Arterial hypertension after influenza, COVID-19 disease and Covid-19 vaccination

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Abstract

In recent decades, the incidence and prevalence of arterial hypertension has been increasing both in the world and in the Republic of Croatia and represents a major public health problem. Almost every year, the healthcare system is faced with an epidemic of influenza, and in the last few years with an new epidemic of the Covid-19 disease caused by the SARS-CoV-2 virus. Hypertension is one of the most important risk factor for the development of severe forms of Covid-19 disease and influenza. On the other hand, after the recovery from these diseases the onset of the de novo development or worsening of existing hypertension is noticed. The association of influenza with the onset of arterial hypertension has been known for many years and occurs in about 16% of hospitalized and about 5% of non-hospitalized patients after the recovery from the flu. More recently, an even higher and more significant incidence of hypertension has been noticed after the Covid-19 disease and occurs in about 21% of hospitalized and 16% of non-hospitalized patients. Pathogenetic mechanisms of the development of hypertension after influenza have not been fully elucidated. It is most likely the interference of viral proteins with the transcription of the ACE 2 (angiotensin converting enzyme 2) gene into a protein. In the case of SARS-CoV-2 viral infection, numerous studies show the destruction of the ACE 2 enzyme expression by the binding of the viral spike protein to this receptor. The ACE 2 enzyme is crucial in the activation of the counter-regulatory mechanism of the renin-angiotensin-aldosterone system (RAAS) that lowers arterial pressure. This mechanism involves the formation and function of angiotensin peptides, especially peptides 1-7. Loss of ACE 2 function leads to the predominance of the classic part of the RAAS system and the prohypertensive effects of angiotensin II and the development of hypertension. Similar effects to SARS-CoV-2 infection are also shown by vector vaccines against Covid-19 disease. They stimulate the synthesis of the spike protein of the coronavirus according to the genetic instructions they carry. Spike proteins in this free, soluble form can bind to ACE 2 and reduce its expression, thereby causing hypertension. It was observed in about 4% individuals, while the proportion of hypertension of the III degree and emergency cases related to hypertension was recorded in 0.6% of the vaccinated individuals. The significance of this unwanted vaccine effect is important considering the wide vaccination coverage of about 67% of the world's population and delivered 13.59 billion doses of the Covid-19 vaccine.

Keywords: Arterial Hypertension; SARS-CoV-2; Influenza and Hypertension; ACE 2 Enzyme; Vaccine-Associated Hypertension

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Sažetak:

Arterijska hipertenzija nakon gripe, bolesti COVID-19 i cijepljenja protiv Covid-19

Posljednjih desetljeća incidencija i prevalencija arterijske hipertenzije raste kako u svijetu tako i u Republici Hrvatskoj i predstavlja veliki javnozdravstveni problem. Gotovo svake godine zdravstveni se sustav suočava sa epidemijom gripe, a posljednjih nekoliko godina i sa epidemijom Covid-19 bolesti koju uzrokuje SARS-CoV-2 virus. Među značajnijim rizičnim faktorima za razvoj težih oblika Covid-19 bolesti i gripe ističe se hipertenzija. S druge strane primarno preboljenje ovih bolesti može voditi u de novo razvoj ili pogoršanje postojeće hipertenzije. Povezanost gripe sa nastupom arterijske hipertenzije poznata je duži niz godina i javlja se u oko 16% hospitaliziranih i oko 5% nehospitaliziranih bolesnika nakon preboljenja gripe. U novije vrijeme primjećena je još veća i značajnija incidencija hipertenzije nakon Covid-19 bolesti i javlja se u oko 21% hospitaliziranih i 16% nehospitaliziranih bolesnika. Patogenetski mehanizmi razvoja hipertenzije nakon gripe nisu u potpunosti razjašnjeni. Najvjerojatnije se radi o interferenciji virusnih proteina sa prepisivanjem ACE 2 (angiotensin converting enzyme 2) gena u protein. U slučaju SARS-CoV-2 virusne infekcije mnogobrojne studije pokazuju uništenje izražaja ACE 2 enzima vezivanjem virusnog proteina šiljka na taj receptor. ACE 2 enzim ključan je u aktivaciji suprotno-regulirajućeg mehanizma renin-angiotenzin-aldosteronskog sustava (RAAS) koji snižava arterijski tlak. Taj mehanizam uključuje stvaranje i funkciju angiotenzinskih peptida, napose peptida 1-7. Gubitak funkcije ACE 2 vodi u predominaciju klasičnog dijela RAAS sustava i prohipertenzivnih učinaka angiotenzina II te razvoj hipertenzije. Slične učinke SARS-CoV-2 infekciji pokazuju i vektorska cjepiva protiv Covid-19 bolesti. Ona potiču sintezu proteina šiljka koronavirusa na temelju genetske upute koju nose. Proteini šiljka i u ovom slobodnom, solubilnom obliku mogu se vezati na ACE 2 i smanjivati mu izražaj te time izazivati hipertenziju. Ona je primjećena u oko 4% cijepljenih dok je udio hipertenzije III stupnja i hitnih slučajeva povezanih sa hipertenzijom zabilježena u 0,6% cijepljenih. Značaj ovog neželjenog učinka cjepiva velik je obzirom na širok obuhvat cijepljenjem od oko 67% svjetske populacije sa isporučenih 13,59 milijardi doza Covid-19 cjepiva.

Ključne riječi: Arterijska hipertenzija; SARS-CoV-2; Gripa i hipertenzija; ACE 2 enzim; Hipertenzija povezana s cjepivom

Covid-19 epidemic

In humans, four types of coronaviruses cause mainly mild symptoms similar to the common cold, while severe, sometimes fatal illnesses are caused by the Middle East respiratory syndrome-related coronavirus (MERS-CoV) and two severe acute respiratory syndrome coronaviruses (SARS-CoV-1 and SARS-CoV-2 viruses). Covid-19 disease is caused by the SARS-CoV-2 virus (1). As of 31 March 2024, there have been 775,251,765 reported cases of Covid-19 disease worldwide and over 7 million deaths (2). In the same period, 1,316,785 cases and 18,751 deaths were reported in the Republic of Croatia (3). Covid-19 disease death toll is probably even higher because excess mortality of 24,026 cases was reported during the period of Covid-19 epidemics, from 01 January 2020 to 31 December 2023 (4,5). The waves of excess mortality coincided with the epidemic waves. It can therefore be concluded that excess mortality is primarily caused by the Covid-19 epidemic, although higher mortality from other diseases cannot be ruled out, considering the overload and limited functioning of the healthcare system during the epidemic waves.

Influenza epidemics

There are four different types of influenza viruses: A, B, C and D. The main source of influenza A virus (IAV) is aquatic birds, although the virus is widespread in populations of various mammals, including humans. In addition to IAV, type B and C influenza viruses infect humans, while influenza D virus is mainly found in cattle and pigs. Within the IAV group, there are several serotypes based on the structure of the viral proteins H (haemagglutinin) and N (neuraminidase). By 2019, a total of 18 H and 11 N subtypes had been identified. However, only the H1-3 and N1-2 subtypes circulate permanently in the human population. From 2018 to date, only the H1N1 and H3N2 subtypes have caused epidemics (6). According to the World Health Organisation (WHO), it is estimated that influenza causes a severe clinical condition in 3-5 million people worldwide each year, with 290,000-650,000 deaths (7). The mortality rate from influenza depends on the type of virus and the age of the patient. For example, the subtype of the H1N1 virus predominantly affects the upper respiratory tract and is rarely fatal, in contrast to the H5N1 virus, which affects the lower respiratory tract and is often

fatal. The overall influenza mortality rate recorded in the US during the 2018–2019 epidemic season was less than 0.1%, but in the population over 65 years of age it was 0.832%, approximately 8.5 times higher (8).
Risk factors for developing severe influenza include a genetic predisposition related to viral recognition and interferon response, smoking, pregnancy and comorbidities such as chronic obstructive pulmonary disease and heart disease. Some of the risk factors for developing severe disease can be found in both influenza and Covid-19, such as obesity, old age and male gender, while others, such as diabetes, chronic kidney disease and hypertension, only contribute to the development of severe disease in Covid-19 infection (9).

Hypertension

More than 25% of the adult population worldwide suffers from hypertension. According to the EHUH study, 37% of the adult Croatian population had hypertension in 2010 (10). The prevalence of hypertension has increased dramatically in recent decades. It increases with age, so that in 2017, 75.2% of men and 73.9% of women over the age of 60 in the USA suffered from high blood pressure (11). According to the WHO, 48% of the entire Croatian population aged 30-79 had hypertension in 2019. The prevalence is slightly higher among men (51%) than among women (45%). Of these, around 1.5 million adults are diagnosed, including 70% of men and 79% of women with a diagnosis and 46% of men and 62% of women receiving treatment, while only around 20% of the population (15% of men and 25% of women) are regularly monitored (12).

Relationship between hypertension and Covid-19

The relationship between hypertension and Covid-19 is bidirectional. Hypertension is a risk factor for the development of severe Covid-19, and conversely, Covid-19 is a risk factor for the development of hypertension. A large meta-analysis of seven separate clinical trials has shown that hypertension is one of the most common comorbidities associated with severe cases of Covid-19 at 21.1%. The likelihood of developing severe Covid-19 is 2.42 times higher in people with previously diagnosed hypertension than in people without hypertension (13).
On the other hand, the likelihood of developing de novo hypertension during Covid-19 disease increases significantly, reaching over 50% in people older than 70 years, while it is over 60% in those over 80 years. This probability increases with the number of comorbidities the patient has, reaching over 50% in those with 2 comorbidities and over 80% in those with more than 4 comorbidities (13).

Relation between hypertension and influenza.

As with Covid-19 disease, the relationship between hypertension and influenza is bidirectional. Hypertension is a risk factor for developing severe influenza illness, while influenza is a risk for developing or worsening hypertension.
A large meta-analysis of 39 separate studies has demonstrated the association between influenza and cardiovascular deaths (14). A prospective Norwegian study involving 182 patients showed a significant association between ICU admission and influenza-related deaths with a previous diagnosis of hypertension (15).
A recently published study showed that of 119 patients who returned for follow-up after influenza-related hospitalisation, 23 (19.3%) developed new-onset hypertension, while the percentage was slightly lower (9.1%) in non-hospitalised patients who returned (16).

Renin-angiotensin system (RAS)

One of the basic mechanisms by which COVID-19 and influenza trigger the development of hypertension is the effect on the renin-angiotensin-aldosterone system (RAAS) (17). In the classic RAS pathway, renin cleaves 451 amino acids long protein angiotensinogen and releases angiotensin I (Ang I), which consists of 10 amino acid residues. Furthermore, the enzyme ACE cleaves decapeptide Ang I, converting it into 8 amino acid long peptide angiotensin II (Ang II). Ang II exerts a number of prohypertensive effects via angiotensin II type 1 receptors (AT1R), such as an increase of the sympathetic tone, decrease of the parasympathetic tone, vasoconstriction, decrease of the baroreceptor sensitivity, decrease of the nitric oxide (NO) secretion, inhibition of the natriuresis, and promotion of the aldosterone and antidiuretic hormone (ADH) secretion. Aminopeptidase converts Ang II to angiotensin III (), which also stimulates the AT1R, while alanyl-aminopeptidase converts Ang III to Ang IV, which acts in the opposite direction to Ang II and via angiotensin II type 4 receptors (AT4R) can lower arterial pressure. However, the effects mediated by AT4R are significantly weaker than those mediated by Ang II via AT1R (18).

Counter-regulatory RAS pathway.

In the balanced arterial pressure regulation within the complete RAS system, the counter-regulatory RAS pathway plays a much greater role in reducing the arterial pressure than Ang IV. This part of the RAS system is mediated by three distinct receptors: AT2R, MasR and MRGD receptors. Several peptides are involved in this signalling pathway. One of the most important is angiotensin 1-9 (Ang 1-9), which is formed from Ang I by the action of the enzyme ACE2. Ang 1-9 acting via AT2R and MasR can lower the sympathetic tone, increase the parasympathetic tone and the sensitivity of the baroreceptors, induce and increase production of NO and stimulate vasodilation, promote natriuresis and finally decrease the arterial pressure. Alamandine shows similar effects via MRGD receptors. Alamandine is formed by the action of the enzyme ACE2 on angiotensin A (Ang A), which can be formed from Ang II by the action of the enzyme ML-DAD (mononuclear leukocyte aspartate decarboxylase) (19).

Angiotensin 1-7 (Ang 1-7) is one of the most important peptides acting via MasR receptors in the opposite direction to the classical RAS pathway. This peptide can be generated in three ways: by ACE2 which breaks down Ang II, by enzyme neprilysin which breaks down Ang I or by ACE which converts Ang 1-9 to Ang 1-7. Ang 1-7 can be converted into alamandine by the action of the enzyme MLDAD. In either case, the counter-regulatory RAS pathway is an important part of the RAS system that balances the effects of Ang II via AT1R (18).

Influenza virus inactivates the ACE2 enzyme

Several different studies have shown that damage to the ACE2 enzyme in influenza leads to the development of more severe disease. With the influenza A H7N9 serotype, increased plasma levels of Ang II lead to significant progression and exacerbation of the disease. Persistently elevated Ang II levels are significantly associated with higher mortality. It has been observed that virus-mediated lung injury in H7N9 is associated with inadequate ACE2 function and increased AT1R stimulation. These results suggest the possibility that Ang II acts as a biomarker for increased mortality in influenza. Experiments with the highly pathogenic H5N1 avian influenza virus have shown that downregulation of ACE2 and consequently decreased expression in the lung are associated with higher plasma levels of Ang II. Elevated levels of Ang II are associated with the development of severe clinical symptoms and increased mortality from this infection. Experiments in mice infected with H5N1 have shown that the AT1R blocker losartan significantly increases the survival rate of mice (20).

The mechanism by which the influenza virus inactivates the ACE2 enzyme is not yet fully understood but appears to involve the degradation of ACE2 mRNA by miRNA. Specifically, H5N1 avian influenza virus induces upregulation of microRNA (miR-200c-3p) targeting the 3′-untranslated region of ACE2 mRNA, increasing its degradation and thus affecting the ACE2 synthesis. It has been shown that non-structural protein 1 (influenza virus NS1) and viral RNA of the H5N1 virus contribute to the induction of miR-200c-3p during infection, and significantly increased levels of miR-200c-3p have been detected in patients with severe pneumonia. It is not known whether less pathogenic influenza viruses such as the H1N1 subtype can affect the function of the RAAS system directly or only indirectly through a strong inflammatory response (21).

The role of ACE2 in SARS-CoV-2 infection

The enzyme ACE2 is found in soluble form and as an enzyme associated with the membranes of endothelial and epithelial cells throughout the body, including the heart, gastrointestinal tract, kidneys and especially the lungs. It is mainly expressed in the epithelium of the oropharynx and nasal cavity and enables the transmission and entry of the SARS-CoV-2 virus into the body (17).

After the SARS-CoV-2 virus spike protein binds to ACE2, the structurally associated serine protease TMPRSS2 cleaves the spike protein, while the enzymes ADAM17 (A-disintegrin and metalloprotease 17) and TMPRSS2 cleave ACE2 and promote viral entry into the cell (17).

Binding of the spike protein to the ACE2 receptor competitively prevents the binding of Ang II, while binding to the virus and enzymatic degradation together with downregulation completely inhibit it. The loss of ACE-2 enzyme function results in an accumulation of Ang II due to reduced hydrolysis of Ang II. Ang II accumulates in the endothelial cells and causes vascular senescence with a strong production of interleukin-6 (IL-6) and reactive oxygen species (ROS), which significantly impairs innate and adaptive immunity. In addition, Ang II is known to be highly toxic for mitochondria (22).

Therefore, loss of ACE2 function leads to dysregulation of the entire RAAS system, which can lead further to the development of cytokine storm, endothelial dysregulation, leukocyte activation, formation of neutrophil extracellular traps (NETs), immune thrombosis in the microcirculation, organ ischaemia and ultimately multi-organ failure and death (23).

As evidence that loss of ACE2 function and the prevalence of toxic Ang II levels are key events in the pathogenesis of Covid-19 disease, a meta-analysis reviewing the results of studies on the effects of ACE inhibitors and AT1R blockers (ARBs, angiotensin II receptor blockers) on the outcome of Covid-19 disease showed that RAAS inhibition with ACE inhibitors, ARBs or their combination reduces the risk of death and/or critical illness by around 24% (24).

In addition to the parameters mentioned above, other factors such as the effects of isolation, stress, reduced physical activity, poor diet and weight gain have also contributed to the development of hypertension in the Covid-19 pandemic (17, 25).

Incidence of newly developed persistent arterial hypertension after Covid-19 disease is higher than after influenza

Persistent hypertension is defined by 3 criteria in patients observed after recovery from Covid-19 or influenza. Firstly, an increase in systolic blood pressure above 140 mm Hg and/or an increase in diastolic pressure above 90 mm Hg during a medical visit, secondly, a new diagnosis based on the ICD-10 code for hypertension, or thirdly, newly prescribed antihypertensive therapy.

The incidence of newly developed persistent hypertension is higher after Covid-19 disease than after influenza. In hospitalised patients with Covid-19 disease, hypertension was found in 20.6% of patients, while it was found in 16.3% of hospitalised influenza patients. In non-hospitalised Covid patients, persistent hypertension was found in 16.3%, while in influenza patients it was found in 4.4% of patients (16).

Covid-19 Vaccination and Hypertension

By 26 November 2023, a total of 13.59 billion doses of the Covid-19 vaccine had been administered. 67% of the world's population had completed the initial Covid-19 vaccination and 32% had received at least one booster dose. In the European Union, 4 types of vaccines have been used according to the European Medicines Agency authorisation, including two mRNA vaccines (BNT162b2 and mRNA-1273), an adenovirus vector vaccine (AZD1222) and a recombinant protein vaccine (NVX-CoV2373).

The first reports of stage III hypertension occurring after Covid-19 vaccination were published in June 2021. Stage III hypertension was documented within minutes of vaccination or during the first 30 days after vaccination in 8 patients who received the BNT162b2 vaccine and one who received the mRNA-1273 vaccine (26).

Following this initial report, several studies have shown the occurrence of hypertensive crises, sometimes with serious consequences such as intracranial haemorrhage, after the administration of mRNA vaccines. In July 2021, based on the World Health Organisation's global pharmacovigilance database, Kaur et al. demonstrated that 5.82% of all adverse events related to the cardiovascular system after three common Covid-19 vaccines (BNT162b2, mRNA-1273 and ChAdOx1-SARS-COV-2) were hypertension (27).

In another large study of healthcare workers, Simonini et al. reported an increase in blood pressure in 8% of participants after vaccination, a new diagnosis of hypertension in 2% of cases, and the need for intensification of antihypertensive therapy in 11% of participants who were already receiving hypertensive therapy (28).

However, the largest study documenting the incidence of hypertension and hypertension-related diseases after Covid-19 vaccination was published in the form of a meta-analysis. This systematic review included six studies with a total of 357,387 subjects analysed and a total of 13,444 cardiovascular events and showed a pooled estimated proportion of elevated blood pressure after vaccination of 3.91% and a proportion of stage III hypertension and hypertensive emergencies of 0.6% of cases (29).

In a recent study of 287 people who received the BNT162b2 vaccine, 5.2% experienced an increase in systolic pressure of more than 20 mmHg 15 minutes after the first dose, although a higher proportion of participants (between 5 and 25%) developed hypotension (with a systolic pressure of more than 20 mmHg) after the first and/or second dose of the vaccine (30).

Mechanisms by which Covid-19 vaccines cause hypertension

The administration of mRNA and adenoviral vaccines leads to the production of spike proteins of the SARS-CoV-2 virus based on the genetic material they carry (RNA in lipid particles or DNA in adenoviral vaccines). Targeted host cells release spike proteins into the environment, stimulating an immune response mediated by B lymphocytes with antibody production as well as T cell response. However, some of the free, soluble spike proteins bind to the ACE2 receptor, inducing downregulation and loss of ACE2 function.

It has been shown that the binding of spike proteins to ACE2 receptors on the cell surface mediates the entry of the virus into cells, thereby promoting the internalisation and degradation of ACE2 and the loss of ACE2 activity. This process is not unique to viral infections, as free, soluble S proteins produced by vaccination also have the ability to bind to the receptor, same as the natural SARS-CoV-2 S protein. ACE2 is a key enzyme in the activation of the counter-regulatory RAS mechanism, i.e. it is important for the conversion of angiotensin 2 (Ang2) to angiotensin 1-7 (Ang 1-7 peptide), which binds to the Mas receptor and inhibits the effects of ANG 2, such as the increase in blood pressure, inflammation, the release of aldosterone and vasopressin, increased sodium reabsorption in the kidneys and fibrosis. Therefore, as in SARS-CoV-2 infection, vaccination-reduced ACE2 expression and an imbalance between ANG2 and ANG 1-7 could directly contribute to an excessive increase in blood pressure after administration of the Covid-19 vaccine.

In recent years, other enzymes that produce Ang 1-7 peptides have been discovered, including prolyl oligopeptidase (POP) and prolyl carboxypeptidase (PRCP) (31). In contrast to ACE2, POP/PRCP levels were found to increase significantly with the age of the subjects (as well as with the presence of various metabolic and cardiovascular diseases). Therefore, some authors have suggested that the adverse effects of Covid-19 vaccines mediated by the interaction of S proteins with ACE2 may be particularly pronounced in younger patients, as they are less likely to have cardiovascular disorders and lower expression of POP and PRCP enzymes. This hypothesis is supported by some, but not all, studies. In a large study, the age of patients with uncontrolled hypertension after Covid-19 vaccination ranged from 35 to 52 years, i.e. in a younger population, which was in line with the proposed hypothesis (32). However, in some studies, no association was found between post-vaccination hypertension and younger age.

Interestingly, many cases of hypertension were reported within minutes of vaccine administration, which is too short for mRNA translation, S protein production and its interaction with ACE2 receptors. This suggests that there are other mechanisms for hypertension evolvent after vaccination, not just a decrease in ACE2 expression. Possible mechanisms include the "white coat effect" as well as an increase in sympathetic tone due to the pain of vaccine administration and a stress response due to the fear of the injection. Headaches, fatigue and fever often occur after vaccination, which can have an indirect effect on blood pressure increase (33).

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