Annals of Clinical Case Reports

Review Article
Published: 25 Mar, 2022

Some Events Linked to SARS-CoV-2 Vaccines Resemble Rare Complications of COVID-19: Are These Events Caused by Spike Protein Binding to ACE2 in Downstream Tissues with Preexisting Dependence on Balanced RAS Actions?

Sven Kurbel*

Josip Juraj Strossmayer University of Osijek , Croatia

Abstract

It seems that the four authorized SARS-CoV-2 vaccines can induce symptoms that resemble some common COVID-19 symptoms; this article is looking whether exceptionally rare events after SARS-CoV-2 vaccines resemble rare COVID-19 complications.

In searching for evidence in favor of this interpretation, COVID-19 vaccine safety updates by European Medicines Agency were used. It turned out that most recognized vaccine-related events can be linked to regulation of local tissue perfusion (myocarditis/pericarditis, capillary-leak syndrome) or coagulation. Similar rare complications were observed during COVID-19.

The matching between rare disease complications and extremely rare vaccine linked events supports the notion that in very few persons, vaccination can resemble COVID-19 complications. An interpretation is proposed that due to preexistent circulatory dependence on balanced RAS actions in some persons, vaccination can lead to ACE2 dysfunctions downstream from areas of spike protein synthesis.

Lungs and the heart muscle are mostly exposed to this scenario due to their central position in circulation that allows them to act as one self-regulatory unit. Different tropisms of used viral vectors and the variable fate of lipid nanoparticles in the four authorized vaccines can possibly explain differences in rare vaccine-related events.

Keywords: COVID-19 complications; SARS-CoV-2 vaccines; vaccine related events; ACE2

OPEN ACCESS

Correspondence:
Sven Kurbel, Josip Juraj Strossmayer University of Osijek, Medical Faculty, J Huttlera 4, Osijek 31000, Croatia, Tel: +385-31512820; Fax: +385-31512833, E-mail: sven@jware.hr

Received Date: *24 Feb 2022*
Accepted Date: *11 Mar 2022*
Published Date: *25 Mar 2022*

Citation:
Kurbel S. Some Events Linked to SARS-CoV-2 Vaccines Resemble Rare Complications of COVID-19: Are These Events Caused by Spike Protein Binding to ACE2 in Downstream Tissues with Preexisting Dependence on Balanced RAS Actions?. Ann Clin Case Rep. 2022; 7: 2150.

ISSN: 2474-1655

Abbreviations

ACE: Angiotensin-I-Converting Enzyme; ACE2: Angiotensin-I-Converting Enzyme 2; Ang I: Angiotensin I; Ang II: Angiotensin II; Ang (1-7): Angiotensin (1-7); Ang (1-9): Angiotensin (1-9); AT1R: Angiotensin II Receptor, Type 1; ET-1: Endothelin-1: RAS: Renin-Angiotensin Systems; TVs: Thebesian Veins

Introduction

Rare and peculiar adverse events possibly related to the COVID-19 vaccination are of great public and scientific attention. This paper is inspired by the author's personal experience: About 24 h after receiving the first dose of VAXZEVRIA AstraZeneca vaccine, the author noticed an unusually high sensitivity to spicy foods that lasted more than six hours and disappeared the next morning. After the second dose of the same vaccine, no changes of taste were noticeable.

Similar peculiar oral symptoms were reported in 19 out of 877 healthcare workers in the Czech Republic, after receiving COMIRNATY Biontech vaccines [1]. Ten participants noticed burning gingiva, tongue tingling reported in five and taste disturbance in four of them.

Based on these data and on the described author's experience, it seems possible that taste alterations after COVID-19 vaccination rely on these premises:

- Altered taste sensations are among common symptoms of COVID-19 infection.

- The cited article [1] reports taste alteration following the mRNA vaccination.

- Similar symptoms have been experienced by the author after a viral vector vaccine.

A possible conclusion is that the rates of oral symptoms after the COVID-19 vaccination are not dependent on the vaccine modality (viral vector or mRNA) or on the certain product by a certain manufacturer. Instead of that, oral symptoms after the COVID-19 vaccination seem partially to resemble oral symptoms of the COVID-19 infection, possibly by the same mechanism as the disease itself.

Besides that, in a review of local and systemic adverse effects reported following three SARS-CoV-2 COVID-19 vaccines (COMIRNATY Biontech, SPIKEVAX Moderna, and COVID-19 Vaccine Janssen), most of them were of mild-to-moderate severity, lasting up to 2 to 3 days. Myalgia was reported in 25.25, 40.35 and 37.5% of participants, respectively, while headaches ranged from 39.5% to 45.65% and fatigue from 46.5% to 51.25% [2]. These symptoms, particularly myalgia, are among the most common symptoms reported by patients suffering from COVID-19.

Is there a link between exceptionally rare events after SARS-CoV-2 vaccines and rare complications of COVID-19?

If we extrapolate the described analogy, suggesting that SARS-CoV-2 vaccination quite commonly induce symptoms that resemble some common COVID-19 symptoms, the open question is whether exceptionally rare events after SARS-CoV-2 vaccines show some resemblance to already recognized rare COVID-19 complications.

This would mean that rare vaccine related events that resemble some COVID-19 complications might use the mechanism of the disease to develop. Important evidence in this direction might be the fact that the simian vector ChAdOx1 is used in VAXZEVRIA AstraZeneca against SARS-CoV-2 and in the ChAd3-EBO-Z vaccine against Ebola virus. The former vaccine is linked to thrombocytopenia. When the latter vaccine was administered to 1,509 adults, no thrombocytopenia was registered [3,4], suggesting that low platelets after VAXZEVRIA AstraZeneca might be related to COVID-19, instead of the viral vector. Likewise, the occurrence of cerebral venous sinus thrombosis is among reported rare complications of COVID-19 [5], but also reported as rare events after two SARS-CoV-2 vaccines that use different viral vectors (VAXZEVRIA AstraZeneca and COVID-19 Vaccine Janssen) [6-8]. When trying to incorporate ACE2 and its products within the Renin-Angiotensin System (RAS) [9], it was pointed out that all mediators in the arterial blood can act only downstream from the point of entry, so we can expect that local perfusion regulators need to enter, or to be produced upstream from the respective arterioles, somewhere in small arteries that distribute blood toward precapillary arterioles. This principle is used here to define relations between lungs and the heart muscle.

The proposed interpretation requires that the vaccine-induced synthesis of spike proteins interact with tissue cells abundant in ACE2 molecules in downstream tissues. Only in very rare individuals, the ACE2 dysfunction can manifest itself through events that resemble rare complications of the disease. It is here proposed that several age-related comorbidities might increase the odds of these events:

- Increased aortic stiffness is associated with major cardiovascular diseases, including heart disease, stroke, and kidney disease, all possibly related to large artery stiffness and increased pressure pulsatility, causing diffuse microscopic tissue damage leading to remodeling of vasculature and impaired regulation of local blood flow [10].

- Impaired microcirculation is of increased dependence on local and regional RAS actions, making older people more susceptible to setting of altered RAS function. The odds for this occurrence are very slim since beside protracted synthesis of spike proteins, preexisting remodeling of regional circulation and high dependence on RAS actions are required. In all other settings rare vaccine related events will not occur.

In search of resemblance between rare COVID-19 complications and exceptionally rare vaccine-related events

When trying to set outlines of this article, few features were here proposed as provisional criteria for identifying events possibly caused by an overexposure to spike protein:

- The event has to resemble some recognized COVID-19 rare complications, OR

- Be attributable to selective tissue exposure, downstream from the place of the spike protein synthesis, OR

- Highly similar events should be reported as linked to more than one vaccine, preferably to vaccines of different types of action.

In searching for evidence in favor of this interpretation, COVID-19 vaccine safety updates for the four EU-authorized vaccines were used as the reference source. They are published by European Medicines Agency (EMA) at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised. Data from safety updates by EMA are summarized in Table 1.

Most recognized vaccine-related events can be linked to regulation of local tissue perfusion (myocarditis/pericarditis, capillary-leak syndrome) or coagulation. All four vaccines seem to share increased chances of myocarditis/pericarditis, although, no clear links are found and only very low apparent risks are expected. Other vaccine-related events in EMA files are mainly linked to the VAXZEVRIA AstraZeneca. Some of them accepted as an extremely rare vaccine-related event, while the rest of them are lacking sufficient evidence that their occurrence was related to this type of vaccine.

The important thing is that the last column in Table 1, lists reports of similar rarely observed complications of COVID-19, clearly suggesting that the specter of rare vaccine related events and the specter of rare disease complications overlap. The matching between rare disease complications and extremely rare vaccine linked events supports the notion that in very few persons, vaccination can resemble COVID-19 complications.

A hypothesis

Can individual preexistent circulatory dependence on balanced RAS actions lead to ACE2 dysfunctions downstream from areas of spike protein synthesis?

Lungs and myocardium as a self-regulated circulatory unit: The peculiar myocardial venous circulation includes Coronary Sinus (CS) that drains venous blood to the right atrium, and Thebesian

Table 1: Rare events linked to SARS-CoV-2 vaccines using mRNA or viral vectors resemble some rare complications of COVID-19 (based on: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised).

Adverse events in EMA safety updates on registered COVID-19 vaccines	Vaccine type and mechanism	EMA safety updates		Apparent risks (event/dose)	Details	Possible analogous complications of COVID-19 infection (refs.)
		Number of events	Number of vaccine doses			
Myocarditis and pericarditis possibly linked to vaccination	COMIRNATY Biontech mRNA	283	177e6	**1.60e-06**	145 cases of myocarditis and 138 cases of pericarditis	[25,26]
	SPIKEVAX Moderna mRNA	38	20e6	**1.90e-06**	19 cases of myocarditis and 19 cases of pericarditis from the EU/EEA,	
	COVID-19 Vaccine Janssen Viral vector HAdV-D type 26	1	2e6	**5.00e-07**	one case of pericarditis, new data needed	
	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	85	40e6	**2.13e-06**	38 cases of myocarditis and 47 cases of pericarditis	
Capillary leak syndrome	COVID-19 Vaccine Janssen Viral vector HAdV-D type 26	3	18e6	**1.67e-07**	to be added in the product information	[27,28]
	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	14	78e6	**1.79e-07**	possibly linked to vaccination	
Immune thrombocytopenia	SPIKEVAX Moderna mRNA	9	20e6	**4.50e-07**	a causal relationship could not be excluded	[29,30]
	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	not reported			new data needed	
Thrombosis with thrombocytopenia syndrome (TTS)	COVID-19 Vaccine Janssen Viral vector HAdV-D type 26	21	7e6	**3.00e-06**	keeping TTS under close monitoring	[31,32]
	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	479	51.4e6	**9.32e-06**	the product information lists the very rare risk of TTS	
Guillain-Barré syndrome	COVID-19 Vaccine Janssen Viral vector HAdV-D type 26	15	7e5	**2.14e-05**	not necessarily related to or caused by vaccination	[33,34]
	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	227	51.4e6	**4.42e-06**	to be added in the product information	
Acute disseminated encephalomyelitis (ADEM) and encephalitis	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	43	40e6	**1.08e-06**	Ten cases of ADEM and 33 cases of encephalitis, not necessarily related to or caused by vaccination	[35,36]
Acute macular neuroretinopathy	VAXZEVRIA AstraZeneca Viral vector ChAdOx1	not reported			new data needed	[37,38]

Veins (TVs) that open in all four heart cavities [11,12], particularly common at the ventricle apex and at papillary muscles base [13]. It was observed that the blood flow through TVs depends on the heart muscle stretching.

This means that pulmonary capillaries are in the upstream serial position to the myocardial capillaries, so mediators from lungs can directly influence myocardial cells after entering the coronary circulation. On the other hand, myocardial veins to the right heart (mainly CS and the right heart TVs) place myocardial capillaries in the upstream serial position to the pulmonary capillaries. Any mediator from the myocardial venous blood, drained through the right heart, will initially affect lungs before being diluted in the systemic circulation.

Both lungs and myocardium are rich in various receptors, so plasma that passes through lungs and myocardium is cleared from many mediators by their binding to receptors:

- Surplus of myocardial mediators leaves the heart muscle through the left-side Thebesian veins and enters the systemic circulation. Some mediators leak from the myocardium to the right heart through CS and the right heart TVs. In the latter case, the right heart veins act as a shortcut from myocardium to pulmonary circulation.
- On the other hand, substances synthesized in lungs enter the left heart and aorta. Some of them can directly affect the myocardium *via* coronary arteries, and their surplus can return to the lungs *via* CS and the right heart TVs. Other, better-known examples of portal circulations in our body are unidirectional, since the tissue of the secondary capillaries (adenohypophysis or liver) has no way of endocrine action directed selectively on the primary organ (hypothalamus or intestines, respectively).

In comparison to other portal systems, cardiopulmonary circulation can be described as a bidirectionally regulated setting in which myocardial and pulmonary capillaries are connected by short endocrine loops of quickly recirculating blood between lungs and

Table 2: Proposed sequence of events following vaccination in individuals whose tissue perfusion is highly dependent on RAS actions? For details and references, see text.

Rare vaccine related events	Vaccine types; viral vectors binding: CAR: epithelial, cardiomyocytes, lymphatic endothelial Sialic acid: many cells lipid nanoparticles: lungs? spleen?	Proposed sequence of events following vaccination in individuals whose tissue perfusion is highly dependent on RAS actions			
		Possible places of spike protein synthesis	Downstream tissues of compromised ACE2 function	Tissue exposed to high Ang II and low Ang(1-7)	Protection of remote peripheral tissues
Myocarditis and pericarditis	viral vector	brachial lymphatics and lymph nodes, pulmonary epithelial cells, cardiomyocytes	myocardial vasculature >> sinus coronarius & right side Thebesian veins >> pulmonary vasculature	pulmonary and myocardial arterioles constrict due to dominant Ang II	soluble ACE & ACE2, secreted by unaffected tissues, degrade Ang I and Ang II to Ang (1-7)
	mRNA		distributive arterial vessels of peripheral tissues	peripheral tissue with RAS dependent perfusion patterns leading to ischemic pain or altered capillary fluid exchange due to dominant Ang II	
Muscle pain	viral vector				
	mRNA				
Capillary leak syndrome	viral vector				
Thrombosis with Thrombocytopenia Syndrome (TTS)	viral vector			At II dominance is procoagulant, particularly in stagnant venous blood	
	mRNA				

the heart muscle. This speed of communication between lungs and the heart muscle puts the heart muscle in a privileged position of regulating the pulmonary circulation. All other peripheral organs are under the control of pulmonary mediators, but they are much slower in returning the blood to the right heart. This makes their mediators susceptible to degradation by various enzymes in the venous blood that protect the lungs from their influence.

The physiological role of ACE2 and Ang (1-7) in perfusion regulation: ACE2 is important in the regulation of cardiovascular function, with ACE2 immunocytochemically detected in myocytes in human heart, in the endothelium of cardiac capillaries, venules, arteries, and arterioles and in vascular smooth muscle cells and adventitia of larger coronary vessels [14,15].

Soluble ACE and ACE2 are able to turn Ang I, Ang II and Ang (1-9) to vasodilatory Ang (1-7), thus preventing excess Ang II to accumulate in blood. The efficacy is probably lower in hyperkinetic circulation, thus allowing residual Ang II in the venous blood to increase pulmonary resistance and limit the left heart preload. In normal conditions, the lungs are better protected by soluble ACE & ACE2 in peripheral venous blood; the resultant Ang (1-7) maintains low pressure and resistance in pulmonary vessels.

Regulation of ACE2 expression in heart myocytes seems complex (based on b01):

- In cardiac myocytes ACE2 was significantly downregulated by Ang II, *via* activated AT1 receptors.
- Myocytes exposed to ET-1 also showed a significant reduction in ACE2.
- Treatment of myocytes with Ang II reduced ACE2, while the presence of Ang (1-7) completely blocked the downregulation of ACE2 by Ang II.

Conclusion: In the heart, the balance between ACE & ACE2 requires sufficient supply of Ang (1-7) *via* coronary vessels, suggesting that any ACE2 dysfunction in lungs can put Ang (1-7) levels below the protective threshold and suppress the ACE2 expression.

The obvious question is what might be the survival advantage of the fact that Ang II and ET-1 exposures (two main systemic vasoconstrictors) suppress ACE2 expression in cardiac myocytes, thus increasing the overall arteriolar constriction by prolonging the presence of Ang II in circulation.

If we look at this regulation of cardiac ACE2 expression in more details, it is not a stable loop aiming to the balanced RAS activity. Instead of that, high Ang II diminishes expression of the enzyme that turns it to its opposite, the Ang (1-7), thus moving toward vasoconstriction. On the other hand, this can be stopped if enough Ang (1-7) is present, although it is the product of the expressed ACE2.

Taken together, it seems that the extremes (high Ang II, low ACE2 or high Ang (1-7) and high ACE2) are much more likely than the balanced situation of normal Ang II presence and normal ACE2 activity that turns some incoming Ang II to Ang (1-7).

This type of cardiac tissue perfusion regulation seems analogous to a flip-flop electronic circuit, a bistable multivibrator that has two stable states. The regular position with sufficient incoming Ang (1-7) and ACE2 expression might be suitable for a setting of undisturbed myocardial homeostasis, while the vasoconstrictive position can help in surviving enduring hypovolemia of any causes, due to prevailing incoming Ang II and low ACE2 expression. Switching from the regular to the vasoconstrictive state is possibly triggered upstream from the heart, by the renin secretion from kidneys. Additional Ang I is produced and this surplus of raw material for pulmonary ACE will increase the myocardial Ang II exposure. Pulmonary ACE2 also produce Ang (1-9) from the additional Ang I and Ang (1-7) from the incoming Ang II. These mediators enter coronary circulation and affect arterioles. Vasoconstriction will gradually increase as regional exposure to Ang (1-7) drops below the threshold and the ACE2 expression is reduced.

In short, the survival pressure favors this bistable regulatory mechanism of myocardial perfusion because it seems well suited to normal conditions and enduring hypovolemia.

Besides that, the survival advantage might lie in the fact that the vasoconstrictive RAS action includes stimulation of aldosterone secretion via Ang II and the AT1R receptors. Aldosterone prevents hypovolemia by urine secretion of K+ instead of Na+ ions, thus allowing some cellular fluid to become extracellular fluid, as the water is distributed by osmosis while the potassium pool decreases due to aldosterone induced kaliuria. For this regulatory mechanism, prolonging activity of Ang II molecules by diminishing the local ACE2 expression is important.

As already mentioned [10], ageing affects microvasculature and remodeling can make the ageing vasculature highly dependent on regional and local RAS action. If an individual with remodeled cardiac muscle perfusion is faced with a condition that compromises the cardiac ACE2 function (like COVID-19, or exposure to spike proteins after vaccination), decreased production of Ang (1-7) can lead to irregular myocardial perfusion, with spots of hypoxia and edema. Besides that, in this setting, sinus coronarius and the right side Thebesian veins would return much more Ang II than Ang (1-7) to the pulmonary arterial tree. The result might be chronic cardiopulmonary vasoconstriction and irregular perfusion patterns in both organs.

Unique features of vaccines that deliver genetic information for the antigen synthesis

For the purposes of this text, all vaccines could be roughly divided into two groups: conventional vaccines with a defined amount of the antigen and vaccines with the introduction of genetic information that produces the antigen in the cells of the vaccinated person in the expected intensity and duration (compiled from various sources):

- Vaccines with a defined antigen load:
- Subunit vaccines contain virus fragments, incapable of causing disease:
- This approach is used in the Hepatitis B vaccine and Pertussis vaccine.
- ZF2001 COVID-19 vaccine (by the Anhui Zhifei Longcom & the Institute of Microbiology, Chinese Academy of Sciences) uses dimers of receptor-binding domains
- The VECTOR Center of Virology EpiVacCorona vaccine uses three spike protein peptides with a chimeric protein
- Some vaccines contain inactivated virulent microorganisms destroyed with chemicals, heat, or radiation: IPV (polio vaccine), hepatitis A vaccine, rabies vaccine, most influenza vaccines, some COVID-19 vaccines:
- Sinovac COVID-19 vaccine (PiCoVacc)
- Sinopharm COVID-19 vaccine (BBIBP-CorV)
- Genetic information vaccines producing an antigen load of expected intensity and duration.
- Both viral vector and mRNA SARS-CoV-2 vaccines inject genetic information needed for the spike protein synthesis in normal cells, regardless of their ACE2 expression.
- The viral vector modality was introduced against Ebola. Viral vector SARS-CoV-2 vaccines:
- Adenoviral tropism defines cells in which DNA genetic material is delivered, DNA is transcripted into mRNA used by ribosomes for the protein assembly:
- VAXZEVRIA AstraZeneca, modified simian adenovirus ChAdOx1
- The Sputnik V (Gam-COVID-Vac), human adenoviruses 26 and 5
- COVID-19 Vaccine Janssen, human adenovirus 26
- The CanSino Biologics vaccine (AD5-nCOV), human adenovirus 5
- Both mRNA SARS-CoV2 vaccines contain nucleoside-modified mRNA of the spike protein closed in lipid nanoparticles that enter cells able to engulf these particles, mRNA is used by cytoplasmic ribosomes without need of transcription in the nucleus:
- COMIRNATY Biontech (tozinameran)
- SPIKEVAX Moderna (elasomeran)

It seems that inactivated and subunit SARS-CoV-2 vaccines are less effective than genetic information vaccines, possibly excepting ZF2001 with a reported result of 92% to 97% of seroconversion after three doses during two months [16].

A possible explanation is in the choice of the antigen. S-protein or its parts are antigens in all authorized vaccines. Synthesized spike proteins bind ACE2 molecules present in various tissues and to soluble ACE2 molecules in the blood. Removal of spike protein from circulation by binding to available ACE2 molecules reduces its presence in blood, lymph, interstitial fluid, and is therefore less presented to the immune system.

Viral vector and mRNA vaccines do not limit the antigen quantity or duration of presence in the body. They ensure the synthesis and secretion of this antigen into extracellular fluids, until the degradation and inactivation of the introduced mRNA and DNA information happen.

There are a couple of new moments with viral vector and mRNA vaccines:

- The existence of tropism of the viral vector that defines the type of cell into which the viral vector will introduce viral DNA with the antigen gene:
- The Coxsackie and Adenovirus Receptor (CAR) [17] is the place of entry for simian adenovirus ChAdOx1 and human HAdV-C type 5
- CAR is a cell adhesion molecule predominantly associated with epithelial tight junctions in adult tissues. CAR is also expressed in cardiomyocytes [18], much more expressed in cultured human, skin-derived lymphatic endothelial cells than in blood vascular endothelial cells [19].
- For human HAdV-D type 26, CAR is less important than sialic acid-bearing glycans as a primary cell entry receptor [20].
- Sialic acids provide a good target for viruses since they are highly conserved and are abundant in large numbers in nearly all cells.

- It was reported for solid lipid nanoparticles containing a toxic traditional drug [21] that the nanoformulation showed significantly longer maximal and mean retention times, significantly decreased maximal concentration.

- This slow absorption might be the most important mechanism for the enhanced efficacy of nanoformulations.

- Tissue-distributions suggest a tendency for nanoparticle slowly to accumulate in the lung and spleen and to decrease in plasma, liver, kidney, and testes.

In short, both viral vector and mRNA vaccines can be expected to offer prolonged delivery of spike protein into circulation. Tissue distribution patterns probably differ (Table 2): Lipoparticles of mRNA are possibly accumulated in the brachial lymph nodes, spleen or lungs, while for vaccines based on HAdV-D type 26 that binds to sialic acid; nearly all cells can be targeted. Vaccines based on CAR targeting viruses are expected to infect lymphatic and epithelial cells and cardiomyocytes.

Separate issues affecting vaccine efficacy and rare vaccine-related events might include:

- Preexistent immunity against the vaccine viral vector

- Innate mechanisms (macrophages etc.) that destroy lipid nanoparticles and their content

- Individual efficacy and reliability of RNA interference mechanisms that limit foreign protein production.

Comparison between the disease and vaccines against it

The main difference between the COVID-19 infection and viral vector or mRNA vaccines against this disease might be in the availability of spike protein molecules in circulation:

- During COVID-19 infection:

- Spike proteins allow viral spreading in all cells with ACE2 expression and these cells produce new viral particles. This can partially explain many faces of this disease, if viremia persists, many organs are affected and their local ACE2 actions are reduced due to damage of ACE2 expressing cells.

- If infection is severe and durable, soluble ACE2 in venous blood will also be diminished, thus leaving the lungs without protection of incoming Ang (1-7) that maintains low pulmonary pressure and resistance.

- Ang II molecules in venous blood that enters the right heart can thus increase pulmonary vascular resistance, thus increasing the right heart after load.

- Arterial blood poor in Ang (1-7) and rich in Ang II, due to depleted pool of pulmonary ACE2 expressing cells, enters coronary arteries. Arterioles are constricted while local ACE2 expression diminishes, thus making the heart muscle situation worse.

- Venous blood poor in Ang (1-7) and rich in Ang II, both due to depleted pool of myocardial ACE2 expressing cells leaves the heart muscle via coronary sinus and the right heart Thebesian veins into the deteriorating pulmonary circulation.

- After vaccination (Table 2):

- Vaccine transfer mRNA or DNA of the spike protein in cells preferred by the viral vector or in cells able to import lipid nanoparticles. These cells lack the ACE2 expression and they produce new molecules of the spike protein that acts as an antigen for developing immune response.

- Only downstream organs are affected by continuous slow inflow of spike proteins into circulation. The ACE2 function is compromised partially in the first organ positioned downstream from the place of spike protein synthesis. This can locally reduce the production of Ang (1-7) and leave more Ang II molecules active in circulation.

- Only in individuals whose regional circulation has already been adapted to a state of high dependence on RAS action, the perfusion modality in the organ downstream from the organ with compromised ACE2 function might slip into the constriction state.

- If this happens in the heart muscle, the local ACE2 expression will diminish in few days after the Ang (1-7) presence in coronary blood fails below the ACE2 protective threshold.

- Increased Ang II presence in downstream tissues can be procoagulant, since Ang II induces the expression of plasminogen activator inhibitor-1 in the endothelial cells [22], and stimulates the local expression of tissue factor, the physiologic initiator of blood coagulation, an effect that can be abolished by ACE or angiotensin II receptor inhibition [23].

- All other, more remote organs remain protected by soluble ACE & ACE2 in venous blood that come from unaffected tissues. This maintains low pulmonary pressure and ACE2 expression in lungs.

Conclusion

Based on known binding sites for simian adenovirus ChAdOx1 (CAR on epithelial, lymphatic endothelial and myocardial cells), HAdV-D type 26 (sialic acid on almost all cells) and probable affinity of lipid nanoparticles toward lungs and spleen, the reported differences in rare vaccine-related events might be less confusing, under the condition that the here proposed vaccine induced downstream ACE2 dysfunctions in certain preexisting settings is found acceptable. Two extrapolations based on this interpretation of rare vaccine-related events and rare COVID-19 complications seem possible:

- Possible variability in fate of lipid nanoparticles in human body might result in more widely distributed synthesis of spike proteins in various tissues and organs, making the vaccinated person less prone to regional ACE2 dysfunctions.

- Differences between the two authorized viral vector vaccines might be in intrinsic affinities of their vectors. If one viral vector infects various cells in diverse organs, regional overexposure to synthesized spike proteins would be less likely than for the vector focused on just a few organs or tissues.

An interpretation of cardiopulmonary circulation as a single self regulatory unit due to rapid exchange of blood between pulmonary and coronary circuits is also proposed. If correct, any disorder caused by direct cardiopulmonary endocrine loops can remain undetectable in the peripheral vein blood samples.

For example, although venous plasma concentrations of ACE2 were higher in men than in women in two independent cohorts of heart failure patients [24], use of neither an ACE inhibitor nor an ARB was associated with higher plasma ACE2 concentrations, clearly suggesting that new diagnostic methods are required to recognize patients with problems caused by an alteration in cardiopulmonary

control loops.

As non-invasive tools, even personal monitors of spontaneous coughing might prove useful here. It would be important to know whether changes in the number of coughs/hour after a single representative dose of an ACE inhibitor (e.g. 10 mg of lisinopril) can detect individuals dependent on the increased cardiopulmonary ACE expression.

Acknowledgement

This review article was financed through Grant VIF2018MEFOS02 from the Croatian Ministry of Science, Education and Sport.

References

1. Riad A, Pokorná A, Attia S, Klugarová J, Koščík M, Klugar M. Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech republic. J Clin Med. 2021;10(7):1428.
2. Nassar M, Chung H, Dhayaparan Y, Nyein A, Acevedo BJ, Chicos C, et al. COVID-19 vaccine induced rhabdomyolysis: Case report with literature review. Diabetes Metab Syndr. 2021;15(4):102170.
3. Lundstrom K. Viral vectors for COVID-19 vaccine development. Viruses. 2021;13(2):317.
4. Tapia MD, Sow SO, Ndiaye BP, Mbaye KD, Thiongane A, Ndour CT, et al. Safety, reactogenicity, and immunogenicity of a chimpanzee adenovirus vectored Ebola vaccine in adults in Africa: A randomised, observer-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2020;20(6):719-30.
5. Tu TM, Goh C, Tan YK, Leow AS, Pang YZ, Chien J, et al. Cerebral venous thrombosis in patients with COVID-19 infection: A case series and systematic review. J Stroke Cerebrovasc Dis. 2020;29(12):105379.
6. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination, March 2nd to April 21st, 2021. JAMA. 2021;325(24):2448-56.
7. Furie KL, Cushman M, Elkind MSV, Lyden PD, Saposnik G. American Heart Association/American Stroke Association Stroke Council Leadership. Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. Stroke. 2021;52(7):2478-82.
8. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med. 2021;384(20):1964-5.
9. Kurbel S. The renin-angiotensin system in COVID-19: Why ACE2 targeting by coronaviruses produces higher mortality in elderly hypertensive patients? Bioessays. 2021;43(3):e2000112.
10. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: Implications for end-organ damage. J Appl Physiol (1985). 2008;105(5):1652-60.
11. Kurbel S, Marić S, Gros M. Do Thebesian veins and arterioluminal vessels protect against myocardial edema occurrence? Med Hypotheses. 2009;73(1):38-9.
12. Ansari A. Anatomy and clinical significance of ventricular Thebesian veins. Clin Anat. 2001;14(2):102-10.
13. Wearn JT. The role of the thebesian vessels in the circulation of the heart. J Exp Med. 1928;47(2):293-315.
14. Gallagher PE, Ferrario CM, Tallant EA. Regulation of ACE2 in cardiac myocytes and fibroblasts. Am J Physiol Heart Circ Physiol. 2008;295(6):H2373-9.
15. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000;87(5):E1-9.
16. Yang S, Li Y, Dai L, Wang J, He P, Li C, et al. Safety and immunogenicity of a recombinant tandem-repeat dimeric RBD-based protein subunit vaccine (ZF2001) against COVID-19 in adults: Two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis. 2021;21(8):1107-19.
17. Vigl B, Zgraggen C, Rehman N, Banziger-Tobler NE, Detmar M, Halin C. Coxsackie- and Adenovirus Receptor (CAR) is expressed in lymphatic vessels in human skin and affects lymphatic endothelial cell function *in vitro*. Exp Cell Res. 2009;315(2):336-47.
18. Mirza M, Pang MF, Zaini MA, Haiko P, Tammela T, Alitalo K, et al. Essential role of the coxsackie- and Adenovirus Receptor (CAR) in development of the lymphatic system in mice. PLoS One. 2012;7(5):e37523.
19. Vigl B, Zgraggen C, Rehman N, Banziger-Tobler NE, Detmar M, Halin C. Coxsackie- and Adenovirus Receptor (CAR) is expressed in lymphatic vessels in human skin and affects lymphatic endothelial cell function *in vitro*. Exp Cell Res. 2009;315(2):336-47.
20. Baker AT, Mundy RM, Davies JA, Rizkallah PJ, Parker AL. Human adenovirus type 26 uses sialic acid-bearing glycans as a primary cell entry receptor. Sci Adv. 2019;5(9):eaax3567.
21. Xue M, Zhao Y, Li XJ, Jiang ZZ, Zhang L, Liu SH, et al. Comparison of toxicokinetic and tissue distribution of triptolide-loaded solid lipid nanoparticles *vs.* free triptolide in rats. Eur J Pharm Sci. 2012;47(4):713-7.
22. Vaughan DE, Lazos SA, Tong K. Angiotensin II regulates the expression of plasminogen activator inhibitor-1 in cultured endothelial cells. A potential link between the renin-angiotensin system and thrombosis. J Clin Invest. 1995;95(3):995-1001.
23. Celi A, Cianchetti S, Dell'Omo G, Pedrinelli R. Angiotensin II, tissue factor and the thrombotic paradox of hypertension. Expert Rev Cardiovasc Ther. 2010;8(12):1723-9.
24. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JGF, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. Eur Heart J. 2020;41(19):1810-7.
25. Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, et al. Systematic review of COVID-19 related myocarditis: Insights on management and outcome. Cardiovasc Revasc Med. 2021;23:107-13.
26. Mele D, Flamigni F, Rapezzi C, Ferrari R. Myocarditis in COVID-19 patients: Current problems. Intern Emerg Med. 2021;16(5):1123-9.
27. Case R, Ramaniuk A, Martin P, Simpson PJ, Harden C, Ataya A. Systemic capillary leak syndrome secondary to coronavirus disease 2019. Chest. 2020;158(6):e267-8.
28. Lacout C, Rogez J, Orvain C, Nicot C, Rony L, Julien H, et al. A new diagnosis of systemic capillary leak syndrome in a patient with COVID-19. Rheumatology (Oxford). 2021;60(1):e19-e20.
29. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: A systematic review. SN Compr Clin Med. 2020;2(11):2048-58.
30. Bomhof G, Mutsaers PGNJ, Leebeek FWG, Te Boekhorst PAW, Hofland J, Croles FN, et al. COVID-19-associated immune thrombocytopenia. Br J Haematol. 2020;190(2):e61-4.
31. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24(1):360.
32. Mei H, Luo L, Hu Y. Thrombocytopenia and thrombosis in hospitalized patients with COVID-19. J Hematol Oncol. 2020;13(1):161.
33. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, et al. Guillain-Barré syndrome related to COVID-19 infection. Neurol Neuroimmunol Neuroinflamm. 2020;7(4):e741.

34. Padroni M, Mastrangelo V, Asioli GM, Pavolucci L, Abu-Rumeileh S, Piscaglia MG, et al. Guillain-Barré syndrome following COVID-19: New infection, old complication? J Neurol. 2020;267(7):1877-9.

35. Koh JS, De Silva DA, Quek AML, Chiew HJ, Tu TM, Seet CYH, et al. Neurology of COVID-19 in Singapore. J Neurol Sci. 2020;418:117118.

36. Pilotto A, Masciocchi S, Volonghi I, Crabbio M, Magni E, De Giuli V, et al. Clinical presentation and outcomes of severe acute respiratory syndrome coronavirus 2-related encephalitis: The ENCOVID multicenter study. J Infect Dis. 2021;223(1):28-37.

37. Gascon P, Briantais A, Bertrand E, Ramtohul P, Comet A, Beylerian M, et al. COVID-19-Associated Retinopathy: A case report. Ocul Immunol Inflamm. 2020;28(8):1293-7.

38. Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, et al. COVID-19 retinal microangiopathy as an *in vivo* biomarker of systemic vascular disease? J Intern Med. 2021;289(1):116-20.