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Clinical Insights

The relationship between COVID-19 vaccines and increased blood pressure: A word of caution

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COVID-19 vaccines substantially changed the course of the pandemic, saving millions of lives on a global scale [1]. According to the latest evidence, 64.85% of the world's population has been fully vaccinated with the last dose of the primary series and more than 30% has received the COVID-19 booster [2]. Together with the growing number of COVID-19 vaccine receivers, a range of vaccine-related complications, including cardiovascular ones, have been reported worldwide [3]. Among the latter, the potential for vaccination to significantly increase blood pressure (BP) levels emerged as a reason for some concern.

To date mRNA vaccines (i.e., mRNA-1273 and BNT162b2), adenovirus vector vaccine (AZD1222), and recombinant protein vaccine (NVX-CoV2373) have been approved by the European Medical Agency (EMA) demonstrating an excellent safety and efficacy profile in randomized clinical trial showing no significant correlations between vaccines and hypertension [4,5]. In June 2021, Meylan *et al.* reported the incidence of stage III hypertension within a few minutes of the vaccination, during the first 30 days, in eight patients out of 12349 who received the Pfizer/BioNTech vaccine and in one who received the Moderna vaccine in the same center (median age 73 years, 7 females and 2 males, 8 with a history of hypertension). No pre-vaccination blood pressure (BP) values were available, but eight patients reported well-controlled home BP before vaccination [6]. After this first series, others reported a potential association between COVID-19 vaccine and acute BP raise [7–9]. In July 2021, based on the global pharmacovigilance database of the World Health Organization (WHO), Kaur *et al.* showed that 5.82% of total cardiovascular-related adverse events after three common COVID-19 vaccines (BNT162b2, mRNA-1273, and ChAdOx1-SARS-COV-2) were hypertension [10]. In particular, the BNT162b2 vaccine was found to be associated with over double the risk of hypertension compared to non-users by others [11]. In a Japanese study on pregnant women receiving the COVID-19 vaccine, increased BP has been observed only in five subjects (0.09%) after the first dose and seven subjects (0.14%) after the second dose [12]. Surveys specifically designed to assess BP changes after vaccination have shown an incidence of about 1% to 5% [13–15]. In June 2021 Zappa *et al.* designed a prospective survey of 113 health workers with referred normal home BP values and who received the Pfizer vaccine (median age 43 years and 18% prevalence of hypertension). Only 6 subjects (5,3%) reported a rise in the average self-measurements home BP by $\geq$ 10 mmHg during the first five days after the first dose of vaccination and in 4 subjects an intensification of antihypertensive treatment was needed. The history of COVID-19 was associated with higher probability of increase in BP values after vaccination [14]. In another large cohort of healthcare workers, Simonini *et al.* reported a BP increase in 8% of the participants, a new diagnosis of hypertension in 2% of the cases, as well as an increase in the antihypertensive therapy in 11% of the subjects already on treatment after vaccination [16]. In this study, headache (39%), general malaise (34%), and dizziness (18%) were reported after the vaccination in association to elevated BP, possibly explaining BP alterations as the consequence of an alarm reaction. In a study by Bouhanick *et al.*, 37% of vaccinated subjects had elevated blood pressure 15 minutes after the

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first injection, a prevalence similar to that reported in the French population of the same age group [17]. In another study on patients with or without history of controlled hypertension undergoing both home and ambulatory BP measurement, a short period of hypertensive response was found at some point in all participants between day 5 and day 20 post-vaccination, irrespective of vaccine type [18]. A systematic overview and meta-analysis including six studies (for a total of 357387 subjects and 13444 events) showed a pooled estimated proportion of increased BP after vaccination of 3.91%, as well as a proportion of stage III hypertension, hypertensive urgencies, and hypertensive emergencies of 0.6% [19]. As of February 3, 2023, a total of 17183 cases of hypertension had been reported to the Vaccine Adverse Event Report System (VAERS) in the US. However, only 159 episodes were reported as hypertensive urgency [20]. In a recent study on 287 individuals receiving the BNT162b2 vaccine, 5.2% of the individuals experienced an increase in systolic BP of more than 20 mmHg 15 min after the first dose, though a higher proportion of participants (ranging from 5 to 25 %) developed significant reductions (even larger than 20 mmHg) in BP levels following the first and/or the second dose injection. No change was observed in the majority of subjects [21] .

Clinical data suggest that SARS-CoV-2 infection also promotes increased BP during the acute phase of the infection [22–24]. Among hospitalized patients, COVID-19 pneumonia was associated with a 7-fold increased risk of uncontrolled hypertension when compared with bacterial pneumonia, which remained significant after adjustment for confounders [25]. However, in the acute phase of the disease, the regular daily use of anti-inflammatory drugs (including paracetamol, NSAIDs and steroids) and the modification of previous antihypertensive drugs because of fever, dehydration, and acute kidney injury and/or in-hospital overinfections might have influenced the results.

The exact mechanism linking SARS-CoV-2 infection and COVID-19 vaccines and acute elevations in BP is still debated but could involve the failure of the counter-regulatory renin-angiotensin-system (RAS) axis [26]. It is well known that the binding of the Spike (S) protein to angiotensin converting enzyme 2 (ACE2) receptors on the cell surface mediates the virus entry into cells, thereby promoting ACE2 internalization and degradation, and loss of ACE2 activities. Free-floating S proteins produced by vaccination exhibit a receptor binding capacity like the native SARS-CoV-2 S protein [27]. ACE2 is the key enzyme in the conversion of angiotensin 2 (Ang2) to angiotensin 1-7 (Ang1-7), which binds to the Mas receptor and counteracts the effects of Ang2, such as inflammation, aldosterone and vasopressin release, renal sodium reabsorption, and fibrosis [28]. The downregulation of ACE2 and the imbalance between Ang2 and Ang1-7 could therefore directly contribute to excessively rise BP both in the acute phase of SARS-CoV-2 infection and following COVID-19 vaccines administration. In the last few years, other Ang1-7 forming enzymes have been identified, including prolyl oligopeptidase (POP) and prolyl carboxypeptidases (PRCP) [29]. Contrary to ACE2, POP/PRCP levels were found to be significantly positively correlated with age and the presence of several metabolic and cardiovascular disorders [30]. Therefore, some authors have suggested that the adverse effects of COVID-19 vaccines mediated by the interaction of S protein with ACE2 may be particularly pronounced in younger patients with a better cardiovascular risk profile [26]. Regarding hypertension, this hypothesis is supported by some, but not all the above studies. In the study by Zappa *et al.*, the age of patients with uncontrolled hypertension following COVID-19 vaccination ranged from 35 to 52 years [14], whereas Tran *et al.* showed that increasing age was associated with a decrease of BP elevation [13]. In the study by Meylan *et al.*, however, the median age was 73 years old [6]. In the study by Kaur *et al.*, the incidence of hypertension was noted to be associated with vaccine use in both genders and all different age groups [10], while others found higher rates in older individuals [15].

Interestingly, many events have been reported within minutes of the injection, which seems to be too short for cellular uptake and translation of mRNA, leading to the interaction between S protein and ACE2 receptors. This suggests the existence of other mechanisms rather than the downregulation of ACE2 [3]. The hypothesis may include a white coat effect, as well as an increase in sympathetic tone caused both by pain and a stress response due to the fear of injections. Headache, malaise, and fever are also frequently observed after vaccination, which may indirectly affect BP [16,31]. The role of excipients, such as polyethylene glycol, represents another explanation of possible link between BP increase and vaccine; however, it does not seem probable due to their insignificant amounts [11]. Further, it should also be noted that several studies reported a delayed occurrence of BP increase after COVID-19 vaccination [11,15], which suggests a role for the failure of the counter-regulatory RAS axis in this scenario.

Although current evidence seems to suggest a possible deleterious effect of COVID-19 vaccines on BP, several points must be made about the studies published so far. First, no control group was included to unmask the real effect of COVID-19 vaccination on BP. Second, the high variability, including a white coat phenomenon and possibly the poor accuracy of BP measurements and the time of recording (from 15 min to several days after the vaccination) clearly impacted the study results. Third, the design of the study largely affected proportions of BP elevation after vaccination, with the highest value recorded in the retrospective study by Bouhanick *et al.* on healthcare workers who received the BNT162b2 vaccine in a French hospital [17]. Forth, the lack of information on BP control before vaccination and the possible presence of hypertension at baseline in several studies limit the interpretability of their results. The lockdown related to the COVID-19 pandemic may have affected the daily management of many chronic diseases, including hypertension. The long interruption of the traditional clinical management of hypertensive patients and the increase of some risk factors for hypertension related to the lockdown period (lack of physical activity, increase in body weight, etc.) could have determined an increase in the incidence of hypertension. Lastly, pharmacovigilance databases provided the largest cohorts of subjects exploring this phenomenon, though they analyzed the rates of BP increase as a self-reported phenomenon [10,11]. Accordingly, even if the BP increase should not be considered a sporadic event after the COVID-19 vaccination, the small number of available studies and their inherent limitations require further investigation. This should include accurate comparisons of BP values before and at various time-points after the vaccination, including 24 hours BP recordings, in both healthy and unhealthy individuals, a rigorous collection of the patient's demographic and clinical characteristics at baseline, as well as a detailed analysis of potential pathophysiological mechanisms of hypertension in this setting.

The SARS-CoV2 infection can have dramatic consequences on the overall health not only in the acute phase but also in the long term, including on the cardiovascular level [32]. In particular, several reports suggest that COVID-19 survivors can develop increased BP in the post-acute phase [22]. Accordingly, the advantages of global COVID-19 vaccination still outweigh the potential risks, and the alleged increased risk of hypertension after administration of COVID-19 vaccines should not lead to vaccination avoidance in any specific category of patient at present. Although more evidence would be necessary, sustained BP increase after COVID-19 vaccination seems to be a rare and transient event [15]. In this respect, one study in Europe using ambulatory 24-hour BP monitoring [33] is recruiting patients and could shed light on these important issues in the near future.

Declaration of Competing Interest

None.

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