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Sublimation-like Behavior of Cardiac Dynamics in Heart Failure: A Malignant Phase Transition?

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Abstract

An abrupt transition from sinus cardiac rhythm to atrial fibrillation (AF) is common in patients with chronic heart failure (CHF). We propose a conceptual framework for viewing this malignant transition in terms of a type of sublimation marked by the switch from highly periodic sinus interbeat interval dynamics characteristic of CHF to a state of random disorganization with AF. Sublimation of physical substances involves an increase in entropy via heat transfer. In contrast, the disease-related sublimation-like behavior involves a loss of information content, associated decreases in cardiac bioenergetic capacity and in multiscale entropy.

Keywords

atrial fibrillation; entropy; heart failure; phase transition; sublimation

1. Introduction

The concept of phase transitions is fundamental to thermodynamics and to understanding the nature of alterations in purely physical states. Relatively abrupt transitions between dynamical “states” are also ubiquitous in biologic systems. Some are integral to healthy physiology. Consider chronobiologic wake-sleep-wake cycles, as well as switches in intra-sleep dynamics associated with dreaming (REM) and non-dreaming (non-REM) states. Phase transition models have also been proposed in understanding the sudden switching from one mode of behavior to another at a distinct (“critical”) frequency in human motor system control [1,2]. At a more basic level, such models have been invoked to explain the emergence of molecular self-assemblies necessary for higher order cytoplasmic organization [3] and other bimolecular changes.

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At a different level of organization are abrupt pathologic events, often leading to death of the organism. Perhaps the most dramatic example is the unanticipated onset of ventricular fibrillation causing sudden cardiac arrest. The relevance of the paradigm of physical phase changes to pathophysiologic transitions is not well established. The goal of this brief communication is to suggest that principles underlying classical phase transitions may have applications to understanding instabilities in biological dynamics. Specifically, we focus on the breakdown of cardiopulmonary interactions reminiscent of those occurring with sublimation. To our knowledge, the possible relevance of sublimation-like behavior to conceptualizing a specific, malignant change in cardiac interbeat interval dynamics has not been previously explored.

Toward this end we seek to address two interwoven sets of questions: 1) What does the physical transition termed *sublimation* have to do with cardiac interbeat interval dynamics in health and disease? 2) How does the purported sublimation-like behavior of the heartbeat relate to classical (single) scale entropy and to more recently proposed multiscale concepts of entropy and of biologic complexity?

In pursuing these questions, we broaden the concept of sublimation beyond its traditional definition of a direct change in physical organization from solid to gas due to heat transfer into a system. The physiologic loss of organization we describe appears related to information transfer out of a system. Furthermore, the specific type of sublimation-like behavior we discuss occurs not (just) with physical (structural) changes, but with the temporal change from a pathologically structured (“lattice-like”) pattern of sinus rhythm heartbeat dynamics to the disorganized (“gas-like”) fluctuations of atrial fibrillation (AF). The onset of this arrhythmia is almost invariably associated with further worsening cardiac status.

1.1. Basic Considerations: Classic Phase Changes

The three most accessible states of matter are solid, liquid and gas. (We omit plasmas from this discussion, as well as amorphous transitions such as liquid to liquid sub-states.) Structural rigidity and the resistance to change in shape or volume characterize the solid phase in which atoms or molecules are tightly bound and arranged in an orderly, repeating pattern (e.g., crystalline lattices). In the liquid phase, the components are less tightly bound, giving the substance the capacity to flow, either in a laminar or turbulent way. The gaseous phase differs from the other two by the vast separation of the individual particles, which have random, uncorrelated motions. The discontinuous transformation of a system from one state to another defines a phase transition [4]. Sublimation constitutes the transformation from solid to gaseous phases. For example, in the case of solid water (ice), sublimation refers to its direct transformation into water vapor, without passing through the liquid phase [5]. This change, as noted above, involves the transfer of heat energy into the system.

1.2. Some Basic Cardiac Electrophysiologic Considerations

Under normal conditions, the human heartbeat is controlled by a multiscale, hierarchical spatio-temporal network, comprising: 1) the sinus (sino-atrial, SA) node, the dominant physiologic pacemaker region of the heart, located in the high right atrium, and 2) the

syncytium (coupled sub-network) of right and left atrial fibers, which are activated by depolarization of the SA node. Electrical stimulation by the SA node, in turn, triggers mechanical contraction of the atria, and also propagates the flow of electrical signals (information) to the ventricles via the fractal-like His Purkinje-myocardial network of branching special fibers and of the myocytes, themselves. This activation process results in synchronized left and right ventricular depolarization, followed by simultaneous contraction.

Of essential importance, the integrated electro-anatomic system of the heart (SA node, atria, AV node and ventricles) is regulated by the autonomic (involuntary) nervous system, with its two major divisions: sympathetic (adrenergic) and parasympathetic (vagal). The autonomic nervous system exerts a self-regulatory, automatic control over heart rate and vascular tone, and, therefore, has a major impact on adjusting cardiac output to meet physiologic, metabolic demands. The autonomic nervous system, which is closely inter-related (coupled) with the pulmonary system, is also largely responsible for the fluctuations in heart rate from beat to beat. The representational, computational and interpretative aspects of cardiac interbeat interval fluctuations have attracted considerable interdisciplinary attention under the rubric of *heart rate variability*. The analysis of heart rate fluctuations is most accurate when based on continuous electrocardiographic (ECG) recordings.

The study of heart rate variability is of both physiologic and clinical importance because of its intimate connection to the overall status of the cardiovascular-pulmonary system. Marked differences in dynamics among the extreme states of health and advanced disease can sometimes be appreciated through a visual inspection of the heartbeat (plotted as interbeat interval or heart rate) time series. As shown in Figure 1a, the sinus heartbeat time series in healthy, particularly young adult subjects under basal (i.e., resting or minimal activity) conditions shows a high degree of variability. Numerous studies have revealed that this healthy heart rate variability is not random, but is characterized by $1/f$ -like (fractal) scaling over several orders of magnitude, ranging from seconds (or less) to hours (or longer) [6–9]. In contrast, heart failure (Figure 1b), is associated with a sharp reduction in the complex variability of sinus rhythm. This alteration is attributable, at least in part, to increased sympathetic and decreased parasympathetic stimulation occurring as an auto-regulatory countermeasure for reduced cardiac output. Finally, in AF (Figure 1c), cardiac rhythmicity appears to break down entirely and is replaced by an erratic (uncorrelated) type of variability. Over time scales ranging from seconds or less to minutes or longer, the dynamics of AF resemble those of white noise [10]. We note that the examples used are from deidentified, freely available data from PhysioNet [11,12]; see figure caption for more details.

2. Spectrographic Visualization of Cardiac Phase-like Changes

Given the factors controlling the heartbeat, a graphical representation that incorporates electrodynamics, autonomic influences and pulmonary interactions might be useful. To help visualize transitions in heartbeat dynamics, we employ the ECG-based method termed cardiopulmonary coupling (CPC) and its three-dimensional spectrographic representation. This technique has been described in detail elsewhere [13–16]. Briefly, CPC was designed to analyze the interactions between the mechanics of breathing and autonomically-mediated

heart rate variability, especially during sleeping hours. CPC makes use of the continuous recording from a single ECG lead, from which two signals are derived: the time series of the interbeat (RR) intervals, representing autonomic influences, and a surrogate respiration signal, termed ECG-derived respiration (EDR). The coupling between cardio-autonomic and respiratory systems is quantified using the cross-spectrum and the coherence of two signals. The information can be graphically displayed as a three-dimensional time-frequency-amplitude plot (spectrogram). Figure 2 shows spectrograms for the three subjects whose RR time series are shown in Figure 1.

The CPC plot for the representative healthy subject's sinus rhythm heartbeat (Figure 2a) shows a broadband spectrum with an inverse ($1/f$ -like) relationship between frequency and power, especially evident here in the range (0 – 0.06) Hz. The spectrogram from a subject with severe chronic heart failure (CHF) (Figure 2b), while still in “normal” sinus rhythm, shows a remarkably structured (“lattice-like”) pattern in which the spectral energy has “collapsed” to a very narrow band of frequencies centered at about 0.02 Hz (corresponding to ~ 1 cycle/min). In contrast to the two previous datasets, the spectral power in AF (Figure 2c) is dispersed across a broad range of frequencies without evidence of scaling or correlations over the bandwidth shown. These graphical representations can be interpreted in the context of transitions from multiscale (fractal-like) $\rightarrow$ single (characteristic)-scale $\rightarrow$ random states. The latter change, from a highly organized temporal “lattice” to a random arrangement (as revealed in the spectrograms) is the one most reminiscent of sublimation-type behavior.

2.1. Cheyne-Stokes Frequency

We note that the highly organized “temporal lattice” in this context represents high amplitude (i.e., tight) cardiopulmonary coupling at the classic Cheyne-Stokes frequency (corresponding to a period of about 1 minute), which is also called periodic breathing or central sleep apnea, the latter when it occurs at night or during daytime naps. Cheyne-Stokes pathophysiology is most apparent in the historically described pattern of breathing abnormality in adults in which respiratory motions go through long cycles marked by progressively deeper and faster breathing, followed by progressively slower and more shallow breathing culminating in a frank apnea. The cycle then repeats itself.

Cheyne-Stokes breathing has been modeled as a type of Hopf bifurcation [17,18] from a steady state of ventilatory control under negative feedback to oscillatory instability induced by either increased circulation time (as observed in heart failure) or increased sensitivity of the brainstem to carbon dioxide (increased brainstem chemoreceptor sensitivity to CO_2). The latter may be seen in a variety of types of brain disorders. While originally described as a pathologic form of breathing, subsequent observations have shown that periodic breathing of this type actually represents a more generalized dynamical state in which a wide number of physiologic variables oscillate coherently at the same frequency, including cardiac interbeat intervals, blood pressure, oxygen saturation, and so forth. Also of interest in the present context is that breathing patterns observed under healthy conditions may represent a bifurcation from fractal-like variability to pathologic periodicity [19–22].

3. Cardiac Sublimation

Up to this point, the notion of cardiac sublimation has been described entirely in the time domain, albeit using three-dimensional spectrographic maps. However, in biologic systems, temporal and spatial features are inextricably linked, as captured in the historically cited interdependence of form and function. For example, the normal pacemaker of the heart, the sinus node, is often treated, in an oversimplified way, as a point source when, in fact, it comprises a complex network of coupled oscillators. Of related interest to the discussion here is that the breakdown of temporal organization associated with sublimation-like behavior has structural correlates. Pathologic deformations may be a cause or sequence of abnormal temporal structures. For example, in healthy atrial tissue, which supports the robust maintenance of sinus rhythm, the atrial cells are linked by gap junctions, which facilitate systemic organization and anisotropic, directional flow (sinus node to AV node) of electrical information. The emergence of AF, with its analogies to gaseous disorganization, has been mechanistically related to the decreased coupling of atrial cells due to organic (e.g., inflammatory and fibrotic changes) autonomic imbalances or electrochemical factors (e.g., increased heterogeneity and other abnormalities of action potential dynamics). The multiscale hierarchical flow of information is degraded or lost entirely.

The initiation and maintenance of AF is thought to be related both to rapid firing of ectopic stimuli from the pulmonary vein orifice areas in the left atrium (thereby over-riding the intrinsically slower rate of the sinus node) and to multiple micro-reentrant circuits that subvert the normal hierarchical organization of atrial depolarization [23–25]. Thus, AF has both temporal and spatial features of impaired coupling (decreased connectivity), reminiscent of the breakdown of atomic or molecular interactions in the transition from solid to gas. Of course, only the former transition is related to the health status of an organism. Physical phase transitions are, of course, “agnostic” with respect to system’s biology!

The discussion of the transition from pathologic sinus rhythm dynamics in heart failure to AF has been over-simplified here to the extent that it suggests an all or none transition. In some cases, an abrupt (sinus to AF) transition is indeed recorded. However, the transition from sinus rhythm to AF is often associated with an intermediate stage in which sinus rhythm is interrupted by frequent premature atrial complexes. In extreme cases preceding AF, each sinus beat may be followed by a premature supraventricular complex, creating a period-2 (ABABAB...) alternans-type dynamic [26], clinically termed *atrial bigeminy*.

4. To What “Phase” Does Healthy Sinus Rhythm Correspond?

The discussion, to this point, has focused on the transition between sinus rhythm in heart failure syndromes and AF. We return to Figures 1 and 2, which also show the time series and spectrograms, respectively, of sinus rhythm in a representative healthy subject. Does this physiologic dynamic have any analogous state in the physical world? The answer remains to be established, but sinus rhythm dynamics in the healthiest individuals has some commonalities to liquid water with turbulent flow. Both represent information-rich states, having fractal/multifractal features [27,28] related to statistical correlations across scales. Healthy sinus rhythm is also associated with the most bioenergetically active, adaptive state

of the heart, associated with the greatest mechanical energy reserves. At the same time, correspondences between turbulent flows and sinus rhythm dynamics are limited to the extent that the latter are constrained by internal feedback mechanisms widely referred to as “homeostatic.”

5. Single and Multiscale Entropy and the Concept of “Complexity”

There is no formal definition of complexity. Its meaning and application vary depending on the scientific field. One approach, derived from information theory, is based on quantifying the degree of compressibility of signals. The first and best-known of these approaches is algorithmic entropy. The underlying notion is that simple sequences can be described concisely, in contrast to complex sequences [29]. Measurements based on algorithmic complexity suggest that the most compressible signals (e.g., highly periodic ones) are the least complex, which is consistent with intuitions about the physical and physiologic worlds. At the other extreme, however, the only signals that are totally incompressible are random uncorrelated signals (white noise), and compressibility-based approaches suggest that such signals are the most complex, a conclusion at odds with biologic intuitions and clinical outcomes.

A closely related area of investigation, motivated by the observation that unpredictability (entropy) frequently reflects complexity, involves the development of entropy-based measures such as approximate entropy (ApEn) [30,31] and sample entropy (SampEn) as surrogate measures for complexity. However, one of their key limitations is they are not universally applicable in this context. As noted above, an increase in the entropy (disorder) of a system is not necessarily always associated with an increase in its biologic complexity [32]. Indeed, the structure and output of complex networks are typically “hybrids” of order and apparent randomness [33].

This limitation prompted the search for entropy-based methods relevant to healthy (adaptive) physiologic systems, which generate signals with temporal “richness.” One such method introduced in 2002 is multiscale entropy (MSE) [10,34,35]. This approach is motivated by the observation that complex signals encode information over multiple time scales [36], whereas uncorrelated random signals or very periodic signals do not. The MSE algorithm was developed to help distinguish uncorrelated random signals from more complex (information-rich) signals (e.g. $1/f$ noise).

The MSE method employs an entropy measure, typically SampEn, to quantify the degree of unpredictability of the time series derived from the original signal by a coarse-graining operation. The original signal is divided into non-overlapping segments of equal length and the mean value of the data points in each of these segments is computed. The process is then repeated for a range of window lengths, i.e., scales. An MSE graph plots SampEn as a function of scale (i.e., coarse graining factor). Both the relative and absolute amplitude of the plots provide insight into the multiscale structure of the data, which may not be apparent by examining just scale 1, corresponding to conventional (single-scale) entropy.

In the analysis of heart rate dynamics, the MSE method shows the highest values for the time series of healthy subjects (equivalent to that of 1/f noise) and lower values for the subjects with CHF (Figure 3a). Furthermore, after about scale 10, both the healthy and the heart failure time series show a plateau on their MSE graphs with a slope close to zero, suggesting “conservation” of information content across scales. AF, on the other hand, presents a different profile, starting with highest values for lowest scales, and a monotonic decrease to values below those of the CHF time series for higher scales. This MSE profile is similar to that of uncorrelated (white) noise, as shown in Figure 3b (right panel). However, even AF is not entirely random, as shown in Figure 3b [37,38].

6. Bioenergetic Capacity

The term *bioenergetic capacity* can be used to describe the heart’s ability to generate the wide range of cardiac outputs necessary to meet metabolic needs at rest and with intense exertion or other stressors. The bioenergetic capacity depends on exquisite orchestration and tuning of components operating over a wide range of temporal and spatial scales. Of interest, the bioenergetic capacity (reserve) of the heart is highest for health and lowest for patients with the combination of CHF and AF (including weakness, shortness of breath, edema formation). Patients with AF and CHF are also among those with highest risk of sudden cardiac arrest or death due to progressive mechanical cardiac dysfunction.

The relationships between the bioenergetic capacity of the heart and entropy values (both classic and multiscale) computed on the cardiac interbeat interval time series are schematically represented in Figure 4. The classic entropy diagram (left panel) shows an inconsistent (non-monotonic) relationship between the two parameters. In contrast, multiscale entropy and the bioenergetic capacity show a consistent directional pattern of changes (right panel). Multiscale entropy is highest for the time series from the healthy subjects in sinus rhythm, lower for that of the subjects with heart failure who are still in sinus rhythm and lowest for that of the time series from AF.

The transition from a healthy cardiac status, with high MSE and high bioenergetic capacity, to severe CHF, where the effective cardiac output is insufficient to meet metabolic needs despite normal or high diastolic filling pressures, is almost universally associated with loss of complex sinus rhythm variability. Visually, this loss of complexity can be identified by the finding that the heartbeat time series in patients with sinus rhythm and CHF show a flattening out and constriction of the overall variability. In addition, in the more extreme cases relevant here, of Cheyne-Stokes dynamics with highly periodic with low frequency oscillation, emerges. This periodicity gives the cardiac interbeat interval time series an oscillatory “envelope,” with its well defined, characteristic frequency of about 0.02 Hz (Figures 1 and 2).

7. Implications of the Sublimation Paradigm

A reasonable question is whether the proposed paradigm for viewing transitions between sinus rhythm in heart failure and AF has any explanatory or predictive clinical value, or is it at best a metaphoric or analogistic connection. One argument for its utility is its relevance in

the context of the complexity loss theory of disease and aging [19,20,39]: the proposed framework accommodates a unified “model” in which bioenergetic capacity (the ability to do physiologically necessary work) and multiscale entropy always go in the same direction. Furthermore, since it is easier to lose information than to recover it, this paradigm is also consistent with the finding that the transition from sinus rhythm to AF in heart failure is more probable than its reverse. Indeed, once AF appears in heart failure, the rhythm becomes more and more difficult to revert back to sinus rhythm, despite pharmacologic interventions, radiofrequency ablation therapy or direct current cardioversion. Eventually, AF in the context of severe CHF most often becomes permanent (chronic), associated with a bioenergetic trough. Not surprisingly, patients with CHF with reduced left ventricular ejection fraction who develop AF are in an especially high risk group for death due to refractory cardiac failure or to sudden cardiac arrest [24,25].

Finally, it is worth noting that the findings here are not in conflict with the second law of thermodynamics. While the entropy of closed systems tends to increase with time, the multiscale entropy (complexity) of biologic systems, which are open, decreases with disease and aging. This consideration invites the search for imaginative therapies for a wide range of pathologies in the form of interventions designed 1) to maintain or restore multiscale complexity, and 2) to avoid those that inadvertently decrease system complexity, since the latter may have unintended “off-target” consequences [40].

8. Coupling vs. Correlations

The two terms are used in related but not synonymous ways in the scientific community. We note that this discussion has adopted the following: 1) ‘coupling’ was used to refer to an interaction between or among physiologic components mediated by electrochemical forces. The coupling between respiration and heart rate via cardiac vagal tone modulation is one example; the physical (molecular) connectivity between heart muscle cells is another. By distinction, ‘correlations’ was used in accord with the parlance of statistical physics [33]. From this perspective, it is important to note that $1/f$ scaling behavior (long-range correlations) of a time series does not ensure that there are complex interactions (coupling) among the components of the underlying control network [33]. Furthermore, from a physiologic perspective, coupling may be due either to healthy (e.g., respiratory sinus arrhythmia) or pathologic (e.g., Cheyne-Stokes breathing) mechanisms. More detailed discussion of these issues and their relationship to complexity/entropy measures lie outside the scope of this essay; see [13,28,33,41] and references therein.

9. Conclusions

We describe a cardiac biodynamical phenomenon reminiscent of sublimation: namely, the abrupt transition from a highly structured temporal pattern of sinus beats, routinely found in severe heart failure states, to the random, disorganized temporal structure of AF. We show how this change in temporal organization can be visualized using a spectrographic method based on cardiopulmonary coupling and heart rate variability analysis. We also show how the transitions from physiologic sinus rhythm in healthy subjects, with its fractal-like behavior → to the highly periodic sinus rhythm dynamics of heart failure → to the random,

uncorrelated pattern of heartbeats in AF can be interpreted as a monotonic decrease in information content (or complexity) of the cardiopulmonary system (as measured by multiscale entropy). This multiscale information loss is associated with a monotonic decrease in the bioenergetic capacity of the heartbeat control system.

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Abbreviations

The following abbreviations are used in this manuscript

AF	Atrial Fibrillation
ApEn	Approximate Entropy
AV	Atrio-Ventricular
CHF	Chronic (congestive) Heart Failure
CPC	Cardiopulmonary Coupling
ECG	Electrocardiogram
EDR	ECG-Derived Respiration
HR	Heart Rate
MSE	Multiscale Entropy
REM	Rapid Eye Movement
SA	Sino-Atrial
SampEn	Sample Entropy

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Figure 1.

Heart rate time series from: **a)** a healthy person in sinus rhythm with normal cardiac mechanical function; **b)** a patient still in sinus rhythm, but with severe chronic heart failure (CHF); **c)** a patient with atrial fibrillation (AF). Note the complex variability in health; the loss of variability (decreased variance) and emergence of periodic oscillations in heart failure, and the random-appearing pattern in atrial fibrillation. The deidentified freely available data used in these examples are from subject #N8 from the CAP Sleep Database (<https://physionet.org/pn6/capslpdb/>), subject #CHF13 from the BIDMC CHF Database (<https://www.physionet.org/physiobank/database/chfdb/>) and subject #07859 from the MIT-BIH atrial fibrillation database (<https://physionet.org/physiobank/database/afdb/>), of PhysioNet [11].

Figure 2.

Cardiopulmonary coupling (CPC) spectrograms computed from the ECG data of the subjects whose cardiac interbeat interval time series are shown in Figure 1: **a)** healthy subject, **b)** patient with chronic heart failure (CHF) and decreased left ventricular ejection fraction, and **c)** patient with atrial fibrillation (AF). The three dimensional graphs plot frequency vs time vs. coupling amplitude. The latter (CPC) is given in normalized units (n.u.). See text for discussion and [13–16].

Figure 3.

a) Multiscale entropy curves for sinus rhythm dynamics from healthy subjects (triangles), sinus rhythm dynamics of patients with chronic (congestive) heart failure (CHF; circles) and of patients with atrial fibrillation (AF) (squares). The interbeat interval time series used in this example are from an open source database of deidentified subjects available at the PhysioNet website [11,12] and the entropy values have been obtained as the average valued of 5 subjects for each category. Symbols represent the group means and the bars represent the standard error mean. Adapted from [34,35]. Note that scale 1 corresponds to the conventional (scale 1) entropy and is highest for the most random (uncorrelated time series).

b) The curve for AF patients is shown together with that obtained as the average over 100 random time series obtained by shuffling each of the RR time series from the AF patients 20 times. The figure shows the trend of the AF curve is similar to that of the random signal (white noise), but the entropy tends to plateau rather than collapse, showing that some information is still contained in the physiological structure of the AF heart, particular at higher time scales (lower frequencies) [37,38].

Figure 4.

Schematic representation of entropy values vs. cardiac bioenergetic capacity in two paradigms. The top panel presents the classic framework in which entropy is measured by irregularity on a single scale. The bottom panel shows the same states, but considers multiscale entropy, not single scale entropy, as the parameter on the abscissa [35].