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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11392
DOI URL: http://dx.doi.org/10.21474/IJAR01/11392

RESEARCH ARTICLE

HYPERCOAGULATION AND VIRAL INFECTION: RATIONALE OF THE USE OF ANTI-THROMBOTIC THERAPIES IN CORONAVIRUS-19 DISEASE:

Giampaolo Palma[1], Pasquale Imitazione[2], Michele Cibelli[3], Giorgio Emanuele Polistina[4] and Giuseppe Fiorentino[4]

1. MD Physician- Cardiologist, "Palma Cardiology Medical Center", Nocera Inf. Azienda Sanitaria Salerno, Italy.
2. MD Physician- Pulmonologist, Department of Intensive Care, AO of Colli, PO Monaldi, Naples, Italy .
3. MD Physician- Cardiologist,Azienda Sanitaria Marche N. 4 - Fermo, Italy.
4. MD Physician - Pulmonologist, Department of Intensive Care, AO of Colli, PO Monaldi, Naples, Italy.

Manuscript Info

Manuscript History
Received: 25 May 2020
Final Accepted: 28 June 2020
Published: July 2020

Key words:-
Covid-19, Viral Infection, Hypercoagulation, Antithrombotic Drugs, Vascular System Disease, Thrombosis

Abstract

The key-events in the clinical evolution of Covid-19 disease are the coagulation disorders. Starting from the evidences of the literature and analyzing the mechanisms involved in the coagulopative process following Covid-19 infection, it is confirmed that Antithrombotic Therapies, associated withAnti-Inflammatory Drugscommonly used in the hospital, often avoid the access of the patients in Intensive Care for assisted ventilation with improved disease prognosis. To avoid the progression of the disease in severe respiratory insufficiency it is of fundamental importance to protect the blood vessels with Antithrombotic Therapy. The administration of heparins (standard orlow molecular weight heparin) improves the prognosis of the disease by reducing the damage of pulmonary thromboembolism, myocardial infarction, heart failure, ischemic stroke and kidney damage avoiding the poor prognosis of the infection.

Introduction:-

Hypercoagulation patterns during Covid-19 disease are confirmed, in the majority of hospitalized patients, by high blood levels of D-dimer and PT, markers of thrombosis, and also by numerous thrombotic manifestations with highly variable phenotypes. Covid-19 viral infection occurs with episodes of acute pulmonary thromboembolism and evolution in severe respiratory failure and often with deep vein thrombosis in the lower limbs. In some patients it has manifested itself with ischemic strokes even in young people in the absence of comorbidity with involvement of the cerebral arteries. In allpatients with damaged endothelium, in diabetics, in hypertensive patients and in patients with previous myocardial infarction,the infection manifests itself with heart failure, severe arrhythmias and acute coronary syndromes such as direct and indirect damage of the myocardium. In other patients, the disease manifests itself in less aggressive forms involving kidneys, intestines, liver and vasculitic dermatitis. In the most serious caseswith poor prognosis, the disease evolves into paintings of Acute Pulmonary Thromboembolism, Disseminated Intravascular Coagulation (DIC) and Septic Shock, with imposing activation of the coagulation cascade, endothelial dysfunction and endothelitis, with characteristic micro- and macro-thrombotic phenomena both in localization pulmonary than extrapulmonary (1) (2) (3).

Corresponding Author:- Giampaolo Palma
Address:- MD Physician – Cardiologist, "Palma Cardiology Medical Center", Nocera Inf. Azienda Sanitaria Salerno, Italy.

The correlation between infection and hyper-coagulation:
The correlation between infection and hyper-coagulation has been widely demonstrated (4).
Numerous inflammatory cytokines such as IL-6, IL-8 and TNF-a (tumor necrosis factor alpha) determine a state of "hyper-coagulation" through the expression of the tissue factor with the movement of leukocytes, platelets, endothelial cells and pericytes (5). In many inflammatory diseases and in sepsis there is an increased release of histones and nucleosomes which are toxic both for the endothelial wall and for the endothelial protective function (6).

In response to infection and inflammation, neutrophils produce strips of extracellular DNA (NETs Neutrophil Extracellular Traps NETs) which should allow neutrophils to cage and destroy "invading" microorganisms. NETs cause deposits of fibrin and platelet aggregation and this has been seen through "in vitro" experiments (7). A fragment of fibrin degradation operated by plasmin is D-dimer. The increase in D-dimer is a recognized marker of disseminated intravascular hyper-coagulation (8). The same D-dimer promotes activation of IL-6, inflammatory storm and activation of neutrophils and monocytes (9).

Evidence of hyper-coagulation in previous viral infections:
In viral infections, both hemorrhagic and non-hemorrhagic, in addition to the evidence of reduced platelet production and destruction of platelets (thrombocytopenia), a decrease in platelet function has also been observed. In the auto-immune body infection causes thrombocytopenia. Another important mechanism is represented by platelet hyper-aggregation and consequent increased consumption of platelets.

In the previous SARS-CoV2 infection both the presence of high levels of Von Willebrand factor in the blood (10) with activation of hyper-coagulation and thrombocytopenia caused by autoantibodies (11) (12) (13) were observed. Furthermore, fibrin clots in the alveoli were an important characteristic of the infection: perhaps the goal of this alveolar hyper-coagulation would be to protect the host by sealing the alveoli by preventing both alveolar edema and alveolar hemorrhages, but the consequence is certainly the limitation of pulmonary gas exchange (14).

Markers of impaired coagulation in viral infection:
A procoagulative state can be evidenced through an increase in the levels of coagulation proteins. Increased levels of fibrinogen, D-dimer, thrombin-antithrombin complex and plasmin-alpha-2-antiplasmin complexes and thrombomodulin have been reported in respiratory infections, influenza and SARS-COV infection. In addition, an increase in the levels of inhibitor of the plasminogen-1 activator, suggestive of impaired fibrinolysis, has also been shown (4).

A recent study by Tang and collaborators has revealed in 15 patients (71.4%) who died for Covid-19 an alteration of the laboratory parameters for DIC according to the diagnostic criteria of the International Society on Thrombosis and Haemostasis. In the advanced stage of the disease, high levels of D-dimer and fibrinogen degradation proteins have been observed (15).

Correlations between viral infection and coagulation disorders:
In several viral infections the clinical picture of the altered coagulation is manifested by bleeding, thrombosis or both. An exaggerated response can even lead to disseminated intravascular coagulation with the formation of microvascular thrombi in various organs (16). Respiratory tract infections increase the risk of deep vein thrombosis and pulmonary embolism (17). Both thrombotic and hemorrhagic complications such as deep vein thrombosis, acute pulmonary thromboembolism, pulmonary hemorrhage with hemoptysis, hematemesis, pet rash and sometimes diffuse petechial cerebral hemorrhage have been reported in the H1N1 swine flu epidemic (4). Avian influenza (H5N1) has been reported in numerous patients with disseminated intravascular coagulation, pulmonary hemorrhage and thrombocytopenia (18). In SARS-COV coronavirus infection, the clinical picture of coagulation consisted of vascular endothelial damage in medium and small-sized pulmonary vessels, disseminated intravascular coagulation, deep vein thrombosis and pulmonary thromboembolism (12) (13) (19). In Covid-19 disease these same clinical pictures have been reported by Tang and collaborators. According to Tang, in an advanced stage of pneumopathy, a consumption coagulopathy induced by sepsis and triggered by the release of cytokines following damage to the vascular endothelium and activation of monocytes would be established. thrombotic phenomena are tissue factor hyper-expression, von Willebrand factor secretion with excessive final fibrin production, platelet activation and fibrinolysis stimulation (15) (Fig.1).

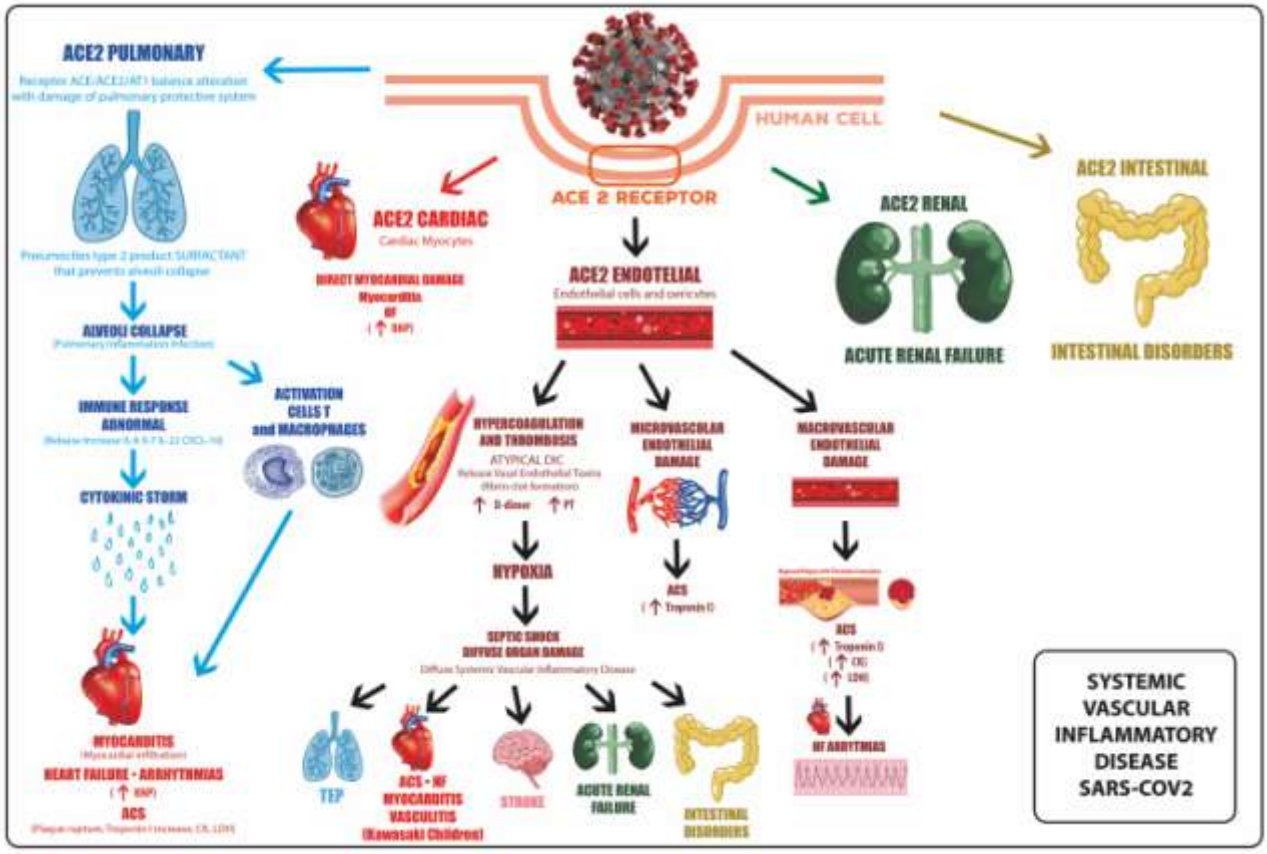

Fig 1:- SARS-COV 2 is a Systemic Vascular Inflammatory Disease.

Importance of the use of anticoagulation in SARS-COV2:

Both standard and low molecular weight heparins are anticoagulant substances used in the prophylaxis and therapy of venous thromboembolism (20). The heparin exerts its anticoagulant properties indirectly by binding reversibly to the anti-thrombin III (AT) by amplifying the inhibitory effect on activated X factor and on thrombin (Xa factor). (21). Heparin indirectly exerts its anticoagulant properties by reversibly binding to antithrombin III and amplifying its subsequent inhibitory effect on activated factor X and thrombin (factor Xa) (21) (22). For its action at the thrombin level, a heparin that contains at least 18 saccharide sequences is required, while the binding at ATIII level, which catalyzes the inhibitory action at the factor Xa level, takes place thanks to a peculiar saccharide sequence (23). This feature has been exploited by pharmacological research for the realization of low molecular weight heparins which are not able to bind to thrombin, but only to Factor Xa (24).

Fondaparinux is a synthetic analogue of the pentasaccharide sequence and compared to heparin it has a longer half-life and does not interact with platelets (25). Fondaparinux binds selectively and irreversibly to antithrombin III. This occurs in a neutralization of Factor Xa, which ultimately inhibits the formation of thrombin and the formation of thrombus. Fondaparinux is also indicated in the prophylaxis and treatment of venous thrombo-embolism (26).

Heparin, used clinically as an anti-coagulant, also has anti-inflammatory properties (27). The proposed mechanisms, although not fully clarified, are: inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of complement factor C5a, sequestration of acute inflammatory phase proteins such as selectin-P and selectin-L, induction of cell apoptosis through the TNF-alpha and NF-kb pathways; also another mechanism proposed to block inflammation is the link with inflammatory cytokines (28) (29).

Viral infection damages endothelial cells that are ubiquitous in the body causing their dysfunction. Furthermore, the histones released by the damaged cells themselves cause endothelial damage (30). Another mechanism is through its effects on histone methylation and on the pathways on the MAPK and NF-Kb signal (31).

For all these reasons, heparin can affect microcirculatory dysfunction and can decrease endothelial damage.

In addition, heparin also has an antiviral role, which is being studied in experimental models. The polyanionic nature of heparin allows it to bind to different proteins and therefore to act as an effective inhibitor of the viral adhesion (32). An example is that of herpes simplex infections in which heparin competes with the virus for the surface glycoproteins of the host cell to limit the infection; in addition, in Zika virus infection, heparin prevents virus-induced cell death of human neural progenitor cells (32) (33). In addition, the use of heparin at a concentration of 100 mcg / mL halved the infection in experimental cells contaminated with sputum from patients with SARS-CoV (34).

In recent work, heparin has been shown to interact with the Spike S1 protein receptor of SARS CoV-2 (35). In the study of Tang et al. a favorable course has been highlighted in severe patients with Covid-19 who meet the criteria for coagulopathy induced by sepsis and with markedly high d-dimer through the use of LMWH (36). Out of 99 patients treated with heparin for at least 7 days, in almost all patients (n = 94), an LMWH s.c. dosage of 4000/6000 UI was used while in 5 patients non-fractionated heparin was administered (10000-15000 UI/day).

Therapeutic results:
Increasing evidence confirms an involvement of the coagulation spectrum on an inflammatory basis in patients with COVID-19 disease. Although the data are contradictory on therapeutic dosage, it is believed that both the use of standard heparin and the use of low molecular weight heparin can have a positive impact in the progression of Covid-19 disease.

The data confirm that the use of heparin is not necessary in asymptomatic patients. However, in the event of the onset and persistence of respiratory symptoms, even in patients in isolation at home, it is considered useful to start a prophylaxis with low molecular weight heparin (LMWH) or with Fondaparinux, the latter characterized by therapeutic coverage in the 24 hours and non-interference with platelets. If the patient develops a clinical picture with worsening respiratory symptoms in association with the increase in hyper-coagulation markers, heparin should be administered at therapeutic/sub-therapeutic dosages based on the patient's characteristics and pharmacological kinetics. In the most advanced stage of the disease there may be a role for unfractionated heparin since a powerful intravascular formation of thrombin and thrombosis occurs. Furthermore, careful monitoring of coagulation parameters is necessary in these patients given the possible progression in intravascular coagulation disseminated in the final phase of the disease (15).

In addition to the antiviral therapies that block the entry and replication of the virus in the cell and the anti-inflammatory therapies in the initial pulmonary and advanced inflammatory phase, in Covid-19 disease it is of fundamental importance to protect the endothelium and vessels to avoid the progressive coagulation and cytokine storm that characterize the serious phases of the illness. (37) (Fig. 2).

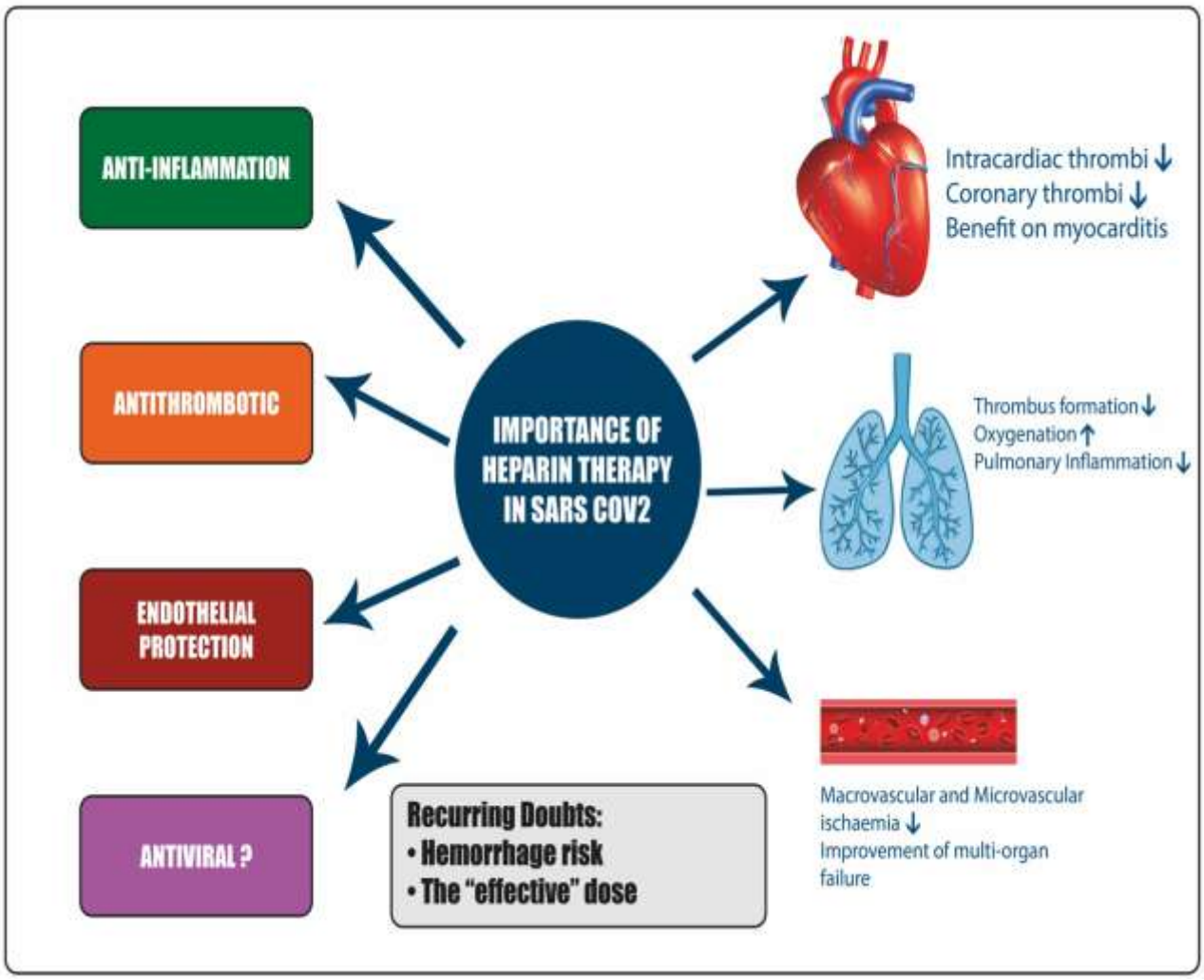

Fig 2:- Importance of the Antithrombotic Therapy in SARS-COV2 infection.

Conclusions and Future Directions:-

The COVID-19 disease is characterized by a wide variability of phenotypes that have viral attack on the endothelium via ACE2 receptors as their common denominator. The disease manifests itself as a coagulopathy with widespread endothelial involvement, from the lungs, to the heart, brain, kidneys, intestines and liver. The pathogenesis of coagulopathy in Covid-19 disease seems to follow the Virchow-Triad and includes anomalies of the blood vessel wall or endothelial surface, alteration of blood flow and prothrombotic components within the circulating blood. In Covid-19 coagulopathy there are inflammation and dysfunction of endothelial cells on a large scale, dynamics of abnormal flow and activated platelets, high concentrations of von Willebrand Factor, cell-free DNA, histones and viral RNA that together cause both activation of Factor XI, both Thrombin generation and Fibrin formation. For this reason, in addition to antiviral and anti-inflammatory therapies, in Coronavirus-19 infection it is of fundamental importance to protect the vascular endothelium and blood circulation with Antithrombotic Drugs for the improvement of the prognosis of the disease.

Acknowledgments:-

1. The authors thank the Doctor Professor Aldo Palma, master of cardiology, at his great heart, culture and humanity.
2. The author Doctor Giampaolo Palma thank Gabriella Tagliamonte, for her great support and her great heart.
3. The authors thank the "Palma Cardiology Medical Center" **www.centrocardiologicopalma.it**.
4. The author Doctor Giampaolo Palma thank for their great support his children Emilia and Nicola Palma.

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