

Detecting Instabilities of Cardiac Rhythm

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Abstract: Diminished beat-to-beat variations in cardiac cycle lengths (CLs) are associated with poor prognosis after acute myocardial infarction and in patients with heart failure. Short-long-short sequences of cardiac cycles, or ultra-short rhythm instabilities, precede initiation of ventricular tachyarrhythmias in some patients. However, little is known about clinical or prognostic significance of abrupt short-term instabilities in CL (AICL) that occur minutes to hours before the event, in part because appropriate analytical methods are lacking. Although various techniques have been used to analyze CL changes, methods for analysis of AICL are limited. We compared performance of time domain, spectral, nonlinear, and pattern recognition techniques with respect to the detection and quantification of AICL. Because of high intra- and inter-subject variability of CL, pattern recognition techniques compared favorably to other studied methods. In continuous ambulatory ECG recordings, AICL occurred hours before spontaneous initiation of sustained atrial and ventricular arrhythmias in different patient populations. AICL were also found prior to the onset of spontaneous ventricular arrhythmias in a mouse model of congestive heart failure. To quantify AICL, we used the number of unstable orthogonal projection coefficients; this number gradually increased hours before the event. Removal of ectopic beats reduced but did not eliminate AICL. To illustrate potential physiological effects and temporal evolution of AICL, we used a simple, continuous, two-dimensional model of cardiac tissue governed by the Morris-Lecar equations. Computer simulations in this model showed that AICL may lead to gradual accumulation of spatial irregularities of the propagation wavefront giving rise to the initiation of reentry. Time-frequency analysis of the most significant eigenvectors of cardiac rhythm in subjects undergoing head-up tilt showed that AICL could indicate instabilities and unsuccessful adaptation of autonomic nervous system activity to physiological stimuli. **Key words:** Prediction of cardiac arrhythmias, Pattern recognition, Biophysical modeling.

It has long been recognized that stable dynamics of cardiac rhythm represents an important feature

of physiological homeostasis. Short-term perturbations, including faster heart rates, more frequent ectopy, and episodes of atrial fibrillation, have been reported hours before initiation of spontaneous sustained ventricular tachyarrhythmias (VTA) (1–3). An increase in atrial ectopic activity and changes in heart rate were also observed prior to the onset of paroxysmal atrial fibrillation (4). These observations suggest that short-term modifications of cardiac rhythm could be pro-arrhythmic. In particular, the short-long-short sequences, which represent ultra-short instability of cardiac cycles, precede the onset of VTA in some patients (5). However, little is

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known about clinical or prognostic significance of the short-term rhythm instabilities that occur minutes to hours before the event. Although various techniques have been used to analyze cycle length (CL) changes, methods for time-series analysis of abrupt short-term instabilities in CL (AICL) are limited.

Traditionally, changes in sinus rhythm and ectopic activity are considered as distinct physiological phenomena. To study sinus rhythm modifications, a time series of sinus beats is extracted from the original sequence of cardiac cycles, whereas frequency of ectopic beats is estimated separately. Recent studies, however, showed that rhythm perturbations from different physiological sources could be studied as a single phenomenon, and this unifying approach revealed general features of rhythm destabilizations that precede initiation of various cardiac arrhythmias (1).

Here we compare performance of the traditional approaches, including time domain, spectral, and nonlinear methods, as well as the recently developed pattern recognition and time-frequency analysis techniques with respect to the detection and quantification of AICL. We describe 1) general features of rhythm perturbations that occur prior to initiation of sustained VTA and atrial fibrillation in humans, and 2) show that these features are independent of species specifics using the data from a genetic mouse model of congestive heart failure. Time-frequency analysis of the most significant eigenvectors derived from cardiac rhythm series in subjects undergoing head-up tilt showed that short-term instabilities could indicate unsuccessful adaptation of autonomic nervous system activity to physiological stimuli. To illustrate potential physiological effects and temporal evolution of AICL, we used a simple, continuous, two-dimensional model of cardiac tissue governed by the Morris-Lecar equations. Computer simulations in this model showed that AICL may lead to gradual accumulation of spatial irregularities of the propagation wavefront giving rise to the initiation of reentry.

Materials and Methods

Data processing. ECG data were digitized at 400 Hz and the QRS complexes were classified using custom software, and pattern recognition analysis was performed as described elsewhere (1). In brief, the series of cardiac cycles is separated into 5-minute segments referred to as the unit vectors. The Modified Karhunen-Loeve Transform (MKLT), allows simplifying the pattern and exposing its most

significant features. The reduction of dimensionality of the unit vector is achieved by projecting it onto linearly independent basis vectors or eigenvectors which represent the most characteristic features of the signal. To reduce the dimensionality of the original data with a minimal information loss, we select the eigenvectors that correspond to the biggest eigenvalues (6). The time series of each MKLT coefficient represents temporal changes in the projection of the signal onto the corresponding eigenvector. Finally, because the time course of the changes does not correspond to the constant, 5-min length of the unit vectors, the window lengths are adjusted to separate the segments with different properties. The first six eigenvectors of the matrix C , which contain most of the information about the signal, were extracted and their coefficients, c_k , were obtained as described above. The time series of c_k were used to estimate the standard deviation of the series of each coefficient (σ_k). A $3\sigma_k$ -threshold was established so that the probability of a random occurrence of the cardiac cycle lengths exceeding $3\sigma_k$ would be less than 0.0013 assuming a normal distribution. The rhythm is said to be at a steady state when all six coefficients are within the limits of $3\sigma_k$. An excursion of one or more coefficients beyond the $3\sigma_k$ -threshold indicates rhythm disturbances. The Dimensionality (Dm) of the disturbances is defined as the number of coefficients that simultaneously exceed the corresponding $3\sigma_k$ -thresholds.

Results

Rhythm Instability Preceding Initiation of Ventricular Tachyarrhythmia and Paroxysmal Atrial Fibrillation in Humans

Figure 1 shows short-term changes in cardiac rhythm that occurred in two patients preceding spontaneous initiation of VTA (left) and paroxysmal atrial fibrillation (right). Series of the most significant MKLT-coefficients reveal instabilities that occurred hours before the event due to the changes in both sinus rhythm and ectopic activity. Note that changes in ectopic frequency prior to the onset of VTA were predominantly associated with the increased number of ventricular extrasystoles, whereas those preceding atrial fibrillation were due to supraventricular ectopy. However, as Figure 1 shows, analysis of the most significant MKLT-coefficients reveals instabilities of cardiac rhythm, independent of underlying physiological mechanisms. Instability of the most significant MKLT-coefficients

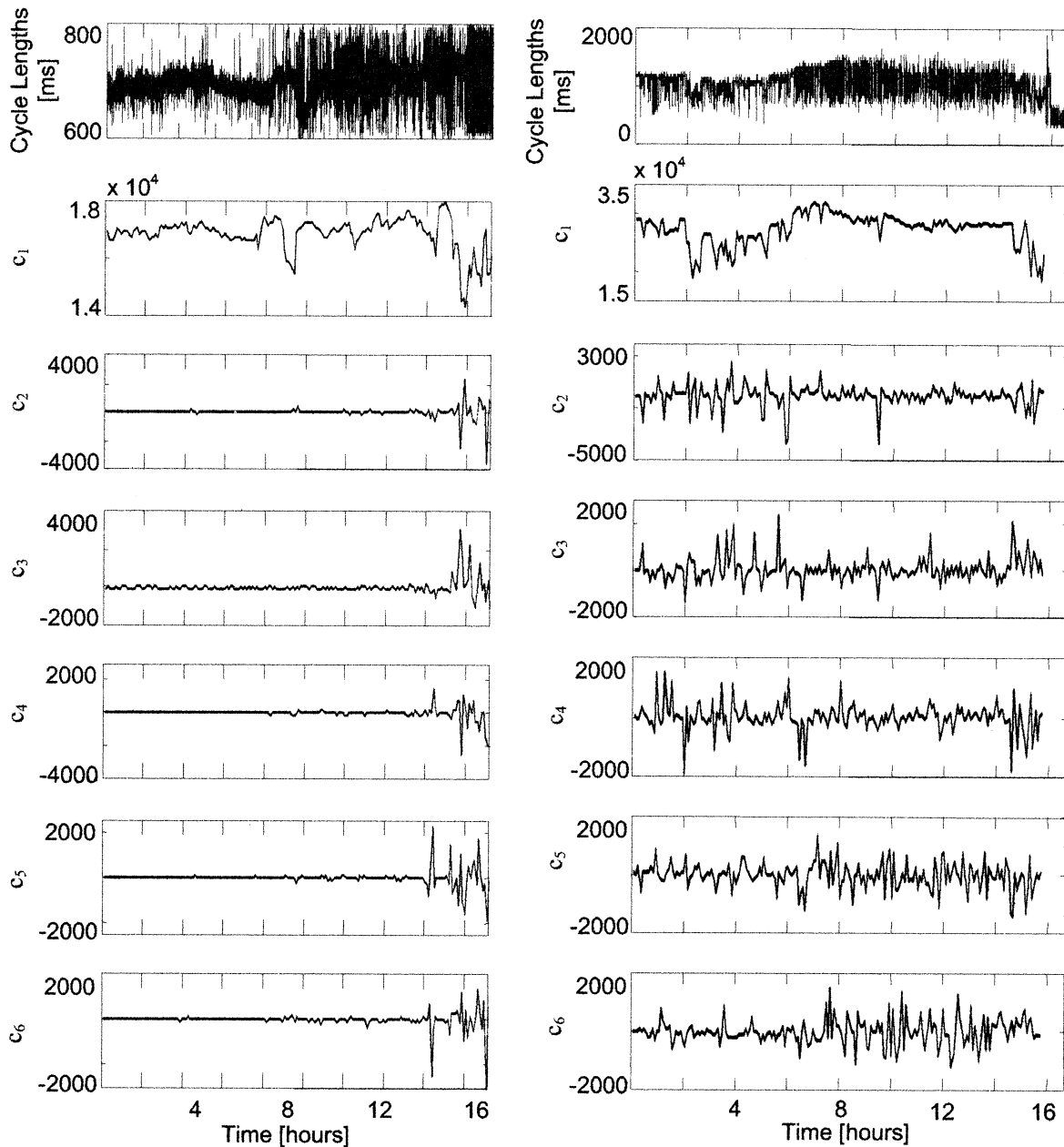


Fig. 1. Changes in cardiac rhythm during 16 hours before the initiation of ventricular tachyarrhythmia (left column) and before initiation of paroxysmal atrial fibrillation (right column). Arrhythmias occurred at the end of the recordings. Top panels show series of cardiac cycle lengths; time series of the corresponding most significant MKLT coefficients are shown in the lower panels.

accurately predicted both the timing of initiation of VTA and paroxysmal atrial fibrillation (1).

Rhythm Instability Preceding Initiation of Ventricular Tachyarrhythmia in a TNF- α Mouse Model of Congestive Heart Failure

To show that characteristics of rhythm instabilities are independent of species, we analyzed

series of cardiac cycles preceding the onset of ventricular arrhythmias in a TNF- α mouse model of congestive heart failure. Four ventricular arrhythmias from 3 mice were selected for analysis because they had at least 60 min of sinus rhythm during the preceding period. In all recordings, an increase in the number of MKLT-coefficients that exceeded 3σ -threshold was observed during 30 min before the event ($P = .058$), whereas tradi-

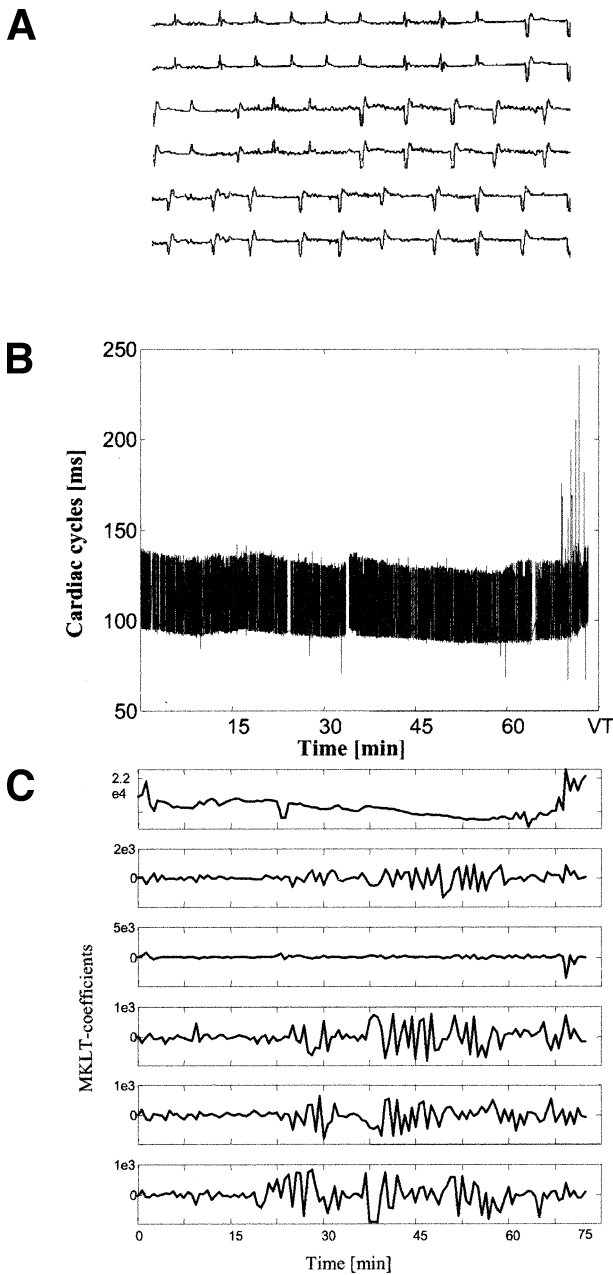


Fig. 2. Initiation of ventricular arrhythmia in a 99-day old TNF- α mouse. Sinus rhythm is followed by isolated premature beats and then by 21 beats of idioventricular rhythm, which had a 134-ms mean cycle length (A), series of cardiac cycle lengths during 75 min before the onset of VTA (B), and series of corresponding MKLT-coefficients (C). VTA starts at the end of the recording.

tional spectral and non-spectral indices of cardiac cycle dynamics did not change. Figure 2 demonstrates a typical example of changes in MKLT-coefficients preceding the onset of spontaneous ventricular arrhythmia.

Time-Frequency Analysis to Reveal Patterns of Adaptation to Orthostatic Challenge

Time-frequency analysis of cardiac rhythm responses to orthostatic challenge provides an insight into the patterns of adaptation of the autonomic nervous system activity to physiological stimulation. Direct time-frequency representation of cardiac rhythm, however, is difficult to comprehend due to multi-component structure of the signal. Therefore, representation of the most significant eigenvectors of the cardiac rhythm in the time-frequency plane revealed underlying rhythm patterns and their relationship to autonomic nervous system activity adjustment to orthostatic challenge. Figure 3 shows the time series of cardiac cycles and the most significant eigenvectors in two subjects undergoing passive head-up tilt. In asymptomatic subject, the eigenvectors bandwidth was stable and concentrated near 0.1 Hz, the frequency of sympathetically mediated vasomotor activity. In a symptomatic subject, the patterns of the most significant eigenvectors were unstable and widely dispersed over the entire frequency range. The instability of the most significant eigenvectors was observed in most symptomatic subjects ($n = 14$), and the bandwidth of the 2nd and the 3rd eigenvectors was significantly wider in the symptomatic subjects compared to asymptomatic ones ($n = 20$) (7).

Mathematical Model

To illustrate the mechanisms that could link cardiac rhythm instability with arrhythmia initiation and to probe their temporal organization, we performed computer simulations. A continuous two-dimensional model of cardiac tissue governed by the Morris-Lecar equations was selected because this simple model allows simulating the prolonged cumulative dynamics of rhythm instability that was observed in the electrocardiographic recordings (8). This is a hybrid FitzHugh-Nagumo/Hodgkin-Huxley model that incorporates a voltage (V) gated Ca^{+2} -channel and a voltage gated, delayed-rectifier, K^{+} -channel:

$$C \frac{dV}{dt} = -I_{ion}(V, w) + I, \quad \frac{dw}{dt} = \phi \frac{w_{\infty}(V) - w}{\tau_w(V)}$$

where $I_{ion}(V, w) = \bar{g}_{Ca} m_{\infty}(V)(V - V_{Ca}) + \bar{g}_K w(V - V_K) + \bar{g}_L(V - V_L)$, w is the fraction of K^{+} -channels open, and the Ca^{+2} -channels instantaneously respond to V .

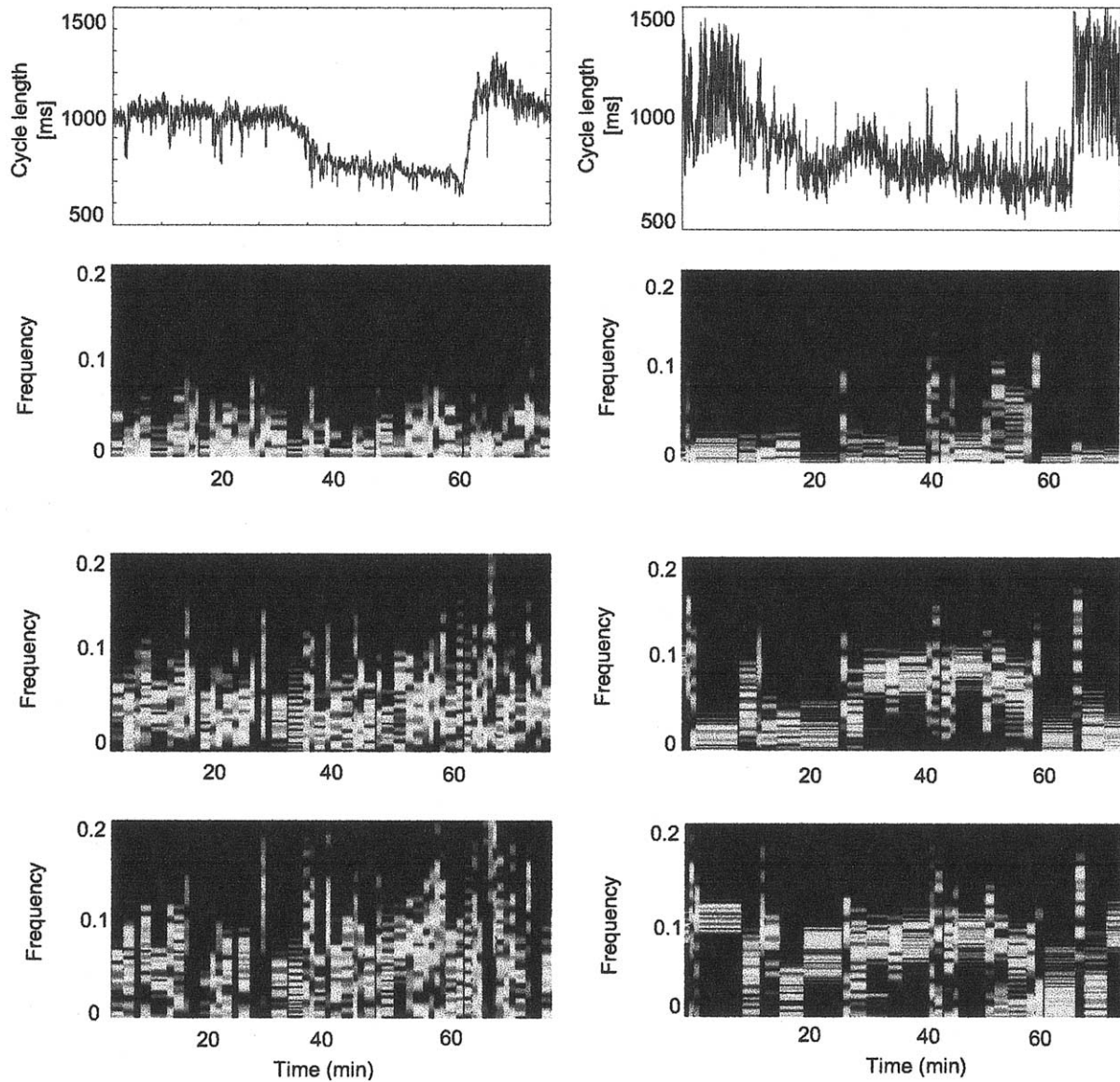


Fig. 3. Changes in cardiac rhythm during head-up tilt in a symptomatic subject (left) and an asymptomatic subject (right). The top panels show series of cardiac cycle lengths; the lower panels show time-frequency representation of the most significant eigenvectors.

$$m_{\infty}(V) = .5 * [1 + \tanh\{V - V_1/V_2\}],$$

$$w_{\infty} = .5 * [1 + \tanh\{V - V_3/V_4\}],$$

$$\tau_w(V) = 1/\cosh\{(V - V_3)/(2 * V_4)\}.$$

Differences in recovery times were assigned in random order and kept constant throughout the simulations. The simulations were performed with isotropic and anisotropic (4:1) propagation. The ratio between action potential duration and stimulation cycle length was kept at 0.45 assuming that the interval between the earliest depolarization and

the latest recovery divided by the square root of the cycle length was 0.4 s (9). A delayed adaptation of repolarization times to changes in pacing cycle lengths was modeled by a scaling restitution parameter. Three types of cardiac cycle dynamics were simulated. Steady-state rhythm was simulated by cardiac cycle sequences that were constant, linearly increasing or decreasing within the physiological range, and by the low and high frequency periodicities that replicated normal cardiac cycle variability (10). Linear trends in the cardiac cycles had ± 2 –20% ranges and -1.5 to 1.5 slopes. Sub-threshold

instabilities were mimicked by changes in cardiac cycles that resulted in MKLT-coefficients variations less than the 3σ -threshold. Super-threshold instabilities were simulated by gradual (slope magnitude <2) or abrupt (slope magnitude >2) changes of cardiac cycles beyond the 3σ -threshold.

The effects of cardiac cycle dynamics on electrical propagation and repolarization simulated in the model are illustrated in Figure 4. Normal elliptical spread of propagation was observed during constant frequency stimulation (Fig 4A, left map), and during periodic changes in cardiac cycles that mimicked normal heart rate variability (Fig 4A, right map). Sub-threshold instabilities resulted in small deviations of the propagation waveform that eventually returned to the steady-state cardiac dynamics (Fig 4, left). In contrast, super-threshold instabilities produced functional slow conduction zones and gradually progressing propagation irregularities that led to initiation of sustained spiral waves (Fig 4, right) of reentrant activity.

Although other models provide a more complete description of cellular kinetics, no model adequately simulates the complex and diverse structural and functional abnormalities present in patients with heart disease. The model we used simulated the effects of cardiac cycle dynamics over relatively long periods permitting examination of the changes that develop gradually (11,12). It is well known that chronic heart disease is accompanied by severe changes in neurohormonal function and abnormal cardiac cycle dynamics (13). Therefore, short-term rhythm instabilities are likely to arise from the interaction between neurohormonal influences, cardiac function and the activity of the sinus node. The model we used provides a plausible explanation of the link between rhythm instabilities and arrhythmogenesis.

Discussion

Descriptors of Cardiac Rhythm Dynamics

Because the cardiac cycle series is complex and individually variable, visual inspection of the series or the traditional statistical tools cannot reveal the changes that preceded the onset of atrial and ventricular arrhythmias. Indeed, the traditional time series estimators, such as mean or variance, can be effective in identifying a unidirectional change in the group. For example, a decrease in heart rate could be readily detectable in the TNF- α mice during the progression of CHF (14). However, this

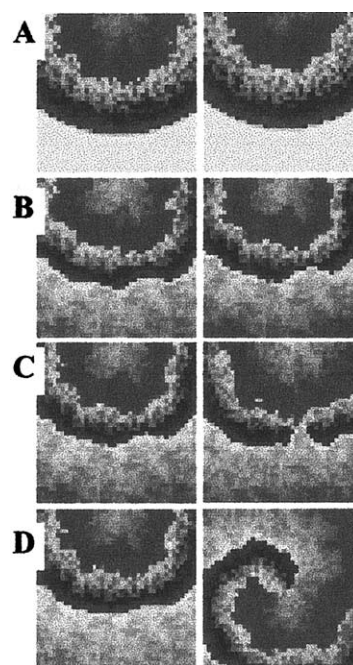


Fig. 4. Computer-generated intracellular potential maps during sub-threshold (left) and super-threshold instabilities (right) of the cardiac rhythm over 8 hours. Black color represents the maximum positive potential during initial depolarization, grey represents less positive potentials during the plateau, light grey represents repolarization. (A) Steady-state rhythm. Maps obtained 50 ms after stimulus impulse at the center of the top edge of tissue during constant interval stimulation (left) and simulated normal cardiac cycle variability (right). Propagation is uniform and spreads through the tissue array in an elliptical pattern until it encounters the edges of the tissue and extinguishes. (B) Propagation during 2 hours of sub-threshold instabilities deviates mildly from normal uniform spread (left). During super-threshold instability (right), more significant nonuniformities in activation and repolarization sequences are observed. (C) After 4 hours of sub-threshold perturbations, propagation remains relatively uniform (left). In contrast, discontinuities of the propagation wavefront are present after 4 hours of rhythm super-threshold instability (right). (D) The propagation pattern has returned to near normal in the tissue subjected to sub-threshold perturbations. In the tissue subjected to super-threshold disturbances, gradual accumulation of propagation irregularities led to initiation of sustained spiral waves of reentrant activity.

analysis may not detect short-term changes if inter-subject variability with respect to the timing and direction of the changes is high. Therefore, we applied a pattern recognition approach that first identifies an individual characteristic pattern of cardiac cycles and then tracks disturbances in this pattern. Specifically, we applied Modified Karhunen-Loeve transform which extracts the basis

vectors from the statistics of the series itself. This method revealed instabilities in the pattern of cardiac cycles that preceded spontaneous initiation of ventricular tachyarrhythmias and atrial fibrillation in humans (1). The number of MKLT-coefficients exceeding the threshold gradually increased hours before the initiation of both atrial and ventricular arrhythmias (1). We also found similar disturbances in the pattern of cardiac cycles preceding the onset of ventricular arrhythmias in TNF- α mice. This strongly suggests that rhythm instability is a general precursor of spontaneous arrhythmias independent of species. The pattern recognition approach provides an accurate description of the homeostatic state and instability of cardiac rhythm.

An increase in the number of ectopic beats and ultra-short irregularity plays an important role in the rhythm destabilization, and inclusion of ectopic beats into analysis improves the accuracy (15). However, the rhythm instability is determined not only by ectopy or ultra-short irregularities but also by the more complex, longer-term relationships between the cardiac cycles (1).

Although the traditional methods could detect some changes, the utility of these methods is limited by the assumptions that 1) the signal is stationary and 2) that the changes occur in a single, a-priori defined property, whereas all other properties remain unchanged. MKLT can be considered as a generalization of the traditional methods that are limited by the assumptions of signals' stationarity and by the single-feature searching capabilities. Indeed, the Fourier transform can be considered as a special case of MKLT in which the basis functions are complex exponentials. The time domain indices, including SD, r-MSSD, and pNN50, also capture certain a priori defined properties of the signal that may or may not represent the changes that occur before the onset of VTA (16). The nonlinear descriptors, ApEn and scaling exponents, also attempt to summarize the complexity of the series using a single measure which is sensitive only to certain types of changes (17). In addition, interpretation of changes in ApEn is obscured by its sensitivity to ectopy, whereas MKLT analysis, as our results demonstrate, is relatively unaffected by ectopy (18).

Rhythm Instability and Initiation of Arrhythmias

To clarify physiological mechanisms of rhythm destabilization, we examined cardiac rhythm adaptation to the tilt-related changes in autonomic ner-

vous system activity. Unstable patterns (Fig. 3) were observed in subjects who exhibited unsuccessful adaptation to head-up tilt. This finding suggests that rhythm instability could be a marker of unsuccessful adjustment of the autonomic nervous system activity to prolonged physiological stimulation.

We used computer simulations to demonstrate a potential link between rhythm instabilities and arrhythmogenesis, which could be related to gradual accumulation of conduction abnormalities and formation of functional slow conduction zones (Fig. 4). Another potential mechanism linking rhythm instability with initiation of arrhythmias could be associated with gradual accumulation of spatial repolarization changes. Delayed repolarization changes have been described after several consecutive periods of rapid atrial pacing and infusion of autonomically active drugs both in humans and animal models (11,19).

Conclusions

Destabilization of cardiac rhythm develops gradually hours before the onset of VTA and paroxysmal atrial fibrillation due to changes in sinus rhythm and/or ectopy. Using the pattern recognition approach, this destabilization could be analyzed without the knowledge of specific clinical context or group reference values.

The gradual development of rhythm destabilization could explain partial success of rate-smoothing pacing in preventing clinically significant arrhythmias. Although short-term rate-smoothing reduces the number of arrhythmic episodes by reducing dimensionality of rhythm destabilization, it cannot eliminate the instability because of its short "viewing" window. A longer-term "smoothing" or modification of cardiac rhythm is required for correction of rhythm destabilization and effective prevention of arrhythmias.

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