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A NOVEL CARDIAC PACING PARADIGM FOR ATRIAL FIBRILLATION AND
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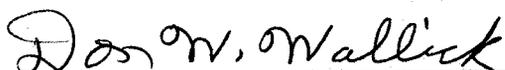
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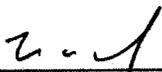
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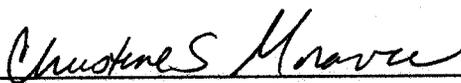
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**This dissertation is dedicated in loving memory of my parents, Emanuel
“Manny” and Dimitroula “Trula” Yanulis**

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I would first like to thank Dr. Don Wallick who has not only served as an outstanding research mentor and advisor; he has helped me in my maturity and development as both a cardiovascular scientist and researcher which I will always be eternally grateful for. Dr. Wallick has always treated me with respect, great patience and has always treated me like colleague. There have been several times where I have felt over-whelmed, but he has always been there to help me maintain my focus and complete my dissertation and research efforts. Dr Wallick has provided me with a great opportunity to pursue my research interests in the areas of cardiac pacing research at an exceptional level of excellence at the Cleveland Clinic. His high level of dedication, intelligence, motivation and mentorship and as a highly regarded researcher by both clinicians and other scientists in this field will always serve as an inspiration in all my future research experiences in cardiovascular medicine.

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**A NOVEL CARDIAC PACING PARADIGM FOR ATRIAL FIBRILLATION
AND HEART FAILURE PATIENTS**

GEORGE EMANUEL YANULIS

ABSTRACT

It has been estimated that 4.6 million persons have heart failure, and 400,000 to 700,000 new cases develop each year and the U.S. Hospital discharges for HF rose from 399,000 in 1979 to 1,099,000 in 2004 according to the National Hospital Discharge Survey. Atrial fibrillation is the most common sustained cardiac arrhythmia in the United States. Recent studies have demonstrated that ventricular rate control is a viable treatment strategy for patients in atrial fibrillation.

In a number of cases, despite the electrical resynchronization of the ventricles using biventricular pacing (cardiac resynchronization therapy), heart failure patients in sinus rhythm do not respond to cardiac resynchronization therapy as with other heart failure patients. These non-responders may respond to our pacing paradigm which is the combined use of cardiac resynchronization therapy which is commonly designated as CRT and coupled pacing (CP) which will be referred to as CRT+CP.

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. And by using the asynchronous mode of a dual chamber pacemaker, the ventricles can be paced at rates sufficient to produce heart failure (180 to 240 beats per minute) which had been successfully accomplished as part of the research protocol in our coupled pacing paradigm studies. These specially designed Y connectors facilitated our coupled pacing and biventricular pacing paradigm studies, i.e. allowed us to induce AF and apply CP under experimental conditions.

My research on this novel pacing paradigm (CRT+CP) has shown that it slowed the contractile rate by half (116 ± 16 cycles per minute vs. 259 ± 15 cycles per minute). And CRT+CP as compared with CRT at a similar contractile rate (CRT-vagal stimulation at 103 ± 14 cycles per minute) also dramatically increased both the diastolic period ($48 \pm 6\%$ vs. $27 \pm 3\%$, $p=0.02$) and the left ventricular ejection fraction ($51 \pm 10\%$ vs. $25 \pm 4\%$, $p<0.001$) as well.

This research has further demonstrated that the addition of a coupled paced beat significantly increased the left ventricular strain. The addition of coupled pacing to biventricular pacing also improved the left ventricular ejection ($51 \pm 10\%$) to that of sinus rhythm despite the continual acute atrial fibrillation. CP may be combined with biventricular pacing (CRT+CP) to slow the ventricular rate of mechanical contractions and further improve contractility to a greater extent than what has been observed by CRT alone in patients with dyssynchronized heart failure and atrial fibrillation.

TABLE OF CONTENTS

	Page
ABSTRACT.....	vii
TABLE OF CONTENTS.....	ix
LIST OF TABLES.....	xii
LIST of FIGURES.....	xiii
LIST OF ABBREVIATIONS	xv
CHAPTER	
I. Introduction to Coupled Pacing (CP) and CP with CRT.....	1
1.1 Overview	1
1.2 Background	2
1.3 Research Aims.....	4
1.3.1 Experimental Paradigm for AF.....	5
1.3.2 Coupled Pacing.....	6
1.3.3 CRT + CP Pacing.....	6
1.3.4 Simulation flow in the Great cardiac Vein (GVC)	7
1.4 References.....	8
II. Use of Conventional Pacemakers to Induce Atrial Fibrillation in Dogs.....	11
2.1 Introduction.....	11
2.2 Materials and methods.....	12
2.3 Results.....	14
2.4 Discussion.....	20

2.5	References	23
III.	Coupled Pacing Reverses the Effects of Atrial Fibrillation on the Left Ventricle	25
3.1	Introduction.....	25
3.2	Methods.....	26
3.2.1	Surgical Preparation.....	26
3.2.2	Conscious Testing.....	26
3.2.3	Pacemaker Implantations and Pacing Protocols.....	27
3.2.4	Echocardiography	28
3.3	Results.....	29
3.4	Discussion.....	33
3.5	References.....	38
IV.	An Improved Cardiac Resynchronization Therapy.....	42
4.1	Introduction.....	42
4.2	Methods.....	43
4.2.1	Pacing protocol.....	44
4.3	Results.....	47
4.4	Discussion.....	50
4.5	References.....	54
V.	Simulation of Flow in the Great Cardiac Vein and the Use of Sensors for Monitoring Flow for Use in Cardiac Pacing Monitoring.....	60

5.1	Introduction.....	60
5.2	Simulation of the Great Cardiac Vein (Mock Circulatory Circuit).....	64
5.3	Methods.....	65
	5.3.1 Bench Testing Phase I	65
	5.3.2 Experimental methods/tools (Mock II Circuit).....	69
5.4	Results (Mock II Circuit).....	71
5.5	Conclusions.....	73
5.6	Future Work.....	75
5.7.	References.....	78
	BIBLIOGRAPHY.....	80

LIST OF TABLES

	Page
I. Experimental Protocol for Data Acquisition.....	69
II. Illustrates the Statistical Analysis for Two Trial Runs.....	72

List of Figures

	Page
1. Photo of customer Y-adaptor	12
2. Schematic diagram showing the placement of the leads, adapters, and pacemakers	13
3. Schematic-timing diagram shows the effects of activating either atrial or ventricular pacemaker alone	15
4. Diagram of ECG tracings.....	17
5. Electrograms of animal in chronic atrial fibrillation.....	19
6. ECG tracings during 3 periods of the study.....	30
7. The effects of persistent AF and sustained CP on LV function.....	31
8. The effects of persistent AF and sustained CP on LV volumes.....	32
9. Hemodynamic tracings.....	34
10. A schematic diagram of electrical stimulation applied to the heart...	45
11. Composite data.....	49
12. Schematic diagram of components for simulation of flow.....	69
13. Photograph of the Mock I Circulatory Circuit.....	70

14.	Photograph of Mock II Circulatory Circuit.....	70
15.	Photograph of data being obtained using the Mock II Circuit.....	71
16.	Change in Pressure vs. Flow for Trial #3 on 8-20-07.....	73
17.	A diagram of our proposed new monitoring system for pacing...	77

LIST OF ABBREVIATIONS

ACC = American College of Cardiology

AF = atrial fibrillation

AHA = American Heart Association

Ao_{mean} = mean aortic pressure

AP = atrial pacemaker

AV = atrioventricular

AVD = atrioventricular delay

BL = baseline during sinus rhythm

Bi-V = biventricular

BPM = beats per minute

CBF = Coronary blood flow (ml/min)

CDC = Centers for Disease Control and Prevention

CHD = coronary heart disease

CHF = congestive heart failure

CI = the interval estimate of a population parameter

CO = cardiac output (L/min)

CP = coupled pacing

CRT = cardiac resynchronization therapy

CRT+CP = cardiac resynchronization therapy and coupled pacing

CRT-VS = cardiac resynchronization therapy and vagal stimulation

CS = coronary sinus

CVR = coronary vascular resistance (mmHg/ml/min)

DATAQ = a data software analysis package (DATAQ® Instruments)

DBP = diastolic blood pressure (mmHg)

EDV = end diastolic volume (mL)

ESV = end systolic volume (mL)

FHS = Framingham Heart Study

GCV = great cardiac vein

HF = heart failure

HR = heart rate (min^{-1})

LA = left atrial

LAD = left anterior descending coronary artery

L/min = liters per minute (unit for representing cardiac output)

LV = left ventricular

LV dP/dt = 1st derivative of LV systolic pressure development

LVEDP = left ventricular end-diastolic pressure (mmHg)

LVE = left ventricular electrograms

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter (mm)

LVESV = left ventricular end-systolic volume (mL)

LVEDV = left ventricular end-diastolic volume (mL)

LVP = left ventricular pacing

LVP = left ventricular pressure (mmHg)

mmHg-s = millimeters of mercury second

mL = milliliter

ml/min = milliliters per minute

min⁻¹ = 1/minute

ml/kg-min = milliliter per kilogram minute

mmHg = millimeters of mercury

mm Hg/ml-min = millimeters of mercury per milliliter minute

MVO₂ = myocardial oxygen consumption (mlO₂/min)

NASPE = North American Society of Pacing and Electrophysiology

NCHS = National Center for Health Statistics

NHDS = National Hospital Discharge Survey

NHLBI = National Heart, Lung, and Blood Institute

NYHA = New York Heart Association

ODO = cardiac pacing turned off

ORIGIN[®] = Data Analysis and Graphing Workspace

Ponemah = a physiology software and hardware platform (DSI)

RA = right atrial

RCA = right coronary artery

RV = right ventricular

RVE = right atrial electrogram

RVP = right ventricular pressure

SBP = systolic blood pressure (mmHg)

SR = sinus rhythm

SV = stroke volume (mL)

SVC = superior vena cava

VCO_2 = minute carbon dioxide production

VO_2 = minute oxygen consumption

VO_{2max} = maximum amount of oxygen in milliliters that is being used by per kilogram of subject's body weight (ml/kg-min)

VP = ventricular pacemaker

VREA = ventricular rate of electrical activations

VRMC = ventricular rate of mechanical contractions

VS = vagal stimulation

VT-HF = ventricular tachycardia induced heart failure

VTI = velocity-time integral

VVD = ventricular-ventricular delay

WINDAQ/XL = is a software add-on to WinDaq (DATAQ[®] Instruments)

CHAPTER I

Introduction to Coupled Pacing (CP) and CP with CRT

1.1 Overview

The 5-year mortality of patients newly diagnosed with chronic heart failure (CHF) is 50%, despite the best of medical efforts [1]. Approximately 15-30% of heart failure patients are in concurrent atrial fibrillation (AF) [1]. At least 25% of heart failure patients develop major left ventricular conduction abnormalities. Last year 200,000 patients in the USA alone receive defibrillators at a cost of over \$20,000 per unit. Hospital cost per implantation is currently set at a cost of approximately \$10,000 [1]. These numbers are growing at an annual rate of 15-20%. As the U.S. population ages, the incidence and prevalence of CHF are expected to dramatically increase according to Gregg C. Fonarow, MD (Director of the Ahmanson-UCLA Cardiomyopathy Center). He also articulated that CHF is the primary diagnosis for 875,000 hospitalizations annually, and it is the most common diagnosis among hospitalized patients 65 years of age or older. Fonarow further articulated that CHF had been the primary cause of death in approximately 250 000 people per year in 2001 [2]. Hospital discharges for CHF increased from 399,000 in 1979 to 1,099,000 in 2004 an increase of 175%

(NHDS and NHLBI). The estimated direct and indirect cost of CHF in the United States for 2007 is \$33.2 billion [1]. In 2001, \$4.0 billion (\$5912 per discharge) was paid to Medicare beneficiaries for CHF [1]. The prevalence and incidence of heart failure and hospital discharges associated with this disease demonstrates the need for several life-style changes in order to decrease the increasing trends in this cardiovascular disease entity [2].

1.2 Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the United States [3]. By increasing ventricular rate, AF can cause a tachycardia-mediated cardiomyopathy. Previous work [4] has shown that when sinus rhythm can not be restored, ventricular rate control is a viable treatment option. For the last several years, our laboratory has been investigating the implementation of coupled pacing (CP) [5-8], a novel pacing paradigm, for controlling ventricular rate of mechanical contraction (VRMC). CP involves application of electrical stimuli to the ventricles after the effective refractory period. VRMC reduction by CP is the result of blocked conduction of rapid supra-ventricular activations to the ventricles during AF. We propose a new pacing regimen which is a combined therapy of CRT and CP. Rather than the CRT ending during episodes of AF, the new pacing regimen could be applied. Briefly, (CRT+CP) will be applied as follows: the 1st stimuli will be applied to the left ventricle and the 2nd stimuli to the right ventricle simultaneously in the same manner as CRT is used clinically today. Thus, these first 2 stimulations will result in a more synchronized electrical activation and

subsequent contraction of both ventricles. We will then apply a 3rd premature paced beat to activate both ventricles electrically but not mechanically. This 3rd paced beat to CRT will 1) block rapid supra-ventricular activation of the ventricles during AF, causing the ventricles to contract at a slower rate and 2) provide positive inotropic support [9] in a similar manner as we found for CP [5-8]. Electrical activity in the heart is spontaneously generated by the SA node which is also designated as the physiological pacemaker. This electrical impulse is propagated throughout the right atrium, and through Bachman's Bundle to the left atrium, stimulating the myocardium of the atria to contract [10]. The conduction of the electrical impulse continues throughout the atria is seen on the ECG as the P wave. As the electrical activity is spreading throughout the atria, it travels via specialized pathways, known as internodal tracts, from the SA node to the AV node. This latter node functions as a critical delay in the conduction system

Biventricular pacing also known as cardiac resynchronization therapy (CRT) is for the most part an effective pacing therapy in restoring a more uniform electrical activation and contractile performance in heart failure (HF) patients who are in sinus rhythm but have ventricular conduction system disturbances [11]. The pacemakers which are used in CRT follow the NASPE designation of pacing codes. Although CRT is effective in many HF patients with LBBB, CRT is not effective in some HF patients despite resynchronization (non-responders) even during sinus rhythm. CRT can only be effective if the ventricular rate is controlled during AF. If CP is added to CRT, this could be an effective means of rate control.

Today's cardiac pacemakers that perform CRT generally sense atrial activity and also track their rate. After sensing atrial activation, the device paces both ventricles at a shortened atrioventricular interval in order to insure that the ventricles are activated more uniformly by the biventricular pacing. However, if the rate of atrial activation suddenly increases or the atria fibrillate (paroxysmal AF), these pacemakers automatically will end atrial tracking and mode shut off. That is, when their upper atrial tracking rate is exceeded, the biventricular pacing is shut off. Therefore, the beneficial effect of CRT is lost until the episode of AF ends and CRT can resume.

1.3 Research Aims

For the past 3 years, Dr. Wallick and I have been studying a novel pacing modality called coupled pacing (CP) which is designed to improve cardiac function during atrial fibrillation (AF) and heart failure [8,12,13]. This pacing therapy both slows the rate of ventricular contraction and increases contractility. CP first senses the intrinsic electrical activation of the heart. Then a delayed stimulation coupled to this intrinsic activation is applied, resulting in a second electrical activation with minimal mechanical contraction. However, the secondary electrical activation causes the subsequent intrinsic activation to result in a stronger contraction.

The rationale for the use of the canine as the animal model for our cardiac pacing research study for the evaluation of the CRT and CRT and CRT+CP is based on the similar anatomical and physiological similarities which exist between the canine and human cardiovascular systems [14] The canine model is a well-

established model for studying AF and HF [15] The dogs are large enough that pacemakers and their leads could be implanted. Additionally, the dog has a similar heart rate to that of a human. Another important reason for the use of dogs is the ability to monitor them in the conscious state. Finally, dogs are robust experimental animals and this helps assure success for our proposed experiments.

1.3.1 Experimental Paradigm for AF

Protocols for producing experimental heart failure by rapid ventricular pacing are well established [16,17]; 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 chapter 2, the experimental protocol for establishing AF using standard dual chambered cardiac pacemakers [12] will be discussed. More specifically rapid ventricular pacing was achieved by modifying a single-chamber pacemaker. In this study [12], we describe the use of a dual-chamber pacemaker and a custom “Y”-lead adapter (Figure 1), 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 [12]. 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, the method described as follows facilitates AF induction without the need for pacemaker modification [12].

1.3.2 Coupled Pacing

In chapter 3, my studies [13] using sustained coupled pacing will be discussed. Coupled pacing has both a negative chronotropic effect (decreases the heart rate) and as a positive inotropic effect (increases the myocardial contractility). Our research to date has demonstrated that the addition of a coupled paced beat significantly increased left ejection fraction (LVEF), and the 1st derivative of left ventricular pressure development (LVdP/dt), and the left ventricular strain [8,12,13] which improves overall myocardial performance in HF and AF patients. In Chapter 3, I will also discuss how the use of coupled pacing (CP) and how it dramatically reverses the effects of persistent atrial fibrillation on the left ventricle [8].

1.3.3 CRT + CP Pacing

In Chapter 4, I will discuss how the addition of coupled paced beat to biventricular pacing improved the left ventricular ejection at a level which is comparable to that of sinus rhythm despite the continual acute atrial fibrillation occurring.

This chapter will also discuss how CP may be combined with biventricular pacing (CRT+CP) to slow the ventricular rate of mechanical contractions and further improve contractility to a greater extent than what has been observed by

CRT alone in patients with dyssynchronized heart failure and atrial fibrillation [13]. And by controlling the time delay of the application of CP, one can balance the negative chronotropic vs. positive inotropic effects of this pacing therapy in a manner that provides the most judicious treatment for each patient. With the development of modern sensing capabilities of these pacemaker devices, one could easily make appropriate adjustments for each patient.

1.3.4 Simulation flow in the Great Cardiac Vein (GVC)

Finally in chapter 5, the development of a mechanical simulation of flow patterns in great cardiac vein (GCV) will be presented as well as future work related to the use of implantable pressure sensors will be presented. These sensors would have to be 1) accurate, 2) small enough to fit on pacing leads, 3) require simple electronics to function, and 4) most importantly require little energy.

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CHAPTER II

Use of Conventional Pacemakers to Induce Atrial Fibrillation in Dogs

2.1 Introduction

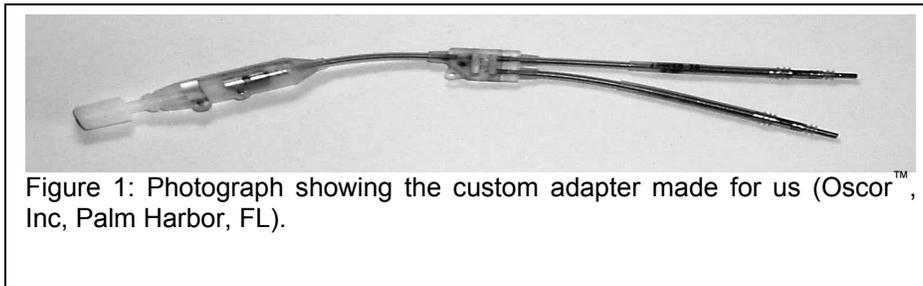
Protocols for producing experimental heart failure by rapid ventricular pacing are well established [1]; however, for safety reasons, commonly used clinical pacemakers do not allow pacing rates that are sufficient to induce either heart failure (HF) or atrial fibrillation (AF). In one previous study, rapid ventricular pacing was achieved by modifying a single-chamber pacemaker [2]. We had been able to 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.

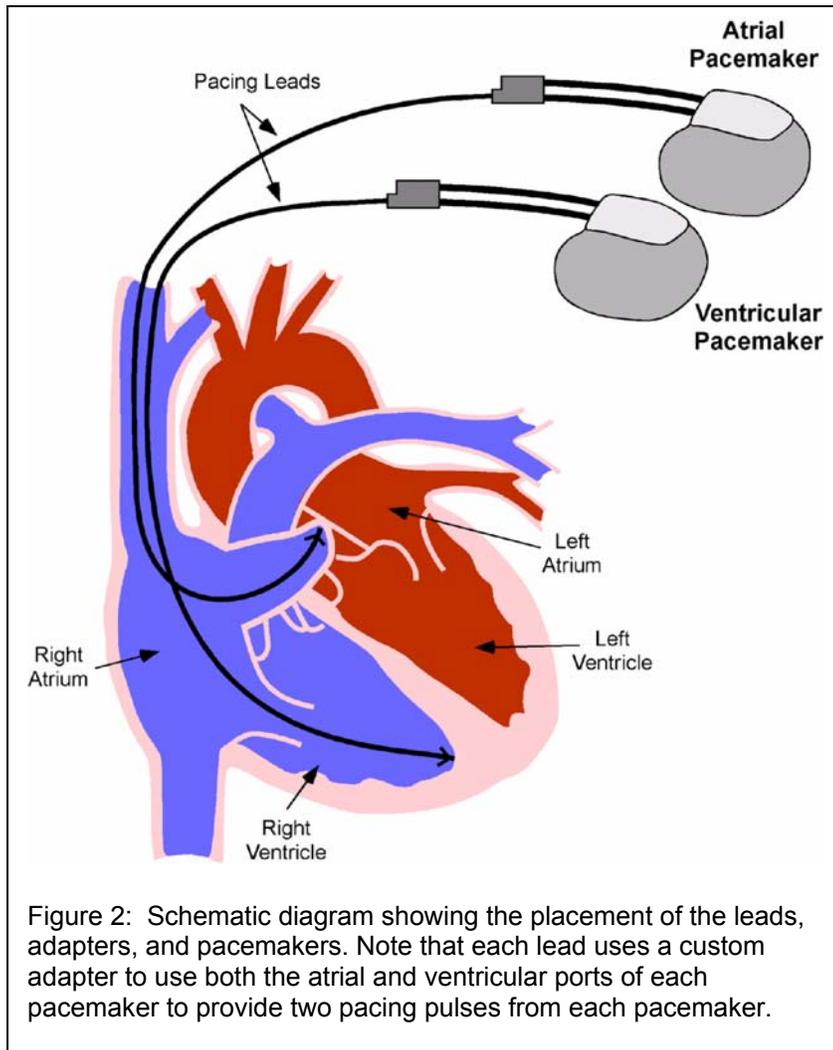
2.2 Materials and Methods

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 (Figure 1). The “Y” adapters were attached to both ports of two dual-chamber pacemakers (Figure 1). The two pacemakers were then subcutaneously positioned 3 to 4 inches apart so that they could be separately interrogated and



programmed [6].

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 [6].



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

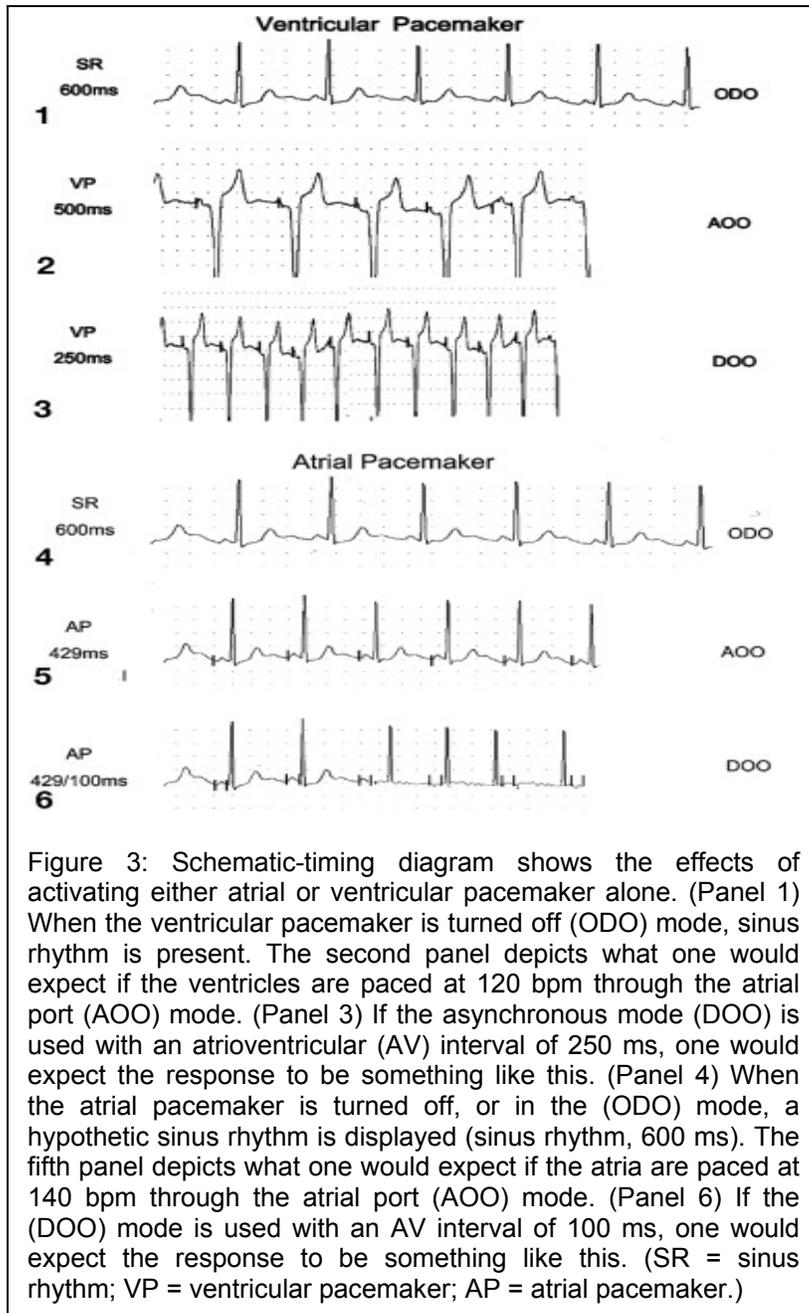
sufficient to produce heart failure (180 to 240 bpm). For example, if the pacing interval is set at twice the desired interval (500 ms) and the atrioventricular (AV) delay (250 ms) is set such that a pacing pulse from the ventricular port fires at exactly half this interval, the ventricles can be paced at shortened intervals (i.e. stimulation pulses from both ports) without having to modify the clinical pacemaker [3].

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 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.

2.3 Results

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 [6] 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 manufacturer 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 , (approximately 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 approximately 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 [3].

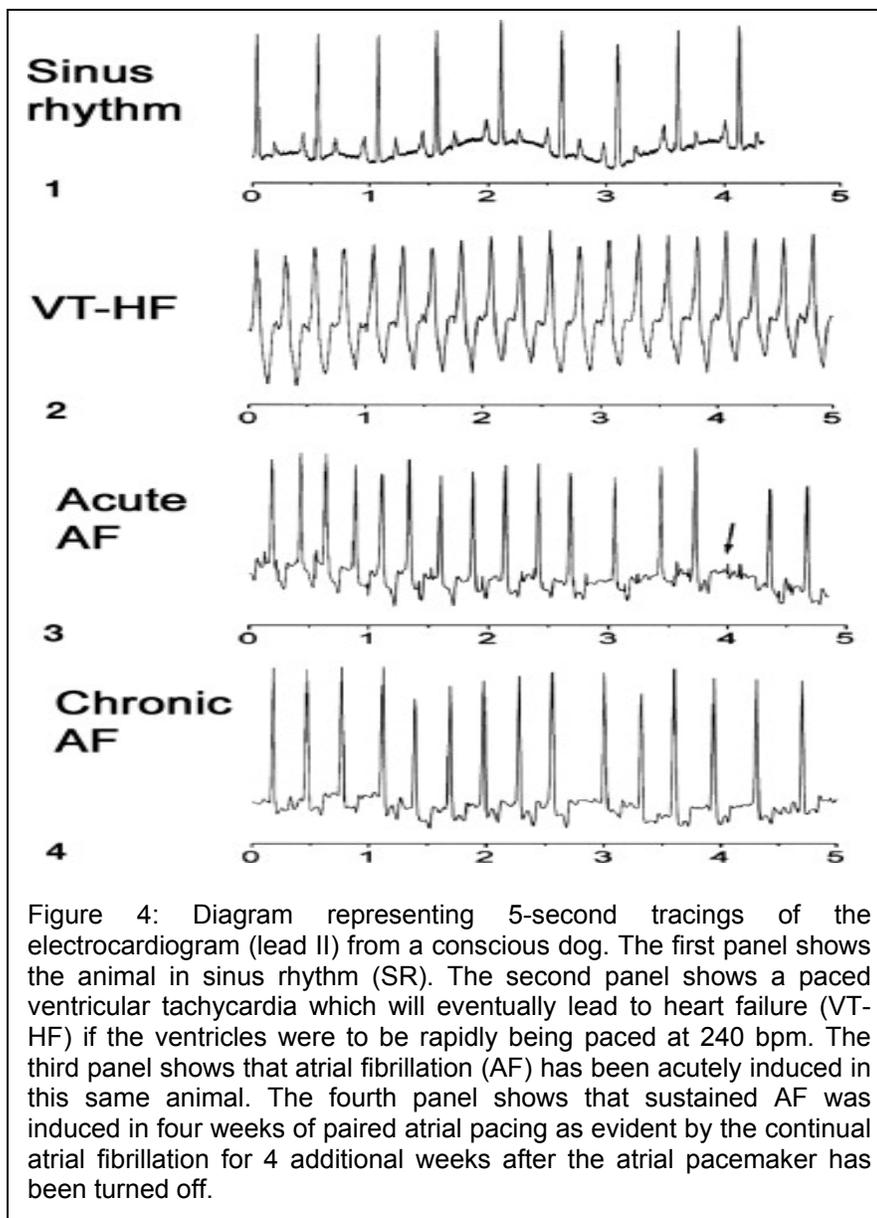
The distal end of the atrial lead was always placed in the right atrial appendage. Other activation sites in the atria may result in AF more readily (e.g., the pulmonary veins). However this location

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

All pacing to the ventricles was applied through bipolar leads. Individual pulses were routinely initially set at 5 V, 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 Figure 3).

All pacing to the atria was applied through bipolar leads. Individual pulses were routinely initially set at 5 V, 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, still 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 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

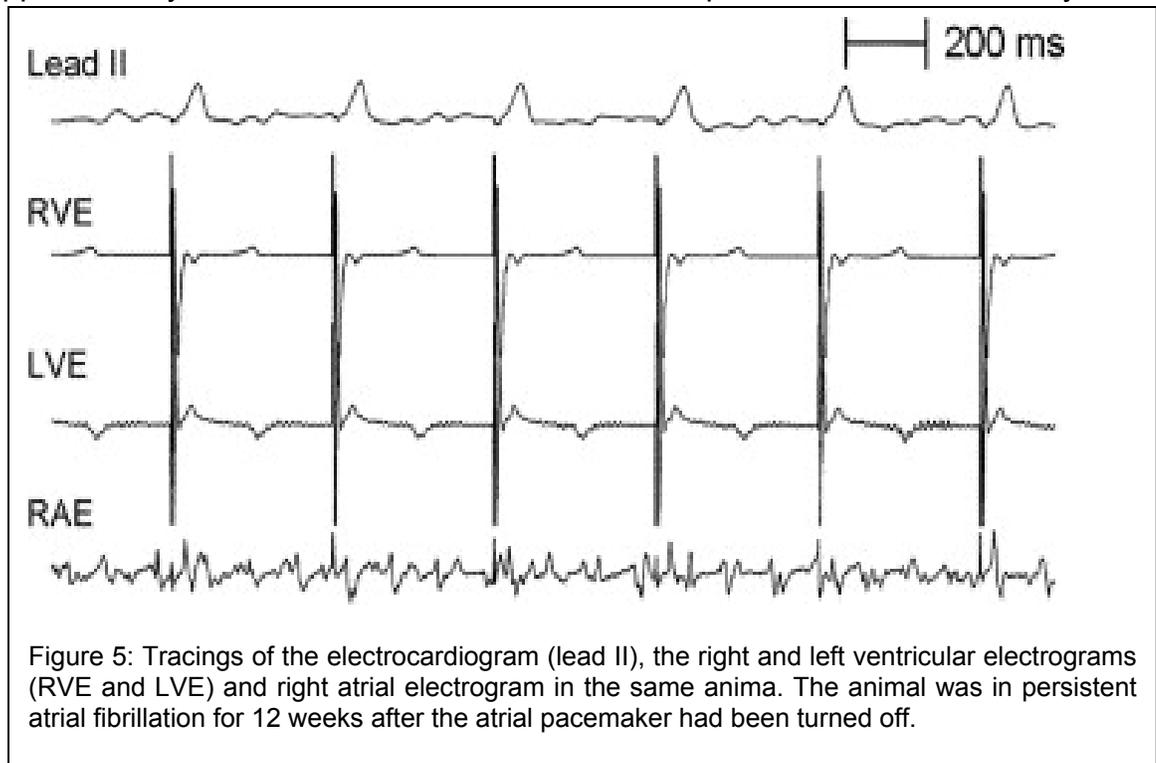
Figure 3). The classical work of Wijffels and coworkers [4] showed that there is electrical remodeling of the atria as AF is being produced (i.e. the atrial refractory period decreases and sometimes necessitates a shortening of the coupling interval).

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 (i.e. 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 lower tracking rate was set 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 [6]. 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 appears to be 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 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 (i.e., 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.

2.4 Discussion

The major finding of this study [6] 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 and eventual heart failure [1-2, and 7]. 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 and 7] (i.e. 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 [7], 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 study had been 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 (i.e. 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 and 8-10], 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 in ensure that sinus rhythm would not return [6]. This could be done using our technique [6].

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 [6] 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.

2.5 References

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Chapter III

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

3.1 Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the United States [1]. By increasing ventricular rate, AF can cause a tachycardia-mediated cardiomyopathy. Recent studies have shown that when sinus rhythm can not be restored, ventricular rate control is a viable treatment option [2]. For the last several years, our laboratory has been investigating the implementation of coupled pacing (CP), a novel pacing paradigm, for controlling ventricular rate of mechanical contraction (VRMC). CP involves application of electrical stimuli to the ventricles after the effective refractory period. In previous studies [3-5], 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 AF. VRMC reduction by CP is the result of blocked conduction of rapid supra-ventricular activations to the ventricles during AF. When CP slowed the

VRMC, stroke volume increased markedly as a result of moderate increases in left ventricular end diastolic volume and a decrease in end systolic volume. In addition, the positive inotropic effects of CP (resulting from postextrasystolic potentiation) increased LVdP/dt and LV ejection fraction. The purpose of this study [6] was to determine if the hemodynamic benefits of sustained CP could be maintained in the setting of persistent AF.

3.2 Methods

3.2.1 Surgical Preparation

The experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic. 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’s Animal Care facility is accredited by the American Association for the Accreditation of Laboratory Animal Care. Six mongrel dogs (20-30 kg) were included in this study.

3.2.2 Conscious Testing

All animals were trained to lie on a couch on their left side for echocardiographic examination. Echocardiographic data were acquired (Sequoia™, Seimens System with a 3MHz probe) at 1) baseline during sinus rhythm, 2) after persistent AF but just before the beginning of CP therapy and 3)

after 3-4 weeks of continual application of CP. LV end systolic and diastolic as well as left atrial (measured at end systole of LV) volumes were computed from standard apical views (2 and 4 chamber views) by using the Simpson biplane method. Left ventricular ejection fraction (LVEF) was calculated from these measurements $[(EDV-ESV)/EDV]$. Measurements from three cardiac cycles were averaged for all volumes and these mean values were expressed as a single value. The surface ECG was recorded during conscious testing via a Dataq™ acquisition system. Origin® plotting software was used to plot representative ECG traces and other results.

3.2.3 Pacemaker Implantations and Pacing Protocols

Under sterile conditions, dogs were chronically implanted with 2 endocardial pacemaker leads, one placed in the right atrial appendage and the other in the right ventricular apex. As previously described [7], two standard dual chamber pacemakers were used for each animal. Each device used a custom Y lead adapter (Oscor™) in order to induce AF and to apply coupled pacing. With a Y-adapter, we connected the atrial pacemaker lead to both the atrial and ventricular ports of a dual chamber pacemaker. Similarly, the ventricular lead was connected to a second dual chamber pacemaker via a second Y-adapter. The Y-adapter permitted us to use both the atrial and ventricular ports of a dual chamber pacemaker to either pace (DOO mode) the heart via one lead, or to sense the intrinsic electrical activation of the heart via the atrial port and then apply a paced beat via the ventricular port (DDD mode). Both pacemakers were

implanted subcutaneously, positioned sufficiently far apart that they could be separately interrogated and programmed.

After animals had fully recovered from pacemaker implantation surgery, rapid right ventricular pacing was applied at a rate of 240 bpm using the DOO mode of the ventricular pacemaker. The lower tracking rate was set at 120 bpm and the AV interval was set at 250 ms, as previously described [7]. Ventricular pacing was continuous at 240 bpm for two weeks. Rapid ventricular pacing promoted ventricular dysfunction and atrial fibrosis that accelerates the development of persistent AF [8].

3.2.4 Echocardiography

Cardiac function was assessed using echocardiographic imaging when the pacemakers were turned off. When LVEF was reduced by approximately 20% from the baseline value during normal sinus rhythm, the ventricular pacemaker was programmed off (from DOO to ODO). At this time, the atrial pacemaker was programmed in AOO mode to pace the atria at a rate approximately 20 bpm above sinus rate. The mode of the atrial pacemaker was then switched to DOO and the AV interval setting was adjusted to an interval sufficiently short that stimuli from the ventricular port would still capture atrial tissue. This pacing paradigm eventually induces persistent AF [7]. The AV interval varied from 80 to 120 ms, depending on the individual animal and its autonomic state. Weekly ECG measurements were obtained in order to confirm that the atrial pacing continually fibrillated the atria. During the induction of AF, echocardiographic

assessments of left ventricular function were continued until the ejection fraction was reduced by approximately 30% from baseline levels. Then the atrial pacemaker was turned off and the animals remained in atrial fibrillation.

Coupled pacing was initiated through the use of the ventricular pacemaker programmed in DDD mode once ventricular dysfunction had developed and persistent AF was established (after ventricular and then atrial pacing, 6-8 weeks total). The lower tracking rate of ventricle pacemaker was set at 30 bpm and the upper tracking rate was set at 180 bpm. As in our acute experiments, the individual coupling interval was adjusted for each animal. With the use of the DDD mode of the ventricular pacemaker, the AV interval was adjusted to alter the CP time delay to intervals ranging from 160-220 ms. Time delay adjustments were made while monitoring LV contractions via echocardiography such that virtually no secondary contractions were observed [5].

Analysis of variance was used to determine if any of echocardiographic measurements (LVEDV, LVESV, LVEF, and LAV) were significantly changed [6]. In addition, we measured the ventricular rate of mechanical contractions (VRMC) as previously described [5]. These continuous variables were expressed as means \pm SE. Paired comparisons were made between these 3 periods, i.e., BL vs. AF, AF vs. CP and BL vs. CP (Fisher LSD). A probability of < 0.05 was considered significant.

3.3 Results

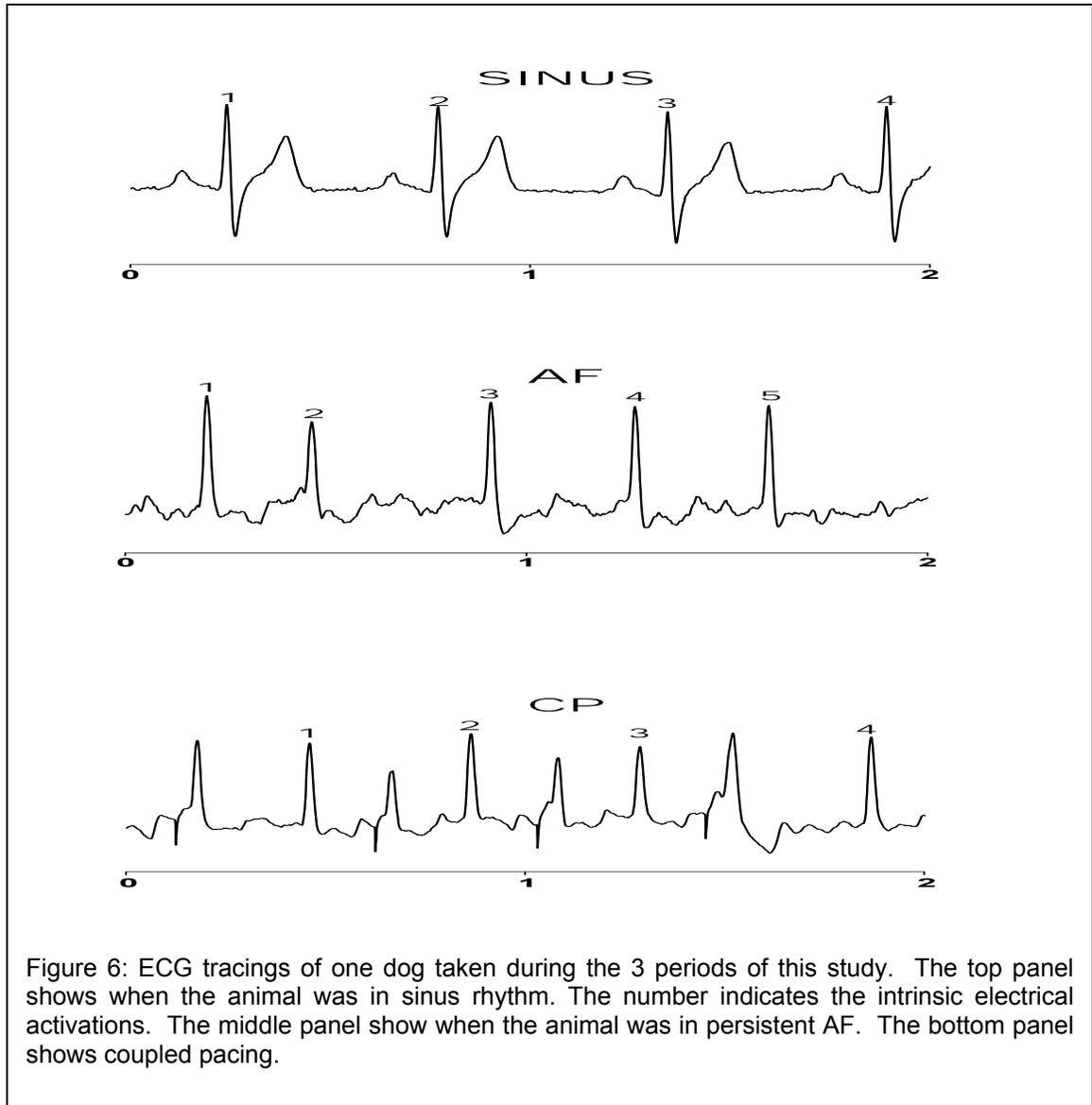
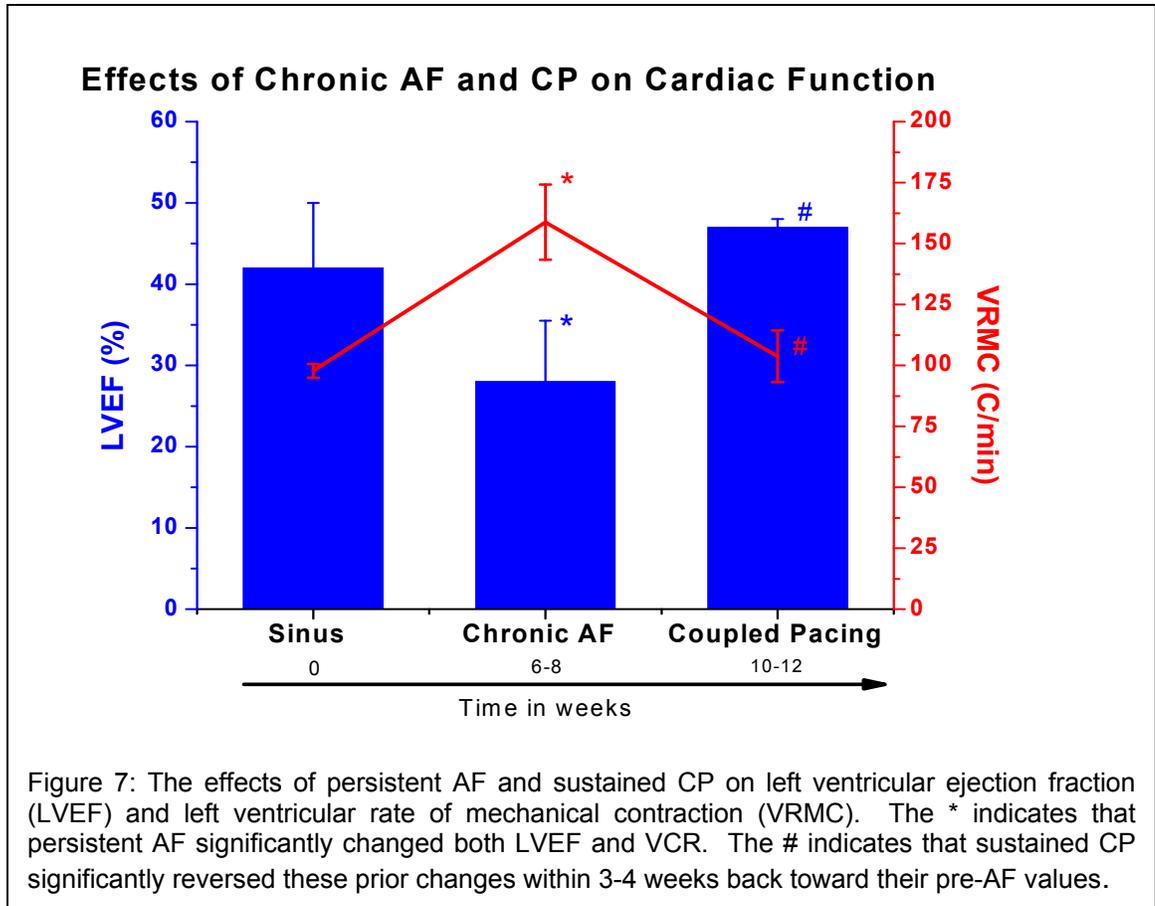


Figure 6 displays representative ECG tracings of one dog during the three phases of this study [6]. The top panel shows normal sinus rhythm prior to the induction of persistent AF. The middle panel show persistent AF just prior to the application of CP. The bottom panel shows that AF persisted even after CP had been applied for 4 weeks. The numbers above each R wave indicate intrinsic electrical activations that resulted in mechanical contractions. The CP stimulus

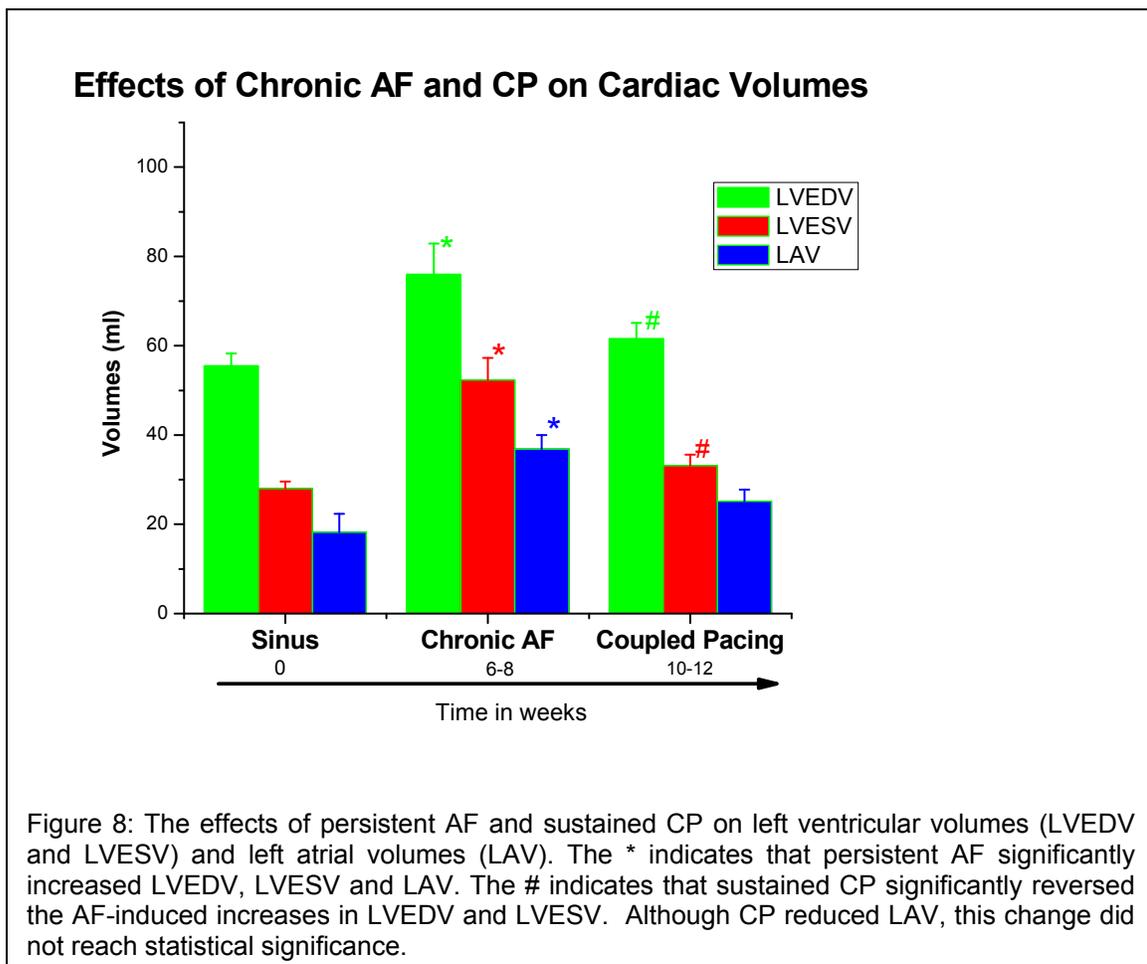
following each of the intrinsic activations in the bottom panel is indicated by the stimulus artifact.



Persistent AF significantly increased the average VRMC (Figure 6, baseline to AF, 103 ± 2.5 bpm to 174.5 ± 14.5 contractions/min (C/m), $p < 0.001$). CP brought the average VRMC back to 95.8 ± 9.2 C/m, ($p < 0.001$). As shown in Figure 7, LVEF was quite sensitive to supraventricular tachycardia, decreasing from 52 ± 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 ± 4.78 mL to 75.5 ± 6.65 mL (BL vs. AF, Figure 8, $p < 0.01$). Similarly, LVESV increased from 30.7 ± 2.57 mL to 51 ± 4.57 mL ($p < 0.001$), and LAV increased from 20.2 ± 3.84 mL to 34.8 ± 4 mL ($p < 0.01$) during persistent AF (Figure 8). After sustained CP had been applied for 3-4 weeks, LV volumes were significantly reduced (AF vs. CP, Figure 8) and returned toward the values measured prior to the induction of persistent AF. The LVEDV decreased from 75.5 ± 6.65 mL to 65 ± 3.22 mL (AF vs. CP, $p < 0.05$) and the LVESV decreased



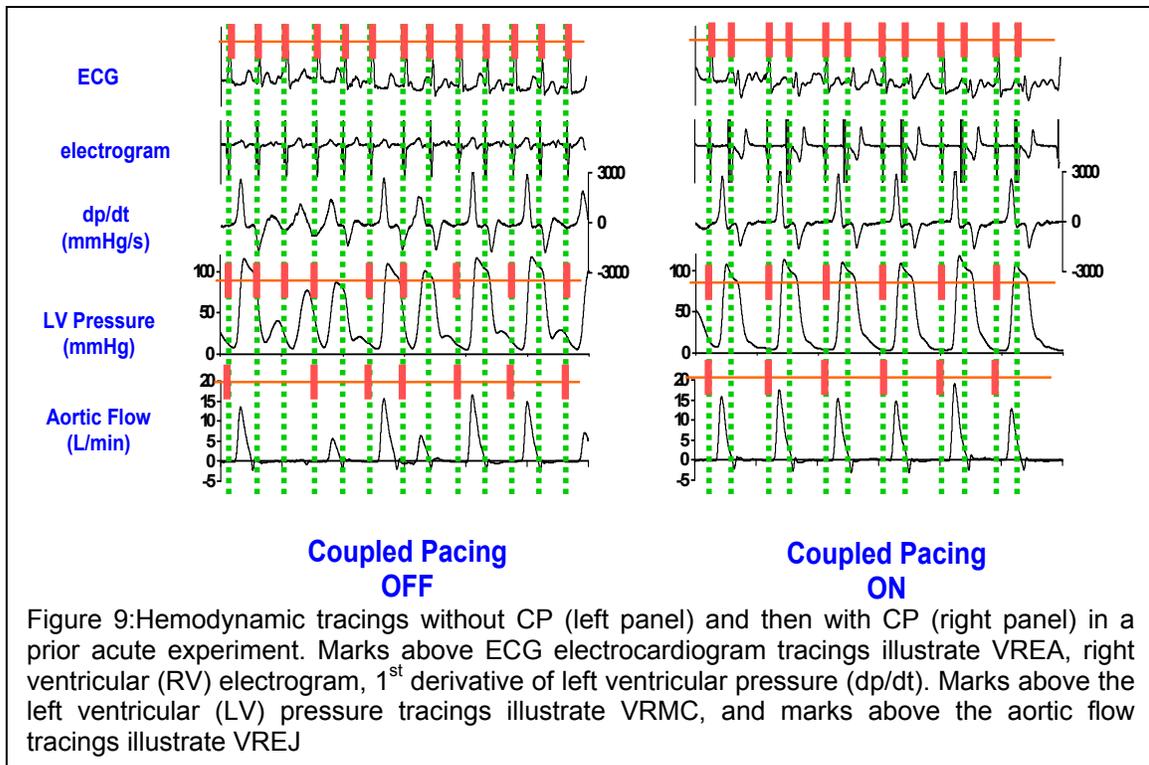
from 51 ± 4.57 mL to 34.5 ± 2.41 mL ($p = 0.001$). The reduction in LV volumes also resulted in a partial reduction of LAV towards baseline values, despite the

continued presence of AF. That is, LAV decreased from 34.8 ± 4 mL to 27.7 ± 2.6 mL ($p > 0.05$).

3.4 Discussion

The first major finding of this study [6] is that the effects of CP were sustained for 4 weeks. Sustained CP dramatically reduced the ventricular rate of mechanical contraction (VRMC) and increased contractile performance (LVEF), in a manner similar to that previously observed during acute AF. 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. Reverse remodeling results in decreased wall stress.

Normally when the ventricles are electrically activated, there will be corresponding subsequent mechanical contractions which in turn results in ejection of blood. However, during rapid AF this is not always the case. Hemodynamic measurements from a prior acute experiment illustrate this point (Figure 9). That is, the 13 electrical activations result in 9 contractions and these contractions in turn lead to 6 ejections of blood (see the left panel of Figure 9). In contrast, the application of CP during AF changes this relationship (see right panel of Figure 9). The application of CP results in the blockage of every other rapid supraventricular activation. However, since a coupled beat (no subsequent contraction) followed each intrinsic electrical activation, the ventricular rate of electrical activation (VREA) remained approximately the same with the application of CP during AF as the rate of AF alone. The positive inotropic effect



of CP via 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 (note the marks above events).

In our prior work examining the effects of acute CP on acute AF [3], we found that the rate of ventricular rate of electrical activation (VREA) changed from 135 to 226 to 225 activations / min from sinus to AF to CP. However the ventricular rate of mechanical contraction (VRMC) changed from 135 to 197 to 112 contractions / min. Finally the ventricular rate of ejections (VREJ) changed from 135 to 136 to 111 ejections / min. Note, that without the application of CP, the VRMC would not be one half of the VREAs, but they would have remained high.

In the present study [6], the cardiac responses to persistent AF and then to sustained CP were somewhat different than previously observed during acute AF. Our coupled pacing resulted in no change in the VREAs but there was a

change in VRMC that is similar to the prior pre-tachycardia rate despite the persistence of AF. In the current study, under persistent AF and chronic CP, the VRMC changed from 103 to 175 to 96 contractions / min. Note, the application of CP at a shortened delay resulted in no contractions both in our prior acute studies (3-4) and in this present study [6].

In most cases, heart rate is defined in terms of VREA rather than VRMC. So what is the concern of VREA vs. VRMC? In both acute and chronic conditions of AF, CP reduces the VRMC but has little effect on VREA. In an earlier study [3], the inotropic effect of CP via 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 (note the marks above events).

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 ejection fraction in dogs [9-12]. These studies also showed that after the termination of this tachycardia, there was a rapid return of their ejection fraction. However, there remained a residual dilatation in their left ventricular volumes that eventually started to return towards pre-tachycardia levels. In contrast, our present study showed that the left ventricular volumes returned back to their pre-tachycardia levels during the same time course as the ejection fraction 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 rather than the VREA. This reduction of left ventricular

volumes induced by sustained CP reduces wall stress.

Heart rate, contractility and wall stress are all major determinants of myocardial oxygen consumption (MVO_2 , [13-15]. Increases in both heart rate, that is, VRMC and wall stress via ventricular volume dilation during persistent AF leads undoubtedly increases metabolic demand and oxygen consumption. Our present results suggest that both the reduced VRMC and wall stress caused by persistent CP should reduce MVO_2 and therefore counteract the effects of increased contractility [13] on MVO_2 that are also the result of CP. However, additional experiments are needed to validate these assumptions.

In our present study [6], the remodeling induced by ventricular pacing and persistent AF is the result of a uniform ventricular dysfunction, similar to that which occurs during dilated cardiomyopathy [16]. Bi-ventricular pacing has been shown to reverse the remodeling of the failing left ventricle [17]. Beta-adrenergic receptor antagonists (β -blockers) can also cause reverse remodeling [18]. Both β -blockers and CP result in slower VRMC, although via quite different means. Whereas β -blockers are negative inotropic agents, CP has a positive inotropic effect. Prior studies [17-18] suggest that reverse remodeling occurs when the ventricle become more efficient. This improvement of ventricular function occurred as a result of either a more synchronous contraction, or by a slower rate of contraction. In both cases, the time course required for reverse remodeling was several months. In contrast, the reverse remodeling caused by CP here appears to have occurred more rapidly. The increased rate of reverse

remodeling may be due in part to the positive inotropic effects of CP in addition to the reduced VRMC.

In summary, sustained application of CP appears to reverse the LV dilation and functional impairment (LVEF) that resulted from LV dysfunction during persistent AF. Therefore, following additional studies CP should be considered as a means to achieve ventricular rate control and to improve cardiac function in many cases of persistent AF, particularly in the presence of non-ischemic dysfunction. Finally, by adding this pacing paradigm to a pacemaker/defibrillator device, these stimuli could be applied safely.

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Chapter IV

An Improved Cardiac Resynchronization Therapy

4.1 Introduction

Cardiac Resynchronization Therapy (CRT) has been shown to improve symptoms and survival in patients with drug-refractory symptomatic heart failure (HF) and conductive disturbances [1-8]. However, in AF patients, CRT can be efficiently delivered only if the ventricular rate is controlled. If rate can not be controlled, atrioventricular (AV) nodal ablation and implantation of a permanent ventricular pacemaker may be required [9-10]. Therefore, we propose to apply a supplemental stimulation to the right ventricle, coupled pacing (CP), in addition to the standard CRT when AF occurs. For the past four years, our laboratory has been studying the potential application of this CP for the treatment of AF when there are no ventricular conductive problems [11-13]. In these prior cases, the intrinsic electrical activation of the ventricles which initiated the contraction was sensed and then an electrical stimulation (CP) was applied after the ventricular refractory period but prior to the time that the ventricles were capable of contracting again. CP activated the ventricles electrically resulting in retrograde

activation of the AV node which in turn prevented rapid supra-ventricular activation of the heart during AF. Thus, CP slowed the ventricular rate of mechanical contraction (VRMC) and increased LV filling. In addition, this CP beat increases contractility via elevated intracellular calcium levels [14]. Based on these prior works, we hypothesized that CP may be combined with biventricular pacing (CRT+CP) to slow the VRMC and further improve contractility to a greater extent than what has been observed by CRT alone in patients with dyssynchronized HF and AF.

4.2 Methods

The experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic. 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’s Animal Care facility is accredited by the American Association for the Accreditation of Laboratory Animal Care.

The dogs (n=6, body weight 22-29 kg) were initially anesthetized with thiopental 25 mg/Kg IV and maintained with 1-2% isoflurane vaporized in oxygen-enriched air during positive pressure ventilation. A mid-sternotomy was performed and the heart was placed in a pericardial cradle. A custom quadrapolar plate electrode was sutured to the right atrium and was connected to a Grass stimulator.

4.2.1 Pacing protocol

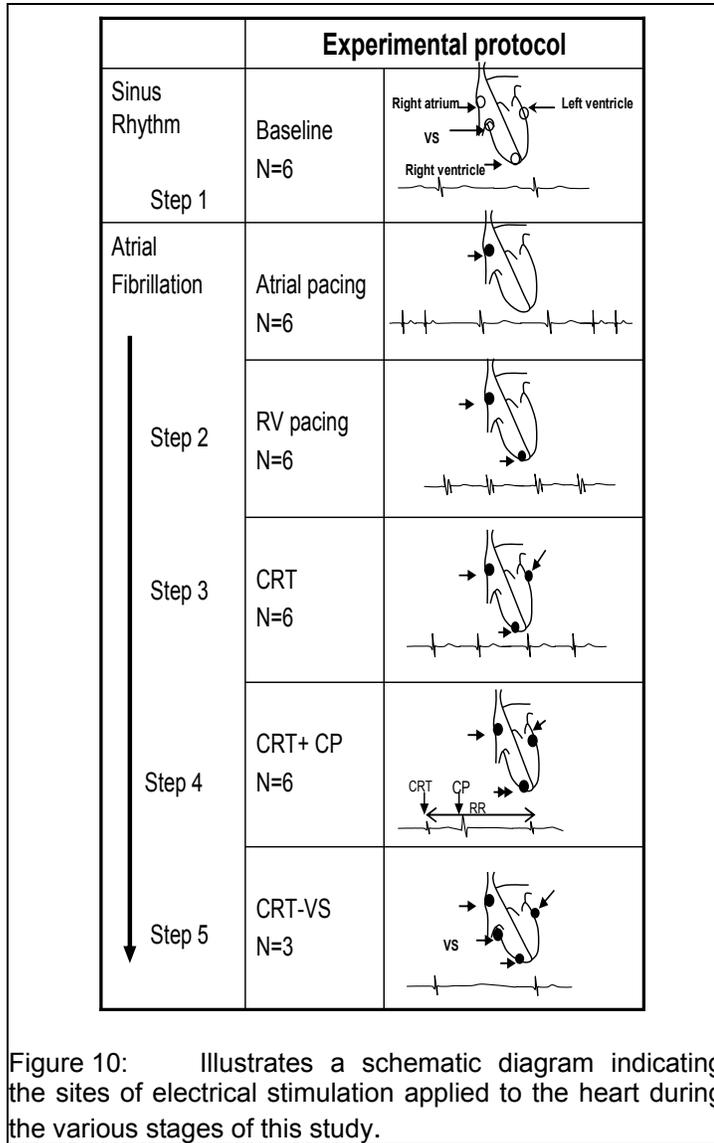
Rapid right atrial pacing (20 Hz, 1 ms, 3-5 V) was used to induce and to maintain a rapid but continual acute AF after baseline measurements were obtained in sinus rhythm. A second quadrapolar plate electrode was sutured on the right ventricular (RV) apex and was connected to the first channel of a Bloom stimulator. A third quadrapolar plate electrode was sutured on the lateral wall of the LV for CRT delivery and connected to the 2nd channel of our Bloom stimulator. The remaining 2 poles of these 3 quadrapolar electrodes were connected to our recording system to record their corresponding electrograms. Finally, a bipolar electrode was sutured on the inferior vena cava-left atrial epicardial fat pad of 3 animals to stimulate the parasympathetic nerve that innervates the AV node to slow A-V nodal conduction [15]. This nerve stimulation allowed us to apply the CRT at a rate to be similar as the response during AF and CRT+CP.

First, we obtained baseline measurements during sinus rhythm (step 1). Next we simulated the effects of AF and left bundle branch block (LBBB) with 5 minutes of rapid RV pacing and acute AF via rapid atrial pacing (step 2). During AF, the rate of RV pacing (2 ms, 2-4 mA) was increased to a rate sufficient to prevent intrinsic ventricular activation over the AV node. This pacing paradigm reduced ejection fraction to less than 35%. This mode of pacing resulted in LV dysfunction [16] and dyssynchrony [17]. Then, we applied a rapid biventricular pacing for 5 min such that the CRT rate was sufficient to pace both ventricles directly (Step 3) without supraventricular activation. The pacing paradigm here

would be somewhat analogous to when a pacemaker would pace the ventricles rapidly by continually tracking atrial activity. Clinically, the biventricular

pacemakers that are in an atrial tracking mode will normally mode switch when atrial rate reaches a prescribed limit, that is, atrial tracking limit. As long as AF persists, effective CRT will not be applied.

Next, we applied CRT (step 4) during acute AF at rate close to sinus rate because of the addition of the CP. CRT+CP, which consisted of simultaneous biventricular pacing (2 ms, 2-4 mA, both channels of



the Bloom stimulator) of both ventricles was followed by an additional stimulation or CP (2 ms, 2-4 mA, 1st channel of the Bloom stimulator) applied only to the RV lead after the RV ventricle refractory period. Before we added the CP, we increased the basic cycle length of the biventricular pacing by approximately 50 % above the level needed to pace both ventricles during AF. Then we added the

CP beat at a delay of 250 ms. Next, we progressively shortened this time delay until we observed by echocardiography that there was no subsequent LV mechanical contraction resulting from the CP. Finally we extended the basic biventricular pacing rates to be close to sinus rates such that the rates of ventricular contractions were similar.

Finally, we applied CRT alone at a rate close to sinus rate (step 5). We were able to apply CRT at this rate because we selectively simulated the parasympathetic nerves that innervate the AV node (pulses = 20 Hz, 0.1ms, 10 mA).

We systematically collected the data at the end of each pacing mode as described above with a current echocardiograph system (Vivid 7, GE Healthcare). For each measurement, five consecutive cardiac cycles were acquired and all images were stored on optical disk for further analysis. LV contractility was quantified by 1) LV ejection fraction, 2) stroke volume and 3) the peak value of the circumferential global strain (ϵ -peak). LV ejection fraction (EF) was computed from standard apical views by using the Simpson biplane method. Circumferential global strain curve was computed by averaging the 6 segmental circumferential ϵ curves derived from 2D short axis view (basal segment) by using speckle tracking analysis (EchoPac GE Healthcare). For all ϵ analysis, end-diastole was chosen as the reference time-point for each cardiac cycle. Peak ϵ had been defined as strain curve, when it reached its maximum value during the cardiac cycle. The time for each of the 6 segments to reach their peak strain was expressed in terms of the percentage of the RR interval for that

particular cardiac cycle because of the wide range of RR intervals for these pacing paradigms in this study. The measure of LV dyssynchrony is the standard deviation of percentage of the time to peak circumferential ϵ for each cardiac cycle. For example, if all 6 segmental peak ϵ occurred exactly at the same time in the cardiac cycle the standard deviation would be zero. Conversely if the 6 segmental peaks of ϵ were reached over a wide range of time, the LV dyssynchrony would be large. Diastolic period was defined as the time duration of the Doppler early diastolic filling velocity profile (E) during atrial fibrillation and as the sum of E and atrial velocity waves multiplied by the duration during sinus rhythm. This measurement also was normalized to the RR interval for each cardiac cycle. Again, because CP does not cause contractions, this electrical activation of the ventricles was not considered in the above calculations.

Normally distributed continuous variables were expressed as a mean \pm SD. To compare numerical data between two or several groups, paired and unpaired student test or analysis of variance was used as appropriate. Two-tailed *P*-values <0.05 were considered statistically significant. Analysis was performed using StatView[®] software (Version 5.0 for Windows[®], SAS institute Inc., Cary, NC, USA).

4.3 Results

The average LV dyssynchrony during sinus rhythm was approximately $7\pm 2\%$ (Figure 11A). The induction of simulated LBBB by right ventricular pacing (RV) increased LV dyssynchrony to an average of $19\pm 3\%$ ($p < 0.0001$ vs. SR). The application of biventricular pacing (CRT) dramatically reduced this LV

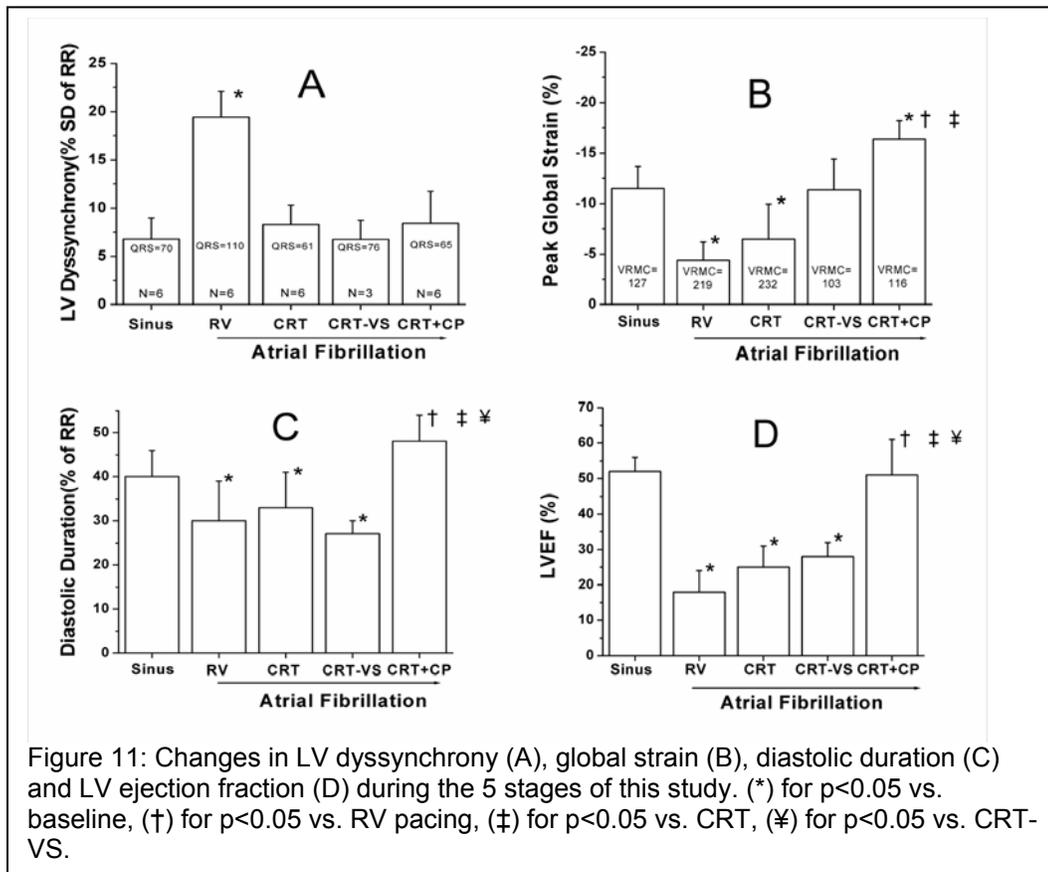
dyssynchrony virtually back to the level of sinus rhythm ($SD=8\pm 3\%$). In three animals we stimulated selectively the parasympathetic nerves innervating the AV node (CRT-VS). This is analogous to those LBBB patients with concurrent AF in which their ventricular rate can be controlled by pharmacological agents such that the CRT could be applied at a more appropriate rate. In this case, the LV dyssynchrony was similar to that during sinus rhythm ($SD = 7 \pm 2\%$). Finally, when we applied an additional paced beat to only the right ventricle (CRT+CP), LV dyssynchrony did not increase ($SD = 8 \pm 3\%$). Note the average corresponding QRS durations were measured during these echocardiographs and are shown for all 5 steps of this study.

During sinus rhythm, the average peak global strain was $-12 \pm 2\%$ (Figure 12B) when the VRMC was $128\pm 17\text{cpm}$. With the induction of acute AF and rapid RV pacing (VRMC= $219\pm 39\text{cpm}$), the peak global strain decreased to $-4 \pm 2\%$. The application of CRT during acute AF slightly improved peak global strain ($-6 \pm 3\%$) despite the rapid VRMC ($232 \pm 15\text{cpm}$). The reduction in VRMC ($103 \pm 14\text{cpm}$) during CRT-VS further improved the strain until it approached that found in sinus rhythm ($-11 \pm 3\%$). Finally, the addition of the CP beat (CRT+CP) increased peak global strain to a level greater than that found during sinus rhythm ($-16 \pm 2\%$). Note that the VRMC was $116 \pm 17\text{cpm}$ during this pacing paradigm.

During sinus rhythm, the average diastolic duration was $40 \pm 6\%$ of each cardiac cycle (Figures 11C). The tachycardia of acute AF plus LV dyssynchrony of RV pacing decreased this percentage duration to $30 \pm 9\%$ ($p = 0.02$ vs. SR).

The reduction in LV dyssynchrony and rapid pacing of CRT did not improve the percentage of diastolic duration ($33 \pm 8\%$). The reduction in rate by CRT-VS also did not prolong the diastolic duration in relation to the cardiac cycle length ($27 \pm 3\%$). Finally, the CRT+CP pacing paradigm did increase this percentage ($48 \pm 6\%$).

Finally, the LV ejection fraction dramatically decreased from $52 \pm 4\%$ to $19 \pm 6\%$ ($p < 0.0001$, Figure 11 D) as the result of the tachycardia and LV dyssynchrony. The resynchronization of the rapid contractions did improve the LVEF slightly ($25 \pm 6\%$). Also the reduction in the ventricular rate by parasympathetic nerve stimulation also improved LVEF ($25 \pm 4\%$). However, once again the addition of CP to CRT (CRT+CP), improved the LVEF ($51 \pm 10\%$) to that of sinus rhythm despite the continual acute AF.



4.4 Discussion

The major finding of this study is that if atrial fibrillation should occur with heart failure patients that are utilizing CRT, the beneficial effects of CRT could continue if the biventricular pacemaker had the capabilities of applying coupled pacing. Normally if the atrial rate exceeds a prescribed limit, the atrial tracking by biventricular pacemakers would stop and the pacemaker would mode switch to VVIR. This new pacing mode results in a less effective pacing therapy than would occur if CRT was being applied. In the present study, we demonstrated that CRT+CP is capable of slowing supraventricular activation of the heart by half in a similar manner as coupled pacing does when the ventricular conductive system is intact. As a consequence, if AF should occur, the CRT could continually be applied at an optimal rate. Additionally, CP added to the CRT provides positive inotropic effect. This increase of contractility and diastolic filling provided by CRT+CP should also be considered as an option for therapy in non responder patients with sinus rhythm in which CRT alone has not improved their cardiac function as it does in others (responders).

In patients with severe heart failure (NYHA III-IV), depressed LV function (EF<35%) and a wide QRS complex (QRS>120ms), the beneficial effects of CRT have been documented with improvement of symptoms [1-8] and prognosis [8]. Reduced mechanical dyssynchrony with CRT decreases wall stress, mitral regurgitation volume [2, 4, and 18] and increases stroke volume [18-21], LV dP/dt [17 and 22] and ultimately leads to LV reverse remodeling [1-2, 4, and 8]. In most cases, the beneficial effect of CRT seems effective in both sinus rhythm and AF

patients [23]. However, efficient CRT delivery during either paroxysmal or chronic AF required a pharmacological control of ventricular rate because CRT devices which use an atrial tracking mode are set at an upper tracking limit to avoid a rapid ventricular tachycardia. In drug-refractory AF patients, AV nodal ablation with permanent pacemaker implantation or pulmonary vein ablation may be needed [9]. An alternative therapy to these procedures would be a simple modification of the CRT algorithm, i.e., CRT+CP, which consists of delivering a supplemental beat after the biventricular pacing.

Published results showed that CP reduces the mechanical rate of contraction during acute AF [11-13]. Coupled pacing differs from paired stimulation in that it uses the spontaneous ventricular depolarization as the first of the 2 electrical activations [14]. This intrinsic activation determines when the second of the paired stimuli is applied. Since the second beat travel retrogradely into the AV node and blocks approximately half of the supraventricular activation of the heart, coupled pacing results in a rate of ventricular contraction approximately half that which occurs prior to the application of stimulation. These techniques had been successively used to reduce ventricular rate during ventricular tachycardia [24], atrial tachycardia and fibrillation [11-13]. Consistent to our previous findings, we found that CRT+CP also permitted us to apply the biventricular pacing at half the rate that CRT alone that would have to be applied during AF. This negative chronotropic effect of CRT+CP resulted in an increased in the diastolic period for improved LV filling and presumably the coronary flow. In addition to the subsequent beneficial impact of a slower heart rate, the addition of the CP beat

appears to increase the diastolic/systolic time ratio (Figures 11C). These results suggest CRT+CP not only increase the intracellular calcium ions supply but may also affect the subsequent re-sequestering of this ion.

In addition to the negative chronotropic effect of CRT+CP, this new pacing paradigm (CRT+CP) resulted in a positive inotropic effect similar to coupled pacing. This increase in contractility has been termed “postextrasystolic potentiation”. The mechanism for this potentiated response is the increased release of calcium [14]. In 1965, Ross and Braunwald [25-26] termed this positive inotropic effect “electro-augmentation” because it was induced by electrical pacing rather than pharmacological agents. Paired stimulation, first proposed as a heart failure therapy more than 50 years ago, increases systolic function of the heart [14 and 26-27]. The effects of paired stimulation are generally achieved by applying two closely paced stimuli to the right ventricle.

However, when compared to intrinsic activation of the ventricles, continual right ventricular pacing can be detrimental because of the dyssynchrony produced by such a pacing paradigm [17]. Prior application of paired stimulation has been shown to increase MVO_2 proportionally to its positive inotropic effect [25]. In addition to the dyssynchrony, paired stimulation normally is applied at a rate equal or greater than the intrinsic rate. In contrast, when CP is applied, the contractile rate is one half the intrinsic activation rates and CP does not induce dyssynchrony. As a result, we did not observe a marked increase in MVO_2 during the application of CP [12]. In the present study, we did not measure the

oxygen consumption. However, CRT+CP like CP reduces the contractile rate and does not cause dyssynchrony as does paired pacing.

Since stimuli are applied prematurely, there is a risk that these stimuli could induce ventricular tachycardia, which might lead to ventricular fibrillation. However, extending the delay of coupled stimuli (less prematurely) still maintains improved cardiac function [13]. In addition, Mischke et al [24] had recently demonstrated that in the worst clinical situation, paired ventricular stimulation can be safely delivered during ventricular tachycardia in patients with predominantly ischemic LV dysfunction (17/22 ischemic, LVEF=38 ± 14%). Additionally, we have never observed any ventricular arrhythmia with a premature stimulation appropriately delivered as described. However, if ventricular tachycardia were induced, the episode could be quickly terminated with a pacemaker/internal cardiac defibrillator system. Importantly, in symptomatic heart failure patients with severe LV dysfunction requiring an Implanted Cardiac Defibrillator (ICD), CP could be assessed with a high degree of safety.

In acute dyssynchronized dysfunctional heart with concurrent AF, CRT+CP slows the ventricular contractile rate and provides a greater increase in myocardial contractility and the diastolic filling compared to CRT alone in which the ventricular rate can be controlled by parasympathetic nerve stimulation. The addition of a coupled beat permits the CRT to be applied at a slower and more appropriate rate for optimal cardiac function.

4.5 References

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Chapter V

Simulation of Flow in the Great cardiac Vein and the Use of Sensors for Monitoring Flow for Use in Cardiac Pacing Monitoring

5.1 Introduction

In order to effectively use pacing paradigms such as coupled pacing, it is essential that the pacing device have some measure of the response of the heart to this pacing other than just sensing intrinsic electrical activations. In the past, and T. Bennett et al [1] and D. Steinhaus et al [2], had been involved in the development of implantable hemodynamic monitoring systems for the management of heart failure patients. Bennett and his colleagues at the Medtronic Corporation had developed the Chronicle[®] System which is an implantable hemodynamic monitor (IHM). Their IHM system comprised a monitor (which included pressure sensing circuits and a means for storing continuous pressure trends, pressure sensors, and a pressure data storage monitoring device. These implantable pressure sensors had been sealed and included a means for indicating changes in the right ventricular pressure [1]. Medtronic's Chronicle[®] System had been designed to be implanted in the same manner in which pacemakers are implanted. Bennett et al concluded from their IHM studies

that their implantable hemodynamic monitor could be permanently placed in heart failure patients.

Since the right ventricular pacing lead enters the heart via the cephalic vein, one could measure blood flow returning to the heart via 2 pressure sensors on this lead at the level of the superior vena cava. Although measurement would only represent a portion of the cardiac output, this measurement should reflect changes in cardiac output. In those cases where left ventricular pacing is needed such as CRT, one implants a pacing lead into coronary sinus. On this second lead, 2 additional pressure sensors could be attached to measure coronary sinus flow via differential pressure. I have developed 2 different mock circulatory systems, designated as Mock I and II Circulatory Circuit which provides a means by which the flow profiles which exist in both the great cardiac vein (GCV) and the Superior Vena Cava (SVC) structures can be simulated in order to confirm that the differential pressure obtained in this system is representative of flow.

Historically, The Bernoulli Equation had been considered to be a statement of the conservation of energy principle which is appropriate for the flow of fluids.

The Bernoulli equation [3] is shown below (the original form):

- **$V^2 + gh + (p/\rho) = \text{constant}$ Equation (1)**

Where:

- **(V)** represents the fluid velocity at a point on a streamline;
- **(g)** Represents the acceleration due to gravity,

- **(h)** Represents the height of the point above a reference plane,
- **(p)** Represents the pressure at the point,
- **(ρ)** Represents the density of the fluid at all points in the fluid.

And the fluid must be:

- Must be incompressible even though the pressure is varying and the density must remain constant.
- The streamline cannot enter the boundary layer
 - A boundary layer is defined as that fluid layer that is adjacent to the bounding surface
- Turbulent flow occurs when the fluid particles move in a random fashion in the (x), (y), and (z)-directions in a blood vessel
- And there are no viscous forces present [4].

Since the pressure sensors may move from the boundary layer and the streamline as the heart contracts. And since blood flowing through the native great cardiac vein (GCV) is turbulent and viscous in nature, the simulation does take these limitations into account as will be discussed later. I can theoretically assume that the flow as produced in our mock circulatory circuit does follow the differential pressure as measured by the two Millar pressure sensors. And that the Bernoulli equation is not applicable for our simulation of flow profiles in the GVC since the fluid flowing through the mock circuit has a high viscosity and is

undoubtedly turbulent.

This mock circulatory circuit is simulating the pulsatile flow of the great cardiac vein through a conduit and should also be addressed in order to realistically model flow profiles through this cardiac vein. DA McDonald discussed the relationship that exists between the pressure gradient to the derivative of pressure with respect to time [5]. If the distance between two points which is represented as (Δz) is very small, this pressure gradient can be expressed after being differentiated as:

- $(dp/dz) = (dp/dt) * (dt/dz)$ Equation (2)

where:

- (dp/dz) represents the “space coefficient” with respect to time. [5]

And if (c) is used to represent the velocity of the “pulse wave” which develops, then equation (2) can now be written as:

- $(-dp/dz) = (1/c) (dp/dt)$ Equation (3)

Since the flow rate is dependent on the pressure gradient, it is also “dependent on the rate of change of the pulse pressure” [5]. This time derivative calculation of flow had been with the assumption that blood as a fluid had no viscosity and traveled through a conduit (blood vessel) without any type of distortion which has been found not to be the case. That is blood is a highly viscous fluid and blood flow through a blood vessel with a lot of variation since it is a pulsatile flow [5]. And as discussed by McDonald [5], the viscous nature of blood results in a dampening of its “amplitude” and decreases its velocity. Thus the pressure

gradient as represented by Equation (3) is “directly related to flow” as stated in the McDonald text [5]. And the factors which “modify” this pressure gradient should be taken into account these factors, e.g. “wave reflections”, non-linear effects, distensibility and viscosity effects, in order to more accurately represent pulsatile flow in blood vessels.

There are some limitations of my mock circulatory circuit such the fluid used does not have the same viscosity as blood and the fluid flow is somewhat Newtonian whereas blood is somewhat non-Newtonian in nature. However, it should be stated that this mock circulatory circuit (Figure 12) does approximate the flow rate through a conduit or vessel, taking into account the flow analyses done by Womersley and Bernoulli [5]. Also the vessels as represented by the conduit have to be curved and this curvature changes with each contraction since the great cardiac vein is in fact highly curved in nature. Thus, the mock circulatory circuit simulates the flow profiles in the great cardiac vein do approximate the pulsatile flow of blood which is related to differential pressure.

5.2 Simulation of the Great Cardiac Vein (Mock Circulatory Circuit)

1. Simulate the flow profiles of the Great Cardiac Vein (GVC) in a mock circulatory circuit which will simulate flow profile changes of the native GVC.
2. Perform post-sampling techniques on the raw data obtained from mechanical model to determine the extent of processing required to measure flow via differential pressure using standard acceptable signal processing techniques.

3. Confirm that preliminary flow profile data obtained using this mock circulatory testing system follows the differential pressure measurements obtained from the pair of Millar pressure sensors in a linear fashion.
4. Re-design mock circulatory circuit as necessary to improve simulation results if aim 1 is feasible and based on 1st phase of our acute animal studies.
5. The results of this part of my dissertation work can be used as a basis for others to modify implantable pressure sensors which can be attached to pre-existing pacing leads to optimally provide a means for adjusting the pacing regimens in both CRT and CRT+CP pacing paradigms.

5.3 Methods

5.3.1 Bench Testing Phase I: I used the mock circulatory circuit for simulating flow profiles in the great cardiac vein, as discussed during my Candidacy. This mock circulatory circuit (Figure 12) is comprised of the following components: a reservoir which represents blood flow returning from the capillary beds; a peristaltic pump mechanism (A Harvard Systems Ventilator). The movement of the shaft of this pump was used to change the curvature of the tubing used to emulate the movement of the GCV during ventricular contraction as well as provide a pulsatile flow. A flow probe; a screw clamp which represents the thoracic cavity's pressure change; a flow meter; two Millar pressure transducers, for obtaining a differential pressure; and a DATAQ Data Acquisition System for digitalizing all analog signals obtained for performing post sampling analysis. All

data collection had been obtained using the DATAQ D1-720 Hardware and WINDAQ acquisition software.

Prior to the collection differential pressure and flow data, all mock circulatory circuit components had been calibrated, i.e. the flow meter and both Millar transducer boxes both calibrated and balanced. Separate experimental trials of flow data were collected over a period of 5 minutes for each individual run. The sample rate was set at 3000 (actual computer sample frequency had been 2999.625) for the three recording channels with a moving average value-set to a value of 50. DATAQ's moving average algorithm involves the use of a smoothing factor. More specifically, this algorithm allows one to specify the number of actual waveform data points or samples that the moving average will span. It accomplishes a moving average by taking two or more of these data points from the acquired waveform, adding them, dividing their sum by the total number of data points added, replacing the first data point of the waveform with the average just computed, and repeating the steps with the second, third, and so on data points until the end of the data is reached. This results in the generated waveform to consist of averaged data which has the equivalent number of data points as the original waveform had. It should also be noted that the distance between the two Millar sensors had been measured to have a length of 3.0 centimeters. And the distance between the end of the 2nd Millar sensor and flow probe had been set at 5 cm.

Based upon the work of Cohen [6] and the preliminary results of D. Wallick et al, I completed the development of a mechanical mock circulatory system that

generated both flow and pressures similar to that measured in the great cardiac vein of dogs. This was achieved by means of changing the stroke volume of a pulsatile pump, changing the curvature of the tubing (“GCV”) and altering the outflow resistance of this system. Since the great cardiac vein is located around the circumference of the base of the left ventricle, the vessel undergoes a significant amount of movement during normal contraction. I collected initial simulated GVC Flow Profiles to determine that that the flow produced by the Mock Circuit does follow differential pressures obtained by the two Millar pressure sensors. I then confirmed that the flows produced by the mock circulatory circuit are representative of the approximate baseline flow measurement for the GVC, as determined by Cohen et al [6], i.e. 42.9 +/- 4.1 ml/min.

2nd Phase of Bench Testing Phase: In two separate experiments I used markedly different construction of leads in which the pressure sensors could be mounted. In the first series (Mock I Circuit as shown in Figure 13), I used sensors that had been mounted on a very flexible catheter system. In the second series of experiments (Mock II Circuit as shown in Figure 14), I used a stiffer catheter system in to ensure that I had effectively changed the arc of the great vein system and substituted in a Gilson Minipuls 2 Peristaltic Pump in place of the A Harvard Systems Ventilator in order to remove any negative pressures that had been observed in my Mock I Circuit. The purpose of the second series of experiments is to determine how pressure measurements would have to be obtained in order to accurately reflect the flow within the simulated vessel. This

was the worst-case scenario, in which pressures measurements would be affected by the movement of the heart. In the first two series of experiments, I used water as a medium to measure blood flow. In the second group of experiments I used a medium that would better emulate the viscosity of blood (ethylene glycol). These experiments would be used as a basis for re-designing my Mock Circulatory Circuit to obtain more accurate and precise GVC flow profiles. Once the appropriate modifications were made to my mock circuit, simulated flow profiles had been collected as well as performing both post sampling and statistical analysis on this phase of simulated flow profile data (Table II) to optimize the results.

Mechanical simulation of blood flow in the great cardiac vein: Using a pulsatile pump, a Windkessel capacitor, and a flexible tube that is distorted in a similar manner as occurs to the cardiac vein during ventricular contraction, I have simulated the pressure and flow characteristics of blood in the great cardiac vein of a dog's heart using the Mock Circulatory Circuits as illustrated in Figure 13-14. The mock circulatory testing system as shown in this Figure 12 comprised the following components: a reservoir (A) which will include a roller pump; a peristaltic pump or roller pump (B) which is representative of the torsional motion of the heart caused by the pressure sensors moving within the coronary vessels; a differential torque mechanism (C) which is representative of the torsional force changes of the heart itself; a flow probe (D); a screw clamp (E) which represents the thoracic cavity's pressure change; a flow meter (F); two pressure transducers (G) and (H), respectively, for obtaining a differential pressure as illustrated by (I);

and Data Acquisition System (DAQ) represented as (J). With 2 Millar pressure sensors for measuring cardiac vein flow and an extracorporeal flow probe for comparison, I was able to determine that measurements of differential pressure will adequately measure flow in this system (refer to Table II).

5.3.2. Experimental methods/tools (Mock I and II Circuits):

1. DATAQ® Software with WINDAQ/XL add-on software
2. (2) Millar pressures sensors
3. Acquisition period for each trial (5 minutes)
4. Origin® plotting software

Table I: Experimental protocol for Data Acquisition

Channel Number (#)	Channel Designates
#1	Pressures from 1 st pressure sensor
#2	Pressures from 2 nd pressure sensor
#3	Flow being recorded
#4	Smoothed data from 1 st pressure sensor
#5	Smoothed data from 2 nd pressure sensor
#6	Channel # 4 – Channel #5
#7	Smoothed data from channel #3

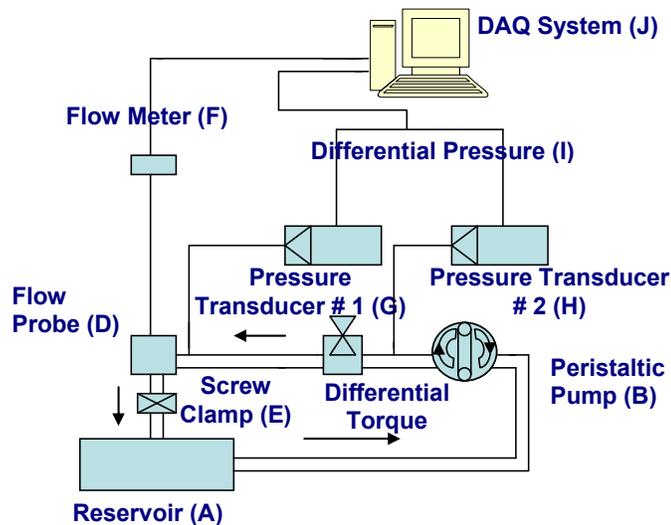


Figure 12: Schematic of components for simulation of the flow in the great cardiac vein (GVC).



Figure 13: Photograph of the Mock I Circulatory Circuit.



Figure 14: Photograph of the Mock II Circulatory Circuit.

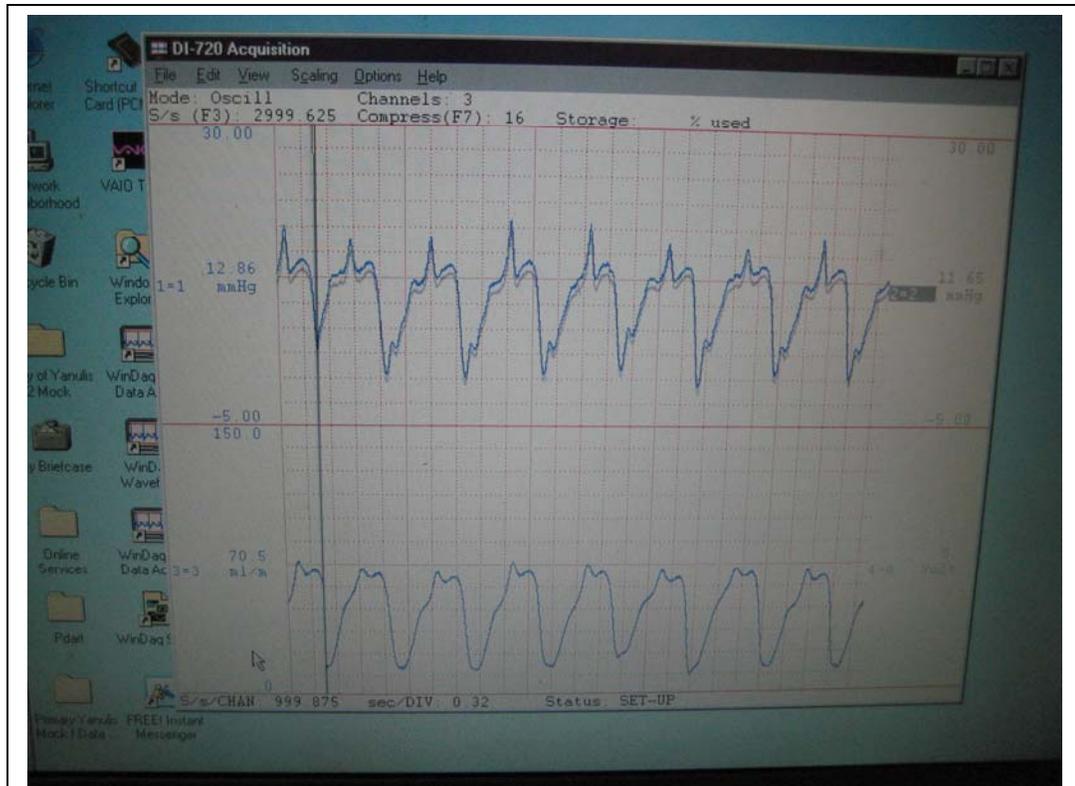


Figure 15: Photograph which shows an actual recording of differential pressures as recorded by 2 Millar Pressure Transducers for two recording channels using the Mock II Circuit and DATAQ software.

5.4 Results (Mock II Circuit)

Origins plotting software for data which obtained for 20 seconds using the Mock II Circuit is shown in Figure 16. From this origin plot, it can be concluded that flow does follow differential pressure as measured by a pair of Millar pressure sensors. DATAQ[®] software with WINDAQ/XL, which is a software add-on to WinDaq (DATAQ[®] Instrument), had been used to as a post-sampling analysis tool for establishing the foundation for future acute studies. Note that only results obtained from the Mock II circuit (Figure 16) will be presented. As

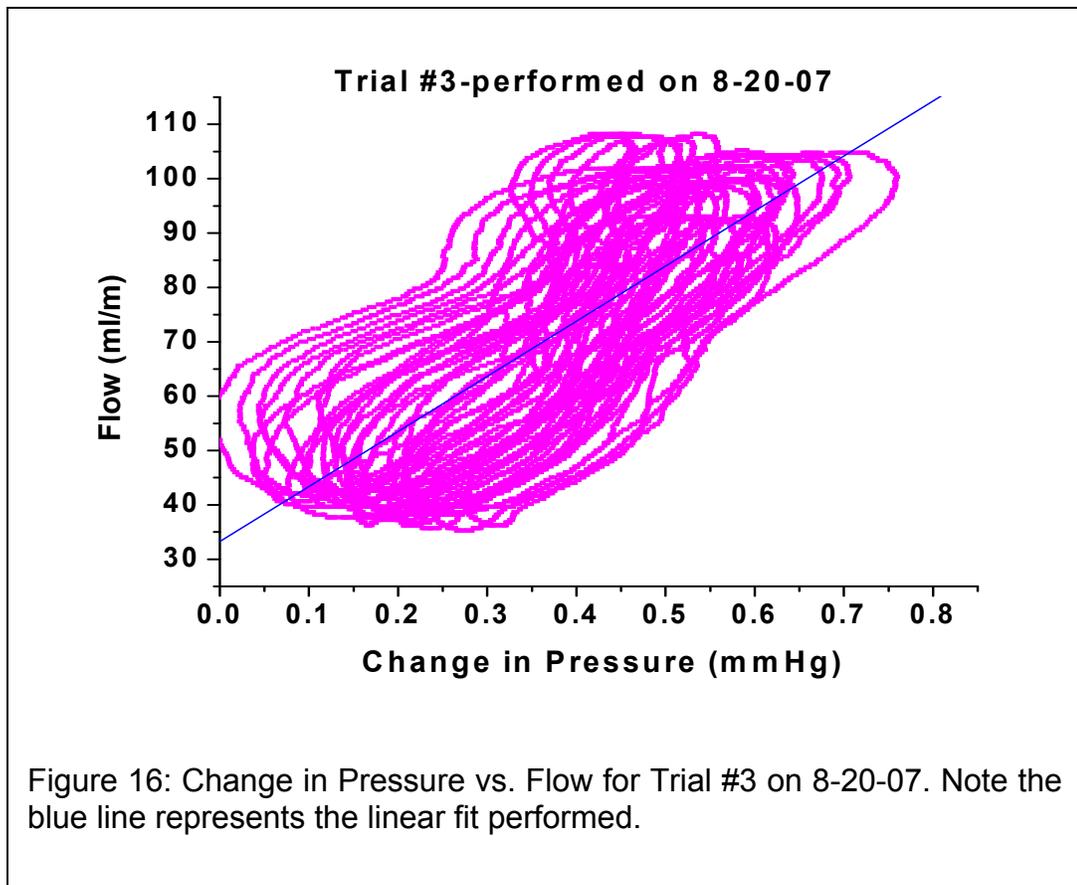
was discussed earlier, I had made changes to the 1st mock circulatory circuit to develop a more realistic simulation of flow profile in the GVC, e.g. used a stiffer catheter system in order to ensure that the position of the catheter and therefore the pressure sensor moved as the simulated contraction occurred. The plots as shown in (Figure 16) had been obtained using the Origin plotting software; illustrates the relationship between the changes in pressure vs. flow. Several experimental runs using the Mock II Circuit (Figure 14) had been performed and the plots of some of these trials had been presented in these figures. Figure 32 as shown is a photograph illustrating an actual recording of differential pressures as recorded by 2 Millar Pressure Transducers for two recording channels using the Mock II Circuit and DATAQ software. Table III illustrates the statistical analysis for two of the experimental trial runs using the Mock II circuit.

Table II Illustrates the Statistical Analysis for Two Trial Runs

<u>DATE PERFORMED, TRIAL #.</u>	<u>X VARIABLE</u>	<u>Y VARIABLE</u>	<u>NUMBER OF DATA POINTS</u>	<u>ST. DEV</u>	<u>P VALUE</u>	<u>R VALUE</u>
8-20-07, #3	Change in Pressure (mmHg)	Flow (ml/m)	20181	14.057	< 0.0001	.74156
9-2-07, #15	Change in Pressure (mmHg)	Flow (ml/m)	20095	14.529	< 0.0001	.79073

5.5 Conclusions

Our prior results [7-9] demonstrate that an effective treatment of AF and heart failure results in an increase in the ratio of external cardiac work to myocardial energy consumption, i.e. an increase in myocardial efficiency [8]. This ratio can be increased if the cardiac work is preserved or increased while the therapy decreases the total amount of energy used by the heart. In contrast, the efficiency of the heart diminishes if the heart uses energy that does not lead to



external work. One such example occurs during AF when the rapid ventricular activations result in isovolumic contractions that result in no ejection of blood from the heart, thus no external work. Prevention of partial isovolumic

contractions would stop the use of energy that results in no external work, thus increasing the efficiency of the heart. It has been previously demonstrated that CP prevents these non-ejecting beats and increases the heart's mechanical efficiency [7-8]. In order to obtain these values, one would normally have to measure ventricular pressures and volumes as well as myocardial oxygen consumption. There are now pacemaker systems that can measure right ventricular pressure [1]. Our work indicates that CP does not significantly alter mean systemic pressure. However, the measurement of both changes in and absolute ventricular volumes values can be quite difficult to obtain. Thus, the measurement of external cardiac work would be challenging in the clinical setting. Next, the durability of oxygen sensors and their ability to measure coronary sinus oxygen content is questionable. In addition, in order to measure myocardial oxygen consumption, one has to measure coronary blood flow as well as the extraction of oxygen. However, our previous results indicate that changes in coronary blood flow parallels the changes in myocardial oxygen consumption [8]. That is, the extraction of oxygen from the heart remains relatively constant despite changes in metabolic demand. Therefore, the short-term changes in coronary blood flow generally indicate corresponding changes in myocardial oxygen consumption, a measure of total energy used by the heart.

Based on both the bench trials and the previous work, a modified ratio of a portion of cardiac output to coronary sinus blood flow appears as the most feasible cardiac parameter that could be used as a control system to provide optimal pacing. Since it is standard practice to secure a ventricular pacing lead to

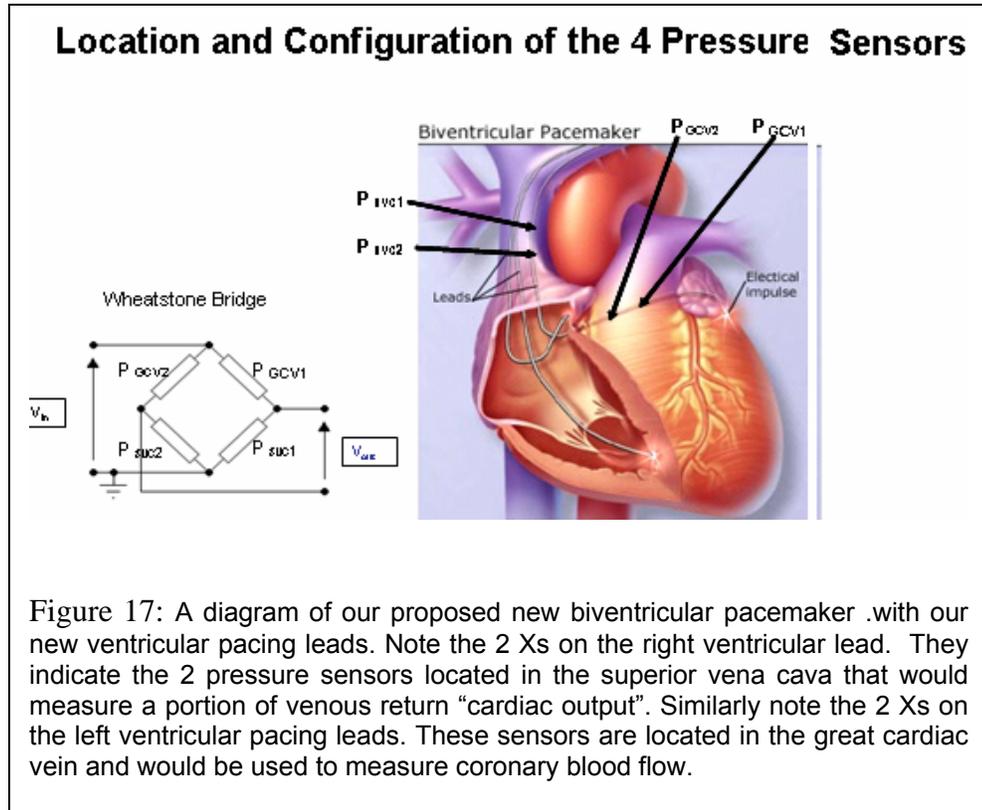
the right ventricular apex via the cephalic vein for ventricular pacing, one could measure blood flow returning to the heart via a proximal flow sensor on this lead in the superior vena cava. Although measurement would represent only a portion of the cardiac output, it would be a simple representative measurement of cardiac output. In those cases where left ventricular pacing is needed, one could implant a pacing lead into the coronary sinus, now a standard clinical practice for biventricular pacing. On this second lead, an additional flow sensor could be attached to measure coronary sinus flow. Also 4 of these sensors could be incorporated onto the lead that enters the great cardiac vein (see Figure 17). By periodically determining the ratio of “cardiac output” to coronary sinus flow, one could determine if this index of cardiac efficiency changes. Then based on the changes in this index, the pacing algorithm could be adjusted. In order to validate that this ratio is the best cardiac parameter to use in our control system, we could compare this proposed index to other standard measurements such as average ventricular rate and right ventricular pressure.

5.6 Future Work

There is the potential for using implantable pressure sensors as shown in (Figure 17) for optimizing either CRT and or our novel pacing paradigm (CRT+CP). Future acute animal studies could involve comparing the responses of predetermined sensors, e.g. implantable pressure sensors in the GVC and SVC veins (Figures 17) which provide a means for measuring cardiac output and

coronary sinus blood flow. As flow is increased in the great cardiac vein or the superior vena cava vein, the differential pressure ($\mathbf{GCV}_1 - \mathbf{GCV}_2$) or ($\mathbf{SVC}_1 - \mathbf{SVC}_2$) would change the balance of the Wheatstone bridge circuit configuration. If the changes are similar the balance would remain the same. But if flow is increased proportionally at a greater value in the GVC than in the SVC, there would now be a change which reflects that the heart's efficiency is decreasing. Thus the appropriate changes could be made to optimize cardiac pacing in heart failure patients.

In order to test our hypotheses and compare the sensors, we could adjust the time delay for CP and CP+CRT in order to obtain the maximal efficiency index under conditions similar to those described in previous work [4]. We could use



this

value of efficiency as a set point and then use a negative feedback control system to monitor deviations from the set point with our sensors. Our control system could then adjust the values toward the predetermined set point values for the purpose of varying the pacing parameters within clinically acceptable ranges. Most likely, we would change the time delay of the stimuli and/or apply the stimuli intermittently as needed. Post-sampling techniques could then be used to determine the optimal set points.

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