

Beyond the Lungs: A Literature Review of COVID-19's Impact on Carotid Artery Disease and Treatment Challenges in Pandemic Era

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ABSTRACT

Introduction: To explore the impact of COVID-19 on carotid artery disease, with a focus on the virus-induced vascular complications, changes in management strategies during the pandemic, and the role of antiplatelet, anticoagulant, and novel therapeutic approaches in mitigating thrombotic risks.

Methods: A comprehensive review of the pathophysiological mechanisms linking COVID-19 to carotid artery disease was conducted, with an emphasis on endothelial dysfunction, hypercoagulability, and inflammation. Current evidence on antithrombotic therapies, surgical interventions, and alternative treatments during the pandemic was evaluated. Additionally, data on the impact of vaccination and associated thrombotic events were analyzed to provide a holistic understanding of the challenges in managing carotid artery disease in the context of COVID-19.

Results: COVID-19 exacerbates vascular dysfunction by triggering systemic inflammation, endothelial damage, and a hypercoagulable state, leading to heightened risks of carotid atherothrombosis and ischemic strokes. The pandemic disrupted elective surgical interventions like carotid endarterectomy (CEA), leading to delays in treatment and poorer outcomes. Antiplatelet and anticoagulant therapies remain crucial but require careful balancing due to the increased risk of bleeding and thrombosis in COVID-19 patients. Vaccination significantly reduced COVID-19-related complications but revealed rare cases of thrombotic events, including vaccine-induced immune thrombotic thrombocytopenia (VITT), necessitating vigilance in post-vaccination care.

Conclusion: The COVID-19 pandemic has significantly impacted the management of carotid artery disease, necessitating adaptive care strategies and innovative therapeutic approaches. Delayed surgical interventions, complexities in antithrombotic therapies, and rare vaccine-associated thrombotic events highlight the need for personalized and multidisciplinary management.

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Introduction

The outbreak of pneumonia in Wuhan, China, in December 2019 marked the discovery of SARS-CoV-2, the virus responsible for Coronavirus Disease 2019 (COVID-19)[1]. While COVID-19 is primarily known for its respiratory complications, it has increasingly been recognized as a vascular disease[2]. SARS-CoV-2 triggers widespread vascular dysfunction by causing endothelial injury, inflammation, and a hypercoagulable state, leading to thrombotic complications such as pulmonary embolism, deep vein thrombosis, and arterial thrombosis [3, 4]. These vascular abnormalities contribute significantly to disease severity, increasing the risk of multiorgan failure and poor outcomes in COVID-19 patients [4].

COVID-19 increases the risk of carotid artery thrombosis and ischemic stroke, particularly in patients with pre-existing atherosclerosis, through mechanisms like endothelial damage, hyperinflammation, and platelet activation[5]. Additionally, delays in elective procedures, such as carotid endarterectomy (CEA), during the pandemic have further complicated the management and treatment of carotid artery disease, underscoring the need for adaptive care strategies.

In this article, we explore the vascular implications of COVID-19, specifically focusing on carotid artery disease and its management and treatment challenges during the pandemic.

Pathophysiology of Carotid Stenosis and thrombosis due to COVID-19

In COVID-19, various pathophysiological mechanisms may explain increased thrombosis in the context of arterial stiffness of carotid disease: SARS-CoV-2 supports systemic hyper-inflammation characterized by the release of cytokines and diminishes the bioavailability of Nitric oxide (NO) necessary to increase arterial stiffness; likewise, direct infection of endothelial cells occurs by the viral interaction through ACE-2 receptors [6-10]. This, subsequently, creates an insult with loss of normal function among endothelium. This dysfunction further affects vascular smooth muscle cells and extracellular matrix behavior, increasing central aortic stiffness [11-13]. Systemic inflammation and endothelial lesions enhance a hypercoagulable state, impairing vascular tone regulation and promoting a prothrombotic state [12-14]. This disruption in vascular homeostasis favors the development of atherosclerosis and the creation of thrombosis even in young patients with minor

atherosclerotic disease, as seen in COVID-19-associated carotid atherothrombosis [15-17].

Carotid atherothrombosis in COVID-19 infection appears to be unique because of the combination of endotheliitis and COVID-19-induced coagulopathy. Less severe atherosclerotic plaques are more prone to rupture with subsequent thrombosis and formation of large thrombi in these patients in the context of SARS-CoV-2 endotheliitis and hypercoagulability [5, 18-21]. This process is further enhanced by the cytokine storm that instigates instability in the atherosclerotic plaques and extension of the clot. Some patients with COVID-19 developed large, free-floating thrombi that conferred a high stroke risk rather than a TIA. The strongly elevated D-dimer levels among these patients reflect immunothrombosis, a pathologic condition wherein immune activation contributes to coagulation [22]. The latter agrees with a thrombotic response, which may be pronounced in the carotid arteries because of high endothelial ACE-2 receptor expression and could account for a higher thrombus burden in COVID-19 patients [9].

Role of Antiplatelet and anticoagulant Therapy in Carotid diseases during COVID-19

Antithrombotic therapy, encompassing both antiplatelet and anticoagulant agents, plays a pivotal role in the management of carotid artery disease (CAD), including carotid stenosis and dissections, to prevent ischemic events and strokes [23, 24]. Antiplatelet therapy, typically with aspirin, is strongly supported for symptomatic carotid stenosis, particularly in patients with transient ischemic attacks (TIA) or minor ischemic strokes, as it significantly reduces the risk of recurrent events [23-26]. While single antiplatelet therapy is generally recommended for asymptomatic carotid stenosis due to its limited role in preventing myocardial infarction or other vascular events, symptomatic patients may benefit from dual antiplatelet therapy (DAPT) with aspirin and clopidogrel [25, 27-31]. However, DAPT carries a heightened risk of bleeding, particularly following carotid endarterectomy (CEA) or carotid artery stenting (CAS), warranting careful consideration of bleeding risk and individual patient factors [32-34].

Anticoagulants play a limited role in carotid artery disease (CAD) without other indications like atrial fibrillation [23, 35]. Novel oral anticoagulants (NOAC), particularly in combination with low-dose aspirin, have shown promise in reducing major cardiovascular events in stable CAD but at the cost of

increased bleeding risk. Compared to warfarin, NOACs offer better safety profiles, especially in reducing intracranial bleeding. However, adding anticoagulants to antiplatelet therapy increases bleeding risks without significant added benefit [36, 37]. Short-term dual therapy is recommended for patients undergoing revascularization, but further studies are needed to refine anticoagulation strategies in CAD management [38].

However, with the emergence of COVID-19, the role of these therapies has become more complex due to the virus-induced hypercoagulable state. COVID-19 induces a hypercoagulable state, with mechanisms such as endothelial injury, platelet activation, and systemic inflammation contributing to a heightened risk of thrombotic events, including ischemic stroke [12-14]. Observational studies and trials have shown that aspirin, a commonly used antiplatelet agent, may help mitigate some of these risks, reducing mortality and preventing thrombotic complications. However, the benefit of antiplatelet therapy in COVID-19 patients is not universally accepted, with randomized controlled trials (RCTs) showing no significant reduction in mortality, although aspirin did result in a modest improvement in hospital discharge rates and a slight reduction in the length of stay [39-44].

While the role of antiplatelet therapy in COVID-19 is debated, its application in carotid-related stroke prevention remains important. In patients with symptomatic carotid stenosis or acute ischemic stroke related to large vessel occlusion, aspirin or P2Y₁₂ inhibitors like clopidogrel are still recommended as the first-line therapy [45, 46]. For secondary stroke prevention in these patients, antiplatelet therapy remains standard [45, 46]. However, in critically ill COVID-19 patients with elevated D-dimer levels and coagulopathy, anticoagulation therapy, such as low-molecular-weight heparin (LMWH), is preferred [47, 48]. This anticoagulation approach addresses the hypercoagulable state seen in COVID-19, which significantly increases the risk of arterial and venous thrombosis, including strokes while minimizing bleeding risk. Combining anticoagulants with antiplatelet agents remains controversial due to potential increased bleeding risk and limited additional benefit in managing thrombotic complications.

The integration of anticoagulants and antiplatelet therapies in COVID-19 patients with carotid artery disease poses a delicate balance. While anticoagulants like LMWH or novel oral anticoagulants (NOACs) are effective for managing thromboembolic events, their

combination with antiplatelet therapy often increases the risk of hemorrhagic complications without providing significant added benefit in preventing ischemic events. This has been especially evident in hospitalized COVID-19 patients, where trials have shown that adding antiplatelets to anticoagulation therapy offers minimal additional clinical benefit. For patients undergoing carotid revascularization, short-term dual therapy with antiplatelets and anticoagulants may be necessary, but the overall risk-benefit ratio should be carefully evaluated, considering the patient's condition and bleeding risk. Further research is required to refine these therapeutic strategies, particularly in the unique context of COVID-19, to optimize outcomes for patients with carotid artery disease [48-51].

To address the limitations of current strategies, emerging treatments like Crizanlizumab, which targets P-selectin-mediated platelet activation, and sodium-glucose cotransporter-2 (SGLT2) inhibitors have gained attention. These agents aim to disrupt platelet-endothelial interactions and modulate inflammatory responses, potentially offering safer alternatives to traditional therapies. Additionally, targeting neutrophil extracellular traps (NETs), a key driver of immunothrombosis in COVID-19, represents a promising avenue for reducing thrombotic complications [51-55].

Management of Carotid Surgery in COVID-19 Patients

The COVID-19 pandemic significantly disrupted the management of carotid artery disease, as healthcare systems faced resource shortages, staff limitations, and stringent infection control protocols. Hospitals, overwhelmed with critically ill COVID-19 patients, had to balance the urgent need for care with the ongoing treatment of patients with vascular conditions like carotid artery stenosis [56-58].

In response to the strain on healthcare resources, the American College of Surgeons (ACS) and the Centers for Disease Control and Prevention (CDC) recommended postponing non-emergency surgeries, including elective carotid endarterectomies (CEA) [59, 60]. This led to significant delays in surgical intervention, particularly for patients with asymptomatic carotid stenosis (ACS). A global study reported an 11% in-hospital mortality rate for 1,103 vascular operations across 19 countries during the COVID-19 pandemic. Mortality rates were consistent across different procedures. In comparison to pre-pandemic data, mortality was notably higher. For

example, 30-day mortality for carotid interventions was typically 1% pre-pandemic, while elective aneurysm surgery had a mortality rate of 3% for open surgery and 0.5% for endovascular procedures. In this study, mortality for aneurysm procedures was double that, with delays in treatment possibly contributing. The study also found that Caucasian patients were twice as likely to die, and factors like chronic obstructive pulmonary disease (COPD), pneumonia, and urgent surgery were linked to higher mortality [61].

Additional data from a large tertiary care center in Virginia further highlighted the impact of delays on patient care. In April and May 2020, there was a 22.1% and 39.5% decrease in acute ischemic stroke admissions, respectively, reflecting challenges in stroke care. Delays in thrombolysis and thrombectomy times also increased significantly, from 38 to 94.5 minutes and 86 to 244 minutes, respectively, further exacerbating patient outcomes [62]. In response to these challenges, the UK's Vascular Society recommended aggressive medical management for newly symptomatic carotid patients when surgical options were unavailable [63]. Internationally, a 2020 study by the Vascular and Endovascular Research Network surveyed 53 countries and found that 17.7% of hospitals performed carotid surgery only on crescendo TIA patients, while 43.5% adopted a case-by-case approach, and 36.4% maintained their pre-pandemic surgical practices [64].

As traditional surgical procedures were increasingly limited during the COVID-19 pandemic, many healthcare providers turned to alternative treatments, such as carotid artery stenting (CAS), which became a popular choice for managing carotid artery disease. CAS offers several advantages: it is minimally invasive, typically does not require general anesthesia, and allows for shorter hospital stays. These benefits were particularly crucial during the pandemic, as reducing patient exposure to COVID-19 and alleviating the strain on intensive care units (ICUs) became top priorities. For high-risk patients, especially those with symptomatic carotid stenosis who were not suitable candidates for open surgery, CAS emerged as a viable, research-backed option [56, 65, 66].

In addition to changes in surgical practices, telemedicine played a critical role in maintaining patient care throughout the pandemic. Hospitals in countries like Portugal, Italy, and the United States adopted virtual consultations for non-urgent cases, significantly reducing the need for in-person visits. This strategy not only minimized the risk of COVID-

19 transmission but also allowed patients to continue receiving necessary care remotely. Telehealth platforms enabled doctors to monitor patients' neurological health and carotid function through remote tools, ensuring timely interventions if a patient's condition worsened [58, 67, 68].

However, patients undergoing carotid surgery during the pandemic faced heightened risks of complications. These included cervical hematomas, thrombosis, and respiratory distress, complications that were exacerbated by COVID-19-related factors such as limited ICU capacity and heightened infection risks. To address these challenges, hospitals implemented strict safety protocols, including the mandatory use of personal protective equipment (PPE) for healthcare staff, and modified perioperative management guidelines. These measures were vital for safeguarding both patients and healthcare workers while ensuring that urgent procedures could proceed safely [66, 69].

Role of Vaccination in Carotid Vascular Complications

In COVID-19 pandemic, the development and deployment of vaccines were heralded as critical tools to curb the virus's spread, mitigate its severe outcomes, and reduce mortality. As of December 2021, billions of vaccine doses have been administered globally, representing a monumental public health achievement. However, the swift development and emergency rollout of these vaccines have also unveiled rare but notable complications, particularly concerning vascular and cardiovascular health.

Among the vaccines developed, those based on mRNA technology (Pfizer-BioNTech and Moderna) and adenoviral vectors (AstraZeneca, Johnson & Johnson, and Sputnik V) have garnered attention for their efficacy and safety profiles [70, 71]. Despite rigorous phase III trials, where major safety concerns were minimal, real-world data have identified rare cases of thrombotic events [72-75]. These occurrences, while statistically insignificant when weighed against the benefits of vaccination, demand thorough investigation due to their potential severity.

COVID-19 itself is known to precipitate a hypercoagulable state, increasing the risks of thromboembolic events, such as stroke and deep vein thrombosis. Similarly, the vaccines, particularly those utilizing adenoviral vectors, have been linked to conditions such as vaccine-induced immune thrombotic thrombocytopenia (VITT). This syndrome, characterized by low platelet counts and unusual

thrombosis sites, including cerebral venous sinuses, mimics heparin-induced thrombocytopenia (HIT) in its pathophysiology [76-80]. The interaction of anti-PF4 antibodies with platelets appears central to its development, triggering a cascade of coagulation and inflammation. While mRNA vaccines have a much lower association with thrombosis, isolated reports of arterial thrombotic events, such as acute ischemic strokes, warrant further exploration [77, 80, 81].

Emerging evidence suggests potential links between vaccination and carotid artery thrombotic events, though the data remain sparse. Cases of acute ischemic stroke (AIS) involving free-floating thrombi (FFT) within carotid arteries have raised questions about vaccine-associated vascular risks [18]. Observational studies have documented cases of FFT in otherwise healthy individuals following mRNA vaccination, with some presenting within days of administration. Despite this temporal association, causation remains elusive due to the multifactorial nature of thrombotic pathologies and the relatively low incidence of these events post-vaccination [82, 83].

The pathophysiology underlying carotid involvement post-vaccination may parallel mechanisms seen in VITT. The presence of circulating procoagulant factors, endothelial activation, and immune-mediated platelet aggregation could contribute to thrombus formation. However, it is crucial to distinguish these occurrences from the thrombotic sequelae directly attributable to SARS-CoV-2 infection, which pose a significantly higher risk and longer duration of vascular complications compared to vaccination.

Prompt recognition and management of vaccine-associated thrombotic events are imperative to mitigate adverse outcomes. Non-heparin anticoagulants, intravenous immunoglobulin (IVIG), and corticosteroids remain the mainstays of treatment for VITT [84-86]. For FFT in the carotid arteries, therapeutic strategies may extend to combined medical and interventional approaches, including mechanical thrombectomy in cases of AIS.

Conclusion

The COVID-19 pandemic has revealed a complex relationship between SARS-CoV-2 infection and vascular health, particularly in the context of carotid artery disease. This article highlights the multifaceted mechanisms through which COVID-19 exacerbates endothelial dysfunction, systemic inflammation, and hypercoagulability, leading to increased risks of carotid stenosis, atherothrombosis, and ischemic stroke. These

insights underscore the significant challenges posed by the pandemic in managing carotid artery disease, from delays in surgical interventions to the complexity of balancing antiplatelet and anticoagulant therapies.

The management of carotid artery disease in the COVID-19 era demands a multidisciplinary approach, incorporating advances in pharmacological strategies, such as the use of NOACs, antiplatelet therapy, and emerging treatments like P-selectin inhibitors and SGLT2 inhibitors, to address the unique thrombotic and inflammatory milieu induced by the virus. The adoption of alternative procedures, including carotid artery stenting (CAS), alongside innovations in telemedicine, highlights the adaptability required to sustain vascular care during a global crisis.

Vaccination has been a cornerstone in combating the pandemic, significantly reducing the severity and mortality associated with COVID-19. However, rare thrombotic complications, such as vaccine-induced immune thrombotic thrombocytopenia (VITT) and potential carotid thrombotic events, necessitate ongoing vigilance and refinement in clinical practice. The pandemic has emphasized the importance of personalized risk assessment and targeted treatment strategies, ensuring optimal outcomes for patients with carotid artery disease.

In conclusion, the COVID-19 pandemic has profoundly transformed the landscape of vascular medicine, revealing vulnerabilities while catalyzing innovation. By integrating these lessons, advancing research, and fostering collaboration across disciplines, the medical community can better address the ongoing challenges of carotid artery disease and other vascular complications in a post-pandemic world.

Consent for Publication

Not applicable, as this study does not involve patient data requiring informed consent.

Ethics Approval and Consent to Participate

This study is a review and does not involve primary research or human participants. All references have been appropriately cited in adherence to copyright regulations.

Authors' contributions

All authors contributed equally and approved the final article.

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Data Availability Statement

The data supporting the findings of this review are derived from publicly available sources cited throughout the article. Any additional information can be obtained from the corresponding author upon reasonable request. Due to ethical and copyright considerations, raw data is not publicly accessible.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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