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Review article

A review of acute limb ischemia in COVID-positive patients

Nicole Ilonzo[a,*], Dejah Judelson[b], Wissam Al-Jundi[c], Yana Etkin[d], Leigh Anne O'Banion[e], Aksim Rivera[f], Giovanni Tinelli[g], Rafaello Bellosta[h], Ageliki Vouyouka[a]

[a] Division of Vascular Surgery, Icahn School of Medicine at Mount Sinai, The Mount Sinai Medical Center, 1425 Madison Avenue, 4th Floor, New York, NY 10029
[b] Division of Vascular Surgery, University of Massachusetts, Worcester, MA
[c] Norwich Vascular Centre, Norfolk and Norwich University Hospital, Norwich, UK
[d] Division of Vascular and Endovascular Surgery, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY
[e] University of California- San Francisco Department of Surgery
[f] Division of Vascular Surgery, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY
[g] Unit of Vascular Surgery, Fondazione Policlinico Universitario Gemelli IRCCS-Università Cattolica del Sacro Cuore
[h] Divisions of Vascular Surgery, Department of Cardiovascular Surgery, Fondazione Poliambulanza, Brescia, Italy

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ABSTRACT

This literature review discusses the current evidence on acute limb ischemia (ALI) in patients with COVID-19. Throughout the pandemic, these patients have been at increased risk of arterial thrombotic events and subsequent mortality as a result of a hypercoagulable state. The exact mechanism of thrombosis is unknown; however arterial thrombosis may be due to invasion of endothelial cells via angiotensin-converting enzyme 2 (ACE2) receptors, endothelial injury from inflammation, or even free-floating aortic thrombus. Multiple studies have been performed evaluating the medical and surgical management of these patients; the decision to proceed with operative intervention is dependent on the patient's clinical status as it relates to COVID-19 and morbidity of that disease. The interventions afforded typically include anticoagulation in patients undergoing palliation; alternatively, thrombectomy (endovascular and open) is utilized in other patients. There is a high risk of rethrombosis, despite anticoagulation, given persistent endothelial injury from the virus. Postoperative mortality can be high in these patients.

1. Introduction

Acute limb ischemia (ALI) occurs in 1.5 cases per 10,000 persons per year [1]. During the coronavirus disease 2019 (COVID-19) pandemic, ALI occurred approximately five times more frequently in COVID-positive patients [2]. COVID-19

* Corresponding author.
E-mail address: nicole.ilonzo@mountsinai.org (N. Ilonzo).

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may be the first of its kind to precipitate arterial thrombotic events through mechanisms inducing endothelial injury; other viruses, such as severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome, and influenza, have been associated with venous thrombosis but not arterial thrombosis [3,4]. During the COVID-19 pandemic in Brescia, Italy, there was an increase in patients with ALI from 1.8% in the same timespan for 2019 to 16.3% in 2020 [2]. Similarly, during the peak pandemic in the region of Lombardy, Italy, ALI was observed in 64% of COVID-positive admissions to the vascular service and in only 23% of COVID-negative admissions from March 9, 2020 to April 28, 2020 [5]. This was similar to the experience in New York City during the peak of the pandemic from March 1 to April 15, 2020; in one report by Ilonzo et al [6], there was a relative increase of lower extremity revascularization cases from 10.7% of total volume of cases to 29.8% likely secondary to ALI [6]. Similarly, Indes et al [7], from a different institution, reported a greater distribution of aortoiliac thrombosis in COVID-positive patients compared to COVID-negative patients admitted during the same period.

There have been numerous retrospective reports and case series denoting ALI in patients with COVID-19. A literature review was performed using the keywords *arterial thrombosis*, *thrombectomy*, *embolectomy*, *acute limb ischemia*, *COVID-19*, and *coronavirus*. This yielded 254 articles and 60 were selected for review. These case reports, review articles, and cohort studies made up the literature for this review.

2. Coagulopathy and COVID-19

The first reports of arterial thrombosis arose in the spring of 2020 from Klok et al [8], who analyzed 184 patients admitted to the intensive care unit with COVID-19 at a Dutch hospital. In this cohort, there were three patients with arterial thrombosis. It must be noted that the arterial events that occurred in this study were all cerebrovascular accidents, not limb ischemia. These patients developed complications despite chemoprophylaxis; therefore, this study suggests that therapeutic anticoagulation be given to critically ill patients with COVID-19. This is the first time that COVID-19–related arterial coagulopathy was noted to be different from the disseminated intravascular coagulation seen in septic patients or other patients in shock from usual catastrophic events [8].

In typical disseminated intravascular coagulation, the primary phenotype is disordered bleeding and it is associated with prolonged activated clotting time, prothrombin time, and thrombocytopenia. In patients with COVID-19 that have diffuse coagulopathy, there are few bleeding complications [9]. Markers usually elevated in patients with COVID-19–related arterial thrombosis are D-dimer, fibrinogen, and C-reactive protein [10].

Later, additional data supported the conclusion that therapeutic anticoagulation reduced mortality in their population of critically ill patients with COVID-19 [11]. In February 2020, Tang et al [12] published data showing that abnormal coagulation was associated with worse prognosis in patients with COVID-19. This was revealed through an examination of coagulation markers in 183 patients with COVID-19. The markers assessed included D-dimer, prothrombin time, platelet count, and fibrinogen. The coagulation markers were analyzed in these patients on day 1 of admission and then again on day 14. There was increased mortality in patients with elevated D-dimer [12]. In evaluating the series of case reports and cohort studies in patients with ALI from arterial thrombosis, there was a steep increase in D-dimer immediately before diagnosis and values declined after intervention [7,13]. Along these lines, the International Society of Thrombosis and Haemostasis published a series of guidelines on management of COVID-19 coagulopathy. These included trending coagulation factors in patients with COVID-19 and subsequently using prophylactic low-molecular-weight heparin in all hospitalized patients unless there were contraindications [14].

3. Proposed mechanisms of COVID ALI

The exact mechanism of acute ALI in patients with COVID-19 infection is not yet well understood, but several theories have been proposed. These include viral invasion of endothelial cells via angiotensin-converting enzyme 2 (ACE2) receptors, endothelial injury from inflammation, and free-floating aortic thrombus [15,16]. Initial case reports speculated that ALI may have been an embolic phenomenon, due to free-floating aortic thrombus [15,16]. Patients with COVID-19 are hypercoagulable and this procoagulant state contributes to arterial thrombosis [12]. The causes of hypercoagulability are multifactorial. Hypoxia, for instance, contributes to coagulopathy by converting the normal phenotype of the endothelium (resistant to thrombotic activity) to a prothrombotic phenotype through the increased transcription of the early growth response gene 1 and hypoxia-inducible factor 1 [17]. COVID-19 is also associated with a cytokine release that contributes to hypercoagulability [18]. Specifically, interleukin-1 is produced in excess in the setting of COVID-19 and this initiates a cytokine cascade and stimulates interleukin-6, inflammatory cells invade the tissue and induce endothelial injury, and fibrinogen production is increased [18]. Endothelial injury leads to exposure of ultra-large von Willebrand factor multimers, which leads to further thrombotic activity [17].

It is important to emphasize the effects of the hyperinflammatory state, endotheliitis, and associated endothelial injury, not only on acute thrombosis but also on re-thrombosis after surgical or endovascular intervention [19]. Arterial thrombosis occurs in the acute phase in patients that present with active COVID disease and abnormal inflammatory markers. The associated endothelial injury persists even in patients that have recovered from COVID and have normalization of the inflammatory markers [19]. Additional mechanisms of endothelial injury have been described. The severe acute respiratory syndrome coronavirus 2 itself binds ACE receptors found on endothelium of several cell types, including lungs, vascular endothelium, and even kidneys [3]. The binding of the severe acute respiratory syndrome coronavirus 2 not only leads to infection, but also endothelial injury through the initiation of an inflammatory cascade [17]. Studies have detailed the theory of endothelial dysfunction in vessels as a result of the virus binding to the ACE2 receptor on the endothelial cells [20]. However, some authors have significant reservations regarding the va-

lidity of viral invasion of vascular endothelium in explaining arterial thrombosis in patients infected with COVID-19 [21].

In fact, currently, the most prevailing theory is that COVID-19 results in endotheliitis that leads to thrombosis and, in many cases, ischemia. Endotheliitis has been found in the coronary circulation [22]. One study reviewed four cases of COVID-positive patients who underwent major lower extremity amputation for Rutherford III ALI. Pathologic examination revealed inflammation in the major arteries of the amputated lower extremities. Primary findings in the specimens were lymphocytic infiltration, apoptotic bodies, and plasma cell infiltration, demonstrated on hematoxylin and eosin staining [23]. Similarly, lymphocyte infiltration was also seen by different authors in the vessels of another two patients with COVID who underwent amputation and lower extremity bypass for ALI [24].

4. Presentation

One of the interesting findings regarding the clinical presentation of ALI among patients with COVID-19 infection is that it is rather unpredictable and not necessarily associated with severity of the disease and viral load [25,26]. A significant number will present in the setting of critical illness. One study showed that 13% of 358 patients in the intensive care unit were found to have a thrombotic event, including but not limited to pulmonary embolism, deep vein thrombosis, and ALI [27]. However, in another study, 38.1% of thrombotic events were seen in patients with mild COVID-19 [25]. In fact, some patients with ALI were completely asymptomatic from a respiratory standpoint and were incidentally found to be COVID-positive on screening before the operating room [26]. In one case report by Schweblin et al [28], the patient had respiratory symptoms from COVID-19 two weeks earlier, but presented later with an arterial thrombotic event. This is a phenomenon, described by Bozzani et al [19], in which patients present in a delayed fashion likely due to prolonged global endothelial dysfunction even beyond the acute phase of the COVID-19 disease.

In studies that reported Rutherford classification at presentation, most patients presented with Rutherford IIA or IIB ALI. In fact, 28% to 77% presented with Rutherford IIA and 17% to 75% presented with Rutherford IIB [2,25,29]. It is important to note that few patients will also present with a thrombotic event, despite having been on therapeutic anticoagulation. In one study, 19.1% of patients had been on anticoagulation before their arterial thrombotic event [25]. There is also no clear correlation between timing of the COVID infection and the arterial thrombotic event. Obviously, it is difficult to estimate this in asymptomatic patients, but many hospitalized patients will develop ALI during their hospitalization and it varies between 6.6 and 15.77 days after their admission for other COVID-related symptoms [30,31].

There are some sex-related correlations in ALI due to COVID-19. Men tended to present more frequently with ALI than women in most of the series [7,29,30]. In the Peruvian cohort, 76.6% of COVID-positive patients with ALI were male [29]. Similarly, 76% of patients that presented with ALI in a New York City medical center were male [30]. In one study from Spain, 92.3% of patients with ALI were also male [31]. There is no clear pathway to explain why men would present more frequently with ALI than women. Although men are more likely to have more severe disease from COVID-19 than women, and higher mortality (as mentioned above), there is no substantial evidence so far that ALI is associated with severe disease [32]. It is possible that sex-related differences in coagulation patterns may play a role in this discrepancy [33]. Although women with COVID-19, compared to men, have generally lower mortality and are less likely to develop ALI, there is an observed trend, in one study, toward increased mortality in women with COVID-19 disease and ALI compared to their male counterparts [25].

5. Diagnosis and management

Most of the studies used either computed tomography angiography or arterial duplex to identify occlusive lesions. Thrombosis of the arteries typically occurred in the lower extremities [29]. The most common location of thrombus was the femoropopliteal region in one cohort [25]. In another cohort, 64.7% of patients experienced thrombosis in this region, followed by tibial disease in 29.4% of patients, followed by "desert foot" (neither the dorsalis pedis artery nor the plantar arteries are patent) in 23.5% of patients requiring thrombolysis [2]. The tendency for COVID-19 thrombus to present in more proximal regions of the circulation has been confirmed in multiple studies [34]. One study compared computed tomography angiography scans of patients that presented with concerns for lower limb ischemia during the COVID-19 pandemic to propensity-matched patients with concerns of ischemia from the prior 2 years when there was no pandemic. They created a grading system by which "aortic" disease (thoracic and abdominal aorta), "proximal" disease (iliac and femoral arteries), and "distal" disease (tibials) were compared. They identified a tendency for a more proximal location of the arterial thrombus in patients with COVID-19 compared to COVID-19–negative patients [34].

6. Anticoagulation strategies

Patients with COVID-19 will present with an acute thrombotic event despite having been on anticoagulation [31]; therefore, it is clear that anticoagulation alone is not preventative against thrombosis. In fact, 14% to 23.3% of patients were anticoagulated before ALI in numerous studies [29–31]. Furthermore, rethrombosis was seen in these studies after revascularization, despite full anticoagulation with heparin-based therapy. One study supported the use of heparin-based therapy because it has been associated with increased survival postoperatively [2]. Novel oral anticoagulants, specifically apixaban and rivaroxaban, were used in one cohort study [25]. Low-molecular-weight heparin at therapeutic dosing [29] was also used. There is no clear consensus as to the type of anticoagulation to use in this setting and, therefore, the choice in the absence of determining evidence will be based on patient and physician preference.

7. Patient selection for interventions: type of interventions

7.1. *Anesthesia type*

Certainly, in thinking about operating on COVID-19–positive patients, there is consideration of using local or regional anesthesia when possible, given the morbidity of intubation in patients with severe pulmonary disease. COVIDSurg data show >50% of COVID-positive patients develop pulmonary complications and 23.8% die within 30 days [35]. Anesthesia used in the cohort studies has ranged from general with endotracheal intubation to strictly local/regional. In patients undergoing surgery for ALI, there was 40% mortality postoperatively after receiving local or locoregional anesthesia [2]. Mortality after general anesthesia ranges between 23.3% and 69% [29,31]. There is no substantial difference between outcomes in the two anesthetic approaches [2].

7.2. *Operative interventions: open, endovascular, and medical*

The management of thrombosis varied according to the symptoms and overall severity of the disease; anticoagulation and palliative care was offered to patients who were terminally ill, and amputation was performed in patients with nonsalvageable limb ischemia [2,25,29,30]. Patients with Rutherford IIB were less likely to undergo thrombolytic therapy, and the main surgical modality was surgical thrombectomy in these patients [25]. In one study, 76% of patients underwent thrombectomy and 6 of the 30 patients required fasciotomy; this was the only study that used surgical thrombectomy alone without endovascular adjuncts [29,30]. Other groups used hybrid therapies, such as angioplasty or stenting of hemodynamically significant lesions [25,30]. Primary amputation ranged from 0% to 30% [2,7,25,30]. Interestingly, few studies used pharmacomechanical thrombectomy for these patients [25].

7.3. *Mortality*

Patients with ALI in the setting of COVID-19 are at high risk for mortality. In fact, a retrospective review of 2,943 patients with COVID-19 demonstrated an increased mortality risk in those with ALI on both univariate and multivariate analysis (10.3-fold after peripheral arterial thrombosis on univariate analysis and 7.5-fold increase on multivariate analysis) [31]. Another study from Italy demonstrated mortality of 40% in patients with ALI. Of the 17 patients in this cohort that underwent intervention, five died of either acute renal failure, multiorgan failure, or acute respiratory distress syndrome [2]. One study by Ilonzo et al [25] from New York demonstrated a 33% mortality rate in patients that presented with ALI in great contrast to 0% mortality rate seen in patients with venous thrombosis. Indes et al [7], also from New York City, demonstrated a 5-fold increase in mortality rate in COVID-19–positive patients with arterial thrombosis compared to those that were COVID-negative (40% *v* 8%; $P = .041$).

8. Conclusions

The approach to classic disease processes, such as ALI, has been questioned in the setting of this novel pathogen. COVID-positive patients are at increased risk of ALI and resultant mortality, given the hypercoagulable state. The etiology of thrombosis is unclear but may be due to invasion of endothelial cells via ACE receptors, endothelial injury from inflammation, and free-floating aortic thrombus. The decision to proceed with operative intervention is dependent on the patient's clinical status as it relates to COVID-19 and morbidity of that disease. The interventions afforded typically include anticoagulation in patients undergoing palliation versus thrombectomy (endovascular and open) in other patients. These patients are at high risk of rethrombosis, given significant endothelial injury from the virus [19]. Mortality can be high in these patients.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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