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RESEARCH ARTICLE

THE NOVEL CORONAVIRUS IS A COAGULATIVE DISEASE WITH DIFFUSE THROMBOSIS OF THE VASCULAR SYSTEM: THE FUNDAMENTAL ROLE OF THE ANTITHROMBOTIC THERAPY.

[1]Palma Giampaolo, [2]Imitazione Pasquale, [3]Tarro Giulio, [2]Polistina Giorgio Emanuele and [2]Fiorentino Giuseppe

[1]MD Physician-Cardiologist, Director of the "Palma Cardiology Medical Center - Thrombosis and Heart Failure Center", Nocera Inf. - Azienda Sanitaria Salerno, Italy
[2]MD Physician-Pulmonologist, Department of Intensive Care, AO of Colii, PO Monaldi, Naples, Italy
[3]MD, PhD, President of the de Beaumont Bonelli Foundation for Cancer Research, Naples, Italy

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Corresponding author:

ABSTRACT

A key event in the evolution of the Covid-19 disease is represented by coagulation disorders and this is confirmed by more and more evidence and observations. Coagulopathy (CAC) associated with Covid-19 has been defined as a fulminant activation of coagulation, resulting from diffuse thrombosis, which falls within the ISTH criteria for Disseminated Intravascular Coagulation (DIC). Clinical evidence, laboratory tests, histological tests, and radiological techniques have confirmed that Covid-19 attacks not only directly the pulmonary parenchyma but is above all a "widespread systemic vascular disease affecting all organs" and not only the lungs. The coagulation disorders had already been hypothesized when in hospitalized patients, although increasing the pO2, respiratory performance did not improve because the lungs appeared "insensitive"; all this confirmed that there had to be another physio-pathological mechanism of the evolution of the disease in severe respiratory failure. The clinic chart at the patient entry to hospital for worsening dyspnea, chest pain, heart failure with evolution often in septic shock, accompanied by high coagulation indices at the entrance (D-dimer, PT, fibrinogen) and the numerous diagnoses of confirmed pulmonary thromboembolism from the chest CT Angio and numerous cardiac arrests for coronary syndromes and severe heart failure confirm the pathogenetic mechanism of hypercoagulation. The clinical manifestations of coagulation disease from Covid19 are : pulmonary thromboembolism in the lung; acute coronary syndromes (ACS) - heart failure and threatening arrhythmias in addition to heart myocarditis, stroke also in young patients with no brain comorbility, in vasculitis with increased prevalence of Kawasaki syndrome in children often asymptomatic and acute renal failures such as kidney damage and intestinal disorders such as damage to the small intestine. Therefore, therapies that have reduced considerable numbers statistically access to Intensive Care Unit (ICU) patients for assisted ventilation for severe respiratory insufficiency have proven to be the therapies that block a fundamental physio-pathological mechanism of Covid-19 disease, i.e. hyper-coagulation. and inflammation. As confirmed by the COVID departments in Italy, it was essential to block the storm of coagulation and inflammatory toxins with anticoagulants and steroids at therapeutic doses and administered at the right time to reduce access to ICU for patients. The COVID-19 disease is an endothelial disease; it is a systemic inflammation of the blood vessels that can generate serious micro-disturbances in the bloodstream and damage to the lungs, heart, brain, kidneys, and intestines. At the therapeutic level, this means that viral multiplication and inflammation must be combated but, at the same time, "it is of fundamental importance to protect the cardiovascular system of patients with drugs that act on hyper-coagulation".

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INTRODUCTION

Italy, after China, was the first country in the western world to be affected by SARS-CoV-2. The experience of Italian doctors who have had to deal with an unknown virus and a new disease has allowed us to face a "viral storm" that has caused, in Italy alone, almost 35,000 deaths.

Waiting for the vaccine, the experience in the field with the first numerous autopsies has made it possible to establish the first effective therapeutic strategies that have slowly reduced mortality and improved the prognosis with almost zero current access of patients in intensive care for assisted ventilation. The disease, which was initially considered only interstitial pneumonia, turned out to be a widespread systemic vascular

disease with impairment of the endothelial wall of the vessels of all organs, especially of the heart and lungs (American Society of Haematology; Tang, 2020; Lillicrap, 2020; Zsuzsanna Varga *et al*., 2020).

Aetiology: SARS-CoV-2 is a new capsule of RNA coronavirus identified as the cause of Covid-19 disease that started in Wuhan, China in late 2019 and has spread worldwide. This coronavirus, which causes serious respiratory infections and widespread systemic vascular damage, is a zoonotic pathogen that begins in infected animals and is transmitted from animals to humans.

Pathogenesis: SARS-CoV-2 attacks humans through "droplets" and breath by binding via the wall receptor (RBD receptor binding domain) present Spike protein on the external wall to the ACE2 cell receptors present in many organs such as vessels, heart, lungs, kidneys, and intestines (Zsuzsanna Varga, 2020; Jun Lan *et al*., 2020; Alexandra *et al*., 2020) (Fig. 1). Once entered into the host cell, the virus can replicate itself through protease enzymes and move freely using "replication correctors" which prevent the virus from being recognized by the immune system; used as "high beams" that prevent its recognition (Zhang, 2020) This leads to an "abnormal" reaction of the immune system and release of inflammatory toxins, cytokines, lung congestion, fibrosis, and loss of lung elasticity, often permanent. Inflammation of the lung parenchyma causes activation of T cells and macrophages with the release of IL-6, Il-7, IL-22, and CXCL-10 (Conti, 2020; Xinjuan Sun, 2020) (Fig. 2). This indirectly leads to heart failure (with an increase in BNP), SCA (increased troponin I), and severe arrhythmias (Indranil Basu-Ray, 2020; Brit Long, 2020; Clerckin, 2020). A recent study has shown that SARS-CoV-2 can infect the organs of engineered blood vessels in vitro (Monteil V 2020). Varga *et al*. in a recent study published in "The Lancet" demonstrated vascular damage and involvement of endothelial cells from different organs in a series of patients with Covid-19 (Zsuzsanna Varga, 2020).

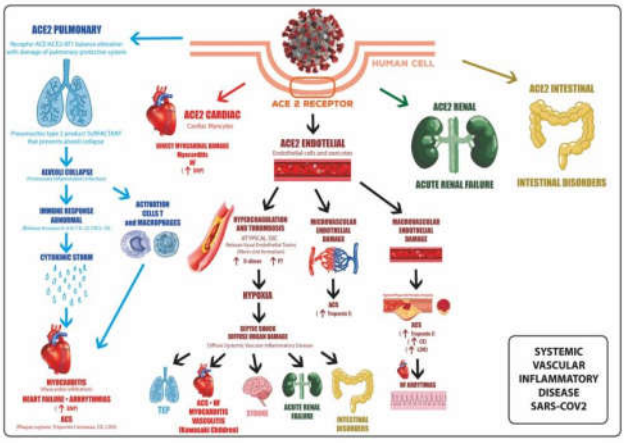

Figure 1 Pathogenesis of Sars-Cov-2 disease with involvement of the pulmonary, cardiac, diffuse vascular, renal and intestinal circulation

Vicious circle lung-heart, hyper-coagulation, and thrombosis: Patients die not only from severe respiratory failure in the final phase but also from a heart attack and cardiovascular system both direct and indirect. Observational data from Covid-19 patients confirm that the lung does not appear as rigid and hard as in the ARDS and the low response to pO2 has made it possible to understand that the contribution of the circle in the evolution of the disease in severe forms is undoubted. Covid-19 causes the greatest damage by attacking the ACE2 receptors present on the endothelial wall of vessels, the heart and in any case, even at the level of the pulmonary capillaries, kidneys, brain, and small intestine (Zsuzsanna Varga, 2020).

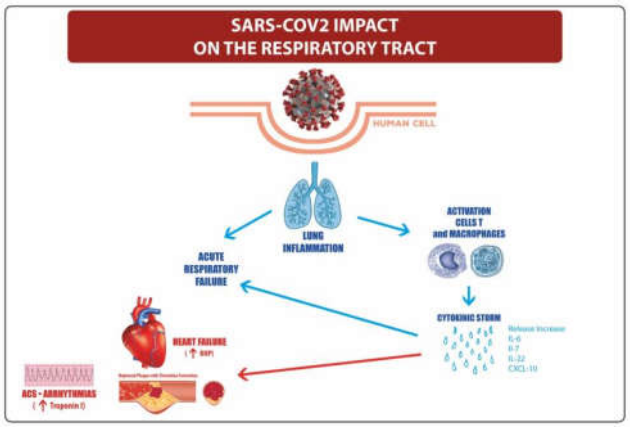

Figure 2. Sars-Cov-2 impact on the respiratory tract

After the attack on the ACE2 receptor, the endothelium loses its protective function resulting in hyper-coagulation and thrombosis, hypo-oxygenation of all organs, and evolution in septic shock (Flammer, 2012; Bonetti, 2003). A vicious circle between lungs and heart has also been observed: pulmonary interstitial disease acts on the one hand on hypoxemia, hyperventilation, and heart failure and the other the reduced lung elasticity causes in itself lung congestion; at the same time the attack on endothelial ACE2 and the consequent ACE / ACE2 imbalance causes hypercoagulation-thrombosis-hypoxia and septic shock and at the lung level pulmonary thromboembolism with an intrapulmonary shunt and consequent increased pulmonary arteriolar wedge pressure (PAWP increase) (Samar Farha, 2020; John J Ryan, 2020).

As in sepsis, the poor capillary flow due to this shunt, together with the capillary obstruction by microthrombi, reduces the release of O2 and compromises the removal of CO2 and "waste products". The reduced perfusion causes the failure of one or more organs including the heart, kidneys, brain, intestines, and liver. An "atypical" DIC develops with consumption of the main coagulopathies factors, in addition to excessive fibrinolysis in the reaction and usually an association of both. The increase in cardiac output with intraventricular pressure overload is badly endured by a stiffer heart and remodeled by the imbalance of the ACE / ACE2 receptors, with consequent increased vicious circulation and increased lung congestion. Pulmonary congestion has, as a final result, an increase in rigidity pulmonary with an increase in the vicious circle of lungs and heart which leads to the patient's death (John J Ryan, 2020; Vetta *et al*., 2019) (Fig.3).

It is a systemic multi vascular disease: Covid-19, as we have said, attacks human ACE2 receptors at multiple levels (Zsuzsanna Varga, 2020). Attacks lung pneumocytes ACE2 with ACE / ACE2 / AT1 imbalance and damage to the pulmonary protective system. We recall in this regard that type 2 pneumocytes normally produce surfactant which prevents the collapse of the pulmonary alveoli. Alveolar collapse causes inflammation of the pulmonary parenchyma with consequent

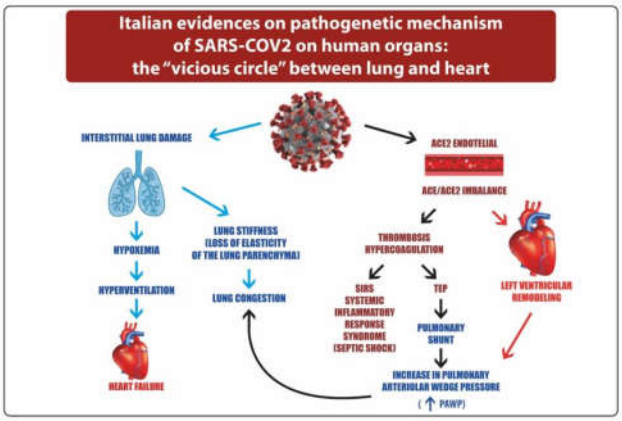

Figure 3 Italian evidences on pathogenetic mechanism of SARS-COV-2 on human organs: the "vicious circle" between lung and heart.

"abnormal" immune response and release of cytokine toxins and activation of T cells and macrophages. All this affects the myocardium that undergoes, in addition to myocarditis and ventricular arrhythmias with direct damage of the infection, also indirectly heart failure (evidenced by the high release of BNP), and SCA (evidenced by high blood levels of troponin I, CK and LDH).In Covid-19 patients, the indicators of myocardial damage, in addition to the clinical signs and the echocardiogram, are represented by high levels of myocardial damage markers, such as Troponin I (at a high intensity) both in coronary arteries and in case of plaque rupture, and from BNP Pro, a peptide released from the damaged myocardium up to 3-4 times higher than normal values, a sign of patients with heart failure and overload of end-diastolic pressure from viral infection. Data from China confirmed in Italy by the Istituto Superiore di Sanita' (ISS) with an increase in mortality in Covid-19 patients who had co-morbidity for endothelium already damaged (ischemic heart disease, atrial fibrillation, heart failure, previous stroke, high blood pressure, type 2 diabetes mellitus), but heart failure, arrhythmias, heart attack, and myocarditis also significantly increased in patients who had a perfectly healthy heart before infection (Zhou *et al*., 2019; Zhou, 2020). Besides, Covid-19 directly attacks the cardiac and vascular ACE2 of endothelial cells and pericytes with consequent multi-organ damage from "hyper-coagulation", "macrovascular" damage, and "microvascular" damage (Zsuzsanna Varga, 2020). Hyper-coagulation and thrombosis are confirmed by increased levels of D-dimer, PT, and fibrinogen upon entering the hospital (Zhou, 2020), italian researchers have defined diffuse thrombosis as the release of "micro clots" and fibrin with consequent hyper-coagulation cascade with hypoxia and widespread multi-organ septic shock; in patients, there is a very high incidence of episodes of pulmonary thromboembolism, acute heart failure, and arrhythmias in addition to SCA (Ciceri *et al*., 2020). Vasculitis, with a higher incidence of Kawasaki syndrome in positive Covid-19 children (Viner Russel, 2020), as well as dermatological damage in adult patients confirm the involvement of the endothelium in this disease (Viner Russel, 2020; Suarez-Valle, 2020). "Macro-vascular" endothelial damage occurs with "plaque rupture", HF and arrhythmias, and "micro-vascular" endothelial damage with SCA. In addition to pulmonary, cardiac, and vascular ACE2 receptors, Covid-19 also attacks renal ACE2 with acute renal failure and the use of hemodialysis. (Zsuzsanna Varga, 2020; Henry, 2020) Particularly exposed are the renal ACE2 receptors placed in correspondence with the nephrons assigned to filtering blood. In the autopsies performed so far, it has been seen that a third of the patients have died from acute renal failure due to hyper-coagulation (Zsuzsanna Varga *et al*., 2020; Henry, 2020). Intestinal ACE2 receptors are more rarely affected with less severe gastrointestinal disorders such as diarrhea, anosmia, and dysgeusia (Zsuzsanna Varga, 2020; Qin Yan Gao, 2020). In this regard, it can be assumed that the lower prevalence of the disease in women and the greater intestinal involvement in women can be explained by the lower expression of ACE2 in women who develop a less serious, often intestinal, infectious form.In a report from the Istituto Superiore di Sanita' (ISS) in Italy based on the medical records of deceased patients, diarrhea, anosmia and dysgeusia were detected in 7% of cases; these conditions associated with the gastrointestinal tract suggest an interaction between SARS-CoV-2 and the cells of the gastro-intestinal tract rich in ACE2 and this confirms that the gastrointestinal tract and intestinal ACE2 are also attacked by the infection with less serious gastrointestinal disorders. A high incidence of ischemic strokes with brain damage even in young patients without co-morbidity has been observed in these patients (Avila, 2020). As far as the brain is concerned, Covid-19 invades the central nervous system both by attacking the vessels, as evidenced by numerous ischemic strokes and by the same mechanism as the SARS and MERS viruses through the cerebrum-spinal fluid (Mao, 2020). Patients admitted to Ditan Hospital in Beijing have been observed with neurological symptoms with decreased consciousness and negative brain CT (Fig. 4).

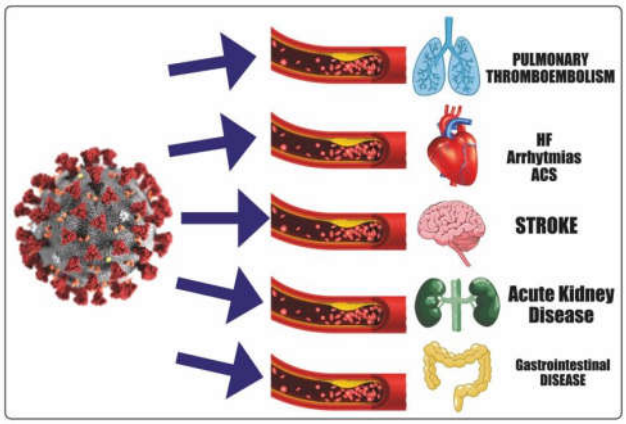

Figure 4 Covid-19-attack on human ACE2 receptors.

DISCUSSION

High coagulation markers have been found in Covid-19 patients hospitalized in the middle and advanced stages of the disease and in these patients, the prognosis is worse (2, 29). High D-dimer values, high PT, and fibrinogen values are found. D-dimer, a fibrin degradation product, is a marker of hyper-coagulation and a high value safely indicates ongoing thrombosis: deep vein thrombosis, pulmonary thromboembolism or disseminated intravascular coagulation. Fibrinogen is a plasma glycoprotein synthesized by the liver and endothelial cells which is altered in the case of coronary artery disease, stroke, and thrombosis. Already from the first admissions to China, the observational data of the patients confirmed the coagulative disease from Covid-19. A study by Tang *et al*. showed that 71.4% of patients who died in Wuhan met the ISTH criteria for DIC (Tang, 2020).

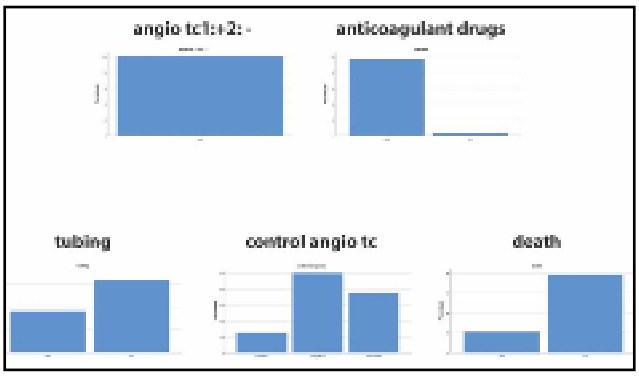

Figure 5. Covid-19 patients upon entering the hospital with pulmonary thromboembolism positive CT angio. Treatment with antithrombotics improves or normalizes the pulmonary CT angio pictures. And impacts on mortality.

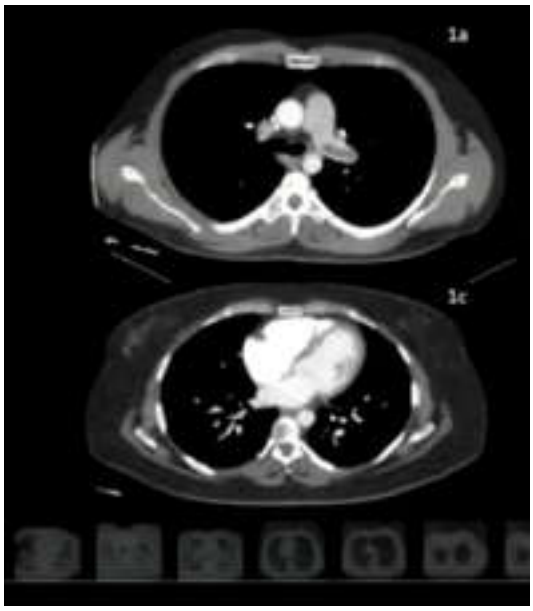

Figure 5/a Patient n.1: Chest CT angio: opacification defect of the left pulmonary artery to refer to thromboembolism of the left pulmonary artery.

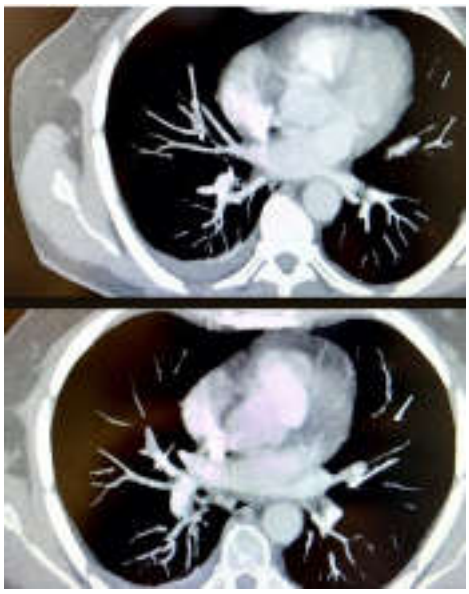

Figure 6/b Patient n.2: Chest CT angio: opacification defect of the right upper lobar branch due to suboclusive thromboembolism; opacification defect affecting the apical, dorsal and ventral segmental branches for the upper right lobe, for segmental branches for middle lobe, latero-basal for lower right lobe and postero-basal of the lower left lobe; due to diffuse pulmonary thromboembolism.

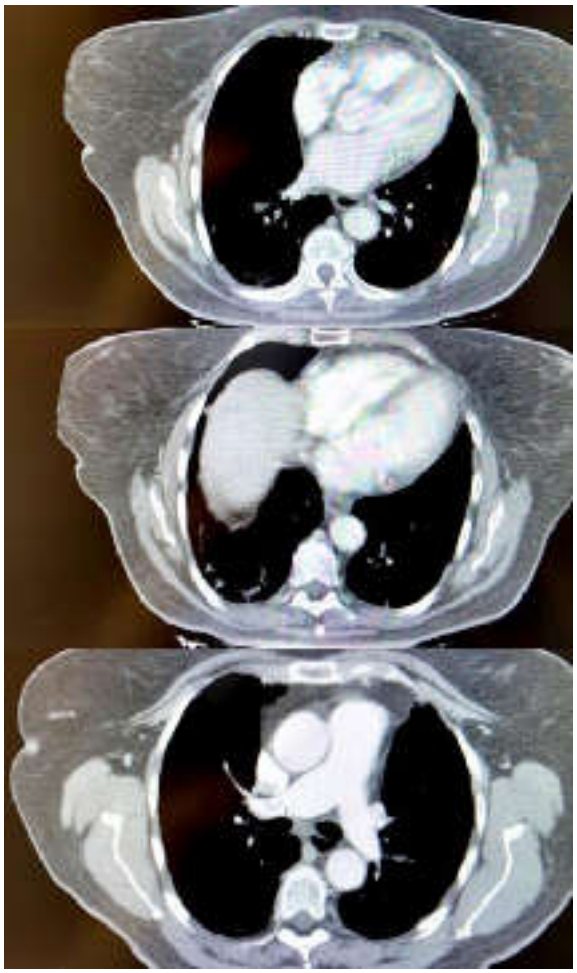

Figure 6/c Patient n.3: Chest. CT angio: RIGHT: thrombotic hypodensities of the non-occlusive type affecting the right pulmonary artery and the lower lobar branch and of the non-occlusive type affecting the branch for the anterior basal segment and its subsegmental branches, and of segmental branches of the branch for apical of lower. LEFT: thrombotic hypodensities of the non-occluding type at the level of certain segmentary branches of the lower lobar artery

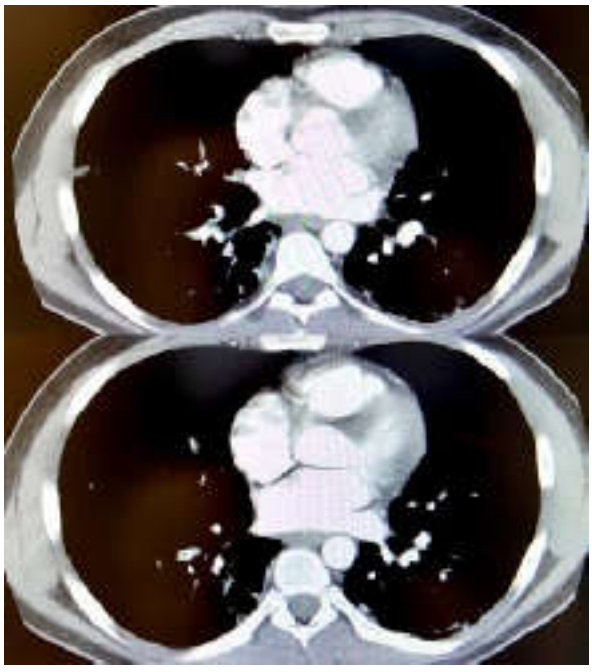

Figure 6/d Patient n. 4: Chest CT angio: endoluminal filling defect of a thromboembolic nature depending on some segmentary and subsegmental branches of the right upper pulmonary artery and, with greater evidence, of the right lower pulmonary artery

In the case studies of Zhou *et al*. high values of D-Dimer at the entrance represented a negative prognostic factor for hospitalized patients (19). In a study by Zhang *et al*. on serological tests the patients were positive for IgG and IgA, that is, anti-phospholipid antibodies and this could be the basis of the "aberrant activation of the coagulation response" (Zhang *et al*., 2020). Another study by Tang *et al*. highlighted that the administration of both standard heparins and LMWH reduced mortality in patients with high D-dimer at the entrance; D-dimer was elevated in all patients during disease progression and in 100% of deceased patients (Tang *et al*., 2020). Covid19 patients show clear manifestations of hyper-coagulation: more often pulmonary thromboembolism, but also myocardial infarction and heart failure, cerebral ischemia, deep vein thrombosis and this has confirmed the Chinese data. In Wuhan patients, in addition to patients with cerebral ischemia, numerous episodes of pulmonary thromboembolism were observed; this was to be suspected in patients entering the hospital with chest pain, dyspnoea, hypoxemia and hemoptysis not explained by other causes; also, DVT was to be suspected in patients with pain and swelling and edema in the lower limbs upon entry and also numerous cases of gangrene have been reported (Tang, 2020; Lillicrap, 2020; Zhou *et al*., 2020; Zhou *et al*., 2020).

In our case history, 32 patients affected by Covid-19 infection hospitalized with fever> 37.5 ° C chest pain and dyspnoea, aged between 26 and 75 years, mainly males, with BMI> 25, almost all hypertensive, often with other cardiovascular risk factors (smoking, diabetes, previous CAD) showed high average values of D-dimer at the input of 6412.04 (+ - 1439.68), the average value of PT 74.29 (+ - 2.23) and the average value of fibrinogen 636.34 (+ -38.58); all patients had a positive CT Angio picture for pulmonary thromboembolism of large right or left pulmonary arterial vessels (Fig. 5). After treatment with LMWH (from 4000 to 12000 IU / day), together with other standard therapy, the patients presented a favorable evolution of the clinical picture with an improved CT Angio picture (residues of thromboembolism) or negative at the discharge of the patient (Fig. 5 CT Angio and spreadsheet). A significant figure is the manifestation of the disease with TEP pictures at the entrance and severe respiratory failure. Pulmonary CT angiograms often show either blurred thromboembolism pictures and thrombosis pictures of the right or left pulmonary arterial branches and evolution in right heart failure. At the lung level therefore endothelial damage is widespread and confirmed by CT Angio. (Fig. 6/a) (Fig. 6/b) (Fig. 6/c) (Fig. 6/d) (Fig. 6/e). Covid-19 can cause serious cardiovascular complications including heart failure, heart attacks and blood clots that can lead to stroke heart failure is a particular concern in patients with COVID-19. A recent study showed that 24% of patients entering the emergency room showed signs of heart failure and almost half of these had no high blood pressure or previous heart disease. The article highlights that Covid-19 and other diseases that cause serious inflammation of the whole body, increase the risk that the fatty plaque accumulated in the blood vessels will break, leading to heart attacks and strokes (Brit Long, 2020). In addition to and as a consequence of heart damage, numerous episodes of acute ischemic stroke have been described in patients with Covid-19 (Avila, 2020). Also at the brain level, SARS-CoV-2 attacks the endothelium of the cerebral arteries and the role of ACE2 receptors is also hypothesized in this case; hospitalized patients in some cases develop coma and posture in decerebration; intubated and subjected to CT angiography of the cerebral

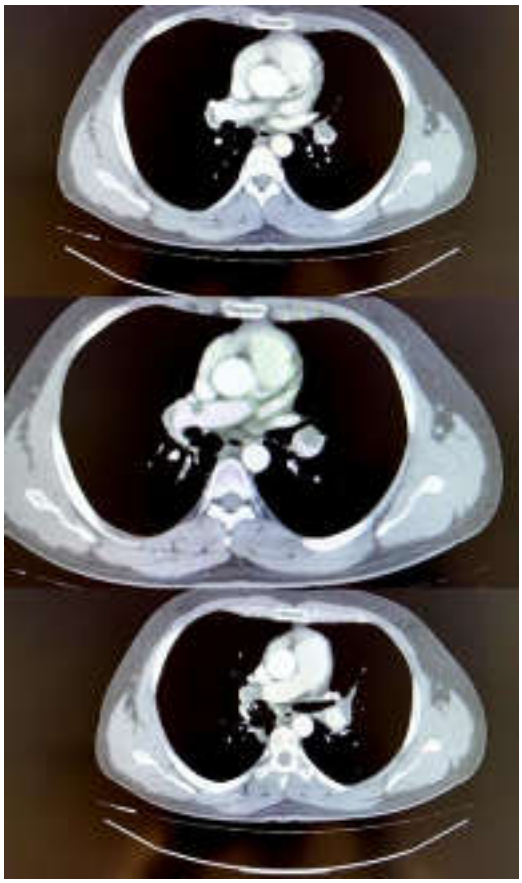

Figure 6/e Patient n.5: Chest CT angio: opalization defect as from thrombotic formations corresponding to the right pulmonary artery and its main lobar branches with massive stenosis to the upper and lower segment, and in correspondence of the left pulmonary artery at the level of the main lobar branches with massive stenosis to the upper segment.

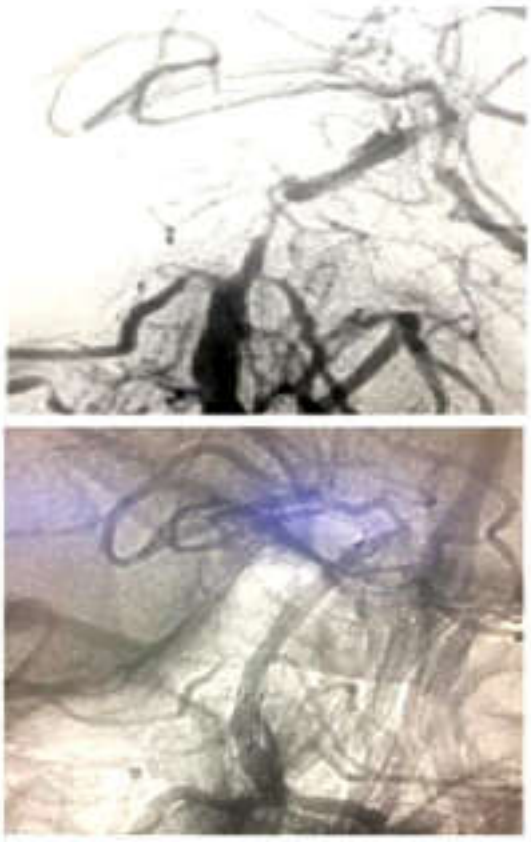

Figure 6 Cerebral CTA: Middle Segment Thrombosis Basilar Cerebral Artery in Patient Covid19 and after tPA and PTA + Stenting.

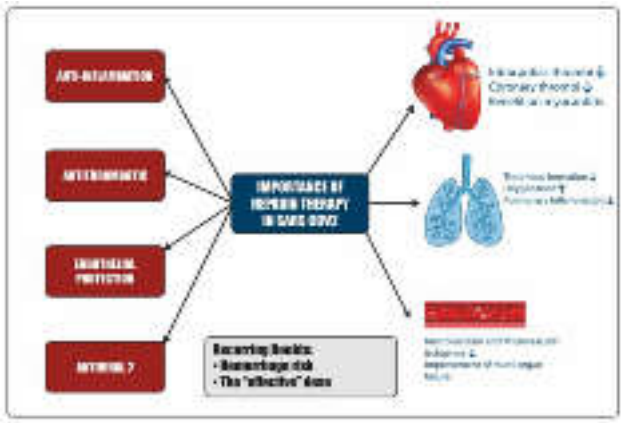

Figure 7 Rationale of the use of anticoagulants in the COVID-19 infection

arteries show occlusion of cerebral arteries of large, medium and small caliber. Treatment with fibrinolytic and subsequent PCI and stenting has often improved the prognosis of patients. These data from hospitalized patients confirm that Covid-19 patients can develop strokes with a mechanism other than traditional ischemic stroke with hypothesized pathogenesis of virus attack on brain ACE2 receptors (Fig. 7). Dermatological manifestations in Covid-19 patients also appear to be attributable to vasculitis and damage to the capillaries and microcirculation. Dermatological manifestations ranging from chilblains to true varicelliform exanthematic manifestations highlight acro-ischemic lesions in more or less young patients. The theory postulated to explain these manifestations refers to the alteration of one of the 3 parameters of the Virchow triad. Further biopsies and bio-humoral investigations will be essential to confirm this hypothesis (De Giorgi *et al*., 2020; Suarez-Valle, 2020).

Pathological anatomy: The pathology of endothelial cell dysfunction in Covid-19 has been demonstrated by the analysis of infected tissues with electron microscopy and histopathological analysis (Menter, 2020). Anatomic-pathological tests have shown that in the lungs, heart, and small intestine there are inflammatory cells associated with the endothelium and apoptosis. At the renal level, electron microscopy of Covid-19 patients evolved into acute renal failure and hemodialysis showed the inclusion of viral structures in endothelial cells of the renal vessels. In these patients with evolution in multi-organ disease, they have demonstrated mesenteric ischemia with the endothelium of the submucosal mesenteric vessels which required resection of the small intestine (Zsuzsanna Varga, 2020). Patients with evolution in heart failure and right ventricular failure experienced STEMI myocardial infarction and cardiovascular arrest and death: in these patients, histology showed myocardial infarction without signs of lymphocytic myocarditis and lymphocytic endothelium in the lungs, heart, kidneys, and liver as well as necrosis of liver cells (Zsuzsanna Varga, 2020).

Rationale of the use of anticoagulants in the COVID-19 infection: Heparin is drugs widely used in cardiology in ACS and DVT, in anti-thromboembolic prophylaxis in bedridden patients and patients undergoing major surgery, orthopedic and gastrointestinal (Alquwaizani, 2013.). The heparin indirectly exerts its anticoagulant properties by binding reversibly with antithrombin III and amplifying its inhibitory effect on activated factor X and thrombin. Fondaparinux is a synthetic analog and compared to heparin it has a longer half-life and does not interact with platelets and binds selectively and irreversibly to antithrombin III with consequent inhibition of the formation of thrombin and thrombosis (Johnston *et al*., 2018). In addition to the anticoagulant activity, heparins also possess anti-inflammatory and immuno-modulating properties (Mousavi *et al*., 2015). Some proposed mechanisms include binding with inflammatory cytokines, inhibition of neutrophil chemotaxis and lymphocyte migration, neutralization of factor C5a of the Complement and sequestration of Selectin, inflammatory proteins (Oduah *et al*., 2016). The heparin can also neutralize the release of histones by damaged endothelial cells and protect the endothelium (Xu *et al*., 2009; Iba, 2015; 40). Another interesting effect is the potential antiviral role of heparin; the polynomic nature of heparin allows it to bind to different proteins by blocking viral adhesion (41). A recent study has shown the binding of heparin with the RBD Receptor Binding Domain of the viral Spike protein by interfering with the attack of the virus on the human cell. The growing evidence emphasizes the involvement of the coagulation spectrum on an inflammatory basis in patients with Covid-19 pneumopathy. The addition of heparin to the standard therapy used in Covid-19 infection is believed to have a positive impact on disease progression (Tang *et al*., 2020).

The data reported show that in Covid-19 patients with onset and persistence of respiratory symptoms in pulmonary phase 2, even in patients in home isolation, it is useful to administer low molecular weight heparin (LMWH) even in patients without D-dimer elevation and this could have positive effects in patients (43); alternatively, Fondaparinux, can be used is characterized by coverage in 24 hours and without interference on platelets. A small pilot study by Wang *et al* showed that the off-label use of tPA (25mg i.v./ 2h, 25mg / 22h) in 3 patients with severe clinical picture induced a temporary improvement in coagulation without bleeding complications. Since there were no benefits to survival, the authors conclude that more aggressive therapeutic regimes should be tested (Wang *et al*., 2020). If the patient develops a progressive worsening of respiratory symptoms in association with the increase in hyper-coagulation markers, anticoagulant therapy must be carried out with EBPM at therapeutic or sub-therapeutic doses taking into account the patient's clinic and pharmacological kinetics. In advanced stages of the disease, at the moment that potent intravascular thrombin production may occur, there may be a role for unfractionated standard heparin. In such patients, careful monitoring of coagulation parameters due to the very probable evolution in DIC in the final phase of the disease (Tang, 2020; Tang *et al*., 2020) (Fig. 8).

Conclusion

Thrombosis and coagulopathy are associated with high mortality in patients with Covid-19 disease. Heparin treatment improves survival in patients with CAC and could have positive effects on the pathophysiology of the infection, from the interrelation between inflammation, thrombosis, and hypoxia, to an antiviral inhibiting effect on S protein. The effects of SARS-CoV-2 in patients, especially those hospitalized in intensive care and very often intubated for assisted mechanical ventilation refer to the so-called Virckow Triad, that is, the set of 3 conditions that are still considered today invariably at the basis of the development of a thrombotic condition and, in full, thrombo-embolic.

The 3 pathogenetic moments refer to 1) alteration of the blood flow; 2) endothelial damage 3) hypercoagulability of the blood. In particular, it seems that SARS-CoV-2 can modify the delicate pro- and anti-thrombotic balance, increasing the "Philia" of the blood towards the formation and deposition of thrombi which migrating become real emboli and *"micro-bombs"*. But even "endothelial damage" would seem to play a fundamental role in the pro-thrombotic genesis. In any case, do not forget the possibility that bedridden patients, despite all the necessary precautions, are likely to face slowdowns and / or obstacles to blood flow with consequent harmful effects. This etiopathogenesis of Covid-19 disease has suggested the large-scale prophylactic and therapeutic use of LMWH in an attempt to limit the coagulative events that aggravate the patient's clinical picture so much. The use of these anticoagulant therapies has significantly improved the prognosis of Covid-19 disease in Italy, with almost zeroing of ICU hospitalizations for patients with severe respiratory failure and intensive care.

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