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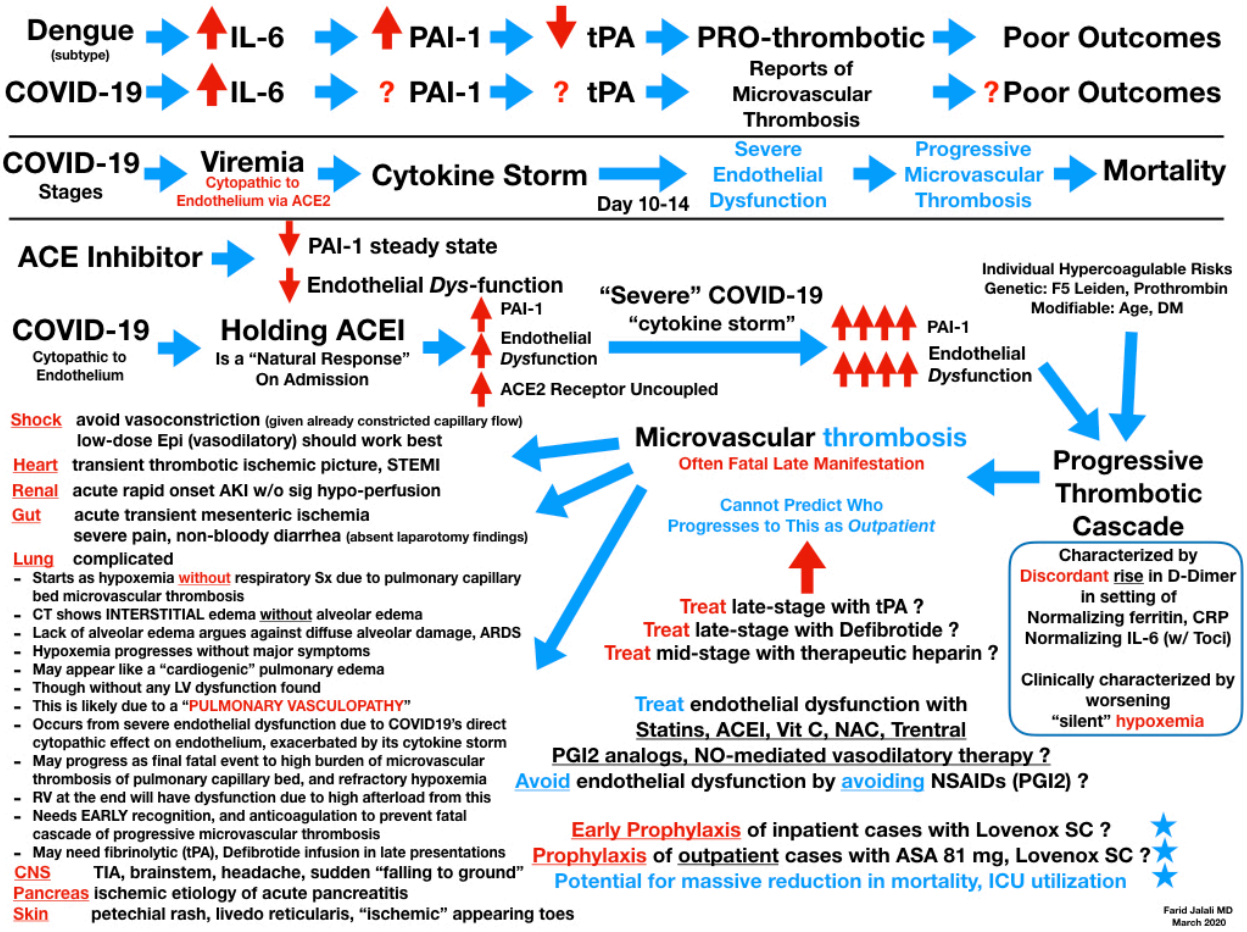
COVID19 = "multiorgan thrombotic microvasculopathy" with mild URI symptoms (hypothesis below)



1) *Possible* reason for ACE inhibitor use as risk for severe COVID-19, due to,

2) MICROVASCULAR THROMBOSIS as the unifying fatal insult in severe COVID-19, due to progressive SEVERE ENDOTHELIAL DYSFUNCTION *(NSAIDs worsen endothelial dysfunction via inhibition of PGI2 - Glucocorticoids COULD worsen endothelial dysfunction but more controversial than NSAIDs - Statins/ACEI/Vit C/NAC could stabilize endothelial dysfunction in theory).*

3) Possible Role for tPA / heparin / DEFIBROTIDE to treat LATE-stage severe COVID-19 complicated by high burden of microvascular thrombosis across many organs (i.e. outpatients who are "toughing it out" at home, sudden decompensation on day 10-14, with ensuing rapid death).

4) Possible role for prophylaxis against this microvascular thrombotic cascade for early MILD confirmed cases discharged from ED, using LMWH or anti-thrombotic for 14 days.

5) A pathway *proposed* via PAI-1 surge and endothelial destabilization effects of ACEI cessation as a risk factor for developing severe COVID-19, by contributing to an existing prothrombotic state created in the first place by the direct cytopathic effects of COVID-19 on endothelium via ACE2 receptor, leading to severe endothelial dysfunction and subsequent late-stage microvascular thrombosis and its associated fatal events via lungs, heart, CNS, etc.

6) Should a discordant RISE in D-dimer, or severe elevation in D-dimer, in the face of otherwise normalizing trend of other inflammatory markers (CRP, Ferritin - all with longer half-life than D-dimer) be a telltale sign that a pro-thrombotic process is occurring, leading to microvascular thrombosis and poor outcomes? This elevation in D-dimer has been widely reported in severe COVID-19 cases, and Chinese have reported improved outcomes with anticoagulation. In outpatient cases, where we don't have the luxury of checking D-dimer trends, should we pursue prophylaxis of all confirmed cases to prevent this late-stage fatal outcome that occurs in a subset of cases?

7) Is predilection for worse MORTALITY (not infectivity) in Southern Europe, Middle East, and New York (with high Italian heritage) due to a higher prevalence of both Factor V Leiden and Prothrombin G2021A gene mutation, predisposing this population to a higher risk of thrombosis, in the setting of the proposed pro-thrombotic and hypercoagulable nature of COVID-19, as hypothesized here? Is this the reason Washington and California, Japan, and China, South

Korea, and South East Asia, all with less notice and less preparedness have far less mortality than the aforementioned area? Is this the reason why children are at very low risk of mortality, given their natural decreased prothrombotic tendencies established in literature? Could children affected with severe outcomes have genetic predisposition to hypercoagulable state?

8) We are seeing incidental radiographic findings of COVID-19 in patients presenting for otherwise unrelated symptoms (i.e. abdominal pain). These patients have a widened A-a gradient (hypoxemia) but have NO significant respiratory symptoms yet despite significant radiographic findings. These radiographic findings on CT have been described to be one of INTERSTITIAL EDEMA -- without -- Alveolar edema. ARDS, by definition, should have both alveolar edema (due to diffuse alveolar damage, hallmark of ARDS) as well as interstitial edema, with alveolar edema rapidly developing after interstitial edema. In contrast to ARDS, the entire CT findings of early, asymptomatic COVID-19 may be due to a cytokine storm causing PULMONARY VASCULOPATHY due to severe endothelial dysfunction from COVID-19, if untreated ultimately resulting in late-stage fatal microvascular thrombosis of pulmonary capillary bed, at a scale too small to detect radiographically (as PE). This process may explain how hypoxemic respiratory failure in COVID-19 is reportedly NOT behaving as ARDS, NOT requiring high PEEP, and appearing as "high compliance". This pulmonary interstitial edema is often in typical cases attributed to a "CARDIOGENIC" cause, but LV dysfunction is not seen in vast majority of COVID-19 cases. This argues that perhaps there is outflow obstruction through pulmonary capillary bed due to severe endothelial dysfunction, behaving like a case of high afterload "cardiogenic" cause without any actual LV dysfunction. An argument is to use steroids to reduce this vasculopathy, but anecdotally this has not been helpful in SEVERE COVID-19 cases per Chinese and Italian experience. NSAIDs have a deleterious effect on endothelial dysfunction via inhibition of PGI2, and perhaps, based on this hypothesis, should be avoided. However, anticoagulation has been reported, by now widely, to improve mortality in SEVERE COVID-19. This hypothesis of an exaggerated endothelial dysfunction and resultant microvascular thrombosis as the unifying theme in late-

stage COVID-19 respiratory failure may account for why anticoagulation helps per Chinese data, why cases behave NOT like ARDS from a physiologic standpoint, why interstitial edema without alveolar edema is seen on CT in these cases, and why there is a large A-a gradient initially without any respiratory symptoms. Should Lovenox SC QD or BID be instituted on every admitted case of COVID19 to prevent this proposed pathway from occurring? Could heparin drip or defibrotide used in hepatic VOD help in late-stage presentations with presumably a high thrombotic burden to reverse this process? Could the multifocal CT findings be due to a vasculopathy with associated infarct, and if we assess each individual area on CT away from the bigger picture, could it be resembling a single area of vasculopathy and infarct?

9) Could abdominal pain (which I propose presents clinically as a brief acute mesenteric ischemia due to the severe endothelial dysfunction and microvascular thrombosis) be a telltale sign that the thrombotic cascade is in effect and will likely affect the lungs and cause worsened outcomes? There are wide reports of patients presenting with severe abdominal pain and non bloody diarrhea as the only presenting symptom (to be found to have characteristic CT findings of COVID19 and confirmed for it later on). There are reports of several laparotomies done due to very high suspicion for acute mesenteric ischemia clinically, and no actual ischemic intestine has been noted. Given the excellent collaterals of the mesenteric vessels, it is plausible that a redundant flow quickly establishes to prevent full blown mesenteric ischemia, and hence the clinical findings and lack of surgical findings.

10) Could CNS / brainstem plausibly be affected by microvascular thrombosis and lead to a TIA as clinically reported widely as SUDDEN fall to ground and paralysis-like sudden presentation of patients we see so much on social media from China, Iran and Italy? Could this explain the reports of severe headaches and even large CVAs associated with COVID19? Original SARS has been reported to have neurologic disturbances with neurotropic effects affecting brainstem. There are now reports of "acute hemorrhagic necrotizing encephalopathy" associated with COVID-19, described to be similar

to rare influenza presentations, and due to a cytokine storm followed by breakdown of blood-brain-barrier. Could a severe endothelial dysfunction and eventual microvascular thrombosis lead to brainstem (thalamic) ischemic microvascular infarct, followed by reperfusion hemorrhage, leading to the described "acute hemorrhagic necrotizing encephalopathy"? Could this explain the reports of SAH in COVID19 patients? I think it would be reasonable to assume nobody with severe COVID19 in ICU would be suffering from severe hypertensive crisis to be causing SAH.

11) Could skin rash reported from Asia and Italy in regards to COVID-19 be due to microvascular occlusion based on above or similar pathway? This rash has been reported as Lived Reticularis by some Dermatologists. This rash has also been anecdotally reported to be indistinguishable from that of Dengue by SE Asian publicaiton. Also, ischemic and very indurated toes have been reported in presentations in Italy and China associated with COVID-19, often as the only presenting symptom.

12) Could "MI" picture seen with often "normal LHC", as well as reports of STEMI cells in young people with LHC showing coronary thrombi without any identifiable risk factor be due to be due to the severe endothelial dysfunction (via ACE2 receptors on endothelium of heart vessels), and microvascular thrombosis of these vessels? Could the sudden LVEF drop reported toward fatal stages of COVID-19 be related to this microvascular thrombotic event? Microvascular thrombosis has been, allegedly, reported in cardiac autopsies from China.

13) Could seemingly unrelated presentations of young people with acute pancreatitis (and some reports of sudden death soon after) be a manifestation of endothelial dysfunction and ischemic etiology of acute pancreatitis, given that most reports cite no association with alcohol use or any evidence of gallstones on US or MRCP? Could this presentation (often the only symptom, with incidental ground glass opacities noted in the chest portion of CT Abdomen) be a telltale sign of COVID-19, and possibly point to this thrombotic cascade already

occurring? Could these patients require a check on D-dimer and Lovenox SC for 14 days to prevent these catastrophic outcomes?

14) Could sudden AKI development reported DESPITE reportedly no evidence of hypo-perfusion or other identifiable etiology be due to renal microvascular thrombosis in the capillary beds and/or glomeruli?

15) Should we have a very heightened level of suspicion for COVID-19's variety of unusual presentations across many organs as described above, until this pandemic is suppressed?

16) Could shock in COVID19 be better responsive to low-dose epinephrine with its vasodilatory effects, as opposed to vasoconstrictive pressors with alpha-1 activity, because of the proposed severe endothelial dysfunction and the resultant existing constrictive capillary flow?

17) Could Plaquenil possible mild benefit be also via its anti-thrombotic effects documented in APS?

18) Statins, ACEI, NAC and Vitamin C, and Trental all can possibly stabilize endothelial dysfunction which seems to be the precursor for microvascular thrombosis. Why not try these harmless therapies? None cause arrhythmia at least.

19) NSAIDs are established to cause endothelial dysfunction and have pro-thrombotic effect. Endothelial dysfunction occurs by inhibiting COX2 and reducing the levels of PGI2 (which affects endothelium by inhibiting platelet aggregation and by vasodilation). Could this be reason that anecdotally (and unconfirmed obviously) NSAIDs have received a bad "rep" in COVID19? Is there truth to it based on this pathway?

This is a ***possible*** pathway that could explain role of HTN, ACE inhibitors being associated with severe COVID-19, and the potential role for tPA in COVID-19 treatment. Please be patient and read my thoughts and let know what your thoughts are.

1) A common thread in the fatality of COVID-19 has been the well described, very sudden, development of cardiomyopathy and idiopathic AKI and need for CRRT, as well as sudden neurologic insults (i.e. sudden fall to ground while walking to store or school without respiratory distress or loss of pulse). **To think that ARDS or septic shock is causing fatality is not accurate, as most reports clearly mention patient even coming off the vent, coming off vasopressors, even almost ready for downgrade from ICU, and suddenly crashing with low EF, AKI, and death within 2 days. To think the virus somehow has not affected the heart and kidneys until day 11 of severe illness is also not too convincing. There has to be a sudden event, such as a vascular compromise, such as in thrombosis.**

2) In several reports and autopsies by Italian and Chinese, **microvascular thrombi** have been identified in cardiac tissue and renal tissue of severe fatal COVID-19. Even massive PEs and large arterial thrombosis were noted in young healthy people with severe COVID-19.

3) We do know that some infections are PRO-THROMBOTIC, as in DIC with thrombosis, such as some subtypes of Dengue fever. Among many factors, elevated PAI-1 levels are associated with significantly worse outcomes in Dengue.

4) We also have some anecdotal evidence that patients with HTN (inevitably a lot on chronic ACE inhibitors) possibly have higher incidence of severe illness from COVID-19.

5) Fact: ACE inhibitor REDUCES **PAI-1** production.

6) Fact: PAI-1 inhibits tPA, thereby causing thrombosis, as described in MI literature. PAI-1 antigen levels are higher in **men**, and higher with **advancing age**, among many other factors.

7) Fact: Dengue, as an example, in certain subtypes causes **elevated PAI-1**, described in literature, and elevated PAI-1 has been associated with subtypes of **Dengue to predict severe outcomes associated with thrombosis.**

8) IL-6, and other cytokines increase PAI-1 release/production during acute inflammatory response.

9) Could it be that ACE inhibitor depletes steady state PAI-1 levels in the serum —> Upon admission of COVID-19 patients with severe illness, ACE inhibitor is naturally held —> this increases the prothrombotic levels of PAI-1 by holding ACEI, eliminates the protective effect of ACEI on endothelial function, and frees up ACE2 receptors that are now uncoupled from ACEI —> COVID19 binds ACE2 receptors on endothelium of a variety of organs, with more affinity and more widespread attachment due to ACEI cessation —> This leads to severe endothelial dysfunction due to direct cytopathic effects of COVID 19, worsened by cessation of ACEI (which protects endothelium naturally) —> Severe exaggerated endothelial dysfunction —> progressive microvascular thrombosis —> Fatal events due to sudden thrombosis in coronaries and myocardium (STEMI), renal vasculature (AKI), CNS (TIA, severe headache), mesenteric vessels (acute transient mesenteric ischemia), and most importantly lung with progressive thrombotic cascade leading to hypoxemia without respiratory symptoms.

10) Could there be a role for tPA infusion or anticoagulation in severe cases of COVID-19? Yes, tocilizumab will stop the IL-6 from wreaking more havoc, but what if the cat is out of the hat, and the thrombotic cascade has begun as described above (as well evidenced by continuous rise in D-dimer despite its short half-life compared to all other inflammatory markers with longer half-life (ferritin, CRP) normalizing). Perhaps a role for therapeutic Lovenox anticoagulation even in moderate cases to prevent the fatal thrombotic outcome that has been seen on autopsies and biopsies?

Perhaps, to stabilize endothelium, a role for **STATINS, NAC, Vit C, Trental, and ACEI itself to stabilize the severe endothelial dysfunction and reduce prothrombotic tendency**? Perhaps a role for NO-mediated vasodilatory effects, and PGI2 agonists to stabilize and vasodilator endothelium?

Perhaps also **prophylactic anti-thrombotic such as ASA 81 mg (less inhibition of COX2, and less inhibitory effect on endothelial-stabilizing PGI2 compared to the 325 mg dose) for mild cases to PREVENT these thrombotic outcomes on day 10-14 of illness, since we cannot tell apart at this time which patients progress to the cytokine storm, endothelial dysfunction, and thrombotic cascade? This could potentially have significant ramifications in the mortality of this illness and the ICU utilization.**

11) Could this explain why HTN (inevitably a lot on ACE inhibitors) has been somewhat anecdotally associated with worse outcomes? A lower PAI-1 state in homeostasis with tPA in the body due to chronic ACE inhibitor use, followed by a sudden surge of PAI-1 and severe endothelial dysfunction due to the cytopathic effect of COVID-19 on endothelium, resulting ultimately in progressive microvascular thrombosis and mortality due to this thrombosis?

12) If you have a case with CRP improving, Ferritin improving, sepsis improving, IL-6 improving, but D-dimer RISING and patient clinically worsening, would it not make sense that the discordant D-dimer rise (which has the shortest half-life of all three and should technically be falling if it were only due to acute inflammation) is due an impending or present thrombotic cascade? Perhaps consider treating this subset first to see if fatal outcomes can be prevented?

13) Could it be that some of the mild cases discharged will go to cytokine storm, microvascular thrombosis, and show up late-stage with hypoxia without any significant lung auscultation findings (as has been reported), because of this process, essentially a thrombosis of pulmonary microvascular bed (think PE, just in the microvasculature, with silent hypoxemia, not detectable on CTA obviously due to the microscopic nature of it)? And succumb to a quick death in this late stage?

15) Should we risk stratify mild cases based on the D-dimer level before discharging a seemingly mild case? Should we prophylaxis everyone we send out with some sort of agent to avoid thrombosis if we cannot tell exactly who gets it and who doesn't?

16) Should we across the board just assume every case's "thrombotic" tendency from cytokine storm is at the same intensity? Should we have a way to assess where each patient belongs in the current burden and the rapidity of progression of this proposed thrombotic cascade by measuring anti-factor-Xa and TEG to risk stratify the thrombotic tendency and trend more accurately than D-dimer? Should we obtain an accurate personal and family history for hypercoagulable states, including familial and incidental personal history of thrombotic events? Could there be cases that need a therapeutic dose of LMWH as opposed to prophylactic dose, in someone with a higher thrombotic burden, depending on how late they've presented for inpatient care? What about those cases that roll into ER without prior care at the very late stage, very elevated D-dimer, and suspicious findings for a wide range of microvascular thrombosis in several organs? Is a prophylactic dose of Lovenox SC enough to stem the thrombotic cascade in these cases? Should we not individualize each case, if this theory pans out? Could they need a higher dose? Could some late presenters need tPA or Defibrotide as used in hepatic VOD?

17) Can Italian, Chinese, or WA/NY doctors tell the rest of us how well did patients do that were NOT on ACEI/ARB but on chronic ASA/ Plavix or anticoagulation? If they did the best, then perhaps we have more reason to believe that this proposed pathway is actually occurring.

<u>Commentary:</u>

If this thrombotic cascade is truly the common denominator for the mortality in COVID-19 (which I am beginning to believe it is), and if we have no current way to tell who ends up in this thrombotic cascade, and who doesn't (perhaps ACEI cessation is a risk factor, perhaps those populations with higher prevalence of genetic hyper coagulable states), then we should try to prevent these catastrophic events that typically seem to occur on days 10-14, and have been reported as sudden demise

despite good oxygenation and perfusion (while at home), suddenly to decompensate and show up to ED, ICU and death within 48 hours.
In short, I believe we will face a shortage of ICU beds due to NOT knowing which one of the mild cases that we see and discharge from ED are going to end up in this thrombotic fatal cascade on Days 10-14 without any significant symptoms otherwise until then.

Patients admitted to hospital are going to receive anti-coagulation (I'm arguing, and Italians and Chinese are recommending, for this to become protocol with at least Lovenox SC QD) to reduce the risk of this fatal clotting.

However, patients that are sent home from the ED early on, as they should because they have good oxygenation and good perfusion, are at risk of developing this clotting cascade on day 10-14. And these people quarantining at home are NOT on any blood thinner or anti-platelet agent to PREVENT this fatal clotting cascade that occurs on Days 10-14. We are asking them to "tough it out" at home, rightfully so, but we are not equipping them with any prophylactic therapy to avoid the microvascular thrombotic cascade that seems (to me at least) to be unifying late fatal insult of severe COVID19.

Is there a role to check D-dimers on every outpatient and ED patient that is confirmed or suspected to have COVID19, in order to better risk stratify the possible severity of the course later on?

Some of these people show up to ED (including a family member of mine in Iran who passed away from this) late-stage with thrombosis of heart (sudden EF drop without precedent CAD), kidneys (sudden AKI), and sudden drop in A-a gradient (which I suspect is due to pulmonary capillary bed thrombosis, as the ARDS picture is simply not present per widespread reports of the respiratory failure physiology), and die within 48 hours, overwhelming our ICU and medical capacity. Potentially these late-presenters in catastrophic situation should be treated with fibrinolytics such as Defibrotide or tPA to reverse the high burden of thrombosis, given that not much can be done to the virus or the cytokine storm itself quickly enough to achieve a meaningful recovery of what I propose to be a widespread microvascular thrombosis.

What I'm thinking is that, if above proposed pathway can be confirmed, and if we can finally confirm that tPA or Defibrotide can reverse the late-stage fatal thrombotic cascade (a trial being cautiously pursued case by case), then we should also assume that all mild cases that we send home from ER early on CAN end up in this fatal cascade on days 10-14. And if we assume this, then we should try to PREVENT this from happening while patients sit at home quarantining. This prevention is the KEY to prevent overwhelming ICU resources.

To prevent this outcome, could we have a situation where **an anti-platelet (Aspirin) or anticoagulant (LMWH) be used for 14 days upon confirmation of all COVID-19 cases to prevent this thrombotic cascade from occurring, and reducing ICU utilization and reducing mortality? I believe there are reports from Italians that DOACs may have variable absorption (possibly due to the GI effects of COVID19) and may not be reliable.**

I suspect that once data is sifted through from Italy and China, we will see a trend that

1. Chronic ACE inhibitor use, and its cessation upon hospital admission, is a RISK FACTOR for severe fatal COVID-19 (mechanism described above in diagram)
2. Chronic anticoagulation use, and possibly ASA or Plavix use, are possibly PROTECTIVE FACTORS, most likely preventing the clotting cascade that is the fatal step of COVID-19.

<u>Commentary #2</u>

This is my response to someone asking whether HAPE could be a better explanation for the findings, and whether the reported COVID-hemoglobinopathy could better account for the underlying pathophysiology of COVID19 in case anyone cares to read:

"My goal from this hypothesis was to generate some thought in smarter people than me to hopefully figure out what we lack so much in understanding of the clinically unusual manifestations of this disease. So thank you for your input. And please keep the discussion going.
Having said that, just from my unintelligent perspective and correct me please, HAPE and what I've proposed have the same underlying pathophysiology as it pertains to pulmonary microvascular vasoconstriction. In HAPE this occurs due to hypoxemia itself. In COVID, I

propose this starts with viral cytopathic effect on endothelium but worsened in a subset due the sepsis and resultant cytokine storm that ensues leading to a cascade of severe endothelial dysfunction. In vasculitis it occurs too via purely inflammatory pathways but widely known to respond well to steroids. HAPE and septic endothelial dysfunction do not respond to steroids in any meaningful way.

So yes underlying vasoconstriction exists but three distinctly separate insults lead to it. And knowing which insult leads to it allows for proper treatment, 1) oxygen for HAPE, 2) steroids for vasculitis, and in absence of proper antiviral treatment (and even with it, if case has progressed enough), 3) anticoagulation and endothelial stabilization for COVID-induced endothelial insult.

Additionally, HAPE is characterized by alveolar leakage in addition to interstitial edema. This is why HAPE *** is *** actually symptomatic early on, as patients present within 2 days usually with dyspnea on exertion and rest (as we've all felt to some degree probably on that ski trip to Rocky Mountains). It is this alveolar leakage of proteinaceous fluid that leads to significant symptoms, and pink frothy sputum on cough in severe cases. And finally, HAPE's vasoconstriction responds rather quickly to supplemental oxygen and disease process is essentially reversed after several hours of supplemental O2, as this addresses the primary insult for the underlying vasoconstriction.

None of above are what's happening with COVID-19 proposed pulmonary microvascular vasoconstriction. Supplemental O2 does not reverse the process (because again the insult is not due to hypoxemia itself, but due to viral cytopathic effect on endothelium itself, exacerbated I believe, by a severe cytokine storm causing further severe endothelial dysfunction). Additionally COVID's CT findings are one of predominantly interstitial edema without alveolar edema (from what I understand, I'm not a radiologist), signifying that alveolar-capillary barrier has not broken down somehow to lead to alveolar edema. And this accounts for the predominantly symptom-free (lower airway) presentation of many cases who are found to be hypoxemic by incident.

Also, HAPE cannot account for the clinical response observed now widely reported to anticoagulation. Neither does AC work in vasculitis induced pulmonary microvascular involvement.

In terms of a hemoglobinopathy, COVID effect on hemoglobin should be, in absence of antiviral treatment, a one way street at least until viral presence is abolished, a process that even in best estimates reportedly takes longer than 14 days from first symptoms. Given the onset of hypoxemia is often early in the course of COVID-19, again mostly found incidentally (as reported by many patients and providers) without respiratory distress, the ensuing (10-14 or so) days until the virus is neutralized by immune system or therapy should technically allow a persistent hemoglobinopathy to be present.

This does not seem to correlate with most of the clinical presentation in organs seen affected in COVID. For instance, you wouldn't expect reports of "STEMI" with normal LHC, only to have spontaneous resolution of the "STEMI" without any PCI soon after (presumably patient will be given temporary heparin drip, ASA/Plavix, etc until LHC is found to be negative). If hemoglobinopathy was the primary driver of this cardiac ischemic episode, it should not be reversed spontaneously, as this COVID-induced hemoglobinopathy should persist for many days until the virus is somehow neutralized by the immune system or therapy (which we lack currently). And none of the standard treatment prior to LHC in STEMI (ASA/Plavix, heparin drip) should reverse or alter the hemoglobinopathy (but they do improve thrombosis obviously). This lack of progressive injury reported in COVID (transient "STEMI", transient mesenteric ischemia symptoms) argues against a progressive process such as hemoglobinopathy, and instead argues for a transient process, as what may be seen in a microvascular thrombosis and subsequent innate fibrinolysis. This process of thrombosis (I propose) and innate fibrinolysis will keep occurring with transient end-organ damage, until the end-stage fatal events of COVID when the innate fibrinolysis is overwhelmed and incapable of dealing with the profound burden of progressive microvascular thrombosis.
This hemoglobinopathy-induced pathology, if present, in my mind, should also not be able to be treated with anticoagulation unless a sickle-cell-like picture of, again, microvascular thrombosis is occurring as opposed to a pure hemoglobinathy-induced-hypoxemia as the primary insult to lungs, heart, CNS, skin, etc. And if thrombosis is occurring via a similar pathway as sickle cell, in an acute fashion, then the treatment probably (given the rapidity of this proposed thrombosis) would be to 1) stem the thrombosis by anticoagulation or thrombolytics, and to 2) stabilize the endothelial dysfunction (ACEI / Statin / Vit C / NAC all have such effect), possibly NO

(vasodilatory), and avoidance of factors that worsen endothelial dysfunction (avoid NSAIDs). Furthermore, if hemoglobinopathy is the primary insult, perhaps pRBC transfusion, as in sickle cell, should reverse the underlying pathology occurred in COVID, and we do not have reports to this effect yet.

Commentary #3:
If the microvascular thrombosis due to severe endothelial dysfunction turns out to be true, I think it's very important for providers to put their thinking hats on, as they always do.

What I mean by this is that you CANNOT treat every case the same and have a protocoled feel-good D-dimer number above which you treat with XYZ dose of Lovenox and below which you don't treat.
D-dimer is just a surrogate marker for thrombosis, particularly, as I'm proposing, if other inflammatory markers are coming down or staying stable.

All this means is that you're thrombosing these microvascular channels, based on this proposal.

However, the true RAPIDITY of thrombosis and the BURDEN of thrombosis needs to assessed case by case and with better markers, possible TEG and other factors that I'm not even going to remotely claim I know. These are times when Hematologist needs to be front-lines for COVID19 patients. Their role will be life-saving.

What determines RAPIDITY of thrombosis depends on:

1) Each patient's GENETIC predisposition for hyper-coagulable state: think Factor V Leiden and Prothrombin mutation. This is, I propose, why MORTALITY is so much more evident and higher in Italy, Spain (Southern Europe) and Iran, as well as NY. Asians have very little prevalence of these genetic factors. Japan is just as dense as NY, but less mortality, and they had the virus before NY. Washington had the virus spread without notice for weeks before even being identified, and they have far less mortality.
2) Each patient's MODIFIABLE risk factors for hyper coagulability. These are your typical factors, DM, aging, etc. This is why kids below age 16 will be very much protected from MORTALITY, but not infectivity. They simply

have less prothrombotic tendencies, unless they have a genetic factor involved in hypercoagulability.

What determines the BURDEN of thrombosis once the patient SHOWS up to hospital (they were toughing it out at home, but now have rapidly decompensated on day 10 or so or even earlier):

1) What's the absolute D-dimer value?
2) What about TEG?
3) What about anti-factor-Xa?
4) How severely hypoxemia are they on XYZ FiO2?
5) Have they had other, proposed, thrombotic process occur? TIA? Mesenteric ischemia picture? "STEMI"? Etc.

To protocolize EVERY CASE is a mistake - even case needs to be assessed carefully. All the way to the FAMILY HISTORY of whether anyone in the family has had clotting disorder, anyone with Factor V Leiden, etc.

Commentary #4:
Again, I don't know all the answers but in terms of the UW path report, here is my take - just my opinion - I'm sure I'm wrong:

You will not see microvascular thrombi everywhere as the body's innate fibrinolytic system will try its best to resolve these as they occur - it depends how the demise occurred - if this was a sudden cardiac event, sudden drop in EF, STEMI picture, then you will see it in heart - to say someone has myocarditis histologically can be interpreted in many ways - sure the virus is THERE in the myocardium we all know that - ACE2 receptors are there in the endothelium (clearly why ACEI are cardioprotective) - but the clinical picture is not likely one of myocarditis - nobody is reporting a typical myocarditis with prolonged EF drop for days before death - unless they had an MI obviously due to this theory. So to see the virus and call it myocarditis doesn't mean clinically much as it's not going along with the typical COVID19 picture.

However, most deaths will be occurring due to pulmonary microvascular thrombosis. If you wait until death to autopsy these people (obviously we do), then the chicken or egg argument is this: the profuse progressive microvascular thrombosis of pulmonary capillary bed WILL inevitably at the very end cause enough buildup of hydrostatic pressure that the

alveolar capillary barrier will break down and it will cause alveolar edema and diffuser alveolar damage. However, diffuse alveolar damage is NOT the primary insult that started it. It's the end result. It's when you require high PEEP. For the vast majority of this hypoxemic respiratory failure you do not need high PEEP. Because the ARDS picture hasn't set in. That's the explanation.

And yes diffuse SAH could mean also endothelial dysfunction as well. I'm sure nobody from this autopsy group had hypertensive crises during their ICU stay to cause the SAH.

And yes if you wait too long until the endothelial damage and thrombosis has broken down every capillary wall then with anticoagulation you WILL have hemorrhagic outcomes - no doubt. The key is to PREVENT this from happening.

Thoughts?

Disclaimer: I'm your average not too bright GI doctor 10 years out from any biochemistry. Smarter people need to chime in like yourself. So many thanks for spending the time reading all of this. **Please do not alter your medical therapy or medications based on this document or its hypothesis. These are just food for thought, to bring in, perhaps, a different view to COVID19 compared to the current practice. Critically appraise it and judge the validity of it for yourself. Please do not take this hypothesis as confirmed or validated, and do not change your practice blindly based on this.**