Title

COVID-19: comprehensive synopsis of suggested pathophysiological mechanisms and repurposed drugs

Running title

Pathophysiology of COVID-19

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Abstract

During the current COVID-19 pandemic caused by SARS-CoV-2, clinicians and scientists are working assiduously to unravel its pathophysiology and find effective treatments. An impressive number of papers has been published on SARS-CoV-2, exposing the complexity of the disease, the tendency of scientists to form hypotheses within their area of expertise, and the lack of orchestration of research. Hypotheses and research findings mainly complement each other, though sometimes controversies can be discerned among various theories and study results. Our overview aims to portray the 'big picture' of COVID-19, visualising the interwovenness of different pathophysiological pathways, with a focus on cytokine-induced pathology, the sequelae of ACE2 downregulation, and thrombosis associated with microvascular injury. It aids in overseeing the effects of repurposed drugs on intended targets, but also alerts to the (adverse) effects on interacting pathways. The overview shows how comorbidities probably increase susceptibility to (severe) COVID-19 and provides the possible pathophysiological origin of signs, symptoms, and biochemical abnormalities.

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Introduction

The world is currently facing a relentless pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease that results from infection with this novel human betacoronavirus (coronavirus disease 2019, COVID-19) is most often characterised by a mild, self-limiting upper respiratory tract infection and/or gastro-intestinal complaints. Nevertheless, in a substantial fraction of the population it escalates into a severe and life-threatening condition with the development of pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure. Individuals with underlying morbidities, such as cardiovascular disease, hypertension, obesity, diabetes, pulmonary disease, and immunocompromising conditions, are especially susceptible to this severe disease course. Male gender and advanced age are also established risk factors.[1] A maladaptive, hyperinflammatory immune response, featuring a 'cytokine storm' reminiscent of the macrophage activation syndrome (MAS),[2] a disbalanced renin-angiotensin system (RAS),[3] a hypercoagulable state with poorly controlled 'immunothrombosis' and contact system activation, either localised to the lungs or more disseminated,[4,5] and endothelial/microvascular dysfunction are all held responsible for disease exacerbation.[6] These homeostatic derangements largely explain the findings in the later stages of COVID-19, of which fever, hypoxia, respiratory failure, lymphocytopenia, and elevated levels of D-dimers, C-reactive protein (CRP), lactate dehydrogenase (LDH), cytokines (e.g. interleukin (IL)-6), and ferritin are the most notable (and prognostic) features.[1,2]

Lately, clinicians and scientists have been involved in an unprecedented international crusade to unravel the precise pathophysiological processes that occur in COVID-19. This endeavour is exemplified by the myriad of papers that have been published since the World Health Organisation (WHO) declared COVID-19 a pandemic earlier this year. By the end of June 2020,

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PubMed contained more than 20,000 articles on SARS-CoV-2. When including non-peer reviewed articles (preprints), more than 30,000 articles relating to the recent coronavirus outbreak can be found on the Internet. Pathophysiological concepts and possible treatment options have been conceived based on patient descriptions in observational studies, expanded in medical hypotheses, and subsequently submitted to the scrutiny of randomised controlled trials (RCT). The majority of the RCTs testing a certain concept by investigating the effects of the associated treatment are still ongoing, and the results are anxiously anticipated. Although much research is needed to increase our understanding of COVID-19, scientific efforts have not been truly concerted, which has resulted, among others, in the simultaneous performance of multiple studies with similar or overlapping aims (e.g. >100 registered studies on hydroxychloroquine (HCQ)).[7] This raises some questions about the correct allocation of time, funds, and resources.

Methods

We desired to contribute to the global endeavour of elucidating the pathophysiology of COVID-19 and finding effective treatments. Therefore, we extensively searched for publications regarding pathophysiological mechanisms (purportedly) underlying COVID-19 and pharmacological interventions targeting these pathways. We confined our research to repurposed drugs, inasmuch as these existing medications are generally available, have a known profile, and are presently the only reasonable alternative, for it will take some time before newly developed, tailored anti-coronaviral drugs and vaccines will become available.

Results

Having read hundreds of papers and contributions identified on PubMed, medRxiv, bioRxiv, and websites, we selected 70 peer reviewed articles, 27 preprints, and 3 websites

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(Supplementary Material), which were used for the construction of a comprehensive overview of suggested pathophysiological mechanisms and redirected drugs (Figure 1). Some speculations of the authors themselves (e.g. bowel wall angioedema, ADAMTS-13 deficiency, and the therapeutic use of C1-esterase inhibitor) were also incorporated in the overview. The sheer volume of publications on COVID-19 prevented us from creating an exhaustive overview. Moreover, it was practically impossible to fit all theories and suggestions into one diagram. An all-encompassing enumeration of experimental treatments can be found in the landscape document of the WHO.[8] We mainly included pathophysiological considerations that were corroborated with research findings, described in various publications, amenable to targeting by repurposed drugs, and linked to the core concepts mentioned in the first paragraph, on which there seems to be consensus in the scientific community. We deliberately omitted medications that are not truly expected to have a significant impact on COVID-19, based on their mode of action (lopinavir/ritonavir, oseltamivir), unrealistic dosing requirements (favipiravir, ribavirin, ivermectin), questionable status (umifenovir), and the results of RCTs (lopinavir/ritonavir).[9,10] Notwithstanding the (retracted) report by Mehra *et al.* and the even more recent study by Boulware *et al.*,[11,12] we did include chloroquine (CQ) and HCQ in our overview, for reasons outlined below.

Discussion

The pathophysiology of COVID-19 is apparently complex. Our overview aids in the visualisation of this complexity. It is also meant to remind clinicians and researchers of the intricate interwovenness of various pathways. When describing an individual pathophysiological pathway and suggesting a possibly beneficial drug, one might not oversee the 'big picture', thereby missing the (potentially deleterious and wide-ranging) effects on interrelated pathways and/or downstream cascades. Hopefully, our diagram contributes to a

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more 'holistic' view of COVID-19 pathophysiology, and a more integral approach to the repurposing of existing drugs and the development of targeted therapies.

The overview is basically self-explanatory, especially with the information contained in the elaborate legend. Nonetheless, we will concisely clarify the following concepts, which constitute the 'backbone' of the overview: (1) SARS-CoV-2 spike glycoprotein binding to angiotensin-converting enzyme 2 (ACE2) and priming of this interaction by transmembrane serine protease type 2 (TMPRSS2) (and Furin), which causes viral cell entry;[13] (2) ACE2 downregulation, causing a lack of conversion of Angiotensin II (Ang II) into Angiotensin(1-7) (Ang(1-7)). This leads to high Ang II levels – aggravating the situation that may already exist in patients with cardiovascular disease – and low Ang(1-7). The disrupted balance between the ACE/Ang II/Angiotensin II receptor type 1 and ACE2/Ang(1-7)/Mas receptor pathways leads to increased vasoconstriction, proliferation, fibrosis, thrombosis, and inflammation, culminating in acute lung injury;[3] ACE2 downregulation also results in decreased inactivation of des-Arg^9-bradykinin, which potentiates the formation of pulmonary angioedema;[4] (3) 'Cytokine storm', which entails a state of hyperinflammation, contributing to multiple organ involvement and ARDS;[1,2] (4) Thrombotic microangiopathy (TMA), probably caused by virus-induced endothelial injury, complement activation, and cytokine effects.[6,14] Microvascular injury is possibly more pronounced in patients with pre-existing endothelial dysfunction. Together with uncontrolled localised and/or systemic 'immunothrombosis' and activation of the contact activation system, this may explain the hypercoagulable state, exemplified by thrombo-embolic events in a considerable number of COVID-19 patients.[4,5]

It should be noted that published pieces of evidence and proposed theories are sometimes conflicting. For example, there are reports in favour and against the association between vitamin

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D deficiency and COVID-19 vulnerability and severity.[15,16] The effects of ACE inhibitors and angiotensin receptor blockers on ACE2 expression are not unequivocally established.[3] It remains to be determined whether increased ACE2 expression is beneficial (due to the Ang II opposing effects) or deleterious (more entry sites for SARS-CoV-2). Perhaps both are true. Studies reported contrasting data regarding the expression of ACE2 in different sexes, ages, and ethnicities.[1,17] Another intriguing controversy concerns the effects of soluble ACE2. On the one hand, complexes of SARS-CoV-2 bound to soluble ACE2 enzymes may be recognised as antigens and may not only elicit an immune response to the virus, but also instigate auto-immunity against ACE2. The generated auto-antibodies may contribute to ACE2 demise and, as a result, acute lung injury.[18] On the other hand, human recombinant soluble ACE2 has been shown to inhibit SARS-CoV-2 infection in an experimental setting, by acting as neutralising agent that prevents binding of SARS-CoV-2 to membrane-attached ACE2. This property, and the fact that soluble ACE2 can be supplemented to compensate for the loss of endogenous ACE2, may be exploited as therapeutic strategy in COVID-19 patients.[19] And then there is bradykinin: should it be cherished as a cardioprotective, compensatory substance in the relative absence of Ang(1-7), or should it be antagonised considering its purported role in the development of pulmonary angioedema and ARDS?[4] The answer may lie in the adequate differentiation of the effects of the des-Arg^9-bradykinin/BK1-receptor/iNOS and bradykinin/BK2-receptor/eNOS pathways.

Timing is important when using repurposed drugs. Van de Veerdonk *et al.* provided a useful timeline, indicating the possible contribution of each (class of) drug(s) to the treatment of the consecutive phases of COVID-19.[4] An example: the antimalarials HCQ and CQ are probably not suitable for use in patients with advanced disease. Negative results from trials investigating hospitalised patients with moderate to severe disease are perhaps not so much surprising as

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anticipated.[11] Considering their modes of action (inhibition of viral entry and endosome fusion/uncoating, reduction of cytokine production, and inhibition of platelet aggregation),[20,21] these slow-acting drugs hold more promise as prophylaxis or early symptomatic treatment. In an early phase, HCQ/CQ toxicity (e.g. QT_c-prolongation) is probably less of an issue, since liver, kidney, and myocardial function are not importantly affected yet. Boulware *et al.* reported that HCQ was not beneficial as postexposure prophylaxis.[12] However, their study population was not a representation of those most at risk of developing (severe) COVID-19, the large majority of cases were not PCR-confirmed, data acquisition relied on self-reporting by the participants, and adherence in the HCQ group was only 75%. More evidence from ongoing trials is needed on this matter. Parenthetically, the way in which HCQ/CQ inhibit viral cell entry – by disrupting terminal glycosylation of ACE2 and, as a result, its interaction with the spike protein of SARS-CoV-2[20] – may also be responsible for a lack of adequately glycosylated ACE2 to convert Ang II into Ang(1-7). This may explain some of the cardiovascular side-effects of these agents. Remdesivir may also be more effective in the early stages of COVID-19. Based on their properties (Figure1), Baricitinib – a Janus kinase inhibitor used in rheumatoid arthritis – and the serine protease inhibitors camostat and nafamostat mesylate may have advantageous effects in early and advanced disease. Drugs counteracting the (maladaptive) immune response (i.e. corticosteroids and anti-cytokine antibodies) should probably be reserved for the hyperinflammatory phase, and not used during the initial phase when an adequate immune response is necessary to ensure viral clearance.[4]

In their discussion of the pathophysiological role of endotheliitis/endothelial dysfunction in COVID-19, Varga *et al.* mentioned statins as a means to improve endothelial function.[6] Statins have pleiotropic effects that may explain their positive contribution, including anti-inflammatory/immunomodulatory activity, reduction of oxidative stress, improvement of

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endothelial function (enhanced nitric oxide generation), and antithrombotic action (inhibition of platelet aggregation, stimulation of tissue plasminogen activator release, decrease in tissue factor expression, and reduction in thrombin formation).[22,23] More research will have to point out whether statins are indeed useful agents in COVID-19.

Conclusion

In this paper, we have put several pieces of the COVID-19 puzzle together in an attempt to create a first impression of the complete picture. Much work still needs to be done to elucidate the exact pathophysiology underlying this disease. We would like to emphasise that all the repurposed drugs in our overview are still 'experimental' and that their effect in COVID-19 patients remains to be proven. The cornerstone of treatment consists of supportive care and adequate ventilatory support, if needed. Finally, let us not forget about the importance of preventive interventions, such as social distancing, quarantine, proper hygiene, protective equipment, and vaccines.

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Contributors

MB and AKO contributed to the conceptualisation of the manuscript, the literature review, the construction of the comprehensive pathophysiological overview, the composition of the figure legend, and the writing of the text. JGvdH contributed to the creation of the overview and critically appraised the manuscript.

Declaration of interests

The authors declare that they have no conflicts of interest, neither financial, nor in terms of personal relationships.

Informed consent and ethical approval

Not applicable.

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Supplementary Material

Enumeration of all references used for the construction of our comprehensive overview.

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Caption of Figure 1

Suggested pathophysiological pathways and repurposed drugs.

Legend to Figure 1

A1AT, alpha-1 antitrypsin, serine protease inhibitor (serpin). AAK1, AP2-associated kinase 1. ACE, angiotensin-converting enzyme. ACE2, angiotensin-converting enzyme 2, a glycosylated zinc metalloprotease and carboxypeptidase, SARS-CoV-2 receptor. ACEi, angiotensin-converting enzyme inhibitor. ADAM-17, a disintegrin and metalloproteinase domain 17, cleaves and sheds ACE2 from the cell surface, releasing soluble and active ACE2 enzymes. ADAMTS-13, a disintegrin and metalloproteinase with thrombospondin type 1 motifs member 13, cleaves von Willebrand factor and is deficient in congenital and acquired thrombotic thrombocytopenic purpura. AKI, acute kidney injury. Ang(1-7), angiotensin(1-7), a peptide functioning within the renin-angiotensin system (RAS), predominantly generated by ACE2-mediated hydrolysis of Ang II, opposing the actions of Ang II through Mas receptor activation. Ang(1-9), Angiotensin(1-9). Ang I, angiotensin I. Ang II, angiotensin II. ARB, angiotensin receptor blocker. ARDS, acute respiratory distress syndrome. AT1R, angiotensin II receptor type 1. AT2R, angiotensin II receptor type 2. Azithro, Azithromycin, a macrolide antibiotic with immunomodulatory effects. BCG, Bacillus Calmette-Guérin, vaccine against tuberculosis. BK, bradykinin. BK1 receptor, bradykinin receptor type 1, induced by inflammation/tissue injury. BK2 receptor, bradykinin receptor type 2, constitutively expressed. C1-INH, C1-esterase inhibitor, inhibitor of the complement cascade and the contact activation system, the latter comprising the intrinsic coagulation pathway and the pro-inflammatory kallikrein-kinin system. (C)APS, (catastrophic) antiphospholipid syndrome. CCL2, C-C motif ligand 2, a chemokine. CCS, corticosteroids. COPD, chronic obstructive pulmonary disease. CP, convalescent plasma. CPM, carboxypeptidase M. CPN, carboxypeptidase N. CQ, chloroquine.

CRP, C-reactive protein. cTnI, cardiac troponin I. cTnT, cardiac troponin T. CVD, cardiovascular disease. CXCL10, C-X-C motif ligand 10, a chemokine. DAMPs, damage-associated molecular patterns. DIC, disseminated intravascular coagulation. EDHF, endothelium-derived hyperpolarising factor, a vasodilator. eNOS, endothelial nitric oxide synthase. EP3, prostaglandin E2 receptor 3. ER, endoplasmic reticulum. GAK, cyclin G-associated kinase. HCQ, hydroxychloroquine. HLH, hemophagocytic lymphohistiocytosis. HMWK, high-molecular-weight kininogen. IL-1, interleukin 1. IL-6, interleukin 6. iNOS, inducible nitric oxide synthase. JAK/STAT, Janus kinase/Signal transducer and activator of transcription, a signalling pathway mediating cellular responses to multiple cytokines, growth factors, and other ligands, such as Ang II, after binding to their respective receptors. LDH, lactate dehydrogenase. LMWH, low-molecular-weight heparin, also has anti-inflammatory and antiviral activity, it can cause a conformational change of the S-protein, thereby possibly impeding binding to ACE2. MAS, macrophage activation syndrome. mPGES1, microsomal prostaglandin E2 synthase 1. NETs, neutrophil extracellular traps, web-like structures composed of DNA and antimicrobial proteins that bind and kill pathogens, activate FXII, and promote platelet aggregation. NF-κB, nuclear factor-kappa B, an inducible transcription factor. NO, nitric oxide. PAMPs, pathogen-associated molecular patterns. PAR1, protease-activated receptor 1, thrombin receptor. PGE2, prostaglandin E2. PGI2, prostacyclin. PIC, pulmonary intravascular coagulopathy. PRR, pattern recognition receptor. RdRp, RNA-dependent RNA polymerase, responsible for SARS-CoV-2 replication. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, an enveloped, single-stranded, positive-sense betacoronavirus. SCF, stem cell factor, a hematopoietic cytokine. S-protein, surface spike glycoprotein of SARS-CoV-2. -/+ssRNA, negative/positive single-stranded RNA. Tα1, Thymosin alpha 1, an immune stimulating and cytokine modulating peptide. TF, tissue factor. TLR, Toll-like receptor.

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TMPRSS2, transmembrane serine protease type 2, primes the spike protein for ACE2 binding.

TNF-α, tumour necrosis factor alpha. t-PA, tissue-type plasminogen activator.

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