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Use of Conventional Dual Chamber Pacemakers With Custom Lead Adapters to Induce Atrial Fibrillation or Heart Failure in Dogs

Faruk Cingoz, MD, George Yanulis, MS, Elizabeth Ching, RN, Kiyotaka Fukamachi, MD, PhD, and Don W. Wallick, PhD

Departments of Biomedical Engineering and Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio

Purpose. The purpose of this article is to show how custom “Y”-lead adapters and standard dual-chamber pacemakers can be used to produce pacing paradigms that will lead to stable experimental models of heart failure and atrial fibrillation.

Description. With two custom lead adapters we used both ports of two dual-chamber clinical pacemakers to independently apply various pacing paradigms to either the ventricles or the atria of dogs.

Evaluation. Because both ports of the ventricular pacemaker were used to apply stimuli through one lead, the device did not have to be modified to obtain ventricular pacing rates that are sufficiently elevated to lead to tachycardia-induced heart failure. Similarly, simultaneous use of both ports of the atrial pacemaker can be used to apply stimuli through one atrial lead to induce sustained atrial fibrillation.

Conclusions. These techniques facilitate induction of experimental models of heart failure and atrial fibrillation without the need for modification of the clinical pacemaker.

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Technology

Protocols for producing experimental heart failure by rapid ventricular pacing are well established [1]; however, for safety reasons, commonly used clinical pacemakers do not allow pacing rates that are sufficient to induce either heart failure (HF) or atrial fibrillation (AF). In one previous study, rapid ventricular pacing was achieved by modifying a single-chamber pacemaker [2]. In this article, we describe the use of a dual-chamber pacemaker and a custom “Y”-lead adapter, and we show how rapid pacing can be achieved without the need to modify the circuitry or programming of a standard clinical pacemaker.

In a similar manner, experimental atrial fibrillation has been previously induced by the use of rapid atrial pacing [3, 4]. Because of the shorter refractory period of atrial tissue, the pacing rate needs to be very rapid (400 to 600 bpm) to induce AF. Although specially modified clinical pacemakers have been built for the purpose of induction of chronic atrial fibrillation [3–5], the method described as follows facilitates AF induction without the need for pacemaker modification.

Material and Methods

This investigation was approved by the Institutional Animal Care and Use Committee at the Cleveland Clinic and conforms to the “Guide for the Care and Use of Laboratory Animals” published by the United States National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Technique

Surgical Preparation

Under sterile conditions, three dogs were chronically implanted with one endocardial lead in the right atrial appendage and another in the right ventricular apex through the right jugular vein. Leads were tunneled subcutaneously toward the interscapular region. Each lead was attached to a custom “Y” adapter (Fig 1). The “Y” adapters were attached to both ports of two dual-chamber pacemakers (Fig 2). The two pacemakers were then subcutaneously positioned 3 to 4 inches apart so that they could be separately interrogated and programmed.

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Address correspondence to Dr Wallick, Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: wallickd@ccf.org.

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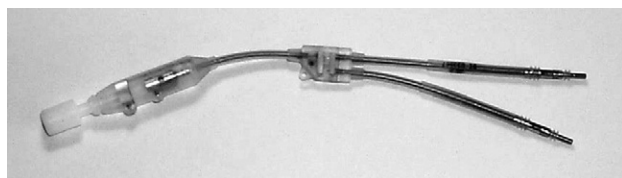


Fig 1. Photograph showing the custom adapter made for us (Oscor, Inc, Palm Harbor, FL).

Description of the Pacing Procedure

The atrial and ventricular pacemakers were programmed at separate times. In this study they were not activated at the same time. Using the asynchronous mode (DOO) of the dual chamber pacemaker, the ventricles can be paced at rates sufficient to produce heart failure (180 to 240 bpm). For example, if the pacing interval is set at twice the desired interval (500 ms) and the atrioventricular (AV) delay (250 ms) is set such that a pacing pulse from the ventricular port fires at exactly half this interval, the ventricles can be paced at shortened intervals (ie, stimulation pulses from both ports) without having to modify the clinical pacemaker.

Similarly, by using the DOO mode of the dual chamber pacemaker, both outputs can be connected to the atrial lead through the new lead adapter, and experimental atrial fibrillation can be induced if given sufficient time for pacing. For example, if the rate is set just above the intrinsic sinus rate and the AV delay of the dual chamber pacemaker is set to be sufficiently short enough, the first

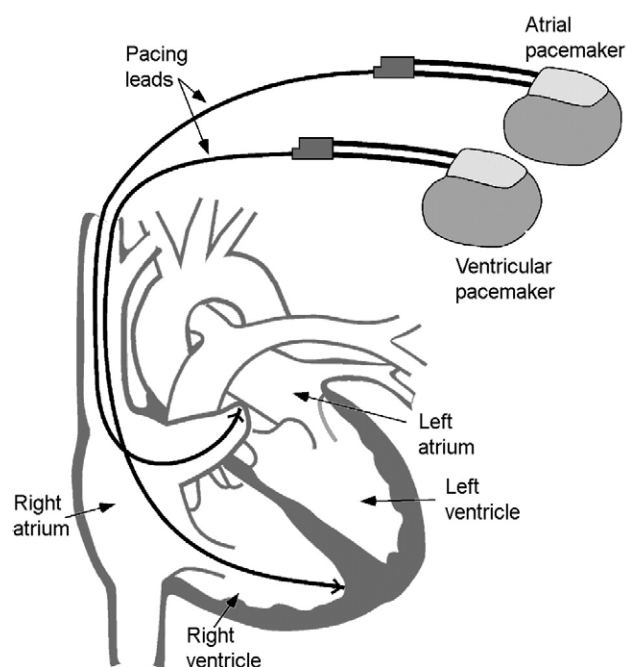


Fig 2. Schematic diagram showing the placement of the leads, adapters, and pacemakers. Note that each lead uses a custom adapter (as shown in Figure 1) to use both the atrial and ventricular ports of each pacemaker to provide two pacing pulses from each pacemaker as described in the text.

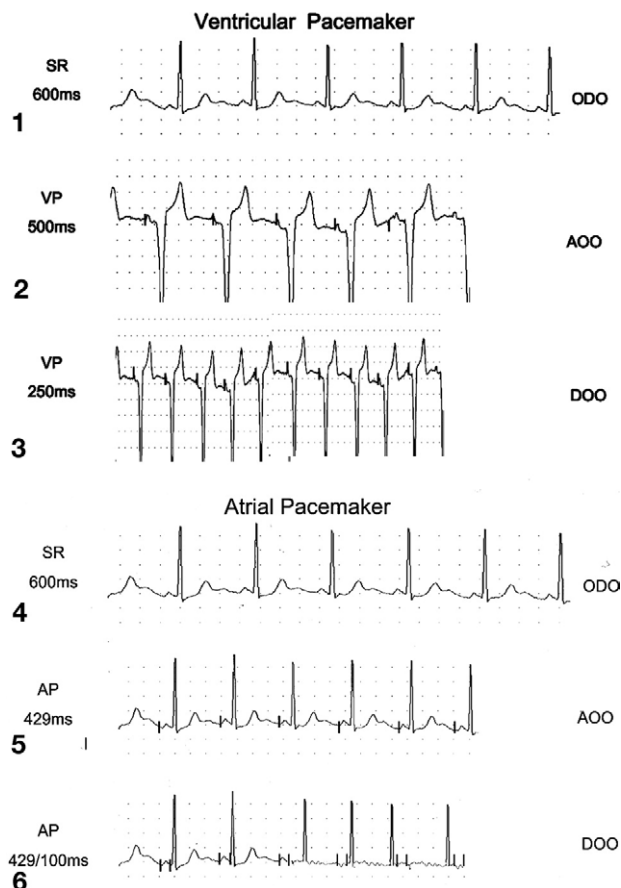


Fig 3. Schematic-timing diagram shows the effects of activating either atrial or ventricular pacemaker alone. (Panel 1) When the ventricular pacemaker is turned off (ODO) mode, sinus rhythm is present. The second panel depicts what one would expect if the ventricles are paced at 120 bpm through the atrial port (AOO) mode. (Panel 3) If the asynchronous mode (DOO) is used with an atrioventricular (AV) interval of 250 ms, one would expect the response to be something like this. (Panel 4) When the atrial pacemaker is turned off, or in the (ODO) mode, a hypothetical sinus rhythm is displayed (sinus rhythm, 600 ms). The fifth panel depicts what one would expect if the atria are paced at 140 bpm through the atrial port (AOO) mode. (Panel 6) If the (DOO) mode is used with an AV interval of 100 ms, one would expect the response to be something like this. (SR = sinus rhythm; VP = ventricular pacemaker; AP = atrial pacemaker.)

stimuli from the atrial port will pace the atria. The interval between the 2 pulses was shortened so that only a portion of the atria could be re-excited by the second stimuli originating from the ventricular port of the atrial pacemaker. This latter pacing paradigm (two tightly coupled stimuli) frequently initiates acute AF rather than a rapid and sometimes sustained atrial tachycardia.

Results of Testing the Pacemaker-Adapter-Lead Combination

Because the atrial and ventricular ports of both pacemakers were alternately used to stimulate the heart, there could have been significant leakage current from one

port into the other port when our custom “Y”-lead adapter is connected to both ports. Because pacemakers are not constant current devices, this alternating firing from both ports could possibly deplete the battery of these devices prematurely. We consulted the manufacture of the pacemakers that we were using and was informed that the input impedance of these devices is extremely high (1 M Ω). Because the impedance of the pacemaker lead-heart interface was always less than 1 K Ω , ($\sim$ 500 Ω), the leakage current back into the device and away from the heart should be less than 1% with the use of the “Y” adapter as previously described. In all animals, we used bipolar pacing for both leads. In addition, bench testing showed that the lead impedance from the atrial port changed minimally (decreased $\sim$ 1%) when both ends of the “Y” adapter were connected to the ventricular port compared with the impedance when only one end of the “Y” adapter was connected to the ventricular port. Thus battery life should not be appreciably shortened because of current leakage into one port when the other port is applying a pacing pulse.

Results of Lead Placement

The distal end of the atrial lead was always placed in the right atrial appendage. Other activation sites in the atria may result in AF more readily (eg, the pulmonary veins). However this location for lead placement was chosen to better assure that the distal end of the lead would not migrate into the right ventricle and induce ventricular tachycardia or fibrillation because of the short coupled pacing from the atrial-ventricular ports of the atrial pacemaker. Similarly the distal end of the ventricular lead was always placed into the apex of the right ventricle because of the stability of this location. After both endocardial leads were attached, lead impedances and pacing thresholds were evaluated. At 0.5 ms pulse duration, both the atrial and ventricular leads captured the heart at less than 1 volt. The impedance of each lead-tissue interface was less than 1,000 ohms.

Results of Pacing Paradigm (Heart Failure)

All pacing to the ventricles was applied through bipolar leads. Individual pulses were routinely initially set at 5 volts, 0.5 ms. The atrial port (AOO) mode was used to pace the ventricles at a rate sufficiently fast enough to capture the ventricles (120 bpm = 500 ms). Once ventricular pacing was achieved, the mode of pacing was changed to the DOO mode, and the ventricular port was activated at a 250 ms delay (see Fig 3).

Results of Pacing Paradigm (Atrial Fibrillation)

All pacing to the atria was applied through bipolar leads. Individual pulses were routinely initially set at 5 volts, 0.5 ms. In one case, atrial pacing at this intensity resulted in some phrenic nerve stimulation. Therefore the voltage was decreased to 3 volts and atrial pacing was maintained, resulting in induction of AF. Because pacing measurements were set when the dogs were conscious and each dog had a different autonomic tone resulting in quite different sinus rates, pacing measurement settings

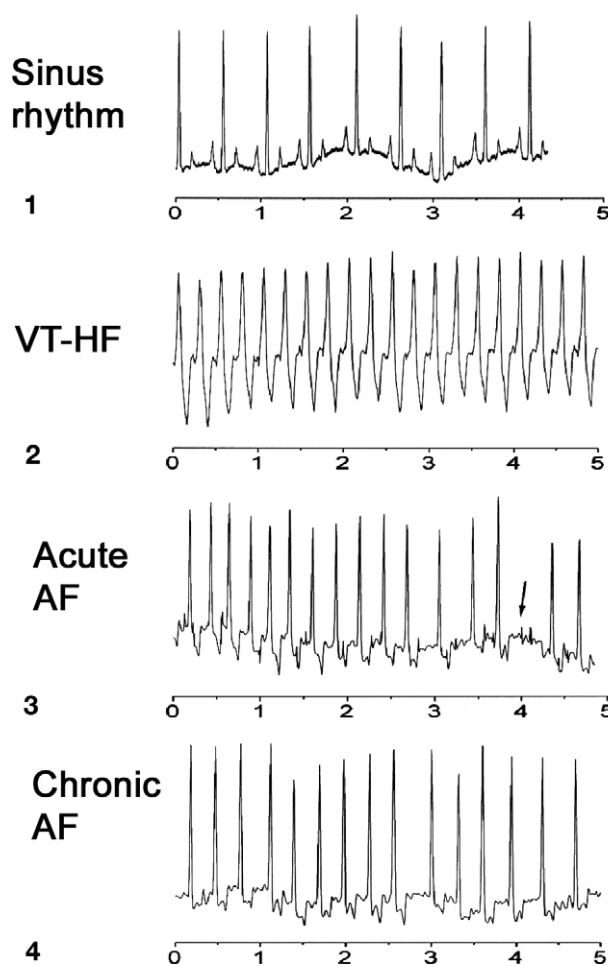


Fig 4. Diagram representing 5-second tracings of the electrocardiogram (lead II) from a conscious dog. The first panel shows the animal in sinus rhythm (SR). The second panel shows a paced ventricular tachycardia which will eventually lead to heart failure (VT-HF) if the ventricles were to be rapidly being paced at 240 bpm. The third panel shows that atrial fibrillation (AF) has been acutely induced in this same animal. The fourth panel shows that sustained AF was induced in four weeks of paired atrial pacing as evident by the continual atrial fibrillation for 4 additional weeks after the atrial pacemaker has been turned off.

for each animal had to be individually set and in some cases adjusted. The atrial port (AOO) mode was used to pace the atria at a rate sufficiently fast enough to capture the atria (range, 140 to 180 bpm). Once the atrial pacing was achieved, the mode of pacing was changed to the DOO mode, and the ventricular port was activated at an 80 to 100 ms delay (see Fig 3). The classical work of Wijffels and coworkers [4] showed that there is electrical remodeling of the atria as AF is being produced (ie, the atrial refractory period decreases and sometimes necessitates a shortening of the coupling interval).

Results of Representative Responses

Figure 4 contains four panels of electrocardiographic recordings from one dog during conscious testing. In the first panel, the dog is in sinus rhythm, because both

the ventricular and atrial pacemakers are off (or in the ODO mode). The second panel of the electrocardiographic recording (ie, the ventricular tachycardia which will eventually lead to heart failure [VT-HF]) demonstrates the dog being paced for 5 seconds at 240 bpm, because the ventricular pacemaker is programmed in the DOO mode. The average daily living rate was adjusted to set the lower tracking rate at 120 bpm (500 ms). In addition, the AV interval was set at 250 ms. These settings resulted in a ventricular pacing rate of 240 bpm, or a pacing interval of 250 ms, with this adapter and the dual output ventricular pacemaker. Then the ventricular pacemaker was turned off (ODO) mode. In all three animals, the ventricular pacemaker was not left in the DOO mode for more than 5 to 10 minutes. The purpose here was to show how heart failure could be induced if the pacemaker had been left on.

The third panel illustrates how AF can be induced when the atrial pacemaker is programmed in the DOO mode. In this particular case, the rate is set above sinus rate at 140 bpm to capture the atria. In addition, the AV interval is set at 100 ms in this case (note the pacing artifacts in the tracing). The arrow shows two stimuli separated by 100 ms. Thus, the second paced beat from the ventricular port of this atrial pacemaker stimulates the atrial tissue when only a portion of the atrial tissue is excitable, a condition which leads to AF. Both the pacing rate and the AV interval can be readily modified as the atria undergo electrical remodeling to perpetuate the AF. We periodically turned off the atrial pacemaker to evaluate whether the heart would spontaneously return to sinus rhythm. In this particular animal, after 2 weeks of pacing sinus rhythm returned within 20 minutes when the pacing was stopped. After 4 weeks of atrial pacing, the atrial pacemaker was turned off and sustained AF continued for another 4 weeks (bottom panel). Because of the more rapid pacing rates used and the increased pacing stimulus intensity, battery life had decreased by approximately 3 months. However, this is a small portion of the total battery life for a commercial pacemaker.

After 16 weeks of persistent AF (as the pacemaker had been turned off for 12 weeks), the pacemakers from the previously described animal (from Fig 4) were explanted during an acute experiment. Figure 5 shows the tracing of the right atrial electrocardiograms as well as 2 ventricular electrocardiograms and lead II. Note the rapid erratic activity of the atria found in AF is still present (ie, right atrial electrocardiograms). The ventricular cycle length is regular in this part of the experiment because we were pacing both ventricles at a cycle length of 400 ms.

Comment

The major finding of this study is the observation that using a custom “Y”-lead adapter, an unmodified dual chamber clinical pacemaker can be used to achieve almost any combination of an experimental stimulation paradigm.

For more than 20 years it has been known that rapid ventricular pacing can result in ventricular dysfunction



Fig 5. Tracings of the electrocardiogram (lead II), the right and left ventricular electrograms (RVE and LVE) and right atrial electrogram in the same animal (as shown in Figure 4). The animal was in persistent atrial fibrillation for 12 weeks after the atrial pacemaker had been turned off.

and eventual heart failure [1, 2, 6]. In these studies, the pacing interval was held constant for various prescribed times. The time needed to produce tachycardia-induced heart failure is for the most part a function of the average pacing rate [1, 6] (ie, the faster one paces the heart, the faster heart failure symptoms develop). However, the time needed to develop heart failure for a given pacing rate is variable from animal to animal and therefore, sometimes it is unpredictable. Furthermore, many investigators monitor cardiac functional measurements, such as ejection fraction and vary the time of pacing to produce a more uniform state of heart failure. In a recent study [6], the investigators found that pacing at a slower rate for a longer period of time resulted in a model of heart failure that was more stable after the pacing was stopped. The purpose of this article is to show how (with the use of a custom “Y”-lead adapter) rapid ventricular pacing at almost any rate can readily be accomplished without modification of the pacemaker or the rapid depletion of its battery. With the ease of programming commercial pacemakers, pacing measurements can readily be modified to fit the goals of a variety of protocols.

In the same manner, persistent AF can be induced by use of electrical rapid atrial stimulation [3–5]. These atria can be stimulated using either periodic bursts (ie, when sinus rhythm is sensed) or using a very rapid but constant stimulus paradigm. Both of these methods required modification of clinical pacemakers and they greatly increased battery life consumption. Battery consumption is a function of the pacing rate, pulse amplitude, and duration, as well as whether or not the monitoring functions are turned on. In the representative animal previously described, the battery life of the atrial pacemaker was decreased by 3 months, even though the atrial pacing was continued for only 1 month. With lower stimulus intensity in the pacing pulses, it might have been possible to somewhat extend battery life; however, that may have resulted in the need to pace the animal for a longer period. Increased battery life consumption is primarily due to the higher than normal pacing rate (compared to that which is used clinically) and increased intensity of pacing, rather than the current leakage into

the other port of the pacemaker. Despite our higher consumption settings, commercial pacemakers have the capacity to provide these pacing paradigms many times longer than needed.

Although the induction of AF by rapid pacing results in electrical remodeling of the atrial tissue and a shortening of the effective refractory period of the atrial tissue [4], both the pacing rate and the AV interval of the dual chamber pacemaker are readily adjusted to assure that the stimuli from the ventricular port of this atrial pacemaker perpetuated the AF. All of our animals eventually developed persistent AF. We continually paced for 4 to 5 weeks to insure that the animals did not revert back to sinus rhythm once the pacemaker was turned off. In addition to our electrocardiographic measurements, we never observed the normal mitral inflow patterns seen in sinus rhythm while performing our weekly echocardiograms when the atrial pacemaker had been turned off.

In prior studies, persistent AF occurred only after structural remodeling of the atria had occurred [3, 4, 7–9], a phenomenon that generally occurs long after electrical remodeling. Thus, pacing may have to be applied for several months. For some unknown reason, our three animals remained in persistent AF after a shorter period of pacing. Even if the process should take 3 to 4 months, the battery of a conventional dual pacemaker should be adequate for the induction process. In a prior study, a modified atrial pacemaker was left on continuously to ensure that sinus rhythm would not return [5]. This could be done using our technique.

Because clinical leads and pacemakers are rugged, readily implantable, and can provide pacing for extended periods of time, they are ideal for these types of experiments. Thus, our present study shows how with the addition of a “Y”-custom lead adapter, an unaltered dual-chamber pacemaker, and some imagination, AF or heart failure can be induced in a large animal model when given sufficient time.

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, analysis, and the reporting of this work. The study is intended to advance basic mechanisms of cardiac arrhythmias.

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