Review

Modification of Sympathetic and Hypothalamic Responses to Prevent Complications of COVID-19 "Dam and Wall Concept"

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Abstract: We are in amidst of COVID-19 pandemic. Since Dec 2019, severe acute respiratory corona virus (SARS-CoV-2) has infected more than half a billion people killing nearly 7 million people worldwide. Now the BA.5 variant of SARS-CoV-2 is causing mayhem and driving the global surge. Epidemiologists are aware of the fact that this virus is capable of escaping immunity and likely to infect the same person multiple times despite adequate vaccination status. Elderly people and those with underlying health conditions are considered as high-risk who are likely to suffer complications. While it is tempting to frame complications and mortality from COVID-19 as a simple matter of too much of a virulent virus in too weak of a host, much more is at play here. Framing the pathophysiology of COVID-19 in the context of the Chrousos and Gold model of the stress response system can shed insight into its complex pathogenesis. Understanding the mechanisms by which pharmacologic modification of the sympathetic and hypothalamic response system via administration of clonidine and/or dexamethasone may offer an explanation as to why a viral pathogen can be well tolerated and cleared by one host while inflaming and killing another.

Keywords: stress response system; sympathetic activity; HPA(Hypothalamic-Pituitary-Adrenal) axis; SARS-CoV-2; catecholamine; corticosteroids; clonidine; dexamethasone

1. The role of sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axes that drive homeostasis in the stress response system

Body homeostasis is defined as complex dynamic yet balanced physical and biological status maintained by all living creatures for survival. The term was first coined by Walter Cannon [1]. Body homeostasis leading to uneventful recovery can become easily disrupted in the face of various intrinsic and extrinsic stressors such as bacterial and viral infections and environmental factors such as physical or psychological trauma. As a result, maladaptive responses can occur with sympathetic hyperactivity leading to neurohormonal immune activation that may continue inexorably even after absence of the perturbing forces. This complex brain-body response is known as stress system response as first described by Chrousos and Gold [2,3]. In this model, two axes are primarily described, A) A Sympathetic nervous system (SNS) outflow axis and B) the Hypothalamic-pituitary-adrenal (HPA) axis. During stress, homeostasis is achieved via fine-tuned control of the SNS and HPA axes so that they remained tightly coordinated to produce an appropriately measured response toward host recovery (Fig 1A).

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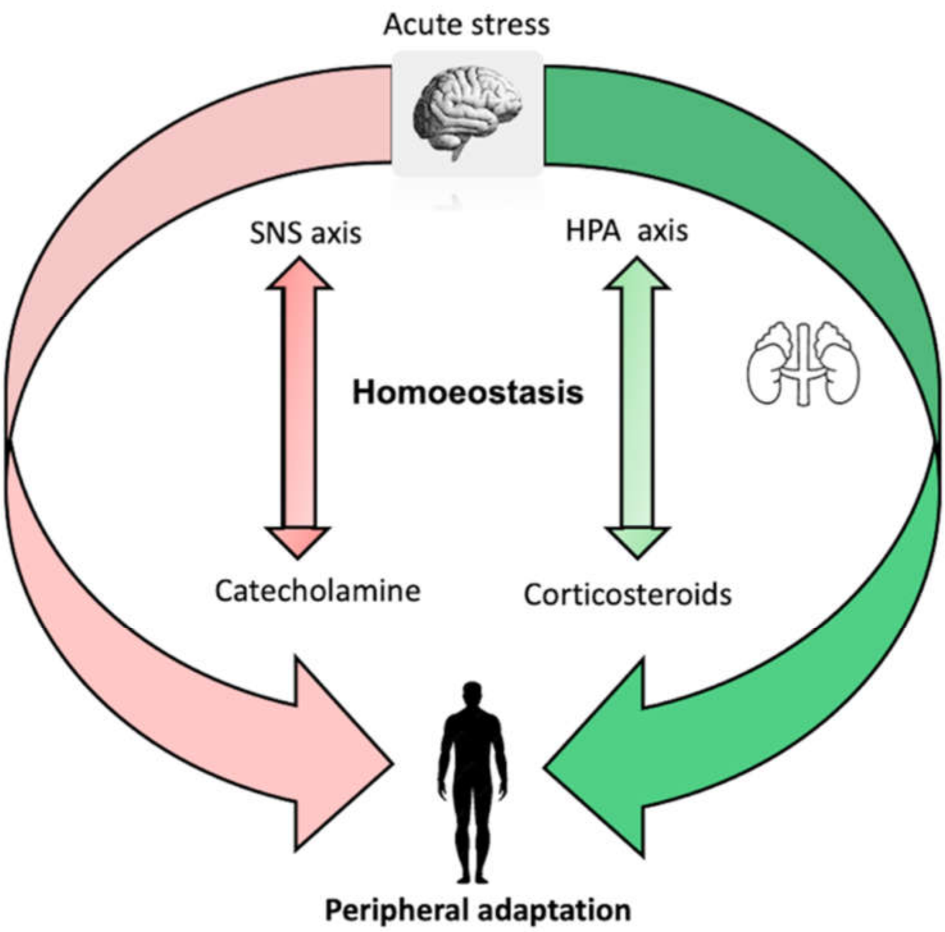

Figure 1. A: Processing of acute stress: Acute stress activates Sympathetic nervous system (SNS) axis and hypothalamic-pituitary adrenal (HPA) axis to maintain homeostasis. Repetitive acute stress lead to peripheral adaptation.

The SNS axis is mediated by catecholamines. This system's input and output signals drive the interaction between the brain and the immune system. During acute stress, catecholamines surge in the body to prepare for a "fight and flight response" queueing up various behavior (increase arousal, alertness, loss of sleep and appetite) and physiological changes (increase heart rate and blood pressure). As a result, immunomodulatory pathways are activated via various adrenoreceptors (ARs) present on immune cells. Evidence for this coordinated response can be observed by sympathoadrenergic nerve fibers that are abundantly present on immune cells that respond to catecholamines released during stress [4]. Yet once this system is activated at the whole organ level, it can be both beneficial or deleterious depending on its intensity, duration and whether prior pre-conditioning of immune cells has occurred. Additionally, the density and affinity of ARs and the concentration of norepinephrine in local organs can differentially express the intensity of the immune response. For example, it has been shown that norepinephrine has preferentially stronger affinity for αARs 1 and 2 on immune cells resulting in a predominantly pro-inflammatory response. In contrast, high concentration of norepinephrine activates βARs [5 6 7]. β_2 adrenoreceptor activation inhibits the production of pro- inflammatory cytokines such as IL-12, TNFα, and interferon gamma while also stimulating the production of anti-inflammatory cytokine IL-10 [8]. Hence, depending upon the type of ARs population activated on immune cells, the immunomodulatory response might be either pro- or anti-inflammatory. Similarly, to the SNS axis, the HPA axis plays an equally important role in maintaining homeostasis following stress-related perturbations. The HPA axis increases peripheral levels of glucocorticoids (GCs). Glucocorticoids bind to intracellular glucocorticoids receptors (GRs) in peripheral immune cells and translocate to the nucleus; this downregulates NFκB pro-inflammatory genes transcription that can encode various cytokines such as IL-6, IL-1, TNF-α [9]. Thus, peripherally released glucocorticoids have a primarily anti-inflammatory effect. Likewise, both SNS and HPA axis play major role in redistributions of T cells. An increase in plasma cortisol reduces the blood lymphocyte count whereas catecholamines generally cause a leukocytosis. Both CD8+ T cells and natural kills cells rapidly yet transiently increase in the blood following catecholamine infusion which can be mitigated by catecholamine inhibition [10].

As a fight or flight response, sympathetic SNS axis activation not only prepares the body physically to manage stress, but it also induces a pro-inflammatory response that can decrease and shift to an anti-inflammatory response. Activation of SNS axis aims to localize the inflammatory response and protect the body from any detrimental effects of released pro-inflammatory cytokines [11]. Concomitant activation of an anti-inflammatory HPA axis further shuts down ongoing inflammation in an effort to maintain homeostasis by preventing excessive collateral damage to organs. Thus, there is coordination of both a central and peripheral stress response that adaptively interact to mitigate stress (Fig 1A).

2. Chronic stress disrupts the stress response resulting in maladaptation and impaired recovery.

Selye et al [12] defined the physiologic stress response as a biological phenomenon that seeks to balance host defense against the stressor while limiting internal damage. Repetitive and continuous stress eventually results in a maladaptive response to a harmful stimulus. Allostasis, the process by which the body responds to stressors in order to regain homeostasis [13] includes recalibration of the SNS axis and HPA axis to realign immunological functions of body toward recovery. An excessive "allostatic load" can result organ damage [14], despite the body continuing to calibrate itself to the ongoing stressor [15]. Prolonged duration of the allostatic load can lead to complete failure of the system to recalibrate itself. In some cases, the SNS and HPA axes may develop a new set point [16] to minimize collateral damage. This causes an imbalance of central stress response system by affecting the calibrating efficiencies of these axes. Goldstein et al refer to this condition as dyshomeostasis [3]. The predominant outcome in dyshomoestasis is overactivity of SNS axis perturbating immune cells function locally due to continuous release of norepinephrine (NE), leading to perhaps a "gain of function" i.e hypersensitization with increase response with same level of stimulation, primarily leading to pro-inflammatory response. Such gain of function can augment the production of macrophage derived TNFα through α_2ARs [17], drive CD8+T lymphocytes toward more pro-inflammatory phenotype, and activate more β_2 adrenoreceptors on immune cell, producing a pro-inflammatory response instead of usual anti-inflammatory response [18] [19]. Another outcome is HPA axis overactivity lead to decrease sensitivity of glucocorticoids receptors to glucocorticoids, perhaps could be "loss of funtion" i.e desensitization with decrease response with same level of stimulation, reducing its anti-inflammatory effects. Such biological changes attribute to pro-inflammatory phenotype [20]. Because of altered phenotype of immune cells during dyshomeostasis and superimposed stress due to virus infection [21], NE loses its ability to localize the inflammation and fails to protect the host from the detrimental effect of cytokines. Perhaps this response might be erratic and detrimental to health [22].

3. Body dyshomeostasis and the role of sympathetic hyperactivity.

The current literature supports the notion that chronic health diseases such as obesity, hypertension, diabetes, autoimmune diseases and cardiovascular disease have been linked to chronic sympathetic hyperactivity and hence a chronic proinflammatory response [23]. The rapid evolution of civilization and its accompanying changes in living style, psychological stress, diet (i.e., Western diet consumption) and resultant dysbiosis

[24] [25] [26] [27] are major contributors to the chronic disease state. As such, high risk populations are likely to be disproportionately impacted following any form of additional stress. A model developed in the Alverdy lab captures many of the features of this so called “dyshomeostasis” state. In this model, mice consuming their normally high fiber low fat of chow all survived after subjected to a major operative stress (i.e., a partial hepatectomy) whereas a 60-70% mortality rate was observed among similarly treated mice consuming a western type diet. Both groups of mice received antibiotics prior to operation, were starved overnight as in routine and underwent surgery under strict aseptic conditions. Yet the consumption of a western diet while led to such a dramatic alteration in outcome in this model such as dysbiosis and the emergence of a gut pathobiome that caused marked endogenously derived stress to the mice [28]. Intriguingly, this model may represent a state of dyshomeostasis induced obesity whereby there is chronic sympathetic hyperactive inflammation that contributes to the organ failure and death (Fig 1B).

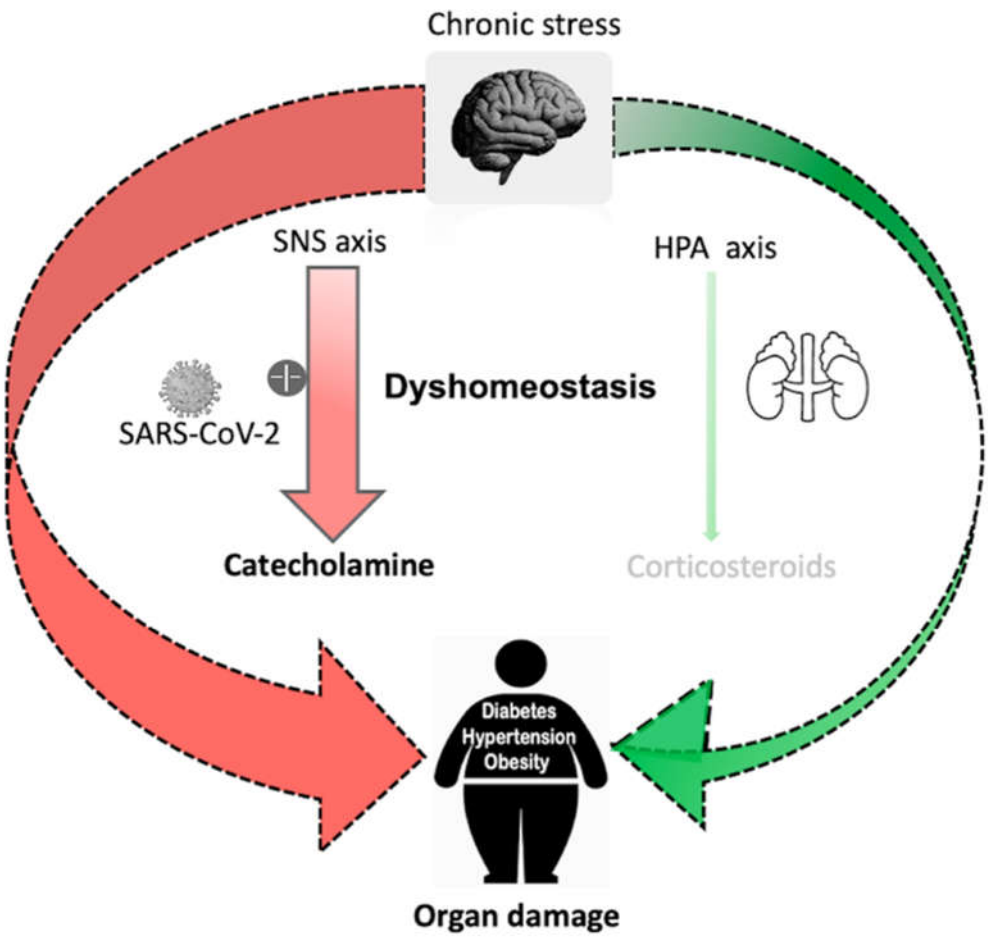

Figure 1B. Imbalanced stress response system during chronic stress with gain of function of Sympathetic nervous system (SNS) axis and loss of function of HPA axis causing dyshomeostasis. SARS-CoV-2 over activates SNS axis causing a pro-inflammatory catecholamine surge leading to organ damage in the susceptible person.

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4. SARS-CoV2 imbalance central stress response system in vulnerable populations.

It is noteworthy to acknowledge, that 80% patients who develop a SARS-CoV-2 infection have mild symptoms. These populations are mainly young and healthy individual with presumably a balanced central stress response system. Older people and those living in a state of dyshomeostasis with underlying medical comorbidities are at risk of developing severe COVID-19 symptoms and are more predisposed to die from organ failure (Fig 1B). It has now been well established that COVID-19 cause autonomic nervous system dysfunction in human beings [29]. This is the neurotropic virus that is known to reach directly or indirectly to brainstem leading to impaired autonomic function with increasing SNS axis hyperactivity [22 30 31 32]. The pathogenesis of COVID-19 reveals a significant role of a sympathetic hyperactivity mediated imbalanced in Angiotensin converting enzyme 1 (ACE1) Vs ACE2 in the evolution of its disease sequalae and mortality [31 33 34 35]. One of the leading causes of death is hypoxia from acute respiratory distress syndrome secondary to viral pneumonia. One possibility to explain the differential response of young healthy versus older infirm patient's outcome following COVID-19 infection could be excessive reactive malfunction of the autonomic nervous system with sympathetic hyperactivity and hyperinflammation as observed for other infections [36]. For example, stellate ganglion blockade with local anesthesia to interrupt sympathetic outflow to lung has been proposed as an intervention to prevent acute respiratory distress syndrome [37]. Animal studies have demonstrated attenuation of acute lung injury following this approach [38]. Similarly, human long COVID-19 symptoms have been significantly improved after a similar intervention [39.]. These observations may indicate a central theme across these disease states as applied to COVID-19 that the stress response systems with SNS axis overactivation is a main driver for the immunopathology observed in COVID-19 pneumonia [31 33]. Hypercoagulability, myocardial infarction, thrombosis and stroke are other spectrum of severe COVID-19 sequalae leading to morbidity and mortality. Biological markers in COVID-19, such as low platelets count deranged PT, PTT, protein C level and elevated D- dimer indicating coagulopathy, have been associated with increased circulating catecholamines [40 41]. Similarly, an increased incidence of Takasubo cardiomyopathy in COVID-19 patients has been linked to cytokine storm and sympathetic hyperactivity related stress [42]. It is well known that increased catecholamines induces release of IL-6 and TNFα cytokines, causing leukopenia and orchestrating immune dysregulation, perpetuating cytokine storm through a self-amplifying loop within macrophages [43]. Such phenomena have been observed in COVID-19 patients. Disturbances of HPA/SNS axis responses have been implicated for the increase in C reactive protein, IL-6 and incidence of leukopenia in the setting of metabolic syndrome with chronic diseases [44]. Derangement of such biomarkers in chronic disease patients after infected with SARS-CoV-2 [45] is suggestive of exacerbation of disturbances in SNS and HPA axes response and thus may correlate with poor outcome [46 45].

5. Clonidine and Dexamethasone acts synergistically to prevent complication during SARS-CoV-2 infection

We and others have previously hypothesized, that SARS-CoV-2 infection leads to overactivation of SNS axis and drives uncontrolled inflammation in the chronic sympathetic hyperactive population leading to poor outcome. Pharmacologic attenuation of SNS overactivation can be addressed by an FDA approved agent, clonidine, an alpha$_2$ agonist that may have clinical benefit and prevent COVID-19 complications [22 32 34 35 47]. In a small case series, we demonstrated early administration of clonidine mitigated SARS-CoV-2 related symptoms thus preventing complications [47] Other has used clonidine lately in CCU as sedation and ventilation method to manage respiratory distress SARS-CoV-2 patients[48]. Similarly, retrospective analysis done by Hamilton et al demonstrated that early used of an alpha$_2$ agonist is associated with reduced 28 days mortality and later use of the medication is not effective [49]. Baller et al recommended to use clonidine as prophylaxis against delirium in SARS-CoV-2 patients [50].

Counterintuitively, pharmacologic enhancement of the HPA axis with corticosteroid treatment has been found to be of clinical benefit in COVID-19 patients, however the timing of administration seems to play important role [51]. Multiple clinical trials have tested the effectiveness of dexamethasone in COVID-19 patients. The RECOVERY trial provided evidence that treatment with dexamethasone is beneficial for COVID-19 patients who required oxygen support although it was not helpful for those patients who did not require oxygen [52]. Although the CoDex randomized clinical trial demonstrated significant increase in the number of ventilator- free days over 28 days with dexamethasone treatment in moderate to severe COVID-19 patients, there was no difference in the mortality rate. Early treatment with dexamethasone has no added benefit in SARS-CoV-2 infection outcome, perhaps could possibly harm [53] the patients due to secondary infection [54]. Recently, it has been revealed that SARS-CoV-2 targets the adrenal gland and can cause adrenal insufficiency [55].

Taken together, much evidence suggests that disruption of central stress response system with gain of function of SNS axis and loss of function of HPA axis can lead to a worse outcome during the course of SARS-CoV-2 infection. Therefore, here I propose that timely administration of a combination of two drugs (clonidine and dexamethasone) in high risk patients has the potential to prevent complications and death (Fig 1C).

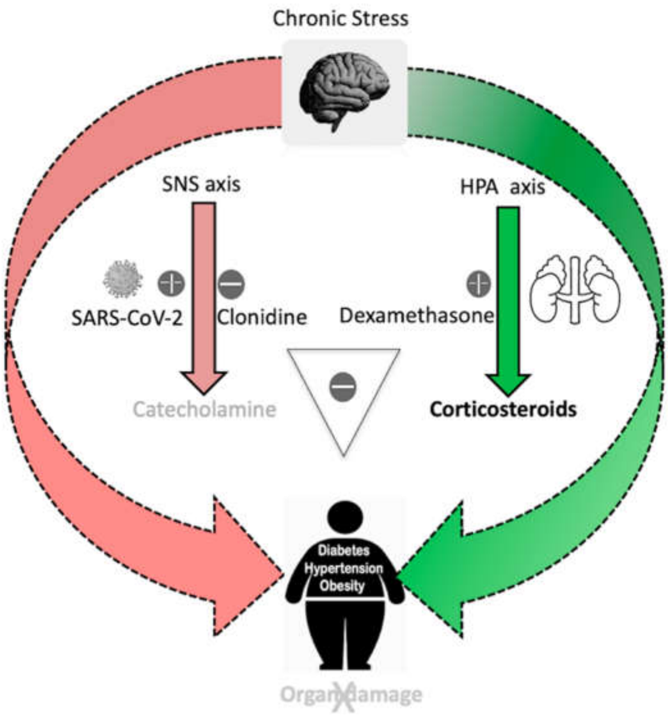

Figure 1C. Clonidine block SNS axis and dexamethasone enhance the HPA axis acting synergistically to balance the stress response system during SARS-CoV-2 infection and prevent organ damage in dyshomeostatic person.

Clonidine should be started early during the course of disease in high risk population and increase gradually while monitoring blood pressure and heart rate. If the patient's condition has not improved or the patient requires oxygen, and/or has deranged biomarkers (i. e. serum CRP, D-dimer, serum ferritin), dexamethasone should be administrated without delay at a tolerable dosage (Fig 2).

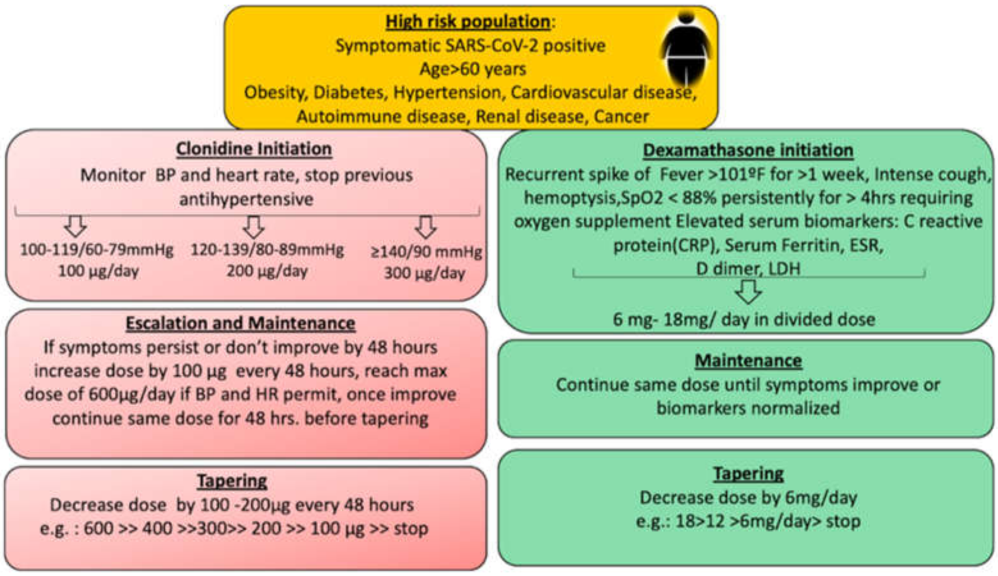

Figure 2. Protocol design for initiation, maintenance and tapering of clonidine and dexamethasone for high risk SARS-CoV-2 positive patient.

A case has been discussed to further in detail to support the hypothesis. 54-year old over weight, female with past medical history of hypertension and depression, who tested positive for SARS-CoV-2 via nasopharyngeal swab PCR. She presented to emergency department with history of fever for 3-day, T-max up to 39°C, cough for 10 days, shortness of breath with excessive fatigue for 1day on august 3rd 2021 during acute surge of COVID-19 with delta variant. She was admitted in COVID ICU and started on continuous positive airway pressure (CPAP). She was on IV dexamethasone 6 mg twice daily along with board spectrum antibiotics, antifungal and heparin. Her condition deteriorated over the period of time requiring 80% FiO_2 to maintain SpO_2 above 90%. Blood tests demonstrated an elevated serum ferritin, D-dimer, CRP, PT, and LDH (Table 2). High resolution CT scan of chest demonstrated scattered areas of ground glass opacities and consolidation in bilateral lungs with subcutaneous emphysema with CT severity score of 24/25 and CORAD score 6 (Fig 3). Her condition was not improved and consulted us virtually on Day 15th of onset of symptoms. After explicitly consented, clonidine 100 microgram 8hourly was started on same day and gradually increased up to 200 microgram 6hourly by day 20th of onset of symptoms monitoring her heart rate and blood pressure. Both the hypoxia and tachypnea improved from day 21st onwards and clonidine and dexamethasone were tapered gradually and eventually stopped on day 30th. Other cases of moderates to severe COVID-19 patients treated with clonidine and/or dexamethasone during acute surge of cases in Kathmandu valley from May 2020 - September 2021 has been outlined (Table 2).

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Table 2. COVID-19 patients treated during acute surge in Kathmandu valley between May,2020-Sep,2021. 1 2

Demographic profile	PCR date and result	Symptoms / Lowest recorded SpO_2 /Oxygen requirement	Abnormal Laboratory reports (Normal value)	Home/ Hospital based treatment	Highest doses of Clonidine and/or Dexamethasone treatment per day.	Total Duration of treatment	Outcome
61yrs/female	May 20,2020 PCR: unknown	High grade fever, cough, shortness of breath. SpO_2< 85, oxygen supplement required.	ESR:64mm/hr. (0-10) CRP: ++ D dimer: 1.61µg/ml (<0.5) Ferritin: 721ng/ml (6.24-264) AST: 138 U/L (5-40) ALT: 153 U/L (5-45)	Home based treatment	Clonidine 300microgram/day	7 days	Recovered
49yrs/female	Sep10, 2020 PCR: Positive	Fever, cough, hemoptysis, shortness of breath. SpO_2 <90. Yes.	D dimer 1.01mg/L (<0.5)	Home based treatment	Clonidine 300 microgram/day	10 days	Recovered
51yrs/male	Oct 10,2020. PCR: Positive	Fever, cough, loss of smell, loss of taste, weakness, SpO_2>92, Oxygen supplement not required	CRP: ++ ESR:16mm/hr (0-10) LDH: 486U/L (<460) AST:124U/L (5-40) ALT:101U/L (5-45) CT Chest: CORADS-6	Home based treatment	Clonidine 300microgram/day	10 days	Recovered
79yrs/female	Dec 12, 2020 PCR: Positive	Fever, cough, shortness of breath SpO_2 < 85, oxygen supplement required	TLC <3500 (4000-11000)	Home based treatment	Clonidine 300 microgram/day	10 days	Recovered
67 yrs./female	March 21,2021 PCR: Positive	Fever, shortness of breath, weakness, SpO_2<88. oxygen supplementation required.	ESR:52 mm/hr (0-20) CRP:48 mg/L (0-6) Ferritin: 389ng/ml (11-307)	Home and Hospital based treatment	Clonidine 300microgram/day Dexamethasone 6 mg/day	10 days	Recovered
32yrs/male	April 27,2021 PCR: Positive	Fever, cough, shortness of breath, SpO_2 <75, high flow oxygen required	CRP:31mg/L (0-6) CT Chest: CORADS-6 LDH:400U/L (120-246)	Hospital based treatment	Clonidine 600microgram/day Dexamethasone 12 mg/day	30 days	Recovered
48yrs/ female	May 4 2021 PCR: Positive	High grade fever, cough, shortness of breath, loss of appetite, loss of smell, loss of taste, SpO_2<75, Oxygen supplement required	CRP=59mg/L (0-6) ESR: 53mm/hr (0-10)	Home based treatment	Clonidine 600microgram/day and Dexamethasone 9 mg/day	14 days	Recovered
59 yrs. / male	May 4 2021 PCR: Positive	High grade fever, cough, shortness of breath, anosmia, agusia, loss of appetite SpO_2< 80, Yes	ESR: 38mm/hr (0-10) CRP:42mg/L (0-6) NT-Pro BNP: 20211pg/ml (<220)	Home based treatment	Clonidine 600microgram/day and Dexamethasone 12mg/day	21 days	Recovered
43 yrs./male	May 4 2021 PCR: Positive	High grade fever, cough, shortness of breath, anosmia, agusia, loss of appetite SpO_2< 80,	ESR: 54 mm/hr (0-10) CRP: 57mg/L (0-6) NT-Pro BNP: 8567pg/ml	Home based treatment	Clonidine 600microgram/day and Dexamethasone 9 mg/day	18 days	Recovered
38yrs/male	May 14,2021	High grade fever, cough, Shortness of breath, SpO_2<90,	CRP: 211mg/l (0-5). ESR: 83mm/hr. (0-12)	Home based treatment	Clonidine 300 microgram/day	14 days	Recovered

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	PCR: Positive	Oxygen supplement required.	Serum ferritin >3000 ng/ml (25-350) LDH: 535U/l (125-220) D dimer: 600 ng/ml (<500) AST: 361 U/L (16-63) ALT: 125 U/L (16-37)		Dexamethasone 16mg/day		
69yrs/female	May 12,2021 PCR: Positive	Fever, Cough, Shortness of breath, SPO_2<85, Oxygen supplement required.	ESR: 30mm/hr (0-9) CRP: 24mg/L (<6) Procalcitonin 0.81ng/ml (0-0.5)	Home based treatment	Clonidine 300 microgram/day Dexamethasone 12mg/day	21 days	Recovered
72yrs/male	May 11,2021 PCR: Positive	Fever, cough shortness of breath, SPO_2<80, Oxygen supplement required	CRP: 38mg/L (0- 10) CT Chest: CORADS-6	Isolation center-based treatment	Clonidine 300 microgram/day Dexamethasone 6 mg/day	15 days	Recovered
59yrs/female	May 15,2021 PCR: Positive	Fever, Cough, shortness of breath, SpO_2 <82,	ESR: 33mm/hr. (0-12) CRP: 19.8 mg/L (0-6) Glucose (R): 206	Home based treatment	Clonidine 300microgram/day Dexamethasone 6mg/day	12 days	Recovered
58yrs/male	July 17,2021 PCR: Positive	Fever, cough, whole body ache, shortness of breath, Intense headache, BP >197/117mmHg, SpO_2< 82. Oxygen supplement required.	CRP: 89mg/L (<10) D-Dimer: 1133ng/ml (30-400)	Home based treatment	Clonidine 900microgram/day. Dexamethasone 12mg/day	18 days	Recovered
45yrs/male	Aug 24,2021 PCR Positive	Fever, cough, hemoptysis, SpO_2<90, oxygen supplementation not required.	CRP: 88mg/L (0-6) Ferritin: 544 ng/ml (17-464) AST: 48 U/L (5-40) ALT: 86U/L (5-45)	Home treatment	Clonidine 300microgram/day Dexamethasone 12mg/day	14 days	Recovered
96yrs/ male	Sep,20,2021 PCR Unknown	Fever, shortness of breath, SpO_2<86, oxygen	Not done	Home based treatment	Clonidine 400 microgram/day and Dexamethasone 6 mg/day	10 days	Recovered

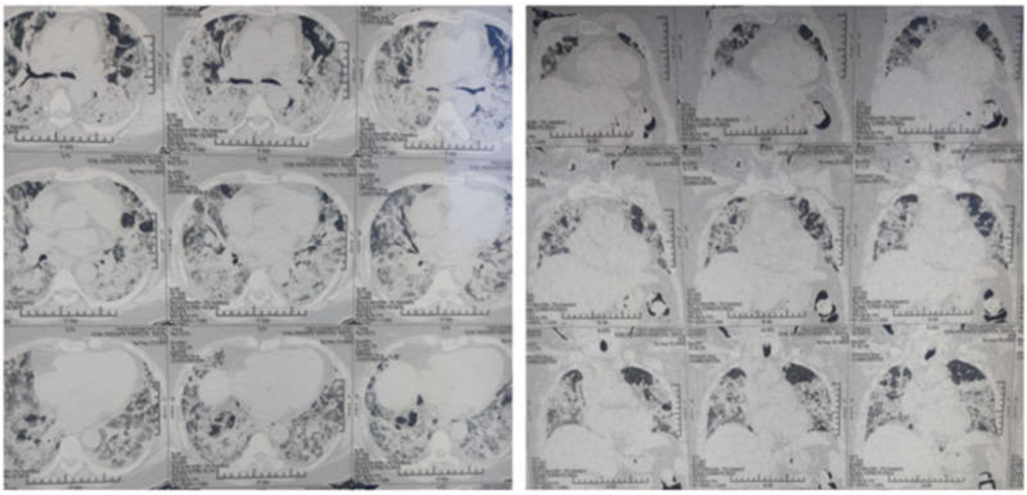

Figure 3. High resolution CT scan of chest demonstrating scattered areas of ground glass opacities and consolidation in bilateral lungs with subcutaneous emphysema with CT severity score of 24/25 and CORAD score 6.

Table 1. Lab investigation of patient: Blood parameters CRP: c reactive protein, PT: prothrombin time, LDH: Lactate dehydrogenase.

Parameter		Normal range
Serum ferritin	1006.4	11.0-306ng/ml
D-dimer	4.6	<0.5mg/l
CRP	138.47	<10mg/dl
PT	20.5	11-16 sec
LDH	926	0-246ng/ml

Given the variable and potentially opposing effects of clonidine and dexamethasone, either drug alone may not be sufficient to control the ongoing inflammation. Randomized clinical trials to test the hypothesis that clonidine and dexamethasone can act synergistically to stop the ongoing overt inflammation centrally at the brainstem level and peripherally at the lung should be encouraged. Generation of the appropriate biomarkers and proper internal controls would yield considerable mechanistic information useful to those unfortunate individuals who develop severe symptoms following COVID-19 infection. This combined approach recapitulates the idea of "closing dam (centrally) and building wall (peripherally) to protect the home field (major organ)" from excessive adrenergic flooding (catecholamine). It should be emphasized that late administration of either drug is not beneficial as observed by other studies, since significant organ damage has already occurred.

6. Concluding Remark.

The COVID-19 pandemic remains a clear and present danger to mankind. Multiple variants are now emerging and hospitalizations are increasing. In healthy population, repetitive infection with SARS-CoV-2 causes a flu like phenomenon because of a balanced central stress response system. With an imbalanced central stress response system, additional stress due to infection lead to substantial morbidity and mortality. Given the multiple ongoing emergence of new variants of SARS-CoV-2 virus, early recognition of high-risk patients whose response represents "dyshomeostasis" is critical and treatment with already available agents should be encouraged. Randomized clinical (CLODEX) trial using combination of clonidine and dexamethasone as mentioned in design protocol (Fig 2) is necessary to test this challenging "Dam and Wall" concept to prevent any further damage caused by emerging new variants of SARS-CoV-2 in high risk population.

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Informed Consent Statement: Informed consent has been taken form the patients, if require consent form is available with author.

Conflicts of Interests: Author declares no competing interest. Author continue volunteer treating COVID-19 patients in Kathmandu, Nepal via Facebook based telehealth platform COVID-19 response group Nepal and Sanjiv Hyoju Free online health clinic Facebook page. The protocol has been drafted after gaining significant experience from treating COVID-19 patients.

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