Thrombectomy for Treatment of Acute Stroke in the COVID-19 Pandemic

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Abstract

This commentary will focus on the role of thrombectomy for the treatment of embolic stroke during the 2019 novel coronavirus disease (COVID-19). We will begin with review of recently promulgated guidelines for use of thrombectomy in COVID-19-associated stroke. We will then survey the reported experience of thrombectomy applied to treatment of large-vessel occlusion (LVO) stroke in COVID-19. We will conclude by discussing unusual challenges confronted by neuro-interventionalists seeking to perform thrombectomy in COVID-19 patients with acute LVO stroke.

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Introduction

In December 2019, several cases of atypical pneumonia of unclear etiology were reported in Wuhan, China [1] and were subsequently attributed to infection with

“severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). Designated by the WHO as “2019 novel coronavirus disease” or the coronavirus disease (COVID-19) pandemic, nearly 7,400,000 cases of SARS-CoV-2 infection were reported worldwide among 188 countries or regions by June 2020.

Stroke has been described as an unusual neurologic complication of COVID-19 and may result from large-vessel occlusion (LVO) of cerebral arteries. Mao and colleagues [2] found acute cerebrovascular disease in 6 of 214 (2.8%) patients hospitalized with SARS-CoV-2 infection. Two of these 6 patients had acute onset of hemiplegia that preceded COVID-19 pneumonia, implying LVO caused by cerebral embolism that could have been treated by mechanical thrombectomy.

In this commentary, we will focus on the role of thrombectomy for treatment of embolic stroke in COVID-19. We will begin with review of recently promulgated guidelines for use of thrombectomy in COVID-19-associated stroke. We will then survey the reported experience of thrombectomy applied to treatment of LVO stroke in COVID-19. We will conclude by discussing unusual challenges confronted during the application of thrombectomy in victims of SARS-CoV-2 infection, such as management of COVID-19 coagulopathy.

Guidelines for Use of Mechanical Thrombectomy to Treat Acute Ischemic Stroke in COVID-19

LVO in ischemic stroke occurs when a major intracranial artery or a distal extracranial carotid, or vertebral segment becomes obstructed by thromboembolus. Since 2015, an expanding number of clinical trials have been published to confirm the benefit of mechanical thrombectomy in the management of LVO stroke and have been summarized in meta-analyses [3, 4].

The Stroke Council of the American Heart Association/American Stroke Association has reiterated the need to adhere to established procedures for management of acute ischemic stroke and for patient selection for mechanical thrombectomy, despite the challenges posed by COVID-19 [5]. Khosravani and others [6] have published recommendations for protected “code stroke” (PCS) to be performed during the COVID-19 pandemic. The PCS must precede selection of patients to undergo mechanical thrombectomy for treatment of acute thromboembolic stroke. The proposed COVID-19 stroke code begins with screening for infectious contacts, respiratory or gastrointestinal symptoms of SARS-CoV-2 infection, and recent travel, as performed by paramedics or triage personnel in Emergency Departments (EDs). Once a patient is identified to be at risk for harboring SARS-CoV-2 infection, and then the PCS conducted in the hospital ED would involve the use of personal protective equipment (PPE) to limit exposure of medical personnel to aerosolized viral particles and rapid diagnostic testing to begin verification that the patient is infected. In the COVID-19 PCS, 2 coordinated teams would work in parallel. The members of the first team would be garbed in PPE to examine the patient and initiate treatment with recombinant tissue-plasminogen activator (rt-PA) if warranted. The second team would remain outside the patient treatment area to oversee safety procedures and monitor use and consumption of PPE by the first team.

Noncontrast computed tomography (CT) of the brain would be preferred over MRI for stroke diagnosis and to exclude intracranial hemorrhage or mass lesions before rt-PA administration. The choice of CT over MRI would be justified by expediency and greater ease in cleaning the imaging device after potential SARS-CoV-2 exposure. To select patients for thrombectomy, CT angiography of the head/neck and/or CT perfusion imaging may be required and could be bundled with the screening noncontrast CT brain scan.

In many EDs, patients who are identified at risk for COVID-19 are directed to travel along a defined path that

may include entry into rooms that are dedicated for endotracheal intubation and performance of other minimally invasive procedures, before referral for thrombectomy. Rapid diagnosis of suspected SARS-CoV-2 infection would be essential, preferably by reverse transcription-PCR assays that qualitatively show viral nucleic acid in nasal swabs.

Accumulated Experience with Mechanical Thrombectomy for Treatment of Acute Stroke in COVID-19

To date, there are only 3 publications of the results of mechanical thrombectomy performed for treatment of acute thromboembolic stroke in patients known to be infected with SARS-CoV-2. For additional details, not addressed in the succeeding paragraphs, refer to Table 1 and to the original publications.

In the first article, Al Saiegh and colleagues [7] described performance of thrombectomy for recanalization of the proximal left middle cerebral artery (MCA) in a 62-year-old woman with acute onset of right hemiparesis and aphasia. The left MCA was successfully reopened, and the patient was referred to a rehabilitation facility but was readmitted 10 days later for management of post-reperfusion hemorrhage within the ischemic left hemisphere. During this second hospitalization, the patient underwent placement of an external ventricular drain (EVD) for removal of spinal fluid, hemicraniectomy for relief of malignant cerebral edema, and tracheostomy to secure the airway after prolonged intubation. Infection with SARS-CoV-2 was confirmed by routine screening by nasal swab undertaken as the patient was prepared for tracheostomy. There were no overt symptoms of COVID-19 pneumonia, and chest radiograph showed no “ground-glass” opacities. Two samples of spinal fluid removed through the EVD tested negative for the presence of SARS-CoV-2 nucleic acid. Four days after positive nasal swab was obtained, repeat testing was negative to show clearance of SARS-CoV-2 from the nasopharynx.

Oxley and others reported the second case series reflecting experience with thrombectomy used to treat COVID-19-associated LVO in the Mt. Sinai Health System in New York City [8]. Five patients of youthful age between 33 and 49 years presented with characteristic LVO syndromes and radiographic evidence of intraluminal thromboembolic occlusion of major extra- or intracranial arteries. An unusual feature of this case series was of delay between best estimated time of onset of stroke

Table 1. Published studies of stroke thrombectomy in COVID-19

Reference	Study population	Status of SARS-CoV-2 infection or associated systemic inflammation/coagulopathy at stroke onset	Outcome of thrombectomy or intervention
Al Saiegh et al. [7]	Sixty-two-year-old woman with acute onset of right hemiparesis and aphasia; pre-stroke vascular risk factors not reported	No overt symptoms of SARS-CoV-2 infection at stroke onset and subsequent performance of thrombectomy; active infection confirmed by nasopharyngeal swab assay during second hospital admission	Successful clot retrieval from the proximal left MCA; post-thrombectomy TICI score not reported; after initial hospitalization that included thrombectomy, patient had delayed post-reperfusion intraparenchymal hemorrhage within the left cerebral hemisphere and was readmitted 10 days after prior discharge
Oxley et al. [8]	One woman and 4 men aged 33–49 years; pre-stroke vascular risk factors: diabetes ($n = 2$), hyperlipidemia/hypertension ($n = 1$), and history of mild stroke ($n = 1$); affected vascular territories included MCA ($n = 3$), ICA ($n = 1$), and PCA ($n = 1$); baseline NIHSS 13–23 points; delay between stroke symptom onset and arrival ranged 2–28 h	Definitive evidence of SARS-CoV-2 respiratory infection in only 2/5 patients at stroke symptom onset; 1 patient with lethargy; 2 patients with no evidence of SARS-CoV-2 respiratory infection at stroke onset; hematological abnormalities suggestive of underlying systemic inflammation and/or coagulopathy: prolonged aPTT ($n = 2$) or elevated fibrinogen level, D-dimer, or ferritin ($n = 3$ each)	One patient (R ICA occlusion) treated only by anticoagulation with factor Xa inhibitor; clot retrieval by thrombectomy in 4/5 patients ($n = 3$ MCA occlusion/1 PCA occlusion); post-thrombectomy TICI score not reported; 1 patient (L MCA occlusion) treated with IV rt-PA before thrombectomy and required hemicraniectomy for management of malignant cerebral edema
Escalard et al. [9]	Two women and 8 men aged 54–71.5 years; pre-stroke vascular risk factors: hyperlipidemia/hypertension ($n = 8$), diabetes ($n = 4$), pre-stroke anticoagulation ($n = 4$), and smoking/AF ($n = 1$ each); 5 patients with multi-territory LVO on diagnostic cerebral angiography; baseline NIHSS 19–25.7 points; thrombectomy started ≤ 6 h after stroke onset in all 10 patients	Definitive evidence of SARS-CoV-2 respiratory infection in only 3/10 patients at stroke symptom onset; 3 patients hospitalized for treatment of SARS-CoV-2 respiratory infection and 2 with no evidence of active infectious disease at stroke onset; hematological abnormalities not reported	Successful recanalization in 9/10 patients with post-thrombectomy TICI ≥ 2 B; no first-pass effect; 5/10 patients treated with IV rt-PA before thrombectomy; early arterial reocclusion ≤ 24 h in 4/10 patients; 24-h NIHSS ranged 19.75–42 points; in-hospital mortality in 6/10 patients: sepsis, poststroke malignant brain edema, or acute respiratory failure ($n = 2$ each); no symptomatic intracranial hemorrhage

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MCA, middle cerebral artery; TICI, thrombolysis in cerebral infarction; ICA, internal carotid artery; PCA, posterior cerebral artery; NIHSS, NIH Stroke Scale; aPTT, activated partial thromboplastin time; rt-PA, recombinant tissue-plasminogen activator; AF, atrial fibrillation; LVO, large-vessel occlusion.

symptoms and presentation for medical treatment, which extended up to 28 h. The authors noted that 2 of the 5 patients hesitated to call for paramedic ambulance transport for fear of contracting COVID-19 upon being admitted to the receiving hospital. At stroke onset, only 2 of the 5 patients had coexisting symptoms of COVID-19 respiratory infection with fever, cough, or chills. Two of the remaining 3 patients had no respiratory symptoms or fever when stroke occurred clearly indicating that LVO was the presenting clinical sign of SARS-CoV-2 infection in these individuals. In the ED, the mean baseline National Institutes of Health Stroke Scale (NIHSS) was 17 points, as expected with LVO. All 5 patients underwent CT angiography that revealed thromboembolic occlusion of the MCA (3), posterior cerebral artery (1), or internal carotid artery (ICA; 1). One patient presented with cough and chills at 28 h after stroke symptom onset and was shown

to have occlusion of the right ICA. By CT perfusion imaging, there was no identified mismatch between infarcted and at-risk tissue in the affected cerebral hemisphere. This patient was not considered eligible to undergo mechanical clot retrieval by thrombectomy and was managed with anticoagulation. The remaining 4 patients underwent thrombectomy for treatment of LVO. Pre-procedural cerebral thrombolysis by systemic infusion of rt-PA was performed in only one patient who presented with proximal left MCA occlusion at 2 h after stroke symptom onset. Despite aggressive stroke management with cerebral thrombolysis followed by mechanical thrombectomy, the patient developed malignant cerebral edema and required hemicraniectomy. In this case series of patients <50 years with few vascular risk factors and no history suggestive of preexisting arterial or venous coagulopathy, it is noteworthy that hematologic abnormalities

were prevalent. Varying combinations of the 5 patients had prolonged activated partial thromboplastin time (2) or elevated levels of fibrinogen (3), D-dimer (3), or ferritin (3).

Escalard and colleagues [9] published the third case series of thrombectomy for treatment of acute LVO in COVID-19 patients at the Rothschild Foundation Hospital in Paris, France. In this group of 10 patients with median age of 60 years (range 54–71.5 years), 7 (70%) had no or only mild symptoms of COVID-19 at stroke onset. Two patients (20%) were <50-year old and were asymptomatic at stroke onset. Three patients (30%) had already been hospitalized for treatment of COVID-19 at the time of stroke occurrence. Median time from onset of COVID-19 symptoms to LVO was 6 days (range 2–18 days). Eight patients (80%) had vascular risk factors, including atrial fibrillation (1). Four patients (40%) were fully anticoagulated (1 was anticoagulated while on dual antiplatelet therapy after myocardial infarction) at stroke symptom onset but still had LVO. The median NIHSS was 22 points (range 19–25.7 points). Five patients (50%) underwent cerebral thrombolysis with median time of administration of rt-PA of 175 min.

Angiographic procedures culminating in mechanical clot retrieval were initiated within 6 h of stroke onset for all 10 patients. Overall, 9 patients (90%) had successful trans-vascular reperfusion achieving modified thrombolysis in cerebral infarction score $\geq 2B$, with median time from stroke onset to recanalization of 302 min. However, in this case series, there were 3 unusual features that highlighted the complexity of thromboembolic cerebral arterial occlusion in association with COVID-19. In the first instance, there were 5 patients (50%) who had simultaneous, multi-territory LVO (proximal MCA and either anterior or posterior cerebral artery occlusion) on presentation. This ominous finding echoed the description of multi-territory LVO during the SARS epidemic of 2002 that was caused by SARS-CoV [10], a beta-coronavirus of the same genera as SARS-CoV-2. Second, in none of the 10 patients was recanalization achieved after only one intraluminal pass of the clot retrieval device (“first-pass effect”). A median number of 3.5 catheter passages were required per patient. Third, there were an unusually high number of intraluminal thrombotic reocclusions that affected 4 of the 10 patients (40%). None of the 10 patients had dramatic early neurological improvement after thrombectomy. The overall in-hospital, all-cause mortality rate was 60% among the 10 victims of LVO associated with COVID-19, compared to 11% among uninfected patients.

Challenges Confronted during Application of Mechanical Thrombectomy for Treatment of Acute Stroke in COVID-19

As highlighted by the case series reviewed in the preceding section, there are several potentially adverse contributors to the clinical and/or angiographical outcome of thrombectomy in a patient with COVID-19. Significant delays in performing thrombectomy may be the most important factor in negatively affecting clinical outcome. In the second case series presented by Oxley and colleagues [8], some patients with easily recognized signs of acute LVO delayed seeking medical attention (and undergoing thrombectomy) for fear of contracting COVID-19. Time metrics that are so vital to the successful outcome of thrombectomy (door-to-CT, door-to-reperfusion, and stroke symptom onset to arteriocentesis) may be dramatically affected due to delayed recognition or denial of LVO stroke symptoms in the field. Interinstitutional transfer of patients who may be affected by COVID-19 could be delayed, thereby restricting access to thrombectomy for treatment of LVO. Overburdened EDs, struggling to implement time-consuming procedures required for rapid diagnosis of SARS-CoV-2 infection in large volumes of patients, may be less efficient in identifying and transporting candidates for thrombectomy to the angiography suite. Anticipation of SARS-CoV-2 infection has forced comprehensive stroke treatment centers to implement changes in the complex, multistep pathway that results in a successfully performed thrombectomy. The most significant demand elements in this pathway would be (1) timing and speed of completion of SARS-CoV-2 diagnostic testing and (2) timing and place of performance of endotracheal intubation for general anesthesia in patients who may be symptomatic with COVID-19 pneumonia. In a patient for whom the diagnosis of COVID-19 has been established or must be assumed, the decision for general anaesthesia or conscious sedation would be made differently than in routine clinical practice, which could impact negatively on the performance of the operator and the timeliness of the thrombectomy. Choosing conscious sedation would avoid the risk of exposure of medical personnel to aerosolized SARS-CoV-2 originating from the patient, even though the interventionalist may prefer endotracheal intubation and general anesthesia.

The most daunting challenge that may complicate thrombectomy performed for treatment of LVO in COVID-19 would be increased intraluminal thrombus burden caused by an associated, as yet undeciphered, coagulation disorder, or microvascular injury. To illustrate,

the patient reported by Al Saiegh and colleagues [7] had delayed intracerebral hemorrhage after thrombectomy. Oxley and others [8] described coagulation abnormalities in most of their patients. Escalard and coauthors [9] remarked on LVO presenting simultaneously in multiple arterial irrigation zones, absence of “first-pass effect,” and the frequent occurrence of post-thrombectomy arterial reocclusion. Symptomatic patients with COVID-19 may have lymphocytopenia, thrombocytopenia, prolonged prothrombin and activated thromboplastin times, and elevated levels of D-dimer, fibrinogen, ferritin, and fibrin-degradation products [1, 11, 12]. Zhang and colleagues [13] described 3 patients with multiple arterial irrigation zone infarcts in brain and elevated levels of anticardiolipin- or beta-2 glycoprotein 1 autoantibody levels, implying the occurrence of an immune-mediated arterial coagulopathy. Varga and others [14] described endotheliitis or arterial endothelial cell injury as a possible contributor to the prothrombotic state observed in association with COVID-19. During the SARS epidemic of 2002 caused by a beta-coronavirus with structural similarity to SARS-CoV-2, several patients with multi-territory cerebral infarction were described and may have been affected by a similar viral-mediated coagulopathy [10].

When confronted with COVID-19-associated coagulation abnormalities, neuro-interventionalists may have to undertake procedures called for during treatment of LVO in disseminated intravascular coagulation, cancer-associated coagulopathy, and sepsis. These include use of intraluminally administered fibrinolytics or antiplatelet agents, multiple passes to retrieve clot, aspiration devices, stent deployment, and other complex maneuvers.

Conclusions

Acute stroke is a recognized neurological complication of SARS-CoV-2 infection in COVID-19. Large-vessel occlusive stroke caused by arterial thromboembolism

is encountered with unusually high frequency among patients with COVID-19-attributed cerebrovascular disease. Victims of COVID-19-associated LVO may be atypical, in regard to youthful age, and noted absence of vascular risk factors. Mechanical thrombectomy to reperfuse ischemic brain has been applied successfully to treat LVO in COVID-19, but overall outcome may be affected adversely by the severity of the underlying viral pneumonia. Challenges confronting the neuro-interventionalist seeking to treat LVO in COVID-19 include delayed presentation due to patient fear of contracted infection, disruptively complicated patient management pathways, and viral-mediated arterial coagulopathy of unknown cause.

Statement of Ethics

Approvals for publication of the described results were obtained from individual Ethics Committees by the original authors of the cited work. As this Commentary includes no previously unpublished information about any patient, informed consent for publication was not requested or obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.C.P. wrote the first and final draft; P.P. and G.P. contributed to revisions.

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