of heart conduction and has a big impact on heart electrophysiology. COVID-19 is an infectious disease characterized by pneumonia but complications affecting the cardiovascular system are the most serious and fatal (42). Myocarditis, thromboembolic events, hypertensive emergency but also arrhythmias are frequent (48) and are the second most common cardiac complications (49-51). Pathophysiology of arrhythmias involved inflammation and hypoxia, but also a direct interaction with the spike protein and cardiac conduction system in patients who died from arrhythmias was found. Immunohistochemical analysis detected the presence of the spike and nucleocapsid protein in the conduction system of a patient who died from heart rhythm disorders (52). Moreover, heart rhythm disorders have been reported in patients not presenting with severe inflammatory response (44,53).

Like in other cardiovascular complications, spike protein interfering with ACE2 and unbalancing ACE, might be the key in understanding the occurrence of SARS-COV-2 and vaccine related heart

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rhythm disorders (54,55). The cardiac conduction system has a high density of ACE receptors (56). The effect of AT II has been under investigation for a long time. Already in 1981 Kass and Blair demonstrated that nanomolar concentrations of AT II have marked effects on the electrical and mechanical activity of the Purkinje system (57).

Angio 2 induced changes in membrane current and increased the height and duration of the plateau phase of the action potential in isolated cardiac Purkinje fibers (57). Saito et al., demonstrated that there are Angio II binding sites highly localized in the conduction system of the heart, using autoradiography and computerized microdensitometry of tissue section of the rat heart, and that could influence the chronotropy (58). De Mello and coworkers described the role of Angio II in arrhythmogenesis. They identified the capacity of Angio II to reduce the refractoriness and the resting potential of the myocardium acting on specific Angio II receptors (59). Besides, they reported Angio II to reduce coupling at the gap junctions altering the junctional conductance and favoring electrical uncoupling (59,60).

This data supports the hypothesis that the peptide has deleterious effect on heart conduction favoring reentrant rhythms and abnormal automaticity (61). Reentry is the cause of the most lethal tachyarrhythmias and is caused by a decrease in conduction velocity and/or the reduction in refractory period (59). In a porcine model of myocardial infarction, AT II infusion reduced ventricular refractoriness favoring spontaneous ventricular arrhythmias (62). Different studies have also investigated in depth the molecular mechanisms underlying Ang II-related arrhythmias in ventricular myocytes (63,64). Zankov et al., demonstrated that Angio II can act on the delayed rectifier K current (IK), the major repolarizing outward currents of action potentials (65). Gunasegaram et al., described regulation of sarcolemmal Na (+)/H (+) exchanger activity by angiotensin II in adult rat ventricular myocytes and the opposing actions of AT1 and AT2 receptors in this contest (66). Wagner et al., showed that Ang II increase diastolic Ca leak from the sarcoplasmic reticulum, increase late Ca and sodium currents favoring Ca channel re-opening and early afterdepolarizations (67) demonstrating that Ang II is also important for cellular conductance and coupling. Finally, Sotoodehnia et al., described the association between genetic variation in ACE-related pathways with sudden cardiac death "that support the need for further investigation of ACE-related pathways in arrhythmogenesis" (68). This data confirmed that ACE system balance is crucial in the cardiac electrophysiology and conductance homeostasis, influencing all the steps of cardiac conduction from depolarization to cellular coupling and repolarization.

We described the strong impact of the ace system on cardiac conduction, but there are some points that has to be clarified. If the pathophysiology is Angio 2 related, why vaccine related side effects are not especially affecting patient with baseline deficiency of ACE2 receptor activity (advanced age, cardiovascular risk factors, and previous cardiovascular events) like in SARS-COV-2 infection does? Indeed, younger patients seems to be more involved. 2) Why vector-based vaccines and mRNA-based vaccines share the same target protein but present different complication? And 3) how can we explain long standing arrhythmias and/or tardive arrhythmias? In particular the arrhythmias tend to be worst after the II or III dose

Angeli et al., highlighted that ACE2 are not the exclusive angiotensinases in nature. Other angiotensinases involved in the processing of Ang II to Ang1,7 may exert a counterbalance influence in the detrimental interactions between Spike proteins and ACE2 receptors. Specifically, the AngioII-Angio1,7 axis of the RAS encompasses three enzymes (carboxypeptidases) that form Angio1,7 directly from (by cleavage) Angio II: ACE2, prolyl carboxypeptidases (PRCP), and prolyl oligopeptidase (POP). PRCP has protective effects cleaves the C-terminal amino acid of Ang II to form Ang1,7, but increased catalytic activity of POP and PRCP is not typical in the young, but more pronounced in elderly individuals with comorbidities or previous cardiovascular events (69). Thus, the adverse reactions to COVID-19 vaccination associated with Angio II accumulation in younger subject could be related to this aspect. Important to remark that activity of these two carboxypeptidases and neprilysin pathway (other pathway described) remains substantially unchanged during the acute phase of COVID-19 infection so plasma concentration of Angio 1-7 remains stable in COVID-19 patients and it appears to be insufficient to prevent the harmful effects of Ang II. This could explain the

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increased risk of severe COVID-19 among patients with specific phenotypes of ACE2 deficiency and could explain the paradox of the vaccine-protective/Covid-unprotective effect (69,70)

Adenovirus-vector and mRNA vaccines promote substantially different innate responses that will certainly influence the nature of characteristics of immune responses and possible adverse reactions Oxford-AstraZeneca vaccine might induce higher levels of specific T cells, whereas mRNA vaccines might induce higher antibody titers (71,72).

One way to explain the long-term side effect of the covid disease but also the Covid vaccine is through the lens of antibiotype immune response. Every antibody that is induced and specific for an antigen (termed "Ab1" antibody) has immunogenic regions capable of inducing specific antibodies against Ab1 antibodies (Ab2 antibody). These Ab2 antibodies that are specific for Ab1 can structurally resemble that of the original antigens themselves (73). As a result of this mimicry, Ab2 antibodies also have the potential to bind the same receptor that the original antigen was targeting, mediate profound effects on the cell that could result in pathologic changes, particularly in the long term. Ab2 alone can even mimic the deleterious effects of the virus particle itself (74). Myocarditis after vaccine administration bears striking similarities to the myocarditis associated with Ab2 antibodies induced after some viral infections (75), anti-bodies could also mediate long standing cardiovascular effects and heart rhythm disorders of SARS-CoV-2 infection or vaccines, given the expression of ACE2 in the heart (73, 76-78). It was demonstrated the presence of antibodies specific for ACE2 in patients with COVID or history of infection and was hypnotized to result from anti-idiotypic antibodies to the spike protein (77). Autoantibodies against ACE2 increase the severity of COVID-19, lowering the activity of soluble ACE2 in plasma also after the infection and bad outcome and was speculated the potential implication of autoantibodies against ACE2 also in post vaccination complications (77,78).

Donoghue et al., showed that also ACE2 overexpression could cause conduction disturbances and lethal ventricular arrhythmias due to a connexin dysregulation, gap junction remodeling and profound electrophysiologic disturbances (79). So ACE2 protection works in a contest of balance where also an overactivity of ACE2 could be unfavorable (80-81). Gitelman's and Bartter's syndromes (GS/BS) are rare genetic tubulopathies that have endogenously increased levels of ACE2 and was demonstrated that these diseases are characterized by microvascular disfunction and in particular by increased risk of cardiac arrhythmias that could not only be justified by the electrolyte's alteration (82-83). These syndromes are good opportunity to investigate the pathophysiology of covid complication. Interestingly Caló et al., demonstrated these genetic disorders to be protective in covid infection and complication, confirming the protective role of ACE 2 in Covid and the ambiguous role in pathophysiology of the arrhythmias (84).

In conclusion spike protein, whether from Covid or from vaccine, binding with high affinity ACE2, could potentially bring an ACEs unbalance, that is the player of covid and vaccine complication. Heart rhythm conduction is very affected by ACEs and its alteration could provoke heart rhythm disorders. Cardiac arrhythmias are not so minor issue and has to be properly investigate. Our patients were treated with metoprolol, not only because its demonstrated efficacies on arrhythmias but also because its effect on the Angio II (85,86). Actually, the treatment was very effective.

The spike protein - whether from Covid or from vaccine – could represent the key for understand the molecular pathway of the heart conduction abnormality. Binding with high affinity to ACE2, could potentially result in ACE imbalance promoting cardiac complication (87,88). Heart rhythm conduction is highly affected by ACEs and its alteration may promote heart rhythm disorders. Cardiac arrhythmias have a high mortality and morbidity and need to be investigated further. Metoprolol has beneficial effect on the AT II pathway (89,90) and the treatment with this drug was very effective.

4. Discussion

SARS-CoV-2 vaccination offered the opportunity to come out of the global pandemic and prevent a worldwide health, social, and economic crash. However, in addition to efficacy, safety is an important issue for any vaccine. The mRNA-based vaccine platform is considered safe but side-effects are being reported more frequently with increasing numbers of vaccinations and booster shots.

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Myopericarditis is the major cardiovascular complication of this vaccination, however, there are other important side effects such as heart rhythm disorders that must not be underestimated. We report the presence of cardiac arrhythmias post mRNA vaccine in several patients with structurally normal hearts in the absence of any other organic reason for the arrhythmia. Data from the literature supports our finding that heart rhythm disorders after Covid vaccination are common and should receive closer attention. Since Covid vaccine is the only vaccination to have been related to this side effect the question remains whether these vaccines have a pathophysiologic impact on heart electrophysiology. We speculate that the molecular mechanism for the Covid vaccine to alter the heart conduction via the production of spike protein with high ACE2 affinity resulting in an imbalance of the ACE system.

Since cardiac arrhythmias have high morbidity and mortality and taking in consideration the red flags in the literature describing the risk of malignant arrhythmias in patients with genetic arrhythmic predisposition (18), the topic has to be further investigated (72).

Finally, it is important to note that for Covid-19 the risk benefit and despite our findings is clearly in favor of the vaccination. However, we should consider thorough risk-benefit assessment in specific populations.

5. Conclusion

We experienced several patients complaining palpitations or worsening of palpitations after mRNA Covid vaccination in our clinical practice. Concordantly, data from the vigilance database and literature report cases of heart rhythm disorders in the post-mRNA vaccination period and malignant arrhythmias in predisposed patients, suggesting a potential impact on the cardiac conduction system. Otherwise, we have not encountered heart rhythm disorders after administration of other vaccines, and found no hints for arrhythmias in the vigilance databases.

We investigated the molecular pathways through new mRNA vaccines may potentially provoke electric disturbances, specifically their effects on the ACE system. These observations rise concerns regarding the central role of the ACE system on heart conduction homeostasis and remark the detrimental impact that an iatrogenic interference with this system could have in this contest.

Although the risk benefit of the Covid vaccine is clearly in favor of the vaccination, cardiac arrhythmias can result in serious health conditions and should not be underestimated.

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