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# Hypertensive Crisis Following COVID-19 Vaccination

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Recently, hypertensive crisis, mainly following messenger RNA (mRNA)-based vaccines, has raised concerns. Meylan et al[1] reported 9 cases with stage III hypertension just a few minutes following administration of mRNA-based coronavirus disease 2019 (COVID-19) vaccines, mainly with the Pfizer/BioNTech (BNT162b2) vaccine. Accordingly, Athyros and Doumas[2] reported a case of hypertensive crisis with blood pressure (BP) of 210/110 mm Hg and an intracranial hemorrhage 3 days after the Moderna (mRNA-1273) COVID-19 vaccine in a 71-year-old woman, who died after 9 days. However, the potential link between COVID-19 vaccines and the BP rise remains unclear. It is well known that the cell entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strongly depends on angiotensin-converting enzyme 2 (ACE2) receptors of host cells. Also, recent evidence has shown that ACE2 receptors are downregulated following interaction with the receptor-binding domain of the virus spike (S) protein. Pfizer/BioNTech (BNT162b2) and the Moderna (mRNA-1273) COVID-19 vaccines work by triggering an individual's cells to produce the S protein that could bind to the ACE2 receptors.[3]

ACE2 is the key enzyme in the conversion of angiotensin 2 to angiotensin 1-7, which binds to the Mas receptor and reduces the effects of angiotensin 2, such as inflammation, reabsorption of renal sodium, the release of vasopressin and aldosterone, and fibrosis.[4] Therefore, the downregulation of ACE2 receptors and imbalance between angiotensin 2 and angiotensin 1-7 might describe the rise of BP following COVID-19 vaccines. A higher rate of adverse reactions after the first dose of vaccine in previously infected patients with SARS-CoV-2 might support this theory.[5]

This hypothesis seems to fit the hypertension crisis after adenovirus-based vaccines, which use double-stranded DNA for S protein production. For example, Oxford-AstraZeneca used a chimpanzee adenovirus, ChAdOx1, in the AZD1222 vaccine to add the SARS-CoV-2 S protein gene, which subsequently can be read by the cell and copied into an mRNA. After getting an AZD1222 shot, cases of hypertension were reported, mostly after 3 hours.[6] However, it should be noted that stage III hypertension caused by mRNA vaccines occurred only within minutes of the shot, which seems to be too short for cellular uptake and translation of mRNA, leading to the interaction between S protein and ACE2 receptors.[1] This may highlight the existence of other mechanisms rather than the downregulation of ACE2 receptors. Although stress response, white coat syndrome, and the possible role of polyethylene glycol as an excipient were suggested by Meylan et al, further studies are required to recognize the exact mechanism of hypertension after COVID-19 vaccines.[1]

Of note, an ongoing clinical trial planned to recruit 100 participants to study the short-term effects of COVID-19 vaccines on BP using ambulatory BP monitoring.[7] The future results of this trial might provide a detailed description of the effects of COVID-19 vaccines on BP. However, monitoring of BP before and after vaccination and symptom screening should be conducted to detect changes associated with the vaccine.

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## Conflicts of Interest

The authors declare no conflicts of interest.

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## References


1. Meylan S, Livio F, Foerster M, Genoud PJ, Marguet F, Wuerzner G. Stage III hypertension in patients after mRNA-based SARS-CoV-2 vaccination. *Hypertension*. 2021;77(6):e56-e57.
2. Athyros VG, Doumas M. A possible case of hypertensive crisis with intracranial haemorrhage after an mRNA anti-COVID-19 vaccine. *Angiology*. 2022;73(1):87.
3. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines*. 2021;6(1):28.
4. Simões e Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br J Pharmacol*. 2013;169(3):477-492.
5. d'Arminio Monforte A, Tavelli A, Perrone PM, et al. Association between previous infection with SARS CoV-2 and the risk of self-reported symptoms after mRNA BNT162b2 vaccination: data from 3078 health care workers. *EClinicalMedicine*. 2021;36:100914.
6. Tran VN, Nguyen HA, Le TTA, Truong TT, Nguyen PT, Nguyen TTH. Factors influencing adverse events following immunization with AZD1222 in Vietnamese adults during first half of 2021. *Vaccine*. 2021;39(44):6485-6491.
7. Short-term effect of COVID-19 vaccine on blood pressure. https://clinicaltrials.gov/ct2/show/NCT05013931. Accessed February 6, 2022.