2005

Design, implementation, and validation of an implantable multichannel telemetry system for chronic study of sudden cardiac death.

Wei Kong
University of Alabama at Birmingham

DESIGN, IMPLEMENTATION, AND VALIDATION OF AN IMPLANTABLE MULTICHANNEL TELEMETRY SYSTEM FOR CHRONIC STUDY OF SUDDEN CARDIAC DEATH

by

WEI KONG

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham,
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA
2005

ABSTRACT OF DISSERTATION
GRADUATE SCHOOL, UNIVERSITY OF ALABAMA AT BIRMINGHAM

Degree Ph.D. Program Biomedical Engineering

Name of Candidate Wei Kong

Committee Chair William M. Smith

Title Design, Implementation, and Validation of an Implantable Multichannel Telemetry System for Chronic Study of Sudden Cardiac Death

Sudden cardiac death (SCD) is one of the leading causes of death in the United State, but the prediction and prevention of SCD have not generally been successful. Dimension, flow, and pressure measurements will be instrumental in further the understanding of the arrhythmic events. I designed and tested a new multichannel telemetry system with dimension, flow, pressure, and electrogram measurements with lower power, smaller size, and less weight. This telemetry system can be divided into three parts: front end, backpack, and host PC. In the front end, I have designed and calibrated sensor electronics for dimension and blood flow measurement. I have adopted the electronics of pressure channels and cardiac electrograms from the previous telemetry system to better fit in the new system. A stainless steel watertight package for the front end was also designed, manufactured, and tested. The backpack included a control unit, Bluetooth radio, and batteries. The control unit digitized the analog signals from the front end and transmitted the data to the host PC. The host PC had another Bluetooth radio as a receiver and the data were archived and displayed on the host monitor. The whole system was powered by six AA batteries for 24 h. The peak power consumption in the new telemetry system was reduced from 5 W to 0.46 W, the weight for the system was reduced from 2.1 kg to 1.1 kg, and the volume was reduced from 2.6 L to 1.3 L. The whole system was suc-

cessfully tested on the bench and in animals. To our knowledge, this is the first telemetry system that has integrated dimension, flow, and pressure measurements with cardiac electrograms. It is novel to bring dimension measurement and Doppler flow into one system. Dimension, flow, and pressure measurements are more direct indicators of heart function. The availability of these measurements in the chronic study of sudden cardiac death will help us to better characterize cardiac arrhythmias and will greatly enhance our ability to study events leading to spontaneous sudden cardiac death.

DEDICATION

I dedicate this work to my mother, Lanqin, and my wife, Jane, the two most important women in my life, for their support and encouragement for this work.

ACKNOWLEDGMENTS

I thank my advisor, Dr. William M. Smith, for giving his guidance and support in this challenging project and for serving as chair of my committee. Dr. Smith spent countless hours of his busy schedule to advise me on system design, experiment setup, manuscript revision, and so on. while he supervised my progress closely; he gave me freedom in laying out the design, setting up the experiment, and approaching and solving problems and always respected my choices. I thank Drs. Raymond E. Ideker, Jack M. Rogers, Jian Huang, and Greg P. Walcott for serving on my committee. I thank Drs. Jian Huang and Kangan Cheng for their help in many of the animal tests. I thank Jack M. Rogers for his generosity in lending me his laboratory equipments and tools. I thank Dennis L. Rollin and Kenneth Kuhn for their technical assistance during the circuit design and debugging. I also thank the support staff of the Cardiac Rhythm Management Laboratory of the Department of Biomedical Engineering for support in this work.

This research was supported in part by the National Institutes of Health.

TABLE OF CONTENTS

Page

LIST OF FIGURES

Figure *Page*

DESIGN AND INITIAL EVALUATION OF AN IMPLANTABLE SONOMICROMETER AND CW DOPPLER FLOWMETER FOR SIMULTANEOUS RECORDINGS WITH A MULTICHANNEL TELEMETRY SYSTEM

IMPLANTABLE MULTICHANNEL TELEMETRY SYSTEM USED FOR CHRONIC STUDY OF SUDDEN CARDIAC DEATH

LIST OF ABBREVIATIONS

A/D	analog-to-digital
CPU	central processing unit
CW	continuous wavelength
dc	direct current
ECG	electrocardiogram
ICD	internal cardioverter defibrillator
LAD	left anterior descending coronary artery
LV	left ventricle
PC	personal computer
RC	resistance-capacitance
SCD	sudden cardiac death
VF	ventricular fibrillation

INTRODUCTION

Sudden cardiac death (SCD) accounts for over 50% of cardiovascular deaths annually in the United States [1]. SCD is largely due to ventricular fibrillation (VF) or ventricular tachycardia which degenerates into VF. Because it is the main cause of unexpected death, VF has been widely studied worldwide. Tremendous progress has been made in the understanding of the mechanism of VF. Thanks to extensive basic and clinical research, there are many therapeutic strategies such as drug therapy and electrical defibrillation used in practice. However, SCD prevention with drugs has not been shown to be effective clinically. By far the most effective way to terminate VF is to apply an electrical shock, which terminates all electrical activity in the heart briefly; then the heart recovers on its own [2]. The shock can be applied externally with a strong shock but this requires quick response and available devices at the onset of VF. A more effective treatment for SCD is the internal cardioverter defibrillator (ICD). Since being first implanted in a patient in 1980, the ICD has reduced mortality in patients with coronary artery disease and heart failure [3]-[5]. However, an ICD implant is expensive, and the criteria and risk assessment of the ICD implant are not foolproof. To improve the prevention, therapy, and cost-effectiveness of ICD implants, prediction and a thorough understanding of VF are necessary. During the past four decades, there has been considerable interest in the identification of patients at increased risk of death following myocardial infarction. Accumulating knowledge of postinfarction risk stratification has provided a rational foundation for individualizing diagnostic and therapeutic strategies. However, the prognostic

significance of some of the techniques used for risk stratification after myocardial infarction remains controversial. The most commonly used techniques are as follows:

(1) Ejection fraction,

(2) T-wave alternans,

(3) Signal-averaged electrocardiogram (ECG),

(4) QRS intervals,

(5) Heart rate variability,

(6) Electrophysiological testing, etc [6], [7].

Most of these measurements are from electrograms and could be obtained noninvasively. These predictive parameters were proven to have reasonable accuracy by various studies [8]-[10]. For example, the signal-averaged ECG has a negative predictive value and T-wave alternans has a positive predictive value for mortality from SCD [7]. However, not a single measurement could predict SCD alone. By far the most widely used predictor for SCD is ejection fraction. The ejection fraction is the volume of blood pumped from the heart divided by the whole volume of the heart during one contraction. It measures the efficiency of the activity of the left ventricle (LV) and is a good indicator of cardiac function. The predictive power of the ejection fraction perhaps results from the fact that it is a more direct assessment of the heart function than the ECG parameters have been found to be. Besides the ejection fraction, the pressure-volume loop is another direct and important way to assess LV function.

Only limited clinical data are available due to many restrictions in hospital environments. In acute animal models variables other than electrograms can be collected in a controlled situation, but the physiological status of available acute animal models may not reflect what is really happening in patients at risk of SCD. Killingsworth et al. con-

ducted a chronic study of 12 dogs with induced ischemia using a previous eight-channel electrogram telemetry system [11]. They found that 5 of the 7 animals with SCD died of VF or of tachycardia-associated VF with small infarcts, and 2 of the 7 showed bradycardia degenerating into VF with larger infarcts. They concluded that the two bradycardia deaths might be mistakenly classified without continuous recording. This finding confirmed the advantage of the telemetry system. They also found that the majority of the dogs with SCD had histopathologic evidence of thrombus or serum clot in the left circumflex coronary artery at the time of death. This suggests that major contractile and subsequent hemodynamic failure may have occurred, leading to death from bradyarrhythmia death. However, none of the hemodynamic measurements were available. The association of pressure, heart volume, and coronary flow with cardiac arrhythmias is not clear. It is still largely unknown what happens immediately before the ventricular fibrillation. Does the hypotension happen before the VF, or does the autonomic tone change first and subsequently affect the coronary flow, eventually leading to ischemia and VF? Chronic study of free-roaming animal models with myocardial infarction or ischemia may simulate the clinical situation better. Recordings of dimension, flow, and pressure, along with electrograms, will provide us with the tools to evaluate which factor is more important in the initiation of VF by allowing analysis of all variables immediately before the VF.

However, no currently available telemetry systems can record heart volume, pressure, blood flow, and cardiac electrograms at the same time. To deal with this problem, I redesigned an eight-channel telemetry system to include these parameters. Furthermore, it was important that the system minimize the trauma to the animal and drastically reduce the power consumed. The original system used a generic CPU and wireless local area

network which were inefficient since they were designed for generic use. The design goals were as follows:

(1) A telemetry system will record one heart dimension, blood flow, blood pressure, and five cardiac electrograms.

(2) The controller for the system will be a specific task microcontroller.

(3) Data will be telemetered by a low power wireless transmission protocol.

(4) Power consumption will be minimized to reduce the size of the battery pack while extending battery life.

(5) The size of the implant and associated electronics will be minimized to reduce the burden on experimental animals.

With these requirements in mind, I have developed a low power sonomicrometer for one-dimension measurement and an ultra low power continuous wave Doppler flowmeter suitable for coronary artery use [12]. The pressure was implemented from the previous design. The 386 computer in the original system was replaced with an ultra low power microcontroller, and the wireless local area network was replaced with a low power Bluetooth link. The system has been designed, implemented, and validated on the bench and in an animal. The biggest concern for this telemetry system is the power consumption since this system is powered with batteries. We have successfully reduced the power, size, and weight for all parts. Part of the work has been published in a paper and the other is ready for submission. These two manuscripts make up the main body of this dissertation.

The first article in this dissertation reports the design and evaluation of two channels for dimension and flow measurement: sonomicrometer and flowmeter. The circuit design emphasized power, size, and accuracy. In other telemetry systems, the sonomi-

crometer and flowmeter are not generally used together because of the potential interference present from high voltage excitation pulse. Keeping the two channels at the lowest working power reduced the interference. The two systems use the same 10-MHz clock, so common background noise was eliminated. The circuits for the two channels were separated with low-pass RC filters to further reduce interference. It is novel to have a sonomicrometer and flowmeter working together. The two channels were validated on the bench with artificial bench settings and in animals.

The second article describes the development and validation of the whole telemetry system. The telemetry had three main parts:

(1) An implantable front end used for data collection and conditioning;

(2) A backpack with control unit, wireless radio, and battery pack for system control, data transmission, and power supply; and

(3) A host PC with another Bluetooth radio for data display and archiving.

All circuits were miniaturized on a small six-layer printed circuit board. This circuit board was hosted in a custom-made stainless steel case. A Teflon lid with IS-1 connectors connects the transducers and seals the package from the outside environment. The data are forwarded to the microcontroller in the backpack for processing and then streamed to the host PC. The data received on the host are displayed on the monitor and saved on a disk. When in use, the front end will be implanted inside the animal, with the backpack on the back on the animal. The host PC will be placed within 10 m of the animal to ensure successful data transmission. The whole system was validated in a pig model. The animal care complied with Section 6 of the Animal Welfare Act, 1989, and adhered to the guiding principles outlined in the "Guide for the Care and Use of Animals," National Institutes of Health Publication #85-23. The Institutional Animal Care and Use Committee

Approval letters are attached in the appendix. The simultaneous recordings of dimension, flow, pressure, and electrograms from the pig model under normal conditions and in VF are shown in the second manuscript.

DESIGN AND INITIAL EVALUATION OF AN IMPLANTABLE SONOMICROMETER AND CW DOPPLER FLOWMETER FOR SIMULTANEOUS RECORDINGS WITH A MULTICHANNEL TELEMETRY SYSTEM

by

WEI KONG, DENNIS L. ROLLINS, RAYMOND E. IDEKER, AND WILLIAM M. SMITH

IEEE Transactions on Biomedical Engineering 2005; 52: 1365-1367

Abstract

We have developed a sonomicrometer and continuous wavelength (CW) Doppler flowmeter for a multichannel telemetry system. These developments will enable us to measure ventricular dimension and coronary artery blood velocity, which are valuable parameters to characterize sudden cardiac death (SCD) in ambulatory animal models of ventricular arrhythmias. The design goals for the sensors were accuracy, low power consumption, small size and compatibility with each other. The circuits were designed successfully and tested simultaneously in vivo. The CW Doppler flowmeter draws 9 mA and the sonomicrometer draws 28 mA on a 5-V supply. The ability to measure heart dimension and blood velocity will add significantly to our understanding of the sequence of events leading up to spontaneous sudden cardiac death.

Introduction

Sudden cardiac death (SCD) is one of the leading causes of death in the United States. It is frequently related to coronary artery disease and myocardial infarction. SCD has been intensively studied with acute animal models and clinical data. However, study of the episode leading to spontaneous SCD has not been possible with these methods. Chronically implanted telemetry in conscious, ambulatory animals may provide useful information to test hypotheses about the cause and effect among coronary artery occlusion, reperfusion, left ventricular (LV) pressure-volume relationships, and bradyarrhythmias [1].

While commercial and specially designed telemetry systems have been used to study spontaneous arrhythmias, they have either an inadequate number of channels, limited battery lifetimes, or unsuitable sensors for cardiac study [2], [3]. We have previously

built an eight-channel implantable telemetry system for this purpose [4], [5]. This system was implemented successfully and collected significant data [6]. However, since a major goal was expedient development time, available physiological signals were limited to cardiac electrophysiological signals and pressure, and power consumption was not optimized.

Previous studies showed that the temporal relationship between electrophysiological and mechanical phenomena was important in understanding modes of SCD [6]. For example, the relationship between pressure and volume is a useful tool for the assessment of ventricular performance [7]-[9]. A pressure channel is available on our present system but dimension sensors are required for an appropriate estimate of cardiac mechanical function.

Blood velocity is another important variable in understanding events leading to SCD. The flow in coronary arteries provides less ambiguous information about the relationship of ischemic events to arrhythmias than indirect measures such as ST segment changes in the electrocardiogram. Results of a few implantable ultrasound flow measurement systems using telemetry have been reported [10]-[14]. They have demonstrated their usefulness in various animal models but they consume more power than our design goal and the modulation techniques used limited their flexibility.

Our goal was to build an ultra low power, small size sonomicrometer and a continuous wavelength (CW) Doppler flowmeter for use in telemetry in acute [15] or chronic [6] animal models of SCD. The CW Doppler flowmeter will be used to detect presence or absence of flow in coronary artery in this specific study. In this paper we describe two sensors that we have fabricated and characterized for measuring dimension and blood

flow. These sensors complement those already in use for pressure and electrograms and will be valuable in the study of spontaneous ventricular arrhythmias.

Design

A. Sonomicrometer

The circuit of the sonomicrometer channel for telemetry consists of two parts. The first part of the circuit is a pulse generator. A 10-MHz crystal is used as the clock. A 0.5-μs pulse at a 1-KHz rate switches on a 67.5-V battery to generate an excitation pulse for the transmitter. The second part of the circuit is a two-stage amplifier, a comparator, and an integrator. The received signal is amplified and low-pass filtered at 4-MHz and compared to a preset level in the comparator. The transmitted signal starts the beginning of a pulse and the received signal marks the end of the pulse. This pulse is integrated to generate an output voltage that is proportional to the distance between the two crystals.

B. Ultrasound Flowmeter

Because of the low power requirement of our telemetry system, we developed the flowmeter with nondirectional CW Doppler [16], [17]. Our design is based on that of Franklin and Yonezawa [11], [14], modified for ultra low power consumption. The 5-V and 15-V power supplies were replaced with one 5-V supply, and all the integrated circuits were replaced with ultra low power devices. A on board oscillator within a balanced mixer generates a 10-MHz sine wave to excite the transmitter. The ultrasound waves are scattered from the particles in the fluid and the receiver detects the reflected signals. The signal received is multiplied by the original sine wave using a balanced mixer to derive the Doppler shifted signal. After amplification, the signal is bandpass filtered with cutoff

frequencies at 300 Hz and 30-KHz. Finally, a zero crossing frequency to voltage converter is used to convert the frequency information to a proportional voltage output.

C. Noise Reduction

In order to reduce noise for simultaneous operation, both circuits use the same 10-MHz frequency and the common background noise is filtered out. The two circuits are separated with a low-pass RC filter on the 5-V power line and bypass capacitors were used. Noise was further reduced by the selection of ultra low power parts to reduce emissions.

Validation

Two 2-mm circular piezoelectric crystals (Sonometrics, Inc., London, ON, Canada) were used to test the sonomicrometer. Two transducers were placed on holders so that they were approximately 1 cm above the supporting surface. Then the holders were placed on the bottom of a 25 x 25 x 50 cm aquarium half filled with tap water. The transmitter was fixed to one end of a ruler and the receiver was moved away from the transmitter along the ruler to test the range. Measurements were taken at 1.27 cm intervals and the output voltage was compared to the true distance by linear regression.

The ultrasound flowmeter was tested by pumping Doppler test fluid (ATS Laboratories, Inc., Bridgeport, CT) through polyimide tubing (Small Part, Inc., Miami Lakes, FL) that formed a closed loop. The transducer was a 10-MHz CW Doppler flow probe from Iowa Doppler Products, Inc. (Iowa City, IA). The output voltage of the flowmeter was compared to the true velocity by linear regression.

The Doppler flowmeter and sonomicrometer were tested together in one animal. A pig was prepared as described previously [18]. The chest was opened and the left anterior descending coronary artery (LAD) was exposed. A flow cuff was wrapped around the artery. Two sonomicrometer crystals were fixed to the base and apex of LV. A unipolar electrogram from a mapping plaque placed over the posterior LV was simultaneously recorded with dimension and flow.

Results

The sonomicrometer measured over a range from less than 1.27 cm to more than 15 cm with spatial resolution of 0.15 mm. The linear regression fit the data with a value of R^2 of 0.99. The current draw of this sonomicrometer circuit is 27 mA measured with an ammeter.

The Doppler flowmeter was able to measure velocities from less than 3 cm/s to more than 90 cm/s. The linear regression fit the data with an R^2 of 1. The flowmeter draws 9 mA from a 5-V supply.

Fig. 1 shows simultaneous recordings of electrogram, dimension measurement and descending coronary artery flow. There is no interference between dimension and flow measurements.

Discussion

A CW Doppler flowmeter and sonomicrometer were built and tested for future use in a chronically implanted multi-channel telemetry system. Our CW flowmeter was designed for ultra low power consumption. The power consumption for the front end of Yoshiharu's flowmeter is 48 mW, the transmitted power for Franklin's flowmeter is less

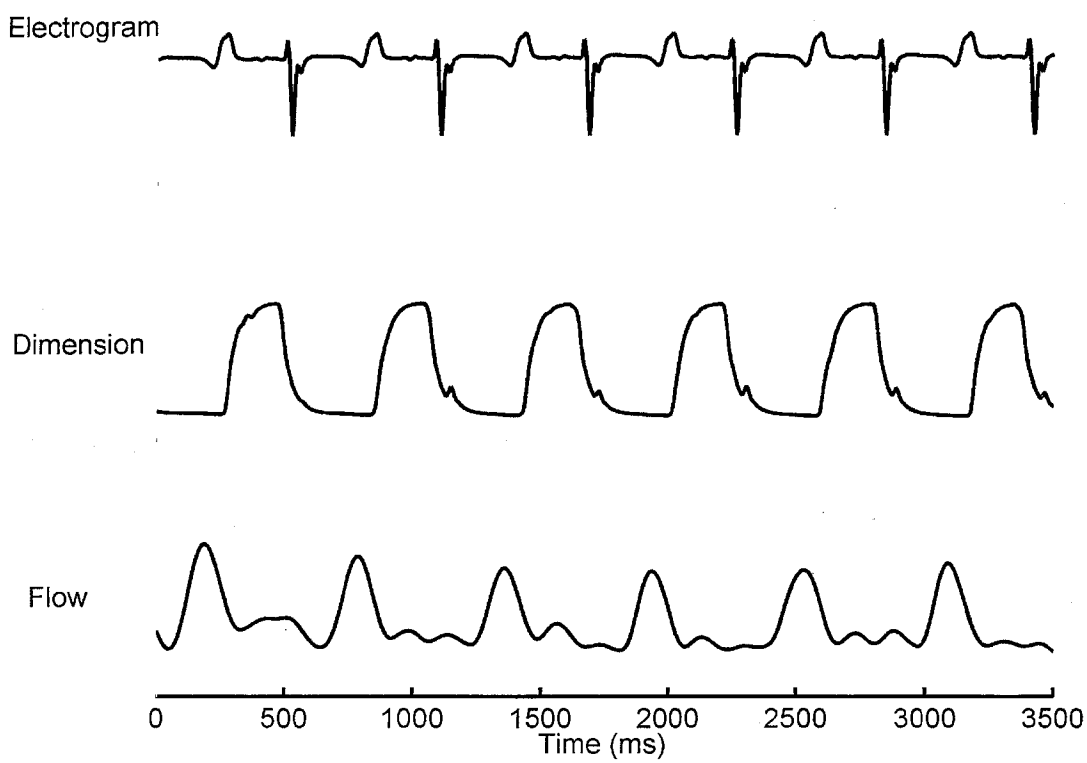

Fig. 1. Simultaneous recordings of electrogram (top trace), dimension measurement (middle trace), and descending coronary artery blood flow (bottom trace).

than 500 mW, and the transmitted power for Wyatt's pulsed flowmeter 40 mW while our whole system consumes 45 mW [14], [17], [19]. Power consumption for other sonomicrometers was not found in literature [20]. The printed circuit board with both flowmeter and sonomicrometer should be about 3.8 cm x 3.8 cm.

The ultrasound flowmeter and sonomicrometer generate high energy pulses as a normal consequence of their individual operation. This interference is generally present for commercial instruments, but not present in our system. The result is that the baseline noise of flow trace with the sonomicrometer operating is comparable to that of flowmeter when operating alone, and vise versa.

The diastolic diameter of the canine LV has been reported to range from 3.0 to 4.7 cm (mean 3.7 cm) and systolic diameter from 1.9 to 3.3 cm (mean 2.6 cm) [21]. Our test shows this sonomicrometer is adequate for measuring these dimensions.

Chilian and Marcus reported that the mean frequency shift, proportional to blood velocity, in the LAD was about 1.5 KHz shift and peak LAD artery frequency shift was 5 KHz [22]. The corresponding velocities are calculated to be 8.3 cm/s (mean) and 27.7 cm/s (peak) [16]. The measurable velocity in our system ranges from less than 3 cm/s to more than 90 cm/s and thus should be adequate to measure canine coronary velocity.

The addition of a sonomicrometer and a flowmeter to an implantable system will allow measurement of coronary artery flow and pressure-volume relations which will greatly enhance the ability to evaluate cardiac function and the changes associated with the spontaneous occurrence of cardiac arrhythmias and sudden cardiac death.

Acknowledgment

The authors would like to thank K. Kuhn, Adjunct Professor of Electrical and Computer Engineering at UAB, for his assistance with circuit design.

References

[1] T. B. Fryer and H. Sandler, "A review of implant telemetry systems," *Biotelemetry*, vol. 1, pp. 351-374, 1974.

[2] E. N. Smith and T. J. Salb Jr., "Multichannel subcarrier ECG, respiration, and temperature biotelemetry system," *J. Appl. Physiol.*, vol. 39, pp. 331-334, 1975.

[3] S. J. Gschwend, J. W. Knutti, H. V. Allen, and J. D. Meindl, "A general-purpose implantable multichannel telemetry system for physiological research," *Biotelem. Patient Monit.*, vol. 6, pp. 107-117, 1979.

[4] D. L. Rollins, C. R. Killingsworth, G. P. Walcott, R. K. Justice, R. E. Ideker, and W. M. Smith, "A telemetry system for the study of spontaneous cardiac arrhythmias," *IEEE Trans. Biomed. Eng.*, vol. 47, no. 7, pp. 887-892, Jul., 2000.

[5] M. D. Yarger, D. L. Rollins, C. R. Killingsworth, G. P. Walcott, R. E. Ideker, and W. M. Smith, "An eight channel telemetry system for chronic ECG recording," in *Proc. 15th Int. Symp. Biotelemetry*, 2000, pp. 602-608.

[6] C. R. Killingsworth, D. E. Ritscher, G. P. Walcott, D. L. Rollins, R. E. Ideker, and W. M. Smith, "Continuous telemetry from a chronic canine model of sudden cardiac death," *J. Cardiovasc. Electrophysiol.*, vol. 11, pp. 1333-1341, 2000.

[7] E. N. Simantirakis, K. E. Vardakis, G. E. Kochiadakis, E. G. Manios, N. E. Igoumenidis, M. Brignole, and P. E. Vardas, "Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation," *J. Am. Coll. Cardiol.*, vol. 43, pp. 1013-1018, 2004.

[8] K. Fukamachi, Z. B. Popovic, M. Inoue, K. Doi, S. Schenk, Y. Ootaki, M. W. Kopcak Jr., and P. M. McCarthy, "Changes in mitral annular and left ventricular dimensions and left ventricular pressure-volume relations after off-pump treatment of mitral regurgitation with the Coapsys device," *Eur. J. Cardiothorac. Surg.*, vol. 25, pp. 352-357, 2004.

[9] H. Takano and S. A. Glantz, "Left ventricular contractility predicts how the end-diastolic pressure-volume relation shifts during pacing-induced ischemia in dogs," *Circulation*, vol. 91, pp. 2423-2434, 1995.

[10] H. F. Stegall, M. B. Kardon, H. L. Stone, and V. S. Bishop, "A portable, simple sonomicrometer," *J. Appl. Physiol.*, vol. 23, pp. 289-293, 1967.

[11] D. L. Franklin, N. W. Watson, and R. L. Vancitters, "Blood velocity telemetered from untethered animals," *Nature*, vol. 203, pp. 528-530, 1964.

[12] A. Benchimol, I. G. Maia, J. L. Gartlan Jr., and D. Franklin, "Telemetry of arterial flow in man with a Doppler ultrasonic flowmeter," *Am. J. Cardiol.*, vol. 22, pp. 75-84, 1968.

[13] H. V. Allen, J. W. Knutti, and J. D. Meindl, "Totally implantable directional Doppler flowmeters," *Biotelem. Patient Monit.*, vol. 6, pp. 118-132, 1979.

[14] Y. Yonezawa, W. M. Caldwell, J. C. Schadt, and A. W. Hahn, "A miniaturized ultrasonic flowmeter and telemetry transmitter for chronic animal blood flow measurements," *Biomed. Sci. Instrum.*, vol. 25, pp. 107-111, 1989.

[15] S. Zhang, J. L. Skinner, A. L. Sims, D. L. Rollins, G. P. Walcott, W. M. Smith, and R. E. Ideker, "Three-dimensional mapping of spontaneous ventricular arrhythmias in a canine thrombotic coronary occlusion model," *J. Cardiovasc. Electrophysiol.*, vol. 11, pp. 762-772, 2000.

[16] J. W. Peter Atkinson, *Doppler Ultrasound and Its Use in Clinical Measurement*, 1st ed. London,UK: Academic, 1982.

[17] G. R. Wyatt, "An implantable pulsed doppler ultrasonic blood flowmeter using custom integrated circuits," Ph.D. dissertation, UMI Dissertation Information Service, Ann Arbor, MI, 1975.

[18] J. Huang, X. Zhou, W. M. Smith, and R. E. Ideker, "Restitution properties during ventricular fibrillation in the in situ swine heart," *Circulation*, vol. 110, pp. 3161-3167, 2004.

[19] D. L. Franklin, W. A. Schlegel, and N. W. Watson, "Ultrasonic Doppler shift blood flowmeter: Circuitry and practical applications," *Biomed. Sci. Instrum.*, vol. 25, pp. 309-315, 1963.

[20] J. W. Knutti, E. Wildi, J. D. Marshall, H. V. Allen, and J. D. Meindl, "Totally implantable dimension telemetry," *Biotelem. Patient Monit.*, vol. 6, pp. 133-146, 1979.

[21] I. Mashiro, R. R. Nelson, J. N. Cohn, and J. A. Franciosa, "Ventricular dimensions measured noninvasively by echocardiography in the awake dog," *J. Appl. Physiol.*, vol. 41, pp. 953-959, 1976.

[22] W. M. Chilian and M. L. Marcus, "Phasic coronary blood flow velocity in intramural and epicardial coronary arteries," *Circ. Res.*, vol. 50, pp. 775-781, 1982.

IMPLANTABLE MULTICHANNEL TELEMETRY SYSTEM USED FOR CHRONIC STUDY OF SUDDEN CARDIAC DEATH

by

WEI KONG, JIAN HUANG, DENNIS L. ROLLINS, RAYMOND E. IDEKER, AND WILLIAM M. SMITH

In preparation for *IEEE Transactions on Biomedical Engineering*

Format adapted for dissertation

Abstract

We have developed an eight-channel telemetry system for studying experimental models of sudden cardiac arrest. The system is an extension of a previous device that has been miniaturized, reduced in power consumption, and provided with increased functionality. We previously developed sensors for ventricular dimension and coronary artery blood flow that are suitable for use with the system. The telemetry system consists of a front end, backpack, and host PC. The front end is a watertight stainless steel case with all sensor electronics sealed inside; it acquires dimension, flow, pressure, and five cardiac electrograms from selected locations on the heart. The backpack includes a control unit, Bluetooth radio, and batteries. The control unit digitizes eight channels of data from the front end and forwards them to the host PC via Bluetooth link. The host PC has a receiving Bluetooth radio and Labview programs to store and display data. The whole system was successfully tested on the bench and in an animal model. This telemetry system will greatly enhance our ability to study events leading to spontaneous sudden cardiac death.

Introduction

Sudden cardiac death (SCD), the leading cause of death in the industrialized world, accounts for 400,000 deaths yearly in the United States alone [1]. About 80% of SCD results from ventricular fibrillation (VF) and ventricular tachycardia [2]. The mechanism of VF is still not clear. Prevention of VF with anti-arrhythmic agents has not been effective [3]. The most effective way to terminate VF is timely electrical shocks. The internal cardioverter defibrillator (ICD) is by far the most effective way to terminate spontaneous VF but requires good risk assessment by clinicians determining who should have an ICD implanted. Current management of SCD is still not satisfactory for the following

reasons: 1) the prevention of SCD is not successful; 2) we are not able to predict SCD in patients with preserved left ventricular (LV) function, although these patients account for over 50% of SCD [3]. As a result, people who have an ICD implanted may never have VF and people without an ICD often die of SCD [3]. These problems in prevention and treatment of SCD raise a question: how to predict VF? Most of the studies dealing with prediction of VF used electrogram variables such as heart rate variability, signal-averaged electrocardiogram, and T-wave alternans. However, the specificity, sensitivity, and accuracy of these predictive variables are yet to be proven [4]. Ejection fraction is the main standard in use today to screen patients for ICD implant [2], but its sensitivity and specificity are also in question [5]. In the meantime, other important parameters such as heart volume index, flow, and pressure were not readily available. These parameters may be instrumental to prediction of VF since they are directly related to cardiac function. Although these measurements are available in acute, anesthetized, open chest animal models of ischemia and infarction, the applicability of these data to clinical situations is limited because of the unphysiologic conditions present during their acquisition. In addition, arrhythmias in acute studies are typically artificially induced, while the onset of clinical cardiac arrhythmias is spontaneous and random. Because of the artificial conditions introduced by thoracotomy, anesthesia, and the induction of VF, chronic studies may provide more insight into the nature and mechanisms of cardiac arrest. To target prediction of VF with chronic study of spontaneous VF, we designed this new telemetry system to include dimension, flow, and pressure parameters, in addition to five cardiac electrograms. The wire free data transmission makes the physiological condition of the animal more realistic and removes obstacles for researchers and animal care personnel.

There are commercial telemetry systems available but their channels and usability are limited [6]-[8]. To study the chronic animal models, we have previously designed an eight-channel implantable telemetry system for our special needs [9], [10]. This system was useful but it was developed with a goal of rapid development time and convenient implementation. Most components were off-the-shelf parts and thus not optimized for implantable needs. Neither size nor power consumption was minimized.

The ability to record many physiological variables is limited in many current telemetry systems [8], [11], [12]. In a previous study, the final event in 2 of 7 animals that experienced sudden cardiac arrest was bradycardia. Because all of the recorded signals were electrograms, it was impossible to determine the temporal relationship between mechanical and electrophysiological derangements [12]. As a result, we have designed and implemented sonomicrometer and flowmeter channels [13]. The pressure channel had been designed but was not implemented in the original telemetry system. The full system integrated dimension, flow, pressure, and five channels of cardiac electrograms for a more complete characterization of SCD. Critical design goals were 1) low power consumption for long battery lifetime, 2) ability to use multiple sensors simultaneously without their interfering with each other, and 3) sufficient information to characterize phenomena associated with SCD.

System Design

The system consists of the implantable front end, backpack, and a host PC. Fig. 1 shows the diagram of the telemetry system. The front end consists of electronics and sensors for the sonomicrometer, flowmeter, pressure meter, and five cardiac electrogram channels. The desired physiological data are collected and amplified in the front end and

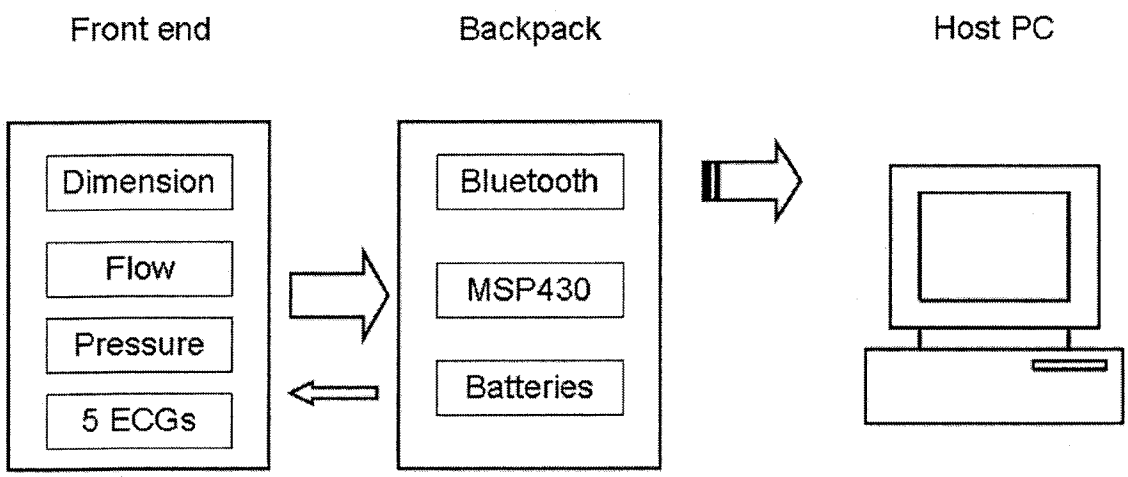

Fig. 1. A block diagram of the telemetry system. This telemetry had a front end, backpack, and host PC. The front end included electronics and sensors. The data collected were forwarded to the backpack through a cable. The front end also received power from the backpack via the same cable. The backpack had a control unit, Bluetooth radio, and batteries. The control unit in the backpack digitized the data and sent them to the host PC through the Bluetooth radio. The host PC archived the data and displayed them on the screen.

experimental animal. The front end also receives power from the backpack. The backpack contains the control unit, Bluetooth radio, and batteries. The control unit in the backpack digitizes the data with eight channels of onboard A/D converters. The data are conditioned and forwarded to the Bluetooth radio for transmission. The host PC has a receiving radio and the received data are saved to the hard drive and displayed on the screen. This telemetry system was designed in modules so that partial upgrade could be easily accomplished without affecting other parts.

A. Front end

The front end consists of all of the implantable sensors and electronics. The design and test of the sonomicrometer and flowmeter have been published previously [13]. The pressure meter is a simple amplifier with an INA114 instrumentation amplifier (Texas Instruments, Inc., Dallas, TX) with a gain of 600. The pressure sensor was a Millar Mikro-Tip pressure transducer catheter, SPR-524 (Millar Instruments, Inc., Houston, TX). Cardiac electrical channels were imported from the original system with modifications. The electrodes were custom-made unipolar screw-in electrodes adopted from Medtronic electrodes (Minneapolis, MN). The gain for the cardiac electrograms was 50.

All of the sensor electronics were built on a 4.7 cm x 5.9 cm six-layer printed circuit board. The components were soldered with reflow solder. The printed circuit board was housed in a custom-made stainless steel case measuring 8.9 x 5.5 x 2.3 cm. There is a plastic lid with two O-rings which, when pushed into the stainless steel case, made the package watertight. All transducers except the pressure probe were connected to the front end case with commercial IS-1 lead connectors (Oscor, Inc., Palm Harbor, FL) for easy replacement and waterproofing. All IS-1 female connectors were fixed inside the lid with

implantable grade silicone adhesive (Rhodia Silicones, Inc., Ventura, CA). The front end, with sensors and electronics, was implanted inside the animal. A wire through the skin connected the front end and the backpack. Power was supplied to the front end through this cable and collected data were forwarded from the front end to the backpack.

B. Backpack

The backpack had the control unit, Bluetooth module, and batteries. The MSP430F149 microprocessor (Texas Instruments, Inc., Dallas, TX) was chosen as the control unit for its ultra low power and small form factor. It has a 16-bit CPU and two on-board universal asynchronous receiver/transmitters. The main timing for the MSPF149 is provided with an external 3.58-MHz clock. This clock provides a good balance between performance and low power consumption. The development board MSP-TS430PM64 of the MSP430F149 was used directly for easy debugging (Texas Instruments, Inc., Dallas, TX). The MSP430F149 was programmed in assembly language. MSP430F149 was programmed to stay in lower power mode. An interrupt wakes up the microcontroller at 1 kHz. Then analog data from the front end were digitized with eight channels of A/D converters. The universal asynchronous receiver/transmitter was then configured to a baud rate of 115 kbps. One start bit, 8 data bits, and 1 stop bit were used. The data were conditioned and sent to serial send buffer for transmission to the host PC via the Bluetooth link. The microcontroller went into lower power mode afterward and this continued in a loop. The front end and backpack were powered with six AA batteries. The MAX1864 regulated the 9-V to two power voltages, 3.3-V and 5-V. The microcontroller MSP430-F149 and Bluetooth module were powered with 3.3-V and the front end was powered by 5-V. There is also a 67.5-V battery in the battery pack for sonomicrometer excitation

[13]. The control unit and the dc-dc converter were hosted in a watertight aluminum box measuring 14.5 x 9.4 x 5.0 cm. The batteries were in another box measuring 13.2 x 7.4 x 5.0 cm. The battery box was connected to the control unit box with a general purpose connector (Tyco Electronics, Harrisburg, PA) for easy and fast replacement of batteries.

C. Host PC

The host PC had another Bluetooth serial adapter to receive the radio signal. The Bluetooth adapter in the backpack and the Bluetooth adapter on the PC were configured to talk only to each other, and the data transmission was password protected. Data throughput was verified at 115 kbps when the telemetry system and the host PC were placed 10 m apart across one wall.

On the PC end, we have developed two applications in Labview (National instrument, Inc., Austin, TX). One application received the data and saved it on a disk every 10 s. It used current time to generate a unique file name. The application was preset to record for 10 s, close the file, and create another data file. The data can be joined together when analyzed later. The data display was accomplished by another application program. This program read the latest written data file and displayed it on the screen.

Validations

Each channel was extensively tested on the bench and in animals. The battery life was tested by powering up the telemetry system with six AA batteries until the batteries were depleted. The front end package was tested by submerging the front end package and all leads and transducers in tap water at room temperature. The front end was powered on and stayed underwater for 3 days. The currents of front end and backpack were

measured with an ammeter. The power consumption was calculated by multiplying respective currents and voltages. Since this system will be used in animal models and since a bench test may not simulate the animal environment perfectly, we did a test in a pig model. The animal preparation followed the methods described in Killingsworth et al.'s paper [12]. Basically, the animal was placed in dorsal recumbency on the surgical table. The chest was opened via a median sternotomy. The locations for all sensors are shown in Fig. 2. The places chosen for the sensors were only for testing purposes and the sensors can be moved to other places if necessary. The animal was allowed to recover for 30 min from the screw-in electrode injuries. The flow and pressure channels were verified against commercial instruments by making simultaneous measurements at adjacent locations. For the flow measurement, the flow transducer from a pulsed Doppler flowmeter (the University of Iowa, Iowa City, IA) was placed next to a telemetry flow cuff on the left anterior descending coronary artery (LAD). The audio signal from the pulsed Doppler flowmeter and the flow signal from the telemetry system were recorded at a sampling rate of 100 kHz with an NI DAQcard-6024 E (National Instrument, Austin, TX) on a laptop. The audio signal was then analyzed and frequency changes were converted to flow. Pressure measurement was verified with pressure channel of a Hewlett Packard monitor (78534 C; Hewlett Packard, Palo Alto, CA). The pressure sensor of the Hewlett Packard monitor was placed in the aorta near the pressure sensor of telemetry system. Pressure from the Hewlett Packard monitor was recorded by replacing an electrogram channel with signals from the pressure channel of the Hewlett Packard monitor. Then VF was induced by applying a dc current to the epicardium. The VF was allowed to continue for about 20 s and then a defibrillation shock was applied. Acute ischemia was simulated by tying a 4.0 suture to the LAD just above the flow cuff for 30 min. The animal died of

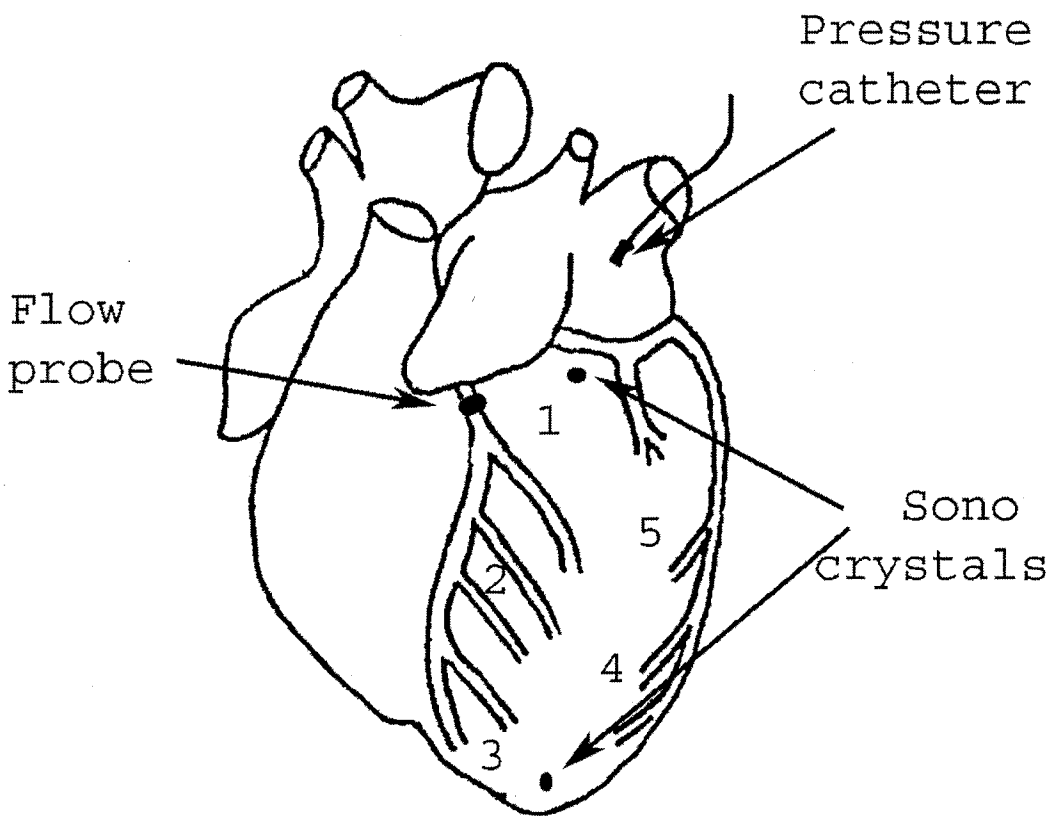

Fig. 2. Locations for sensors. Five custom-made screw-in epicardial electrodes were place over the coronary arterial beds to monitor electrograms. The left leg served as the ground for electrograms. The pressure sensor was placed in the lumen of the ascending aorta. Two sono crystals were placed on the base and apex of the LV to measure one dimension of the heart. A segment of the LAD was isolated and one 1.5-mm Doppler flow probe was wrapped around the vessel. Sono = sonomicrometer.

spontaneous VF before the end of the 30 min. Data were recorded for more than 4 h continuously throughout the study. The implant was examined and there was no damage to the front end package and transducers.

Results

A new telemetry system with expanded capabilities has been designed, built and tested successfully. We can acquire dimension, flow, and pressure measurements, as well as five cardiac electrograms, with this system. Compared to the size and power consumption of our original telemetry system, both were greatly reduced in the new system. The combined front end and backpack volume was reduced from 2.6 L to 1.3 L. The weight was reduced from 2.1 kg to 1.1 kg. The average power consumption was reduced from 2.5 W to 0.46 W with additions of sonomicrometry, flow, and pressure measurements [9]. The batteries were reduced from eight AA batteries and twelve C batteries to six AA batteries but the battery life was extended from 12 h to more than 24 h. The front end and backpack lasted more than 24 h on six AA batteries. The submerge test for the watertight front end package lasted 3 days and no leak was found. Verification recordings of flow and pressure are shown in Fig. 3 and 4, respectively. Fig. 5 shows simultaneous recordings of all eight channels in a pig model. The recordings from top to bottom are dimension of the LV from apex to base, flow speed in LAD, pressure in aorta, and five electrograms on the surface of the anterior LV. Fig. 6 shows an induction and termination of VF with a shock from a Lifepak 12 defibrillator (Medtronic, Minneapolis, MN).

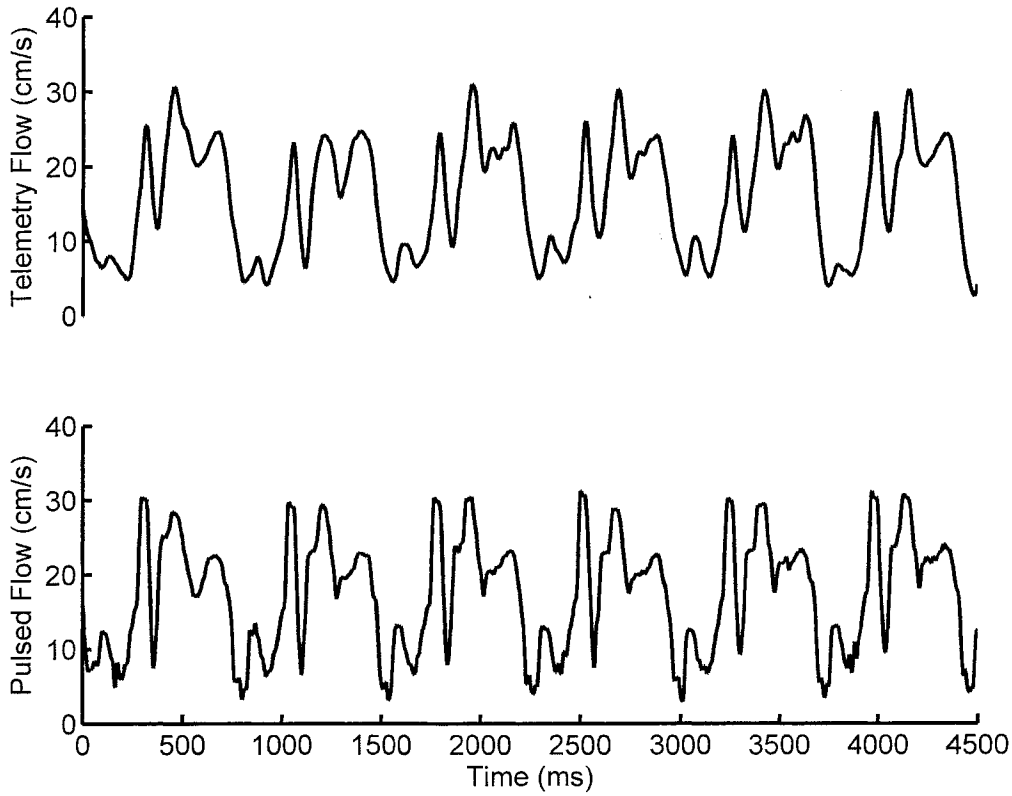

Fig. 3. Verification recordings of flow. Flow measurements from the telemetry system and pulsed Doppler flowmeter are shown. They were recorded simultaneously from the LAD. The top trace was from the telemetry system and the bottom trace was from the pulsed Doppler flowmeter.

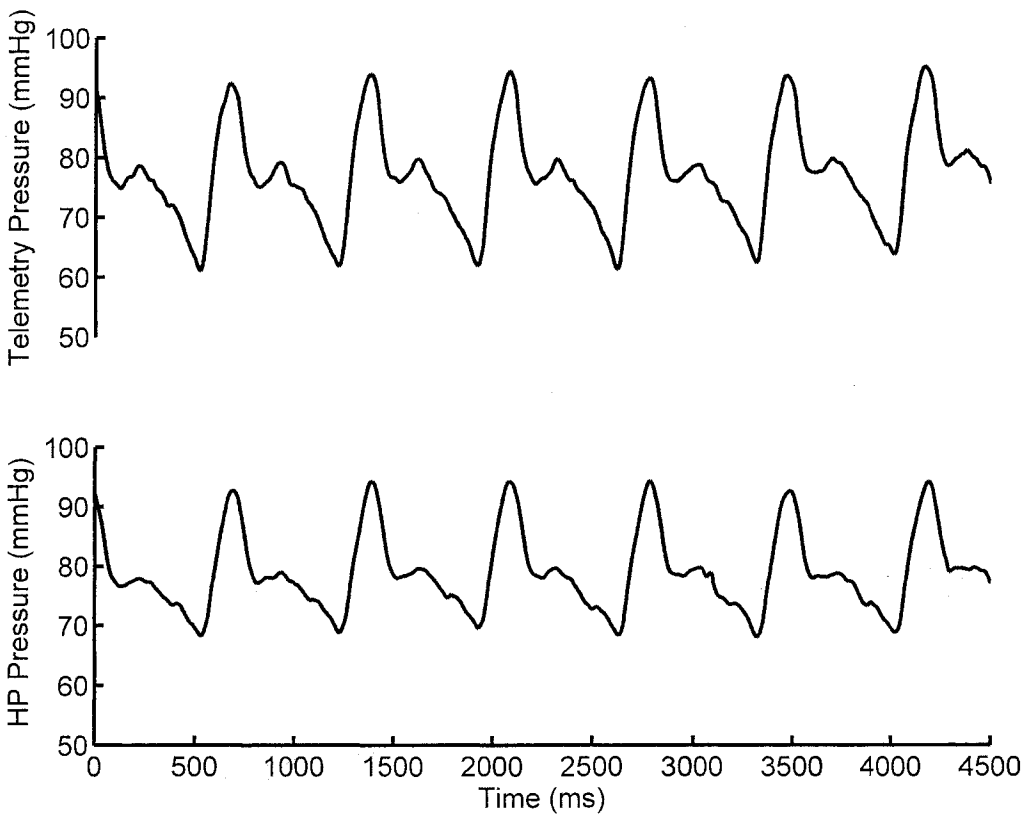

Fig. 4. Verification recordings of pressure. Pressures recorded simultaneously in the aorta are shown. The top trace was from the telemetry system and the bottom trace was from the pressure channel of a Hewlett Packard monitor.

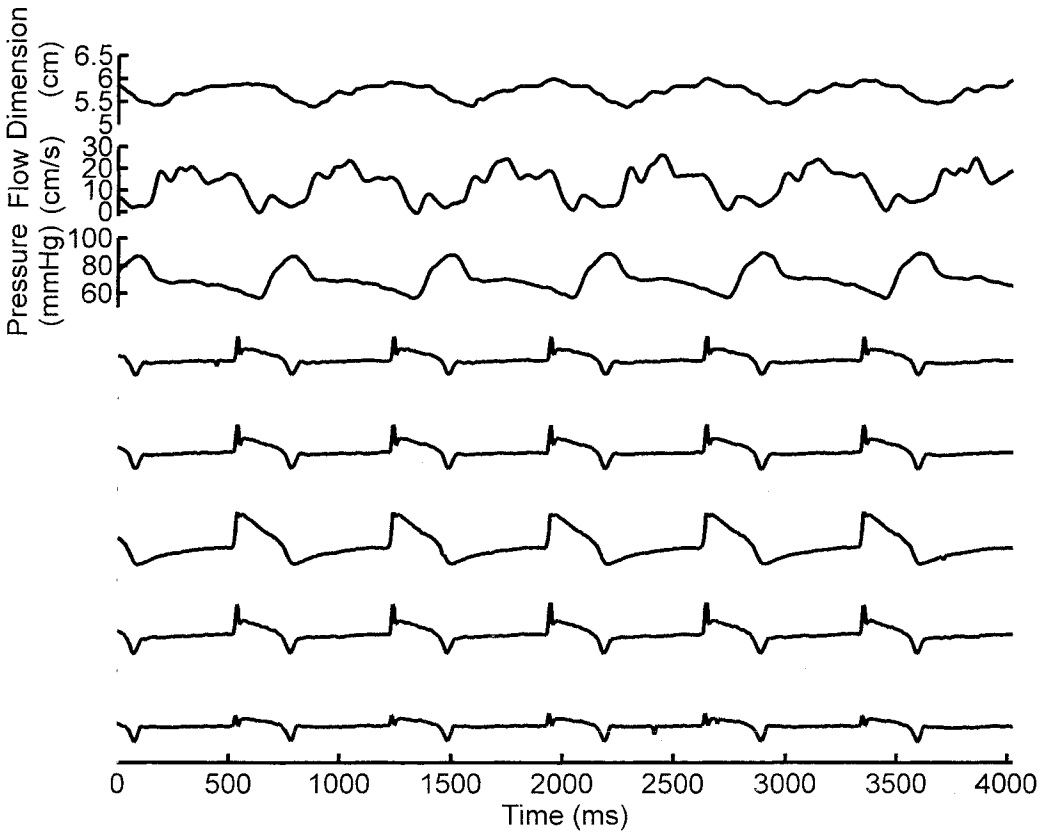

Fig. 5. An example of eight simultaneous recordings. Simultaneous recordings for dimension, flow, pressure, and five cardiac electrograms (in that order) are shown from top to bottom.

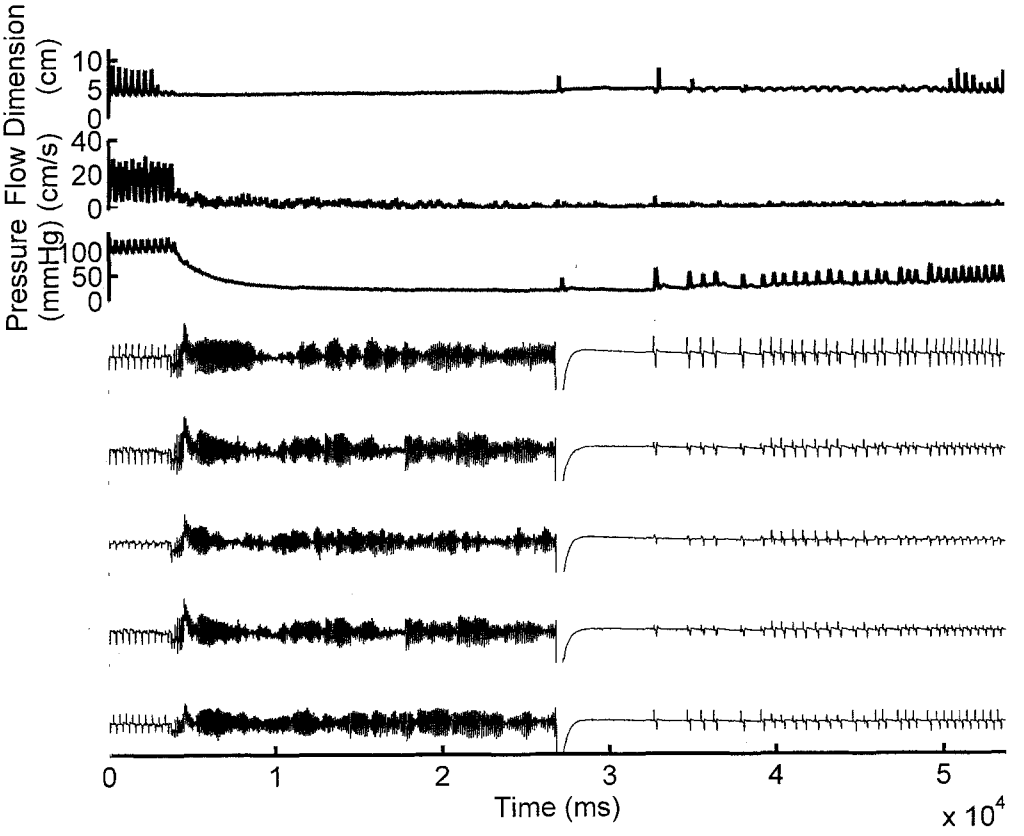

Fig. 6. Recordings of induced VF and defibrillation. A VF was induced by applying a dc current to the epicardium of the LV. The VF was sustained for about 20 s and was terminated by a defibrillation shock.

Discussion

A complete eight-channel telemetry system was designed, implemented, and tested. This work brought dimension, flow, pressure, and cardiac electrograms into one implantable system. SCD is a major problem in the industrialized world and VF is one of the main causes of SCD. Prediction and prevention of VF will greatly reduce mortality and improve patients' quality of life if successfully done. Most attempts to predict VF tried to identify electrogram patterns that may lead to VF [14], [15]. Many other important, more direct parameters were not available, especially for spontaneous VF. This deficiency in clinical therapy requires better understanding of events preceding spontaneous VF. The measurements of dimension, flow, and pressure, along with cardiac electrograms, will greatly enhance our ability to evaluate cardiac functionality and then events surrounding the onset of cardiac arrhythmias. This new technique may improve our understanding of VF mechanism in terms of mechanical electrical coupling and autonomic tone changes. If prediction of VF is successful, the significance is two fold: 1) long term prediction may improve the cost-effectiveness of the ICD implant since this capability will dramatically decrease the incidence of unnecessary expensive heart surgeries and ICD implants, and 2) short term prediction of VF may improve the therapy algorithm in devices like ICDs and pacemakers.

For future improvements, the microcontroller can be incorporated into the front end to reduce the number of wires through the skin. Multiple signals can be multiplexed at this level. This modification will leave only the battery box outside and it also makes the cable thin and imposes fewer burdens on the animal. By far, the low power Bluetooth radio still consumed most of the total power in the current system. The Bluetooth link can be replaced with an Ultra Wide Band for wider bandwidth and lower power when the

Ultra Wide Band becomes available. The sonomicrometer should be expanded to two or three channels so that heart volume can be estimated from these measurements [16], [17]. The cardiac electrograms should be expanded to more channels for a more precise definition of activation fronts of action potentials.

References

[1] R. Mayerburg and A. Castellanos, "Cardiac arrest and sudden death," in *A textbook of cardiovascular disease*, E. Braunwald, Ed. Philadelphia: WB Saunders, 1997, pp. 742-779.

[2] M. L. Ashwath and F. O. Sogade, "Ejection fraction and QRS width as predictors of event rates in patients with implantable cardioverter defibrillators," *South. Med. J.*, vol. 98, pp. 513-517, 2005.

[3] P. S. Spector, "Diagnosis and management of sudden cardiac death," *Heart*, vol. 91, pp. 408-413, 2005.

[4] H. V. Huikuri, T. H. Makikallio, M. J. Raatikainen, J. Perkiomaki, A. Castellanos, and R. J. Myerburg, "Prediction of sudden cardiac death: Appraisal of the studies and methods assessing the risk of sudden arrhythmic death," *Circulation*, vol. 108, pp. 110-115, 2003.

[5] A. E. Buxton, "Risk stratification for sudden death: Do we need anything more than ejection fraction?" *Card. Electrophysiol. Rev.*, vol. 7, pp. 434-437, 2003.

[6] E. N. Smith and T. J. Salb Jr., "Multichannel subcarrier ECG, respiration, and temperature biotelemetry system," *J. Appl. Physiol.*, vol. 39, pp. 331-334, 1975.

[7] S. J. Gschwend, J. W. Knutti, H. V. Allen, and J. D. Meindl, "A general-purpose implantable multichannel telemetry system for physiological research," *Biotelem. Patient Monit.*, vol. 6, pp. 107-117, 1979.

[8] M. Shiotani, T. Harada, J. Abe, Y. Sawada, K. Hashimoto, Y. Hamada, and I. Ho rii, "Practical application of guinea pig telemetry system for QT evaluation," *J. Toxicol. Sci.*, vol. 30, pp. 239-247, 2005.

[9] D. L. Rollins, C. R. Killingsworth, G. P. Walcott, R. K. Justice, R. E. Ideker, and W. M. Smith, "A telemetry system for the study of spontaneous cardiac arrhythmias," *IEEE Trans Biomed. Eng.*, vol. 47, pp. 887-892, 2000.

[10] M. D. Yarger, D. L. Rollins, C. R. Killingsworth, G. P. Walcott, R. E. Ideker, and W. M. Smith, "An eight channel telemetry system for chronic ECG recording," in *Proc.15th Int. Symp.Biotelemetry*, 2000, pp. 602-608.

[11] P. Mohseni, K. Najafi, S. J. Eliades, and X. Wang, "Wireless multichannel biopotential recording using an integrated FM telemetry circuit," *IEEE Trans. Neural. Syst. Rehabil. Eng.*, vol. 13, pp. 263-271, 2005.

[12] C. R. Killingsworth, D. E. Ritscher, G. P. Walcott, D. L. Rollins, R. E. Ideker, and W. M. Smith, "Continuous telemetry from a chronic canine model of sudden cardiac death," *J. Cardiovasc. Electrophysiol.*, vol. 11, pp. 1333-1341, 2000.

[13] W. Kong, D. L. Rollins, R. E. Ideker, and W. M. Smith, "Design and initial evaluation of an implantable sonomicrometer and CW Doppler flowmeter for simultaneous recordings with a multichannel telemetry system," *IEEE Trans. Biomed. Eng.*, vol. 52, pp. 1365-1367, 2005.

[14] L. S. Klein, N. Fineberg, J. J. Heger, W. M. Miles, J. M. Kammerling, M. S. Chang, D. P. Zipes, and E. N. Prystowsky, "Prospective evaluation of a discriminant function for prediction of recurrent symptomatic ventricular tachycardia or ventricular fibrillation in coronary artery disease patients receiving amiodarone and having inducible ventricular tachycardia at electrophysiologic study," *Am. J. Cardiol.*, vol. 61, pp. 1024-1030, 1988.

[15] P. V. Bayly, E. E. Johnson, P. D. Wolf, W. M. Smith, and R. E. Ideker, "Predicting patterns of epicardial potentials during ventricular fibrillation," *IEEE Trans. Biomed. Eng.*, vol. 42, pp. 898-907, 1995.

[16] R. F. Appleyard and S. A. Glantz, "Two dimensions describe left ventricular volume change during hemodynamic transients," *Am. J. Physiol.*, vol. 258, pp. H277-284, 1990.

[17] M. C. Visner, C. E. Arentzen, M. J. O'Connor, E. V. Larson, and R. W. Anderson, "Alterations in left ventricular three-dimensional dynamic geometry and systolic function during acute right ventricular hypertension in the conscious dog," *Circulation*, vol. 67, pp. 353-365, 1983.

DISCUSSION

The focus of basic research is often driven by a need in the real world. Only then could basic research flourish. SCD is a serious problem in the western world. Thanks to the brilliant work of thousands of elite researchers in cardiology, successful therapy such as the implantable defibrillator has been saving people's lives every day. However, there are still many unanswered questions regarding the mechanism of cardiac arrhythmias and SCD. Most research done in clinical settings or with acute animal models has limited available data, altered physiological environments, or both. A more realistic physiological animal model is needed to improve our understanding of the clinical phenomenon. As a result, members of our laboratory proposed to study the episodes preceding spontaneous VF and SCD in animal models with prior myocardial infarction or ischemia. This research will create a real world model of patients at risk of SCD. In this animal model, we will study direct heart function indexes such as heart dimension, coronary artery flow, and pressure, along with electrograms. For this purpose, I have successfully developed a new low power telemetry system which can acquire one dimension variable, one flow measurement, and one pressure, along with five cardiac electrograms. This system was tested chronically on the bench and acutely in an animal. A series of chronic studies will further test the stability and durability of this telemetry system and provide feedback for future developments. The current system has one-dimension measurement but could be expanded to three-dimension measurements. The ejection fraction could be obtained real time from three-dimension measurement. The pressure-volume

loop could be plotted from simultaneous pressure and dimension measurements. The implementation of this system is the first successful step in preparing hardware necessary for this kind of study. As we discussed in the second article, there are still improvements to be made. Future upgrades should be straightforward because of the modular design of the whole system.

GENERAL LIST OF REFERENCES

[1] R. J. Myerburg and A. Castellanos, "Cardiac arrest and sudden death," in *Heart Disease: A Textbook of Cardiovascular Medicine*, E. Braunwald, Ed. Philadelphia: WB Saunders, 1997, pp. 742-779.

[2] G. P. Walcott, S. B. Knisley, X. Zhou, J. C. Newton, and R. E. Ideker, "On the mechanism of ventricular defibrillation," *Pacing Clin. Electrophysiol.*, vol. 20, pp. 422-431, 1997.

[3] M. Mirowski, P. R. Reid, M. M. Mower, L. Watkins, V. L. Gott, J. F. Schauble, A. Langer, M. S. Heilman, S. A. Kolenik, R. E. Fischell, and M. L. Weisfeldt, "Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings," *N. Engl. J. Med.*, vol. 303, pp. 322-324, 1980.

[4] S. Nisam, S. A. Kaye, M. M. Mower, and M. Hull, "AICD Automatic cardioverter defibrillator clinical update: 14 years experience in over 34,000 patients," *PACE*, vol. 18, pp. 142-147, 1995.

[5] T. D. Brennan and G. J. Haas, "The role of prophylactic implantable cardioverter defibrillators in heart failure: Recent trials usher in a new era of device therapy," *Curr. Heart. Fail. Rep.*, vol. 2, pp. 40-45, 2005.

[6] M. Harvey and R. Malkin, "T wave alternans: A marker of myocardial instability," *Prog. Cardiovasc. Nurs.*, vol. 18, pp. 99-107, 111, 2003.

[7] H. V. Huikuri, T. H. Makikallio, M. J. Raatikainen, J. Perkiomaki, A. Castellanos, and R. J. Myerburg, "Prediction of sudden cardiac death: Appraisal of the studies and methods assessing the risk of sudden arrhythmic death," *Circulation*, vol. 108, pp. 110-115, 2003.

[8] A. Gradman, P. Deedwania, R. Cody, B. Massie, M. Packer, B. Pitt, and S. Goldstein, "Predictors of total mortality and sudden death in mild to moderate heart failure. Captopril-Digoxin Study Group," *J. Am. Coll. Cardiol.*, vol. 14, pp. 564-70; discussion 571-572, 1989.

[9] J. A. Gomes, M. E. Cain, A. E. Buxton, M. E. Josephson, K. L. Lee, and G. E. Hafley, "Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction," *Circulation*, vol. 104, pp. 436-441, 2001.

[10] A. K. Gehi, R. H. Stein, L. D. Metz, and J. A. Gomes, "Microvolt T-wave alternans for the risk stratification of ventricular tachyarrhythmic events: A meta-analysis," *J. Am. Coll. Cardiol.*, vol. 46, pp. 75-82, 2005.

[11] C. R. Killingsworth, D. E. Ritscher, G. P. Walcott, D. L. Rollins, R. E. Ideker, and W. M. Smith, "Continuous telemetry from a chronic canine model of sudden cardiac death," *J. Cardiovasc. Electrophysiol.*, vol. 11, pp. 1333-1341, 2000.

[12] W. Kong, D. L. Rollins, R. E. Ideker, and W. M. Smith, "Design and initial evaluation of an implantable sonomicrometer and CW Doppler flowmeter for simultaneous recordings with a multichannel telemetry system," *IEEE Trans. Biomed. Eng.*, vol. 52, pp. 1365-1367, 2005.

APPENDIX

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Provost

NOTICE OF APPROVAL

DATE: November 4, 2003

TO: William M. Smith, Ph.D.
VH-B140 0019
FAX: 975-4720

FROM: Suzanne M. Michalek, Ph.D., Vice Chair
Institutional Animal Care and Use Committee

SUBJECT: Title: PPG: Mechanisms and Therapy of Ischemic Sudden Cardiac Arrest (Ideker); Project # 1: Chronic Monitoring of Ischemic Models of Sudden Death
Sponsor: NIH
Animal Project Number: 031005443

On October 29, 2003, the University of Alabama at Birmingham Institutional Animal Care and Use Committee (IACUC) reviewed the animal use proposed in the above referenced application. It approved the use of the following species and numbers of animals:

Species	Use Category	Number in Category
Dogs	B	24
Pigs	B	40

Animal use is scheduled for review one year from October 2003. Approval from the IACUC must be obtained before implementing any changes or modifications in the approved animal use.

Please keep this record for your files, and forward the attached letter to the appropriate granting agency.

Refer to Animal Protocol Number (APN) 031005443 when ordering animals or in any correspondence with the IACUC or Animal Resources Program (ARP) offices regarding this study. If you have concerns or questions regarding this notice, please call the IACUC office at 934-7692.

Institutional Animal Care and Use Committee
B10 Volker Hall
1717 7th Avenue South
205.934.7692 • Fax 205.934.1188
iacuc@uab.edu
www.uab.edu/iacuc

The University of
Alabama at Birmingham
Mailing Address:
VH B10
1530 3RD AVE S
BIRMINGHAM AL 35294-0019

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Provost

NOTICE OF APPROVAL

DATE: November 3, 2004

TO: William M. Smith, Ph.D.
VH-B140 0019
FAX: 975-4720

FROM: Suzanne M. Michalek, Ph.D., Vice Chair S.M.M.
Institutional Animal Care and Use Committee

SUBJECT: Title: PPG: Mechanisms and Therapy of Ischemic Sudden Cardiac Arrest (Ideker); Project # 1: Chronic Monitoring of Ischemic Models of Sudden Death
Sponsor: NIH
Animal Project Number: 041005443

On October 27, 2004, the University of Alabama at Birmingham Institutional Animal Care and Use Committee (IACUC) reviewed the animal use proposed in the above referenced application. It approved the use of the following species and numbers of animals:

Species	Use Category	Number in Category
Dogs	B	24
Pigs	B	40

Animal use is scheduled for review one year from October 2004. Approval from the IACUC must be obtained before implementing any changes or modifications in the approved animal use.

Please keep this record for your files, and forward the attached letter to the appropriate granting agency.

Refer to Animal Protocol Number (APN) 041005443 when ordering animals or in any correspondence with the IACUC or Animal Resources Program (ARP) offices regarding this study. If you have concerns or questions regarding this notice, please call the IACUC office at 934-7692.

Institutional Animal Care and Use Committee
B10 Volker Hall
1717 7th Avenue South
205.934.7692 • Fax 205.934.1188
iacuc@uab.edu
www.uab.edu/iacuc

The University of
Alabama at Birmingham
Mailing Address:
VH B10
1530 3RD AVE S
BIRMINGHAM AL 35294-0019

GRADUATE SCHOOL
UNIVERSITY OF ALABAMA AT BIRMINGHAM
DISSERTATION APPROVAL FORM
DOCTOR OF PHILOSOPHY

Name of Candidate Wei Kong

Graduate Program Biomedical Engineering

Title of Dissertation Design, Implementation, and Validation of an Implantable Multichannel Telemetry System for Chronic Study of Sudden Cardiac Death

I certify that I have read this document and examined the student regarding its content. In my opinion, this dissertation conforms to acceptable standards of scholarly presentation and is adequate in scope and quality, and the attainments of this student are such that he may be recommended for the degree of Doctor of Philosophy.

Dissertation Committee:

Name		Signature
William M. Smith	**, Chair**	
Jian Huang		
Raymond E. Ideker		
Jack M. Rogers		
Gregory P. Walcott		

Director of Graduate Program

Dean, UAB Graduate School

Date 12/22/05