Effects of coupled pacing on cardiac performance during acute atrial tachycardia and fibrillation: an old therapy revisited for a new reason

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Yamada, Hirotsugu, David O. Martin, Kent A. Mowrey, Neil L. Greenberg, and Don W. Wallick. Effects of coupled pacing on cardiac performance during acute atrial tachycardia and fibrillation: an old therapy revisited for a new reason. Am J Physiol Heart Circ Physiol 285: H2630–H2638, 2003. First published July 31, 2003; 10.1152/ajpheart.00393.2003.—Atrial tachycardia (AT) and fibrillation (AF) result in rapid ventricular rates that are detrimental to optimal cardiac function. The purpose of this study was to determine whether the application of a coupled pacing (CP) regimen would improve ventricular function by decreasing the ventricular rate of mechanical contractions (VRMCs). We simulated AT by pacing either atrium at a rate that resulted in a rapid but regular ventricular rate in seven anesthetized dogs. AF was induced by increasing the atrial pacing rate until atrial activation did not follow the pacing. After the induction of either AT or AF, we applied CP after each intrinsic atrial activation. We measured the VRMCs and left ventricular (LV) pressures and volumes via a pressure-conductance catheter. The marked reductions in VRMCs during CP resulted in increases in LV end-diastolic volume. The CP resulted in virtually no mechanical contractions, whereas the strength of contractions from the normal electrical activation increased. The increases in the positive LV rate of pressure development over time and LV ejection fraction during CP were the result of postextrasystolic potentiation. The average stroke work (area of the pressure-volume loops) increased as a result of CP during both AT and AF. Despite the large increases in stroke volume (≈2×) during CP, the changes in cardiac output were moderate because the VRMCs markedly decreased (≈½). We conclude that CP therapy may be a viable therapy for slowing the heart rate and improving cardiac performance in patients with AT and AF.

METHODS

Animal preparation. Our experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic Foundation. All animals used in this study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals published by National Institutes of Health. The Cleveland Clinic Foundation’s Animal Care facility is accredited by the American Association for the Accreditation of Laboratory Animal Care.

Seven dogs (body wt, 22–29 kg) were given morphine (1 mg/kg im) and were then anesthetized with α-chloralose (80 mg/kg iv). Supplemental doses of a α-chloralose (20 mg/kg iv) were given hourly. We started positive-pressure ventilation. Arterial blood gas and pH values (PO₂, >80 mmHg; PCO₂, 30–40 mmHg; and pH, 7.35–7.45) were maintained by ap-

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propriate adjustments in ventilation rate and volume and by the administration of sodium bicarbonate throughout the experiment. The right femoral and left carotid arteries were isolated to insert a micromanometer-tipped catheter (model SPC-570, Millar; Houston, TX) and a pressure-conductance catheter (model SPC-560, Millar). These catheters were soaked in warm saline for 30 min before insertion and were precalibrated. A mid-sternotomy was performed, and the heart was placed in a pericardial cradle.

A custom quadrupolar patch electrode was sutured to the right or left atrium to induce either AT or AF. We used a stimulator (SD-9, Grass) to rapidly pace the atria (pulses of 1 ms and 3–5 V) to induce either AT or AF. We gradually increased the rate of atrial pacing and monitored the ventricular rate. Our goal in inducing AT was to pace the atria at a rate that would result in a consistent yet rapid AV activation. We increased this rate of pacing ~80% (range, 174–222 beats/min). In some cases, the ventricular contractions exhibited marked pulse alternans. Therefore, we backed off the rate until the pulse alternans disappeared, because we wanted to test the effects of CP during rapid but uniform contractions. In some cases, there were two atrial activations to one ventricular activation. The extent by which ventricular rate could follow atrial rate depended largely upon the filtering state of the AV node and the refractoriness of the atrial tissue. That is, we obtained resultant ventricular rates and contractile strengths that were rapid but regular. We increased the atrial pacing rate further until the activation of the atria could not follow the pacing rate; thus we induced AF. In both cases (AT and AF) we continually applied atrial pacing. Again the resultant ventricular rate during AF was a function of the filtering capacity of the AV node. For this initial study, we wanted to evaluate the effects of CP over a wide range of ventricular rates to show that it may be a viable clinical means of rate control during AF. Thus we did not use the same atrial pacing rate during all of the experiments before the application of CP.

Coupled pacing. A second quadrupolar electrode on the right ventricular apex was used to sense the electrical activation of the ventricles and then apply CP. We used a Bloom stimulator to apply this CP. These paced beats were 1 ms in duration and 2× the diastolic threshold in amplitude (1–5 mA). While monitoring the left ventricular (LV) pressure and using the external mode of this stimulator, we progressively decreased (starting at 250 ms) this coupling interval until we obtained the maximal slowing of the ventricular contractions with minimal contraction of the ventricles from these electrically paced beats. If the CP interval was too long, there would be small secondary contractions, and/or another electrical activation of the ventricles could possibly occur during AF or AT before the application of CP. Therefore, we shortened this delay to 180–220 ms. These intervals were short enough to minimize any mechanical contractions that may have resulted from these CPs yet long enough to maximize the reduction in the ventricular rate of mechanical contractions (VRMCs). Once this optimal delay was found, the timing delay remained constant throughout each experiment. In this study, we reported VRMC rather than heart rate. We calculated VRMC as follows: we defined ventricular contraction as a developed pressure (>10 mmHg) that occurs after electrical activation. Thus if the left ventricle developed this pressure, this activation sequence was used in the calculation of VRMC whether or not there was ejection of blood. In the present study, we kept the delay of the paced beats sufficiently short enough to prevent a secondary contraction (>10 mmHg). All of the above hemodynamic signals were continuously monitored and periodically recorded (Cardio Lab, GE Medical Systems).

Pressure-volume analysis. Epicardial two-dimensional echocardiography was performed using a commercially available ultrasound diagnostic machine (Vingmed System Five, GE Medical Systems; Milwaukee, WI) at every stage of this study. The LV end-systolic and end-diastolic volumes (LVEV and LVEDV, respectively) were measured from two- and four-chamber views using a modified Simpson’s method. The volume curves obtained from the conductance catheter were calibrated by these echocardiographic measurements of both LVEDV and LVEV during SR. Prior work shows the accuracy of these echocardiographic measurements to be within 6%–7% (20). From these calculations via echocardiographic measurements, we could generate individual beat-by-beat LV pressure-volume loops. During AF, there are a number of nonejective or abortive beats. In these cases, the stroke volumes (SVs) were zero, because the LVEDVs and LVEVs were equal for that particular cardiac cycle. However, when the CP is applied, there are two ventricular electrical activations to every one mechanical contraction. Instead of the loop representing stroke work (SW). With no ejection (SV = 0), there was no external work performed. External cardiac power (ECP) was calculated as average SW x average VRMC. All measurements from the echocardiographic images and conductance catheter were analyzed offline.

Data and statistical analysis. Data were collected in the following five stages: normal SR, AT, AT + CP, AF, and AF + CP. The order of the stages was fixed. The duration of each stage was 2 min. The hemodynamic data collected from ~50 consecutive cycles (range, 40–60) were averaged and used as a single value for further analysis. The seven values during SR are displayed as means and standard deviations (see Figs. 3–6). In comparing the effects of CP during AT and AF, we used a nonparametric Wilcoxon paired signed-rank test, as there was variance inequality. Again, we used each parameter as a single value from each animal for further analysis. A P value < 0.05 was considered significant. We compared the changes in all measured and derived parameters in response to CP during both AT and AF. No statistical comparisons were made between SR and AT, AT + CP, AF, or AF + CP.

RESULTS

Representative responses of CP during AF. We acutely induced AF via rapid atrial pacing (Fig. 1). Note that during AF alone, there were a large number of rapid but weak ventricular contractions that did not result in ejection. These weak beats did not result in the ejection of blood as indicated by lack of a rise in arterial pulse. Thus without ejection of blood, the hearts are not performing external work. However, the development of pressure in the ventricle from abortive beats utilizes energy (internal energy). In contrast, when we carefully applied timed CP, these coupled paced beats electrically activated the ventricles but resulted in no significant mechanical contractions. Thus the CP was delayed enough to permit ventricular electrical activation but premature enough to prevent the mechanical contractions. These CP beats undoubtedly partially conducted into the AV node retrogradely and prevented the frequent antegrade AV conductions from atrial electrical activations that would have oc-
curred during AT and AF. Thus properly timed electrical activation of the ventricles by CP can reduce the mechanical contraction rate of the ventricles and ensure that each ventricular mechanical contraction results in strong contractions as indicated by the large arterial pulse. The representative changes in the pressure-volume relationship in response to the application of our pacing paradigm during AF is also shown (Fig. 1). During AF, the rapid, erratic, ventricular contractions are displayed in pressure-volume loops. Both the LV volumes and developed pressure changes were quite variable. The loops with no change in volume represent the aborted beats. The vertical lines represent isovolumic pressure development and relaxation. Because the shape of the left ventricle changes during these isovolumic periods, there appears to be a change in the volume of the left ventricle. These small changes are due probably to motion artifact. However, when the CP was applied, variability of both the SV and the LV systolic pressure (LVSP) dramatically diminished. The average SV (differences in the vertical lines of the loops) and to some degree the developed pressure (differences in the horizontal lines of the loops) of the left ventricle increased as the result of the CP.

Representative responses of CP during AT. We paced the atria at a slower rate than that used to simulate AF to produce simulated AT. At this slower atrial pacing rate, there were either one or two atrial activations for each ventricular activation. The VRMC was rapid but regular (Fig. 2). When CP was applied to the ventricles after their intrinsic ventricular activations, the ventricular mechanical contraction rates were reduced. Note the slight LV pressure rise (Fig. 2) after the coupled beats in this particular incidence. Figure 2 also shows the representative changes in the pressure-volume relationship in response to the application of our pacing paradigm during AT. The SV increased largely due to the increased LVEDV (from 16 to 30 ml; right vertical lines from each loop). In this particular case, the CP resulted in partial contractions of the left ventricle (small loops with no change in LV volume).

Effects of CP on ventricular rate, aortic blood pressure, and LV contractility. We applied this pacing paradigm after the induction of AT and AF to reduce the rapid VMCRs. The means ± SD of VMCRs and all the other parameters during SR are shown in Fig. 3 and all figures. During our acutely simulated AF and AT (via atrial pacing), the CP was able to reduce the average VMCR by approximately half. During AF, the rate changed from 215 ± 30 to 111 ± 14 contractions/min, and during AT it changed from 200 ± 20 to 104 ± 9 contractions/min. The VMCR during SR was 117 ± 16 contractions/min. These marked reductions in VMCR caused by CP occurred despite the 84 and 71% increases in VMCR that were the result of our simulated AF and AT. The CP increased aortic pulse pressure.
Fig. 2. A representative response to CP during atrial tachycardia (AT). Typical electrical and hemodynamic traces were displayed before and during CP (top). Changes in the LVP-LVV relationship from the representative experiment resulting from CP during AT are shown (bottom).

Fig. 3. Average changes in ventricular rate of mechanical contraction (VMCR), aortic pulse pressure (AoPP), and mean AoP to CP during AF (top) and AT (bottom).
(AoPP) values from 21 ± 10 to 62 ± 10 mmHg during AF, whereas during AT, the AoPP rose from 31 ± 12 to 55 ± 12 mmHg. The AoPP during SR was 50 ± 17 mmHg. The CP increased LVSP from 86 ± 18 to 139 ± 18 mmHg during AF, whereas during AT, the pressure rose from 127 ± 13 to 140 ± 15 mmHg (Fig. 4). The LVSP during SR was 133 ± 15 mmHg. This pacing paradigm (CP) resulted in a dramatic increase in the peak-positive LV rate of pressure development over time (dP/dt) value; that is, this isovolumic index of contractility went from 1,547 ± 413 to 3,454 ± 755 mmHg/s as the result of the CP during AF. Similarly, the rate of developed pressure rose from 2,365 ± 412 to 3,953 ± 623 mmHg/s as the result of CP during AT. The LV dP/dt value during SR was 1,730 ± 144 mmHg/s. Finally, the mean left atrial pressure decreased (15 ± 6 to 11 ± 4 mmHg) during AF as the result of the CP. During AT, the CP reduced the mean left atrial pressure from 13 ± 5 to 10 ± 5 mmHg. The left atrial pressure during SR was 13 ± 9.

**Effects of CP on changes in LV volumes and ejection fractions.** The effects of CP on various ejection indices of cardiac performance during both AT and AF are summarized in Fig. 5. Because CP reduced the VRMC during AF, the average LVEDV increased from 26 ± 8 to 31 ± 7 ml, whereas during AT, the same application of CP increased LVEDV from 25 ± 8 to 33 ± 5 ml. The LVEDV during SR was 36 ± 14. CP increased SV from 9 ± 3 to 18 ± 5 ml during AF. During AT, the same CP increased SV from 11 ± 3 to 21 ± 4 ml. The SV during SR was 19 ± 4. Because SV increased to a greater extent than LVEDV as a result of CP, LV ejection fraction (LVEF) increased. That is, CP increased LVEF from 31 ± 4 to 55 ± 6% during AF, whereas during AT, the same CP increased LVEF from 42 ± 6 to 65 ± 3%. The LVF during SR was 58 ± 8%.

**Effects of CP on cardiac output, SW, and external cardiac power.** Despite the doubling of the SVs, cardiac output changed moderately (Fig. 6) because CP decreased VRMC to approximately half its rate before this pacing paradigm during AF. That is, cardiac output went from 1.7 ± 0.6 to 1.9 ± 0.6 l/min as the result of CP during AF. During AT, cardiac output did not change (from 2.1 ± 0.6 to 2.1 ± 0.3 l/min) as the result of CP. The cardiac output during SR was 2.2 ± 0.4 l/min. As illustrated in Figs. 1 and 2 (area of pressure-volume loops), SW increased as the result of CP during both AT and AF. These increases in SW were caused by the marked increases in SV and moderate increases in developed pressure. CP increased SW from 0.12 ± 0.05 to 0.31 ± 0.09 J during AF. During AT, the same CP increased SW from 0.17 ± 0.04 to 0.37 ± 0.08 J. The SW during SR was 0.3 ± 0.1 J. Because the VMRC decreased due to CP, the average external cardiac power (ECP = SW × VMRC) during acute AF or AT did not change as much as SW. That is, ECP increased from 0.39 ± 0.12 to 0.55 ± 0.17 W as a result of CP during AF. During AT, CP increased from 0.56 ± 0.15 to 0.63 ± 0.15 W. The ECP during SR was 0.6 ± 0.1 W.

**Effects of CP on total systemic vascular resistance and aortic stiffness.** The total systemic vascular resistance (TSVR) rose from 44.6 ± 21.3 to 56.6 ± 20.5 mmHg·l⁻¹·min⁻¹ as a result of CP during AF. In contrast, the TSVR did not change during AT as the result of CP (44.9 ± 10.6 to 42.6 ± 11.9 mmHg·l⁻¹·min⁻¹). The aortic stiffness rose from 2.4 ± 0.9 to 3.8 ± 1.2 mmHg/ml as a result of the CP during AF. The aortic stiffness did not change during AT as a
result of CP (3.1 ± 1.8 to 2.7 ± 0.7 mmHg/ml). Thus during AF, CP resulted in both enhanced resistance and impedance of the arterial vascular bed. Despite these vascular changes, CP enhanced the ejection of blood during AF.

**DISCUSSION**

The major finding of this study is that when premature ventricular stimulations are applied after a critical time delay following ventricular electrical activa-

![Fig. 5. Average changes in LV end diastolic volume (LVEDV), stroke volume (SV), and LV ejection action (LVEF) to CP during AF (top) and AT (bottom).](image1)

![Fig. 6. Average changes in stroke work (SW), external cardiac power (ECP), and cardiac output (CO) to CP during AF (top) and AT (bottom).](image2)
tion, the VRMC dramatically decreases and the ventricular contractile state improves during acute AT and AF. This pacing paradigm is unique in that it is both a negative chronotropic and positive inotropic, nonpharmacological therapy. Unlike pharmacological therapy, this therapy has an immediate effect, yet it can be stopped immediately if inappropriate side effects occur.

In an earlier study, premature ventricular depolarizations were applied to reduce the rate of ventricular contractions during AF (11). In the lone AF patients, the mean pulse rate decreased from 137 to 75 beats/min ($P < 0.001$) with “interventricular” pacing. Their interventricular pacing was similar to our CP. They found that their pacing resulted in an increase in the pulse pressure without a change in the mean blood pressure. These increases in arterial pulse pressure suggest that the SV increased as the pulse rate decreased. In our present study, we found that the degree of ventricular slowing is similar; that is, a reduction of arterial pulses by approximately half because of the application of the CP and a doubling of the pulse pressure (see Fig. 3). In the present study, we found that the SV indeed doubles (see Fig. 5). The increases in pulse pressure and cardiac function would undoubtedly increase the activity of arterial baroreceptors. This increase in afferent nerve activity would reflexively increase parasympathetic nerve activity to the AV node. Increased vagal activity would in turn increase the filtering capacity of the AV node and result in additional slowing of the ventricular rate of activation.

In the clinical study of Lau et al. (11), the optimal time delay of the stimuli was much longer than we observed in the present study. This difference in optimal delay is not surprising, because the ventricular action potential duration of humans is longer than that of dogs (8, 14). When the delays of our CP were extended, we started to observe a secondary contraction of the ventricles. Because the prior study did not measure LV pressure in patients (11), the effects of interventricular pacing on myocardial contractility are not known. In addition, there is no way to know whether the longer delays resulted in secondary contractions of the ventricles. In the mitral stenosis group from the study of Lau and colleagues (11), CP resulted in significant reductions in pulse rate (102 to 57 beats/min) that were attended by decreases in pulmonary arterial and wedge pressures and an increase in cardiac output. Before this clinical study (11), Braunwald’s group (9) showed that the application of “paired stimulation” always increased myocardial contractility, but it increased cardiac output only when heart failure was present. In our study, we found that the cardiac output increased moderately (see Fig. 6).

Recently we have been able to reduce ventricular rate and improve hemodynamics during acute AF by selectively increasing parasympathetic nerve activity to the AV node in dogs (15, 16, 23, 24). In these studies, we have shown that slowing (despite its irregularity) but maintaining the intrinsic activation patterns of the ventricles improved cardiac function to a greater degree than when we performed AV nodal ablation and paced the ventricles at a regular rate equivalent to the averaged rate obtained during the parasympathetic stimulation. However, this new method of ventricular slowing requires thoracotomy and careful placement of a stimulating electrode on the epicardial AV fat pad. In addition, this type of limited nerve stimulation alters the effective refractory period of a portion of atrial tissue. This heterogeneous shortening of the atrial effective refractory period may increase the propensity of AF to perpetuate itself (12). In contrast, the present study suggests that the simple use of a transvenous lead placed in the right ventricle and connected to a modified pacemaker could potentially be an effective means for rate control during AF. However, more experiments are needed to validate the present pacing paradigm.

The rate of pressure development increased dramatically as a result of applying this pacing therapy during acute AT and AF (see Fig. 4). Peak-positive LV dP/dt is an index of contractility that assesses cardiac function during the isovolumic contraction period. This index of contractility, as are others, is influenced by preload and afterload (13). On average, there were moderate increases in both LVEDV and LVSP as a result of CP (see Figs. 4 and 5). Because influences of preload and afterload were moderate (see Figs. 4 and 5), the large increases in peak LV dP/dt during the CP in this study are probably too large to be the result of these factors alone. Finally, increases in heart rate also cause increases in this isovolumic index of contractility (13). The CP applied in this study resulted in a rate reduction of mechanical contraction to less than half of its prior rate. However, there were two electrical activations for every one mechanical contraction. Because there were no increases in the rate of electrical activations of the ventricles and less than half the rate of mechanical contraction, one can rule out an increase in heart rate as a cause for the increase of this isovolumic index of contractility. The application of the CP resulted in greater ejection of blood with each mechanical contraction (see Fig. 5). Because the rate of mechanical contraction decreases dramatically, cardiac output (see Fig. 6) did not markedly change as the result of CP. Previous work has shown that decreasing heart rate per se while maintaining other factors as constant improves the efficiency of the heart (1, 2). However, the application of the CP alters preload and afterload as well as contractility (see Figs. 5 and 6). Thus one cannot say with certainty that CP will improve the efficiency of the heart as a pump during acute AT and AF. However, for this therapy to be effective, the efficiency of the heart should improve or at least not decrease. The present study shows that external work increased as a result of CP during AF. Because the VRMC decreased by one-half while LVSP did not double as a result of CP during AF, one might suspect myocardial oxygen consumption would not increase. However, further experiments to evaluate possible changes in the efficiency of the heart during CP are needed.
Mechanisms for inotropic effects of CP. A pacing therapy similar to ours was proposed many years ago as a therapy for heart failure (3, 7, 9). The purpose of the present study was to show that CP can reduce the rate of ventricular contractions that occur during acute AT and AF and improve cardiac function. It is well established that premature activation of the heart results in impaired mechanical contractions for that beat (10). The greater the prematurity, the weaker the contraction. If the cardiac interval following this prematurity is prolonged, the subsequent contraction is increased. This phenomenon is known as postextrasystolic potentiation (6). When pairs of stimuli are applied to the heart in which the second stimulus is placed immediately after the electrical refractory period of the ventricles, minimal mechanical contractions occur. In contrast, the first stimulus of each pair results in a potentiated contractile response. This paired stimulation can result in sustained increases in myocardial contractility (3, 4). Cooper's insightful review (6) points out the various mechanisms for this potentiation. Most work cited indicates that increased release of cellular calcium is the underlying mechanism. However, the exact source and controlling mechanisms of this released calcium are still disputed. In this review, Cooper points out that comparing the various studies is difficult because there is no standardized pacing protocol. The precise extent to which our CP uses postextrasystolic potentiation is difficult to quantify, because we did not control heart rate. Our pacing paradigm is different from that of paired stimulation in that our paradigm first senses the intrinsic activation of the ventricles and then applies a stimulus similar to the second paced beat in the previous paired stimulation rather than electrically pacing the ventricles twice to obtain increases in mechanical contractile strength. Because the intrinsic electrical activation of the ventricles is the initiator of the mechanical contraction in our pacing paradigm, a more rapid electrical activation of the ventricles and thus presumably a more uniform contraction should occur than with paired pacing. In addition, our CP beat presumably enters into the AV node retrogradely and blocks many of the atrial activations of the ventricles that would have occurred during either AF or AT. Thus the VRMC is decreased by approximately one-half, because half of these antegrade conductions are blocked that would have caused weaker contractions during AF had they not been blocked (see Fig. 1).

In Cooper's review (6), evidence is presented that changes in autonomic tone may alter the extent of postextrasystolic potentiation, but the mechanism for this potentiation is independent of neural control. This independence is important because chronic AF and heart failure alter autonomic tone.

Limitations. We did not use the same rate of atrial pacing to induce acute AT and AF for each animal. The purpose of this initial study was to determine whether CP could be applied over a wide range of ventricular rates. The resultant ventricular rates of these experiments are a function of the filtering capacity of the AV node as well as the atrial rate. The filtering capacity of the AV node is a function of the autonomic state of the animal. If CP improves cardiac performance, autonomic tone would undoubtedly change, i.e., sympathetic tone would decrease and parasympathetic tone would increase. Lack of complete control of heart rate prevents a rigorous evaluation of the effects of our CP on cardiac performance. However, in this study we have shown that CP might be applied clinically over a wide range of ventricular rates.

Because the effects of CP in this study were performed during both acute AT and AF, we are uncertain whether the bradycardic and positive inotropic effects of this pacing paradigm can be maintained. Because CP applied to the atria resulted in chronic bradycardia (5), we suspect the negative chronotropic effect of our pacing paradigm applied to the ventricles could also be sustained for months if needed. On the other hand, the chronic effects of paired stimulation on postextrasystolic potentiation have not been evaluated, although the chronic effects of pacing the right ventricle have been evaluated indirectly (17) and found to be deleterious to cardiac function compared with intrinsic ventricular activation. Thus the sustained effects of postextrasystolic potentiation from the second electrical stimuli from paired stimulation may become masked if the chronic right ventricular pacing (first electrical stimuli) gradually results in dysfunction. On the other hand, our pacing paradigm utilizes the intrinsic activation of the ventricles (a sense rather than paced beat of the pair) that results in mechanical contraction. Thus CP as opposed to paired stimulation may be able to provide a chronic positive inotropic effect. Further experiments are needed to validate these assumptions.

Clinical implications. The recent AFFIRM clinical trial revealed that the mortality rate for some AF patients is equal for ventricular rate control and rhythm control (21, 22). If normal SR cannot be maintained, the use of CP may be an attractive strategy for ventricular rate control. Advantages of this therapy include: 1) it has a positive inotropic effect while slowing the rate of ventricular contraction, 2) the stimuli can be applied via a right ventricular pacing lead connected to a modified clinical pacemaker programmed with the proper algorithms, and finally 3) its effects are immediate. Because CP cannot only decrease the rate of ventricular contraction but also increase contractility independent of the adrenergic system, it may be a novel and viable therapy for ventricular rate control and improvement of cardiac function during concurrent chronic AF and heart failure. Before this therapy could be applied clinically, additional experiments are needed to address the following issues: 1) its potential proarrhythmic effects (application of premature electrical stimuli), 2) the detailed determination of optimal pacing delay and site in terms of both effectiveness and safety, 3) possible chronic changes in myocardial oxygen consumption that could alter the chronic efficiency of the heart, and 4) whether its effects (negative chronotropic and positive inotropic) can be sustained.

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In conclusion, if it can be safely and effectively applied to patients with chronic AF, this therapy could provide a new means for rate control and improved cardiac function.

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**DISCLOSURE**

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