33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Potential of Gallium-Based Leads for Cardiac Rhythm Management Devices

Aaron M. Kyle, *Member, IEEE*, Nichole Leahy-Glass, William Combs, and Keith L. March

***Abstract*—We propose the use of gallium (Ga), a metal that is liquid at physiological temperatures, or one of its alloys,for use as the conducting material in the leads of implantable pacemakers or cardioverter defibrillators. It is proposed that a liquid conductor will make these leads more pliable and thus less susceptible to fracture *in situ*. As an initial step towards utilizing liquid gallium in leads, the biocompatibility of Ga was investigated via cytotoxicity, hemocompatibility, and intracutaneous injection testing. Unipolar pacing Ga prototypes were fabricated by adapting existing pacemaker leads. The electrical impedance and pulse transmission ability of these leads were examined. Ga was well tolerated both *in vitro* and *in vivo*. Additionally, the Ga prototypes conductors behaved as low magnitude resistances that did not distort pulses as generated by conventional pacemakers. These results indicate that Ga is an appropriate material for implantable cardiac stimulators and will be a focus of our liquid metal prototypes.**

I. Introduction

Heart diseases persist as the top causes of death in the United States and may result in bradycardia, tachycardia and heart failure which may be treated in selected patients. There are over 5 million people living with heart failure, with 670,000 new occurrences per year and an annual mortality rate of 266,000 people. Arrhythmias, which are often precursors to catastrophic heart failure, are commonly treated using cardiac rhythm management devices (CRMDs), such as cardiac pacemakers or implantable cardioverter defibrillators (ICDs). Pacemakers and ICDS both contain the same basic components: an electrical generator and a conducting lead for transmitting signals to and from the myocardium. Implantable leads are made of metallic (MP35N or stainless steel) conductors, insulating sheath(s) to isolate lead conductors from each other and the surrounding environment, and external electrodes for interfacing the lead with the generator and the myocardium. There are approximately 3 million pacemakers in worldwide use with 600,000 new pacemakers implanted per year [1]. There were over 100,000 ICDs implanted in the USA in 2004 [2, 3].

In situ, CRMD leads are subject to significant stresses that accompany the nearly 37 million annual heartbeats. One of the most common modes of lead failure is conductor fracture, which presents a serious problem because electrical signals may not be transmitted across the large impedances created by a breakage. Also, the electrical interference from overlying muscles could be interpreted by ICD sensing circuitry as an arrhythmic event, triggering unnecessary ICD shocks and possibly inducing fibrillation or fatal cardiac arrest [4]. Lead fracture / failure occurs in 1%-4% of implanted devices over the device lifetime, with annual lead failure rates as high as 1% in all implanted devices [5-10], making this both a costly and dangerous mode of CRMD failure.

Rather than using a solid metal conductor, such as MP35N, we propose the use of a liquid metal, gallium (Ga) or one of its alloys, as a conductive element in a CRMD lead. Ga has good conductivity and a low melting point, 29°C, thus it is liquid at physiologically relevant temperatures, i.e., 35 °C – 40 °C. It is reasonably predicted that leads utilizing liquid Ga as their conducting element(s) will be more pliable than leads containing solid conductors, making Ga-based leads less susceptible to fracture. To explore safety and feasibility of Ga for use in implantable devices, the biocompatibility of Ga was evaluated via a battery of *in vitro* and *in vivo* compatibility tests. Further, liquid metal leads were fabricated by replacing the solid conductors in an existing commercial CRMD lead with Ga or one of its alloys. The electrical impedance was then measured and compared to that of an intact lead. Additionally, the liquid metal leads' ability to transmit pulses from a pacemaker to a resistive load was evaluated.

II. Materials and Methods

A. Ga and Ga Alloy

Solid ingots of highly pure Ga (Recapture Metals) were heated to 37 °C until completely liquefied. For components of the study utilizing a Ga alloy, Ga-In (Indium Corp, 75% Ga, 25% In) was utilized. The Ga-In alloy was examined because of its lower melting point than pure gallium, ensuring liquidity at room and physiological temperatures.

B. Biocompatibility Testing

1) Cytotoxicity

Human umbilical vein endothelial cells (HUVECs, Lonza, passage 5) were cultured in 12-well plates on tissue culture plastic in fully supplemented endothelial growth media (EGM-2MV, Lonza). The cells were cultured at 50% and 100% confluence and allowed to attach overnight. Media was subsequently replaced with fresh EGM-2MV, then

Manuscript received on April 15, 2011.
N. Leahy-Glass is an Engineer with Gallilead, Inc.
W. Combs is a consultant with Gallilead., Inc.
K.L. March is Professor of Medicine, Physiology, and Biomedical Engineering at Indiana University School of Medicine, Indianapolis, IN
Send correspondence to A.M. Kyle at (aaron.kyle.gallilead@gmail.com)

30 µL of liquid Ga, which had been previously sterilized with 70% ethanol, were pipette-dropped onto the cell monolayers; controls did not receive any Ga. The cells were -placed in an incubator (37 °C, 5% CO_2, 100% Humidity) for 24 h and 48 h. At each time point, viability and proliferation were assessed using trypan blue exclusion and hemacytometer counts of the cells.

2) In Vitro Hemocompatibility

A hemocompatibility assay was performed to ensure that Ga does not adversely affect the cellular components of blood. Extracts of Ga were created by boiling liquid Ga in 0.9% saline solution for 1 h (200 mg Ga per mL of saline solution). A negative control was created by boiling an inert plastic sample in saline solution under similar conditions (3 cm^3 of sample per mL of saline). Whole human blood was collected and complete blood counts (CBC), platelets, hematocrit, and platelet indices were quantified. In three tubes, Ga extract and blood were mixed (1:9 extract-blood ratio). Negative and untreated control extracts were mixed at the same ratios (three tubes per condition). The tubes were incubated in a warm water bath at 37 °C for 1 h. Post incubation, CBC values, including platelet, hematocrit, leukocyte, and erythrocyte indices were determined.

3) In Vivo – Intracutaneous Injections of Ga

Liquid Ga was intracutaneously injected into rabbits to examine the acute inflammatory response to Ga exposure. Two rabbits, one male and one female, received intracutaneous injections of 40 µL of liquid Ga (heated to 37 °C) or 0.9% saline solution (control). The Ga was injected on the rabbits' anterior sides, while the control material was injected on the posterior sides. The injection sites were marked with histology ink. The animals were weighed immediately prior to injections and 72 h post-injection. Response was assessed by total body temperature and examination of the injection sites for erythema and edema. Observations were scored according to the Classification System for Scoring Skin Reactions (Draize Scale). Measurements and photographs of the injection sites were obtained immediately pre-dose, immediately post-dose (0 h) and at 24 h, 48 h, and 72 h post dose.

At the end of the observation period, the animals were sacrificed by barbiturate injection. The injection sites were excised and fixed in 10% neutral buffered formalin. After macroscopic examination for inflammation, encapsulation, hemorrhage, necrosis, and discoloration, the tissues were sectioned into histological slides. Slides were stained with hematoxylin and eosin (H&E). A ToxiKon, Inc. pathologist examined the slides and provided a narrative report regarding the injected test article.

C. Unipolar Ga Leads

Portals were created at the proximal and distal ends of a Medtronic 5076-45CM pacemaker lead (6F, 450 mm long). The solid MP35N anodal and cathodal conductors and the leads' inner sheaths were extracted. 20 mm long portions of the solid conductors at the ends were retained to maintain contact between the liquid metal and the interfacial conductors. Two liquid leads, one containing Ga and another containing Ga-In alloy, were created by infusing the metals into the insulating sheaths. The portals were sealed with a medical grade adhesive, forming unipolar Ga prototypes.

D. Impedance Measurements

The impedances of the prototype leads were measured using a current-voltage (I-V) test circuit. Each test lead was connected in series with an ammeter (Fluke 87IIA) and a 500 Ω load resistance to simulate the impedance at the distal electrode-myocardium interface. The series circuit was energized by a sinusoidal constant voltage source whose frequency was varied from 1 Hz – 8 kHz. The differential voltage across the prototype lead was buffered/amplified (AD620, Analog Devices), and the resultant voltage measured using an oscilloscope (Agilent HP33120A). The ratio of the voltage amplitude to current amplitude (Ohm's Law) was used to determine the magnitude of the of the test lead impedances.

E. Pacing Pulse Transmission

Each of the prototypes and an intact 5076-45CM lead were connected to a commercial pacemaker (Medtronic E2DR01 Dual Chamber Rate Response Pacemaker). The lead's distal electrode was connected in series with a 500 Ω load. The voltage across the resistive load was differentially measured for 16 pulse cycles. The resultant measurements were averaged in the time domain to qualitatively compare the signals' transmitted through the Ga prototypes to those through the conventional lead.

F. Statistics

Statistical comparisons were performed using one-way ANOVA with $\alpha = 0.05$.

III. Results

A. Ga Is Biocompatibile

1) Cytotoxicity

The monolayers of HUVECs were microscopically examined at each time point post-Ga exposure. Besides regions where the liquid metal was initially deposited on the cells, there was not an evident adverse effect of Ga on the cell monolayers. Cells in direct contact and proximate to the Ga droplets appeared normal and healthy at both timepoints (see Fig. 1). These observations were corroborated by hemacytometer counts: there were no significant differences in the numbers of cells with Ga exposure compared to controls (Fig. 2, excluding 24 h at 85E3 cells/well which likely resulted from mechanical trauma induced by Ga dropping onto cell monolayers).

Fig. 1 Representative microscopic image (4x) of cells cultured at 170E3/well with exposure to Ga (dark regions) at 24 hours post exposure.

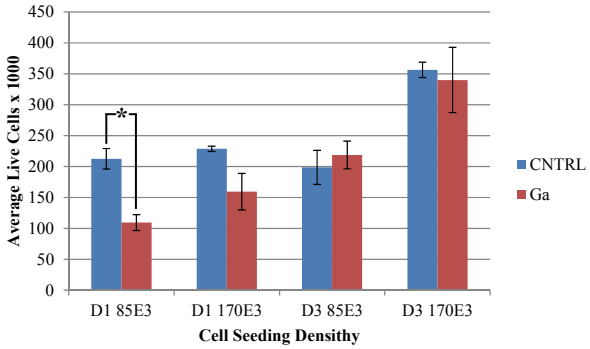

Fig. 2 Mean cell counts (n = 3) from cells exposed to Ga compared to controls (Cntrl). *~ $p < 0.05$.

2) *Hemocompatibility*

For each of the hematological parameters, there was not a statistically significant difference between the Ga extracts and the negative or untreated controls (see Fig. 3).

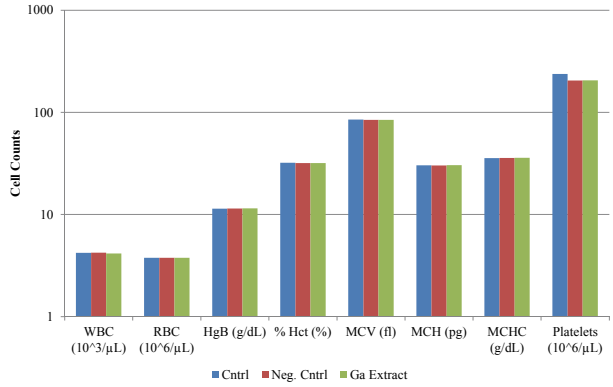

Fig. 3 Mean blood content counts (***n*** = 3) for untreated controls (Cntrl), negative controls (Neg. Cntrl), and Ga extract samples (Ga Extract). The blood contents of interest: WBC ~ White Blood Cell Count, RBC ~ Red Blood Cell Count, HgB ~ Hemoglobin concentration, Hct ~ Hematocrit, MCV ~ Mean Corpuscular Volume, MCH ~ Mean Corpuscular Hemoglobin, MCHC ~ Mean Corpuscular Hemoglobin Concentration, Platelets ~ Platelet Count.

3) *Intracutaneous Injection*

The animals' temperature variations and weight changes throughout the study were minor. There was no visible evidence of erythema, edema, or necrosis at any time point or injection site in either animal: The overall mean scores for the Ga injection and control injection sites were both 0.0 ± 0.0. Macroscopic examination of the tissue sections did not exhibit gross evidence of inflammation, encapsulation, hemorrhage, necrosis, or discoloration. Microscopic examination in Ga tissue samples from both animals displayed particulate materialnear the injection sites. At the interface between the Ga and surrounding tissues there were variable mixed cell infiltrates – primarily granulocytes and macrophages.

B. *Electrical Characterization*

1) *Ga Lead Impedance*

Unipolar Ga and Ga-In lead prototypes were fabricated as previously described. The measured impedances of the liquid metal leads were on the order of 4 Ω and 1 Ω for the Ga and Ga-In, respectively. These impedances were significantly less than the cathodal impedance of a lead containing solid MP35N conductor, which was ~26 Ω. The impedances of the liquid metal leads were fairly consistent throughout the test bandwidth (Fig. 4). Additionally, the outputs voltages across the liquid metal leads were in phase with the input voltage at all frequencies.

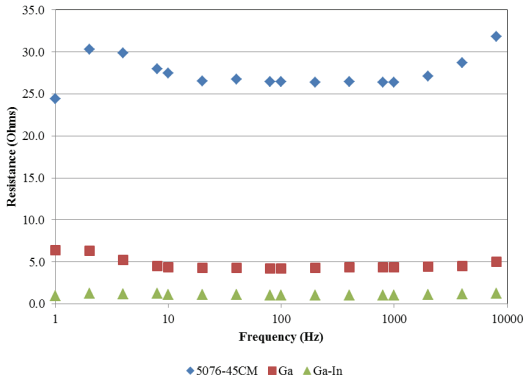

Fig. 4 Measured impedance (resistance) as a function of frequency for Medtronic 5076-45CM, Ga prototype, and Ga-In prototype pacing leads.

2) *Pacing Pulse Transmission*

The average time domain signals in both the Ga and Ga-In leads were in good agreement with the signals observed with the conventional pacing lead: There was no apparent phase or amplitude distortion (Fig. 5).

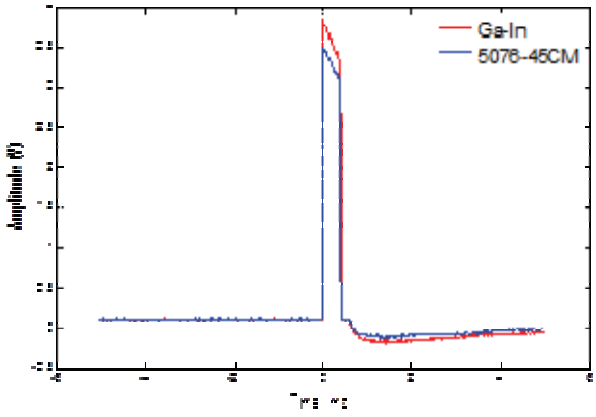

Fig. 5 Average time domain recording (n = 16) of cardiac pacing pulse signals transmitted across Ga-In test lead and conventional lead (5076-45CM) to a resistive load

IV. Conclusions and Future Work

In this study, the biocompatibility and electrical capability of Ga were evaluated to determine if Ga or one of its alloys could be used as the conducting element in CRMD leads. Ga has been used for imaging purposes and explored as potential dental amalgam material [11, 12]; however, its specific biological responses are not well-defined. In our work, acute exposure of Ga to blood did not induce hemolysis or adversely affect total blood cell counts. Additionally, intracutaneous injection of liquid Ga into a mammalian model resulted in a minimal macroscopic inflammatory response. The results indicate that acute exposure to elemental Ga does not induce evident harmful responses.. Accordingly, we conclude that a Ga-based lead would be potentially biocompatible. Of course future iterations of the Ga CRMD leads will be designed and constructed to ensure that Ga does not leak from lead capsule(s). This design feature will be paramount for both the transmission capability of the lead and to minimize the possibility of inflammatory response or potential embolisms that could result from Ga leakage *in situ*.

The Ga lead must be capable of accurately transmitting stimulatory pulses to the myocardium while transmitting cardiac electrograms from the heart. Impedance measurements show that the Ga and Ga-In leads were primarily low magnitude, resistive impedances. These outcomes were desirable to ensure reduced losses with transmission across the lead. Primarily resistive Ga leads are also highly desirable because they will minimize distortion that may occur with transmission of the multi-band pacing or defibrillation pulses.

It was noted that the Ga leads' impedances were (a) significantly lower than those of an intact solid lead and (b) that the amplitudes of pacing pulses transmitted through these leads was larger than their solid lead-transmitted counterparts. These results were not unexpected and are clearly interrelated. The lower impedance with the Ga lead is due to a combination of material and configuration properties of these leads. Let us consider the lead as a wire resistance, R, whose magnitude can be determined using:

$$R = \rho l / A \qquad (1)$$

Where $\rho \sim$ conductor resitivity (Ω•cm), $l \sim$ conductor length (cm), and $A \sim$ conductor cross-sectional area (cm^2). Ga has a lower resistivity than MP35N (17.4 μΩ•cm vs. 103 μΩ•cm). The Ga conductor fills the entire lumen of the lead's insulating sheath, a diameter of 2 mm compared to 254 μm of MP35 wire. Finally, the MP35N wire is typically coiled in multifilar strands in the lead sheath, providing redundant current paths, but also forming a significantly longer conduction path than a single column of Ga. This combination of factors makes the Ga lead less resistive, effectively shorter, and effectively larger in cross-sectional area than a solid metal conductor lead. As a result of the decreased impedance, less of the stimulatory pulse is lost due to i^2R losses that occur with transmission through the lead. Increased efficiency was manifested in the average pulse recordings, where it was observed that the amplitudes of pulses transmitted through the Ga leads were greater than those transmitted through the solid conductor. It is predicted that the increased efficiency will be particularly relevant with ICDs, where the impedance of the lead (2 Ω - 6 Ω) is comparable to the load impedance (50 Ω). The resultant improvement in energy efficiency with Ga leads may have substantial effects on the strength of shocks, number of shocks that can be administered during device lifetime, or battery/ICD size.

Utilizing these highly encouraging preliminary results, efforts are underway to evaluate the design feasibility and ultimate utility of a Ga-based leads for CRMDs. Modern CRMD leads are multipolar. Thus, we are developing multi-lumen, co-axial Ga leads, in which the liquid metal forms both the anodal and cathodal paths. These leads will be subjected to similar electrical testing as that described in this report. Future prototypes will be subjected to cyclical load testing to simulate the deformations experienced by a lead during cardiac contractions. The mechanical testing will empirically demonstrate the improved durability of these leads. The results of these studies will form the basis for the design of a Ga lead prototype that will be appropriate for further pre-clinical testing.

References

[1] M. A. Wood and K. A. Ellenbogen, "Cardiac Pacemakers From the Patient's Perspective," *Circulation,* vol. 105, pp. 2136-2138, May 7, 2002 2002.

[2] R. G. Hauser, "Monitoring an Imperfect Lead," *Pacing and Clinical Electrophysiology,* vol. 32, pp. 541-542, 2009.

[3] M. Josephson and H. J. J. Wellens, "Implantable Defibrillators and Sudden Cardiac Death," *Circulation,* vol. 109, pp. 2685-2691, June 8, 2004 2004.

[4] P. P. Borek and B. L. Wilkoff, "Pacemaker and ICD leads: Strategies for long-term management," *J Interv Card Electrophysiol,* vol. 23, pp. 59-72, 2008.

[5] E. Alt, R. Volker, and H. Blomer, "Lead Fracture in Pacemaker Patients," *Thorac. Cardiovasc. Surgeon,* vol. 35, pp. 101-104, 1987.

[6] S. Hecht, R. Berdoff, A. Van Tosh, and E. Goldberg, "Radiographic pseudofracture of bipolar pacemaker wire," *Chest,* vol. 88, pp. 302-304, August 1985 1985.

[7] H. Olgun, T. Karagoz, A. Celiker, and N. Ceviz, "Patient- and lead-related factors affecting lead fracture in children with transvenous permanent pacemaker," *Europace,* vol. 10, pp. 844-847, July 1, 2008 2008.

[8] G. Tyers, P. Mills, J. Clark, M. Cheesman, J. Yeung-Lai-Way, and R. Brownlee, "Bipolar leads for use with permanently implantable cardiac pacing systems: a review of limitations of traditional and coaxial configurations and the development and testing of new conductor insulation, and electrode designs," *J Invest Surg,* vol. 10, pp. 1-15, 1997.

[9] A. Udyavar, U. Pandurangi, K. Latchumandhas, and A. Mullasari, "Repeated fracture of pacemaker leads with migration into the pulmonary circulation and temporary pacemaker wire insertion via the azygous vein," *Journal of Postgraduate Medicine,* vol. 54, pp. 28-31, 2008.

[10] B. L. Wilkoff, "Lead failures: Dealing with even less perfect," *Heart Rhythm,* vol. 4, pp. 897-899, 2007.

[11] V. Psarras, A. Wennberg, and T. DÃ©rand, "Cytotoxicity of corroded gallium and dental amalgam alloys: An in vitro study," *Acta Odontologica Scandinavica,* vol. 50, pp. 31-36, 1992.

[12] J. Wataha, H. Nakajima, C. Hanks, and T. Okabe, "Correlation of cytotoxicity withh elemental release from mercury- and gallium-based dental alloys *in vitro*," *Dental Materials,* vol. 10, pp. 298-303, 1994.