

# Coupled Pacing Reverses the Effects of Persistent Atrial Fibrillation on the Left Ventricle

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**Purpose.** Recent studies have demonstrated that ventricular rate control is a viable treatment strategy for patients in atrial fibrillation (AF). The purpose of this study was to determine whether or not the benefits of coupled pacing (ie, a proposed rate control therapy) could be used during persistent AF.

**Description.** Six mongrel dogs were chronically implanted with endocardial atrial and ventricular pacemaker leads and two standard dual-chamber pacemakers. With the use of two custom "Y"-lead adapters, the pacemakers were used to induce AF and to apply coupled pacing. Left ventricular end-diastolic and systolic volumes were measured by echocardiography to determine ejection fractions.

**Evaluation.** Persistent AF significantly increased both ventricular rate and left ventricular dimensions. After sustained coupled pacing had been applied for 3 to 4 weeks, left ventricular volumes and contractile rate were significantly reduced and returned toward the values measured prior to the induction of persistent AF. Coupled pacing increased the ejection fraction that had been reduced by persistent AF.

**Conclusions.** Coupled pacing reversed the left ventricular remodeling caused by the tachycardia resulting from AF.

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## Technology

For the last several years, our laboratory has been investigating the implementation of coupled pacing (CP) (a novel pacing paradigm) for controlling the ventricular rate of mechanical contraction (VRMC). Using CP involves the application of electrical stimuli to the ventricles after the effective refractory period. In previous studies [1–3], we reported that acute application of CP resulted in both a negative chronotropic (mechanical not electrical rate) and a positive inotropic response during acutely induced atrial fibrillation (AF). Reduction in ventricular contractions by CP is the result of blocked conduction of rapid supraventricular activations to the ventricles during AF. When CP slowed this ventricular rate of contraction, stroke volume increased markedly as a result of moderate increases in left ventricular end-diastolic volume and the decrease in end-systolic volume [1, 3]. In addition, the positive inotropic effects of CP (resulting from postextrasystolic potentiation) increased left ventricular (LV) first derivative of left ventricular

pressure (dp/dt) and LV ejection fraction (EF). The purpose of this study was to determine if sustained CP could be used in the setting of persistent AF.

## Technique

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. Six mongrel dogs (20 to 30 kg) were included in this study.

During echocardiographic imaging, all pacemakers were temporarily turned off to assess cardiac function, except during CP therapy. Echocardiographic data were acquired (Sequoia, with a 3-MHz probe [Seimens System, Mountain View, CA]) at (1) baseline during sinus rhythm, (2) after persistent AF, but just before the beginning of CP therapy, and (3) after 3 to 4 weeks of continual application of CP. Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV), as well as left atrial volumes (LAV) (measured at end systole of the left ventricle), were computed from standard apical views (ie, 2-chamber view and 4-chamber view) by using the Simpson bi-plane method. Left ventricular EF was calculated from these measurements ( $[LVEDV - LVESV]/$

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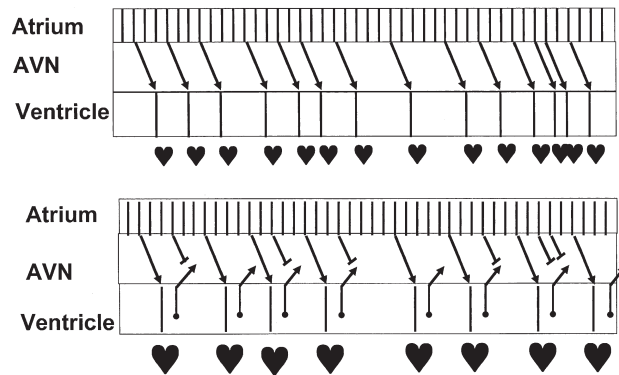


Fig 1. Concept of coupled pacing (CP) during atrial fibrillation (AF). A diagram illustrating the effects of applying coupled pacing to the right ventricle during AF. Note the CP results in atrioventricular nodal (AVN) block and the reduction in ventricular rate of mechanical contraction as illustrated by the spacing of the hearts.

LVEDV). Measurements from three cardiac cycles as defined by visible contractions were averaged for all volumes, and these mean values were expressed as a single value.

Rapid right ventricular pacing was applied for 2 weeks at a rate of 240 bpm using asynchronous mode (DOO) of the dual chamber ventricular pacemaker as previously described [4]. When the LV EF was reduced by approximately 20% from the baseline value during normal sinus rhythm, the ventricular pacemaker was turned off. At this time, the atrial pacemaker was programmed to induce AF [4]. The atrial volume interval varied from 80 to 120 ms, depending on the individual animal and its autonomic state. Weekly electrocardiographic measurements were obtained to confirm this pacing continually fibrillated the atria. During the induction of AF, echocardiographic assessments of LV function continued until the EF was reduced by approximately 30% from baseline levels. Then the atrial pacemaker was turned off.

Once ventricular dysfunction had developed and persistent AF was established (ie, in 6 to 8 weeks total), we initiated coupled pacing. We used the ventricular pace-

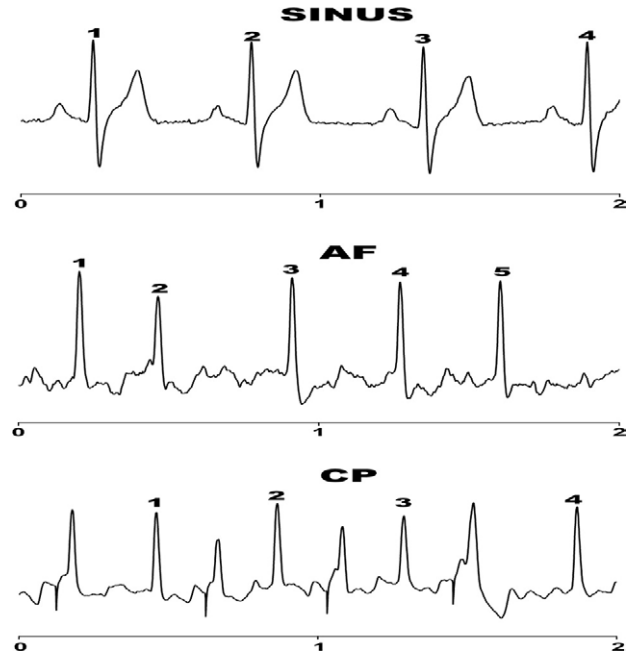


Fig 3. Electrocardiographic tracings of one dog taken during the three periods of this study. The top panel shows when the animal was in sinus rhythm. The number indicates the intrinsic electrical activations. The middle panel shows when the animal was in persistent atrial fibrillation (AF). The bottom panel shows coupled pacing (CP).

maker which was programmed in its dual chamber synchronous pacing (DDD) mode to apply the coupled pacing. The AV interval of the ventricular pacemaker was adjusted to alter the CP time delay to intervals ranging from 160 to 220 ms (Fig 1). These adjustments were made while monitoring LV contractions by echocardiography such that no secondary contractions were observed.

Normally when the ventricles are electrically activated, there will be corresponding subsequent mechanical contractions, which in turn result in ejection of blood. However, during rapid acute AF this is not always the case (ie, prior acute hemodynamics illustrate this point) (Fig 2).

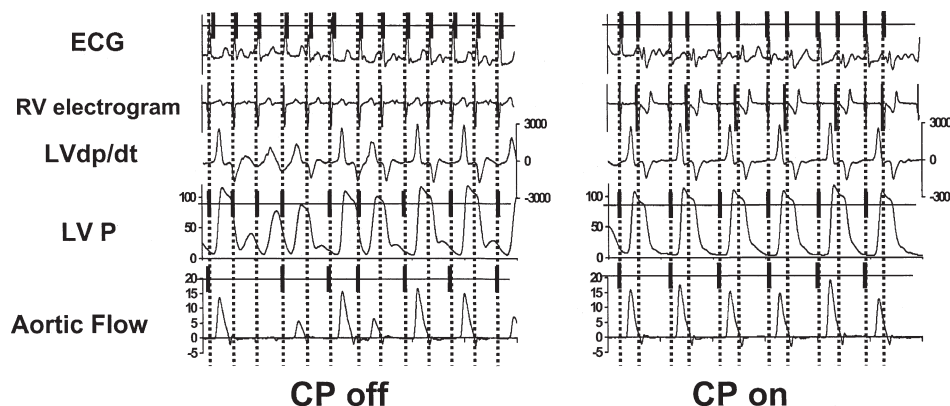


Fig 2. Hemodynamic tracings without coupled pacing (CP) (left panel, CP off) and then with CP (right panel, CP on) in a prior acute experiment. Marks above electrocardiogram (ECG) tracings illustrate ventricular rate of electrical activation, right ventricular (RV) electrogram, first derivative of left ventricular pressure (LVdp/dt). Marks above the left ventricular pressure (LV P) tracings illustrate ventricular rate of mechanical contraction, and marks above the aortic flow tracings illustrate ventricular rate of ejections.

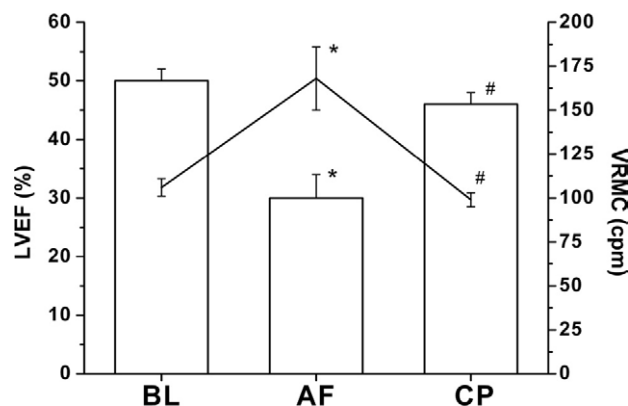


Fig 4. The effects of persistent atrial fibrillation (AF) and sustained coupled pacing (CP) on left ventricular ejection fraction and left ventricular rate of mechanical contraction (VRMC). The asterisk (\*) indicates that persistent AF significantly changed both left ventricular ejection fraction (LVEF) and VRMC. The pound sign (#) indicates that sustained CP significantly reversed these prior changes within 3 to 4 weeks back toward their pre-AF values. (BL = baseline.)

The ventricular rate of electrical activation (VREA) resulted in 13 electrical activations that resulted in the VRMC causing 9 contractions, which in turn led to a slow ventricular rate of ejections (ie, 6 ejections) (Fig 2, left panel). In contrast, the application of CP during AF changes this relationship (Fig 2, right panel). The application of CP results in the blockage of every other supraventricular activation. Since a coupled beat followed each intrinsic electrical activation, the VREA remained approximately the same with the application of CP. The positive inotropic effect of CP by postextrasystolic potentiation now resulted in each intrinsic activation to result in a subsequent contraction and then ejection of blood. That is, there were 12 VREAs, 6 VRMCs, and 6 ejections. For this chronic study, we reported only the VRMC obtained while performing the echocardiographic measurements.

Analysis of variance was used to determine if any echocardiographic measurements (LVEDV, LVESV, LV EF, and LAV) were significantly changed. In addition, we measured the VRMC as previously described [2]. These continuous variables were expressed as means  $\pm$  standard error of the mean. Paired comparisons were made between these 3 periods: (1) baseline (BL) versus AF, (2) AF versus CP, and (3) BL vs CP (Fisher Least Significant Difference). A probability of  $< 0.05$  was considered significant.

### Clinical Experience

Figure 3 displays representative electrocardiographic tracings of one dog during the three phases of this study. The top panel shows normal sinus rhythm prior to the induction of persistent AF. The middle panel shows persistent AF just prior to the application of CP. The bottom panel shows that AF persisted even after CP had been applied for 4 weeks.

Persistent AF significantly increased the average

VRMC (Fig 4, baseline to AF,  $103 \pm 2.5$  contractions per min [cpm] to  $174.5 \pm 14.5$ ;  $p < 0.001$ ). Using CP brought the average VRMC back to  $95.8 \pm 9.2$  cpm, ( $p < 0.001$ ). As shown in Figure 4, LV EF was quite sensitive to supraventricular tachycardia, decreasing from  $52 \pm 2$  to  $32 \pm 4\%$  ( $p < 0.01$ ) during persistent AF, and returning to  $47 \pm 2\%$  ( $p < 0.01$ ) during CP.

We observed significant tachycardia-mediated LV remodeling, resulting in both left atrial and left ventricular dilatation. All ventricular dimensions significantly increased as a result of persistent AF. The LVEDV increased from  $62.3 \pm 4.78$  to  $75.5 \pm 6.65$  mL (BL vs AF;  $p < 0.01$ ) (Fig 5). Similarly, LVESV increased from  $30.7 \pm 2.57$  to  $51 \pm 4.57$  mL ( $p < 0.001$ ), and LAV increased from  $20.2 \pm 3.84$  to  $34.8 \pm 4$  mL ( $p < 0.01$ ) during persistent AF.

After sustained CP had been applied for 3 to 4 weeks, LV volumes were significantly reduced (AF vs CP) (Fig 5) and returned toward the values measured prior to the induction of persistent AF. The LVEDV decreased from  $75.5 \pm 6.65$  to  $65 \pm 3.22$  mL (AF vs CP;  $p < 0.05$ ) and the LVESV decreased from  $51 \pm 4.57$  to  $34.5 \pm 2.41$  mL ( $p = 0.001$ ). The reduction in LV volumes also resulted in a partial reduction of LAV toward baseline values, despite the continued presence of AF. That is, LAV decreased from  $34.8 \pm 4$  to  $27.7 \pm 2.6$  mL ( $p > 0.05$ ).

### Comment

The first major finding of this study is that the effects of CP were sustained for 4 weeks. Sustained CP dramatically reduced the VRMC and increased contractile performance (LV EF). Second, the sustained effects of CP resulted in a decrease of left ventricular volumes (reverse remodeling) that had become dilated during the induction of persistent AF.

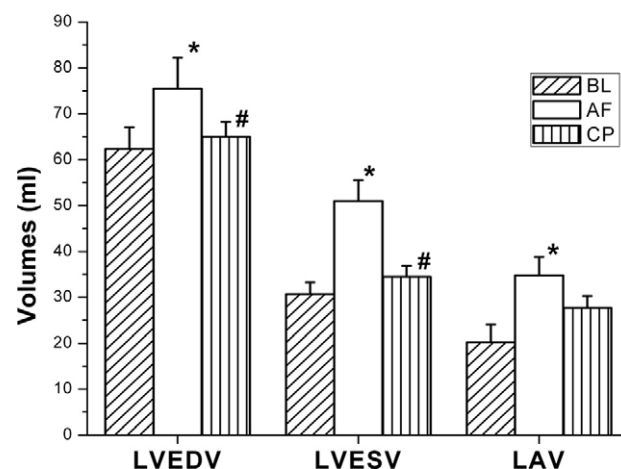


Fig 5. The effects of persistent atrial fibrillation (AF) and sustained coupled pacing (CP) on left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left atrial volume (LAV). The asterisk (\*) indicates that persistent AF significantly increased LVEDV, LVESV, and LAV. The pound sign (#) indicates that sustained CP significantly reversed the AF-induced increases in LVEDV and LVESV. Although CP reduced LAV, this change did not reach statistical significance.

The changes in left ventricular volumes in this study were remarkably different than we observed acutely [1]. In our earlier study, mean LVEDV decreased during acute AF. This reduction in LVEDV was undoubtedly due to the marked tachycardia during our other study of acute AF [1]. Acutely, the reduction in VRMC by CP increased LVEDV. In contrast, with concomitant LV dysfunction, persistent AF increased the mean LVEDV in this present study. Sustained application of CP reduced the mean LVEDV (Fig 5). In summary, sustained application of CP in this present study reversed the remodeling of the left ventricle chamber dimensions caused by persistent AF.

A number of laboratories have reported that both chronic supraventricular and ventricular tachycardia caused significant left ventricular dilation as well as a reduction in the EF in dogs [5–8]. After the rapid pacing was stopped in these prior studies, the EF rapidly returned to normal. These studies also showed there remained a residual dilatation in their left ventricular volumes that eventually started to return toward pre-tachycardia levels. In contrast, our present study showed that the left ventricular volumes returned rapidly back to their pre-tachycardia levels as the EF improved. Thus, the positive inotropic effect of our CP may be partially responsible for the reverse remodeling as well as its negative chronotropic effect as defined by the VRMC, despite the continual rapid VREA.

A limitation of this study is short observational periods that were made during the conscious testing. However, during these periods of conscious testing, we observed that the CP consistently reduced the VRMC. Finally, there was no separate group of animals in which sustained CP was not applied. The purpose of this control group would have been to determine if the rapid VREA developed by the persistent AF would have spontaneously diminished in the same 4-week period that CP had been given in this study. If this would have occurred to a measurable degree in this study, then the VRMC (one half of VREA) following the sustained CP would be less than one half of the VREA measured after the induction of persistent AF, but prior to the beginning of CP. This was not the case (see Fig 4). These preliminary results suggest that further experiments should be pursued in which long-term hemodynamic measurements of electrocardiograms, left ventricular pressures and volumes, and aortic and coronary flow were obtained for longer periods to further elucidate the mechanism of action of this pacing paradigm.

In summary, we have shown that with new technology, the sustained application of CP can reverse the LV dilation and functional impairment (LV EF) that resulted from LV dysfunction during persistent AF. Therefore, further tech-

nology using CP as a therapy should be considered as a means to achieve ventricular rate control and improve cardiac function in many cases of persistent AF, particularly in the presence of nonischemic dysfunction.

## Disclosures and Freedom of Investigation

We would like to thank Medtronic and St. Jude Medical for their unrestrictive supply of standard dual pacemakers and leads. Ocor generously provided the custom “Y”-lead adapters at no cost. We had full control of the design, execution, and analysis, and the reporting of this work. This study is intended to advance basic mechanism of cardiac arrhythmias.

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