Mechanisms of ventricular arrhythmias: a dynamical systems-based perspective

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Cherry EM, Fenton FH, Gilmour RF Jr. Mechanisms of ventricular arrhythmias: a dynamical systems-based perspective. Am J Physiol Heart Circ Physiol 302: H2451–H2463, 2012. First published March 30, 2012; doi:10.1152/ajpheart.00770.2011.—Defining the cellular electrophysiological mechanisms for ventricular tachyarrhythmias is difficult, given the wide array of potential mechanisms, ranging from abnormal automaticity to various types of reentry and kk activity. The degree of difficulty is increased further by the fact that any particular mechanism may be influenced by the evolving ionic and anatomic environments associated with many forms of heart disease. Consequently, static measures of a single electrophysiological characteristic are unlikely to be useful in establishing mechanisms. Rather, the dynamics of the electrophysiological triggers and substrates that predispose to arrhythmia development need to be considered. Moreover, the dynamics need to be considered in the context of a system, one that displays certain predictable behaviors, but also one that may contain seemingly stochastic elements. It also is essential to recognize that even the predictable behaviors of this complex nonlinear system are subject to small changes in the state of the system at any given time. Here we briefly review some of the short-, medium-, and long-term alterations of the electrophysiological substrate that accompany myocardial disease and their potential impact on the initiation and maintenance of ventricular arrhythmias. We also provide examples of cases in which small changes in the electrophysiological substrate can result in rather large differences in arrhythmia outcome. These results suggest that an interrogation of cardiac electrical dynamics is required to provide a meaningful assessment of the immediate risk for arrhythmia development and for evaluating the effects of putative antiarrhythmic interventions.

Information accumulated to date indicates that multiple mechanisms, ranging from abnormal automaticity, triggered activity, and various forms of reentry, are capable of provoking ventricular arrhythmias (6, 43, 68, 105, 128, 148, 158, 201, 209). Several of these mechanisms can be attributed to specific abnormalities of cellular electrophysiology, such as mutations in a single ion channel, transporter, or pump (14, 172). However, the vast majority of ventricular rhythm disturbances appear to be multifactorial in origin and associated with various combinations of derangements in ion channel distribution and function, intracellular ion dynamics, cardiac innervation, metabolic and signaling pathways, as well as in gross and microscopic anatomical features [for reviews, see (3, 12, 97, 108, 110)].

It has also become apparent that arrhythmia development is not solely a function of a static set of electrophysiological properties but also depends on changes that occur over multiple time scales ranging from seconds to months. Beat-to-beat changes in electrophysiological properties occur over seconds during irregular or rapid cardiac activation and appear to be important determinants of the propensity to develop and sustain arrhythmias, particularly as they relate to the development of dynamical heterogeneity of refractoriness (23, 83, 84, 186). On a longer time scale of minutes to hours, key electrical

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properties such as action potential duration (APD) are importantly influenced by an accumulation and dissipation of short-term cardiac memory, as occurs during prolonged pacing (30, 71, 79, 106). At a still longer time scale of days to months, the heart can remodel, both structurally and functionally, in response to various stressors (3, 146, 196). Along with the presence of multiple time scales, the nonlinearity of cardiac tissue (67, 86, 117) can result in complex dynamics from such properties as multistability (53, 68, 103, 150, 188, 199) and dependence on initial conditions (34, 42, 68).

It seems possible that the combination of short, intermediate, and long time scales and nonlinear properties governs the evolution of cardiac dynamics and may account for some of the features of arrhythmia development that up to now have defied explanation. Accordingly, this review focuses on the importance of certain aspects of these temporal and nonlinear dynamics in the initiation and perpetuation of ventricular tachyarrhythmias. With regard to the temporal dynamics, we segregate the discussion according to those that occur over short (beat-to-beat to seconds), intermediate (minutes to hours), and long (days to months) time scales, recognizing that these classifications, although useful for organizing the discussion, are somewhat arbitrary and that some of the dynamics may evolve over a continuum of time. In addition to reviewing the relevant literature, we provide preliminary evidence for a somewhat different perspective on arrhythmia development and propose corresponding future directions for research.

**Triggers and substrates.** Mechanisms for the development of ventricular arrhythmias traditionally have been considered in the context of triggers and substrates (107), where particular characteristics of each are required to produce a permissive environment for the initiation and maintenance of sustained arrhythmias. In that regard, the normal heart can be easily fibrillated by the application of high-frequency stimuli (36) or even by contact with a 9-V battery (56). However, normal hearts are subjected to few, if any, arrhythmogenic triggers [outside of unusual events such as inadvertent electrical shock or *commotio cordis* (8)]. Consequently, symptomatic ventricular arrhythmias are rare in individuals with normal cardiac function. On the other hand, sequences of potential triggers (e.g., premature ventricular complexes) that ordinarily would be benign in an otherwise normal heart may precipitate more sustained rhythm disturbances in infarcted or myopathic hearts. Thus, understanding the relationship between trigger and substrate at any given moment is essential for predicting when (or if) an arrhythmia is imminent.

**Nonlinear dynamics and the heart.** One of the signature features of nonlinear systems is that they exhibit sensitivity to initial conditions, where small changes in the initial state of the system can lead to very different outcomes over time (98, 198). Rather extreme examples of this phenomenon are common in the physics and mathematical literature (e.g., the “butterfly effect”) and may contribute to the apparently chaotic fluctuations in the behaviors of various biological systems (87). However, fluctuations in heart rate and blood pressure, for example, typically are not abrupt. From a functional standpoint, the lack of sharp transitions in cardiac rhythm makes sense, in that such changes would be counterproductive, given that the heart requires a balance between electrical and mechanical systole and diastole to optimize the relationship between filling and ejection and to maintain optimal excitation-contraction coupling. Nevertheless, certain functions of the heart, notably restitution of APD, are known to exhibit a sensitive dependence on initial conditions. (34, 42, 68, 103, 150, 188). Perhaps these properties and other nonlinear effects, such as multistability, where a system may oscillate between two quasistable states, underlie the seemingly unpredictable emergence of some ventricular tachyarrhythmias. Although this idea is intuitively attractive, it is, at least for the time being, insufficiently validated. That said, we will review some of the existing evidence for it in the following sections.

**Role of Cardiac Dynamics in the Generation of Ventricular Arrhythmias**

**Evolution of dynamics over short times scales.** Although several hypotheses regarding cellular electrophysiological mechanisms for VF have been proposed [for reviews, see (68, 105)], substantial evidence has accumulated over the past few years to suggest that fibrillation is a state of spatiotemporal chaos consisting of the perpetual nucleation and disintegration of spiral waves (38, 90, 224), often in association with a period-doubling bifurcation of local electrical properties (115, 158, 219). Nucleation of the initiating spiral wave pair is caused by local conduction block (wave break) secondary to spatial heterogeneity of refractoriness in the ventricle (105, 127, 158, 222). Until recently, spatial heterogeneity was thought to result solely from regional variations of intrinsic cellular electrical properties [e.g., (192, 230)]. However, it is now appreciated that purely dynamical heterogeneity can be sufficient to cause conduction block (68, 115, 177, 217, 219).

For the case of pacing at a fixed cycle length, the period-doubling bifurcation implicated in the transition to conduction block is manifest as alternans, a beat-to-beat long-short alternation in the duration of the cardiac action potential (147). Previous investigators have hypothesized that alternans can be accounted for by a simple unidimensional return map called the APD restitution function (44, 58, 60, 91, 125, 147). The combination of a steeply sloped APD restitution function and a monotonically increasing conduction velocity (CV) restitution function has been shown to be sufficient to produce dynamical conduction block during sustained pacing at a short cycle length (78, 174, 217). This combination of restitution functions promotes the development of so-called “discordant alternans,” in which the alternations in APD are out of phase with one another at different locations in the tissue (162). However, when the APD restitution relation is considered as a function of more than one variable (e.g., to account for memory), its steepness is neither necessary nor sufficient for the development of alternans under certain circumstances, as has been observed experimentally (19, 92) and verified numerically (41, 55, 68, 113, 206).

The cellular mechanism for APD alternans is complex, but Ca^{2+} cycling appears to be an important determinant in many cases (48, 76, 89, 195). Moreover, blockade of L-type Ca^{2+} current has been shown to reduce the slope of the APD restitution relation and convert VF into monomorphic ventricular tachycardia in vitro (181, 226) and to suppress the induction of VF in vivo (83).

Although constant pacing studies may provide a generic mechanism for wave break and the onset of ventricular tachycardia and fibrillation, it is unlikely that the conditions used to
demonstrate this phenomenon experimentally apply to the clinical situation, where the induction of ventricular tachyarrhythmias is typically associated with the interruption of normal cardiac rhythm by several premature beats. In addition, APD dynamics during rapid sustained pacing at a constant cycle length rely on the steady-state APD restitution relation, where APD is solely a function of the preceding diastolic interval. More realistic descriptions of APD restitution require consideration of multiple rate-dependent effects, as characterized by restitution portraits (113) and by determination of restitution kinetics during random or cyclical pacing protocols (46, 225). Marked differences in APD dynamics derived from the steady-state restitution relation and the restitution relations determined after abrupt changes in pacing intervals raise questions as to whether studies conducted during constant rapid pacing are relevant to the development of clinical ventricular tachyarrhythmias.

To address this issue, studies were recently conducted to determine whether dynamic heterogeneity and conduction block occur in one-dimensional cardiac fibers in which pacing at a slow rate was interrupted by one to four premature stimuli at variable intervals (77). This protocol simulated the interruption of sinus rhythm by one to four premature ventricular complexes, a situation that can lead to the onset of VF clinically. Computer modeling studies indicated that a short-long-short-long coupling interval pattern of premature stimuli induced marked spatial dispersion of repolarization and conduction block at some distance from the stimulus site, as predicted by interactions between APD and CV restitution (58, 77, 152, 217). Thus the dynamical mechanism for the development of block was the same as for the development of discordant alternans during sustained rapid pacing. Other premature stimulus interval patterns, such as short-long-long-short, also created conduction block, with each family of such patterns depending on both the steepness and the shape of the APD and CV restitution functions (77, 152). The predictions generated by the computer models subsequently were validated in vivo in normal dogs (83) and in dogs with an inherited predisposition to the development of polymorphic ventricular tachyarrhythmias.

These results are consistent with other studies that have examined related aspects of this problem. For example, Watanabe et al. (217) demonstrated that multiple beats at one site and a single premature beat at a different location from the pacing site are both sufficient to cause spatial heterogeneity in the form of discordant alternans, and Qu et al. (175, 176) studied how preexisting gradients in refractoriness can interact with one or more premature stimuli to produce conduction block. Moreover, Comtois et al. (52) have demonstrated that two properly timed stimuli following the passage of a propagating wave can produce unidirectional block and spiral wave reentry with a large window of vulnerability. Other studies have demonstrated that the development of conduction block does not necessarily require steep APD restitution, in that interactions between regions of ventricular myocardium having different APD restitution relations may be sufficient, as has been shown both numerically (16, 25, 50) and experimentally (69).

Taken together, these studies provide a rationale for the development of conduction block and reentry following certain patterns of premature stimuli (but not others) and indicate that heterogeneity of refractoriness is a function of not only preexisting or intrinsic heterogeneity but dynamical heterogeneity as well and that the latter can fluctuate on a beat-to-beat basis.

Although the destabilizing effects of an APD restitution curve that decreases monotonically with the pacing period have received the most attention, other types of APD restitution curves can also be associated with chaotic behavior and spiral wave breakup. For example, biphasic APD restitution curves, which contain a range of pacing periods over which APD increases as the period is decreased (negative slope region), have been shown to yield complex dynamics for one-dimensional maps (216), spatiotemporal chaos for one-dimensional rings (178), and spiral wave instability (68, 161). It is not necessary in this case for the absolute value of the slope of the APD restitution curve to exceed one for spiral wave breakup to result; the altered morphology of the restitution curve can lead to complex dynamics and breakup even when the curve is not steeply sloped over any range of periods (68). Biphasic APD restitution curves have been observed experimentally in different cardiac tissue preparations (80, 100, 200), although it has been suggested (68) that biphasic curves may result only when restitution curves are measured using a particular protocol, namely, the S1-S2 protocol (80, 122).

Similarly, a CV restitution curve that is not monotonically decreasing with the pacing period also can be associated with complex dynamics. An increase in CV as the period is decreased is also known as supernormal conduction and is associated with supernormal excitability (33, 45, 62, 63). The existence of supernormal CV restitution curves has been questioned (74); however, nonmonotonic CV has been observed in cell cultures (129). Along with chaotic dynamics in one-dimensional maps (45), increasing CV with decreasing period has been shown in simulations to lead to the bunching of propagating waves, which in turn can produce conduction block and generation of reentry (68, 85).

Factors other than APD and CV restitution may also vary over short time scales and account for spiral wave breakup. For example, the trajectories followed by spiral waves can affect their behavior. Meandering or drift of a spiral wave can produce a Doppler effect, in which the movement of the spiral wave affects the period at which the tissue is stimulated in a spatially dependent manner. Such an effect has been observed in cardiac tissue (57, 64, 163) and has been shown numerically to be capable of producing spiral wave breakup (20, 21, 68). Spiral wave trajectories can also play a role in the breakup of spiral waves when structural features such as the periodic boundary conditions of the ventricles are included. If the reentry follows a hypermeandering trajectory whose length is comparable to the length of the tissue, periodic boundaries can lead to wavefront-waveback interactions that produce localized conduction block and nucleation of additional reentrant waves (70, 73).

Spiral wave breakup can also result over short time scales from a negative tension property of the medium associated the stability of three-dimensional scroll waves. Specifically, tension in this setting describes the propensity of the organizing center of a scroll wave, called a filament, to remain straight if perturbed from an initially straight state. Scroll waves initiated in tissue with normal filament tension will quickly become straight again if perturbed, whereas scroll waves in tissue with negative filament tension will amplify small perturbations,
resulting in long, complicated filaments that are prone to breakup into multiple scroll waves (29, 68). Although healthy cardiac tissue is in the normal filament tension regime, some types of heart disease, including ischemia, are associated with electrophysiological modifications that modulate the filament tension to the negative regime, so that this mechanism of breakup may be associated with such pathophysiological conditions.

Anatomical structure also may interact with and destabilize reentrant waves. For example, the intrinsic transmural rotation of fibers from the epicardium to the endocardium (rotational anisotropy) (197, 205) has been shown numerically to produce an instability in the presence of meandering scroll waves that can give rise to complex dynamics and breakup of waves (65, 66, 73, 179). Although other destabilizing factors such as steep APD restitution may exacerbate the effect of fiber rotation (177), the instability caused by fiber rotation requires only a minimum tissue thickness and fiber rotation rate in combination with a sufficiently meandering tip trajectory (65, 66, 68, 73, 179). Even without considering such factors as fiber rotation, the complex geometry of realistic cardiac tissue has been shown in simulations to be capable of producing spiral and scroll wave breakup (40, 184).

Evolution of dynamics over intermediate times scales. Initial conditions and the resulting dynamics may also change over intermediate time scales, such as following periods of sustained pacing, during which memory may accumulate (30, 71, 75, 79, 106, 151, 206, 218). Typically, accumulation of memory flattens APD restitution, an effect that results from augmented rate-dependent activation of the delayed rectifier (75, 101, 102) and by increased inward rectifier (221).

Although the flattening of APD restitution resulting from sustained pacing at rapid rates is expected to reduce the probability of conduction block and reentry initiation, rapid pacing also promotes the transition from concordant to discordant APD alternans (41, 78, 162, 217), which would be expected to facilitate the development of reentry, secondary to the development of marked dispersion of APD and refractoriness. Consequently, arrhythmia initiation under these circumstances requires a rather specific interplay between APD alternans and memory. It should be noted that steep APD restitution is neither necessary nor sufficient for the development of alternans; along with memory, electronic effects arising from intercellular coupling together with CV restitution can interact to either suppress alternans when the APD restitution curve is steep or to produce alternans when the APD restitution curve is relatively flat (41, 55, 58, 151, 206).

Changes in triggering mechanisms for ventricular arrhythmias also may occur secondary to the rate and duration of pacing, with delayed afterdepolarization (DAD)-induced triggered activity typically being promoted by sustained rapid pacing and early afterdepolarization (EAD)-induced triggered activity being facilitated by slow pacing (223). Given that induction of triggered activity is rare in normal myocardium, the arrhythmogenic effects of sustained pacing at fast- or slow-pacing rates also will depend on the type and severity of underlying myocardial disease, as discussed in more detail in the following section.

Evolution of dynamics over prolonged times scales. Initial conditions may evolve over rather long time scales as the result of disease-induced electrophysiological and anatomical remodeling [for recent reviews, see (3, 97, 108, 110, 146)]. Several forms of myocardial disease have been shown to produce changes in ionic currents (density and type) and intracellular concentrations of various ions (Na+, K+, Ca2+), secondary to changes in ionic currents, as well as alterations in exchangers, pumps and the Ca2+-sequestering capacities of the sarcoplasmic reticulum (SR), nucleus, and mitochondria. Although the specific changes in individual ionic currents vary in different experimental models and clinical manifestations of heart failure, patterns of alterations are apparent, as discussed briefly in the following sections, which emphasize those changes that occur in nonspecific heart disease. Ultimately, alterations in ionic currents, in association with abnormalities of cell coupling and intracellular Ca2+ dynamics, conspire to create a permissive substrate for arrhythmia development, as well as an increased incidence of arrhythmogenic triggers.

RESTING MEMBRANE POTENTIAL: INWARD RECTIFIER K+ CURRENT. Inward rectifier K+ current (I\textsubscript{K1}) is significantly reduced at negative voltages in terminal human heart failure (28) and in rapid pacing-induced heart failure in the dog (112, 133), but not in the rabbit (187, 207). Reduction of I\textsubscript{K1} in the canine model is not accompanied by changes in the steady-state level of Kir2.1 mRNA, suggesting that the reduced current results from post-translational alterations of the channel protein (185). Kir2.1 and 2.2 knockout (234) and Kir2.1 dominant negative overexpressing mice (143) exhibited evidence of reduced I\textsubscript{K1} in the form of prolonged APDs, but as in most other models, there were no significant changes in resting membrane potential.

ACTION POTENTIAL UPSTROKE: Na+ CURRENT. It has been well established that Na+ current (I\textsubscript{Na}) is reduced in the setting of a subacute canine myocardial infarction (173). Myocytes isolated from the infarct border zone exhibit reduced I\textsubscript{Na} current density, accelerated inactivation, and slowed recovery from inactivation. These effects are manifest as reduced upstroke velocity and slow conduction, effects that resolve as the infarct heals (210). It might be expected that reduction of I\textsubscript{Na} would contribute to slow conduction in other forms of myocardial disease [e.g., (6, 130)], but the direct recordings of I\textsubscript{Na} available to date indicate that I\textsubscript{Na} is unchanged in human heart failure (112, 189).

EARLY REPOLARIZATION: TRANSIENT OUTWARD K+ CURRENT. Reduction of the transient outward K+ current (I\textsubscript{to}) occurs in a wide variety of heart disease, ranging from Chagas’ disease to chronic heart failure (28, 81, 111, 112, 144, 154, 155, 208). Although a reduction in current density occurs under all of these conditions, changes in current kinetics vary from no change (28) to rather profound changes (154, 155).

In human heart failure, reduced I\textsubscript{to} current is associated with reduced steady-state levels of Kv4 mRNA (7, 111, 144, 235). Studies in experimental models indicate that the downregulation of I\textsubscript{to} expression in heart failure may be mediated by the Ca2+/calmodulin-dependent protein kinase II (CaMKII) and calcineurin/nuclear factor of activated T-cells signaling cascades (157, 228).

ACTION POTENTIAL PLATEAU: Ca2+ CURRENT AND LATE Na+ CURRENT. Changes in L-type Ca2+ current (I\textsubscript{Ca,L}) density in diseased ventricles are variable, depending on the type of disease and its severity. In the early stages of heart failure marked by hypertrophy, I\textsubscript{Ca,L} may be increased (31, 37), whereas in the failing heart it may be unchanged (27, 112) or
decreased (97, 166, 182). Studies of $I_{\text{Ca-L}}$ density in human heart failure suggest that current density is held near normal levels by increased phosphorylation, despite the fact that the response to β-adrenergic receptor-mediated phosphorylation is attenuated (39, 153). In that regard, single channel studies in failing myocytes suggest that phosphorylation may offset a reduction in channel number by increasing open channel probability (193).

The molecular bases for changes in $I_{\text{Ca-L}}$ density in failing ventricles are incompletely understood, as reflected by reports of variable subunit mRNA expression (202) and isoform switching of both α1C- (231) and β-subunits (104). A role for the latter is suggested by studies in which knockdown of the β-subunit reduced $I_{\text{Ca-L}}$ density and the development of hypertrophy in an experimental model, with minimal negative inotropic effects (49).

With respect to late $I_{\text{Na}}$ during the action potential plateau, several studies have indicated that this current is increased in human and canine heart failure (209, 211), possibly resulting from a slowing of inactivation kinetics and a shift of the voltage dependence of steady-state inactivation, as mediated by intracellular Ca$^{2+}$/CaMKII signaling (140, 214).

**TERMINAL REPOLARIZATION: DELAYED ($I_{\text{Kr}}$, $I_{\text{Kr}}$, and $I_{\text{Ks}}$) AND INWARD ($I_{\text{K1}}$) RECTIFIER K+ CURRENTS.** Reduced $I_{\text{K1}}$ density, slower activation, and faster deactivation kinetics have been observed in hypertrophied feline ventricles (82). Downregulation of both $I_{\text{Kr}}$ and $I_{\text{Ks}}$ have been reported in a rabbit model of rapid ventricular pacing-induced heart failure (207, 208), whereas $I_{\text{Ks}}$ but not $I_{\text{Kr}}$ was downregulated in all layers of the left ventricular myocardium in a canine model of tachycardia-induced heart failure (133). The molecular basis for $I_{\text{K1}}$ down-regulation in heart failure remains unclear. Studies of mRNA levels of the genes encoding the α-subunits for the rapidly human ether-a-go-go gene (HERG) and slowly voltage-gated K$^+$ channel long Q-T mutant (KvLQT1) activating components of $I_{\text{K}}$ found no statistical difference between normal and failing canine hearts (185). Reduced $I_{\text{K1}}$ density in heart failure also may contribute to a prolongation of APD (133, 148, 169, 185).

**Ca$^{2+}$ TRANSIENTS.** The initiation and termination of the Ca$^{2+}$ transient in cardiac myocytes is a complex interplay between Ca$^{2+}$-induced Ca$^{2+}$ release from the SR via the ryanodine receptor (RyR2), reuptake of Ca$^{2+}$ into the SR by the sarco-(endo)plasmic reticulum Ca$^{2+}$-ATPase 2 (SERCA2a), and extrusion of Ca$^{2+}$ via the Na$^+$/Ca$^{2+}$ exchanger (NCX). Each of these components of intracellular Ca$^{2+}$ dynamics is altered during heart failure (3, 95, 108, 110, 142).

First and foremost, the amplitude of the Ca$^{2+}$ transient and its rate of decay are reduced (149). The reduction in the amplitude reflects a reduction in the density of RyR2 (15, 180), resulting in less Ca$^{2+}$ release from the SR, whereas the prolongation of the transient is caused, in part, by a reduction in the density and uptake rate of SERCA2a (149, 190, 191). NCX density and function are upregulated in heart failure (17, 26, 99), perhaps as a compensatory mechanism to counteract the reduction in SR Ca$^{2+}$ uptake.

In addition to being downregulated during heart failure, RyR2 receptors are “leaky,” secondary to hyperphosphorylation of RyR by protein kinase A (141) or by CaMKII (2, 54, 123, 135, 139) or possibly by redox modification (204). Excessive SR Ca$^{2+}$ may increase diastolic Ca$^{2+}$ concentration.

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**Fig. 1.** Nonsustained ventricular fibrillation in rabbit ventricles initiated by rapid pacing at a period of 80 ms. A: anterior and posterior views. B–E: optical signal during nonsustained fibrillation; color represents voltage. Frames show anterior and posterior views at 4 different times (600, 1,200, 2,000, and 2,400 ms). F: spatial frequency domain showing a maximum frequency of about 10 Hz. Color bar indicates frequency in hertz. Hearts were Langendorff perfused with oxygenated Tyrode solution at 37°C with 10 μM blebbistatin.
and generate spontaneous Ca\textsuperscript{2+} waves and delayed afterdepolarization-induced triggered activity.

Although altered Ca\textsuperscript{2+} dynamics are likely to contribute importantly to the development of ventricular tachyarrhythmias, particularly in the setting of heart failure, the exact nature of that contribution has yet to be established (94, 109, 132, 138, 227). As discussed briefly below, Ca\textsuperscript{2+} participates in the development of arrhythmogenic triggers (EAD and DAD), as well as permissive substrates for arrhythmia initiation and perpetuation. In particular, a complex interplay between voltage and Ca\textsuperscript{2+} alternans may lead to multiple arrhythmogenic scenarios, as reviewed recently by Weiss et al. (220).

**CONEJECTINS.** The density, distribution, and molecular properties of the predominant cardiac gap junction protein connexin 43 (Cx43) are altered in various forms of myocardial disease (6, 35, 167, 232). Cx43 typically is downregulated and is redistributed from the intercalated disk to the cell border, a process known as lateralization (4, 6, 114, 126, 165). In rapid pacing-induced heart failure, Cx43 downregulation is associated with an overall reduction in Cx43 mRNA, yet a hypophosphorylated component of the protein is actually more abundant than in control myocardium (4, 6). Other studies have supported the concept that changes in gap junction function and concomitant alterations of cell coupling and CV may not be solely functions of gap junction density but also may relate to Cx43 localization, colocalization with other gap junction proteins, trafficking, and phosphorylation status (22, 61, 96, 194, 233).

Alterations in intercellular coupling are known to contribute to the development and maintenance of reentrant waves in cardiac tissue (32, 57b, 93, 121). Although a reduction of coupling in experimental settings is unlikely to occur homogeneously and may be considered as promoting wave break by increasing tissue heterogeneity, uniform reduced coupling has been shown in numerical simulations to give rise to the breakup of reentrant waves, especially in the setting of rotational anisotropy (10, 68, 118–120, 159, 160).

**ARRHYTHMOGENIC TRIGGERS AND SUBSTRATES.** The predominant electrophysiological changes that accompany heart failure-induced remodeling are slowing of conduction and prolongation of APD (3, 5, 146). Prolongation of APD typically is heterogeneous (5, 88), amplifying the intrinsic APD dispersion of the normal heart, including base-to-apex (51, 57c) and transmural gradients (13, 213), where the magnitude of the latter is still a matter of some debate.

The electrophysiological alterations associated with heart failure promote the development of arrhythmia triggers. Specifically, the combination of prolonged APD, abnormal Ca\textsuperscript{2+} cycling, and increased late Na\textsuperscript{+} current is conducive to the generation of EAD-induced triggered activity (133, 148, 209, 229). In addition, increased SR Ca\textsuperscript{2+} leak and increased NCX promotes DAD-induced triggered activity (169, 212).

Afterdepolarizations provide a potential triggering mechanism for arrhythmias both in the setting of bradycardia (EADs) and tachycardia (DADs), although the clinical manifestations of these phenomena have yet to be demonstrated conclusively. Triggered activity also may be the underlying mechanism for sustained tachycardias in the setting of ischemic cardiomyopathy and dilated or hypertrophic cardiomyopathy, where in many cases the arrhythmias appear to be generated by a focal, as opposed to reentrant, mechanism (11, 116, 168, 170, 171).

With respect to arrhythmogenic substrates, the combination of heterogeneously prolonged repolarization and slowed conduction in diseased hearts is expected to facilitate the initiation

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**Fig. 2. Sustained ventricular fibrillation in rabbit ventricles initiated by rapid pacing at a period of 80 ms preceded by a conditioning period (15 min) of fast pacing at 250 ms in the same heart as shown in Fig. 1. A–E: optical signal during sustained fibrillation; color represents voltage. Frames show anterior and posterior views at 5 different times (600, 1,200, 1,800, 2,400, and 3,000 ms). F: spatial frequency domain showing a maximum frequency of about 10 Hz. When compared with the nonsustained VF episode shown in Fig. 1, a larger fraction of the tissue exhibits the maximum frequency. Color bar indicates frequency in hertz.**
and maintenance of reentrant arrhythmias. The requirements for reentrant excitation—unidirectional conduction block, slow conduction, and reexcitation of the previously blocked region—are satisfied by dispersion of refractoriness secondary to heterogeneous APD prolongation and by slow conduction secondary to decreased $I_{Na}$ and connexin lateralization and hyperphosphorylation, as discussed above. Dispersion of refractoriness may be exacerbated in some forms of myocardial disease secondary to alterations of APD restitution (124, 145, 156). Reentrant arrhythmias are most commonly observed in the setting of a healed myocardial infarction (35, 57a, 164), but evidence of reentry also has been observed in models of nonischemic heart failure (5, 6, 131).

A systems-based perspective on arrhythmia development. As is evident from the foregoing, the changes in cellular electrophysiology that accompany myocardial disease are many and varied, impacting virtually every aspect of ventricular electrical activity (and an equally long list of alterations in mechanical activity could easily be generated). Consequently, it does not seem reasonable to expect a single root cause for ventricular arrhythmias, the identification and eradication of which would return the system to normal function. The cardiovascular system reacts to disease as a system, often in counterintuitive or even counterproductive ways, such as by remodeling the atria in response to paroxysmal atrial fibrillation to promote more sustained fibrillation. Understanding the adaptations of the cardiovascular system to disease and their consequences for arrhythmia development might best be accomplished using a systems-based approach.

By a systems-based approach, we mean an approach similar to that used in systems biology, where various known inputs are delivered to the system (a.k.a. a “black box”) and the resulting output characteristics of the system are measured. The properties of the system are then derived from the differences between the inputs and outputs. If the system is sufficiently well characterized using this method, its behavior can be understood without a detailed knowledge of its component parts. Moreover, if something (but not everything) is known about the system, control theory can be applied to predictably alter its behavior (47).

The effectiveness of a purely systems-based approach begins to break down, however, if one wants to develop specific therapies for arrhythmias, pharmacological therapy in particular. Whereas knowing that a given behavior of the system depends on the properties of the “slow variable” in a simple computer model can be very useful for defining the dynamics of the system, it is not very useful for defining therapy, in that there are no “slow variable”-specific drugs. It is necessary to know what ionic current (or, more likely, currents) underlies the slow variable and then design drugs to bind to the relevant ion channels with the appropriate affinities and kinetics. Given the apparently infinite number of potential interactions between the large number of ion channels, transporters, pumps, second-messenger systems, etc., that determine cardiac electrical activity and the equally large number of alterations of those determinants with various forms of heart disease, the chances of developing an effective antiarrhythmic therapy based on a reductionist approach seem small compared with what might be achieved using a systems-based approach. However, that conjecture remains to be validated.

Examples of different arrhythmia outcomes depending on initial conditions. As discussed above, the characteristics of a given ventricular arrhythmia may importantly depend on the electrophysiological state of the ventricles at the time of arrhythmia initiation, where small changes in the initial state can lead to large differences in outcome. To illustrate that point, we present in this section examples of different arrhythmia outcomes following perturbations to the initial state of isolated perfused rabbit hearts and a mathematical model of the canine ventricle.

![Fig. 3. Stable and unstable spiral waves in a computer simulation of the FMG mathematical model. A: initiation of a spiral wave with transient breakup that results in a stable spiral wave. The spiral ultimately follows a complex hypermeandering trajectory. B: sustained spiral wave breakup initiated following tissue preconditioning by pacing at 300 ms for 30 s. C: sustained spiral wave breakup initiated following tissue preconditioning at 220 ms for 30 s, resulting in more waves with shorter wavelengths. The domain in all cases is 30 cm × 30 cm, and the spatial resolution is 0.0125 cm.](image-url)
Figure 1 shows an example of nonsustained fibrillation initiated in rabbit ventricles using a rapid pacing protocol following a training period of pacing for 5 min at 500 ms. Although immediately after initiation multiple waves are present in the tissue, the propagation pattern in the ventricles soon becomes more regular, eventually leaving a single long-wavelength wave that cannot fit in the tissue and extinguishes itself. Despite the apparent difficulty of inducing sustained fibrillation in rabbit ventricles (19, 136), it is possible to initiate sustained fibrillation in rabbit ventricles by pacing at a faster rate before inducing an arrhythmia. Figure 2 shows an example of sustained fibrillation initiated in the same preparation as that shown in Fig. 1 using the same rapid pacing protocol, but in this case following a training period of pacing at 250 ms for 5 min. In this case, the difference in pacing history between the two episodes affected the initial state of the system so as to allow fibrillation to be sustained following more rapid pacing. For both instances of fibrillation, the dominant frequency is between 8 and 10 Hz and the frequencies appear more spatially uniform in the sustained case, although the average frequency is also somewhat higher in that scenario. Results were replicated in five different preparations.

A comparable sensitivity to initial conditions has been observed in computer simulations as well. For the model of ten Tusscher et al. (203), it was previously observed that although a spiral wave remains stable when initiated in a domain conditioned by pacing at a relatively slow period of 1,000 ms, the same initiation protocol gives rise to sustained breakup when the tissue had been previously paced at a period of 300 ms (34). As shown in Fig. 3, the model of Fox et al. (76) exhibits similar behavior, with a stable spiral wave resulting in tissue paced for 30 s at a period of 500 ms and sustained breakup resulting after pacing for 30 s at periods of 300 ms and 220 ms, with the shorter period producing more complicated behavior with a larger number of waves having shorter wavelengths. The dynamics of a reentrant wave may also depend on the timing of a premature beat used to initiate it, especially when the reentrant wave follows a hyperbolic trajectory (42).

Conclusion

Given the dynamical nature of cardiac arrhythmia initiation and perpetuation, the likelihood of identifying a therapeutic “magic bullet” along the lines of penicillin for infection or insulin for diabetes seems remote (59, 215). In addition, the apparent dependence of arrhythmia development on initial conditions is likely to confound predictions of arrhythmia risk based on static measures of electrophysiological properties. Consequently, for the near-term arrhythmia therapy is likely to be dominated by brute-force approaches such as ablation and high-voltage defibrillation defibrillation [although lower-energy alternatives may be on the horizon (9, 72, 134, 137)]. It should be noted that even the draconian therapies are not uniformly effective and that their efficacy depends on the state of the myocardium at the time of delivery (e.g., the efficacy of defibrillation varies depending on how soon after the onset of fibrillation the shocks are delivered and on the disease-dependent state of the myocardium). Even with substantial improvements in electrical and pharmacological therapy, however, an elimination of most lethal arrhythmias will not occur unless and until the root causes of those arrhythmias—heart failure and coronary artery disease—are eradicated. Nevertheless, a successful antiarrhythmic therapy has clear benefits with respect to quality of life and longevity and should continue to be pursued vigorously.

REFERENCES


Review

VENTRICULAR ARRHYTHMIA


