**REVIEW ARTICLE**

# The extended autonomic system, dyshomeostasis, and COVID-19

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## Abstract

The pandemic viral illness COVID-19 is especially life-threatening in the elderly and in those with any of a variety of chronic medical conditions. This essay explores the possibility that the heightened risk may involve activation of the "extended autonomic system" (EAS). Traditionally, the autonomic nervous system has been viewed as consisting of the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system. Over the past century, however, neuroendocrine and neuroimmune systems have come to the fore, justifying expansion of the meaning of "autonomic." Additional facets include the sympathetic adrenergic system, for which adrenaline is the key effector; the hypothalamic-pituitary-adrenocortical axis; arginine vasopressin (synonymous with anti-diuretic hormone); the renin-angiotensin-aldosterone system, with angiotensin II and aldosterone the main effectors; and cholinergic anti-inflammatory and sympathetic inflammasomal pathways. A hierarchical brain network—the "central autonomic network"—regulates these systems; embedded within it are components of the Chrousos/Gold "stress system." Acute, coordinated alterations in homeostatic settings (allostasis) can be crucial for surviving stressors such as traumatic hemorrhage, asphyxiation, and sepsis, which throughout human evolution have threatened homeostasis; however, intense or long-term EAS activation may cause harm. While required for appropriate responses in emergencies, EAS activation in the setting of chronically decreased homeostatic efficiencies (dyshomeostasis) may reduce thresholds for induction of destabilizing, lethal vicious cycles. Testable hypotheses derived from these concepts are that biomarkers of EAS activation correlate with clinical and pathophysiologic data and predict outcome in COVID-19 and that treatments targeting specific abnormalities identified in individual patients may be beneficial.

**Keywords** COVID-19 · Autonomic · Stress · Dyshomeostasis · Homeostasis · Catecholamines · Sympathetic · Adrenaline

## Abbreviations

| | |
|---|---|
| ACE | Angiotensin-converting enzyme |
| ACTH | Adrenocorticotropin (corticotropin) |
| ADH | Anti-diuretic hormone |
| AII | Angiotensin II |
| Ang 1–7 | Angiotensin 1–7 |
| ANS | Autonomic nervous system |
| AVP | Arginine vasopressin |
| COVID-19 | Coronavirus disease-2019 |
| CRH | Corticotropin-releasing hormone |
| DA | Dopamine |
| DOPA | 3,4-Dihydroxyphenylalanine |
| DRD1 | Type 1 dopamine receptor |
| ENS | Enteric nervous system |
| EPI | Epinephrine (synonymous with adrenaline) |
| NLRP3 | NOD-, LRR- and pyrin domain-containing protein 3 |
| HPA | Hypothalamic-pituitary-adrenocortical |
| IL-6 | Interleukin-6 |
| LC | Locus ceruleus |
| NE | Norepinephrine |
| PNS | Parasympathetic nervous system |
| POTS | Postural tachycardia syndrome |
| PVN | Paraventricular nucleus of the hypothalamus |
| RAS | Renin-angiotensin-aldosterone system |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SAS | Sympathetic adrenergic system |
| SNS | Sympathetic noradrenergic system |
| TNFα | Tumor necrosis factor alpha |

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## Introduction

Coronavirus disease-2019 (COVID-19), the acute illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now pandemic, so far without effective treatments or vaccines. Biomedical researchers worldwide have shifted their focus urgently to COVID-19.

One of the major challenges posed by COVID-19 is that the disease is much more likely to be lethal in the elderly and in people with pre-existing chronic disorders such as diabetes, coronary artery disease, and obesity than in other populations. No conceptual framework has been offered to account for this phenomenon.

Pneumonitis and pulmonary dysfunction usually dominate the clinical picture, but it is by now clear that COVID-19 importantly involves other body organs and systems, including the heart, gut, kidneys, and brain. The purpose of this essay is to convey a perspective that can account for the age-relatedness of COVID-19 mortality and the multi-organ—and therefore multi-disciplinary—aspects of the disease. The thesis is that both of these aspects may reflect dysautonomia, broadly defined as a condition where changes in functioning of one or more components of the autonomic nervous system adversely affect health.

The presentation begins with some integrative physiologic concepts—homeostasis, allostasis, dyshomeostasis, and stress—and introduces the notion of the "extended" autonomic system (EAS). The main take-home message is that biomarkers of EAS activation might predict outcome in COVID-19, and treatments targeting specific EAS abnormalities in individual patients might be more effective than one-size-fits-all approaches.

## Homeostasis

The term "homeostasis" refers to the stability of the body's "inner world." In systems biology, homeostasis is an emergent phenomenon, but in integrative physiology homeostasis is a goal—it is *the* goal [71]. Thus, Claude Bernard, the founding father of integrative physiology, wrote, "The constancy of the internal environment is the condition for free and independent life…All the vital mechanisms, however varied they might be, always have one purpose, that of maintaining the integrity of the conditions of life within the internal environment" [12]. And Walter B. Cannon, who coined the word, homeostasis, wrote, "My first article of belief is based on the observation, almost universally confirmed in present knowledge, that what happens in our bodies is directed toward a useful end" [26].

A classic example of homeostasis is regulation of core temperature (Fig. 1, left). In response to cold
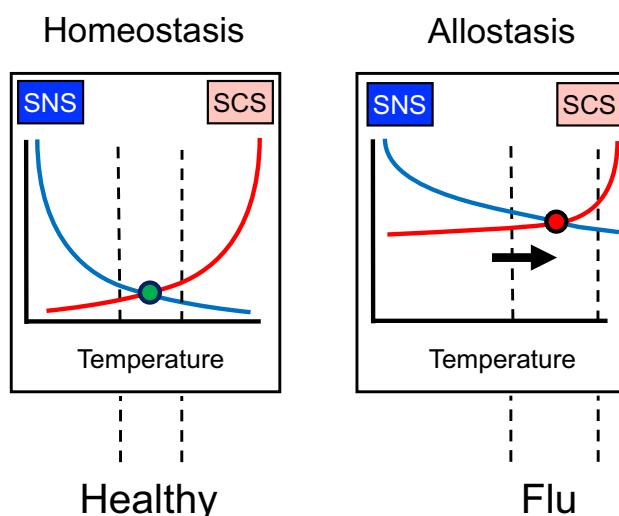


**Fig. 1** From homeostasis to allostasis. In allostasis there is a shift in input-output curves for oppositely acting effectors (yellow and white), resulting in regulation of the monitored variable (in this case body temperature) at a different level. The acceptable bounds are the vertical dashed lines. A low-grade fever associated with a flu-like illness is an example of an allostatic state

exposure, sympathetic noradrenergic system (SNS) outflows increase, resulting in cutaneous vasoconstriction, shivering, and piloerection, all of which tend to maintain the core temperature. In response to heat exposure, sympathetic cholinergic system (SCS) outflows increase, evoking diaphoresis that tends to maintain the core temperature by evaporative heat loss.

## Allostasis

Allostasis, from the Greek words for "other" and "standing still," refers to a shift in input-output curves (Fig. 1, right). A low-grade fever when an individual has a viral disease is an example of allostasis. The temperature is regulated, but at an altered thermostatic setting.

Allostatic adjustments use up more energy than do homeostatic adjustments, but normally allostatic states are temporary and beneficial (whether a fever is helpful in fighting off a viral illness has been debated for decades [130]). Once the individual recovers, the input-output curves revert to those before the acute illness, with no apparent harm done.

Allostatic states, however, also increase wear and tear on both the effectors and the target organs—allostatic load [74]. Declining homeostatic efficiencies (dyshomeostasis) associated with aging and chronic disorders can prolong or intensify the accumulation of allostatic load and eventually decrease thresholds for a variety of vicious cycles (positive feedback loops) that can be lethal.

## Dyshomeostasis in the elderly

That resilience declines with aging is part of humankind's evolutionary heritage. In his *The Wisdom of the Body* Walter B. Cannon devoted an entire chapter to this phenomenon. Cannon summarized already substantial literature that with aging the abilities to maintain body temperature, glucose, blood pH, and circulatory-respiratory delivery of oxygenated blood under baseline conditions are preserved, but for each of these vital functions there are decreased abilities to keep appropriate levels during stress—e.g., heat or cold exposure, glucose ingestion, and exercise.

This viewpoint from about a century ago still applies. For instance, during cooling by intravenous infusion of cold saline, older people 55–72 years old have larger decreases in core temperature and smaller increments in plasma norepinephrine (NE) levels, systemic vascular resistance, and heat generation than younger people 18–23 years old [58].

After taking a high carbohydrate diet, in young adults postprandial plasma adrenaline (epinephrine, EPI) levels follow a biphasic diurnal pattern that is inversely related to glucose and insulin levels. Aging is associated with a dysregulation of this response [139], and insulin sensitivity declines with aging [171].

Baroreflex sensitivity, and consequently the ability to keep blood pressure within bounds, also decreases as a function of age, in a manner associated with hypertension [16]. The rate of pulse-synchronous bursts of skeletal muscle sympathetic nerve traffic increases with aging [170]; however, arterial baroreflex control of muscle sympathetic nerve traffic [117] and of cardiovagal outflow is decreased in the elderly [16].

Plasma NE levels, NE responses to stress, skeletal muscle sympathetic outflow, and cardiac NE spillover all increase with aging [44, 54, 134], probably from a combination of decreased neuronal reuptake of NE and increased sympathetic nerve traffic. For a given amount of reflexively increased sympathetic outflow, however, there is a blunted vasoconstrictor response [44]. Responses of cardiac NE spillover to exercise are similar in elderly vs. young men, but this is due to an aging-related decline in neuronal reuptake of released NE, meaning that the increment in cardiac sympathetic outflow probably is blunted [54].

The ability of catecholamines to break down triglycerides to free fatty acids decreases with aging. This may increase susceptibilities to exercise intolerance, decrease ability to maintain core body temperature during cold exposure, and reduce ability to survive starvation, as well as increase visceral adiposity and indolence.

As people age the efficiency of immune responsiveness also generally declines. Depending on genetics, epigenetics, and life experiences, "immune age" can be estimated and is correlated with all-cause mortality [3]. Unbiased whole-transcriptome analysis of adipose macrophages has revealed that aging upregulates the gene encoding monoamine oxidase-A (MAO-A) in an NLRP3 inflammasome-dependent manner, and MAO-A inhibition restores NE-induced lipolysis [22].

## The extended autonomic system (EAS)

### Autonomic neuroendocrine systems

The autonomic nervous system conceptualized by Langley in the early 20th century has three components—the sympathetic nervous system, the parasympathetic nervous system, and the enteric nervous system [102]. Walter B. Cannon added a neuroendocrine component, here called the sympathetic adrenergic system (SAS), in which EPI is the hormonal chemical messenger [27, 28]. Cannon taught that the sympathetic nervous system and adrenal gland act together in emergencies to maintain homeostasis [23, 24]. This view is still widely held, although by now there is abundant evidence that the neuronal component, here called the sympathetic noradrenergic system (SNS), and the hormonal component, the SAS, are constitutively active [101] and participate in even the mundane aspects of daily life.

Neuroendocrine systems expand the meaning of "autonomic." Modern neuroendocrinology refers specifically to peptides secreted by hypothalamic neurons into the circulation. Even in this sense the neuroendocrine and autonomic systems interact. For instance, thyroidectomy, which increases thyrotropin secretion, also increases plasma levels of the SNS neurotransmitter NE [61]. Release of corticotropin-releasing hormone (CRH) in the brain concurrently increases SNS and SAS outflows [18, 91]. Infusion of the beta-adrenoceptor agonist isoproterenol into humans decreases plasma levels of both corticotropin (ACTH) and EPI [52]; subacute glucocorticoid treatment with prednisone decreases directly recorded skeletal muscle sympathetic outflow [68]. Both hypopituitarism and adrenocortical failure decrease plasma EPI and increase plasma NE levels [152, 172]. Arginine vasopressin (AVP) inhibits SNS responses to hemorrhage [85]. Corticosteroid synthesis by cultured adrenocortical cells is increased ten-fold by co-culture with adrenomedullary chromaffin cells [82]. In general, across a variety of stressors, plasma EPI responses are more closely tied to ACTH responses than to NE responses [73].

### Autonomic neuroimmunology

Another extension of the concept of autonomic relates to the immune system. The field of neuroimmunology focuses on interactions between the nervous system and immune functions. Anti-inflammation exerted by adrenocortical steroids

was fundamental in Selye's stress theory [159], discussed below. A much more modern example of autonomic-immune interactions is regulation of cytokines and the "inflammasome" by the vagus nerve [97, 191]. The inflammasome concept is based on the NOD-, LRR-, and pyrin domain-containing protein 3, or NLPR3 [173]. NLPR3 is conceptualized to be an intracellular sensor that can detect a wide variety of microbes, including RNA viruses. NLRP3 inflammasome formation leads to release of the proinflammatory cytokines IL-1beta and IL-18 and to cell death by pyroptosis. Pyroptosis is a form of programmed cell death that may remove intracellular viral replication niches in the tissue.

The cytokine IL-6 not only activates the HPA axis but also directly stimulates production of aldosterone, cortisol, and androgenic steroids [137]. In conscious, unrestrained rats, TNFα administration increases plasma levels of glucagon, corticosterone, ACTH, NE, and 3,4-dihydroxyphenylglycol (DHPG, the main neuronal metabolite of NE) [43].

It has been proposed that overactivity of myocardial beta-adrenoceptors by SNS activation exerts proinflammatory effects [94]. There actually are three types of peripheral catecholamine system in humans—the SNS, where NE is the locally acting neurotransmitter, the SAS, where EPI is the hormone, and the DOPA-dopamine (DA) autocrine-paracrine system [75], in which DA is produced in, released from, and acts locally on parenchymal cells that take up DOPA from the circulation and decarboxylate the amino acid to form the catecholamine. The latter mechanism is by definition an activity of "APUD" cells (APUD standing for amine precursor uptake and decarboxylation) that release polypeptide hormones in a diffuse neuroendocrine system [124].

In primary human monocytes, alpha-1 adrenoceptor stimulation by phenylephrine has been reported to suppress the NLPR3 inflammasome [87]; however, the same drug has been reported to induce cardiac dysfunction and inflammation in vivo as evidenced by increased expression of IL-6 and NLRP3 [195]. Across a variety of stressful situations, increases in EPI levels are associated with elevations of the proinflammatory cytokine IL-6 [41, 84, 90, 96, 100, 135, 141]; however, bases for this relationship have not been systemically studied.

The sources of endogenous DA outside the brain are relatively poorly understood. In the kidneys DA is formed from uptake and decarboxylation of circulating DOPA [190] by proximal tubular cells and acts as an autocrine-paracrine substance [75] that promotes natriuresis [8]. In patients with decompensated congestive heart failure, levodopa treatment increases urinary sodium excretion [77]. Whether intravenously administered DOPA or DA affects the NLRP3 inflammasome is unknown.

Proinflammatory cytokines increase expression of CRH and AVP in the hypothalamus [34], probably via vagal afferents [64]. In critically ill patients, non-survivors have been reported to have higher ACTH levels in response to exogenously administered CRH and longer release of cortisol, associated with higher levels of IL-6 and IL-8 [46].

In the cholinergic anti-inflammatory pathway [182], efferent nerve traffic from the dorsal motor nucleus of the vagus nerve increases delivery of acetylcholine to α7 nicotinic receptor subunits on celiac-superior mesenteric post-ganglionic neurons that terminate in the spleen and act on splenic immune cells to decrease TNFα generation [97, 150].

## Stress and the "stress system"

Hans Selye defined stress as the non-specific response of the body to any demand imposed upon it [161]. In line with Selye's conceptualization, in the 1990s George Chrousos and Philip Gold at the NIH proposed the existence of a central stress system, activation of which would elicit a "stress syndrome" [36, 168]. Key elements of the stress system as originally proposed were the paraventricular nucleus (PVN) of the hypothalamus, from which CRH is derived, and the locus ceruleus (LC) of the pons, from which NE in most of the brain is derived (Fig. 2, left panel). CRH drives pituitary release of ACTH in the HPA axis.

The original Chrousos/Gold stress system has required modification. For one thing, arginine vasopressin (AVP, synonymous with anti-diuretic hormone, ADH) is another neuroendocrine factor derived from the PVN. For another, the LC does not directly drive SNS or SAS outflows; several other brainstem sites do [40, 48, 49, 79, 125]. A more complex schema embeds the stress system within the "central autonomic network" [10] (Fig. 2, right panel). The central autonomic network is the source of outflows to components of the autonomic nervous system, including the SNS, for which NE is the neurotransmitter, the SAS, for which EPI is the hormone, and the parasympathetic nervous system (PNS), for which acetylcholine is the neurotransmitter [70].

Selye also conceptualized the "General Adaptation Syndrome" [160]. By this he was referring to three stages. The stages were alarm, resistance, and exhaustion, and the three pathologic consequences were adrenal enlargement, gastric bleeding, and "involution of the thymico-lymphatic apparatus." The alarm stage is acute and in the present vocabulary would include HPA, SNS, and SAS activation. The resistance stage, which Selye theorized can go on for variable periods of time, is adaptive and may correspond to an allostatic state. Accumulation of allostatic load decreases thresholds for induction of vicious cycles that usher in the exhaustion stage, the harbinger of imminent organismic death.
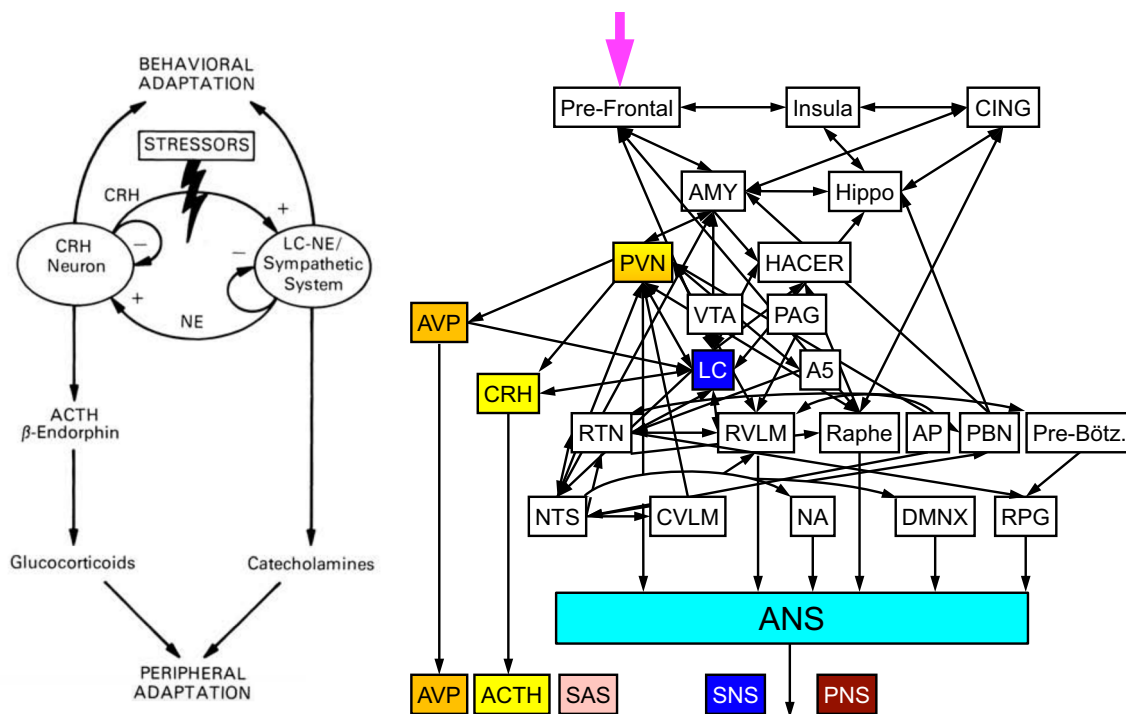
**Fig. 2** Central stress systems. The concept diagram on the left (reproduced with permission of the American College of Physicians) shows the Chrousos and Gold model of "the central stress system." The concept diagram on the right relates the central stress system to the central autonomic network. *CING* cingulate cortex, *AMY* amygdala, *Hippo* hippocampus, *PVN* paraventricular nucleus of the hypothalamus, *HACER* hypothalamic area controlling emotional responses, *AVP* arginine vasopressin (same as anti), *CRH* corticotropin-releasing hormone, *VTA* ventral tegmental area, *PAG* periaqueductal gray, *LC* locus ceruleus, *A5* A5 noradrenergic cell group, *RTN* retrotrapezoid nucleus, *RVLM* rostral ventrolateral medulla, *AP* area postrema, *PBN* parabrachial nucleus, *Pre-Botz.* pre-Botzinger complex, *NTS* nucleus of the solitary tract, *CVLM* caudal ventrolateral medulla, *NA* nucleus ambiguus, *DMNX* dorsal motor nucleus of the vagus nerve, *RPG* respiratory pattern generator, *ACTH* adrenocorticotrophic hormone (corticotropin), *ANS* autonomic nervous system, *SNS* sympathetic noradrenergic system (norepinephrine), *SAS* sympathetic adrenergic system (adrenaline), *PNS* parasympathetic nervous system (acetylcholine)

## Effects of EAS activation

### The sympathetic adrenergic system (SAS)

EPI is a remarkably potent hormone that exerts numerous bodily effects. Most of these are well known, and so only aspects potentially relevant to COVID-19 are noted here. EPI-induced vasoconstriction in the splanchnic bed and kidneys decreases gastrointestinal and renal perfusion. EPI increases sweating [132], and the combination of cutaneous vasoconstriction and adrenergic sweating may explain the "cold sweat" that characterizes people in shock. EPI increases cardiac rate and contractility [121], increasing cardiac output, and increases spontaneous electrical depolarization and the electrocardiographic QTc interval [169].

EPI also increases serum glucose levels [42] by multiple mechanisms, including anti-insulin effects, breakdown of hepatic glycogen, stimulation of hepatic gluconeogenesis [163], and stimulation of pancreatic secretion of glucagon [83].

EPI increases hepatic breakdown of lipids to free fatty acids, generating heat, and evokes thermogenesis via uncoupling protein-1 in brown adipose tissue [179].

EPI activates platelets [122], via occupation of alpha-2 adrenoceptors [103, 104].

EPI stimulates the renin-angiotensin-aldosterone system (RAS) [76]. Angiotensin II is a potent vasoconstrictor and in concert with EPI would be expected to augment splanchnic and renal vascular resistance. Aldosterone, the body's main mineralocorticoid, promotes sodium reabsorption and renal potassium loss.

EPI decreases serum potassium and magnesium levels [42, 129] via augmentation of Na/K ATPases that mediate transmembrane cation influx [9]. The fall in serum potassium may help to explain a dissociation of stimulated plasma renin activity and less clear effects on plasma aldosterone [99].

Finally, EPI intensifies the negative emotional experience of fear [167], probably via afferent information to the brain from physiologic changes exerted by occupation of adrenoceptors.

## The sympathetic noradrenergic system (SNS)

The SNS is tonically active [101] and plays key roles in patterned alterations in the distribution of the cardiac output among the vascular beds during activities of daily life such as standing up [101], eating a meal, mild exercise [158], the Valsalva maneuver, and adjustments to altered environmental temperatures. In addition to the cardiovascular system, SNS outflows to the irises, sweat glands, gastrointestinal tract, and pancreas, and kidneys play important "housekeeping" roles.

It is important to keep in mind that NE is a neurotransmitter, not a hormone. Because of this regional heterogeneity and different roles, measuring plasma NE levels can be uninformative. For instance, in resting humans hypoxia increases skeletal muscle sympathetic outflow without increasing plasma NE [151].

Increases in renal sympathetic outflow promote sodium reabsorption by proximal tubular cells [66]. Both NE and EPI increase cellular uptake of potassium and therefore tend to decrease serum potassium levels [37].

## Arginine vasopressin/anti-diuretic hormone (AVP/ADH)

AVP acting as ADH promotes renal retention of water. In acute illnesses this can manifest with decreased serum osmolality and hyponatremia [59]. AVP acting as a pressor contributes to vasoconstriction and blood pressure; however, the effects may be masked by other determinants of systemic vascular resistance. In addition, in the brain AVP shifts the arterial baroreflex to lower blood pressures, and the maximum amount of sympathetic activation for a given decrease in blood pressure is reduced [85].

## The hypothalamic-pituitary-adrenocortical (HPA) axis

As noted above, the HPA axis has been viewed as the main effector of the central stress system. Regulation of the HPA axis is more complicated than that depicted by Selye's theory or the Chrousos/Gold model. For instance, in critically ill patients there is decreased clearance of circulating cortisol [14, 138]. This may augment negative feedback regulation of CRH and explain attenuated ACTH responses. Studies
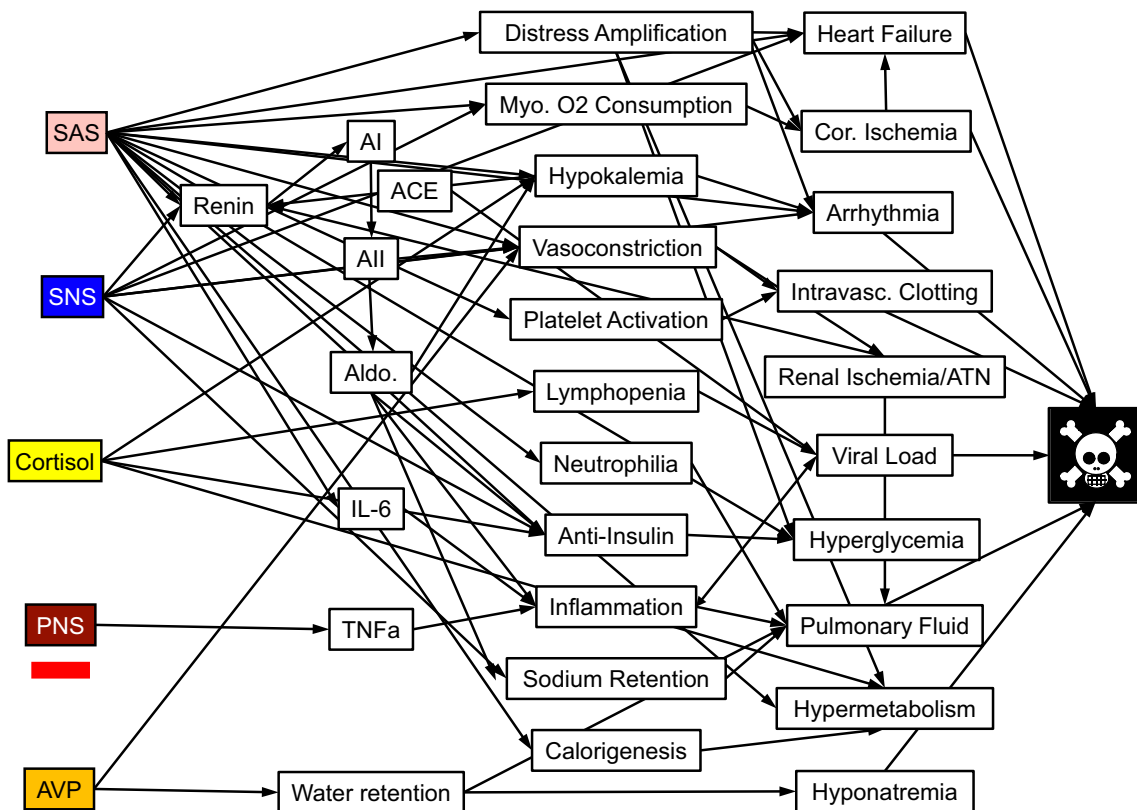


**Fig. 3** From EAS system activation to dyshomeostasis to death. Five effector components of the EAS are on the left. Intervening variables are in the center. Factors contributing the critical illness or death are on the right. The red bar under PNS indicates PNS inhibition. *AI* angiotensin I, *ACE* angiotensin-converting enzyme, *AII* angiotensin II, *Aldo* aldosterone, *ATN* acute tubular necrosis, *IL-6* interleukein 6, *Myo.* myocardial, *Cor.* coronary, *TNFa* tumor necrosis factor alpha

involving real-time dynamics of glucocorticoid hormones and glucocorticoid receptor function indicate pulsatility of the HPA axis and a continuous dynamic equilibrium [111].

In patients treated with intravenous methylprednisolone for multiple sclerosis flareups, there are diverse acute symptomatic side effects, including abdominal pain, nausea, and vomiting, disturbed sleep, and neurobehavioral changes such as confusion, irritability, and restlessness [92]. Common clinical laboratory findings are hyperglycemia, hypokalemia, increased blood pressure, and anti-inflammation. All these aspects may be relevant to neurobehavioral and clinical laboratory abnormalities in COVID-19 because of the frequent use of high-dose steroids as part of management in the intensive care setting.

### The parasympathetic nervous system (PNS)

Unlike other autonomic effectors, the PNS is active in situations that are not distressing and tend to build up rather than use up energy [70]. When the central stress system is activated, PNS outflows generally decrease (red negative sign in Fig. 3). Manifestations of PNS inhibition include tachycardia, decreased gastrointestinal motility, decreased production of saliva and tears, and decreased urinary bladder tone. Vagal stimulation inhibits production of the cytokine TNFα [106, 200].

### The renin-angiotensin-aldosterone system (RAS)

The renin-angiotensin-aldosterone system (RAS) plays major roles in homeostasis of extracellular fluid volume, blood pressure, electrolytes, and immune functions. The main determinants of release of the proteolytic enzyme renin are SNS and SAS activation (acting through beta-a adrenoceptors), decreased renal perfusion, and decreased sodium delivery to the distal tubules of the kidney. Renin cleaves the circulating protein angiotensinogen to form angiotensin I. Angiotensin I is converted to angiotensin II (AII) by angiotensin-converting enzyme (ACE), which is especially abundant in vascular endothelium of the lungs. AII exerts numerous effects. It is a potent vasoconstrictor and augments adrenocortical secretion of aldosterone, the body's main salt-retaining steroid. In adrenomedullary cells AII stimulates secretion of catecholamines via increased cytosolic ionized calcium [203]. In the brain, probably via a separate local RAS, AII evokes AVP release and drinking behavior and increases sympathetic outflows. ACE2, a homolog of ACE, converts AII to angiotensin 1–7 (Ang 1–7), which opposes the effects of AII. Thus, ACE2 inhibition would be expected to build up AII. Relevant to the present discussion, the SARS-CoV-2 virus enters cells via binding to ACE2.

## The EAS and biomarkers of risk, with applications to COVID-19

One of the lessons of the COVID-19 pandemic, and a source of anxiety and worry, is that it seems impossible to predict who among the infected will suffer from rapid evolution to acute respiratory distress syndrome and multi-organ failure. This section describes clinical and laboratory biomarkers that may indicate a high risk of such a transition and are related to altered EAS functions.

There are references here to sudden, unexpected health catastrophes—earthquakes, acute coronary syndromes and stress-related cardiomyopathy (takotsubo cardiomyopathy), and previous viral epidemics (SARS, Middle East respiratory syndrome). To the extent published information is available, each factor is applied to COVID-19.

### Age

Analyses of medical records from before vs. after natural catastrophes such as Hurricane Katrina in 2005 [1, 19] and the 2011 earthquake/tsunami in Japan [39, 131] have indicated disproportionately increased morbidity and mortality among the elderly [118]. This has not been a universal finding, however [183].

The high risk of serious illness or lethality in the elderly from COVID-19 is quite clear. According to the US Centers for Disease Control, hospitalizations, intensive care unit admissions, and case fatality rates are age-related [143]. The case-fatality rate in people 75–84 years old is about 10 times that in people 55–64 years old and about 40 times that in people 20–22 years old.

### Hyperglycemia

Hyperglycemia is a common feature of critical illness, even in individuals without a history of diabetes [65]. In patients with acute, severe head injury, high serum EPI and NE levels have been associated with hyperglycemia, worse Glasgow coma scores, and poor survival [199]. After the Kobe earthquake of 1995, hemoglobin A1c levels and high scores on the General Health Questionnaire were especially evident in diabetic patients who had severe damage to their homes or who had relatives who were killed or injured, indicating long-term effects of the acute stress exposure [88]. After the East Japan earthquake/tsunami in 2011, among diabetic patients followed in a diabetes clinic somatic symptoms and sleep disturbances or anxiety were independently associated with worse glycemic control [60].

In acute coronary syndromes, hyperglycemia upon admission is common regardless of a history of diabetes and is associated with both increased mortality [98] and a variety

of morbidities including ventricular tachycardia/fibrillation, atrial fibrillation, advanced degrees of atrioventricular block, and pulmonary edema [51] and poor outcome after emergency coronary artery bypass grafting [177]. In non-diabetic patients admitted for acute myocardial infarction, concentrations of cortisol, EPI, and NE are the main correlates of circulating glucose concentrations [133]. High glucose levels are an adverse prognostic factor in patients admitting for ST elevation myocardial infarction (STEMI), regardless of the occurrence of diabetes mellitus [162]. Both acute mortality and the subacute event rate are increased in patients with high admission glucose levels [47, 147]. In the pre-hospital phase of cardiac arrest with return of spontaneous circulation, hyperglycemia occurs commonly and is associated with increased mortality [185].

In patients with COVID-19 hyperglycemia at the time of hospitalization is common and related to adverse prognosis [13, 156, 164, 193]. Patients with "new" diabetes noted during the hospitalization have if anything poorer outcomes than those with an already established diagnosis [107].

## Hypokalemia

EPI administration decreases serum potassium levels [169] via agonist effects at beta-2 adrenoceptors [17, 42, 93]. After the Sichuan earthquake in 2008, hypokalemia was associated with ventricular tachyarrhythmias in the ensuing month [202].

In hospitalized COVID-19 patients hypokalemia occurs commonly and is also associated with increased mortality [31]. Low serum potassium may reflect augmented sodium/potassium exchange in the kidneys mediated by aldosterone as well as endogenous and exogenously administered EPI.

## Hyponatremia

Hyponatremia often occurs in critical illnesses [59]. After the Sichuan earthquake of 2008 in Japan and the Bam earthquake of 2003 in Iran there was a high frequency of hyponatremia, and the hyponatremia was an independent mortal risk factor [155, 201]. Among patients with congestive heart failure, ADH levels are increased in a manner associated with hyponatremia [146, 174].

In patients with COVID-19 hyponatremia can be an early or isolated finding [5, 21, 81]. Hyponatremia has been ascribed to inappropriate secretion of ADH [2, 35]. It is unknown whether hyponatremia is an independent predictor of outcome in COVID-19.

## Electrocardiographic Abnormalities

Tachycardia, electrocardiographic changes, and abnormal heart rate variability in the frequency domain occur commonly during catastrophes and in severe illnesses. At the time of the Taiwan earthquake of 1999, 15 patients happened to be undergoing 24-h Holter monitoring, and heart rate variability data were analyzed in the time and frequency domains. Heart rate and the ratio of low frequency/high frequency (LF/HF) power increased after the earthquake and were attributed to PNS withdrawal [112]. After the Great Hanshin Earthquake of 1995, there was an increased frequency of deep negative electrocardiographic T waves and accelerated washout of cardiac $^{123}$I-metaiodobenzylguanidine-derived radioactivity, interpreted as indicating increased cardiac sympathetic outflow [196]. The 2008 Sichuan earthquake was associated with an increased frequency of hemodynamically unstable ventricular tachyarrhythmias [202]. On the other hand, the 2011 Christchurch earthquakes were not associated with increased ventricular arrhythmias, based on analysis of implanted defibrillator diagnostics [30], while in the same year, after the East Japan earthquake there was an increased incidence of tachyarrhythmias in patients with implanted cardiac devices [128]. After the East Azarbaijan earthquake in 2012 there was a reported increased likelihood of arrhythmic events associated with anxiety in patients with implanted defibrillators [145].

In stress-related acute heart failure, prolongation of the QTc interval occurs regardless of left ventricular apical ballooning [188] (see the section below about takotsubo cardiomyopathy).

EPI increases the electrocardiographic QTc interval [42, 169]. In acute stroke, the most common new electrocardiographic abnormality is QTc prolongation [20, 69].

In hospitalized patients with COVID-19 several studies have noted prolongation of the QTc interval; however, interpreting this abnormality has been difficult because of the possibility of iatrogenicity from treatment with chloroquine or hydroxychloroquine [95]. No studies have reported on power spectral analysis of heart rate variability, in either the time or frequency domains. There are numerous mechanisms by which SNS or SAS activation could precipitate cardiac arrhythmias [50]. None of these has been explored specifically in COVID-19-related research.

## Immune functions

Central stress system activation would be expected to produce lymphopenia from HPA axis stimulation. Neutrophilia may reflect effects of glucocorticoids [181] or catecholamines. In healthy volunteers adrenaline infusion acutely evokes leukocytosis, neutrophilia, and lymphocytosis and increases the activity and numbers of natural killer cells [181]. The effects of circulating catecholamines depend on the types of occupied adrenoceptors. Adrenaline, which stimulates both types of adrenoceptor, results more in beta-adrenoreceptor-mediated effects [11].

By now it has been widely publicized and generally accepted that COVID-19 patients are variably susceptible to "cytokine storm." Bases for this variability are unknown. In asymptomatic individuals with COVID-19 there seems to be less active immune responses than in symptomatic individuals [115]. It has been reported that within 19 days of symptom onset, all patients test positive for antiviral immunoglobulin-G (IgG) [114]. These findings suggest that symptomatic patients have more active immune responses.

COVID-19 patients have been reported to have lymphopenia [55, 113], related to decreases in natural killer cells and T cell populations [45]. The numbers of total T cells and CD4(+) and CD8(+) T cells are dramatically reduced, associated with increased serum IL-6, IL-10, and TNF-alpha concentrations and poor survival [45]. Meanwhile, there tends to be neutrophilia [113, 192] and increased neutrophil extracellular traps (networks of extracellular fibers mainly containing neutrophil DNA that bind pathogens), associated with increased COVID-19 mortality [180].

## Heart failure

### Dyshomeostasis and heart failure

As intrinsic cardiac pumping efficiency declines, the SNS is activated [89, 119, 178]. At first, the increase in SNS outflow seems to be confined to the heart [153]. Once cardiac pump function declines to below a certain level despite maximal SNS stimulation, blood backs up into the pulmonary veins, bringing on pulmonary edema. The patient becomes short of breath, and in a distress response experiences the classic "feeling of impending doom" that has been associated from time immemorial with massive activation of the SAS and high circulating EPI levels. Rather than augmenting left ventricular myocardial contractility, EPI can be toxic to myocardial cells. Myocardial contractility could decrease further, and "stress cardiopathy" could set in, worsening the pulmonary edema.

Low LF power is an independent predictor of sudden death in heart failure patients [63]. LF power seems to be less of a marker of cardiac sympathetic outflow than of the ability to modulate that outflow via baroreflexes [72, 144, 166]. Therefore, the absence of LF power in severe heart failure may represent baroreflex failure. Whether severely ill COVID-19 patients have low LF power is unknown.

### Stress-related cardiomyopathy

A particular type of acute heart failure involving non-ischemic myocardial stunning [189] has been called takotsubo cardiomyopathy [94], because left ventricular apical ballooning in this syndrome gives the radiographic appearance of a *takotsubo,* a type of Japanese pottery for catching octopuses. Takotsubo cardiomyopathy is especially common in post-menopausal women, for unknown reasons. Heart failure with apical akinesia can occur in disorders involving high circulating levels of catecholamines such as pheochromocytoma [62].

After the 2004 Niigata earthquake, two patients were reported who had takotsubo cardiomyopathy [175]. Both had stress-associated chest pain, giant T waves in the electrocardiogram, and echocardiographic apical hypokinesia, without evidence of coronary artery disease during cardiac catheterization. Both patients had accelerated loss of $^{123}$I-metaiodobenzylguanidine-($^{123}$I-MIBG)-derived radioactivity, consistent with increased sympathetically mediated exocytosis from myocardial sympathetic nerves. After the 1995 Hanshin earthquake, there was an increased incidence of patients with deep negative T waves, also associated with accelerated loss of $^{123}$I-MIBG-derived radioactivity [196]. After the 2011 East Japanese earthquake/tsunami there was an increased incidence of acute decompensated heart failure in the affected geographic region [127]. The frequency of atrial fibrillation was also increased [126]. Patients admitted to the hospital after the earthquake were characterized by older age, systolic hypertension, infection, increased B-type natriuretic peptide and C-reactive protein (respective biomarkers of heart failure and inflammation), and decreased glomerular filtration rate [197].

In COVID-19 patients heart failure is a major concern. Patients with pre-existing cardiovascular disease are more likely to be infected with SARS-CoV-2 and are more likely to develop severe symptoms. There are several potential mechanisms. Myocarditis can result directly from local infection with SARS-CoV-2 and the local immune response [165]. ACE2 receptor disruption may cause damage by preventing conversion of AII to Ang (1–7) [7]. Toxic effects of endogenous or exogenous catecholamines may evoke a takotsubo cardiopathy pattern [67, 120, 123, 136, 148]. There may be endothelial or microvascular dysfunction or instability of coronary arterial plaque [80].

In heart failure cardiac NE stores become depleted [32]. This is likely from greater NE release with escape of neuronal reuptake compared to catecholamine biosynthesis via tyrosine hydroxylase [53]. The depletion of NE stores in the failing human heart attenuates the ability of indirect-acting sympathomimetic amines to provide inotropic support [142].

## Intravascular clotting

In the COVID-19 pandemic there has been an unexpectedly high frequency of intravascular clotting, manifested by deep vein thrombophlebitis, pulmonary embolism, myocardial infarction, or stroke. It has been proposed that an imbalance between coagulation and inflammation results in

a hypercoagulable state. Thrombosis initiated by the innate immune system may limit SARS-CoV-2 dissemination, but aberrant activation of this system could cause endothelial injury, with dysregulation of fibrinolysis and thrombosis [38]. The roles of neutrophilia, neutrophil extracellular traps, platelet activation, and proinflammatory cytokines are a subject matter of active investigation and ongoing clinical trials.

One should bear in mind that adrenaline is a potent hemostatic agent, not only because of vasoconstriction but also because of promotion of platelet aggregation [104, 122], at least partly via agonism at alpha-2 adrenoceptors [4, 103]. Whether this contributes to intravascular clotting in COVID-19 is unknown.

### Central nervous system

COVID-19 is associated with a variety of central nervous system abnormalities, including stroke, encephalopathy, encephalitis, anosmia, anorexia, headache, nausea, and delerium [184]. A meta-analysis of literature from prior epidemics (SARS, Middle East respiratory syndrome) noted high frequencies of confusion, depressed mood, anxiety, impaired memory, and insomnia [149]. It has been proposed that the SARS-CoV-2 virus may invade the brainstem and alter functions of medullary cardiorespiratory centers [110].

In patients with Parkinson's disease COVID-19 worsens motor and non-motor symptoms, with urinary abnormalities and fatigue being prominent [110]. In this study symptoms and signs one might ascribe to autonomic failure were unaffected. Serum neurofilament light chain levels, a biomarker of axonal damage, have been reported to be increased in COVID-19 patients [116]. Although patients with increased serum neurofilament light chain levels have been reported to be more likely to require intubation, the levels seem unrelated to neurologic symptoms.

There have been no reports about brain regions or pathways of the central autonomic network in COVID-19, although one may reasonably speculate that involvement of the medullary nucleus of the solitary tract or dorsal motor nucleus of the vagus nerve predisposes to symptoms such as nausea, vomiting, and loss of appetite [33].

The dysautonomia postural tachycardia syndrome (POTS) can be a consequence of viral illnesses [56, 157] and may have an autoimmune component [78, 108, 154]. There are substantial concerns—but no published data—about possibly increased risk from COVID-19 in people with POTS. Conversely, one may anticipate an increased incidence of POTS in COVID-19 patients.

One may also anticipate a high frequency of post-traumatic stress disorder [57, 194], which could be related to EAS activation [140].

## EAS activation in COVID-19 may be a double-edged sword

The direct and indirect effects of EAS activation can be understood in terms of enhancing survival in life-threatening emergencies that have threatened homeostasis throughout mammalian evolution, such as asphyxiation, hemorrhage, starvation, salt deprivation, water deprivation, exposure to extremes of temperature, and "fight-or-flight" encounters [24, 25].

This activation may come at a cost. Among other things, activation of the extended ANS increases myocardial oxygen consumption and glucose levels, uses up energy, decreases thresholds for arrhythmias, induces hypokalemia and hyponatremia, can promote renal ischemic injury and intravascular thrombosis, and can evoke a form of stress cardiopathy [189]. Moreover, imbalances in the inflammasome system could contribute to cytokine "storm."

In several ways, in critically ill patients physiologic negative feedback loops could give way to pathophysiologic positive feedback loops. Within a sometimes surprisingly short period of time from the onset of symptoms, the patient could die—within minutes because of a catecholamine-evoked ventricular arrhythmia, hours because of intractable pulmonary edema, or days because of critically decreased perfusion of body organs such as the kidneys.

## Biomarkers predicting COVID-19 mortality

Hyperglycemia, hypokalemia, hyponatremia, prolongation of the electrocardiographic QTc interval, arrhythmias, hemodynamic instability, takotsubo cardiopathy, and neurobehavioral manifestations suggest contributions of the EAS to morbidity and mortality in COVID-19; however, all these indices are indirect and complexly determined.

Quantitative indices of EAS activation such as increases in plasma catecholamines, ACTH, AVP, and AII levels could provide valuable biomarkers by which to test whether EAS involvement explains the high mortality associated with aging and chronic disorders of regulation in COVID-19. To date, no reports have described levels of any of these compounds in COVID-19 patients. A recent correspondence noted associations of both elevated neutrophil/lymphocyte ratios and cortisol levels with decreased survival in COVID-19 patients [176].

## Treatment implications

In COVID-19 patients who have evidence of EAS activation, treatment with already existing drugs such as the benzodiazepine alprazolam [15, 86], the CRH-1 receptor antagonist antalarmin [6], the alpha-2 adrenoceptor agonist

dexmedetomidine [109, 187], a beta-1 adrenoceptor blocker, an IL-6 inhibitor (tocilizumab), or even DOPA or DA might prevent positive feedback loops and improve survival. Some of these are undergoing clinical trials now.

Given that adrenaline promotes platelet aggregation, treatment with dexmedetomidine might be risky in COVID-19 patients with intravascular clotting.

DA, via the type-1 DA receptor-1 (DRD1) and cyclic AMP signaling, inhibits the NLRP3 inflammasome [198]. This introduces the possibility of modulating cytokine "storm" by a DRD1 agonist. Fenoldopam is a catechol-containing DRD1 partial agonist that does not cross the blood-brain barrier. The drug also exerts vasodilator effects in coronary, renal, mesenteric, and peripheral arteries and is used intravenously clinically as an anti-hypertensive agent. The sulfonylurea oral hypoglycemic drug glyburide is a NLPR3 inhibitor [186]; however, effective doses may be high enough to produce cardiovascular side effects.

In patients with sepsis or acute respiratory distress syndrome, high-dose corticosteroid administration does not improve survival; however, low doses of corticosteroids alleviate inflammation and improve survival [29]. A recent news report noted that dexamethasone substantially improved mortality in COVID-19, without reference to a peer-reviewed publication [105].

A randomized, blinded, healthy control pilot trial of non-invasive transcutaneous vagal stimulation reported down-regulation of inflammatory cytokine release [106]. Clinical trials of non-invasive vagal stimulation in COVID-19 are currently under way (NCT04382391, NCT04379037).

# Conclusions

Concepts presented here such as the EAS, allostasis, and dyshomeostasis can account for the age-relatedness of COVID-19 mortality and the multi-organ involvement in the disease. These concepts lead to testable hypotheses about biomarkers of risk in COVID-19 and about possible treatments. Ideas are cheap and easy; data are expensive and hard, and the science of COVID-19 and the autonomic nervous system is in its infancy.

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