

Acute Catecholamine Surge and Cytokine Storm: The Deadly Duo in Severe COVID-19

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Abstract

Catecholamines (norepinephrine, epinephrine, dopamine) are stress hormones which actions are mediated through their adrenoceptors. The multisystem effect of excess secretion of these hormones in severe COVID-19 are manifested variedly as hypertension (cardiovascular and renin-angiotensin systems), marked inflammation and sometimes thrombosis (immune and hematologic systems), hypoxemia and ventilation problem (respiratory system), and hyperglycemia (metabolic and endocrine system). In severe COVID-19, there is systemic hyperinflammation induced by augmented production of proinflammatory cytokines. Such cytokine storm results into multi-organ dysfunction, cardiovascular collapse, and even death. Hypertension, diabetes, obesity, and old age have shown to be risk factors for the untoward events in severe COVID-19. Increased in catecholamine secretion is associated with increase in proinflammatory cytokines. And increased catecholamine levels can augment production of concentrations of proinflammatory cytokines. Takotsubo syndrome is a reversible cardiovascular condition in a setting of physical or emotional stress whereby the excess catecholamines leads to mild to severe myocardial edema. Chronic unabated elevation of these hormones, however, may lead to irreversible cardiomyopathy. Recent reports have shown that there is increased morbidity and mortality in patients with severe COVID-19 and Takotsubo syndrome. The interplay of acute elevation in circulating catecholamines in an already compromised CV function and cytokine storm could influence the clinical course of patients with severe COVID-19. Therefore, early recognition of acute hypercatecholaminergic surge and cytokine storm, so-called the deadly duo, is vital, and a timely and optimal management is critical for increased survival of patients with severe COVID-19.

Keywords: *Catecholamines; Chromaffin Tumors; COVID-19; Takotsubo Syndrome; Cytokine Storm; Acute Catecholamine Surge*

Introduction

Catecholamines are hormones secreted from the chromaffin cells of adrenal medulla and sympathetic and parasympathetic ganglia. The physiologic role and functions of these hormones (norepinephrine, epinephrine, dopamine) are vital as response of the body to cope up with stress. Clinical manifestations in a setting of excess catecholamine secretion are well studied in chromaffin tumors such as pheochromocytoma and paraganglioma (PPGLs). Thru their adrenoceptors actions (α_1 , α_2 , β_1 , β_2 , β_3 , D_1 , D_2) the multi-systemic effect of excess catecholamines are well discernible in PPGLs such as hypertension, palpitations, headache, pallor, diaphoresis, orthostatic hypotension, weight loss, and hyperglycemia [1]. However, in the recent years there is evolution in the clinical picture and course of patients with PP-

GLs manifested as acute cardiac syndrome, heart failure and severe arrhythmia. Untoward clinical events may be reversible with timely removal of chromaffin tumors, worse is death in very morbid occurrences [1].

Severe COVID-19 is characterized by hyperinflammatory state resulting from uncontrolled immune system activation. An elevation in cytokine concentrations can lead to hypercoagulability and thrombosis. Ventilation defect arose from diffused alveolar damage and granulocytic infiltration of bronchi and alveoli. The involvement of angiotensin-converting enzyme 2 in the viral entry phase with its eventual degradation contributes to vasoconstrictive and cardiovascular untoward consequences [2]. Reports have shown that increased morbidity and mortality in severe COVID-19 are observed in patients with cardiovascular risk factors like hypertension, heart disease, diabetes, elderly, and obesity [3].

Acute catecholamine surge can influence the course of severe COVID-19. Increase in catecholamine secretion is associated with increase in proinflammatory cytokines (IL-6, IL-10, TNF- α , granulocyte colony stimulating factor, and IL-2) and can even augment their production [4]. Similarly, IL-6 has shown to influence the chromaffin cell response to a wide range of physiological and parapsychological stressors, particularly when immune and endocrine stimuli converge. Circulating IL-6 levels are closely linked to the severity of COVID-19 infection [5].

Takotsubo syndrome (TTS) is a reversible myositis caused by increased catecholamines from emotional and physical stresses. MRI imaging shows myocardial edema with abnormal functional study of mild to severe dyskinesia with low ejection fraction. In patients with pheochromocytoma, the myocardial edema has shown to resolve after removal of the adrenal tumor [6,7]. However, high burden of myocardial injury (19.7 - 27.8%) in TTS, contribute to significant high mortality in these patients [8].

It has been reported that cytokine release syndrome in COVID-19 patients is often accompanied by acute catecholamine surge, which can predispose patients to develop TTS. COVID-19 patients have shown to manifest decreased left ventricular ejection fraction (LVEF), higher left ventricle (LV) volume, and higher MRI markers of inflammation, which are similar specific cardiovascular features seen in patients with TTS. Over 50% of patients with TTS who incurred COVID-19 infection succumbed to fatal cardiovascular complications like supraventricular tachycardia, acute biventricular heart failure, and cardiogenic shock [8]. Could it be that the deadly duo in severe COVID-19 are --- 1) an acute surge of catecholamines in a patient with pre-existing cardiovascular abnormalities, and 2) an environment of hyperinflammatory state due to cytokine storm?

Adrenoceptor-mediated clinical and evolving manifestations of excess catecholamines

Based on ligand studies and their agonists and antagonists, adrenoceptors are classified into adrenergic (α_1 , α_2 , β_1 , β_2 , β_3) and dopaminergic receptors (D_1 , D_2) and their subtypes. Norepinephrine mainly signals α_1 , α_2 , β_1 receptors, while epinephrine mainly signals β_1 , β_2 receptors. Normally dopamine does not affect the adrenergic receptors, but with increased plasma concentrations, it can stimulate both α and β receptors [9-11]. Pheochromocytoma (PHEO) and paraganglioma are chromaffin tumors (PPGLs) that secrete catecholamines in excess [1,2].

In general, α_1 receptors, mostly found in smooth muscle, peripheral arteries and veins cause vasoconstriction upon stimulating and leads to increased systemic pressure. In PHEO, manifestations include hypertension, headache, and pallor. Headache can also be due to vasoconstriction in the brain mediated by D_1 adrenoceptors. Stimulation of α_2 -adrenergic receptors located on smooth muscles will result in arterial vasodilation and coronary vasoconstriction. In PHEO, typical manifestations may include diaphoresis and orthostatic hypotension. Stimulation of β_1 -adrenergic receptors has a positive chronotropic and inotropic effect in the heart and will also result in release of renin. In PHEO this can contribute to hypertension, palpitations, and tachycardia. Stimulation of β_2 -adrenergic receptors will induce vasodilation of muscular arteries, and some common effects in PHEO include constipation and nausea. β_3 -adrenergic receptors in adipocytes induces lipolysis and can cause weight loss [1].

Recently, there have been reports on young PHEO patients, with no CV risk factors, being admitted for dramatic CV events like acute coronary syndrome, severe congestive heart failure, and arrhythmia. Echocardiographic and angiographic findings have shown consistently with wall motion abnormality and decrease in ejection fraction, but no problems in the coronary arteries. Cardiac MRI demonstrated mild to severe myocardial edema with resolution after removal of the chromaffin tumor. Clinical course has been reported to be benign and uneventful but can be worse with increased fatality [1,6,7,12]. The setting suggests the destructive effect of chronic hypercatecholaminemia that develops insidiously if the diagnosis of PHEO is overlooked leads to dramatic CVD events and death which could be due to the sudden surge in the concentration of the hormones adding significant insult to a compromised cardiac function. Such clinical picture points to a similar earlier reported entity called Takotsubo syndrome, a condition of reversible cardiac myositis arising from emotional and physical stresses. If left unrecognized the problem may lead to irreversible cardiomyopathy that may be fatal if no immediate treatment is instituted.

Cytokine storm syndrome in severe Covid-19 and Takotsubo syndrome

Severe COVID-19 is characterized by explosion of proinflammatory cytokine secretions (IL-6, IL-10, TNF- α , granulocyte colony stimulating factor, and IL-2) resulting into the so-called cytokine storm syndrome [13,14]. This massive cytokine release is often accompanied by acute catecholamine surge and may lead to devastating multisystem dysfunction such as heart failure, ventilation abnormality with respiratory failure, hematologic problem with hypercoagulability and thrombosis, and severe pancreatic β -cell problem with development of frank diabetes mellitus [2,14]. Sharma and colleagues reported in fulminant COVID-19 there is acute catecholamine surge and is characterized by low left ventricular ejection fraction (LVEF), higher left ventricle (LV) volume, high sensitive troponin T (hsTnT), and higher MRI markers of inflammation, which are specific features of Takotsubo syndrome [8]. The group described COVID-19 patients with TTS majority presenting with dyspnea and wall motion abnormalities. Although majority were discharged with uneventful course, over 50% developed arrhythmia, biventricular heart failure and cardiogenic shock. The in-hospital complications included acute respiratory and kidney failures. Of note, there was greater percentage of mortality in patients with COVID-19 and TTS versus those with no TTS (14.8% vs. 5.8%, respectively). Treatment included anticoagulation, antivirals, vasopressors, and β -blockers [8]. Moreover, Titi and his colleagues reported a case of a fatal TTS in a patient with COVID-19-related pneumonia. Her electrocardiogram showed ST elevation with LV mid-apical ballooning on angiogram. After sustained resuscitation, patient died and autopsy showed subepicardial hematoma in the absence of myocardial rupture [15].

In contrast, Japp, *et al.* described three (3) elderly patients tested positive but asymptomatic for COVID-19, admitted for operation of pheochromocytoma. All had markedly increased catecholamines and big tumors but with benign features. The perioperative course of the three patients was uneventful. Obviously, the absence of cytokine surge in these patients with asymptomatic COVID-19 in an environment of excess catecholamines could have explained the nonmorbid clinical course [16].

The Role of α - and β -Adrenoceptors and their Blockade in Curbing the Fatal Course of Severe COVID-19

Epinephrine kinetics in COVID-19

The multifaceted utilization of epinephrine in the clinical practice has been evident for its life-saving use in various emergencies like hypotension and cardiogenic shock (α_1 and β_1 adrenoceptor-mediated) and severe anaphylaxis (β_2 adrenoceptor-mediated). However, it can afford only a narrow therapeutic window that when administered in overdose will lead to myocardial infarction, heart failure, arrhythmia and stroke. Caution must be observed when given to elderly and patients with pre-existing cardiovascular disease [17].

Derakhshan, *et al.* studied the epinephrine micro-pulses and looked at its circadian amplitude in patients with COVID-19. They reported that young patients with COVID-19 do not need hospitalization and with no ICU admission and fatalities as oppose to elderly patients with 6% to 29% ICU admissions, and 10% to 27% case fatalities. Their observation showed the circadian amplitude of the epinephrine

rhythm is higher in children than in the elderly. Similarly, those asthmatic patients maintained on β_2 -agonist have decreased severity of COVID-19 and with lesser risk of hospitalization [18].

Interestingly, epinephrine modulates immune system. For mounting an anti-viral response, a certain degree of adrenergic signaling by catecholamines is required. It has been reported that in H7N9 disease, patients who rapidly recovered had early CD8+ T cell responses. Such immune response has been shown to positively correlated with epinephrine oscillations, and their population increased after low-dose epinephrine infusion [19].

Adrenergic receptor antagonists versus cytokine storm in COVID-19

Catecholamines can augment proinflammatory cytokine secretions in patients with COVID-19. Prophylactic inhibition of catecholamine synthesis with metyrosine, a tyrosine hydroxylase antagonist, reduced levels of catecholamines and cytokine responses with markedly increased survival following various inflammatory stimuli in mice. König and his group reported that α_1 -adrenoceptor antagonist, prazosin, prevented cytokine storm, requirement of mechanical ventilation, and reduced mortality in patients when on this medication prior to hospitalization for COVID-19 [20]. Nonetheless, when on α_1 -adrenoceptor blockade, catecholamine action on β_2 -adrenoceptor can precipitate hypotensive shock or distributive (septic) shock in patients with COVID-19. Propranolol, a non-selective β -blocker has been shown to reduce inflammatory cytokines including IL-6 and TNF α and some inflammation-related transcription factors such as NF κ B and STAT3, it can also decrease platelet aggregation as shown in patients with cancer [21]. Barbieri and colleagues qualified the possible benefit in targeting β_2 -adrenoceptor in patients with COVID-19. β_2 -adrenoceptor blockade in Phase I targets viral replication and vasoconstriction, β_2 -adrenoceptor blockade in Phase II targets macrophage recruitment in lung tissue and infiltration, and β_2 -adrenoceptor blockade in Phase III addresses cytokine storm with decrease in the inflammatory cytokines [21].

Lastly, IL-6 is an inflammatory cytokine reported to be closely linked to the severity of COVID-19 infection. It is an inflammatory cytokine that can fine tune chromaffin response to a wide range of stressors. These observations provide the evidence that IL6 can regulate adrenal chromaffin cell signaling, protein phosphorylation, and gene transcription, with the potential to modulate the secretory output of the adrenal medulla in response to inflammation. IL-6, by modifying both catecholamine and neuropeptide synthesis, and thus the secretory cocktail of the chromaffin cell, may have an important role in integrating and limiting the course of the inflammatory response at the level of adrenal medulla [5]. On the other hand, norepinephrine has shown to be the most potent stimulus to increase the level of IL-6 in rat cardiac fibroblasts [22].

In COVID-19 infection, an increase in IL-6 levels implies a possible shared mechanism of cytokine-mediated lung damage. The highly pathogenic SARS-CoV-2 is associated with rapid virus replication and a tendency to infect the lower respiratory tract, resulting in an elevated response of IL-6-induced severe respiratory distress. In a meta-analysis, Ulhaq, *et al.* demonstrated that IL-6 is a potential biomarker of COVID-19 progression [23]. Tocilizumab is a recombinant humanized anti-interleukin IL-6 receptor monoclonal antibody. It was hypothesized that modulating the levels of pro-inflammatory IL-6 or its effects may improve the course of COVID-19. Initial studies showed tocilizumab treatment lowered the incidence or duration of intensive care unit (ICU) and hospital stays in patients with COVID-19 [23].

Summary and Insights

The following summarize the discussion and issues addressed in this paper:

- Acute catecholamine surge can influence the course of severe COVID-19.
- Increase in catecholamine secretion is associated with increase in proinflammatory cytokines.

- Increased catecholamine levels can augment production of concentrations of proinflammatory cytokines.
- Cytokine storm leads to cardiovascular collapse, multi-organ dysfunction and death in severe COVID-19.
- There is increased mortality in severe COVID-19 patients with Takotsubo syndrome.
- Catecholamine adrenoceptor blockade showed reduction in morbidity and mortality in patients with severe COVID-19.
- So, are catecholamines a friend or a foe?--- timing is critical and vital in using either an α or β receptor antagonist in manipulating the course of severe COVID-19 for patient survival.
- Indeed, the deadly duo are --- 1) an acute surge of catecholamines in a COVID-19 patient with already CV abnormalities, and 2) an environment of hyperinflammatory state due to cytokine storm.
- The early recognition of these duo and managed optimally and timely could be critical in reducing morbidity and mortality in patients with severe COVID-19.

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