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Adrenergic storm-induced Warburg effect in COVID-19: A hypothesis.

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Abstract:

At present, there is no treatment option available for COVID-19 condition and most importantly the underlying pathophysiology in COVID-19 is not known. No theory at present explains all the clinical features in COVID-19. In this article, I had proposed a hypothesis that explains the underlying pathophysiology in COVID-19 and based on it proposed treatment options for COVID-19. I propose that the adrenergic storm-induced Warburg effect (aerobic glycolysis) may be the underlying mechanism in the COVID-19 condition. I propose alpha1 adrenergic blockers in the early phase and beta-adrenergic blockers in the late phase of COVID-19 to inhibit the adrenergic storm and reverse the Warburg effect in COVID-19 condition.

Keywords: COVID-19, SARS-CoV-2, Adrenergic storm, Warburg effect, Aerobic glycolysis, alpha1 adrenergic blockers, beta adrenergic blockers.

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection caused coronavirus disease 2019 (COVID-19) pandemic is causing damage all over the world. It is known that SARS-CoV-2 enters the host cell via angiotensin-converting enzyme 2 (ACE2) and CD147, which is also known as Basigin or extracellular matrix metalloproteinase inducer (EMMPRIN)[1,2]. COVID-19 patients present with a wide variety of clinical features ranging from asymptomatic, mild cases with fever, cough, sore throat to moderate and severely affected patients with complications like acute respiratory distress syndrome (ARDS), pulmonary embolism, acute cardiac injury, acute kidney injury, septic shock[3,4]. Even though many drugs were on the clinical trial for the treatment of COVID-19 including Remdesivir, Hydroxychloroquine, Azithromycin, Tocilizumab, etc., at present, no specific drug is available for the treatment of COVID-19 patients. Cytokine storm due to an increased level of proinflammatory cytokines like IL-1β and IL-6 is known to occur in COVID-19[5], but what causes the cytokine storm and inflammation associated with it, is not known. Most importantly, the underlying pathophysiology of the COVID-19 condition is unknown. In this article, a hypothesis is proposed for both the underlying pathophysiology in COVID-19 and treatment options based on it.

Does adrenergic storm occur in COVID-19?

I speculate that SARS-CoV-2 infection might cause adrenergic storm (increased catecholamine level in the body) in the moderate and severely affected COVID-19 patients in at least three possible ways. 1) It is known that hypothalamic paraventricular neurons (PVN) play a crucial role in sympathetic activity. It is also known that GABAergic interneurons inhibit the pre-sympathetic paraventricular neurons. Interestingly these GABAergic interneurons have ACE2 receptors. It has been already shown that the downregulation of ACE2 leads to increased PVN

sympathetic activity[6]. It is known that SARS-CoV-2 by using the ACE2 receptor for its cellular entry downregulates ACE2[7]. I speculate that SARS-CoV-2 induced downregulation of ACE2 in hypothalamic GABAergic interneurons may increase the PVN induced sympathetic activity, which increases the catecholamine level in the body. 2) SARS-CoV-2 induced downregulation of ACE2 may also increase angiotensin II (AT-II) level[7]. It is well known that increased AT-II causes increased sympathetic activity resulting in increased catecholamine level[8]. Increased sympathetic activity by activation of RAAS may increase the ACE2 and AT-II which may result in a vicious cycle. 3) Neutrophils and macrophages are present in increased numbers in COVID-19 patients[9]. It is known that neutrophils and macrophages release catecholamines. And catecholamines in turn increase neutrophils and macrophages, this vicious cycle leads to proinflammatory cytokines secretion by neutrophils and macrophages[10]. Since in COVID-19 neutrophils and macrophages are increased, these cells may likely release catecholamines.

Based on the above evidence, I speculate that adrenergic storm occurs in the COVID-19 moderate and severely affected patients and the increased catecholamines result in cytokine storm and produce inflammation in COVID-19 patients.

It is interesting to note that catecholamines via beta-adrenergic receptors activate CD147/EMMPRIN and induce matrix metalloproteinases (MMPs) release[11]. In COVID-19, increased catecholamine level in the body may increase the CD147 /EMMPRIN which in turn may increase the SARS-CoV-2 cellular entry. An intricate relationship might exist between catecholamines and both SARS-CoV-2 receptors ACE2 and CD147/EMMPRIN, their details need to be clarified in the future for a better understanding of COVID-19 condition. It is known that EMMPRIN activates MMPs. I speculate that SARS-CoV-2 entry via EMMPRIN may lead to respiratory membrane breach by the degradation of the basement membrane by MMPs. Respiratory membrane breach, in turn, might lead to neutrophil and macrophage infiltration in the alveoli. A similar phenomenon might occur in other affected organs.

As it is likely that adrenergic storm might occur in COVID-19, the addition of exogenous catecholamines, by the use of beta-adrenergic agonists in nebulizer solutions for COVID-19 patients having dyspnoea and use of norepinephrine in COVID-19 patients affected by septic shock may further worsen the condition of COVID-19 patients.

Does the Warburg effect occur in COVID-19?

Warburg effect (aerobic glycolysis) is a well-known phenomenon in cancer and it is considered to be one of the hallmarks of cancer. Recent studies showed that the Warburg effect occurs not only cancers but also in inflammatory and sepsis conditions[12,13]. I speculate that the Warburg effect occurs in COVID-19 in various organs especially in the lungs, the main organ affected by SARS-CoV-2. 1) It is well known that hypoxia-inducible factor 1 alpha (HIF-1α) is known to activate glycolytic enzymes and produce Warburg effect[12]. It is known that hypoxia exists in COVID-19 patients and the level of hypoxemia correlates with the mortality[14]. Since hypoxemia exists in COVID-19 patients, HIF-1α may likely be induced in COVID-19 which might result in the Warburg effect. 2) ^{18}F-FDG PET scan is used mainly to detect cancer and metastatic lesions, as cancer cells have increased glycolysis, these scans will differentiate normal and cancer cell areas based on their glycolysis. It has been already shown that ^{18}F-FDG PET scan of the lungs of COVID-19 patients showed clusters of increased glycolysis areas in the lungs[15]. This increased glycolysis areas in the lungs of COVID-19 patients could be due to anaerobic or aerobic glycolysis. I speculate that it is due to aerobic glycolysis, and the ^{18}F-FDG PET scan results in the COVID-19 patients support the claim that the Warburg effect occurs in COVID-19 patients in the affected organs. 3) SARS-CoV has been shown to activate the Nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome[16]. Clinical trials, focusing on the inhibition of NLRP3 inhibition in COVID-19 patients were already registered[17]. NLRP3 inflammasome activation resulting in the Warburg effect is well known[12]. 4) It is known that the activation of CD147 /EMMPRIN results in Warburg effect[18]. CD147 is

one of the two receptors used by the SARS-CoV-2 for its cellular entry. As mentioned earlier increased catecholamines are known to activate the CD147 via beta-adrenergic receptors. I speculate that increased catecholamine levels due to adrenergic storm in COVID-19 might activate CD147 which might lead to MMPs release and Warburg effect. 5) It is known that increased catecholamines level conditions induce oxidative stress[19], which might damage the mitochondria. It is also known that increased AT-II via reactive oxygen species and activation of NLRP3 inflammasome resulted in mitochondrial dysfunction[20,21]. I speculate that mitochondrial dysfunction occurs in COVID-19, which may exhibit mitochondrial respiration inhibition, and mitochondrial DNA (mtDNA) release might occur. Interestingly, mtDNA is one of the activators of NLRP3 inflammasome[12], which as mentioned earlier might occurs in COVID-19. Based on the above evidence, I speculate that the Warburg effect occurs in the affected organs especially in the lungs in the COVID-19 patients.

Evaluation of the Hypothesis:

1. I speculate that plasma Norepinephrine, epinephrine, and urine Vanillylmandelic acid (VMA) levels may be positively correlated with the severity of COVID-19 condition. Plasma Norepinephrine and Epinephrine level and urine VMA level should be measured in all COVID-19 patients. Increased levels of catecholamines will indicate the existence of an adrenergic storm in COVD-19.
2. Measurement of plasma lactate and if possible, the lactate level of the affected organ, for example, pulmonary lactate level, will indicate the level of glycolysis in the affected organs. Cells taken from the in COVID19 patients by bronchoalveolar lavage, a biopsy from affected organs, and white blood cells in the blood sample may show the Warburg effect and inhibition of mitochondrial respiration.
3. Since beta-adrenergic blockers are common drugs given for cardiovascular illness and regulation of blood pressure, it is likely that a subgroup of adult COVID-19 patients

might already be on these drugs. A retrospective study in this subgroup might show the beneficial effects of beta-adrenergic blockers. A similar study could be conducted for alpha1 blockers and combined alpha and beta-blockers. Also, prospective clinical trials can be conducted to check the effect of alpha1 and beta-adrenergic blocker's effect on the morbidity and mortality of COVID-19 patients. Since in adrenergic storm conditions, it has been shown that alpha1-adrenergic blockers like Prazosin may work in the early phase and beta-adrenergic blockers like Propranolol may work better in the late phase[22]. I speculate that the same could be applied to the COVID-19 adrenergic storm condition. Whether two different phases exist in COVID-19 needs to be found. The author had recently proposed that adrenergic hyperactivation may explain all the complications occurring in the COVID-19 condition[23]. Recently alpha1 adrenergic blockers and beta-adrenergic blockers have been proposed to treat COVID-19 patients[24,25]. This evidence supports the claim that alpha1 and beta-adrenergic blockers can be used in the COVID-19 patients to prevent adrenergic storm and thereby reverse the Warburg effect.

Conclusion: Based on the above details, I hypothesize that an adrenergic storm occurs in COVID-19, which by the activation of the NLRP3 inflammasome, HIF-1A, oxidative stress, and mitochondrial dysfunction might induce Warburg effect (Figure 1). This may be the underlying pathophysiology in COVID-19. I propose that adrenergic blocker drugs by inhibition of adrenergic storm might reverse the Warburg effect in COVID-19. This hypothesis if experimentally and clinically validated will help in understanding the COVID-19 condition and has the potential to save millions of lives.

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Figure Legends:

Figure 1: Adrenergic storm-induced Warburg effect in COVID-19.

Increased catecholamines level in the body (Adrenergic storm) might occur in COVID-19. SARS-CoV-2 downregulation of ACE2 in the hypothalamic interneurons might increase the pre-sympathetic activity of paraventricular neurons (PVN), which might increase the catecholamines level in the body. Increased Neutrophil and macrophages in COVID-19 patients might release catecholamines and further fuel the adrenergic storm. It is likely that the AT-II level in COVID-19 patients might be high due to the downregulation of ACE2 by SARS-CoV-2 and might increase catecholamine levels. Increased catecholamine will further activate all the above three sources of catecholamine release and might lead to a vicious Adrenergic storm cycle. Increased catecholamine level and the SARS-CoV-2 infection in COVID-19 patients might lead to activation of the NLRP3 inflammasome, oxidative stress, HIF-1α activation, mitochondrial dysfunction and shift the metabolic phenotype of the cell from oxidative phosphorylation (OXPHOS) to aerobic glycolysis and cellular phenotype from differentiated state to dedifferentiated state (Warburg effect). Adrenergic storm-induced Warburg effect in various affected organs especially in the lung of COVID-19 patients might cause complications like ARDS, pulmonary embolism, septic shock, etc. Alpha and beta-adrenergic blockers might inhibit adrenergic storm and reverse the Warburg effect in COVID-19 patients.

Figure 1: Adrenergic storm induced Warburg effect in COVID-19