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Coupled pacing improves left ventricular function during simulated atrial fibrillation without mechanical dyssynchrony

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Aims Electrical stimulation [coupled pacing (CP)] applied near the end of the T-wave is able to create a retrograde activation of the atrioventricular (AV) node in turn to prevent rapid ventricular conduction during atrial fibrillation (AF). The impact of this pacing modality associated with cardiac resynchronization therapy (CRT) has been evaluated in the present experimental study.

Methods and results After inducing AF by rapid pacing in six dogs, we applied the following pacing modalities: rapid right ventricular (RV) pacing, rapid CRT, CRT with an additional RV paced beat (CP) at a specific delay (CRT + CP), and CRT with vagal stimulation (CRT-VS). Left ventricular (LV) pressure recordings and echocardiography for 2D strain analysis were performed. CRT + CP reduced the ventricular response rate and increased the LV systolic pressure and cardiac output compared with CRT alone (136 ± 6 vs. 86 ± 13 mmHg, $P < 0.05$ and 2.0 ± 0.4 vs.1.2 ± 0.1, $P < 0.05$ L/m, respectively). Compared with CRT-VS, CRT + CP increased the LV ejection fraction (LVEF = 51 ± 10 vs. 28 ± 4%, $P < 0.05$), peak global circumferential strain (−17 ± 2 vs. −11 ± 3%), and diastolic filling time (49 ± 6 vs. 28 ± 3%, $P < 0.02$) suggesting beneficial effects of CP beyond rate control. CRT + CP did not result in increased dyssynchrony [CRT (8.3 ± 2%) vs. CRTCP (8.4 ± 3%, P = NS)].

Conclusion CRT + CP effectively reduces ventricular contractile rate and leads to an increase in systolic and diastolic performance without inducing mechanical dyssynchrony.

Keywords Rate control • Cardiac resynchronization therapy • Atrial fibrillation

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and survival in patients with systolic dysfunction and prolonged ventricular depolarization (wide QRS).[1–8] However, atrial fibrillation (AF) may cause significant problems in these patients, particularly when the ventricular rate exceeds the device programmable rate. Atrial fibrillation in heart failure patients is often clinically challenging,[9] and if poorly controlled, permanent atrioventricular (AV) nodal ablation when pharmacologic rate control is not possible may be required.[10] For the past 5 years, our laboratory has been studying the potential application of coupled pacing (CP) as a means of rate control when AF occurs.[11–14] Briefly, CP can be explained as follows: after sensing the intrinsic electrical activation of the ventricles which initiate mechanical contraction, an additional electrical stimulation (CP) is applied near the end of the T-wave. Coupled pacing is applied prior to the time that the ventricles are capable of fully contracting again. These critically timed retrograde activations of the AV node in turn prevent subsequent rapid ventricular activations that would have lead to weakened ventricular contractions. An additional advantage of CP in patients with AF and systolic dysfunction is that the CP beat increases contractility via the mechanism of post-extrasystolic potentiation.[15] Since premature stimulations have

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differential effects on Purkinje vs. ventricular muscle refractoriness,[16,17] there is some concern that CP may potentially alter the left ventricular (LV) electrical activation pattern during biventricular pacing. The goal of our study was therefore to better define the effects of CP during biventricular pacing (CRT + CP) on LV function and mechanical dyssynchrony.

Methods

The experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic. All animals received humane care in compliance with the 'Guide for the Care and Use of Laboratory Animals'. The dogs ($n = 6$) were initially anesthetized with thiopental and maintained with isoflurane during positive pressure ventilation. A mid-sternotomy was performed and the heart was placed in a pericardial cradle. A quadrapolar plate electrode was sutured to the right atrium and was connected to a Grass stimulator for the induction of a pseudo AF. A second quadrapolar electrode was sutured on the right ventricular (RV) apex and was connected to the first channel of a Bloom stimulator for RV pacing as the protocol dictates. A third electrode was sutured on the lateral wall of the LV and connected to the second channel of our Bloom stimulator for LV pacing. The remaining two poles of these three quadrapolar electrodes were connected to our Ponemah™ system (Valley View, OH, USA) to record their corresponding electrograms: right atrial electrogram (RAE), right ventricular electrogram (RVE), and left ventricular electrogram (LVE). Finally, a bipolar plate electrode was sutured on the inferior vena cava–left atrial epicardial fat pad to stimulate the parasympathetic nerve that innervates the AV node to slow A–V nodal conduction.[18]

Pacing protocol

Five to ten minutes of each pacing paradigm was applied before obtaining the echocardiographic and invasive haemodynamic acquisitions. Step 1: With the animal in sinus rhythm (SR). Step 2: Subsequently, a simulated paroxysmal AF was induced by continuous rapid right atrial pacing (20 Hz, 1 ms, 3–5 V). Importantly, rapid atrial pacing was maintained continuously to ensure persistent AF for Steps 3–6.[11–13] Step 3: Application of rapid RV pacing (2 ms, 2–4 mA) at a ventricular rate greater than the resultant ventricular rate from rapid atrial pacing alone. The purpose of this rapid RV pacing was to prevent intrinsic ventricular activation over the AV node, thereby inducing dyssynchrony comparable with left bundle branch block (LBBB). Step 4: CRT: Rapid simultaneous biventricular pacing (both channels of the Bloom stimulator set at 2 ms, 2–4 mA) allowing capture by both ventricles in the presence of rapid simulated AF. Step 5: CRT + CP: Simultaneous biventricular pacing (both channels of the Bloom stimulator), followed by an additional stimulation of CP (first channel of the Bloom stimulator) which was applied only to the RV lead near the end of the T-wave. This was done by increasing the basic cycle length during biventricular pacing by ~50% above the length used in Step 4 (CRT alone). We subsequently added CP stimuli at a delay of 250 ms. This delay was then progressively shortened until we observed by both echocardiographic and LV pressure recordings that CP resulted in only minimal LV mechanical contractions (not leading to effective ejection). By adding CP, we were able to finally reduce the biventricular pacing rate to a rate close to SR. Step 6: vagal stimulation (CRT-VS): CRT capture enabled by reducing the ventricular rate response during rapid AF with selective stimulation of the parasympathetic nerves which innervate the AV node (pulses = 20 Hz, 0.1 ms, 10 mA). At this level of intensity, this selective and limited stimulation of the preganglionic parasympathetic fibres projection towards the AV node[18] slowed the rate of ventricular activation from the atria without negative inotropic effect. This allowed applying the CRT at a rate also similar to the SR. In this study, we chose not to apply CP to the LV for the following reasons: (1) The timing of retrograde activation of the AV node/His system would have been difficult to control if left ventricular CP had been applied in the presence of intrinsic LBBB. However, LBBB was not present in our study. (2) Since scar tissue would most likely be in the LV, applying CP close to scar tissue may theoretically increase the risk of fatal arrhythmias.[19] Thus for these reasons, we chose to evaluate the effects of CP when it was applied only from the RV.

Epicardial echocardiographic data

Echocardiographic acquisitions were performed with a Vivid 7 machine (GE Healthcare). During these periods, we turned off the aortic flow meter in order not to interfere with the Doppler measurements from the echocardiograph. The time intervals between two Doppler LV outflow peaks were used to determine the cardiac period. These integrated velocity profiles, times aortic cross-sectional area, were used to obtain an estimate of stroke volume (SV). Left ventricular contractile function was quantified by measuring (1) left ventricular ejection fraction (LVEF) and (2) the peak circumferential global LV strain by speckle tracking. Left ventricular ejection fraction was computed from standard apical views by using Simpson's biplane method. Global circumferential strain curve was derived from the 2D short axis view (basal segment) using 2D strain analysis (EchoPac, GE Healthcare). Peak circumferential global strain was defined as the minimal strain value during cardiac cycle. Left ventricular dyssynchrony was calculated as the standard deviation (SD) of the time (%) to peak circumferential strain of these six different segments with a larger SD indicating an increasing degree of dyssynchrony. Diastolic filling time [duration of the early diastolic filling wave (*E*) during AF or the sum of *E* and late diastolic filling wave (*A*) during SR] was normalized to cardiac cycle for variability in cycle length. All echocardiography parameters used were obtained by averaging five consecutive values.

Haemodynamic data

A Millar™ pressure transducer (Houston, TX, USA) was inserted into the LV in order to record pressure. In addition, we placed a Transonic™ flow probe (Ithaca, NY, USA) around the ascending aorta for cardiac output (CO) measurements. For CO measurement, SV was averaged over 15 cardiac cycles for each step. During the whole experiment, all dogs were invasively monitored to maintain haemodynamic parameters at similar levels.

Statistical analysis

Analysis of variance was used to determine if altering the pacing paradigms significantly changed any measurements. All continuous variables were expressed as means ± SE. We made paired comparisons between the first five steps. All statistical tests were two sided and a probability of <0.05 was considered significant.

Results

Representative experiment

Figure 1 shows representative tracings of the electrical activation sequences and haemodynamic responses. The first step was SR (*Figure 1A*). The response to rapid AF (Step 2) is illustrated in Panel B. In Step 3 (*Figure 1C*), we induced AF and then applied rapid RV pacing in addition to the AF. In Step 4 (*Figure 1D*), we

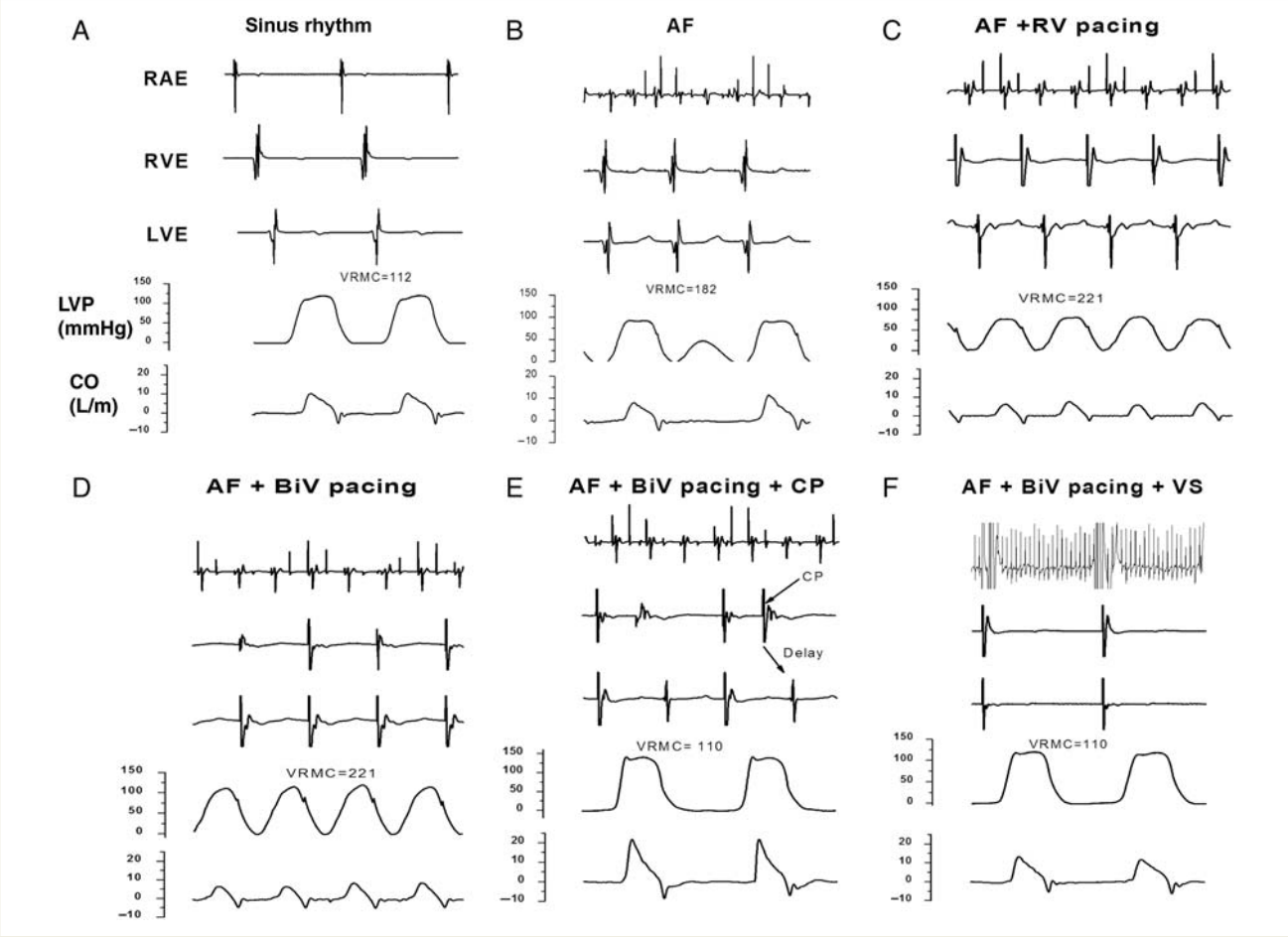

Figure 1 Representative tracings digitally extracted using the Ponemah system and then plotted with Origin graphic software. See Results section for further details.

applied CRT at a rate sufficient to provide ventricular pacing independent of supraventricular activation. In Step 5 (*Figure 1E*), we were able to apply CRT at a similar rate to SR despite the continual AF because we added the CP. Also, note that the activation of the LV is delayed following the CP because this paced beat is initiated from the RV electrode. Finally in Step 6 (*Figure 1F*), we were able to apply CRT at a rate similar to SR because the AV node was suppressed by the selective stimulation of the parasympathetic nerve. Video 1 (Supplementary material online) shows LV function during the pacing paradigms. The corresponding line diagrams below the video illustrate the circumferential strain curves with the dotted line representing the global strain. The left panel (Step 1) of this video shows the results obtained during SR. The next panel illustrates the effect of RV pacing on LV dyssynchrony after AF has been induced (Step 3). The middle panel shows the effect of rapid CRT (Step 4). In spite of CRT, a decrease can still be observed in the peak global strain. The next panel subsequently illustrates the effect of CRT + CP, resulting in a dramatic increase in the peak global strain (Step 5). Importantly, application of CP did not result in increased ventricular dyssynchrony. Finally (Step 6), we tried to differentiate the effects of CP from those of rate control alone achieved by selective parasympathetic nerve stimulation of AV nodal tissue (CRT-VS). Peak global strain is improved compared with rapid CRT, but not to the extent of CRT + CP.

Composite results

Impact of CRT + CP on LV mechanical dyssynchrony

The average LV dyssynchrony during SR and rapid AF was $\sim 7 \pm 2$ and $8 \pm 3\%$ (*Figure 2A*). Rapid RV pacing with AF increased LV dyssynchrony to an average of $19 \pm 3\%$ ($P < 0.0001$ vs. SR and AF), while the application of CRT reduced the extent of LV dyssynchrony, virtually back to the level of SR (SD $= 8 \pm 3\%$). The application of CP (CRT + CP) from only the RV did not increase LV dyssynchrony (SD $= 8 \pm 3\%$). The average time delay of CP from CRT for these six animals was 160 ± 11 ms. Finally, the CRT with parasympathetic nerve stimulation of the AV node (CRT-VS) did not change the extent of LV dyssynchrony compared with SR or CRT alone (SD $= 7 \pm 2\%$, NS). The average corresponding QRS duration during each step is shown in the bars of *Figure 2A*.

Impact of CRT + CP on LV systolic function

During SR, the average peak global strain was $-12 \pm 2\%$ (*Figure 2B*) when the ventricular rate of mechanical contractions

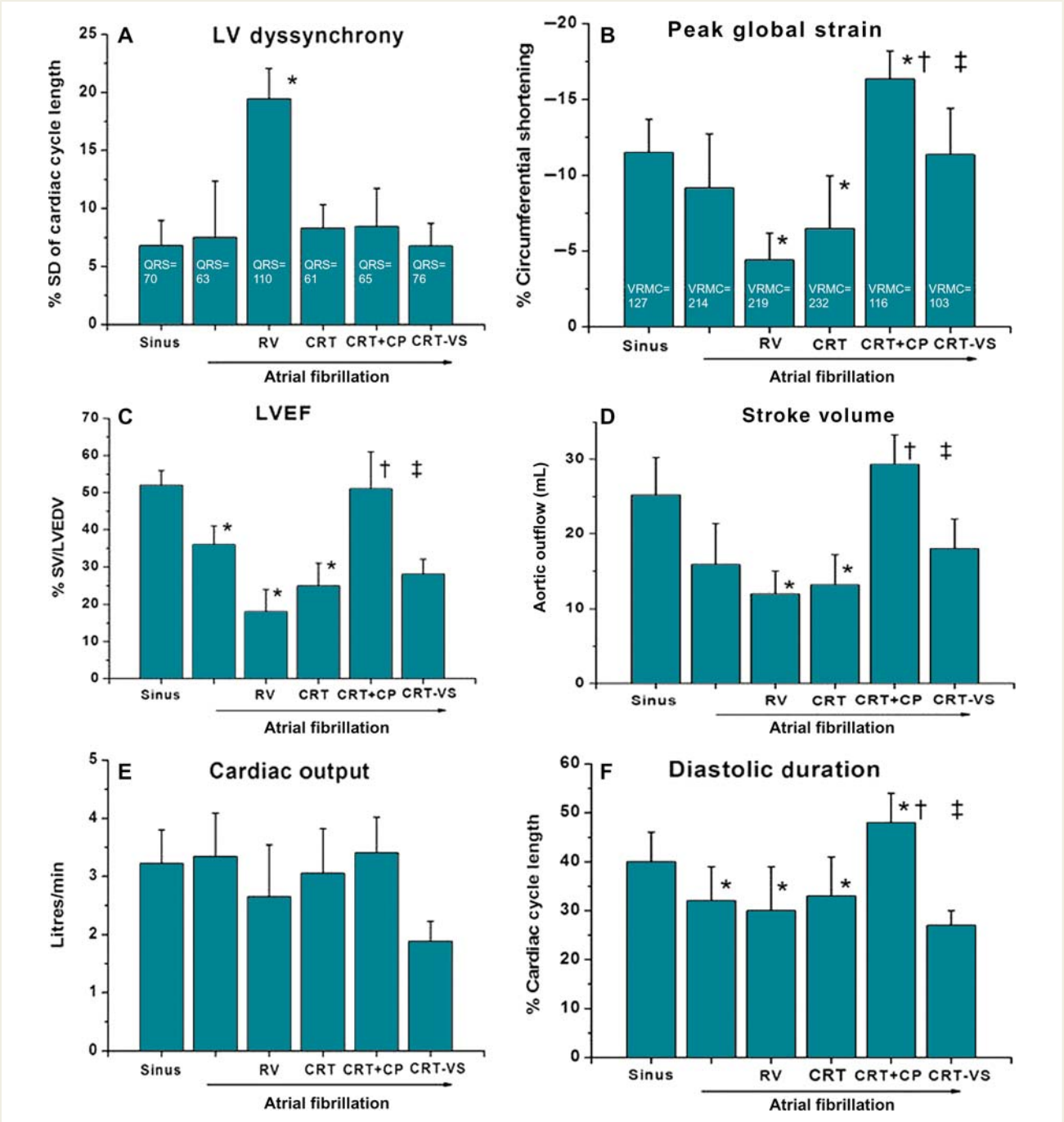

Figure 2 (*A*) Changes in LV dyssynchrony, (*B*) average strain, (*C*) LV ejection fraction, (*D*) stroke volume, (*E*) cardiac output, and (*F*) LV percentage of diastolic duration, during the six stages of this study. (*) for $P < 0.05$ vs. baseline, (†) for $P < 0.05$ vs. RV pacing, (‡) for $P < 0.05$ vs. CRT.

(VRMC) was 127 ± 17 c.p.m. With the induction of acute AF, the peak global strain decreased to −9 ± 6% and to −4 ± 2% when RV pacing was added to AF. The application of CRT during acute AF + RV pacing did not improve significantly the peak global strain (−6 ± 3%). The addition of the CP beat (CRT + CP) increased peak global strain to a level that was even greater than that found during SR (−17 ± 2%, $P < 0.05$). The average VRMC during CT + CP was 116 ± 17 c.p.m. The reduction in VRMC (103 ± 14 c.p.m.) during CRT-VS improved the peak global strain, until it approached values obtained in SR (−11 ± 3%).

Left ventricular ejection fraction closely followed the changes in global strain. Left ventricular ejection fraction decreased from 52 ± 4 to 36 ± 5% with rapid AF and to18 ± 6% (*Figure 2C*) with both AF and RV pacing. Although the resynchronization of the rapid contractions did not significantly improve the LVEF (25 ± 6%) compared with rapid RV pacing, a dramatic increase

Table 1 Measurements and derived parameters of the left ventricular pressure and aortic flow

	Sinus rhythm (Step 1)	AF (Step 2)	AF + RV pacing (Step 3)	AF + BV pacing (Step 4)	AF + BV pacing + CP (Step 5)
VRMC$^{\#}$ (contractions/m)	122 ± 5	164 ± 14*§	211 ± 17*§	196 ± 24*§	115 ± 8
CCL$^{\#}$ (ms)	494 ± 19	370 ± 30*§	302 ± 28*§	335 ± 47*§	535 ± 39
LVSP$^{\#}$ (mmHg)	108 ± 7	102 ± 10§	86 ± 13§	102 ± 8§	136 ± 6
+dP/dt$^{\#}$ (mmHg/s)	2228 ± 114	2490 ± 115	2088 ± 182§	2325 ± 121§	3719 ± 382*
−dP/dt$^{\#}$ (mmHg/s)	2525 ± 164	2413 ± 698	1733 ± 291	2277 ± 332	3007 ± 664
Systolic time$^{\#}$ (ms)	235 ± 5	186 ± 13*	165 ± 16*	180 ± 16*	194 ± 7
% Systole$^{\#}$ (% diastole)	48 ± 1 (52)	50 ± 1 (50)	57 ± 4§ (43)	57 ± 5§ (43)	37 ± 2 (63)
Tau$^{\#}$ (ms)	57 ± 11	67 ± 12	120 ± 34	75 ± 19	69 ± 13
SV$^{\#}$ (mL/beat)	17 ± 4	11 ± 5	5.3 ± 1.4*§	6.6 ± 1.6*§	17 ± 3
CO$^{\#}$ (L/min)	2.1 ± 0.4	1.7 ± 1	1.1 ± 0.2*§	1.2 ± 0.1*§	2.0 ± 0.4

VRMC, ventricular rate of mechanical contractions; CCL, cardiac cycle length; LVSP, left ventricular systolic pressure; dP/dt and −dP/dt, peak rate of rise and fall of LV pressure; ST, systolic time (time from LV end-diastolic pressure to peak −LV dP/dt); % Systole, [(ST/CCL) × 100]; % Diastole, remaining per cent of CCL; Tau, the time constant of isovolumic relaxation; CO, cardiac output; SV, stroke volume (SV = CO/VRMC). Changing overall the above pacing paradigms significantly alter the above parameters, $^{\#}P < 0.05$. Then we performed paired comparisons (*t*-test with Bonferroni correction). (*) for $P < 0.05$ vs. baseline, (§) for $P < 0.05$ vs. CRT + CP.

in LVEF was observed by adding CP to CRT (51 ± 10 vs. 25 ± 6%, $P < 0.05$). That is, the LVEF was virtually equal to SR ($P > 0.05$) despite the presence of AF. With parasympathetic nerve stimulation added, LVEF (28 ± 4%) was unchanged compared with CRT alone (25 ± 6%, $P > 0.05$).

During SR and AF, SV by the echocardiography method (*Figure 2D*) was 25 ± 5 and 16 ± 5 mL, respectively. With acute AF and rapid RV pacing, the SV decreased significantly ($P < 0.05$) to 12 ± 3 mL. The application of CRT during acute AF did not significantly improve the SV, which remained lower than SR (13 ± 4 vs. 25 ± 5 mL, $P < 0.05$). The addition of the CP beat (CRT + CP) increased SV (29 ± 4 mL) to a level slightly greater than that found during SR. The SV during CRT-VS was 18 ± 4 mL.

The echocardiographic measurements of CO (*Figure 2E*) did not significantly change, probably because of the variability of SV echocardiography measurement which may be challenging during epicardial echocardiography. In contrast, CO measurements via the transonic flow meter (Table *1*) showed that AF alone or with RV pacing and rapid CRT both significantly reduced CO. Interestingly, the changes in global circumferential strain by CRT + CP were concordant with similar increases observed in the invasively derived peak rate of LV pressure development (+LV dP/dt) and SV by the high-fidelity pressure transducer and flow probe (Table *1*).

Impact of CRT + CP on LV diastolic filling time and LV diastolic properties

Diastolic filling time was 40 ± 6% of cardiac cycle during SR (*Figure 2F*), decreasing to 32 ± 7 and 30 ± 9% during AF alone and with RV pacing, respectively. In spite of reducing LV dyssynchrony with rapid CRT, diastolic filling time remained unchanged with CRT (33 ± 8%). With CP, however, diastolic filling time increased significantly (48 ± 6%, $P < 0.05$ vs. CRT alone). A notable improvement in LV diastolic properties (−dP/dt, Tau, and invasively calculated duration of diastole shown in Table *1*) was equally observed. It should be noted, however, that contrary to echocardiography where diastolic filling time is limited to the inflow of blood into the LV, the invasively derived duration of diastole includes a portion of the isovolumic relaxation time. In spite of the reduction in rate by CRT + VS, no notable changes in diastolic filling time were noted with vagal AV node stimulation (27 ± 3%).

Discussion

Our study highlights the potential benefit role of right ventricular CP for providing ventricular rate control during simulated paroxysmal AF. This rate control leads to a significant improvement in both LV systolic and diastolic function as documented by both invasive and echocardiographic methods. This study did not address changes in atrial electrical or mechanical properties that would change with the development of AF. In addition, contrary to previous concern,[16,17] these effects were achieved without causing mechanical dyssynchrony.

While the beneficial effects of CRT have been well documented in previous studies,[1–8] rapid AF often occurs in heart failure population and results in acute clinical deterioration of the functional status.[9] Routine biventricular pacing usually does not allow rapid tracking of the atrial rate in acute AF because of the potential for inducing ventricular tachycardia. Although conventional methods of slowing AV nodal conduction may be sufficient to normalize LV function in rapid AF, these clinical strategies of rate reduction by pharmacological agents may not, in some cases, be well tolerated. In case of drug-refractory atrial tachycardia, AV nodal ablation with permanent pacemaker implantation or pulmonary vein isolation is sometimes necessary, procedures that each carry significant risks.[9,10] On the basis of our results of global strain, ejection fraction, and SV, the acute effects of the ventricular tachycardia as the result of acute AF appear to be the major cause for the acute reduction of systolic function. The application of CP to the right ventricle permitted a reduced rate of biventricular pacing needed for synchronized contractions in the presence of acute AF. Our findings show that CP has considerable

potential as a new pacing paradigm by reducing the rate of ventricular contractions, increasing systolic function, and maintaining CO. We therefore believe that the concept of CP deserves further attention, and the most reasonable initial application would be the implementation of CP in patients who already have a biventricular device. Modern and elaborate algorithms associating electrical and mechanical (d*P*/d*t* measurement) sensing could be used to appropriately apply CP when AF occurs. Instead of switching into pacing mode of ventricular inhibited pacing with rate modulation (VVIR) when the atrial rate exceeds a prescribed limit, CP would then theoretically allow further application of CRT at a rate similar to that prior to the induction of supraventricular tachycardia. The addition of CP to biventricular pacing effectively reduces the ventricular rate by approximately one-half in the presence rapid AF. The electrical wave front from the coupled beat would travel retrogradely into the AV node and block approximately half of the supraventricular activations of the heart. This mode of pacing permits the biventricular pacing to be maintained at a rate similar to that prior to the AF. Particularly, patients with advanced systolic dysfunction may benefit from CP as the supplemental beat will increase contractility by the mechanism of 'post-extrasystolic potentiation' due to an increased intracellular release of calcium.[15] This concept is not entirely novel as 'paired stimulation' was first proposed as a heart failure therapy more than 40 years ago.[20–22] However, in these previous studies, paired stimulation was achieved by continuously applying two closely paced stimuli to the RV. It is now well known that continuous RV pacing may eventually lead to adverse effects because of chronic LV mechanical dyssynchrony.[23] Our findings suggest, however, that when added to CRT, right ventricular CP does not induce significant LV mechanical dyssynchrony assessed by 2D strain echocardiography. Since stimuli are applied near the end of the T-wave; there is a theoretical risk that these stimuli could induce ventricular tachycardia, which might lead to ventricular fibrillation. However, extending the delay of coupled stimuli still maintains improved global cardiac function, while reducing the risk of ventricular arrhythmias as shown earlier by our group.[13] In addition, Mischke *et al.* [24] have recently demonstrated that paired ventricular stimulation can be safely delivered during ventricular tachycardia in patients with predominantly ischaemic LV dysfunction. We do believe, however, that the first clinical application of this pacing concept should best be reserved for patients with an internal cardiac defibrillator system, allowing immediate termination of any ventricular tachycardia if it would occur.

Limitations

Our study was performed in the acute heart failure model with systolic LV dysfunction induced by rapid AF and RV pacing and not during chronic heart failure with AF and left branch block. Thus, we acknowledge that our experimental model of pacing-induced LV dysfunction has significant limitations mimicking the complexity of human heart failure. First, RV pacing cannot be assimilated to a LBBB occurring in fibrosis myocardial tissue despite similar mechanical impact with LV dyssynchrony and myocardial dysfunction. Safety and efficiency of CRT + CP may differ in chronic heart failure with less gain in contractility and a higher risk of ventricular tachycardia expected. Therefore, a specific algorithm to determine optimal delay to deliver CP has to be addressed in future study in this setting. However, we believe that the use of this oversimplified model has been helpful in assessing the feasibility and the efficiency of this new pacing algorithm.

Conclusion

The application of CP to CRT during rapid AF in this experimental model of LV systolic dysfunction allows effective ventricular rate control without inducing LV dyssynchrony. In addition, this new pacing modality increases myocardial contractile performance and diastolic properties to a greater extent than observed by simply slowing AV nodal conduction.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: R.A.G. has received consulting fees from GE Healthcare, Medtronic, and St. Jude Medical, honoraria from GE Healthcare and Medtronic, and grant support from Medtronic. The other authors report no conflicts of interest.

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IMAGES IN ELECTROPHYSIOLOGY

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Interventricular septum haematoma following CRT-D implant

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After CRT-D implant, the patient complained of chest pain and presented with frequent polymorphic premature ventricular contractions. Echocardiogram, and subsequent CT-scan (*Figure*), demonstrated a large interventricular septum haematoma (septal thickness 4 cm), probably related to a damaged coronary subsidiary caused by the right ventricular screw-in lead, although no coronary angiogram was performed due to patient instability. The patient status improved and the haematoma spontaneously resolved over 6 weeks with a normal septum on post-recovery echocardiography (*Figure*, inset). RV/LV, right ventricle/left ventricle; RA, right atrium.

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