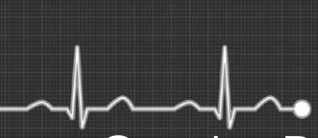

Concise Definitive Review

Slowing Down of Recovery as Generic Risk Marker for Acute Severity Transitions in Chronic Diseases

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Objective: We propose a novel paradigm to predict acute attacks and exacerbations in chronic episodic disorders such as asthma, cardiac arrhythmias, migraine, epilepsy, and depression. A better generic understanding of acute transitions in chronic dynamic diseases is increasingly important in critical care medicine because of the higher prevalence and incidence of these chronic diseases in our aging societies.

Data Sources: PubMed, Medline, and Web of Science.
Study Selection: We selected studies from biology and medicine providing evidence of slowing down after a perturbation as a warning signal for critical transitions.
Data Extraction: Recent work in ecology, climate, and systems biology has shown that slowing down of recovery upon perturbations can indicate loss of resilience across complex, nonlinear biologic systems that are approaching a tipping point. This observation is supported by the empiric studies in pathophysiology and controlled laboratory experiments with other living systems, which can flip from one state of clinical balance to a contrasting one. We discuss examples of such evidence in bodily functions such as blood pressure, heart rate, mood, and respiratory regulation when a tipping point for a transition is near.
Conclusions: We hypothesize that in a range of chronic episodic diseases, indicators of critical slowing down, such as rising variance and temporal correlation, may be used to assess the risk of attacks, exacerbations, and even mortality. Identification of such early warning signals over a range of diseases will enhance the understanding of why, how, and when attacks and exacerbations will strike and may thus improve disease management in critical care medicine. (*Crit Care Med* 2016; 44:601–606)
Key Words: critical slowing down; nonlinear dynamics; recovery of function; resilience

In critical care medicine, the management of acute episodes in chronic disease trajectories is an increasingly dominating patient care. There are several patterns of such acute transitions in the natural course of chronic noncommunicable diseases, of which the most frequently occurring are the following: chronic diseases with episodic attacks and interictal periods without symptoms, such as cardiac arrhythmias, epilepsy, bipolar disorder, and migraine, and slowly progressive chronic diseases with (sub)acute worsening, such as chronic obstructive pulmonary disease with (sub)acute exacerbations of bronchial obstruction. The tipping point concept of acute changes in disease states, probably, is most clearly seen in the acute onset of epileptic episodes, frequently "triggered" or "tipped" by external stimuli, setting off electroencephalographic (EEG) changes, and a characteristic tonic-clonic movement pattern. These acute epileptic changes in EEG, together with the acute cardiac rhythm transitions in EEG, are the clearest examples of the dynamic rhythms with tipping points in critical care medicine. In a wide range of complex systems, slowing down of recovery rates following a perturbation has been hypothesized as a generic early warning signal for critical transitions signaling the proximity of a tipping point, independent of the specific underlying mechanism (1). Although exceptions exist (2), a growing series of empiric studies have confirmed indicators of critical slowing down in complex systems, ranging from controlled living systems in the laboratory to full-scale ecosystems such as lakes and nonlinear physical systems such as the climate (3–7). Arguably, human diseases are analogous to such complex systems in the sense that they can go through critical shifts between alternative states, resulting from self-propagating positive feedback mechanisms. Indeed, there are a number of striking similarities in warning signals for impending attacks or exacerbations in chronic episodic disorders. For example, 1) in syncope and orthostatic blood pressure fall, a slower recovery after changing from supine to standing position predicts future mortality in patients (8, 9) and 2) increased slowness of mood fluctuations predicts a shift from healthy to depressed mood, which ultimately may also result in suicidal ideation and critical care interventions (10). 3) Similarly, increased minute ventilation recovery time following spontaneous breathing trials has been shown to be predictive for failure of extubation and closeness to the tipping point of again being dependent on mechanical ventilation (11–14). This is an example of predictive evidence for slowing down of recovery following an artificial perturbation in a chronic treatment. Probably, the best known example of resilience measured by the time needed for recovery in normal physiology is the time needed for recovery of heart rate following strenuous exercise. Exercise increases the metabolic needs of the skeletal muscle while necessitating a stable blood flow to critical tissues such as the heart and brain. Therefore, sympathetic activity predominates over vagal tone to increase heart rate and cardiac output, and blood flow to visceral areas is reduced and directed to the skeletal muscles. This quickly increases heart rate up to the maximum heart rate at maximum aerobic capacity. When exercise is stopped, the sympathetic output is reduced and vagal tone increased, leading to a decrease in heart rate and peripheral resistance, which also causes a reduction in cardiac output and systolic blood pressure (SBP), with a rapid return to resting levels. For more than 30 years, it is known that shortening of recovery time of heart rate following exercise is a valid measure of cardiac fitness, whereas slowing down of heart rate recovery is seen in declining fitness or following myocardial ischemia (15).

Although the disease mechanisms differ widely, the common finding in the above-mentioned conditions, and many other disease states, is that the risk of acute transitions is associated with slowness of restoration of the former physiologic balance condition after perturbations (**Table 1**).

OBJECTIVE

The aim of this article is to put forward a generic hypothesis that may be support progress in critical care medicine by enabling quantification of the patient's risk of approaching tipping points of acute transitions in chronic diseases to their alternative severe disease states or death. This quantification may be carried out by measuring the recovery rates in physical, physiologic, or mental parameters following small perturbations in bodily or mental functions. *The hypothesis* we put forward here is that by measuring recovery rates in physical or psychologic parameters during recovery to the previous equilibrium state following small perturbations in bodily or psychologic functions, we can quantify the risk of approaching tipping points of acute transitions in chronic diseases to their alternative severe disease states or death. These perturbations can be caused by naturally occurring random stressors or by stress tests.

TABLE 1. Examples of Chronic Dynamic Diseases With Acute and Reversible Transitions of Increased Disease Activity

System	Disease	Transitional State
Chronic diseases with attacks or exacerbations alternating with periods of relative freedom of symptoms		
Brain (neurologic disease)	Epilepsy	Seizures (various types)
	Migraine	Migraine attack
	Cluster headache	Cluster headache attack
	Narcolepsy	Sleep attacks
	Trigeminal neuralgia	Attacks of facial pain
Brain (psychiatric diseases)	Bipolar mood disorder	Depressed or manic episode
Nerve-muscle	Periodic paralysis	Systemic paralysis
Heart	Paroxysmal atrial fibrillation	Atrial fibrillation state
	Long QT syndrome	Torsade de pointes
Chronic diseases with exacerbations and episodes with limited symptoms		
Brain (neurologic disease)	Multiple sclerosis	Relapse (sometimes reversible)
Brain (psychiatric diseases)	Schizophrenia	Psychotic episode
	Major depression	Depressed state
Renal system	Chronic renal failure	Fluid volume disturbances
Cardiovascular system	Heart failure	Acute cardiac decompensation
	Chronic autonomic failure	Syncope
Lungs	Asthma	Asthma attack
	COPD	COPD exacerbation
	Sleep apnea syndrome	Apnea episode
	Cheyne-Stokes respiration	Cheyne-Stokes breathing
Hematologic system	Periodic chronic myeloid leukemia	Periodic leukocytosis
Immune system	Familial Mediterranean fever	Fever episode
Gastrointestinal system	Crohn disease	Relapse of inflammation
	Ulcerative colitis	Relapse of inflammation
	Irritable bowel syndrome	Attacks of abdominal pain
	Remittent bacterial overgrowth	Episodes of *Clostridium difficile*

COPD = chronic obstructive pulmonary disease.

EVIDENCE ON GENERIC EARLY WARNING SIGNALS

Transitions in complex systems can occur when conditions pass a critical threshold, which is commonly called a tipping point. In mathematics, tipping points are modeled to explain how qualitative behavior of a disease system can change, in response to a tiny change in an internal (e.g., physiologic) or exogenous parameters. We explain the terms frequently used in this modeling in **Box 1** (16, 17). Although numerous studies have proposed mathematical models for dynamic transitions associated with disease (3), progress in developing early warning signals of dynamic transitions in disease is still slow. However, recent identification of generic warning signals for a class of tipping points in other domains suggests a scope for novel approaches in critical care medicine. In the vicinity of such a tipping point, the return time to the homeostatic condition upon a perturbation becomes increasingly longer, a phenomenon known as critical slowing down (4–7). This can be understood intuitively from stability landscapes of a dynamic system that can shift between alternative stable states (**Fig. 1**). The simplest way to measure critical slowing down is to analyze the response to (experimental) perturbations (**Figs. 1, *C*** and ***E***; and **2**). Alternatively, it can be inferred from increased correlation of physiologic parameters over time and increased heterogeneity in the fluctuation of such parameters, driven by its slower response to the natural occurrence of perturbations (**Figs. 1, *D*** and ***F–H***, and **3**). For human physiology and other biologic systems that naturally fluctuate strongly, either because of external stressors happening by chance or because of internal physiologic changes, critical slowing down is not expected to indicate the risk of upcoming transitions. Instead, such a system may show "flickering" (3, 18, 19), as it erratically briefly visits the alternative state before permanently shifting to it. Flickering might be a relevant warning signal in some "dynamic disorders" (2), characterized by changes of qualitative dynamics (e.g., emergence of a regular oscillation as in Cheyne-Stokes respiration or an irregular rhythm as in chronic granulocytic leukemia). For instance, paroxysmal atrial fibrillation may be interpreted as flickering in the period before chronic atrial fibrillation. In the remainder of this article, we will focus on critical slowing down as a potential indicator of an imminent acute transition between stable states in physiologic systems.

Empiric evidence consistent with the hypothesis that slowing down indicates the proximity of a tipping point has been shown in a range of complex systems (**E-Appendix Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B622). Although a significant amount of work, directed at detecting risk factors

BOX 1. Terms Used in Relation to the Generic Early Warning Signals of Slowing Down of Recovery

Alternative stable states: Contrasting equilibrium states to which a system may converge under the same external conditions.

Critical slowing down: The tendency that the recovery rate in physiologic or psychologic parameters following disturbances by external stressors decreases when patients get closer to a tipping point of critical transitions (e.g., attacks or exacerbations in their chronic diseases).

Critical transition: The change that occurs when the condition of a patient exceeds the tipping point, which transfers the patient from one health state (set point) to another, clinically mostly observed as a disease attack or exacerbation.

Dynamic disease: A disease that occurs in an apparently intact control system (e.g., respiratory rhythm control) operating in a range of control parameters (e.g., abnormally long circulatory delays) that leads to abnormal dynamics (e.g., Cheyne-Stokes respiration).

Early warning signals: Variables that change in characteristic ways, prior to critical transitions. A full description can be found at: http://www.early-warning-signals.org. In this article, we discuss slowing down of recovery from perturbations, increased autocorrelation, increased variance, and flickering as generic early warning signs.

Equilibrium: Situation in which processes that affect the state of a patient precisely balance out so that the condition of a patient does not change.

Feedback loop: Set of cause-effect relationships that form a physiological closed loop. Multiple negative or positive feedback loops normally operate in parallel or hierarchically to maintain physiological parameters in normal ranges (i.e., "homeostasis").

Frailty: A state of increased vulnerability of patients or organs to poor resolution of homeostasis following a stress, which increases the risk of change to another set point, often an adverse outcome for patients, including seizures, falls, syncope, and depression (frailty is the opposite of resilience).

Resilience: Capacity of a patient to return to its normal state of homeostatic control upon a perturbation (the opposite of frailty).

Tipping point: Critical threshold that marks the border of a subject's homeostatic equilibrium. Exceeding the tipping point results in abrupt change from one (e.g., symptom free) health state to another (less favorable) disease state or vice versa.

and warning signals for disease, has identified abnormal temporal features of physiologic function as conferring a higher risk of acute transitions for specific diseases (**E-Appendix Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B622), it has been difficult to transfer these associations into useful clinical markers. For a more classical discussion of early warning signs and risk prediction for epilepsy, see the article by Frei et al (20), and for sudden cardiac death, see the article Goldberger et al (21). No single technique has emerged so far as the most promising risk prediction measurement (21). However, recent studies using metrics suggested by the current hypothesis suggest potential benefits of this new approach for clinical studies and clinical practice (10, 22, 23). This is in line with the concept that the human physiologic system consists of an interacting network of regulatory systems compensating for external or internal stressors until a tipping point has been reached. Most recently, this resulted, for example, in the finding that quantitative measures of intervals between heartbeats (i.e., the so called "slope of the return") are early warning signals for transitions to abnormal alternating cardiac rhythms, even in noisy cardiac systems (24).

EXAMPLES OF GENERIC EARLY WARNING SIGNALS IN HUMAN DISEASES

In the next three paragraphs, we will explain the possible mechanisms for slowing down in human diseases approaching acute exacerbations by using the three different examples pointed out earlier. First, we will discuss slowing down of recovery of blood pressure, next normalization of mood following perturbations, and finally weaning of from artificial ventilation.

Regulating blood pressure involves cardiovascular, autonomic, neuroendocrine, renal, and neuropsychiatric feedback loops, which compensate for changes due to, for example, orthostatic maneuvers such as getting out of bed, eating (postprandial stress), or exercise to prevent passing the tipping point toward fainting or even ischemic stroke. In case of heart failure or autonomic failure, blood pressure is one of the system's most relevant set points for which the stabilizing effects may progressively fail. External factors such as antihypertensive drugs may also have nonlinear (pharmacodynamic) interactions with feedback loops involved in blood pressure regulation. In patients with syncope or orthostatic hypotension, those who show slow recovery of blood pressure in the first minute after standing up from a supine position are at increased mortality risk supporting the hypothesis that slowing down of recovery can signal closeness to a tipping point (Fig. 2) (8, 9). Frail patients have a longer recovery time in blood pressure regulation (8, 9). Similarly, a slow rise in blood pressure following exercise is associated with a five-fold increased risk of ischemic stroke, whereas the maximum SBP response after exercise is not a risk factor (25).

The second example relates to psychiatric disorders, which can be seen as the result of feedback mechanisms in a network of interacting symptoms (10, 26, 27). For example, in a severely depressed mood, patients are less likely to engage in social contacts or physical exercise. This in turn reduces the likelihood of having positive emotions and hinders mood improvement. In some persons, such feedback mechanisms may be strong enough to divide the depressed and normal mood condition as two alternative stable states separated by tipping points. Here, indications of critical slowing down do not come from experimental perturbations but from time series of self-reported mood variables such as "cheerful" and "sad" (10). Slowing down in systems subject to a natural regime of perturbations results in elevated temporal correlation and variance (Fig. 1). Indeed, these indicators were associated with elevated risk of future

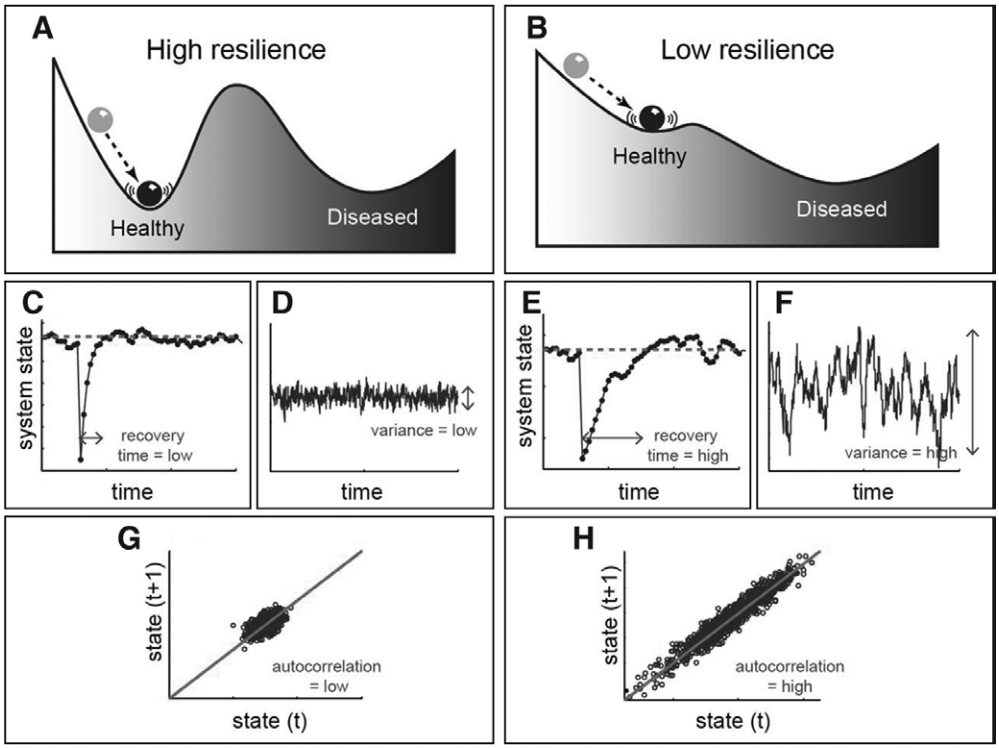

Figure 1. Mathematical model of homeostatic dynamics of a patient approaching a tipping point. Critical slowing down is a generic indicator that the patient has lost resilience in the sense that the patient may shift more easily from his current "healthy" state into an alternative "diseased" state. The patient (represented by the *ball* in the stability landscape in (**A**) and (**B**) can be in a diseased state (e.g., in a major generalized depression) and in a more healthy state (e.g., in a healthy mood state). Far from the tipping point, the patient is highly resilient, and perturbations will not easily flip the subject out of the basin of attraction to the alternative diseased state (A). Changes in conditions (e.g., drug application, stress, and comorbidity) can lower resilience and shrink the basin of attraction (B), so that a perturbation can more easily flip the patient into the severe disease state. As the basin of attraction becomes smaller, its slopes become less steep, implying that the return rate to equilibrium upon small perturbations slows down. Recovery time after a small perturbation is higher (**E** vs **C**) if the patient is closer to the tipping point. The effect of this slowing down can also be measured as (**F** vs **D**) increased variance in randomly induced fluctuations in the current state of the patient, caused by small external stressors, and (**H** vs **G**) in increased "memory" or increased (lag-1) autocorrelation between the serial measurements when the disease state is moving toward its tipping point.

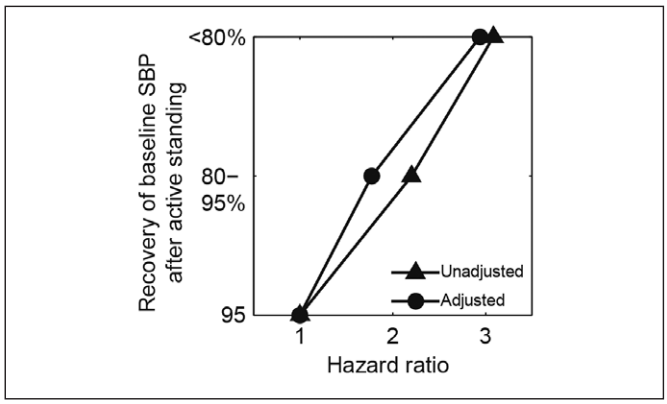

Figure 2. Slowing down in recovery patterns of systolic blood pressure (SBP) after active standing maneuvers. Cox proportional hazards ratios for all-cause mortality unadjusted and adjusted for age, gender, body mass index, comorbidity, SBP, diastolic blood pressure, heart rate, calcium channel blockers, and anti-Parkinson medication use at baseline in frail older subjects ($n = 238$). Mortality is presented for patients ($n = 95$) with a quick (> 95%) recovery of their baseline SBP within 1 min after active standing, for the intermediate recovery group (80–95% in 1 min; $n = 98$), and the slow recovery group (< 80% in 1 min; $n = 45$). Both upward trends of the unadjusted and adjusted model are significant ($p < 0.05$). Reproduced from Lagro et al (9).

transitions between a healthy and a depressed mood (Fig. 3). The link between critical slowing down and increased temporal correlation is intuitively straightforward. For instance, in persons who are close to the tipping point for falling into a major depression, recovery of mood upon stressful events is slow, and this results in increased autocorrelation of mood statements on subsequent moments. In critical care medicine, these warning signals for acute transitions in chronic disease may also resemble the measures that predict transitions in different treatment states, such as the condition of being artificially ventilated, versus being successfully weaned off. Numerous studies have been carried out to define the best predictive measures of this acute treatment transition, which plays a key role in everyday critical care medicine (11–14). The normalizing response to spontaneous breathing trials seems one of the best predictors, but there is no consensus on the exact response measure to be used in analyzing the breathing response (12). Consequently, there also is no consensus on a single gold standard in monitoring and guiding extubation. The common ground between the predictions in these two disease domains and the treatment trajectory of mechanical ventilation is given by the multiple feedback loops that stabilize each disease or treatment state.

CONCLUSIONS

A large number of theoretical studies and computational simulations have been carried out to provide evidence for critical transitions in many complex biologic systems (28, 29). Our data synthesis illustrates that loss of resilience and elevated risk of acute severity transitions in human diseases may be announced by symptoms of critical slowing down, just as in other complex nonlinear systems. The ability to anticipate such transitions could prove beneficial in terms of adding, dosing, and monitoring of new treatments (8, 10, 22–24, 29). Available toolboxes can be used to detect slowing down signals on medical data (an R statistical package is available and updated versions can be found via the **E-Appendix** "Toolbox" [Supplemental Digital Content 1, http://links.lww.com/CCM/B622], which are fully explained and available as open

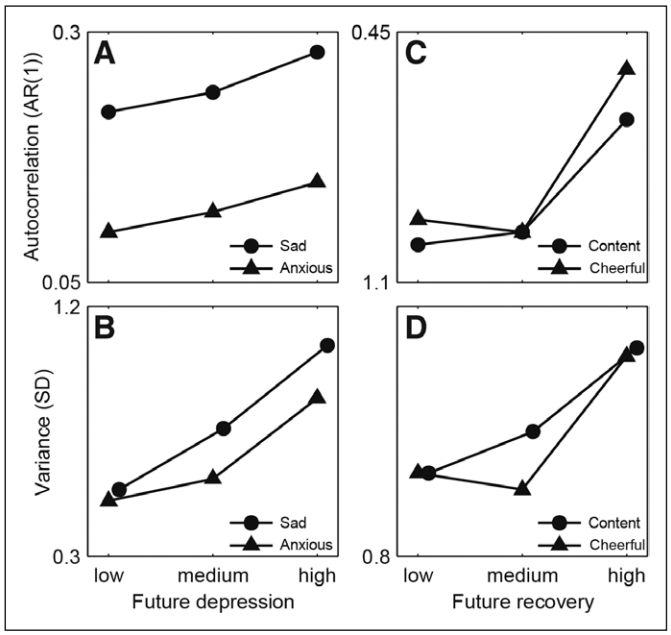

Figure 3. Early warning signs for depression and recovery in time series of self-assessed emotions. Increasing (**A**) autocorrelation (AR (1) = mean lag-1 autoregression coefficient, related to the first subsequent time point) and (**B**) variance (SD) of negative emotions are related to the development of future depressive symptoms in a general population ($n = 535$). Increasing (**C**) autocorrelation and (**D**) variance of positive emotions are related to the development of future recovery in a depressed population ($n = 93$). All upward trends are significant ($p < 0.05$). Reproduced from van de Leemput et al (10).

access [30]). Ultimately, the observation of slowing down of recovery and related warning signals could improve critical care management for acute severity transitions in chronic diseases based on better understanding of their complex disease dynamics.

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