Coronavirus disease 2019 infection in patients with recent cardiac surgery: does chronic anticoagulant therapy have a protective effect?

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\textbf{Aims} The aim of this study was to evaluate the clinical course of COVID-19 in patients who had recently undergone a cardiac procedure and were inpatients in a cardiac rehabilitation department.

\textbf{Methods} All patients hospitalized from 1 February to 15 March 2020 were included in the study (n = 35; 16 men; mean age 78 years). The overall population was divided into two groups: group 1 included 10 patients who presented with a clinical picture of COVID-19 infection and were isolated, and group 2 included 25 patients who were COVID-19-negative. In group 1, nine patients were on chronic oral anticoagulant therapy and one patient was on acetylsalicylic acid (ASA) and clopidogrel. A chest computed tomography scan revealed interstitial pneumonia in all 10 patients.

\textbf{Results} During hospitalization, COVID-19 patients received azithromycin and hydroxychloroquine in addition to their ongoing therapy. Only the patient on ASA with clopidogrel therapy was transferred to the ICU for mechanical ventilation because of worsening respiratory failure, and subsequently died from cardiorespiratory arrest. All other patients on chronic anticoagulant therapy recovered and were discharged.

\textbf{Conclusion} Our study suggests that COVID-19 patients on chronic anticoagulant therapy may have a more favorable and less complicated clinical course. Further prospective studies are warranted to confirm this preliminary observation.

\textbf{Introduction}

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 1.5 million people worldwide, causing over 100 000 deaths in the first 3 months of 2020.\textsuperscript{1,2} Although the estimated fatality rate because of SARS-CoV-2 disease [known as coronavirus disease 2019 (COVID-19)] is about 3\%, the number of deaths registered in recent weeks suggest a distinctly higher mortality, especially in elderly people.\textsuperscript{3,4} The disease is transmitted not only mainly through respiratory droplets but also through contact and has a period of incubation ranging from 3 to 7–9 days.\textsuperscript{5–7} The first phase of infection is characterized by minor respiratory symptoms, fever, dry cough, shortage of breath and myalgia. In 15–20\% of cases, this is followed by interstitial pneumonia with progressive immunomediarediated respiratory insufficiency, which may lead to acute respiratory distress syndrome (ARDS) requiring intensive treatment and mechanical ventilation.

As yet, no vaccine against the virus exists nor do we have any direct therapy for COVID-19 disease. Pharmacological treatments with antivirals or monoclonal antibodies that are already used in other diseases have been proposed in order to reduce viral replication, at least in the initial phase.\textsuperscript{8–14} In-vitro studies showed that the SARS-CoV-2 virus seems to disappear on contact with high concentrations of enoxaparin sodium, an anticoagulant widely used to prevent venous thromboembolism.\textsuperscript{15} This finding has prompted Chinese researchers to undertake clinical studies in which a high dosage of the active principle is administered to patients affected by COVID-19; the preliminary results, while promising, remain to be validated in controlled clinical trials.\textsuperscript{16–18}

Enoxaparin is a low-molecular-weight heparin (LMWH) which exerts a marked antithrombotic activity. Owing to its efficacious anticoagulant effect, it is used in the prophylaxis of venous thromboembolism, particularly in patients undergoing surgery or at risk of developing thrombi.\textsuperscript{19–21} More recently, some evidence has emerged of the role of heparin in the case of COVID-19 infection, leading the WHO to recommend the subcutaneous administration of LMWH for preventing venous thromboembolism in patients with recent COVID-19 infection.
thromboembolism and improving the clinical management of hospitalized patients with SARS. Indeed, the molecular structure of heparin is similar to that of the site of the cell wall to which SARS-CoV-2 adheres before penetrating into the cell. On this basis, many clinical studies on the use of enoxaparin in patients affected by COVID-19 have been initiated worldwide.

It is currently established that patients aged above 70 years with multiple comorbidities are most vulnerable to COVID-19 and may have a more complicated clinical course, leading to death in up to 80% of cases.24,25 Most often, this patient subset has recently undergone a cardiac procedure [e.g. valve replacement or coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI) with stenting, device implantation] and is prescribed with cardiovascular pharmacological therapy, not devoid of possible drug interactions.

The aim of the present retrospective observational study was to evaluate the impact, clinical course and complications of coronavirus infection in a patient population who had recently undergone a cardiac procedure or suffered from severe heart failure, and who were inpatients in a cardiac rehabilitation department for clinical and functional recovery.

Methods
The research was entirely carried out at the Department of Cardiology and Cardiac Rehabilitation of the Istituto Figlie di San Camillo di Cremona (Italy). Between 1 February and 15 March 2020, 35 patients (16 men, mean age 78 years, range 56–90 years) were admitted to our Department for cardiac rehabilitation. All patients admitted to our Rehabilitation Department had been transferred on the seventh to eighth day after a cardiac procedure or for severe heart failure. All patients presented more than five risk factors or comorbidities (Fig. 1). On 19 February 2020, the first case of COVID-19 was reported in Codogno, a municipality located 20 km from our hospital, and COVID-19 was rapidly spreading throughout the surrounding territory.

During hospitalization, 10 patients (group 1: 4 men; mean age 81 years, range 65–89) developed a clinical picture of respiratory infection and were preventively placed in isolation. Among these patients, four had undergone aortic valve replacement, two pacemaker implantation, two mitral valve replacement, one CABG, and one PCI. Nine patients were on chronic oral anticoagulant therapy (with warfarin in three, edoxaban in two, rivaroxaban in two, dabigatran in one, and apixaban in one), whereas one patient was on acetylsalicylic acid (ASA) and clopidogrel (Fig. 2). Because of persisting symptoms of fever and...
coughing, nasopharyngeal swab tests were performed on the 10 symptomatic patients and proved positive COVID-19 infection. A chest computed tomography scan also revealed interstitial–alveolar pneumonia with frosted glass appearance in all 10 patients (Fig. 3), who were then transferred to the COVID-19 dedicated area of our hospital.

The remaining 25 patients (group 2: 9 men; mean age 76 years, range 56–90) were found to be COVID-19-negative (Fig. 2).

**Results**

During hospitalization, our patients received azithromycin 750 mg/day for 5 days and hydroxychloroquine 400 mg/day for 7 days, in addition to their ongoing cardiovascular pharmacological therapy. To treat mild oxygen desaturation, four patients underwent O₂ therapy with a Venturi mask for 2–3 days, which was gradually tapered off following improvement. Neither QT prolongation nor ventricular arrhythmia was observed on ECG after hydroxychloroquine administration. Among group 1 patients, only an 85-year-old woman on ASA with clopidogrel was transferred to the ICU for mechanical ventilation because of worsening of her respiratory
condition. During ICU stay, her condition deteriorated, she suffered irreversible cardiorespiratory arrest and died. The remaining nine patients recovered and were discharged from the COVID-19 unit; swab testing for SARS-CoV-2 infection before discharge proved negative (Fig. 2).

Overall, among the 10 COVID-19-positive patients, the nine patients who were on chronic anticoagulant therapy had a favorable course. Despite the presence of major comorbidities, the picture of interstitial–alveolar pneumonia improved without requiring either invasive or noninvasive ventilation. The only patient who died was not on chronic anticoagulation, but only received antiplatelet therapy.

Discussion
Although COVID-19 infection can have a mild clinical course and may be completely asymptomatic, many patients present with symptoms, such as fever, headache, diffuse pain, rhinitis, conjunctivitis, cough, diarrhea or vomiting, and anosmia. In the initial phase of the disease, individuals with a weaker immune response can develop an abnormal acute inflammatory response, causing more serious symptoms with an increased concentration of proinflammatory cytokines [i.e. tumor necrosis factor-α (TNF-α) and interleukins (IL)]. IL-6, in particular, induces the expression of tissue factor on mononuclear cells, which activates the coagulation cascade and promotes the generation of thrombin. TNF-α and IL-1, on the other hand, represent the main mediators capable of suppressing the endogenous anticoagulant pathways. In severe COVID-19, patients may experience the cytokine storm syndrome characterized by a hyperinflammatory response with a marked increase in the indexes of inflammation and D-dimer levels. This systemic hyper-inflammation results in inflammatory lymphocytic and monocytic infiltration of the lung. Monocytes differentiate in macrophages, which give rise to destruction of functional lung tissue, on the one hand, and to vigorous processes of ‘repair-proliferation’, on the other. These processes involve progressive fibrosis and, in the vascular endothelium, progression toward an obliterating micro-angiopathy, with promotion of thrombus formation in arterioles and great vessels (Fig. 4).

Recently, several reports described excessive activation of the coagulation cascade in COVID-19 patients. In 94 patients with confirmed SARS-CoV-2 infection, antithrombin III was found to be lower than in 40 healthy volunteers (P < 0.001). By contrast, D-dimer, fibrin, and its degradation products (FDP) and fibrinogen were elevated. This observation was confirmed in 183 consecutive patients hospitalized for COVID-19, in whom mortality was strongly influenced by elevated D-dimer levels and FDP (P < 0.05). Noteworthy, 71.4% of the patients who died, as opposed to 0.6% of those who survived, presented criteria for diagnosis of disseminated intravascular coagulation. Moreover, it was observed that anticoagulation with LMWH for at least 7 days improved prognosis at 28 days, at least in patients with sepsis-induced coagulopathy (score ≥4; 40 vs. 64.2%, P = 0.029) or with a circulating D-dimer level six-fold higher than the upper limit of normal (32.8 vs. 52.4%, P = 0.017). Thus, coagulation activation seems to be particularly marked in COVID-17 patients, with consequent worsening of their prognosis.

Recent autopsy findings have documented the presence of interstitial or alveolar infiltrates containing macrophages, microthrombotic formations, and microvascular alterations with pulmonary thromboembolism (Fig. 5), making adequate ventilation challenging in patients with COVID-19 pneumonia associated with acute respiratory distress. Excessive activation of coagulation can give rise to disseminated intravascular coagulation and anoxia because of microvessel thrombosis, ultimately leading to acute pulmonary insufficiency, multiorgan failure, septic shock, and death. Moreover, it has recently been hypothesized that affected patients may present a pattern of pulmonary embolism even in the absence of risk factors and of deep vein thrombosis.

In severe COVID-19, the early use of anticoagulant therapy has been proposed to improve treatment outcomes and survival. This has prompted Chinese researchers to undertake clinical studies on high-dose enoxaparin administration to COVID-19 patients. In addition, LMWH has been used not only as an anticoagulant but also to exploit its anti-inflammatory effect. In the early stage of COVID-19, timely supportive therapies should be implemented including antibiotics and hydroxychloroquine. Antiviral drugs with possible side-effects are also currently under clinical evaluation. However, in the event of a sudden hyperinflammatory response, prophylactic LMWH therapy is indicated in most COVID-19 patients in combination with beta-lactams and azithromycin, maximum gastroprotection, and steroid used. LMWH, which possesses both anti-coagulant and anti-inflammatory properties, should be administered at a dosage of 50 IU/kg twice daily or, preferably, of 100 IU/kg twice daily if not contraindicated.

High-dose heparin for thromboprophylaxis is routinely administered to COVID-19 patients in the ICU. Interestingly, in our small but selected population, although patients were elderly, suffered from heart disease, and had numerous comorbidities, the fact that they were on chronic anticoagulant treatment seemed to have limited the serious complications of interstitial pneumonia. It may therefore be hypothesized that chronic anticoagulant therapy, which was already ongoing in our patients at the onset of the viral infection, may have a similar effect to that of the targeted heparin therapy administered in the
Patterns and pathogenesis of corona virus disease-19. (a) Structure and transmission of COVID-19: the virus enters the body, displaying a certain affinity to the alveolar tissue. (b) Current understanding of key events in COVID-19 pathogenesis: after intratracheal inoculation, the virus infects bronchial epithelial cells through dipeptidyl peptidase 4 before spreading into the lung parenchymal cells, including type I and type II alveolar pneumocytes and endothelial cells. IL, interleukin; MIF, macrophage migration inhibitory factor; PAF, platelet-activating factor; TNF, tumor necrosis factor. Modified with permission from Arabi et al. COVID-19, corona virus disease 19.
Chest computed tomography. Pulmonary thromboembolism in coronavirus disease-19 pneumonia: partial thrombus at the level of the bifurcation of the right lower lobar branch (arrow); multiple bilateral peripheral pulmonary thickening, some still with a partially ‘frosted glass’ appearance, others with substantially complete alveolar occupation. COVID-19, coronavirus disease 19.

ICU. That is to say, it may act not upon pulmonary alveolar damage, but upon the subsequent coagulation in the pulmonary microvessels, which can dramatically complicate infection because of SARS-CoV-2.

Study limitations
The limitations of this observational study are the small sample size and the lack of a control group, though not uncommon in the initial phase of a pandemic.

Conclusion
COVID-19 has spread rapidly throughout the world, displaying a disproportionately high lethality rate among elderly patients with concomitant cardiovascular, pulmonary, and metabolic diseases. As no approved radical therapies exist, every effort is being made to identify an efficacious therapy and to create a vaccine to prevent future infections. The relatively high mortality of severe COVID-19 is a matter of concern. Although the limited sample size cannot allow definitive conclusions to be drawn from our study, patients who are already on chronic anticoagulant therapy, even if elderly and with multiple comorbidities, seem to have a better prognosis because of a lower risk for progressive obliterator microangiopathy and thrombosis of pulmonary arterioles and large vessels. Further prospective studies are needed to confirm this preliminary observation.

Conflicts of interest
There are no conflicts of interest.

References


