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Understanding COVID-19: in the end it is the endothelium—what else?

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First science

The COVID-19 pandemic has changed the world and has refocused science, including cardiovascular (CV) research.[1] This virus not only affects the throat and lungs, but also profoundly impacts the CV system. First of all, male sex, obesity, hypertension,[2] diabetes and cardiac conditions at large increased the risk of infection, possibly related to angiotensin-converting enzyme (ACE) expression,[3,4] and of an unfavourable disease course. Secondly, COVID-19 affects the heart, leading to myocarditis,[5,6] myocardial injury,[7] scar formation and arrhythmias, and heart block,[8] as well as affecting the blood vessels, leading to vascular occlusion due to local thrombus formation or embolism and eventually cardiac death.[9] The mechanisms involved are the usual suspects, as outlined in the *Viewpoint* '**COVID-19 is, in the end, an endothelial disease**', by Peter Libby from the Brigham and Women's Hospital in Boston, USA and myself. It is well known that the vascular endothelium provides the crucial interface between the circulating blood and tissues, and displays remarkable properties that normally maintain homeostasis.[10] This tightly regulated array of functions includes control of haemostasis, fibrinolysis, inflammation, oxidative stress, vascular permeability, and eventually vasomotion and vascular structure. While these functions participate in the moment to moment regulation of the circulation and coordinate many host defence mechanisms, they can also contribute to disease when their usually homeostatic and defensive functions overreach and turn against the host, as is the case with SARS-CoV-2, the virus causing the current pandemic (*Figure 1*).

It produces protean manifestations ranging from head to toe, wreaking seemingly indiscriminate havoc on multiple organ systems including the lungs, heart, brain, kidney, and the vasculature. This *Viewpoint* presents the hypothesis that COVID-19, particularly in the later complicated stages, represents an endothelial disease. Cytokines, protein proinflammatory mediators, are key signals that shift endothelial function from the homeostatic into the defensive mode. The endgame of COVID-19 involves a cytokine storm with positive feedback loops governing cytokine production that overwhelm counter-regulatory mechanisms. This concept provides a unifying concept of this raging infection and a framework for rational treatment strategies at a time when we possess an only modest evidence base to guide our therapeutic attempts to confront this novel pandemic.[11]

Surprisingly, emergency unit visits for acute cardiac conditions have declined markedly.[12] Several reasons have been suggested: first, patients may have been wary of visiting hospitals during the pandemic.[12,13] Secondly, with life on standstill, plaque ruptures and aortic dissections may have become less likely, and, thirdly, the marked reduction in pollution may also have had an influence.[14] The first hypothesis is supported by the *Fast Track* manuscript '**COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests**' by Simone Savastano and colleagues from the Fondazione IRCCS Policlinico San Matteo in Italy.[15] They included all consecutive out-of-hospital cardiac arrests (OHCAs) occurring in the Provinces of Lodi, Cremona, Pavia, and Mantova in the 2 months following the first documented case of COVID-19 in Lombardia compared with those that occurred in the same time window in 2019. The cumulative incidence of COVID-19 from 21 February to 20 April 2020 was 956/100 000 inhabitants and the cumulative incidence of OHCA was 21/100 000 inhabitants, with a 52% increase as compared with 2019 (*Figure 2*). A significant correlation was found between the difference in cumulative incidence of OHCA and the cumulative incidence of COVID-19. Thus, the OHCA excess in 2020 is closely correlated to the COVID-19 pandemic. These findings are important for furthering the understanding of the reduced emergency unit visits and for planning of future pandemics, as outlined in an **Editorial** by Hanno Tan from the Academic Medical Center in Amsterdam, the Netherlands.[16]

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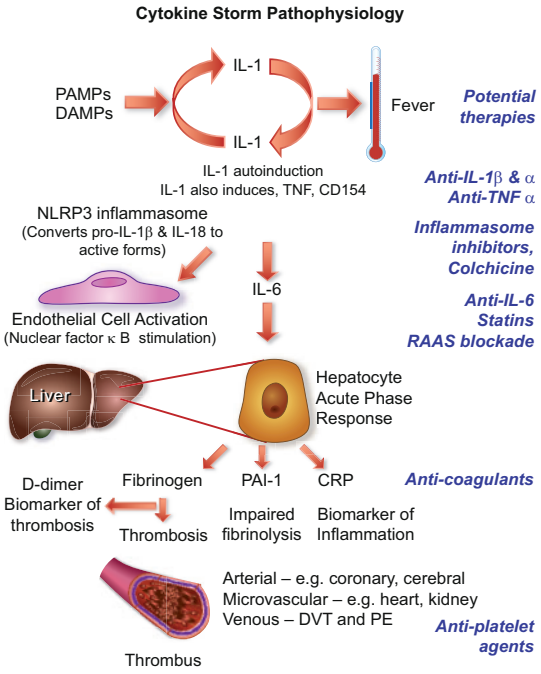

Figure 1 Cytokine storm. Proinflammatory cytokines such as IL-1 and TNF-α induce each other's gene expression, unleashing an amplification loop that sustains the cytokine storm. The endothelial cell is a key target of cytokines, as they induce action of a central proinflammatory transcriptional hub, nuclear factor-κB. IL-1 also cause substantial increases in production by endothelial and other cells of IL-6, the instigator of the hepatocyte acute phase response. The acute phase reactants include fibrinogen, the precursor of clot, and PAI-1, the major inhibitor of our endogenous fibrinolytic system. C-reactive protein, commonly elevated in COVID-19, provides a readily measured biomarker of inflammatory status. The alterations in the thrombotic/fibrinolytic balance due to the acute phase response predisposes towards thrombosis in arteries, in the microvasculature including that of organs such as the myocardium and kidney, and in veins, causing deep vein thrombosis and predisposing towards pulmonary embolism. Thus, the very same cytokines that elicit abnormal endothelial functions can unleash the acute phase response which together with local endothelial dysfunction can conspire to cause the clinical complications of COVID-19. The right side of this diagram aligns therapeutic agents that attack these mechanisms of the cytokine storm and may thus limit its devastating consequences (from Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. See pages 3038–3044).

With a prothrombotic state of the endothelium, thromboembolism should increase during the COVID-19 pandemic.[17] This hypothesis is pursued in a *Fast Track* entitled '**Pulmonary embolism in COVID-19 patients: a French multicentre cohort study**' by Ariel Cohen from the Hopital Saint-Antoine in Paris, France.[18] In a retrospective multicentric observational study, the authors included consecutive patients hospitalized for COVID-19. Among 1527 patients, 6.7% patients had pulmonary embolism confirmed by computed tomographty pulmonary angiography (CTPA). Intensive care unit (ICU) transfer and mechanical ventilation were significantly higher in the pulmonary embolism group. In a univariable analysis, traditional venous thrombo-embolic risk factors and pulmonary lesion extension in chest CT were not associated with pulmonary embolism, while patients under anticoagulation prior to hospitalization or in whom it was introduced during hospitalization had a lower risk of pulmonary embolism, with an odds ratio of 0.37. Male gender, prophylactic or therapeutic anticoagulation, C-reactive protein, and time from symptom onset to hospitalization were associated with pulmonary embolism. Thus, risk factors for pulmonary embolism in COVID-19 do not include traditional thrombo-embolic risk factors, but rather independent clinical and biological findings at admission. In line with the concept outlined above, inflammation is a major driver of pulmonary embolism in COVID-19, as further discussed in a thought-provoking **Editorial** by Adam Torbicki from the Centre of Postgraduate Medical Education in Otwock, Poland.[19]

Inflammation is also a trigger for atrial fibrillation as it changes the electrical properties of the atrial myocardium and eventually favours tissue fibrosis.[20] Furthermore, inflammation may trigger tissue factor expression in the atrial endothelium and favour thrombus formation.[21] On the other hand, life on standstill may reduce sympathetic drive and hence reduce the likelihood of new-onset atrial fibrillation.[22] In their article entitled '**New-onset atrial fibrillation: incidence, characteristics, and related events following a national COVID-19 lockdown of 5.6 million people**', Anders Holt and colleagues from the Copenhagen University Hospital, Herlev and Gentofte in Hellerup, Denmark resolved this conundrum.[23] During 3 weeks of lockdown, weekly incidence rates of new-onset AF were 2.3, 1.8, and 1.5 per 1000 person-years, while during

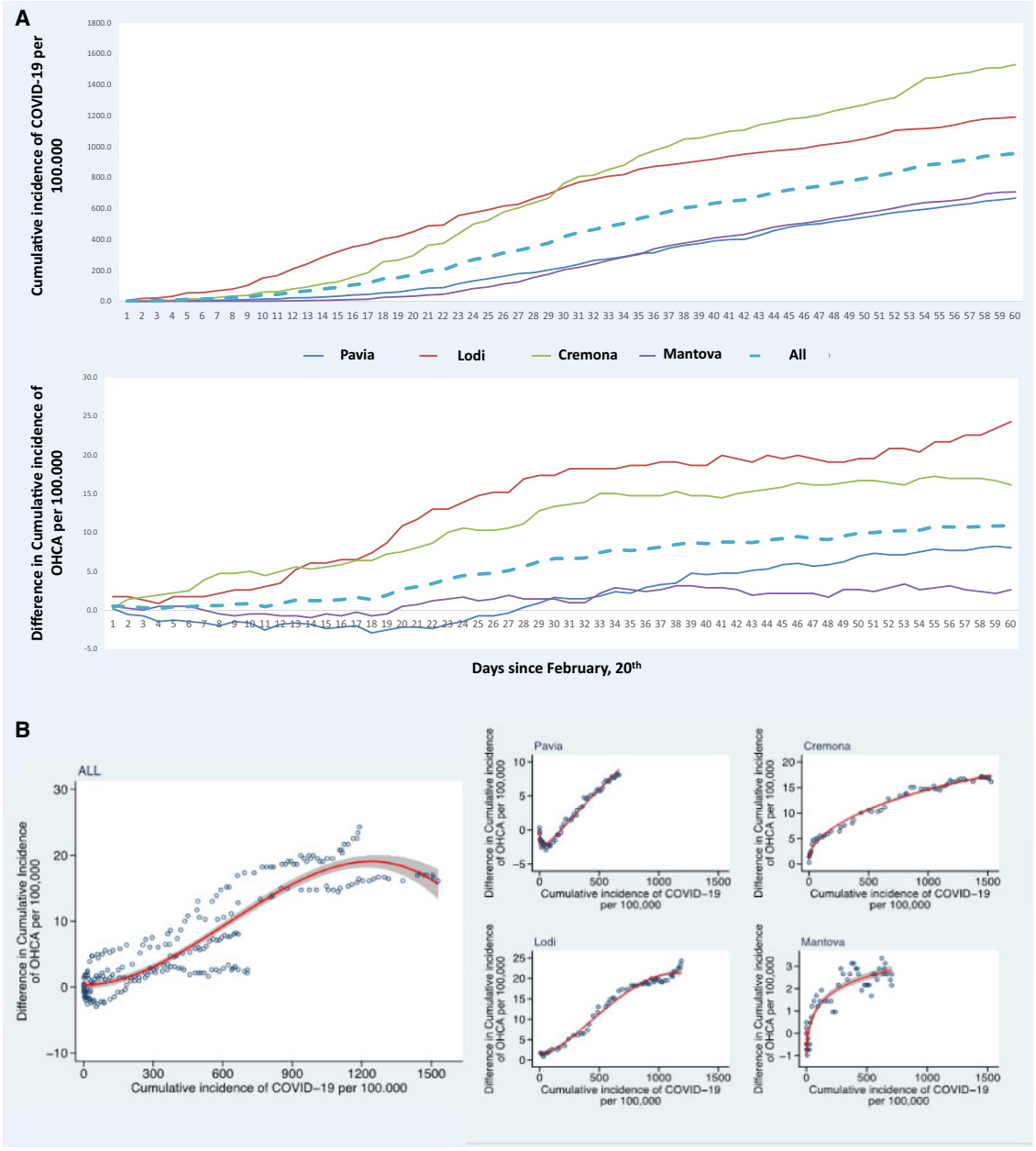

Figure 2 (*A*) Over a period of 60 days from 20 February, the cumulative incidence of COVID-19 per 100 000 inhabitants in the four provinces and in the overall territory (dotted line) (upper part), and the trend of the difference of OHCA between 2020 and 2019 per 100 000 inhabitants in the four provinces and in the overall territory (dotted line) (bottom part). (*B*) The cumulative incidence of the difference in OHCA between 2020 and 2019 per 100 000 inhabitants as a function of the cumulative incidence of COVID-19 per 100 000 inhabitants, since 20 February 2020. Dots are the observed values. The red line is the function fitted using fractional polynomials. The shaded area is the 95% CI for the estimates (from Baldi E, Maria Sechi G, Mare C, Canevari F, Brancaglione A, Primi R, Klersy C, Palo A, Contri E, Ronchi V, Beretta G, Reali F, Parogni P, Facchin F, Rizzi U, Bussi D, Ruggeri S, Visconti LO, Savastano S, on behalf of the Lombardia CARe researchers. COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests. See pages 3045–3054).

the corresponding weeks in 2019, incidence rates were 3.5, 3.4, and 3.6 per 1000 person-years. Incidence rate ratios comparing the same weeks were 0.66, 0.53, and 0.41. Patients diagnosed during lockdown were younger and had lower CHA_2DS_2-VASc-scores. During the first 3 weeks of lockdown, 7.8% of patients experienced an ischaemic stroke or death within 7 days of new-onset atrial fibrillation compared with 5.6% during the equivalent weeks in 2019, corresponding to an odds ratio of 1.41. Thus, following a national lockdown in Denmark, new-onset atrial fibrillation declined by 47%, while ischaemic stroke or death within 7 days increased. These complex findings

are put into context in an excellent **Editorial** by Carina Blomstrom-Lundqvist from the Department of Medical Science in Uppsala, Sweden.[24]

Myocardial injury after non-cardiac surgery or MINS is caused by myocardial ischaemia due to a supply–demand mismatch or thrombus and is associated with an increased risk of mortality and major adverse CV events or MACE.[25] In their review '**Myocardial injury after non-cardiac surgery: diagnosis and management**' Philip Devereaux and colleagues from McMaster University in Hamilton, Canada note that the diagnostic criteria for MINS include elevated post-operative troponin levels with no evidence of a non-ischaemic aetiology during or within 30 days after non-cardiac surgery, and without ischaemic features such as chest pain or ECG changes.[26] Patients with MINS should receive aspirin and a statin, unless contra-indicated, and an NOAC (non-vitamin K antagonist oral anticoagulant) if not at high bleeding risk. Cardiac catheterization is only recommended for those with recurrent ischaemia, heart failure, or high risk based on non-invasive imaging. Troponin should be measured for the first few days after surgery in patients ≥65 years or with atherosclerotic disease to avoid missing MINS and the opportunity for secondary prophylactic measures and follow-up.

Finally, the issue is complemented by various Discussion Forum contributions on this very timely topic. In a contribution entitled '**Should atrial fibrillation be considered a cardiovascular risk factor for a worse prognosis in COVID-19 patients?**', Fabian Sanchis-Gomar from the Faculty of Medicine at the University of Valencia, Spain discuss the recent publication '**Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy**' by Marco Metra and colleagues from Brescia, Italy.[9,27] Metra *et al.* respond in turn. In a comment entitled '***ACE2* is on the X chromosome: could this explain COVID-19 gender differences?**' Felix Hernandez from the Universidad Autonoma de Madrid Centro de Biologia Molecular Severo Ochoa in Madrid, and his colleague Esther Culebras discuss the recent publication entitled '**Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin–angiotensin–aldosterone inhibitors**' by Adriaan Voors and colleagues from the University Medical Center Groningen in the Netherlands.[3,28] Voors *et al.* respond in a separate comment.[29]

In a contribution entitled '**Circulating plasma angiotensin-converting enzyme 2 concentrations in patients with kidney disease**', Insa Marie Schmidt and colleagues from the Boston University in Massachusetts, USA also comment on the article by Voors *et al.*[3,30] Voors and colleagues respond in a separate message to this piece.[31]

Time for the last words

This is my last Issue@aGlance in the *European Heart Journal* in my role of Editor-in-Chief. It has been a pleasure and honour to serve both authors and readers of this fine journal and the European Society of Cardiology over more than a decade. My goal has always been to make it more attractive and informative for clinicians and important and stimulating for scientists worldwide. I hope you have enjoyed it. Needless to say, that was only possible thanks to an amazing team of editors, reviewers, authors, and editorial staff. I hope that you enjoy this very last issue under my leadership. The time has come to hand the *European Heart Journal* over to the new Editor-in-Chief, Filippo Crea from Rome. I am certain Professor Crea will do an excellent job with his new team, retaining some of the experienced editorial staff from Zurich. Thank you for submitting to, reviewing for, and reading the *European Heart Journal*, and goodbye—I am sure we will stay in touch.

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