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CONTEMPORARY REVIEW

Clinical Potential of Beat-to-Beat Diastolic Interval Control in Preventing Cardiac Arrhythmias

Kanchan Kulkarni, PhD; Richard D. Walton, PhD; Antonis A. Armoundas, PhD; Elena G. Tolkacheva, PhD

ABSTRACT: Life-threatening ventricular arrhythmias and sudden cardiac death are often preceded by cardiac alternans, a beat-to-beat oscillation in the T-wave morphology or duration. However, given the spatiotemporal and structural complexity of the human heart, designing algorithms to effectively suppress alternans and prevent fatal rhythms is challenging. Recently, an antiarrhythmic constant diastolic interval pacing protocol was proposed and shown to be effective in suppressing alternans in 0-, 1-, and 2-dimensional in silico studies as well as in ex vivo whole heart experiments. Herein, we provide a systematic review of the electrophysiological conditions and mechanisms that enable constant diastolic interval pacing to be an effective antiarrhythmic pacing strategy. We also demonstrate a successful translation of the constant diastolic interval pacing protocol into an ECG-based real-time control system capable of modulating beat-to-beat cardiac electrical activity and preventing alternans. Furthermore, we present evidence of the clinical utility of real-time alternans suppression in reducing arrhythmia susceptibility in vivo. We provide a comprehensive overview of this promising pacing technique, which can potentially be translated into a clinically viable device that could radically improve the quality of life of patients experiencing abnormal cardiac rhythms.

Key Words: alternans ■ arrhythmias ■ control ■ diastolic interval ■ pacing

Life-threatening ventricular tachyarrhythmias, leading to sudden cardiac death, are often preceded by T-wave alternans (TWA), beat-to-beat oscillations in the morphology of the action potential or the action potential duration (APD), and the T-wave of the ECG. Studies of the mechanisms linking TWA to arrhythmogenesis[1–7] have shown that increased dispersion of repolarization is an important condition for the development of concordant or discordant alternans.[8–10] In turn, localized discordant alternans increases vulnerability of the substrate and susceptibility of the heart to ventricular tachycardia (VT) or ventricular fibrillation (VF).[1] Multiple groups[11,12] have demonstrated that the magnitude of TWA measured using intracardiac electrograms from implantable cardioverters-defibrillators rises sharply before spontaneous VT/VF.[13–15] There is compelling evidence supporting the idea that the same mechanisms responsible for TWA occurrence, such as functional spatial dispersion of repolarization,[1,9,10,16–22] are likely to also lead to VT/VF, implying that heightened TWA can occur either before or in conjunction with VT/VF. This suggests that significantly elevated levels of TWA may serve as a predictor of impending arrhythmias. Indeed, we have shown that TWA is a short-[23–26] and long-term[27,28] predictor of susceptibility to ventricular tachyarrhythmias.

The implantable cardioverter-defibrillator is currently the most effective means of detecting and treating lethal ventricular arrhythmias (ie, VT/VF).[29–31] However, despite its rapid acceptance and growth, the main limitation of the current implantable cardioverter-defibrillator technology is that it applies therapy only on the arrhythmia onset. Therefore, there is substantial clinical interest and a need to develop novel therapeutic approaches that prevent the onset of lethal heart rhythms. One such recent approach uses

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Nonstandard Abbreviations and Acronyms

APD	action potential duration
BCL	basic cycle length
DI	diastolic interval
HR	heart rate
TRI	TR interval
TWA	T-wave alternans

a measurement of the instantaneous beat-to-beat variability in the morphology of ECG waveforms (namely, TWA) to deliver preventive electrical therapy to the heart on a dynamic beat-by-beat basis. Various alternans-controlled algorithms have shown positive results in silico and in vitro.[32–35] In preclinical studies, precise control of APD and diastolic interval (DI) has been used to control alternans and prevent the occurrence of life-threatening cardiac rhythms.[32,33,35–44] Also, prior studies have demonstrated that elimination of alternans could lead to the prevention of VT/VF.[45–48] However, alternans is a spatial phenomenon, and given the structural complexity of the human heart, experimental control of alternans has exhibited limited success, especially in 2-dimensional settings.[36,39,44,49]

A novel control algorithm that successfully prevented the onset of alternans by eliminating the dependence of the DI on the preceding APD was first implemented by Jordan and Christini[37] in a 1-dimensional (1D) Purkinje fiber in silico study and subsequently validated by our group using in silico[42,43,50,51] and ex vivo[40] experiments. The results support the hypothesis that controlling the DI on a beat-by-beat basis can eliminate the interdependency between the APD and DI and in turn ensure that the succeeding APD in every beat is independent of prior electrical perturbations.

Herein, we provide a systematic review of the potential of constant DI pacing in preventing cardiac arrhythmias by eliminating the onset of TWA. We present promising results of this novel technique in TWA control and prevention using in silico, ex vivo, and preclinical in vivo experiments, while elucidating the mechanisms that enable this method to be a compelling antiarrhythmic pacing strategy.

ELECTRICAL RESTITUTION AND FEEDBACK

Electrical restitution is a fundamental property of cardiac myocytes and is responsible for shortening APD in response to an increase in heart rate (HR). Although it is essential for regulating electrical function at moderate HRs, restitution can lead to life-threatening cardiac rhythms, such as alternans,[18,44,45,47,48,52,53] at higher rates. Indeed, it has been proposed that electrical restitution can lead to the bifurcation from a constant APD response to an alternating long-short APD pattern (alternans) when transitioning from slow to faster HRs.[54]

Nolasco and Dahlen were one of the first to investigate the onset of APD alternans and modeled cardiac restitution using a 1D mapping model with the assumption of constant periodic pacing.[55] Specifically, they proposed that the APD generated by the $(n+1)^{st}$ stimulus, APD_{n+1}, was solely determined by the preceding DI, DI_n.

$$APD_{n+1} = f(DI_n) \quad (1)$$

where f is the restitution curve. In addition, periodic stimulation imposes a second constraint on the APD and DI as the time interval between 2 adjacent stimuli, the basic cycle length (BCL), is fixed (Figure 1). In this case, APD and DI are interdependent through the periodic pacing relation:

$$APD_n + DI_n = BCL = \text{constant} \quad (2)$$

Therefore, during periodic pacing (Equation 2), there is a partial dependence of the DI_n on the preceding APD_n, leading to an inherent "feedback." The presence of feedback, in conjunction with restitution (Equation 1), causes small changes in APD_n that translate into changes in DI_n and subsequently into changes in the APD_{n+1}, thus enhancing the electrical instability in the heart.[43,44,56,57] Therefore, maintaining a constant DI_n,

$$DI_n = DI = \text{constant} \quad (3)$$

in Equation 2, eliminates the pacing relation between APD and DI, thus eliminating feedback (Figure 1). Although other theories for the mechanisms of alternans onset have been proposed,[3,10,23,58] this restitution-based mechanism of alternans formation remains the most predominant in the context of periodic pacing.[18,23,40,45–48,52,53,59]

IN SILICO IMPLEMENTATION OF CONSTANT DI PACING

Multiple groups have investigated the control of alternans using in silico and in vitro experiments,[32,33,35–37,42–44,60,61] albeit with mixed results. Positive results in controlling alternans using single-cell models and in vitro preparations were obtained by predominantly using an adaptive feedback algorithm that adjusted the BCL based on the amplitude of alternans,[33–35,62] requiring a precise knowledge of real-time APD and DI.[63] However, in more complex spatiotemporal 1D and 2-dimensional settings, control of alternans has been unsuccessful. Echebarria and Karma[49] reported that the spatiotemporal control of cardiac alternans failed above a critical 1D cable length. These

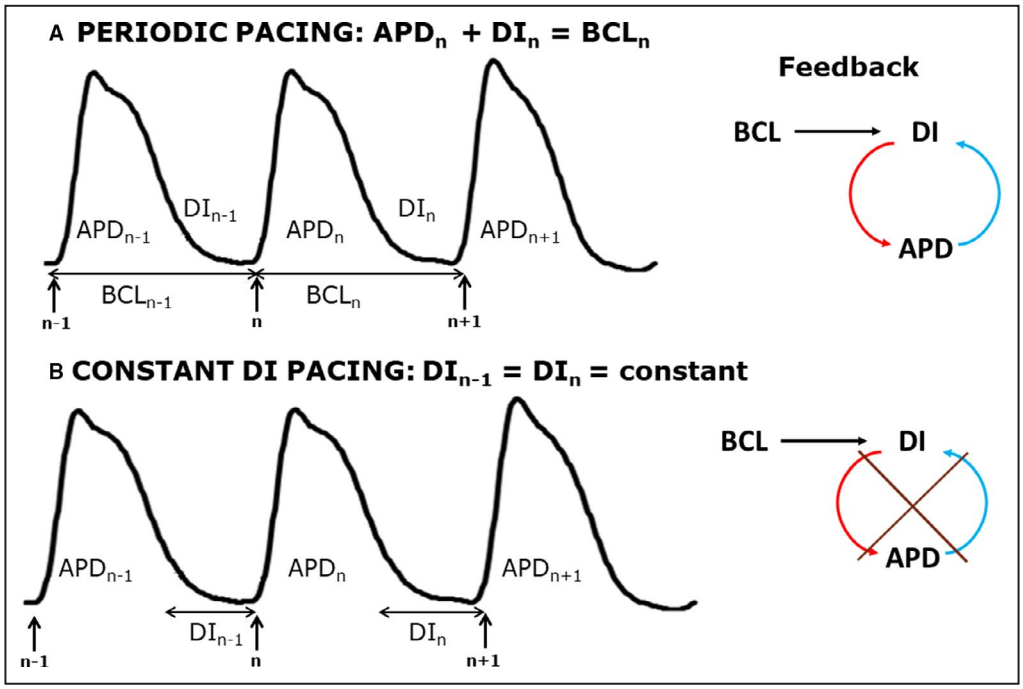

Figure 1. Representative action potential traces demonstrating the functional difference between periodic pacing (A) and constant diastolic interval (DI) pacing (B).
In periodic pacing, the duration between consecutive stimuli (basic cycle length [BCL]) is constant from beat to beat, creating a partial dependence of the DI on the preceding action potential duration (APD) (DI_n=BCL–APD_n) (ie, feedback). Feedback elimination can be achieved by controlling and maintaining a constant DI on a beat-by-beat basis, hence eliminating the inherent dependence of the DI on the preceding APD.

findings were further supported by Christini et al,[36,38,39] who demonstrated that control was spatially attenuated with an increase in alternans amplitude. The novel control algorithm with adaptive DI control, introduced by Jordan and Christini,[37] has been shown to control alternans in a 1D Purkinje fiber in silico study, albeit with limited spatial control.

Initial experiments by our group demonstrated the successful prevention of alternans onset (instead of controlling already existing alternans) by the application of constant DI pacing using a physiological ionic model of a canine cardiac action potential.[43] The model[64] exhibits APD alternans when chronotropically paced at progressively decreasing BCLs using periodic pacing. It is believed that the inclusion of HR variability in periodic pacing is a promising direction toward creating more physiological pacing modalities. However, we have demonstrated (Figure 2) that when HR variability is included in periodic pacing, alternans is still present, even over wider ranges of pacing frequency, suggesting that periodic pacing, with or without HR variability, is proarrhythmic because of the presence of inherent feedback.[43] However, constant DI pacing has been able to completely inhibit the formation of cellular alternans by eliminating feedback between APD and DI, with or without HR variability.

We further extended these results to cable models and investigated the efficacy of constant DI pacing in preventing alternans formation during wave propagation conditions.[51] We applied constant DI pacing to ventricular cable models using human kinetics. The results demonstrated that the onset of both cardiac alternans and conduction blocks shifted to higher pacing rates during constant DI pacing in comparison to periodic pacing (Figure 3A). Figure 3B demonstrates representative traces of APD along the 3-cm length of the cable for 2 consecutive beats, exhibiting alternans (BCL=185 ms) during periodic pacing. In comparison, constant DI pacing successfully prevented the onset of alternans, as observed from the representative traces of APD for 2 consecutive beats along the length of the cable in Figure 3C.

DEPENDENCE OF CONSTANT DI EFFICACY ON UNDERLYING MECHANISMS OF ALTERNANS

The promising in silico effects of constant DI pacing were shown to be effective in preventing primarily voltage-driven alternans. Two main theories have been broadly accepted to explain the pathogenesis of cardiac

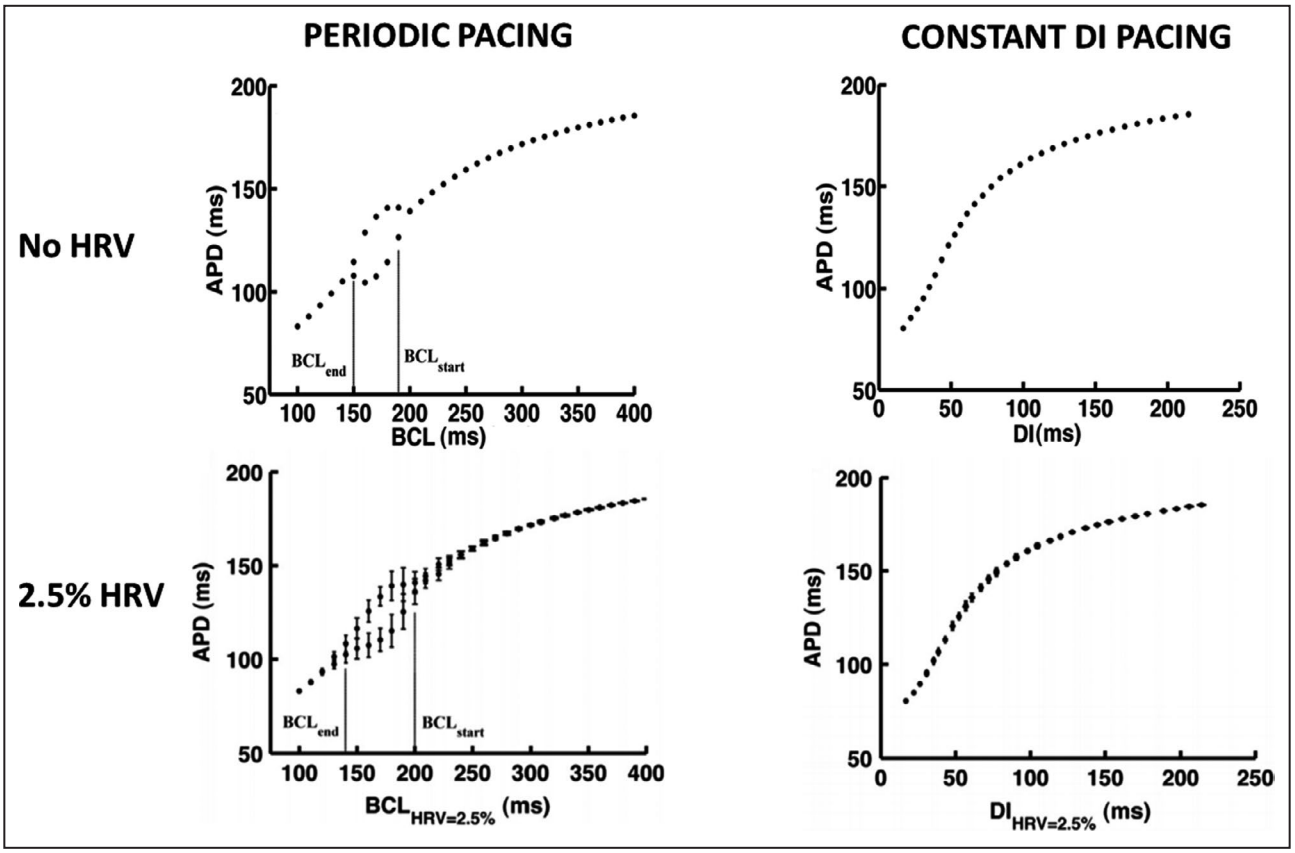

Figure 2. Action potential duration (APD) as a function of basic cycle length (BCL) (or diastolic interval [DI]) for a single-cell ionic model paced with periodic pacing and constant DI pacing with 0% and 2.5% heart rate variability (HRV).
BCL_{start} and BCL_{end} denote the start and end of APD alternans, respectively. Reproduced with permission from McIntyre et al[43] ©2014, Elsevier.

alternans.[23] The first proposes that alternans is an action potential or voltage-driven phenomenon. Subsequently, alternation in cellular sarcolemmal currents and APD drive alternation in intracellular Ca^{2+} concentration, leading to calcium alternans.[58,65,66] However, the second theory postulates that alternans is a calcium-driven phenomenon wherein changes in intracellular Ca^{2+} concentration drive membrane voltage changes and subsequently cause APD alternans.[1,4,59,65,67–71]

More recently, it was reported that constant DI pacing might not effectively prevent alternans in situations involving calcium cycling abnormalities. Indeed, using a combination of a memory model and a calcium cycling model, the presence of alternans during constant DI pacing was reported in a 1D fiber in silico study.[72] Similar results were reported in a study investigating the role of intracellular Ca^{2+} dynamics in the persistence of alternans despite constant DI.[73] The effect of constant DI pacing was evaluated using mathematical models capable of producing alternans through both voltage- and calcium-driven mechanisms, and it was shown that although constant DI pacing effectively prevented voltage-driven alternans, in the case of calcium-driven alternans, its success was limited.[73] Furthermore, the efficacy of constant DI pacing in eliminating alternans was inversely correlated to the strength of the calcium instability and progressively increased as the instability was reduced, making it a possible marker for differentiating between voltage-driven and calcium-driven alternans. Another recent study investigating the effect of applying feedback control on the BCL to suppress alternans demonstrated that APD control induced spatially discordant alternans when the underlying instability was calcium driven.[74]

Following the studies pointing to differences in outcomes caused by differences in underlying mechanisms, we investigated the response of the cardiac cell model to constant DI pacing in the case of voltage-driven alternans, and we demonstrated that the presence of constant DI pacing alters cardiac cell dynamics.[50] Specifically, the response of a single cell to periodic pacing (Equation 2) at certain BCL values was affected by the presence of constant DI pacing. Indeed, we demonstrated that application of periodic pacing after constant DI pacing can lead to either a 1:1 response or alternans, depending on the initial conditions, thus introducing a region of bistability.[50] Furthermore, the size of the region of bistability was

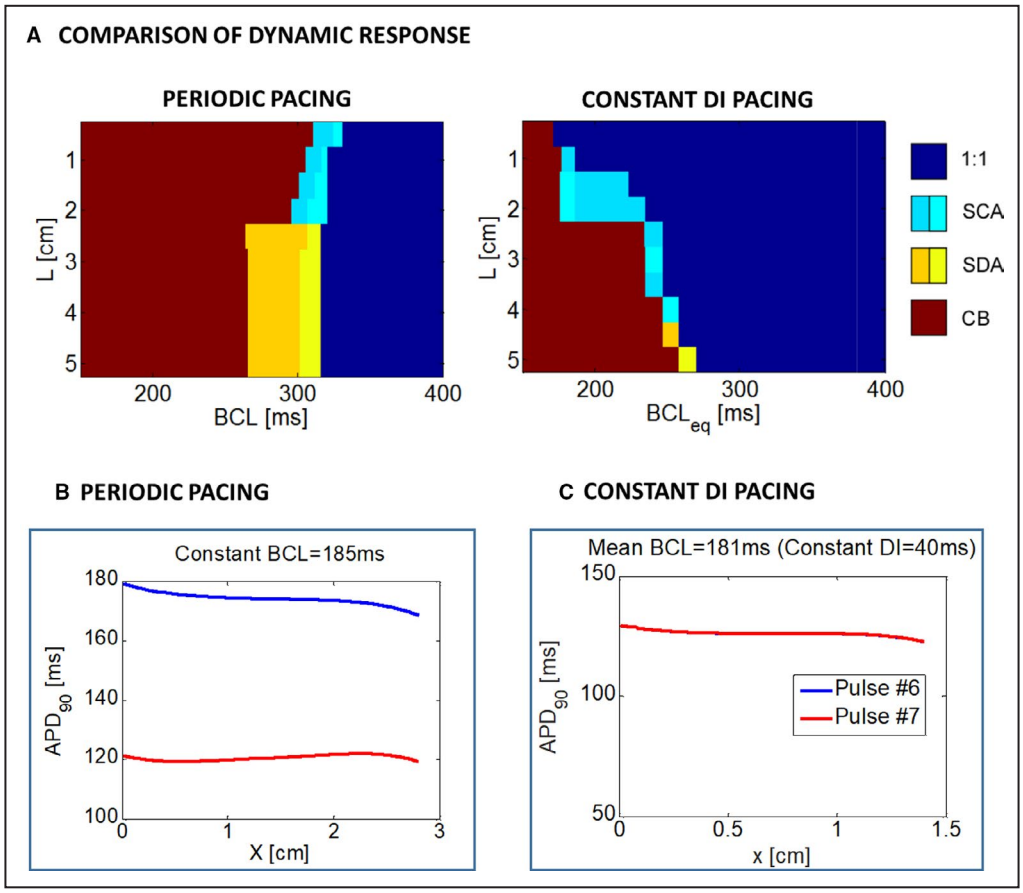

Figure 3. Application of constant diastolic interval (DI) pacing to ventricular cable model using human kinetics.

A, Dynamical response of the human ventricular cable model for periodic pacing (constant basic cycle length [BCL]) and constant DI pacing at varying cable lengths (L). BCL_{eq} represents the calculated BCL for each DI (DI+ action potential duration [APD]=BCL_{eq}). Colors represent different electrical responses: normal 1:1 conduction (dark blue), spatially concordant alternans (SCA) (light blue), spatially discordant alternans (SDA) (yellow), and conduction block (CB) (red). Darker or lighter color shade denotes alternans amplitude being larger or smaller than 50 ms, respectively. **B**, Representative traces of APD corresponding to beats 49 (red) and 50 (blue) along the 3-cm length of the cable exhibiting alternans (BCL=185 ms) during periodic pacing. **C**, Representative traces of APD corresponding to beats 6 (red) and 7 (blue) along the length of the cable during constant DI pacing. No onset of alternans was observed. Reproduced from Zlochiver S, Johnson C, Tolkacheva E. Constant DI pacing suppresses cardiac alternans formation in numerical cable models. *Chaos*. 2017;27:093903, with the permission of AIP Publishing.[51]

directly correlated to the strength of voltage-calcium coupling and increased with stronger voltage-calcium coupling. The results suggest that the application of constant DI in conjunction with strong voltage-calcium coupling may stabilize cardiac cell dynamics during periodic pacing, thus increasing the utility of constant DI pacing in suppressing alternans.

EXPERIMENTAL EVALUATION OF CONSTANT DI PACING USING EX VIVO OPTICAL MAPPING

Implementation of constant DI pacing experimentally has been an extremely challenging task.[44,56] A major constraining factor has been the difficulty in executing precise, local, real-time APD and DI measurements, and translating the local feedback information into a global control strategy capable of preventing the spatial evolution of alternans in the whole heart. To address this shortcoming, we introduced the concept of "global" constant TR interval (TRI) pacing, which is based on ECG recordings and provides an indirect measure of global DI relaxation period in the heart through the TRI assessment.[42] We further compared the efficacy of local constant DI control with global constant TRI pacing in preventing alternans using a 1D numerical model of human ventricular tissue. We observed that although both constant TRI and constant DI pacing prevented the onset of alternans, for longer

cable lengths, constant TRI pacing exhibited greater control on alternans than constant DI pacing.[42]

Next, we extended the concept of TRI pacing to isolated hearts and successfully demonstrated the antiarrhythmic effects of constant TRI pacing in ex vivo whole rabbit hearts using optical mapping studies[40,41] (Figure 4). To incorporate constant TRI pacing, we developed a novel closed-loop cardiac control system, which detects, on a beat-by-beat basis, the instantaneous T waves and applies stimuli after a predetermined fixed TRI to essentially implement global DI control.[40] Optical videos are recorded simultaneously to investigate the efficacy of the control technique in alternans prevention. Figure 5 demonstrates representative 2-dimensional APD maps corresponding to chronotropically decreasing BCLs, for 2 consecutive beats during both periodic pacing (Figure 5A) and constant DI pacing (Figure 5B).[40] Corresponding 2-dimensional alternans maps and action potential traces highlight the absence of spatiotemporal alternans during constant DI pacing as opposed to periodic pacing.

Figure 5C presents summary results across all experiments (n=8), quantifying the presence of alternans during both periodic and constant DI pacing. Although periodic pacing always led to the onset of alternans and even VF, constant DI pacing was able to inhibit the onset of alternans in both the left ventricle (LV) and right ventricle and prevent the spatial evolution of alternans (Figure 5D).[40] This was the first study to demonstrate the prevention of alternans by constant DI pacing using a translational, real-time, beat-by-beat, closed-loop control system capable of global TRI control.

PRECLINICAL UTILITY OF REAL-TIME CLOSED-LOOP CONTROL IN ALTERNANS SUPPRESSION

To further probe the translational potential of constant DI pacing, we recently developed and evaluated a novel closed-loop method to dynamically modulate TWA in an in vivo myocardial infarction swine model.[26,40,75,76] The real-time control system is capable of recording and analyzing TWA from multiple intracardiac leads[11] and delivering stimuli at a fixed interval on a beat-by-beat basis on detection of the T wave.[77] In addition, the algorithm has the ability to identify and exclude/replace abnormal beats (ie, premature ventricular complexes and extrasystoles) based on a template matching technique. Any changes in alternans phase caused by abnormal beats are also addressed by an alternans-phase detection algorithm.[77]

Figure 6 shows data from a single animal where the alternans voltage and K_{score} (a statistical measure of TWA relative to background noise[11,26]) are plotted for 2 intracardiac bipolar leads (CS4LV3 and CS4LV9) from catheters in the coronary sinus (CS; CS1/CS10 correspond to distal/proximal sites, respectively) and LV (LV1/LV10 correspond to basal/apical sites, respectively). During coronary artery occlusion (baseline, beats 0–825), significant spontaneous TWA is present, as evidenced by elevated levels of alternans voltage and K_{score}. On detection of significant TWA, the system applies real-time TWA-suppression pacing on every beat with the following pacing pulse parameters: amplitude, 5 mA; width, 5 ms; and T-wave

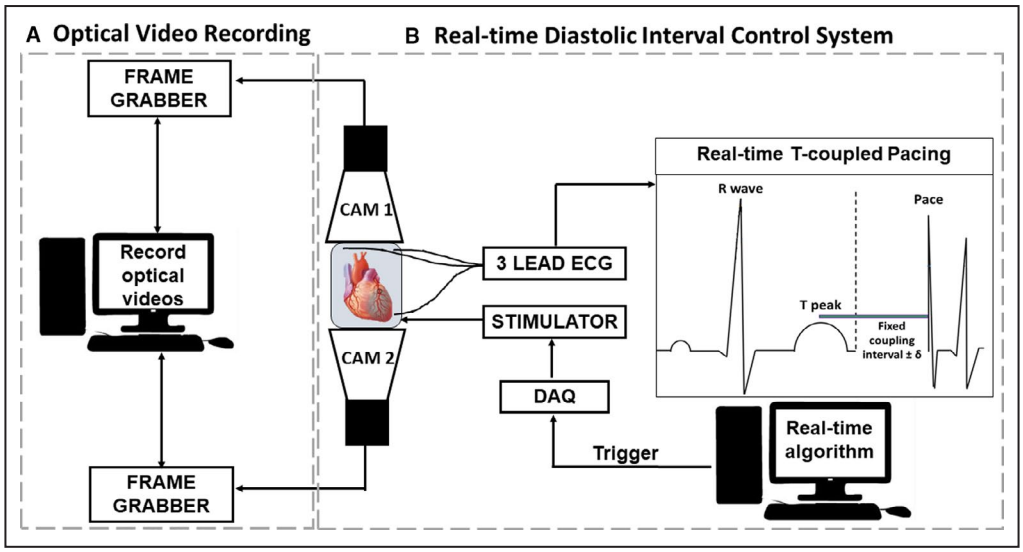

Figure 4. Schematic of the ex vivo whole heart optical mapping system with real-time closed-loop diastolic interval (DI) control.
A, The optical mapping setup records optical videos during periodic and constant DI pacing for offline processing and analysis. **B**, The real-time DI control system detects instantaneous T waves on a beat-by-beat basis using volume-conducted ECG and applies electrical stimuli after a predetermined fixed TR interval. CAM indicates camera. DAQ indicates data acquisition board.

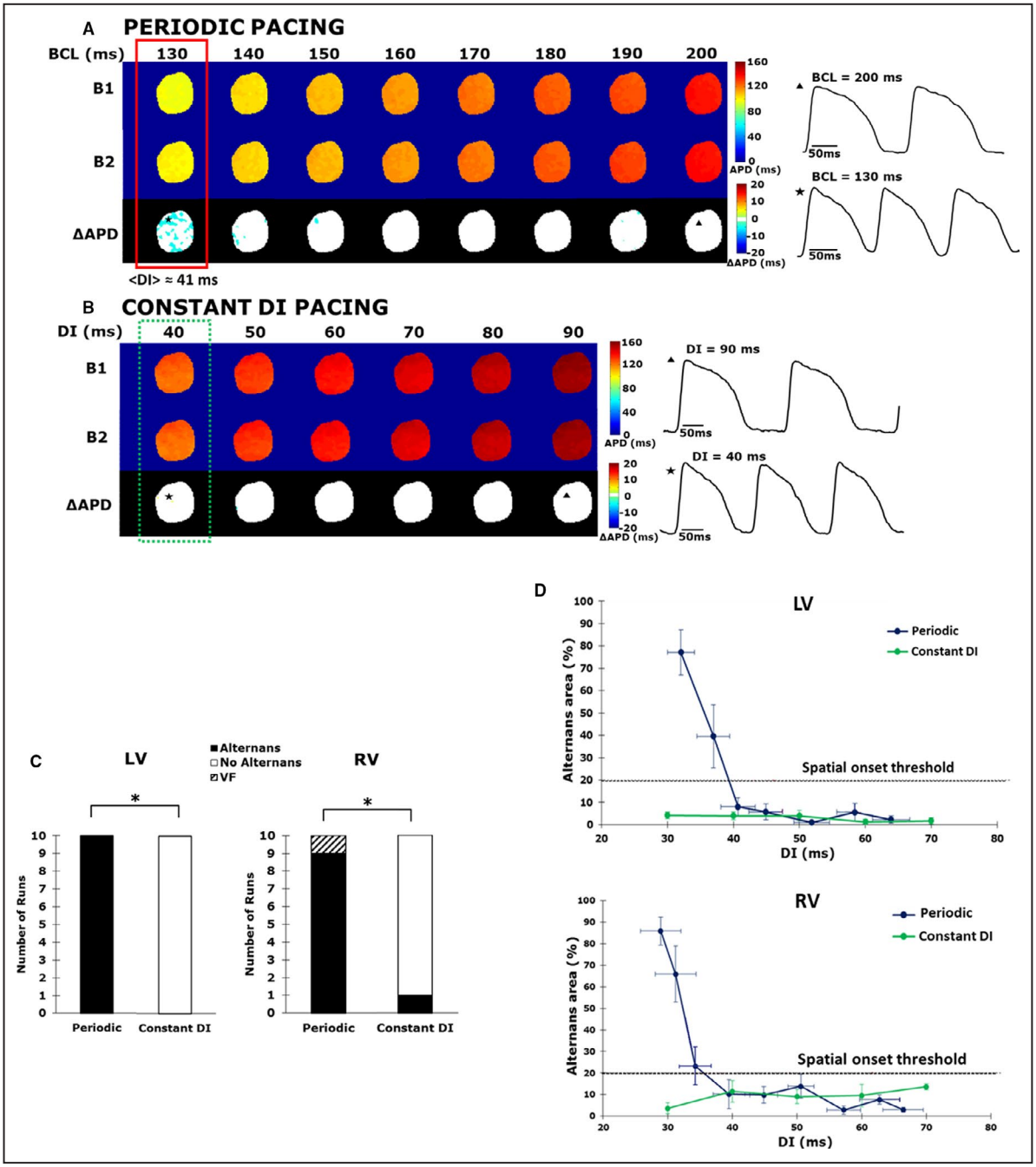

Figure 5. Experimental evaluation of constant diastolic interval (DI) pacing using ex vivo optical mapping of isolated whole rabbit hearts.

A, Representative 2-dimensional (2D) action potential duration (APD) maps depicting the change in APD with basic cycle length (BCL) for 2 consecutive beats during periodic pacing, for the left ventricle (LV). Corresponding 2D alternans maps denote the onset of spatial alternans (blue) at a BCL of 130 ms (BCL onset highlighted by red box). Action potential traces at a BCL of 200 ms (filled diamond) demonstrate 1:1 APD response at steady state and 2:2 APD response, alternans, at a BCL of 130 ms (asterisk). Mean diastolic interval (<DI>) corresponding to BCL onset was ≈41 ms.[40] **B**, Representative 2D APD maps depicting the change in APD with DI for 2 consecutive beats during constant DI pacing. Corresponding 2D alternans maps show the absence of spatial alternans. Action potential traces at DIs of 90 (filled diamond) and 40 (asterisk) ms demonstrate steady state 1:1 APD response, highlighting the absence of temporal alternans during constant DI pacing. Green box highlights the DI equivalent to the <DI> during BCL onset for periodic pacing. **C**, Summary results across all experiments (n=8), quantifying the presence of alternans during periodic and constant DI pacing in both the LV and right ventricle (RV). * denotes statistical significance of $p < 0.05$. **D**, Line plot depicting the spatial evolution of alternans across the LV and RV during periodic and constant DI pacing. VF indicates ventricular fibrillation. Adapted with permission from Kulkarni et al.[40]

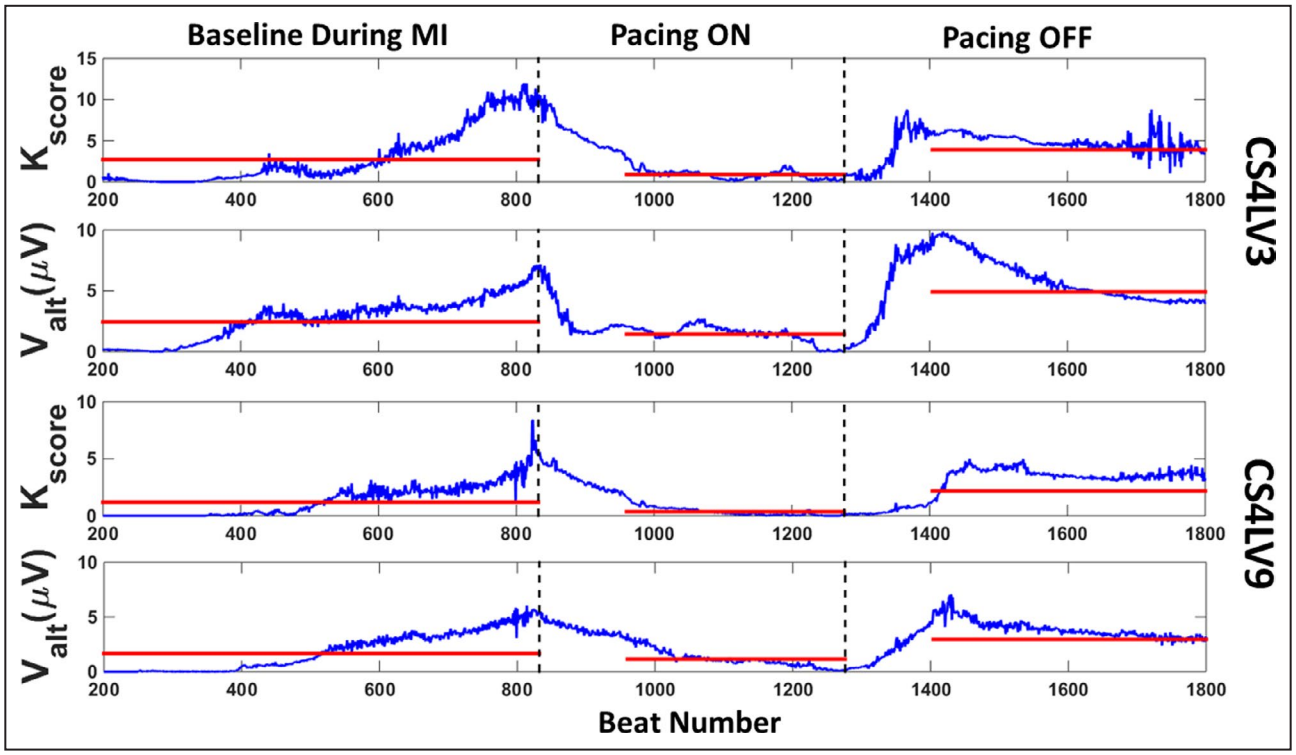

Figure 6. Representative example demonstrating the use of T-wave triggered pacing to suppress spontaneously occurring alternans during acute myocardial ischemia.
Alternans voltage and K_{score} are plotted for 2 intracardiac bipolar leads (CS4LV3 and CS4LV9) during angioplasty balloon-induced, coronary artery occlusion, which demonstrates spontaneous alternans at baseline. Alternans suppression pacing is delivered from the right atrium (amplitude, 5 mA; width, 5 ms; coupling to T wave, 155±40 ms). When triggered pacing is discontinued, both the alternans voltage and K_{score} increase to the baseline level during sinus rhythm. Transitions from baseline to triggered pacing ON to triggered pacing OFF occur correspondingly at times marked by solid vertical black lines, whereas the colored horizontal lines during each intervention indicate the mean value of the alternans voltage/K_{score} during that intervention. T-wave triggered pacing results in a significant reduction of spontaneous T-wave alternans during acute ischemia (alternans voltage, ≈0.63-fold average reduction compared with baseline, P<0.0001; K_{score}, ≈0.32-fold average reduction compared with baseline, P<0.0001). Discontinuation of T-wave triggered pacing leads to an increase of alternans voltage and K_{score} (alternans voltage, ≈3.06-fold average increase compared with alternans suppression, P<0.0001; K_{score}, ≈4.91-fold average increase compared with alternans suppression, P<0.0001). Statistical test used: Kruskal-Wallis. MI indicates myocardial infarction.

coupling, 155±40 ms. Pacing from a catheter in the right atrium (beats 826–1300) results in a significant reduction (to levels below the spontaneously occurring TWA at baseline during ischemia) in both the alternans voltage and K_{score}. Pacing is applied from the right atrium because of ease of access to the right atrium compared with ventricles. In addition, pacing from the right atrium eliminates the possibility of retrograde (ventricle-to-atrium) conduction, which could affect the estimation of alternans or in the long term cause ventricular dyssynchrony, commonly observed with ventricular pacing. Finally, the pacing is discontinued (beats 1301–1800) and alternans voltage and K_{score} increase again to levels similar to those observed before initiation of pacing. In this example, T-wave triggered pacing using a fixed coupling interval on every beat results in a significant decrease of spontaneous TWA during acute ischemia (alternans voltage, ≈0.63-fold average reduction compared with baseline, P<0.0001, Kruskal-Wallis test; K_{score}, ≈0.32-fold average reduction compared with baseline, P<0.0001, Kruskal-Wallis test). Discontinuation of T-wave triggered pacing leads to an increase of alternans voltage and K_{score} (alternans voltage, ≈3.06-fold average increase compared with alternans suppression, P<0.0001, Kruskal-Wallis test; K_{score}, ≈4.91-fold average increase compared with alternans suppression, P<0.0001, Kruskal-Wallis test).

These preliminary data using in vivo myocardial ischemia swine model demonstrate the ability of our real-time algorithm to detect the onset of TWA and initiate appropriate pacing to suppress TWA. Under normal physiological conditions, if no alternans is observed, pacing would be off, whereas on detection of TWA, the algorithm will initiate appropriate pacing. Furthermore, the real-time detection and suppression of alternans using the proposed algorithm can detect the presence of alternans at faster heart rates, in real-time.

DISCUSSION AND FUTURE PERSPECTIVES

In a series of studies, we have demonstrated the ability of constant DI pacing to both prevent as well as suppress the onset of cardiac TWA. Constant DI pacing has been developed on the basis of a purely restitution-dependent hypothesis and to date shown to be successful in predominantly preventing (rather than controlling) alternans induced by chronotropic pacing in ex vivo hearts.[40] The effect of constant DI pacing under diseased states, such as myocardial ischemia, myocardial infarction, and heart failure, remains to be mechanistically evaluated. Studies by our group[50] and others[72,73] have demonstrated that the efficacy of constant DI pacing is altered during the presence of cellular Ca^{2+} cycling abnormalities and metabolic disturbances[78] originating independent of the restitution-based phenomenon; therefore, they remain to be further investigated. Although our results provide proof of concept and highlight the promising translational potential of beat-to-beat TRI pacing by demonstrating its feasibility to control spontaneous TWA in an in vivo myocardial infarction model, further studies are warranted to quantitatively demonstrate the antiarrhythmic effects of constant TRI pacing in a larger animal group.

In addition, under disease conditions, multiple theories have been proposed to elucidate the mechanisms for cellular onset of alternans, such as decreased energy availability in the ischemic cell, the different spatial (epicardial versus endocardial) sensitivity of K_{ATP} channel activation during ischemia, cellular uncoupling, or electrophysiological remodeling during acute ischemia that leads to shortened APD, decreased action potential amplitude, velocity of impulse propagation, and resting membrane potential.[23,24,58,71,79] An assessment of underlying cellular and metabolic dynamics and their influence on the efficacy of constant TRI pacing in vivo remains to be examined.

Several other alternative approaches have been proposed to investigate the suppression of TWA based on autonomic regulation and pharmacological interventions. The autonomic nervous system plays a critical role in the pathogenesis of multiple cardiac arrhythmias, including atrial fibrillation and VT/VF. Multiple studies have investigated the utility of different autonomic modulation modalities, such as vagus nerve stimulation, tragus stimulation, renal denervation, baroreceptor activation therapy, and cardiac sympathetic denervation, in preventing cardiac arrhythmias, presenting promising results in preclinical experiments and preliminary studies in humans.[80,81] Yet, the need for optimization of the stimulation parameters and gaining a mechanistic understanding of the effects of parasympathetic activation on cardiac electrophysiology to identify appropriate biomarkers are warranted by the disappointing results of randomized clinical trials of autonomic modulation therapies.[82–84] In addition, these promising alternatives to suppress TWA based on autonomic regulation, pharmacological interventions, such as ion channel activators or blockers, have demonstrated significant interpatient variability, highlighting the need for rigorous patient selection based on appropriate biomarkers.[81] In comparison, alternans suppression techniques, such as the constant DI pacing, which are based on pure electrical intervention, provide ease of translatability into existing pacemakers, thereby enabling patient-specific adaptation of stimulation parameters of larger/broader patient population.

Our results indicate that a comprehensive evaluation of this pacing technique holds the potential to translate into a clinically viable antiarrhythmic pacing strategy that can radically improve the quality of life of patients experiencing abnormal cardiac rhythms.

ARTICLE INFORMATION

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Disclosures

None.

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