Utility of Monophasic Action Potentials in the Diagnosis and Treatment of Cardiac Arrhythmias

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Dedication

This thesis is dedicated to my parents, Tom and Rhonda. Thank you both for ensuring I had everything I needed to make my dreams a reality.
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Thesis Summary

The object of this thesis was to investigate applications for monophasic action potential (MAP) recordings in the diagnosis and treatment of cardiac arrhythmias. To meet this objective, MAPs were measured in situ and in vitro, during sinus rhythm and cardiac arrhythmias. MAPs were analyzed for potential clinical applications and in novel cardiac mapping and ablation catheter concepts.

MAPs are focal action potential recordings which are directly proportional to the electrical activities of cells adjacent to a contacting electrode. When sufficient force is applied between a contacting electrode and the myocardium, the cells directly beneath become mechanically depolarized; i.e. electrically inactive. As a transmembrane action potential passes through this region, a change in boundary currents between the active and inactive cells, via gap junctions, results in a waveform that is proportional to the original action potential.

The Visible Heart® Apparatus provides us with the ability to study large mammalian hearts, including human, in an in vitro setting; allowing the testing of prototype catheter concepts prior to in situ or in vivo work. To validate MAPs from an in vitro working heart model a comparison study was conducted. Over the course of 2 hours in situ and 2 hours in vitro MAPs were recorded from the right atrium, left atrium, and right ventricle (endocardially and epicardially). Overall, there were no significant differences between recorded signals when compared to in situ baseline recordings. Based on these findings,
systems like the Visible Heart® Apparatus can be used as a platform on which cardiac action potentials can be studied.

The clinical application of MAP recordings, as they pertain to radiofrequency (RF) ablations, was also evaluated. To ensure proper lesion formation, RF ablation requires a catheter contact force (CF) of between 10-20 grams to be maintained throughout energy delivery. It was determined that MAP waveforms could only be recorded when at least 10-15 grams of CF was applied to the myocardium. In other words, the presence of MAP waveforms would indicate that sufficient CF has been applied prior to the delivery of RF energy. Additionally, MAP waveforms were found to correlate with RF lesion size. MAP amplitudes at baseline (pre-ablation) were significantly larger than amplitudes from lesions which matured to greater than 1 mm deep. MAPs were also able to distinguish between lesions between 1-2mm deep, and those deeper than 2mm. Moving forward, MAPs may be used in evaluating cardiac viability, both through recording from induced lesions, as well as in regions of scarred or ischemic myocardium.

Finally, several novel catheter concepts for the recording of MAPs were designed and tested in situ and in vitro. Endocardial MAP recording concepts included catheters designed to target the pulmonary veins and surrounding atrial substrates. Additionally, an epicardial mapping system was developed for detecting ventricular tachyarrhythmias. All concepts illustrated an ability to elicit MAP recordings, however future catheter iterations should focus on optimizing the electrode-tissue interface, as well as the placement of a non-contacting reference electrode.
Section I: The Visible Heart® project as a platform for monophasic action potential recordings

The focus of this section is validating the Visible Heart® project as a viable in vitro platform for the study of monophasic action potentials (MAPs). For the study of electrophysiology catheters, it is critical for the conduction properties of the in vitro specimens to be unaltered from their intrinsic state.

First, in this section I will present the current and historical perspectives on, and utilities of, MAP recordings. I will discuss how these waveforms can be implemented in conjunction with Visible Heart® methodologies to facilitate the rapid prototyping and development of novel catheters for the diagnosis and treatment of tachyarrhythmias, such as atrial fibrillation and ventricular tachycardia.

Secondly, I will describe a validation study comparing in situ MAP recordings to those recorded in vitro, or on the Visible Heart® apparatus. This study provides information on the ability to record MAPs for several hours in situ and in vitro. It also shows the relationship between endocardial and epicardial waveforms from the right ventricle. Finally, this study can provide insight on how MAPs recorded from reanimated human hearts can translate to the clinical setting.
Using the Visible Heart® for studying cardiac monophasic action potentials and evaluating their underlying mechanisms

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Preface

We were invited to write a review article on the utility of the Visible Heart® Laboratory and the latest research we have been performing. We chose to write this review on monophasic action potentials and Visible Heart® applications for prototype mapping and ablation catheters.

The following manuscript provides a detailed review of current and historical literature associated with the recording of monophasic action potential (MAPs). MAPs have been used for a variety of clinical applications: e.g. action potential alternan mapping, arrhythmia susceptibility, lesion assessment and tissue viability. Using Visible Heart® methodologies, we are able to study these applications on a unique pre-clinical platform; with the added capability of in vitro human heart comparisons.

I was responsible for the literature search conducted and documented in this section. I was also responsible for recording the MAP waveforms used in Figure 2. The arrhythmias collected and shown in Figure 3 were collected during a protocol where Dr. Tinen Iles, Maria Seewald, and I simultaneously evaluated cardiac viability through
different methods. Additionally, Dr. Mark Benscoter and I worked together to collect the contact force and MAP data represented in Figure 4. Finally, I developed the prototype catheter seen in Figure 5 with the technical expertise of Julia Campion (Medtronic, Mounds View, MN), Carla Pfeiffer (Medtronic), and Gonzalo Martinez (Medtronic).
**Summary**
The Visible Heart® approach is a platform that allows for direct visualization and imaging of catheters inside of isolated large mammalian hearts. Over the last 20 years more than 1800 porcine, 10 mini-pig, 14 ovine, 14 canine, and 80 human hearts have been reanimated using this technology. This review describes the utilization of the Visible Heart® methodology as it relates to electrophysiologic studies to investigate the recording of monophasic action potentials (MAPs). We will describe the history and proposed mechanisms behind how MAPs are recorded, new catheters for recording these signals, and finally how we can utilize the Visible Heart® methodology to develop and test new MAP recording technologies for electrophysiologic investigations.
Historic perspective
In 1882, the first report of cardiac monophasic action potentials (MAPs) was described by Burdon-Sanderson and Page [1]. Using two electrodes, one on healthy intact myocardium and the other on a nearby injured area, they recorded the first documented MAP waveform. In 1931 Schültz proposed another method of inducing focal myocardial injury, the Herzknoten or heart knot, where a tie was used to prevent local prefusion and produce the injury current [2, 3]. These original studies on MAP waveforms contributed to the belief that MAPs were only produced as a result of injury to the myocardium [2, 4, 5].

Schültz continued his work, and in 1934 he created the first suction electrode technique for documenting reproducible cardiac MAP recordings [5]. Importantly, in 1969, this was taken a step further by recording in situ MAPs from the human ventricular endocardium, using a suction based catheter [6]. This pioneering work was then continued in humans, by Olsson et al., primarily on the right atrium [7, 8]. Despite these preliminary studies, and the development of transvenous catheters, such as those used by Stroobandt, the suction electrode technique was never widely adopted due to multiple concerns regarding patient safety [7, 9, 10]. Ultimately, the risks to the patients associated with using the suction-based catheters were deemed too great despite the identified and discussed clinical benefits that recorded MAP waveforms provided clinicians. However, thanks to the persistent work in this field by numerous subsequent cardiologists, scientists and device design engineers, MAPs can now be recorded safely and reliably in patients with contact catheters thereby opening the door to endless possibilities for improved patient outcomes.
The monophasic action potential recording electrode controversy

In general, it is considered that MAPs are the result of a bipolar recording between two electrodes, where one electrode is located on inactive (blanked or injured) myocardium, and the second electrode is not. The latter could be on viable myocardium or not contacting the tissue at all but is electrically coupled via blood or another conductive medium to the former. Because bipolar MAP waveforms can only be recorded when two nearby electrodes are employed, it has been unclear which one is primarily responsible for the MAP recording. For example, Franz described in his 1999 review – “the extracellular nature of MAP recordings leads to debate over the electrode responsible for recording the waveforms, though many agree that the truth likely is a combination of both” [9]. About five years later Kondo et al. proposed a secondary theory in response, to what they called a “disagreement between these concepts” [11]. In response to these papers and many more, a multitude of studies were conducted over several years in an attempt to conclusively state which electrode, or more specifically “the myocardial electrical activity near which electrode”, was responsible for the resultant recorded MAP waveform. These studies have included a range of observations and conclusions stating MAPs can be the result of: 1) electrical activities near either or both electrodes, 2) injury currents, 3) superimposed electrograms, and/or 4) hybrid action potentials, just to name a few [12-20]. Nevertheless, these studies cumulatively have shown that the origin of the MAP recordings may be more complex than originally thought. Despite many of the aforementioned studies’ claims that one electrode or the other is the definitive source, the truth – as pointed out by Franz – is likely a combination of many of these theories. Nevertheless, all will agree as to the potential clinical investigational values of recording
these focal myocardial waveforms.

**Theories for relative electrode configurations**

As Schültz was introducing the suction electrode method for recording MAPs, another approach was also being simultaneously tested. In 1935, Jochim et al. reported that cardiac MAPs could be recorded by simply pressing a recording electrode against the myocardium [21]. Though discovered in the 1930s, the contact electrode technique was largely undeveloped as a clinically useful method until 1980, when Franz conducted a series of studies where he and colleagues were able to show that MAPs could be recorded by applying gentle pressure with a nonpolarizable electrode to the myocardium [22, 23]. This discovery that MAPs could be recorded without the need of a suction electrode, or the induction of myocardial injury, then opened the door for clinically safe MAP recordings in situ in humans. In addition to reduced patient risks, the contact electrode technique allowed physicians to record MAPs which were found to be stable over several hours. More recently, our lab has performed both in situ and in vitro studies (the latter employing Visible Heart® methodologies) where we have shown that MAPs recorded via the contact electrode technique can be done so both endocardially and epicardially for at least 2 hours with minimal catheter adjustments [24].

The contact electrode technique was supported largely by Franz’s work on the volume conductor theory, where it is claimed that MAP recordings are the result of changes in boundary currents [2, 9]. Franz drew these conclusions based on two key points: extracellular resistances have no influence on the recorded MAP waveforms and the relative numbers of cells contributing to a given MAP waveform has an impact on the
signal amplitude [2, 9]. Shown in Figure 1 is an illustration showing Franz’s hypothesis based on this theory. As the transmembrane action potential (TAP) passes the contact electrode, the boundary currents between the electrically active and inactive tissue are altered; the resulting waveform, or MAP recording, is then directly proportional to the original TAP.

Figure 1. The contact electrode technique for monophasic action potential (MAP) recordings is documented. In the diagram, the transmembrane action potential (TAP) can be seen propagating past the tip electrode, causing changes in the boundary currents. The result is a MAP which is directly proportional to the underlying TAP waveform. Figure taken from: M. R. Franz, “MAPs recorded by contact electrode method,” in Monophasic Action Potentials Bridging Cell and Bedside, Armonk, New York: Futura Publishing Company, 2000.

To the contrary, using an arterially perfused tissue wedge, Kondo et al. presented a scenario in which, by recording intracellular action potentials and traditional MAPs, they concluded that the contact, or KCl electrode in their study, was not the recording electrode; but in fact, it was the opposite, or the noncontact electrode which was the critical component in the resulting waveform [11]. This work also explored Franz’s
theory that the MAP sees deep into the tissue through an injection of ATX-II, which prolongs action potentials, directly beneath the contact electrode (about 3-4 mms deep) [9, 11]. However, it is important to point out that according to Franz’s theory, the cells directly beneath the catheter are inactive – and are never stated to be responsible for the MAP properties, it is the cells adjacent to the contact electrode which are responsible for the MAP and its corresponding properties [2, 9].

**Clinical applications & utility**

Over the last 50 years, the prospect of recording MAPs from human heart tissue in situ has gone from a risky consideration to, for some, the “method of choice for evaluating repolarization” [19]. Specifically, Franz has illustrated many of the reasons why the monitoring of MAPs can or would be advantageous to evaluate cardiac electrical activity over electrograms or intracellular action potential recordings [9]. Numerous studies have documented the utility of recording MAPs in clinical scenarios, including: 1) to assess repolarization behaviors for conditions such as long-QT, or 2) the study of focal action potential behaviors in patients presenting with alternans during and atrial fibrillation (AF) [25-30]. Summarized in Table 1, are the reported MAP waveform properties documented for a variety of investigations performed on various species and/or with different recording catheters and techniques. Furthermore, we have been able to record MAP waveform properties from multiple locations throughout human heart so to critically study the heart’s conduction pathways: Using Visible Heart® methodologies on reanimated human hearts, we were able to record representative MAP waveforms from atrial and ventricular locations. Distinct waveform changes can be seen between all
recorded MAPs; specifically, the nodal like waveforms recorded from near the bundle of His (Figure 2).

Table 1. Monophasic action potential properties reported from literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Endocardial / Epicardial</th>
<th>Location</th>
<th>Cycle Length (msec or bpm)</th>
<th>APD90 (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right Ventricle</td>
<td>250 msec Right Atrium pace</td>
<td>174±16.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right Ventricle</td>
<td>400 msec Left Ventricle pace</td>
<td>227.5±13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Right Ventricle</td>
<td>250 msec Left Ventricle pace</td>
<td>160±14.7</td>
</tr>
<tr>
<td>Kongstad 2005 [74]</td>
<td>Swine</td>
<td>Endocardial – pre sternotomy</td>
<td>Left Ventricle</td>
<td>500 msec Right Atrium pace</td>
<td>277±20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left Ventricle</td>
<td>500 msec Right Atrium pace</td>
<td>292±19</td>
</tr>
<tr>
<td>Tsuburaya 2011 [75]</td>
<td>Swine</td>
<td>Endocardial</td>
<td>Left Ventricle</td>
<td>140±8 bpm</td>
<td>329±9</td>
</tr>
<tr>
<td>Bristand 2012 [76]</td>
<td>Wistar Rat</td>
<td>Epicardial</td>
<td>Ventricular (non-specific)</td>
<td>270±52 msec</td>
<td>60.3±5.4</td>
</tr>
<tr>
<td></td>
<td>Guinea Pig</td>
<td>Epicardial</td>
<td>Ventricular (non-specific)</td>
<td>223±21 msec</td>
<td>127.7±15.3</td>
</tr>
<tr>
<td>Osadchii 2012 [33]</td>
<td>Guinea Pig</td>
<td>Endocardial</td>
<td>Left Ventricle</td>
<td>550 msec Left Ventricle pace</td>
<td>175±3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epicardial</td>
<td>Left Ventricle</td>
<td>550 msec Left Ventricle pace</td>
<td>169±2</td>
</tr>
<tr>
<td>Narayan 2011 [28]</td>
<td>Human (Persistent AF)</td>
<td>Endocardial</td>
<td>Atrial</td>
<td>411±94 msec</td>
<td>223±51</td>
</tr>
<tr>
<td></td>
<td>Human (Paroxysmal AF)</td>
<td>Endocardial</td>
<td>Atrial</td>
<td>372±72 msec</td>
<td>260±37</td>
</tr>
<tr>
<td></td>
<td>Human (Sinus Rhythm)</td>
<td>Endocardial</td>
<td>Atrial</td>
<td>218±30 msec</td>
<td>181±24</td>
</tr>
<tr>
<td>Fossa 2007 [42]</td>
<td>Guinea Pig</td>
<td>Epicardial</td>
<td>Left Ventricle</td>
<td>241±7 msec</td>
<td>138±4</td>
</tr>
<tr>
<td>Osadchii 2009 [77]</td>
<td>Guinea Pig</td>
<td>Epicardial</td>
<td>Right Ventricle</td>
<td>188±6 bpm</td>
<td>134±5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epicardial</td>
<td>Left Ventricle</td>
<td>188±6 bpm</td>
<td>129±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 msec Ventricle pace</td>
<td>54±5</td>
</tr>
</tbody>
</table>
The study of restitution dynamics is one area where cardiac MAPs have provided users with more information on arrhythmias, than a typical clinical electrogram. Initially, Kim et al. set out to test if AF in humans, was related to the slope of the action potential duration (APD) restitution kinetics, and/or how that relationship could vary with chronic vs. paroxysmal AF [31]. Importantly, they observed that the APD restitutions were steeper in patients with AF, verses controls [31]. This publication was followed less than a year later by a report describing the implications of a steeper vs flatter restitution curve, and which of these factors was more indicative of arrhythmias [32]. In addition to the clinical applications, MAPs have been used to study and understand methods to test...
restitution kinetics in both preclinical and translational models. For example, Osadchii, in 2012, conducted a MAP study utilizing extra-systolic stimulation for generating restitution curves which provided results that deviate from those seen when dynamic pacing is used [33]. MAP restitution properties have also been studied with various global mapping models, such as that by Kalb et al., showing further potential for assessing focal arrhythmias [34]. They further described the abilities of MAP recordings to provide information on focal restitution properties, which in turn could be critical in the diagnosis and treatments of arrhythmias. Through further studies, MAP recordings could be used to tailor treatments based on a patient’s observed restitution kinetics to develop a more personalized course of medical treatment.

The recording of MAPs has also been used extensively for the study of the clinical arrhythmias through action potential alternans: much of this research being performed by Narayan and his co-workers [27, 28]. In one of their patients with atrial flutter, MAPs were recorded during atrial pacing and they were able to show that APD rate maladaptation at the isthmus lead to alternans which could further disorganize causing either atrial flutter or AF [27]. Narayan also conducted a MAP study on 33 individuals showing APD alternans were more pronounced in more advanced stages of AF (persistent vs paroxysmal) [28]. In addition to these studies, work has also been done on the use of spectral analysis of MAP alternans to help identify specific patients who would be more likely to have substrates for AF [26]. This work and many more studies are summarized in a 2012 review by Franz [25]. In a manner similar to those mentioned above, the use of MAPs in today’s electrophysiology (EP) lab may lead to more tailored
treatment for all types of arrhythmias. Employing these technologies, it may be possible to predict individuals who are at higher risk for AF, which could lead to earlier diagnosis, treatment, and ultimately a higher quality of life for patients.

As previously mentioned due to their ability to represent the underlying transmembrane action potential, MAPs recording in novel groups of patients may provide unique insights into abnormal myocyte repolarizations (also known as repolarization syndromes). For example, Blana et al. have conducted studies with mice genetically modified to express long QT syndrome type 3: they concluded that this model for long QT demonstrated both structural and electrophysiologic changes in atrial substrates [35]. Similarly, Shimizu et al. conducted some early studies on long QT syndrome and, through the study of afterdepolarizations, concluded that both verapamil and propranolol could help improve these abnormalities [36]. Interestingly, verapamil and propranolol have also been studied by other researchers, focusing on the ability to re-create a Brugada like action potential [37-40]. Recently, using Visible Heart® methodologies, we have initiated similar studies to generate Brugada-like action potentials in the right ventricular outflow tract of reanimated large mammalian hearts. This model would allow us to monitor the focal and global applications of a variety of current and novel therapies for the treatment of early repolarization diseases.

The study of MAP properties, could be greatly beneficial in the development and understanding of both new and existing chemical compounds. For example, previously Kägström et al. studied 12 different drugs with known effects on ventricular repolarization, to evaluate MAPs from guinea pigs compared to the known response in a
dog model [41]. Fossa et al. furthered this research by using the guinea pig model to
demonstrate that Azithromycin as a standalone therapy, as well as in combination with
chloroquine, had no additional arrhythmia risk [42]. Additional drug studies, with MAP
verification, include those by Tabo et al. in 2007, on delayed ventricular repolarization,
and by Cheng et al. in 2011, on the effects of estradiol and progesterone [43, 44]. More
recently, it was described that MAP recordings could also be used to link changes in
electrocardiograms to potential causes through torsadogenic drugs [45]. This research
highlights that as our understanding of arrhythmias evolves, so do the agents we treat
them with. Incorporating the study of MAPs with the testing and development of these
agents could lead to a more detailed understanding of their impact, and consequently the
potential side effects.

The ability to assess tissue viability and ablation lesions was initially studied with MAPs
in 1984, by Franz et al.; they elicited MAP recordings in 41 dogs from ischemic and
healthy regions of epicardial and myocardial tissue [46]. Franz was able to demonstrate
MAP recordings were able to more accurately identify regions of myocardial ischemia
than the study of the ST segment, and were also less dependent on the length of ischemic
time [46]. Studies from our lab were not only able to confirm these early studies but also
expand on them through the employment of multi-modal imaging allowing for direct
visualization of the contact site. In a recent study, we showed that one only needed an
applied MAP catheter force of approximately 7.6 grams to reproducibly record MAPs
over sustained periods; this was then applied to the recording of MAPs from lesions on
the endocardial surface of the left atrium in a reanimated heart [47]. Coupled with the
Visible Heart® imaging, we were able to show the lack of MAP recordings on tissue that had been ablated, through direct visualization with endoscopes. In other words, we consider here that MAPs are able to easily distinguish between focal regions of healthy and ischemic myocardium; depending of catheter design this discrimination ability can be within millimeters: thus, an ablation catheter, with the ability to record MAPs, would provide physicians with feedback related to the device tissue interface as well as tissue viability before and after the applied therapy.

**Visible Heart® methodologies for electrophysiologic investigation**

Visible Heart® methodologies have been employed by our laboratory for over two decades, utilizing the study of large mammalian hearts under physiologic conditions coupled with imaging from endoscopes inside the heart to provide direct visualization of the device tissue interface. The original publications detailing the perfusion methods for large mammalian heart reanimation using a clear perfusate were published in 2000, by Chinchoy et al. (employing animal hearts) and in 2005 by Hill et al. in which human hearts were reanimated: these methods will be described briefly in the following paragraphs [48].

For the study of recovered/reanimated large mammalian hearts, either healthy animals, those eliciting specific cardiac pathologies, or with prior placed cardiac devices are placed under general anesthesia (mean alveolar concentration > 1.2) and ventilated using positive pressure ventilation. Next, a median sternotomy is performed and a cardioplegia cannula is inserted into the ascending aorta to administer a high potassium cardioplegia solution to the heart in a Langendorff perfusion, whilst cooling the organ prior to
excision. As required for reanimation, the major vessels (aorta, superior and inferior vena cava, pulmonary veins, and pulmonary arteries) are cannulated. The heart is then flushed with a modified Krebs-Henseleit buffer and attached to the Visible Heart® apparatus. The heart is continuously perfused and warmed to 37° C during which spontaneous electrical activity will typically occur. Once the ventricular myocardium has reached normothermic temperatures, defibrillation shocks (typically at 34 J) are applied to elicit sinus rhythm: in rare instances spontaneous electrical activity will organize into sinus rhythm without the application of an external shock. At this point the heart is considered to be functioning, using intrinsic conduction pathways with no pacing or electrical stimulation being required. Endoscopes can then be inserted into the various cannulated vessels and the internal anatomy imaged while electrical signals, including MAPs, from a multitude of locations are simultaneously recorded [24, 47, 49-51]. The employed procedures and protocols have been reviewed and approved by the University of Minnesota Institutional Animal Care and Use Committee and ensure humane treatment of all animals as indicated by the “Guide for the Care and Use of Laboratory Animals” from the National Institutes of Health (NIH).

Our laboratory continues to reanimate and study human hearts that were not deemed viable for transplant [52, 53]. Consent for research use is obtained by LifeSource (Minneapolis, MN, our local organ procurement agency) who also assists with procurement and transportation of the organs to our laboratory within 4-6 hours. Again, using typical transplant procedures, these hearts are excised and placed on ice for transport. Upon arrival, each patient’s gifted heart is cannulated and re-perfused and
reanimated, in the manner described above. These research protocols have been reviewed and approved by the Institutional Review Board, Human Subjects Committee at the University of Minnesota.

**Transcatheter electrophysiologic studies**
Using the described Visible Heart® methodologies, we have been able to uniquely study the device tissue interface using a variety of imaging modalities simultaneously. This enables us to directly visualize how both clinical and prototype catheters interact with the tissue alongside how these catheters would be visualized clinically. Relative to EP studies, our laboratory has utilized the Visible Heart® methodologies extensively in the study of both traditional pacing, with one or multiple leads, and more recently with transcatheter delivered leadless pacemakers [54-58]. We also have utilized clinical EP systems to recorded multiple electrical waveforms during an array of cardiac ablation technologies [47, 49, 59-61]. While these studies focus on how conduction pathways were modified through various cardiac therapies (pacing or ablation), the intrinsic, focally recorded conduction patterns have only recently been explored using Visible Heart® methods.

**Monophasic action potentials from reanimated large mammalian hearts**

**Translational research**
Over the last 5 years, the study of MAPs using the Visible Heart® methodologies has been an area of interest. Within this broad spectrum of research one area of particular interest has been the recording of MAPs from a variety of anatomical locations in the reanimated animal and human hearts. To establish baseline comparisons, MAPs were recorded in situ (in the animal) and in vitro (on the Visible Heart® apparatus), from an
array of locations, for up to two hours. We consistently observed that in situ and in vitro MAP waveform recordings over a 2-hour recording period were not significantly different in action potential duration when compared to their baseline in situ recordings [24, 51]. While this work was conducted on swine hearts, it shows that intrinsic conduction pathways and properties are preserved during the reanimation process. This in turn gives us an indication that the MAP recordings obtained in reanimated human hearts would be a realistic representation of those that which would be recorded in a clinical case. It is important to note that the human hearts are deemed non-viable for transplant often because of histories of cardiac disease, myocardial infarcts, or prolonged cardiac downtime. Nevertheless, the use of MAP recording in such cases may be a means to study the pathophysiological behavior of these conditions: i.e. mapping a region of infarct. Additionally, this study also showed a direct beat-to-beat comparison of right ventricular signals recorded from juxtaposed endocardial and epicardial locations [51]. The study of MAPs from the juxtaposed ventricular locations can be directly translated to the study of dispersion of ventricular repolarization; i.e. in the study of Brugada Syndrome where the epicardial and endocardial surface repolarize differently.

*Enhanced understanding of electrophysiology assessments in reanimated hearts*

Through the use of Visible Heart® methodologies our laboratory has been able to place catheters capable of MAP recordings in specific locations, with high accuracy. These locations, both endocardial and epicardial can then be imaged using direct visualization with endoscopes or cameras, and/or simultaneously with fluoroscopy. To date, in several human hearts (n=7) that were reanimated, MAPs were collected from a variety of both endocardial and epicardial locations, as well as on the left and right sides of a given heart.
Using the MAPs collected we were able to construct a diagram illustrating these typical MAP recordings and their corresponding anatomical imaging. The results from these studies can be seen in Figure 2. Notably, bundle of His elicited more dome-like, slow response, action potentials while more traditional fast response action potentials were elicited from the contractile myocardium (both atria and ventricles).

**Monophasic action potential recording for the study of arrhythmias**

In addition to studying reanimated hearts in sinus rhythms, we have been able to collect a significant amount of data recorded during arrhythmias. Recording MAPs during elicited arrhythmias may provide more information on how arrhythmias originate and how they can best be terminated. Swine are known to be a fairly arrhythmogenic species, and during our studies we have recorded a variety of arrhythmias. For arrhythmias studies, MAPs were recorded from four catheters simultaneously: one endocardial right atrial (RAn), one epicardial left atrial (LAp), and two right ventricular catheters (one endocardial, RVn, and one epicardial, RVp). Recordings during sinus rhythm show the activation pattern, and characteristic waveforms for each of the four catheter locations (Figure 3A). Premature ventricular contraction (PVC) are easily inducible in swine through external mechanical stimulation, in Figure 3B it can be see that the RVp MAP (most near the stimulus, or PVC origin) activates first, followed by the RVn catheter. The following atrial contraction does not elicit a ventricular contraction, due to the cells being in a refractory period. Finally, AF is induced through a burst stimulus in the left atrial appendage (note this can be done both in situ and in vitro); see Figure 3C. This rhythm strip shows a heart in AF spontaneously terminating into a sinus pattern. Through studies like these, evaluating multiple MAP recording catheters simultaneously coupled with
Visible Heart® imaging platforms and methodologies, we can better understand these arrhythmias, and how to better diagnosis and treat them.

Figure 3. Shown here are monophasic action potential recordings from the right atrium endocardium (RAn), left atrium epicardium (LAp), and right ventricle endocardium and epicardium (RVn and RVp respectively). The top strip (A) shows the heart in sinus rhythm. The RAn can be seen activation prior to the LAp, and the RV signals occur almost simultaneously. In strip B a premature ventricular complex, indicated by the arrow, was induced through external mechanical stimulation. In strip C the heart is initially in atrial fibrillation, the rhythm organizes and spontaneously terminates near the end of the recording (see arrow).

**Visible Heart® methodologies in the study of cardiac ablations**
The Visible Heart® methodologies have also been used in studying cardiac ablation techniques and outcomes. The Visible Heart® has been utilized in studying multiple aspects of cardiac ablation. Studies have been published on topics ranging from transseptal puncture techniques, perforation forces during ablation, visualization of steam...
pops, and lesion integrity to name a few [59, 60, 62-64]. Most recently MAPs have been
used, in combination with the Visible Heart®, to study the transmurality and continuity
of lesions. In a 2015 publication by Benscoter and Iaizzo, they fixed a fiber Bragg
grating adjacent to a MAP4 (Medtronic, LLC., Dublin, Ireland) catheter (Figure 4A, B).
Using the Visible Heart® preparation, they were able to create linear lesions using
radiofrequency energy on the endocardial surface, specifically a mitral isthmus line. They
then advanced the MAP recording catheter (and the attached fiber Bragg) and recorded
the amount of force required to elicit MAP like waveforms. In areas where no MAPs
were elicited the applied force was also recorded. This method for correlating catheter
contact force with a fiber Bragg was also used to assess catheter angle, with respect to
MAP waveforms (Figure 4C). The authors concluded that MAPs could be elicited from
viable myocardium when around 10 grams of force was applied to the tissue [63]. We
have continued this work in the Visible Heart® lab and have further concluded that the
optimal range to elicit and record MAP waveforms is between 10 and 15 grams [64]. This
force ranged is aligned with the acceptable range for contact forces for RF ablation and
illustrates that MAPs can be used to supplement those recordings.

Figure 4. A) Shown here is an illustration of the MAP4 catheter and attached Fiber Bragg as described in
Benscoter’s work [63]. B) This configuration was then used to assess monophasic action potentials
recorded from an endocardial left atrial line, correlating the recordings with contact force [63]. C) This
method of contact force assessment, in combination with the MAP4’s distinct tip electrodes, could be used
to determine catheter orientation.
Visible Heart® methodologies for prototype catheter testing
Combining our ability to record MAPs on a clinical EP system, with the unique visualization capabilities of the Visible Heart® approach, provides a platform on which concepts and prototype catheters can be rapidly designed, tested, and re-configured. This is most evident though the ability to directly visualize the catheter/device and study how it interacts with the active or inactive myocardium. To illustrate this concept, we have employed a research MAP recording catheter, the MAP4, and placed it into the right ventricle of the reanimated heart. Because of the MAP4 catheter’s tip design with 4 distinct recording (spherical tip) electrodes we were able to determine catheter orientation relative to the myocardium through the recording of MAPs from each tip electrode. In Figure 5A, a MAP catheter can be seen with 2 electrodes clearly embedded in the myocardium, and 2 electrodes not contacting myocardium; this results in MAP recordings from only 2 of the 4 tip electrodes. When the catheter is adjusted slightly (Figure 5B) all 4 electrodes become in good contact with tissue, and MAPs are recorded from all tip electrodes [50].

Figure 5. Shown in this figure are captures from video footage collected using the Visible Heart® apparatus to visualize the device tissue interface. A) The MAP4 catheter is seen with 2 tip electrodes in
poor/no contact with the myocardium; accordingly, 2 of the recording channels lack monophasic action potential (MAP) recordings. B) When the catheter was adjusted, and all 4 tip electrodes were in good contact with tissue, MAPs were elicited on all channels. Additionally, panels C-F show images of a prototype MAP recordings catheter. The catheter is shown exerting low (D), medium (E), and high (F) contact force on the tissue on the mitral annulus of a reanimated swine heart. This figure was modified from M. M. Schmidt, M. R. Franz, T. G. Laske, M. T. Stewart and P. A. Iaizzo, "In Vitro Evaluations of Cardiac Mapping Catheters Designs and Utilities: Employing Visible Heart® Methodologies," Journal of Medical Devices, vol. 10, no. 2, 2016.

Additionally, the Visible Heart® has been used to study the device-tissue interface with a variety of prototype catheters. In Figure 5C-F are images collected during the assessment of a prototype MAP catheter. The catheter is a based off the design of a multi-array MAP catheter, as described in US Patent 8565851 B2 [65]. This catheter was modified from an existing multi-array ablation catheter (MAAC, Medtronic, LLC. Dublin, Ireland) to optimize MAP recordings. The catheter was then placed into a reanimated swine heart so to visualize the device tissue interface. The catheter was advanced against the mitral isthmus at varying contact levels (low, medium, and high) [50]. Subsequently, we have used these obtained images to gather feedback from physicians: this novel imaging has allowed us to develop the next generation of MAP recording catheters. Many of the limitations of the initial prototypes, specifically associated with the device/tissue interface may have gone un-noticed without the ability to directly visualize their applications.

*Expert commentary and five-year view*

The treatment of cardiac arrhythmias with ablation technologies and/or the use of antiarrrhythmic drugs is effective in some patients dramatically affecting their quality of life. As described above, many groups have attempted to use MAP recordings as a means to better diagnose, and ultimately treat these arrhythmias. Despite some sustained degree of interest in MAPs by clinical electrophysiologists, there have been few catheters
designed to record them. This scarcity of devices may be rectified through the design and
development of novel devices, with nearly 15 patents related to novel ways to clinically
record MAPs having been filed or granted in the last year alone. Several of these patents
are related to methods for assessing cardiac conduction through concepts such as basket
style mapping catheters, balloon interfaces, and other multi-array electrode
configurations [66-72].

The considered clinical benefits of utilizing MAP recordings over standard electrical
recordings are currently growing; however, their adoption into EP labs has been slow.
Perhaps, with the FDA approval of the EasyMap MAP diagnostic catheter (MedFact
Engineering GmbH, Lörrach, Germany), MAPs may begin the process of partially
penetrating this clinical field [73]. Yet, the road for MAP adoption will not be an easy
one; with current conventional mapping catheters being designed for specific anatomies
and procedures, an array of MAP catheters will be needed for their use to become
commonplace. Nevertheless, when compared to electrogram recordings, MAP
waveforms can provide clinical information vital to the understanding, diagnosis and
treatment of arrhythmias through their ability to represent focal activation timings,
depolarization rates, durations, and repolarization waveforms. Additionally, the use of
MAP recordings could mitigate the need for mechanical pressure sensors and use the
recording platform of the ablation catheter to ensure contact, orientation, depth, and
effectiveness of an ablation, without added mechanics and sensors to the tip, making the
catheter smaller or adding room for other enhancements.

We have described here how the use of in vitro models, such as the Visible Heart®
methodologies, can illustrate the utilities and applications when developing MAP methodologies and technologies. One such indication has been through the study of current catheters and the pros and cons of working with them. By visualizing their use inside reanimated hearts, engineers and scientists can assess and study nearly all components of a given catheter and how it interacts with a variety of cardiac tissues. For example, when considering the case of designing an endocardially deployed right ventricular ablation catheter: 1) Can it be manipulated to the intended target? 2) What anatomical structures must it traverse to get there? 3) Does the tip of the catheter need to be perpendicular/parallel to the myocardium? 4) How important is contact force? 5) Can the appropriate leverage be applied? Such an extensive list of design criteria can be assessed by employing novel visualization approaches thereby expediting the development, application and physician training associated with bringing a novel catheter design to market.

The nature of the MAP recording requires one contact and one non-contact electrode. Because electrode placements are vital component of the device design, one needs to design the next generation of MAP catheters to allow and maintain the desired focal contacts. Fortunately, such catheters can be constructed with electrodes in a variety of locations via rapid prototyping and consequently tested in realistic, in vitro, functional models. Nevertheless, the ability to visualize the electrodes inside of a functioning heart, allows a designer to optimize the electrode positions/contacts relative to the catheter body and thus ultimately increase the ability to quickly iterate MAP recording catheters.

Our laboratory continues to enhance and expand the Visible Heart® methodologies and
its applications in electrophysiologic studies remain extremely promising. On a daily basis, new catheters and ablation technologies are being assessed on reanimated large mammalian hearts. These abilities combined with continued enhancements in imaging modalities such as endoscopes, fluoroscopy, echocardiography, and with computational systems for electrical mapping are being applied to the MAP catheter design process. In other words, the combined use of these cutting-edge technologies will pave the way for both the rapid prototyping and development of MAP catheter concepts and aid in developing technologies that more rapidly navigate the regulatory process and consequently expedite the journey to clinical use.

**Conclusion**
To improve ablation procedural outcomes, new methodologies and catheters will be required to provide more precise, focalized electrical information of a given patient’s heart. Even with a growing understanding of the disease states associated with cardiac arrhythmias and the highly competent electrophysiological tools currently available, one can still envision the need for MAP recording catheters. The recording of focal MAP waveforms can provide patient information related functional status of the underlying myocardium: e.g., is it arrhythmogenic, has it been ablated, is it a scar. Our laboratory has utilized Visible Heart® methodologies to study the potential clinical utilities of recording MAP waveform, how to optimize their recording and assess varying catheter designs. Through this testing we are hopeful that the time from concept to product can be reduced and that an array of MAP catheters can be put in the hands of physicians, where they will ultimately improve patient outcomes.
The ability to reproducibly record cardiac action potentials from multiple anatomic locations: endocardially and epicardially, in situ and in vitro

Submitted to IEEE: Transactions on Biomedical Engineering, in review.

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Preface
The Visible Heart® Laboratory provides researchers with unique abilities to study cardiac anatomy and electrophysiology in an ex vivo setting of large mammalian hearts, including human. Past work has shown the utility of the Visible Heart® for the evaluation of cardiac pacing and relevant pacing thresholds; however, research on the relationship of in situ and in vitro MAP waveforms has been limited.

I was responsible for protocol development and data collection with the aid of Dr. Paul Iaizzo, Dr. Tinen Iles, and Maria Seewald. I was also responsible for the exportation of data for analysis. Thuy Hoang and I worked together to develop a custom MATLAB script for MAP waveform analysis. I was responsible for all statistical analysis and the composition of this manuscript. Furthermore, I presented the preliminary results of this study at the Design of Medical Devices Conference in Minneapolis, Minnesota in April 2017.
**Summary**  
**Objective:** For cardiac arrhythmia mapping and ablation procedures, the ability to record focal cardiac action potentials could aid in precisely identify lesions, scarred tissue, and/or arrhythmic foci. Our study objective was to validate the electrophysiologic properties of a routinely employed, large mammalian, in vitro working heart model.  

**Methods:** Monophasic action potentials (MAPs) were recorded from 18 swine hearts, during viable hemodynamic function both in situ (post-median sternotomy) and in vitro (using Visible Heart® methodologies). We placed specially designed mapping catheters both in epicardial and endocardial locations. High-quality MAP signals were recorded for up to 2 hours, and MATLAB was utilized to evaluate relative durations and temporal/regional changes in waveform morphologies.  

**Results:** MAPs were reproducibly recorded from both epicardial and endocardial locations in situ and in vitro. No significant differences were noted in right atrial endocardial, right ventricular endocardial, right ventricular epicardial, or left atrial epicardial waveforms when baseline recordings were compared to all other in situ and in vitro time points. Further, MAP duration between right ventricular endocardial and epicardial waveforms was not significantly different, in situ or in vitro.  

**Conclusion:** In vitro models like the Visible Heart® may be considered for the study of cardiac arrhythmias, the development of novel therapies, and/or preclinical testing of future cardiac mapping catheters and systems.
Introduction
The rapidly evolving field of clinically applied cardiac technologies continues to rely on validation via preclinical platforms. For example, relative to cardiac arrhythmia mapping and ablation, the ability to record focal cardiac action potentials would enable precise identification of placed lesions, areas of scarred tissue, and/or the sites of arrhythmic foci. Further, the development of 3D navigation and electrical mapping systems—such as EnSite Precision™ (Abbott, Chicago, IL), Rhythmia HDx™ (Boston Scientific, Marlborough, MA), Carto® 3 (Biosense Webster, Irvine, CA) and CardioInsight™ Noninvasive 3D Mapping System (Medtronic LLC., Dublin, Ireland) – could benefit from focal mapping of myocardial potentials. In other words, with spatial resolutions on the scale of 2 to 7 mm, these aforementioned mapping systems are limited in their abilities to target focal cardiac activations and assess repolarizations [1-3].

One solution is to record focally, extracellular monophasic action potentials (MAPs); collected via the contact method [4]. MAP recordings are focal action potential waveforms, representative of underlying transmembrane action potentials. These signals can be recorded through the application of sufficient contact forces to the myocardium [4, 5]. Given the focal nature associated with MAP recordings, these waveform’s features change in response to the distribution of ion channels in the underlying myocardium, i.e., MAPs recorded from the various heart chambers will have different depolarization and repolarization properties [6-9]. With regard to 3D mapping applications, recent studies have described the benefits of MAP recordings for identifying focal rotors in atrial fibrillation (AF); these investigators identified localized rotors in up to 96% of AF
patients referred for ablation [10, 11]. Therefore, incorporating the ability to record MAPs into clinically used ablation catheters could be critical for improving AF therapeutic outcomes. It should be noted that today, after a mean of 1.3 ablation procedures, recurrence-free success rates are approximately 80%, with rates only as high as 70% without the use of antiarrhythmic drugs; hence there is room for improvements [12].

The utility of employing in vitro studies over in situ work has long been known. In vitro studies can have associated values such as increased relevance, lower costs, abilities for direct visualizations, and/or ease of use [13, 14]. Techniques developed to study isolated hearts include Langendorff preparations and arterially perfused tissue wedges [15, 16]. As with many in vitro setups, such techniques are not without limitations. Frequently, the morphologies of underlying action potentials are modified by changes in activation pathways: e.g., changes caused by cardiac pacing or by underutilization of stretch-activated ion channels because of paralytic drugs, such as blebbistatin [16, 17]. Several investigators have studied the effects of cardiac isolation on altering action potential properties [18-21].

In vitro perfusions and reanimations of intact mammalian hearts, through working heart approaches like the Visible Heart® methodologies (Medtronic/University of Minnesota, Minneapolis, MN USA), have demonstrated added benefits for studying, visualizing, and treating cardiac arrhythmias [22, 23]. More specifically, our laboratory has utilized Visible Heart® methodologies, for testing a variety of pre-clinical prototype devices [24-28].
In the present study, our primary objective was to further validate the electrophysiologic utility of investigating reanimated swine hearts; to do so we compared in situ versus in vitro recorded MAPs from multiple anatomic locations.

**Methods**

Our experimental protocol has been previously described [29]. The University of Minnesota Institutional Animal Care and Use Committee reviewed and approved the employed procedures; all animals were humanely treated per the Guide for the Care and Use of Laboratory Animals.

**In situ setup**

Swine (n = 18) weighing between 60 to 80 kg were initially anesthetized with 500 mg of Telazol and 500 mg of methohexital. Then, each animal was intubated and maintained in a plane of deep anesthesia (mean alveolar concentration > 1.2). To enable access to the epicardial surfaces of a given swine heart in situ, we performed a median sternotomy on each animal and formed a pericardial cradle. Only hearts eliciting normal cardiac functions (native sinus rhythm) were included: pacing was not used.

To record both epicardial and endocardial MAPs, we used four 7 Fr MAP4 catheters (Medtronic LLC., Dublin, Ireland). These catheters contain 4 independent spherical-tip electrodes (diameter, 0.9 mm) and a distal (spaced 5 mm) ring electrode. The catheters were placed on the epicardial and endocardial surfaces such that the tips, or contact electrodes, were perpendicular to the myocardium. For the in situ portion of these studies, the first catheter was placed endocardially in the right ventricle (RV) through an introducer in the jugular vein. Then, similarly the second catheter was placed
endocardially within the right atrium (RA) via a second introducer. These endocardial MAP4 catheters were placed utilizing fluoroscopy (Ziehm Vision R, Nuremberg, Germany). Next, the third and fourth catheters were positioned onto the epicardial surfaces of the RV and the left atrium (LA) using direct visualization. Stabilizing arms were used to hold introducers containing conductive gel so to maintain continuity between the tip and ring MAP4 electrodes.

**In vitro setup**
After completion of the in situ portions of these studies, we excised each heart using standard cardioplegia methodologies [22]. A cold, high potassium solution was delivered through a cannula placed into the aortic root, causing cardiac arrest within 30-60 seconds. Each heart was then carefully explanted, cannulated, and re-perfused within 60 minutes [22]. Subsequently, once positioned onto the Visible Heart® apparatus, each heart was perfused with warmed modified Krebs-Henseleit buffer. Upon reaching 36.5° C a defibrillation shock initiated functional contractions, and only hearts beating in native sinus rhythm were used in these studies.

MAP4 catheters were again placed within and on the reanimated hearts. The endocardial recording catheters (RA and RV) were delivered through a cannula placed within the superior vena cava and visualized with endoscopes. The exact placements of the epicardial catheters (RV and LA) were done with direct visualization. In vitro, all catheters were positioned near their in situ recording locations (± 1 cm). As an additional means to best compare the in vitro waveforms with in situ recordings, all MAPs were recorded only during physiologic “working mode” in these reanimated hearts [22]. While
in working mode, the hearts maintained stable hemodynamic function as assessed by monitoring with echocardiography, pressure waveforms, and sonomicrometry crystals. The remainder of the in vitro time, during non-recording periods, was spent in right-sided working mode to preserve each hearts’ overall function.

**Signal collection and statistical analysis**
To record MAP waveforms, we used a CardioLab Recording System (GE Healthcare, Waukesha, WI) with a wide bandpass filter (0.05 to 1,000 Hz). MAP waveforms from each anatomical location were collected and monitored for 2 hours. Catheter positions and tip pressures were slightly adjusted, as needed, throughout these recording periods, in order to record high-quality MAP signals with these characteristics: (1) stable baselines, (2) sharp upstrokes, and (3) amplitudes ≥ 2 mV for ventricular signals; ≥ 0.5 mV, atrial.

To analyze these high-quality MAP signals, we used a customized MATLAB (MathWorks, Natick, MA) script, optimized to selectively identify the amplitude of each MAP using its plateau phase (Figure 6). For each peak identified, using a built-in peak detection function, we defined a reference window as a means to analyze one signal at a time. To calculate the relative MAP amplitudes, we subtracted the baselines from the peak’s measured voltages. In instances where “spike and dome” morphologies were present, a moving average was used to selectively identify the plateau as the MAP amplitude (Figure 6, top panel).

To determine action potential duration (APD) at 30%, 60%, and 90% repolarization (APD30, APD60, and APD90), we assessed the time from the start of the signal until repolarization to the specified percentage (Figure 6, bottom panel). To evaluate temporal
and regional changes in MAP morphology, we used APD30:APD90 and APD60:APD90.

Figure 6. Top) Quantified amplitudes of monophasic action potentials. The top strip shows the initial amplitudes selected by the software peak detection function. The blue line represents a moving mean used to identify the maximal amplitudes of the plateau phase. Bottom) Properties of monophasic action potentials. Action potential duration at 30%, 60%, and 90% repolarization was determined from the start of the signal until repolarization to the specified percentage.

We performed all MAP waveform analyses at 10-min intervals. The mean value at a given time point represents the averaging of 1 minute of data (i.e., S10 mean represents the mean of the MAPs recorded during the 10th in situ minute). All data are presented as the mean ± standard deviation. We used 1-way analyses of variance (ANOVA) and, after excluding outliers, post hoc Tukey honest significant difference (HSD) tests. A P value of less than 0.05 was considered as significant.

**Results**

We recorded MAP waveforms from a given heart for 120 minutes, both in situ and in
vitro \((n = 18)\). Throughout the in situ recording periods, the mean heart rates were 104 ± 13 bpm versus 94 ± 20 bpm in vitro (Figure 7). For each catheter location, the APD90, APD30:APD90, and APD60:APD90 were determined and are presented below (Tables 2-5). Excluded from our analyses were amplitudes (given its previously reported sensitivity to catheter contact force) \[4\] and the time point immediately after the delivery of a defibrillator shock to initiate reanimation, i.e., in vitro time points start with V10 measurements.

![Average heart rate in situ and in vitro](image)

*Figure 7. Sinus heart rates averaged for all 18 animals. The first portion of the figure shows heart rate in situ (S0-S120), with a transition to in vitro (V0-V120).*

**Right atrium**
Overall, for RA MAP recordings, the mean in situ APD90 values were between 97.4 ± 25.3 msec and 124.2 ± 50.2 msec; in vitro, between 84.9 ± 28.9 msec and 112.0 ± 77.8 msec (Table 2). Per ANOVA with Tukey HSD tests comparing APD90 for all RA time points to the in situ baseline \((S0)\) there were no significant differences in these values (Figure 8).

The mean in situ APD30:APD90 ratios were 58.6% ± 19.1% versus 63.1% ± 18.0% in vitro. The mean in situ APD60:APD90 ratios were 77.7% ± 11.8% versus 81.5% ±
11.8% in vitro. No significant differences in APD30:APD90 or APD60:APD90 ratios were observed for any time point comparisons to baseline.

**Table 2. Right atrial endocardial monophasic action potential properties**

<table>
<thead>
<tr>
<th>Time</th>
<th>RA Endocardial</th>
<th>In vitro</th>
<th>Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>102.6 ± 37.5</td>
<td>118.2 ± 100.8</td>
<td>79.5 ± 9.0</td>
</tr>
<tr>
<td>10 min</td>
<td>113.3 ± 37.4</td>
<td>124.2 ± 102.0</td>
<td>81.0 ± 10.0</td>
</tr>
<tr>
<td>20 min</td>
<td>103.3 ± 37.4</td>
<td>112.1 ± 103.9</td>
<td>75.9 ± 11.0</td>
</tr>
<tr>
<td>30 min</td>
<td>112.1 ± 37.4</td>
<td>112.1 ± 103.9</td>
<td>77.0 ± 10.9</td>
</tr>
<tr>
<td>40 min</td>
<td>105.6 ± 37.4</td>
<td>108.3 ± 106.8</td>
<td>80.7 ± 9.9</td>
</tr>
<tr>
<td>50 min</td>
<td>111.3 ± 37.4</td>
<td>100.3 ± 108.3</td>
<td>74.7 ± 10.5</td>
</tr>
<tr>
<td>60 min</td>
<td>106.8 ± 37.4</td>
<td>97.4 ± 108.3</td>
<td>75.1 ± 12.9</td>
</tr>
<tr>
<td>70 min</td>
<td>106.8 ± 37.4</td>
<td>101.0 ± 103.9</td>
<td>75.5 ± 14.5</td>
</tr>
<tr>
<td>80 min</td>
<td>106.8 ± 37.4</td>
<td>103.9 ± 108.3</td>
<td>79.6 ± 12.0</td>
</tr>
<tr>
<td>90 min</td>
<td>106.8 ± 37.4</td>
<td>103.9 ± 108.3</td>
<td>80.4 ± 10.0</td>
</tr>
<tr>
<td>100 min</td>
<td>106.8 ± 37.4</td>
<td>103.9 ± 108.3</td>
<td>78.8 ± 11.9</td>
</tr>
<tr>
<td>110 min</td>
<td>106.8 ± 37.4</td>
<td>103.9 ± 108.3</td>
<td>77.6 ± 12.4</td>
</tr>
<tr>
<td>120 min</td>
<td>106.8 ± 37.4</td>
<td>103.9 ± 108.3</td>
<td>75.1 ± 13.3</td>
</tr>
</tbody>
</table>

**Figure 8. Action potential durations (APDs) for monophasic action potentials (MAPs) recorded from the right atrial endocardium.** The first portion of the figure shows APDs in situ (S0-S120) with comparisons to those from MAPs recorded in vitro (V10-V120).

**Left atrium**

Overall, for LA MAP recordings, the mean in situ APD90 were between 92.3 ± 25.9 msec and 114.7 ± 69.2 msec versus between 77.1 ± 49.1 msec and 127.7 ± 69.2 msec in vitro (Table 3). No significant differences in APD90 values were noted for any time points comparisons (Figure 9).

The mean in situ APD30:APD90 ratios at baseline were 54.6 ± 20.5% and the mean APD60:APD90 ratios at baseline were 78.4 ± 10.2%. When the in situ baseline values
were compared to all other time points no significant differences were observed.

Table 3. Left atrial monophasic action potential properties

<table>
<thead>
<tr>
<th>LA - Epicardial</th>
<th>In situ time points</th>
<th>In vitro time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFDPD90 (msec)</td>
<td>114 ± 92</td>
<td>107.2 ± 94.7</td>
</tr>
<tr>
<td>APD(0-90)/APD90 (%)</td>
<td>78.4 ± 10.2</td>
<td>78.7 ± 9.4</td>
</tr>
<tr>
<td>APD(60-90)/APD90 (%)</td>
<td>78.4 ± 10.2</td>
<td>78.7 ± 9.4</td>
</tr>
</tbody>
</table>

Figure 9. Action potential durations (APDs) determined for monophasic action potentials (MAPs) recorded from the left atrial epicardium. The first portion of the figure shows APDs in situ (S0-S120) with comparisons to those from MAPs recorded in vitro (V10-V120).

In our experimental design, epicardial LA signals were the most variable and difficult to collect for several key reasons. We observed that because a given heart was functioning within a pericardial cradle in situ, the lateral LA was wrapped closely by the pericardium, so typically the LA appendage was the only accessible portion of this chamber. Further, the LA appendage typically elicited large amount of motion and coupled with nearby left lung filling, these caused issues in terms of relative catheter stabilities. In addition, given its anatomic orientation, the catheter often rubbed against the pericardium during recordings. In the in vitro setup, perfusion to the left side of the heart was reduced during...
Right-sided working mode. This in turn resulted in decreases in left-sided volumes (since only the coronaries were being perfused), as well as reductions in LA catheter contact forces. These factors taken together, were considered to contribute to a reduced ability to consistently record LA MAPs.

**Right ventricle**

For RV MAP recordings, we used 2 catheters: 1 on the endocardial surface and another epicardially. For the endocardial MAPs, the mean in situ APD90 values were between 151.0 ± 75.9 msec and 227.4 ± 68.0 msec; versus between 152.5 ± 54.5 msec and 201.4 ± 33.6 msec in vitro (Table 4). No significant differences in endocardial APD90 values were noted between any studied time points (Figure 10).

### Table 4. Right ventricular endocardial monophasic action potential properties

<table>
<thead>
<tr>
<th></th>
<th>In situ time points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>151.0 ± 75.9</td>
</tr>
<tr>
<td>APD90/VA (%)</td>
<td>63.2 ± 18.5</td>
</tr>
<tr>
<td>In vitro time points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 min</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>82.6 ± 17.3</td>
</tr>
<tr>
<td>APD90/VA (%)</td>
<td>60.3 ± 19.7</td>
</tr>
</tbody>
</table>
Figure 10. Action potential durations (APDs) for monophasic action potentials (MAPs) recorded from the right ventricular endocardium. The first portion of the figure shows APDs in situ (S0-S120) with comparisons to those from MAPs recorded in vitro (V10-V120).

For the epicardial catheter, the mean in situ MAP APD90 values were between 145.6 ± 59.9 msec and 204.3 ± 62.7 msec and between 137.7 ± 29.8 msec and 180.7 ± 36.9 msec in vitro (Table 5). No statistically significant differences in the epicardial APD90s were noted for any time points (Figure 11). No differences in APD90 was noted between the RV MAPs recorded endocardially versus epicardially.

Table 5. Right ventricular epicardial monophasic action potential properties

<table>
<thead>
<tr>
<th>Time Point</th>
<th>In situ time points</th>
<th>In vitro time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV - Epicardial</td>
<td>0 min</td>
<td>10 min</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>137.7 ± 29.9</td>
<td>140.6</td>
</tr>
<tr>
<td>APD90 (%)</td>
<td>60.8</td>
<td>64.2</td>
</tr>
<tr>
<td>APD90 (msec)</td>
<td>84.2 ± 6.7</td>
<td>87.0 ± 6.4</td>
</tr>
</tbody>
</table>
Figure 11. Action potential durations (APDs) for monophasic action potentials (MAPs) recorded from the right ventricular epicardium. The first portion of the figure shows APDs from the in situ (S0-S120) MAPs versus those from in vitro measurements (V10-V120).

For the MAPS recorded with the endocardial catheter, the mean in situ APD30:APD90 ratios were 65.0% ± 22.1% versus 54.3% ± 21.1% when recorded in vitro. The mean in situ APD60:APD90 ratios were 85.4% ± 13.7% versus 79.0% ± 13.6% in vitro. No significant differences in these ratios were noted.

For MAPs recorded from the RV with the epicardial catheter, the mean in situ APD30:APD90 ratios were 67.5% ± 20.4% compared to 64.8% ± 18.4% for the in vitro MAPs. The mean in situ APD60:APD90 ratios were 87.0% ± 8.9% versus 85.2% ± 9.2% in vitro. Again, no statistically significant differences in these ratios were observed.

Discussion
Here we have shown the MAPs can be recorded consistently for up to 2 hours from swine hearts, either in situ or in vitro and from both the endocardial and epicardial myocardium. Overall, MAP durations compared to baseline did not significantly change for signals recorded over 2 hours in situ, as well as for those recorded for an additional 2 hours in vitro (Figure 12). Further, no significant differences in waveforms were noted per our
analyses of APD30:APD90 and APD60:APD90 ratios compared to baseline levels.

Figure 12. Monophasic action potentials recorded at the S0, V30 and V120 time points. Variations in amplitudes were considered to be due primarily to variations in applied contact forces.

While no statistically significant differences were observed for the analyses between the MAP waveforms recorded in situ and in vitro, it should be noted that there were large standard deviations associated with many of the variables measured. As with any such
physiologic study variations can occur, even though steps were taken to minimize these variations. As noted above, our MAP4 catheter placements for endocardial measurements in situ were done under the guidance of fluoroscopy and those in vitro were done with direct visualization for the epicardial catheter. Despite being able to see the catheters using the Visible Heart® preparation, the in vitro MAP4 catheters placements were close to those sites recorded from in situ, but likely not the exact same locations. In addition, because of the arrhythmogenic nature of the swine heart, RV catheter placements were limited deep within the RV apex (due to the induction of ectopic beats).

For the continued development and validation of cardiac medical devices, preclinical animal models, both in situ and in vitro, are of both critical values. To date, various experimental methods have been used to better understand underlying cardiac electrophysiologic principles and to optimize device designs, yet few have met the requirements for eliciting reproducible and accurate cardiac action potentials. As mentioned above, many in vitro approaches (such as Langendorff preparations or isolated tissue wedges) are limited by employing paralytic agents that in turn inhibit stretch-activated ion channels [15-16]. Furthermore, the ability to study in situ electrophysiologic properties in an in vitro setting, is considered invaluable for the study of focal electrical changes. Here we showed that the novel Visible Heart® methodologies, allowed us to preserve intrinsic cardiac functions, with a minimal effect on ones’ ability to record cardiac MAPs throughout the heart including epicardial and endocardial locations: note, many clinical ablations procedures performed today to treat ventricular tachyarrhythmias, utilize an epicardial approach.
The investigation described here, is not without limitations. For example, our laboratory has previously identified that to obtain stable MAP recordings, constant pressure must be maintained by the catheter, on the surface of the myocardium. To minimize force variabilities, we developed customized fixtures to hold and stabilize the catheters in place over the 2-hour recording periods; we did not assess the forces applied. It should be noted that in both in situ and in vitro setups, minor MAP4 catheter adjustments were required to maintain stable tip pressures. As noted above, we did not utilize pacing in this study; yet in future studies one may want to incorporate atrial pacing or perform pace mapping so to study various arrhythmia models. Finally, left ventricular MAP recordings were not included in this study; future studies should be performed to incorporate additional anatomical locations, as well as utilize reanimated human hearts to provide more evidence for the translational values of such preclinical studies.

**Conclusion**
This study validated the utility of employing the Visible Heart® in vitro model, as a means for investigating electrophysiologic behaviors using MAP waveforms. Reproducible, endocardial and epicardial MAP recordings were obtained in situ as well as in vitro from multiple cardiac locations (RA, RV, and LA). The use of pre-clinical in vitro models is considered invaluable for the study of cardiac arrhythmias, the development of novel therapies, and/or the early testing of future cardiac mapping/ablation catheters or other devices.
Section II: Clinical utility of monophasic action potential recordings: contact force and focal tissue viability

The second section of my thesis will focus on the clinical utility of monophasic action potential (MAP) recordings. In the past, MAPs have been used in the study of action potential alternans and their implications in patients with atrial fibrillation (AF). We would like to further explore the applications of MAPs in AF patients, specifically their utilities in radiofrequency (RF) ablation of the pulmonary veins and other AF substrates: i.e. left atrial appendage, posterior wall, and mitral isthmus.

The formation of a proper lesion with RF energy requires a minimum of 10-20 grams of catheter contact force. It is also known that MAP waveforms can only be elicited when sufficient force is applied to the myocardium by the tip electrodes. The first portion of this section will describe in detail a series of studies which were conducted to determine the optimal force for MAP recordings, and how this knowledge can be applied clinically.

While CF is required for lesion formation, the force applied during RF delivery can be unstable and the resulting lesion sizes may vary. As a secondary method to validate lesion formation, MAP waveform properties were correlated to induced RF lesions: qualitatively and quantitatively. Based on the results from these two studies MAPs could be used both as a method to identify catheter CF prior to the delivery of RF energy, as well as a tool to evaluate lesion formation.
Contact force required for monophasic action potential recordings: a supplement to force measurements

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Preface
Radiofrequency (RF) ablation is a common energy modality used in the treatment of cardiac arrhythmias. In order to create a lesion with RF energy, a minimum of 10 grams of contact force (CF) is required. It was hypothesized that because monophasic action potentials (MAPs) require CF to be recorded, they could be used as a supplement to CF measurements.

The experimental protocol described in this section was developed by the co-authors, in which Dr. Mark Benscoter took a lead role. I assisted Dr. Benscoter with the collection of CF and MAP waveforms. Additionally, I was responsible for the detailed data and statistical analyses. I took on the primary responsibility for the preparation of this manuscript.
Summary

Objective: Catheter contact force (CF) plays a major role in radiofrequency (RF) ablation; impacting lesion sizes, arrhythmia recurrence rates, dictating ablation durations, and/or overall patient safety. Our study sought to determine the relative CFs required to elicit reproducible monophasic action potential (MAP) recordings.

Methods: The study utilized 4 swine in which: 1) median sternotomies were performed and MAPs were collected from 7 ventricular locations on the epicardial surface of each heart and 2) a subset of endocardial signals were recorded from a reanimated heart. In such studies, the initial elicitations and then losses of stable MAP waveforms were recorded as were their associated catheter CFs (n=371) using a calibrated optical fiber.

Results: Mean CFs at the onset of MAPs were 14.2±2.9g for epicardial and 16.6±2.5g endocardial locations. Across epicardial locations, no significant differences in CFs were required to elicit MAPs. Additionally, endocardial and epicardial CFs for MAPs did not significantly differ from their respective locations; i.e. right ventricular septum endocardial versus epicardial.

Conclusion: In our study, the catheter CFs required to elicit MAPs were within the ranges previously reported for clinically viable RF ablations. We believe that MAP recordings could be used to estimate the contact force of an RF ablation catheter, providing additional clinical feedback for physicians performing RF ablation.
**Introduction**

In recent years, the incorporation of contact force (CF) sensing into radiofrequency (RF) ablation catheters, such as the ThermoCool SmartTouch® (Biosense Webster, Inc., Diamond Bar, CA) and the TactiCath™ Quartz (Abbott Laboratories, Chicago, IL), has led to increases in both cardiac ablation safety and success [1, 2]. Natale et al. reported the mean CF applied during irrigated RF ablation was 17.9 ± 9.4 g; when they achieved the target CF in patients with paroxysmal atrial fibrillation (AF), the recurrence-free rate at 12 months markedly improved [3]. Studies on mapping ventricular tachycardia have also looked at CF. Percutaneous subxiphoid access has been used as a means for both mapping and ablation of the epicardial substrate [4, 5]. In patients with ventricular tachycardia, Mizuno et al. reported that 9 g of CF was sufficient for mapping both endocardial and epicardial substrates [6].

Presented here is a new approach for estimating contact force by recording monophasic action potentials (MAPs) before applying ablative energy. The focal electrical signals represented by MAPs can be reproducibly recorded only when sufficient catheter CF is applied to the myocardium, resulting in a mechanical depolarization of cells by the electrode on the tip of a given catheter [7, 8]. The relationship between MAPs and intracellular action potentials has been previously explained. MAPs are the result of changes in boundary currents at the tip of the catheter. When sufficient CF is applied to the myocardium, the cells beneath the catheter become mechanically depolarized through the activation of stretch activated channels; thus, these cells are electrically inactive. As a transmembrane action potential passes through a given myocardial region, a change in
membrane voltage can be recorded between tip and distal catheter electrodes. The recorded waveforms provide useful insights into relative activation time, depolarization, and repolarization [7-9]. In other words, given its nature, a MAP cannot be recorded without certain applied catheter CF; however, the specific amount of CF required has not been previously studied.

In this study, MAPs and CFs were simultaneously recorded from the epicardial and endocardial surfaces of swine hearts in situ and in vitro. The MAP waveforms supplemented CF recordings with data on focal electrical activity. If applied clinically, such MAP recordings could improve ablation outcomes in patients with cardiac arrhythmias.

**Methods**
For these studies 4 Yorkshire crossbred swine (weight, 75 to 95 kg) were anesthetized with Telazol® (Zoetis, Parsippany, NJ; 5 to 7 mg/kg) and methohexital (5 to 7 mg/kg), then intubated for general anesthesia with isoflurane (mean alveolar concentration > 2). After performing a median sternotomy, a pericardial cradle was created to enable access to the epicardial surface of each heart [10]. Only specimens that elicited normal cardiac function (e.g., native sinus rhythm) were included. The Institutional Animal Care and Use Committee at the University of Minnesota reviewed and approved these studies, which adhered to the Guide in the Care and Use of Laboratory Animals.

**Epicardial monophasic action potential recordings**
For MAP recordings, a catheter consisting of 4 spherical tip electrodes (diameter, 0.9 mm) and 2 ring electrodes (width, 1 mm) was used (Figure 13). For epicardial recordings
the catheter was fixed to a micromanipulator, enabling precise adjustments to catheter positions in the x, y, and z directions. Using electrode gel, focal transmembrane waveforms were recorded in a bipolar configuration between each of the spherical tip electrodes and the distal ring electrode (spacing, 2 mm). Recordings were filtered using a bandpass filter of 0.05 to 1,000 Hz and a sampling frequency of 1,000 Hz. Signals then passed through an Octal Bio Amp (ADInstruments Ltd, Dunedin, New Zealand) and were recorded using a PowerLab system (ADInstruments Ltd).

Epicardial MAPs were recorded from a total of 7 predefined locations: the right ventricular (RV) apex, the RV anteroseptal border, the RV septum, the RV outflow tract (RVOT), the left ventricular (LV) anteroseptal border, the LV septum, and the LV apex (Figure 14). A reproducible ventricular MAP waveform was defined as a signal with the following characteristics: (1) stable baseline, (2) sharp upstroke, (3) amplitude > 5 mV, and (4) MAP signal duration of 200 to 400 msec, depending on the baseline heart rate.
**Contact force**

To record applied CF by a given catheter, a fiber Bragg grating was mounted along the shaft of the catheter through an attached hypotube. The fiber was aligned so that it and the electrodes simultaneously contacted the myocardium (Figure 13). Each fiber was calibrated using an optical interrogator (HBM Test and Measurement, Darmstadt, Germany) against a compliant sponge to mimic myocardial stiffness. Doing so created linear calibration curves, which were then used to determine the relationship between the change in wavelength and CF. The calibration curves for the fiber Bragg gratings used yielded $R^2$ values of 0.997 and 0.989 (Figure 15). Each experiment included a baseline recording at 37ºC to adjust for frequency variations associated with changes in temperature.
To simultaneously evaluate the relationship between MAP and CF recordings, gradually increasing force was applied to the epicardial surface of the heart until 4 consecutive and reproducible MAPs were recorded (Figure 16A). Upon completion of data collection, force values during diastole and systole were averaged; the mean was defined as the CF required for MAP acquisition, also referred to as CF at “capture”. To account for any possible hysteresis effects, such as those seen while capturing pacing thresholds, CF was substantially increased and then the catheter was slowly retracted until reproducible MAP waveforms were no longer recorded, which was defined as “loss of capture” (Figure 16B) [11]. Throughout the experiments, investigators were blinded to the CF required for MAP recordings. During recordings, breath holds were induced to minimize any effects of respiratory movement against the fiber.
Figure 16. Illustration of collection protocol. A: Slowly increasing contact force (CF) was applied until 4 consecutive high-quality monophasic action potentials (MAPs) were observed. B: At MAP capture, CF was substantially increased. C: The catheter was then slowly retracted until reproducible MAP waveforms were no longer recorded.

**Endocardial monophasic action potential recordings**

A subset of data was collected from the endocardial surface of a reanimated swine heart.

After injecting cardioplegia, the heart was procured and reanimated using previously described Visible Heart® methodologies [12]. Heart rate and blood pressure were both stable throughout the recording period (96 bpm and 80/60 mmHg respectively). To obtain endocardial recordings the catheter was inserted into the right atrium (RA) through the superior vena cava. Then the catheter was manually navigated to 3 RA locations: the RA
appendage ostium (RAAO), the tricuspid valve annulus, and the coronary sinus ostium (CSO). Additional data were collected from these RV endocardial locations: the RV apex, the RVOT, the anterior papillary muscle, and the RV septum. Catheter force was slowly increased until 4 consecutive MAP recordings were captured, then the catheter was retracted and the measurement was repeated.

**Statistical and data analyses**
For each epicardial location, as well as for each anatomic location, statistical assessments of the variations in CF at capture and at loss of capture were made. Continuous variables are presented as the mean ± standard deviation. Both analysis of variance (ANOVA) and the Tukey post hoc test were employed. A probability value of P < 0.05 was considered to indicate statistical significance.

**Results**
MAPs were recorded from 7 epicardial ventricular locations on 4 swine hearts, for a total of 315 measurements. Each of the swine had a stable sinus rhythm; throughout the in situ recording periods, the mean heart rate was 92 ± 10.4 bpm and the mean blood pressure was 106/57 ± 14.7/9.3 mmHg. At MAP capture, the mean CF for epicardial recordings (n = 159) was 14.2 ± 2.9 g; for endocardial recordings (n = 56), mean CF was 16.6 ± 2.5 g. At initial MAP capture, the overall mean CF was 14.8 ± 3.0 g.

**Hysteresis**
For each epicardial location, the relative CF required to initiate, and then lose, reliable MAP recordings were documented (Figure 17). Across all predefined locations, the mean CF at MAP capture was 14.2 ± 2.9 g (n = 159). At loss of capture (n = 156), the mean CF
was 13.5 ± 3.1 g. The mean difference in CF at capture vs. loss of capture was 0.9 ± 3.1 g.

The overall mean CFs at capture vs. loss of capture did not significantly differ. However, for the LV anteroseptal border (n = 16), the mean CF at capture was 15.4 ± 2.8 g, significantly higher (P < 0.05) than the mean CF at loss of capture of 12.2 ± 3.6 g. The mean difference for that location was 4.0 ± 5.1 g. No other significant differences in CF at capture vs. loss of capture were observed.

**Anatomic variations**

At MAP capture, the LV septum (n = 16) required the lowest mean CF, 12.6 ± 1.2 g, while the LV anteroseptal border (n = 16) required the highest, 15.4 ± 2.8 g (Figure 18). Nevertheless, no statistically significant differences were found in CF among the 7 epicardial locations studied.

In all instances, a minimum of 7.5 g of CF was required to elicit reproducible MAP
waveforms. The optimal range of CF for successful RF ablation is 10 to 15 g [4, 6].

Overall, 68.4% of CF values for MAP recordings occurring on the LV (39 of 57) were in that optimal range. In addition, 3 of the 4 RV locations (the RV anteroseptal border, the RV septum, and the RVOT) had a majority of their CF values for MAP capture in the same optimal range (n = 42 of 79 or 53.2%). The RV apex (n = 24) consisted of a larger range of CFs (7.5 to 19.4 g), but the mean CF at capture (14.3 ± 4.1 g) was within the optimal range.

![Figure 18. Contact force (CF) at monophasic action potential (MAP) capture, plotted for 7 epicardial locations where we simultaneously recorded MAP and CF. The shaded region is the optimal range (10 to 15 g) for MAP recording. LV = left ventricular; RV = right ventricle; RVOT = right ventricular outflow tract.](image)

**Endocardial contact force**

From the reanimated swine heart (Figure 19), CF at MAP capture was documented for 7 endocardial locations (n = 8 per location). At capture, the mean CF in the RV was 17.0 ± 2.0 g; in the RA, 16.0 ± 3.0 g. No statistically significant differences in CF between the RV endocardial locations were found. The CSO, in the RA, showed a significantly lower CF at capture than all other endocardial locations (P < 0.05).
Finally, both endocardial and epicardial data at MAP capture for the RV apex, RV septum, RVOT, and RV septum was compared. For the RV apex, the mean endocardial CF was $17.6 \pm 2.8$ g; epicardial, $14.3 \pm 4.1$ g. For the RV septum, the mean endocardial CF was $16.8 \pm 0.6$ g; epicardial, $14.5 \pm 3.3$ g. Finally, for the RVOT, the mean endocardial CF was $16.9 \pm 2.8$ g; epicardial, $14.3 \pm 2.6$ g. We found no statistically significant differences in the endocardial vs. epicardial CF required to capture MAP waveforms.

Discussion
Over the last 10 years, the benefits of real-time CF measurements during the delivery of ablative cardiac RF therapies have been extensively explored. But the described benefits have focused on the size and relative transmurality of lesions. For example, in a canine study, atrial tissue lesions were identified to be transmural with applied catheter CF of 10 to 20 g [13]. Further, other investigators have reported that the application of moderate CF is as important in determining lesion size as the applied RF energy and duration of the
therapy [14]. More specifically, those claims have been validated by the results of both the TOCCATA and EFFICAS I trials. In the TOCCATA trial, all ablations conducted at a CF < 10 g were associated with recurrence of AF by 12 months [15]. A combined analysis of the EFFICAS I and TOCCATA trials revealed that 20 g of CF should be used clinically, and that no less than 10 g should be applied during RF ablation [15, 16].

One of the major obstacles in ablation, even with real-time CF recordings, is catheter stability [1]. In clinical trials using catheters for CF recordings, a high variability in CF was noted within a single ablation, indicating the difficulty of maintaining stable recordings [1]. For example, during a single recording, CF varied by up to 60 g, due simply to cardiac and respiratory movements [1]. While ablation protocols vary between clinics, power settings are typically between 15-50W for AF ablations. In the current study, we demonstrated that, in order to maintain stable MAP recordings, an adequate CF must be applied; any deviation from an adequate CF will result in unstable MAP recordings.

Clinically, electrograms have been used to evaluate lesion viability for decades, nevertheless both unipolar and bipolar voltage recordings have poorly correlated with CF [17]. However, recent studies have shown that the use of mini-electrodes to record electrograms during RF ablation improves lesion formation and can reduce complications [18, 19]. Further preliminary studies assessing lesion quality with MAP recordings have been previously conducted and are ongoing in our laboratory [20, 21].

The main findings of our study can be summarized as follows. First reproducible MAP
recordings require a mean catheter CF of $14.2 \pm 2.9$ g (epicardial) and $16.6 \pm 2.5$ g (endocardial). Second, the mean CF to elicit high quality MAP recordings is in the same range as the target CF for RF ablation, thus MAPs may act to supplement CF measurements and provide instantaneous insights relative to the device-tissue interface. Finally, due to the nature of a MAP, they can provide feedback on the conductivity and viability of the underlying tissue, and ultimately aid in both diagnosis and treatment of cardiac arrhythmias.

Our study has several limitations. First, the fiber Braggs used to measure CF are delicate, limiting the operator’s ability to record from certain locations in and on the heart. Inserting the system into the reanimated swine heart required a precise hand; the slightest movement could offset the fiber from the tip of the catheter. In addition, we collected epicardial data only from the anterior surface of the ventricles (the most accessible from the pericardial cradle); future studies should consider collection from other epicardial locations.

**Conclusion**
An adequate CF of about $14.2$ g (epicardial) and $16.6$ g (endocardial) was required to reproducibly and continuously record MAPs. MAP recordings could mitigate the need for mechanical pressure sensors and use the recording platform of the ablation catheter to ensure contact, orientation, depth, and effectiveness of an ablation, without added mechanics and sensors to the tip, making the catheter smaller or adding room for other enhancements.
The utility of recording monophasic action potentials relative to assessing the radiofrequency ablated myocardium: a tool for identifying lesion properties

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Preface
Today, electrogram (EGM) amplitude is used as the primary method to evaluate tissue viability after the delivery of ablative energies. While EGM amplitude is sensitive to lesion formation, it is also sensitive to adipose tissue, catheter contact, and far-field influence. Monophasic action potentials are sensitive and specific to focal myocardial viability and are absent in the presence of adipose tissue and with insufficient contact force, making them a valuable tool for assessing lesion formation.

For this research investigation, I was responsible for the initial experimental methods presented; however, this work was inspired by preliminary studies conducted by Dr. Mark Benscoter and myself. Due to the complex experimental protocol, I would not have been able to collect this data without the help of Kaleigh Rock, Angela Burgess, Tommy Valenzuela, Erik Gaasedelen, Alex Mattson, Lars Mattison, and Dr. Paul Iaizzo. I was responsible for the data and statistical analyses presented in this manuscript.
**Summary**

**Objective:** Radiofrequency ablations are used to treat a variety of cardiac arrhythmias. The goal of this study was to evaluate the utility of recording monophasic action potentials (MAP) to determine lesion depths, surface areas, and volumes of epicardial radiofrequency ablations.

**Methods:** Lesions were created on the epicardial surfaces of reanimated hearts in vitro using an irrigated, radiofrequency ablation catheter. Several power and duration combinations were utilized to create a range of lesion sizes. MAP amplitudes were measured at 0, 15, 30, 45, and 60 minutes post-ablation. Blinded observers provided qualitative analysis of the waveforms obtained 60 minutes post-ablation.

**Results:** Baseline MAP amplitudes were 4.4±1.9 mV and were found to be significantly reduced in all lesion sets (p<0.05). There were no temporal changes in MAP amplitudes between any measure depths, surface areas, or volumes. At 60 minutes post-ablation, MAP amplitudes were significantly reduced for lesions between 1.00-1.99 mm deep compared to those 2.50-2.99, 3.00-4.00, and ≥4.00 mm deep (p<0.05). Lesion properties (depths, surface areas, and volumes) were inversely associated with recorded MAP amplitudes and MAP qualities.

**Conclusion:** MAP waveforms can provide information on lesion sizes, which may increase a physician’s ability to predict lesion sizes during a radiofrequency ablation procedure.
**Introduction**

Radiofrequency (RF) ablation is a common treatment for persistent atrial fibrillation (AF); however, pulmonary vein isolation (PVI) in such patients has often been met with limited success [1, 2, 3, 4]. Many groups have studied the addition of new ablation targets to eliminate these substrates through creating additional transmural lesions in locations, such as the left atrial roof, the mitral isthmus, and/or within the left atrial appendage [5, 6].

One could argue that often the limited success in ablation can be due to the reconnections, or re-activations within regions, which were thought to have been appropriately ablated [7, 8]. Recently it was reported that there are clinical utilities in recording monophasic action potentials (MAPs) for identifying either small lesion gaps, or a lack of transmurality [9]. Furthermore, studies have illustrated values in monitoring MAPs to elicit focal action potentials from unhealthy myocardium; e.g. diseased, ablated, and/or infarcted. [10, 11, 12, 13].

Previous studies have looked at the “field of view” and/or “depth of view” relative to MAP recordings, however this relationship is still largely undefined. The field of view is considered to be no less than the tip electrode diameter: yet, it has been shown that the angle between the tip, reference electrodes, and the myocardium plays a role, as well as electrode spacing [14]. These investigators concluded that MAP waveforms are likely generated from an area greater than the tip electrode size, but less than 5 mm in diameter [14, 15]. The exact depth of view to which MAP recordings can reach is even less clear, however studies have shown that MAPs likely originate from deeper layers of the

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The primary objective of our current work was to evaluate the utilities of recording MAP waveforms in assessing relative lesion depths, surface areas, and/or volumes for induced epicardial RF ablations. Additionally, we sought to evaluate if temporal changes were present in MAP waveforms, recorded for a 1-hour lesion maturation period.

**Methods**
Yorkshire crossbreed swine were used in this study. The University of Minnesota Institutional Animal Care and Use Committee reviewed and approved the following procedures; all animals were humanely treated per Guide for the Care and Use of Laboratory Animals.

**Ablation procedure**
Hearts were excised and reanimated using previously described Visible Heart® methodologies [18]. A total of n=4 hearts were used for RF induced epicardial ablations (n=62) on the left ventricle. Ablations were delivered utilizing a 7Fr irrigated RF catheter with a 4 mm tip and using an RF generator (Atakr® Plus 990064, Medtronic LLC., Dublin, Ireland). Normal saline was used for this irrigated catheter at 30 cc/min (CoolFlow™ Pump, Biosense Webster®, Irvine, CA). Energies were delivered at a range of power settings and durations, in order to create a variety of lesions sizes (depths and surface areas). Ablations were conducted with power control settings at 10 or 20 watts for either 15 or 30 seconds. The ablation catheter was oriented parallel to the myocardial surface and then shifted slightly during energy deliveries, so to reduce the incidences of steam pops.
**Electrical recordings**

MAPs were recorded using MAP4 catheters (Medtronic LLC., Dublin, Ireland) at each ablation site prior to energy delivery, immediately post-ablation (0 minutes), and at time points of 15, 30, 45 and 60 minutes post-ablation. For all recordings, the MAP catheters were oriented perpendicular to the cardiac epicardial surfaces and placed in the same locations as were the therapeutic ablation catheters.

MAPs were recorded and subsequently evaluated using a CardioLab EP Recording System (GE Healthcare, Chicago, IL). Note, that these MAP waveforms were derived from bipolar recordings between a contact (0.9 mm diameter) and nearby non-contacting electrode (1 mm ring spaced 2 mm proximal to the tip electrodes). Filter settings were set at 0.05 Hz and 1000 Hz. Signal amplitudes were measured from defined time points; 100 msec after the beginning of the QRS complex as means to minimize the effects of far field potentials.

The qualitative assessments of the MAP waveforms at the 60 minutes post-ablation time points were made by 3 blinded reviewers. Two reviewers were familiar with MAP recordings, while the third reviewer had a general knowledge of cardiac electrophysiology, but limited experience with assessing MAP waveforms. The reviewers studied the waveforms and were asked to place each signal into one of following categories: 1) “viable”, indicating normal MAP waveform characteristics, 2) “damaged”, indicating some level of MAP degradation, or 3) “ablated”, indicating the absence or extreme decays of the MAP waveform.

**Lesion assessment**
In addition to the MAP waveform assessments, lesion sizes were also investigated. After the 60-minute time points, the ablated myocardium from each heart was placed in triphenyl tetrazolium chloride (TTC) stain, which was heated to 37° C prior to use. The tissue was submerged for 15 minutes, then removed and the lengths and widths of each lesion were measured. The lesions were then transected through the visible center and the tissue was re-submerged for an additional 15 minutes. The lesion depths were then measured. With these measurements, lesion surface areas were calculated using the equation for an ellipse. A given lesion volume was calculated based on a modified hemisphere equation; similar methods for RF lesion volume calculation are used in literature [19]. The methods for lesion measurements are shown in Figure 20.

Figure 20. The top two panels of this image show lesions created using radiofrequency energy. In both images the scale bar is 5mm in length. The bottom images illustrate how lesions were measured, and the associated volume calculation. RF – radiofrequency, L – length, W – width, D – depth.
**Statistics**
Continuous variables are presented as means ± standard deviations. Categorical variables are represented as percentages only. Statistical significance for continuous variables was evaluated using one-way analyses of variance (ANOVA) with applied Tukey’s honest significant difference (HSD) tests. A P value of less than 0.05 was considered statistically significant.

**Results**
Baseline MAP waveforms were collected prior to each ablation. Mean amplitude at baseline was 4.4±1.9 mV. The APD for baseline recordings was 336.5±59.0 msec. Baseline heart rate was 92±9 bpm. Heart rate was stable over all days and time points, with mean rates at 90±8 bpm.

**Lesion depth**
MAP quality at 60 minutes post-ablation was compared directly to lesion depth. Lesions were separated into the following groups: 1.00-1.99 mm (n=10), 2.00-2.49 mm (n=15), 2.50-2.99 mm (n=11), 3.00-3.99 mm (n=15), and ≥4.00 mm (n=11). Lesions which matured at 1 hour to between 1.00-1.99 mm deep were qualitatively assessed to be viable 23% of the time, 46.7% were noted damaged, and 30.0% were seen as ablated (Figure 21A). Between 2.00-2.49 mm, lesions were considered to be viable, damaged, and ablated in 13.3%, 33.3% and 53.3% of assessments respectively. Lesions over 2.50 mm (n=37) were noted to be viable only 3.6% of the time, and damaged 14.4%; these same regions were assessed to be ablated in 82.0% of measurements.
Waveform amplitudes were evaluated at 100 msec time points after the initial QRS deflections. MAP amplitudes for each lesion group are shown in Figure 21B and were grouped chronologically. There were no significant differences in MAP amplitudes for a given lesion depth at any time point. In other words, the MAP amplitudes immediately post-ablation, were not significantly different than those recorded at 60 minutes post-ablation: or at any measured time points in-between. Amplitudes immediately post-ablation and at 60 minutes were significantly greater for lesions 1.00-1.99 mm of depth, when compared to lesions with depths of either 2.50-2.99 mm, 3.00-3.99 mm, and ≥4.00 mm. Lesions with depths of 1.00-1.99 mm elicited MAP amplitudes at the 30 and 45-minute time points post-ablation, which were significantly greater than all other measured depths. No significant differences were observed between lesions with depths of 2.00-2.49 mm, 2.50-2.99 mm, 3.00-3.99 mm, or ≥ 4.00mm.
Figure 21. A) Depiction of monophasic action potential (MAP) quality with respect to lesion depth in mm. For each lesion 3 response were recorded, 1 per reviewer. B) MAP Amplitude compared to lesion depth. Lesions between 1.00-1.99 mm deep were significantly different than deeper lesions. No differences were observed between time points for a given depth.

Lesion surface area
Lesions were grouped into approximately equal bins according to surface area for analyses: <85.0 mm² (n=11), 85.0-99.9 mm² (n=12), 100.0-129.9 mm² (n=13), 130.0-174.9 mm² (n=14), and ≥175 mm² (n=12). MAP lesion quality was evaluated with respect to lesion surface area at 60 minutes post-ablation. Lesions less than 100 mm² in surface area resulted in viable lesion assessments in 18.8% of cases, damaged in 37.7%,
and ablated in 43.5% of instances. Lesions $\geq 100 \text{ mm}^2$ were noted to be viable in only 5.1% of measurements and ablated in 80.3%. Additionally, with increasing depth (as grouped above) corresponded to a consistent increase in the number of measurements marked as dead, as well as a decrease in those marked as damaged (Figure 22A).

Mean amplitudes for lesions in the aforementioned groups based on surface areas can are presented in Figure 22B. At the 15 minutes time points post-ablation, lesion with depths $<85.0 \text{ mm}^2$ had significantly higher measured amplitudes than those of $\geq 175.0 \text{ mm}^2$. Additionally, at the same time point, lesion depths between 85.0-99.9 $\text{ mm}^2$ had significantly smaller amplitudes than those of 130.0-174.9 and $\geq 175.0 \text{ mm}^2$. MAP recordings from induced lesions with $<85.0 \text{ mm}^2$ depths at both the 30 and 45 minutes time points post-ablation had significantly greater amplitude versus all lesion groups $\geq 100.0 \text{ mm}^2$. No significant differences were observed between any time point comparison for these assessed surface area groups.
Figure 22. A) Depiction of monophasic action potential (MAP) quality with respect to lesion surface area in mm$^2$. For each lesion 3 response were recorded, 1 per reviewer. B) MAP Amplitude compared to lesion surface area. Significant differences were found between lesion groups, however there were no differences between time points for a given area.

**Lesion volume**
Lesion volume was also evaluated with respect to MAP quality at 60 minutes. Lesions were grouped into approximately equal bins according to volume: <30.0 mm$^3$ (n=12), 30.0-39.9 mm$^3$ (n=12), 40-59. 9 mm$^3$ (n=10), 60.0-99. 9 mm$^3$ (n=15), and ≥100.0 mm$^3$ (n=13). Small lesions (those <30.00 mm$^3$) were reported as viable in only 25.0% of instances, about the same number of times they were noted to be ablated (27.8%).
However, as was seen in the depth and surface area results, as the lesion volume increased the instances of viable and damaged tissues decreased and the waveforms were more often reported as being from ablated myocardium (Figure 23A). Lesion between 60.0-99.9 mm³ were reported as viable only 4.4% of the time, damaged 8.9%, and ablated the remaining 86.7%. Overall lesions 40.0mm³ and larger resulted in 3.5% viable, 13.2% damaged and 8.3% ablated myocardium.

Relative MAP amplitudes were also correlated with the induced lesion volumes (Figure 23B). As with lesion depths and surface areas, there were no observed temporal changes in MAP amplitudes for the lesion volume groups analyzed. At the 15 minutes post-ablation time points, the MAP amplitudes for lesion volumes <30.0 mm³ were significantly higher than those for volumes ≥100.0 mm³. When compared across the 30-minute time points, for the MAP amplitude measurements, induce lesions with volumes <30.0 mm³ were significantly greater when compared to all other induced lesion volumes. Additionally, at 45 minutes post-ablation, the MAP amplitudes were larger for the <30.0 mm³ induced lesion volume group compared to those with volumes of 40.0-59.9 mm³, 60.0-99.9 mm³, or ≥100.0 mm³.
Figure 23. A) Depiction of monophasic action potential (MAP) quality with respect to lesion volume in mm$^3$. For each lesion 3 response were recorded, 1 per reviewer. B) MAP Amplitude compared to lesion volume. Significant differences were found between lesion groups, however there were no differences between time points for a given lesion volume.

**Discussion**
An ability to relatively assess the depths of generated myocardial lesions would be invaluable tool for optimizing the ablative treatments of cardiac arrhythmias. Here we evaluated the potential utility of recording MAPs as a means to approximate the underlying lesion depths, surface areas, and/or volumes; i.e., through both qualitative or
quantitative measures. Regardless of the induced lesion size, the relative MAP amplitudes, measured 100 msec after the beginning of the QRS, from known site of applied RF ablation were significantly reduced from the baseline amplitudes (p<0.05); indicating a strong sensitivity to identify lesion formation. Additionally, there were no significant differences associated with measured MAP amplitudes for up to an hour post-ablation.

Clinically, when utilizing RF ablation technologies for treating arrhythmia, electrophysiologists are continuously moving the catheters from one nearby cardiac location to another to create point-by-point lesions so to isolate the pulmonary veins from the left atrium. While technologies such as 3D mapping and navigation systems, fluoroscopy, and intracardiac echocardiography have enabled better visualizations of the relative catheter placements, it can be difficult as well as time consuming if one must backtrack so to ensure proper lesion formations (e.g., transmurality). Therefore, potential benefits in procedural efficacy, could result from better knowledge of the relative lesion depth, which we have indicated here can be determined with MAPs assessments: i.e., immediately post-ablation, with the added abilities to distinguish between unablated tissues, as well as therapeutic locations which will become lesions of 1.00-1.99 mm, 2.50-2.99 mm, 3.00-3.99 mm, and/or ≥4.00 mm depth for up to 1-hour post-ablation.

When the relative MAP waveform quality was compared to the assessed lesion depths, there was an observed strong correlation in the number of recordings evaluated as ablated as lesion depths increased. In other words, the data we present here are supportive for evaluating relative lesion depths using the qualitative assessment of MAPs; this was
especially consistent for identifying lesions greater than 2.5 mm deep. When looking at
the overall assessment of the lesions at the 60-minute time point, only 3.6% were
assessed as viable while 96.4% were deemed damaged or ablated: e.g., of the lesions two
marked as viable, one elicited a minimal lesion surface area which may have impacted
MAP quality.

Lesion depth also correlated significantly with quantified MAP amplitudes at the 60-
minute time points, with the subsequently determined lesion depths. Note, it still is
unclear to what myocardial depths viable tissues can lead to the ability to record a MAP
waveform [14, 16, 17]. However, in this study we demonstrated the abilities of MAPs to
distinguish between lesions with depths of 1.00-1.99 mm compared to those of 2.50 mm
or deeper: the deeper the lesion the more significant the decrease in MAP amplitude.
Therefore, one could hypothesize based on these finding, that the bulk of the MAP
waveforms recorded from healthy myocardium can be from cells between 2.0 and 2.5
mm below the epicardial surfaces: these depths were not significantly different from the
induced shallow lesions.

Induced RF lesion volumes and lesion surface areas also correlated well with the
estimated MAP waveform qualities. While lesion volumes were found to be directly
impacted by overall lesion depths, lesion surface areas were in general independent of
induced lesion depths; however, in general larger surface areas correlated with deeper
lesions. While it is impossible to completely dissociate these parameters, a larger lesion
set may enable a subsequent study evaluating lesions of a specific depth, but a variety of
surface areas. This would allow the determinations of how MAP qualities might be
impacted based solely on depths or areas.

There are a few limitations to note related to our study design. First, as mentioned previously, induced lesion depths, surface areas, and volumes were not independent from one another. For precise evaluations of lesion depths and surface areas, sub-sets of data could be analyzed with groups of like lesion depths and varying surface areas, or vice versa. Additionally, MAP waveform reviewers were allowed to interpret MAP quality based on their existing knowledge only; i.e., a set of parameters, or guidelines, may have resulted in more drastic differences between viable, ablated and damaged tissues; furthermore, the addition of more quality levels may increase the sensitivity of MAP quality as a tool.

**Conclusion**
There is a potential utility of recording cardiac MAPs as means to either quantitatively and qualitatively assess myocardial lesions created with RF ablative therapies. Relative MAP waveform qualities were found to be correlated with induced lesion depths, surface areas, and volumes. In addition, MAP amplitudes at 60 minutes post-ablation, decreased with induced lesion formation with depths greater than 1.00 mm; amplitudes were further decreased associated with lesions 2.50 mm and greater in depth. Finally, MAP amplitudes did not vary temporally for any measured lesion depths, surface areas, or volumes, indicating an ability to accurately assess RF induced lesions immediately post-ablation. Overall, MAP waveforms could provide valuable information relative to induced RF lesion sizes, which should increase a clinician ability to estimate lesion sizes during an ablation procedure.
Section III: Novel catheter concepts for the diagnosis and treatment of tachycardias

This final section focuses on developing catheter-based concepts which incorporate key experimental findings from the previous sections into novel catheters for the diagnosis and treatment of tachyarrhythmias.

Radiofrequency ablation for persistent atrial fibrillation patients has proven less successful than ablation for paroxysmal AF patients; this is likely due to the existence of AF substrates outside of the pulmonary veins. In some cases, these substrates are identified through the recording of complex fractionated electrograms with mapping and ablation catheters. Due to the focal nature of monophasic action potential (MAP) recordings it was hypothesized that the incorporation of MAP recordings capabilities onto various mapping arrays may aid in the identification of AF substrates.

A second catheter concept was tested for initial feasibility in the mapping of epicardial ventricular substrates. Currently, there are no catheters designed for epicardial mapping or ablation of ventricular tachycardias. In lieu of a dedicated device, physicians have made due with adapting endocardial technologies; however, these devices are limited in their ability to detect changes in repolarization properties and limit users to voltage mapping of the epicardial surface. The unique ability of MAPs to represent focal repolarization could aid in the identification of arrhythmic substrates, especially in channelopathies such as Brugada syndrome.
Circular catheter for monophasic action potential recording in the assessment of pulmonary vein isolation

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Preface

Pulmonary vein isolation (PVI) is a primary method in the treatment and ablation of paroxysmal atrial fibrillation (AF). Current catheters used to measure PVI can be limited in their ability to distinguish far-field signals from pulmonary vein potentials. The use of monophasic action potential recording capabilities could reduce these far-field signals and provide more precise information relating to PVI.

The prototypes presented in this work were conceptualized by Dr. Paul Iaizzo and myself. Prototyping was done in combination with the efforts of Julia Campion (Medtronic, Mounds View, MN), Carla Pfeiffer (Medtronic), and Gonzalo Martinez (Medtronic). Additionally, I was responsible for the preliminary testing of these devices with Dr. Mélèze Hocini (Centre Hospitalier Universitaire de Bordeaux, France) at the Visible Heart® Laboratory.
Summary

Objective: High rates of pulmonary vein (PV) reconnection have been reported after ablation for atrial fibrillation, likely due to the reconnection of tissues which were stunned during the ablation. While several catheters exist for PV mapping, these catheters have limited sensitivity due to influences from far-field electrogram recordings, specifically in the left superior PV. Due to the highly focal nature of monophasic action potential (MAP) recordings, it was hypothesized that their incorporation onto circular mapping technologies could improve detection of PV isolation.

Methods: Based on customer inputs and key design requirements, a PV ablation catheter was modified for MAP recording. This was done through the addition of spherical electrodes to the distal portion of the existing catheter design.

Results: The placement of MAP recording electrodes limited the testing of the concept in the PVs; the electrodes extended distally into the vein, and not radially into the tissue. Epicardial signals were collected and indicated MAP recordings were possible with this catheter concept.

Conclusion: MAP recordings with a circular mapping catheter are feasible, however further testing will need to be done. Future concepts should look modifying MAP electrode placement and incorporating a non-contact reference electrode for bipolar recordings. The combination of MAP recording capabilities onto a catheter which could also deliver ablative energy would be ideal for PVI assessment during AF ablation.
Introduction
Pulmonary vein isolation (PVI) with radiofrequency (RF) and cryoablative energies has been shown to have similar procedural success rates in the treatment of atrial fibrillation (AF) [1, 2]. In patients with recurrence post AF ablation, PV reconnection rates have been reported as high as 91%, however other studies have reported high rates of durable PVI (no reconnection) in 75% of PVs [3-5]. These PV reconnections are often the result of tissues, which were stunned or damaged during the initial ablation, later regaining electrical activity, enabling conduction between the PVs and the left atrium (LA).

During RF ablation, a circular mapping catheter (i.e. Lasso®, Biosense Webster, Diamond Bar, CA), is often used to assess PVI [7, 8]. During and after the delivery of point-by-point RF energy the Lasso® catheter is placed into the PV and electrical activity is evaluated. Another tool which can be used in evaluating PVI is the Achieve™ Mapping Catheter (Medtronic LLC., Dublin, Ireland). This mapping catheter is used in combination with the Arctic Front Advance™ Cryoballoon catheter (Medtronic). The Achieve™ catheter is placed into the PV and baseline PV electrical potentials are recorded. These potentials can then be monitored throughout the ablation to determine when PVI occurs. The time-to-isolation, or time from when the freeze begins until PV potentials disappear, has used to titrate the duration of energy application, leading to increased treatment success, reduced procedure times, and decreased adverse event rates [5, 8-10].

Clinical need
Physicians need a tool which can accurately measure the electrical activity at the LA-PV
junction, in order to assess PVI. Current measurement systems have several limitations. The first limitation is in electrode size. Larger electrodes will integrate electrical activity over a larger tissue area, causing a prolonged effect on electrogram recordings. Smaller electrodes allow for more precise electrogram recordings. A second limitation is the inter-electrode spacing. The closer two electrodes are together, the less far-field signal will be recorded. This is especially apparent in the mapping of the left superior (LS) PV, which is in close proximity to the left atrial appendage (LAA). Often when mapping in the vein, the LAA signals may be pronounced and confound interpretation of PV potentials. Unless the disappearance of the vein potentials is evident during real-time ablation, it can be difficult to discern if the PV is isolated. Monophasic action potential (MAP) recordings may reduce the impact of far-field signals and could provide immediate feedback on the viability of the underlying myocardium.

**Key design requirements**
The key design inputs (Table 6) are indicative of system components that would be required for a catheter designed to record MAPs for the assessment of PVI.

*Table 6. Key design requirements for a circular mapping catheter*

<table>
<thead>
<tr>
<th>Electrode Spacing</th>
<th>Contacting electrodes must be spaced to optimize array density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformability</td>
<td>Array must be able to conform to a variety of vein anatomies: oval, circle, large/small diameters</td>
</tr>
<tr>
<td>Electrode Shape</td>
<td>Contacting electrodes must be able to cause focal electrical depolarization</td>
</tr>
<tr>
<td>Reference Electrode</td>
<td>Non-contacting reference electrode needs to be in close proximity to contact electrodes</td>
</tr>
<tr>
<td>Electrode Contact</td>
<td>Array must provide 10-15 grams of contact force without risk of perforation or other tissue trauma</td>
</tr>
</tbody>
</table>
Pugh chart
Based on the above design inputs and the customers’ needs a Pugh chart was created to determine a catheter concept to move forward with (Table 7). The pulmonary vein ablation catheter (PVAC) based design will be explored further.

Table 7. Pugh chart for a circular mapping catheter

<table>
<thead>
<tr>
<th>Design Criteria</th>
<th>Achieve</th>
<th>PVAC</th>
<th>Basket Catheter</th>
<th>Balloon with Electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Design #1</td>
<td>Design #2</td>
<td>Design #3</td>
<td>Design #4</td>
</tr>
<tr>
<td>Weight</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Substrates Coverage</td>
<td>6</td>
<td>2</td>
<td>-2</td>
<td>1</td>
</tr>
<tr>
<td>Non-Contact Electrode Compatibility</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sufficient structural support</td>
<td>3</td>
<td>-1</td>
<td>2</td>
<td>-3</td>
</tr>
<tr>
<td>Weighted Points Total</td>
<td>42</td>
<td>54</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>Unweighted Points Total</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

Initial concepts and prototypes
In this concept a PVAC catheter was modified. To enable the recording of MAPs, rounded spheres were added to each existing base electrode. To do this, on each electrode a small scratch/defect was created in the surface most distal to the catheter handle. A small amount of silver solder was then added onto the existing electrode, taking care not to melt the surrounding catheter components (Figure 24). The solder spheres were approximately 1 mm in diameter. Once the rounded electrode was created, the base electrode was covered in a UV curable polymer to allow electrical recordings from only the rounded portions (Figure 25A and B).
Figure 24. A pulmonary vein ablation catheter electrode ring was modified through the addition of small balls of conductive material to the existing base electrodes.

Figure 25. A pulmonary vein ablation catheter electrode was masked with a UV polymer to allow electrical recording from only the spherical part of the electrode.

Preliminary testing and physician feedback
This concept was tested at the Visible Heart® Laboratory with Dr. Mélèze Hocini.

Initially the catheter was placed into the left atrium through a cannulated PV. While the catheter was easily manipulated within the atrium, there was not sufficient interaction between the MAP electrodes and the myocardium in the PVs. Because of the dome placement on the distal portion of the electrodes, the domes protruded distally into the vein, rather than radially into the tissue.
To evaluate the feasibility of MAP recordings with this concept, the catheter was also placed against the epicardial surface of a reanimated swine heart. The catheter was pressed against the left ventricular epicardium. Unipolar waveforms were recorded from each electrode with respect to Wilson’s Central Terminal (WCT). When force was applied to the catheter shaft some depolarization was seen, however the force was not evenly distributed to each electrode. Additionally, force was manually applied to the entire ring, causing all electrodes to press into the myocardium. This caused waveforms reminiscent of MAPs to be visualized on some unipolar channels (Figure 26).

![Figure 26. Shown here are representative waveforms from the prototyped catheter. These channels are representative of the unipolar MAP recordings. The white arrows indicate representative monophasic action potential waveforms. Amplitudes for these waveforms range between 1-3mV.](image)

**Future directions**

With this initial prototype we were able to obtain valuable feedback for the development of future devices. First, the prototype catheter did not have a non-contact reference
electrode for bipolar MAP recordings. While unipolar MAPs are beneficial, they lack the focal specificity that is recorded with near-field bipolar recordings. While bipolar waveforms can be recorded between contacting electrodes this could lead to the misinterpretation of data. When two electrodes are both causing focal depolarization, it is unclear what tissue is responsible for the resultant MAP waveform. It is hypothesized that if E1 and E2 were both depolarizing electrodes, that then the direction of the MAP waveform (positive versus negative) would indicate which electrode has better contact.

Secondly, the structure of the catheter was not conducive to MAP recording capabilities. The MAP electrodes will need to be angled more radially in order to improve tissue contact. Additionally, the catheter may not provide enough radially force to cause focal depolarizations. Future devices must incorporate the changes in MAP electrode orientation to further evaluate feasibility.

Finally, it was discovered upon the completion of prototype testing that the UV curable polymer, used to mask the base electrodes, was not compatible with the Krebs-Henseleit buffer used in these studies. It is unclear at what point in the experiments the polymer began to disintegrate. It is clear though, that without the masking of the base electrodes, focal MAP waveform quality will be diminished with far-field electrogram recordings. Future prototypes must look into alternative masking agents, or the creation of a custom catheter with only dome like electrodes, eliminating the need for a masking agent.

In conclusion, the recording of MAPs for PVI assessment is possible, however further development of electrode concepts is needed. Future concepts should look at adjusting
the placement of the spherical electrodes so to optimize the electrode-tissue interface. A non-contact reference electrode will also need to be added for proper evaluation of bipolar MAPs. Additionally, the spherical electrodes must be the only active recording electrodes, in other words if an existing electrode is modified the base electrode must remain electrically isolated from the myocardium. The combination of MAP recording capabilities onto a catheter which could also deliver ablative energy would be ideal for PVI assessment during the ablation of AF.
Mapping catheter for monophasic action potential recording in the identification of arrhythmic substrates

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\textsuperscript{2} Department of Surgery, University of Minnesota, Minneapolis, MN

Preface
Pulmonary vein isolation (PVI) is a primary method in the treatment and ablation of paroxysmal atrial fibrillation (AF); however, PVI has been less success in patients with persistent and long-standing persistent AF, likely due to atrial remodeling and the existence of AF triggers outside of the pulmonary veins. The use of monophasic action potential recording capabilities could reduce, or even eliminate, the influence of far-field signals, resulting in more precise identification of AF substrates.

The prototypes presented in this work were conceptualized by Dr. Paul Iaizzo and myself. Prototyping was done in combination with the efforts of Julia Campion (Medtronic, Mounds View, MN), Carla Pfeiffer (Medtronic), and Gonzalo Martinez (Medtronic). Additionally, I was responsible for the preliminary testing of these devices with Dr. Boaz Avitall (University of Illinois, Chicago, Illinois), Dr. Michael Franz (VA Hospital, Washington D.C.), and Dr. Mélèze Hocini (Centre Hospitalier Universitaire de Bordeaux, France) at the Visible Heart® Laboratory.
Summary

Objective: Pulmonary vein (PV) ablation for patients with persistent atrial fibrillation (AF) has been less successful than for patients with paroxysmal AF, presumably because of triggers originating away from the PVs. Efforts have been made to increase ablation effectiveness by targeting non-PV locations, including arrhythmogenic electrophysiological sources. Due to the highly focal nature of monophasic action potential (MAP) recordings, it was hypothesized that their incorporation onto mapping arrays could improve the detection of these arrhythmogenic substrates.

Methods: Based on customer inputs and key design requirements, a multiarray ablation catheter was modified for MAP recordings. This was done through the addition of spherical electrodes to the distal portion of the existing catheter design.

Results: Unipolar MAP waveforms were recorded from endocardial and epicardial locations on the atria and ventricles. Sufficient contact force required for MAP recordings was not obtained in some cases.

Conclusion: MAP recordings with a multiarray mapping catheter are possible, however future concepts will need to optimize the contact force generated by the recording electrodes and included a non-contact reference for bipolar recordings. The combination of ablative energy would be ideal for the subsequent ablation of identified arrhythmic substrates.
Introduction
Atrial fibrillation (AF) is defined by irregularly irregular activation of the left and right atria. Isolation of the pulmonary veins (PVs), using radiofrequency or cryogenic ablation, is a common practice that has been reported to have a high rate of treatment success. Using a pulmonary vein ablation catheter (Medtronic, Dublin, Ireland) success rates were reported as high as 83% in paroxysmal AF [1]. However, treatment success is lower for patients with persistent AF, presumably because of AF triggers originating away from the PVs. As a result, efforts have been made to increase ablation effectiveness by targeting non-PV locations, including ablation of anatomical structures such as the left atrial appendage as well as arrhythmogenic electrophysiological sources, such as rotors and complex fractionated electrograms (CFAEs) [2, 3]. These electrophysiological substrates can be identified through intracardiac mapping and have been implicated in the initiation and maintenance of AF. As a result, novel approaches may be required to facilitate the identification and localization of non-PV targets for ablation [2-5].

Catheter concepts have been developed specifically to map and identify these electrophysiological sources. One catheter developed for the identification of CFAEs is the Multiarray Ablation Catheter (MAAC) (Medtronic). The MAAC is a cross-shaped array with 1 pair of electrodes on each of the 4 catheter arms [6, 7]. The electrodes are 2 mm long with 2 mm inter-electrode spacing; this configuration allows for 4 bipolar, or 8-unipolar recordings. This catheter is used for mapping and ablation of CFAEs, specifically those originating from the posterior, superior, and anterior aspects of the left atrium. Another multiarray catheter is the PentaRay® Catheter (Biosense Webster,
Diamond Bar, CA). The PentaRay® catheter is a 5-spline catheter with 4, 1 mm electrodes on each spline. There are several versions of this catheter with different inter-electrode spacing configuration (either a 4-4-4 mm spacing configuration, or a 2-6-2 mm configuration). The catheter can be used for electroanatomical mapping in conjunction with a navigation system to provide mapping and activation data for all four chambers of the heart [8, 9].

**Clinical need**
Physicians need a tool which can record detailed electrical signals from a large number of atrial locations. Due to the need to cover a large amount of substrate with each catheter placement, a catheter with an array of electrodes is ideal. The catheter must also be able to distinguish slight changes in activation timing and patterns between the electrodes; minimizing far-field input via small inter-electrode spacing will be key in assessing activation sequence and local electrical activity accurately. It is hypothesized that CFAEs will exhibit unique monophasic action potential (MAP) waveforms and that activation patterns will be easily identifiable with MAP recordings. The CFAEs may then be targeted for ablation, potentially increasing the ablation effectiveness for AF treatment.

**Key design requirements**
The key design inputs (Table 8) are indicative of system components that would be required for feasibility testing of a catheter designed to record monophasic action potentials, the identification of CFAEs, and other non-PV arrhythmic substrate in the left and right atria.
Table 8. Key design requirements for a multiarray mapping catheter

<table>
<thead>
<tr>
<th>Substrate Coverage</th>
<th>Array tissue coverage area needs to be large enough to map the chamber with limited catheter manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter Size / Maneuverability</td>
<td>Catheter array must be small enough to be manipulated into all anatomic locations</td>
</tr>
<tr>
<td>Electrode Spacing</td>
<td>Contacting electrodes must be spaced to optimize array density</td>
</tr>
<tr>
<td>Electrode Shape</td>
<td>Contacting electrodes must be able to cause focal electrical depolarization</td>
</tr>
<tr>
<td>Reference Electrode</td>
<td>Non-contacting reference electrode needs to be in close proximity to contact electrodes</td>
</tr>
<tr>
<td>Electrode Contact</td>
<td>Array must provide 10-15 grams of contact force without risk of perforation or other tissue trauma</td>
</tr>
</tbody>
</table>

**Pugh chart**

Based on the above design inputs and the customers’ needs a Pugh chart was created to determine a catheter concept to move forward with (Table 9). Based on the weighted design criteria a MAAC based catheter will be explored.

Table 9. Pugh chart for a multiarray mapping catheter

<table>
<thead>
<tr>
<th>Concepts for MAP recording for CFAE assessment</th>
<th>MAAC</th>
<th>PVA</th>
<th>Basket Catheter</th>
<th>Decapolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Criteria</td>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substrate Coverage</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Catheter Size/Maneuverability</td>
<td>6</td>
<td>1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Electrode Array Configuration</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-Contact Electrode Compatibility</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sufficient structural support</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>-3</td>
</tr>
<tr>
<td>Weighted Points Total</td>
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<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Unweighted Points Total</td>
<td>12</td>
<td>5</td>
<td>2</td>
<td>-1</td>
</tr>
</tbody>
</table>

**Initial concepts and prototypes**

In this concept a MAAC catheter was modified. To enable the recording of MAPs
rounded spheres were added to each existing base electrode. To do this, on each electrode a small scratch/defect was created in the surface most distal to the catheter handle. A small amount of gold-based solder was then added onto the existing electrode, taking care not to melt the surrounding catheter components (Figure 27). Once the rounded electrode was created, the base electrode was covered in a UV curable polymer to allow electrical recording from only the rounded portion. Additionally, a wire was run the length of the catheter and placed in the center of the electrode array, proximal to the tip electrodes (Figure 28). This wire was to serve as a non-contact reference for bipolar MAP recordings. A second prototype design was made using the above methods, however the electrode array was modified to be a 4 electrode configuration versus an 8 electrode configuration (Figure 29).

Figure 27. Electrodes from a multi-array ablation catheter were modified through the addition of small spherical electrodes to existing base electrodes. The sphere sizes were relatively consistent, however in many cases the surrounding electrical and structural components were compromised.


Figure 28. A multi-array ablation catheter was modified for bipolar monophasic action potential recordings. Spheres were added to each existing electrode and the base was coated in a UV curable polymer. A wire was also added to the center of the array to serve as a non-contact reference electrode.

Figure 29. The electrodes array from a multi-array ablation catheter was modified such that there were only 4 electrodes instead of 8 to increase contact force.

Preliminary testing and physician feedback
This concept was tested at the Visible Heart® Laboratory with Drs. Boaz Avitall, Michael Franz, and Mélèze Hocini. Unipolar signals were recorded from each tip electrode to Wilson’s Central Terminal. In cases where a non-contact reference electrode was used, bipolar signals were recorded between a tip electrode and the reference electrode.

During in situ testing the 8-electrode catheter was placed on the epicardial surface of an in situ swine heart, following a median sternotomy. For epicardial recordings a large amount of contact force was necessary to create MAP waveforms. However, when focal
depolarization was successful, unipolar MAP waveforms were recorded from the epicardial right ventricular outflow tract (Figure 30). Additionally, MAP recordings were obtained from the epicardial lateral wall of the left ventricle in situ (Figure 31). A second 8-electrode with silver solder, instead of gold, was also used for epicardial recordings. The silver catheter experienced significantly more drift in recordings; making it virtually impossible to record stable signals (data not shown).

Figure 30. Unipolar monophasic action potentials were recorded from the epicardial surface of the right ventricular outflow tract of a swine heart in situ. The white arrow indicates far-field influence in the recording, due to a lack of a close-bipolar reference electrode.
Figure 31. Unipolar monophasic action potentials were recorded from the epicardial surface of the lateral left ventricle of a swine heart in situ. The white arrow indicates far-field influence in the recording, due to a lack of a close-bipolar reference electrode.

Prototype testing was also conducted on reanimated swine hearts. MAPs were collected from both the left atrium and left ventricle. In the left atrium, the catheter was manipulated to the mitral annulus. Unipolar MAP waveforms were elicited when sufficient force was applied to the myocardium (Figure 32). Additionally, when the MAP catheter was advanced into the left ventricular apex MAPs were also recorded.
Figure 32. Unipolar monophasic action potentials were recorded from the lateral wall of the left atrium, near the mitral isthmus, in a reanimated swine heart. Amplitudes were between 2-4 mV.

**Future directions**

These prototype catheters demonstrated the ability of a multiarray catheter to elicit MAP recordings. However, during these studies there were several key learnings which will help improve future prototypes.

First is the optimization of the electrodes. In these prototypes either silver or gold-based solders were used. It was realized that material selection, even for feasibility studies, was crucial, as it dramatically impacted in the quality of the MAP waveforms. Additionally, the placement of the reference electrode will need to be optimized. For epicardial recordings the reference was a wire attached to the catheter shaft; the wire was then electrically connected to the tip electrodes with a conductive gel. Ideally there would be a unique reference just proximal to each tip electrode. One possible solution is to modify the base electrode such that the cooling fin which extends away from the tip could be
isolated and used as the reference.

Feedback from physicians also brought into question the size and shape of the electrode array and questioned the overall utility. With the 8 electrode array it was difficult to induce sufficient depolarization with the electrodes to record MAPs. While the 4 electrode configuration seemed to provide more mechanical push, the array was not stable enough to be tested adequately. Large electrode arrays can often be difficult to manipulate endocardially, and as pointed out by one physician, may not reach into small gaps between pectinate structures.

Overall a multiarray MAP recording concept demonstrated an ability to record both endocardial and epicardial MAPs from the atria and ventricles. Future concepts will need to optimize the MAP electrodes through modifying the base electrode such that a spherical tip can depolarize the myocardium, while the cooling-fin can serve as a non-contacting reference electrode. Additionally, various array configurations should be evaluated for mapping endocardial atrial anatomies. The combination of MAP recording capabilities onto a catheter which could also deliver ablative energy would be ideal for the identification, and subsequent ablation, of CFAEs and other endocardial arrhythmic substrates.
Pericardial system for monophasic action potential recording in the diagnosis and treatment of ventricular tachyarrhythmias

Patent filed in February of 2017 (US15441501), patent pending.

Megan M Schmidt, BS\textsuperscript{1,2}; Paul A Iaizzo, PhD\textsuperscript{1,2}

\textsuperscript{1} Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN
\textsuperscript{2} Department of Surgery, University of Minnesota, Minneapolis, MN

Preface

Ventricular tachyarrhythmias are responsible for over 325,000 deaths in the United States each year; many of these arrhythmias originate from the epicardial surface of the heart. To date there are no catheters designed for the mapping and ablation of epicardial ventricular arrhythmias. The recording of monophasic action potentials could allow for the unique visualization of repolarization patterns, which would be otherwise impossible with traditional electrogram recordings.

The prototypes presented in this work were conceptualized by Dr. Paul Iaizzo and myself and have been submitted as a US patent application (US15441501). I was responsible for prototype construction, and for the preliminary testing of these devices with Dr. Boaz Avitall (University of Illinois, Chicago, Illinois) and Dr. Michael Franz (VA Hospital, Washington D.C.) at the Visible Heart® Laboratory.
Summary
Objective: Ventricular tachycardias, such as channelopathies like Brugada Syndrome, are often caused by abnormal substrate on the epicardial surface. However, there are no devices available today that were designed for epicardial mapping/ablation of the ventricles. Here we created a custom mapping catheter, with monophasic action potential (MAP) recording capabilities, specifically for the identification of abnormal epicardial substrates.

Methods: Initially a custom balloon concept was created, utilizing two inner balloons for inflation and generation of catheter contact force, and an outer balloon as a structure on which MAP recording electrodes could be placed. A second concept, based off a surgical paddle lead, was also developed through the addition of spherical MAP recording electrodes.

Results: When tested, the initial balloon concept was much too large in comparison to the anterior surface of the heart. Additionally, the catheter was not able to maintain stable contact with the epicardium for MAP recordings. The second concept was able to elicit MAP recording from the epicardial surface of the right ventricular outflow tract, a common target in epicardial ablations.

Conclusion: Epicardial MAP recordings for the identification of irregular ventricular substrates may be feasible. Array size and shape, as well as electrode placement will be critical inputs to elicit high quality MAPs. In combination with ablative energies, this type of system could improve the efficacy of epicardial ventricular ablations.
Introduction
Sudden cardiac death (SCD) from ventricular tachycardias (VT) account for more than 325,000 deaths in the United States each year [1-3]. In individuals under the age of 40, early repolarization diseases such as Brugada syndrome, Wolff-Parkinson-White syndrome, and Long-QT syndrome are often thought to account for many cases of SCD [2, 4]. Brugada syndrome is identified by an elevation in the ST-segment on the right precordial leads [5, 6]. In 2011 it was shown that Brugada syndrome was associated with delayed depolarization in the epicardial surface of the right ventricular outflow tract, thus making this a target for ablations [7, 8]. Monophasic action potential (MAP) recordings could be able to uniquely identify these altered repolarization pathways with higher fidelity than typical electrogram recordings.

There are no devices available today that were designed for epicardial mapping/ablation of the ventricles; however endocardial systems have been used in lieu of a custom epicardial tool. One common system used in the epicardial mapping of VT substrates is the Carto® EP mapping system (Biosense Webster, Diamond Bar, CA) [7-9]. The mapping catheter is often the same catheter used in the ablation, such as the ThermoCool® SmartTouch® catheter (Biosense Webster). In these procedures, access to the epicardial surface is gained through a pericardial access point. The catheter is then used to record electrogram voltages across the desired area. The voltages are then separated into dense scar and border zones, defined by amplitudes <0.5 mV and < 1.5 mV respectively. Additionally, abnormal electrograms can be tagged on the mapping system as those meeting some existing criteria: e.g. wide duration (<80 msec), multiple
electrogram peaks (>3), or those containing delayed components [9]. After identification of the abnormal and/or border regions epicardial ablations are performed to eliminate irregularities.

**Clinical need**
Physicians need a tool with which they can accurately identify the origin of epicardial based VTs. The catheter must be able to access the right and left ventricular epicardium through minimally invasive means such as substernal pericardial access point. The catheter must be able to record from all regions of the ventricular epicardium including the diaphragmatic surface. Additionally, the catheter should be composed of an array of electrodes, to identify regions of earliest activation, as well as the presence of rotors and abnormal repolarization patterns. Finally, the catheter should be able to distinguish regions of low electrogram voltage from epicardial fat or coronary vasculature.

**Key design requirements**
The key design inputs listed below (Table 10) are indicative of system components that would be required for feasibility testing of an epicardial monophasic action potential recording catheter for the identification of ventricular arrhythmic substrates.
Table 10. Key design requirements for a pericardial mapping array

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conformability</td>
<td>Array must be able to conform to the epicardial surface</td>
</tr>
<tr>
<td>Substrate Coverage</td>
<td>Electrode array needs to be large enough to identify action patterns and rotors</td>
</tr>
<tr>
<td>Pericardial Accessibility</td>
<td>Catheter must be collapsible to be used in pericardial and substernal access</td>
</tr>
<tr>
<td>Catheter Stability</td>
<td>Electrode array needs to remain stationary (relative to the epicardial surface) to elicit stable electrical recordings</td>
</tr>
<tr>
<td>Electrode Spacing</td>
<td>Contacting electrodes must be spaced to optimize array density</td>
</tr>
<tr>
<td>Electrode Shape</td>
<td>Contacting electrodes must be able to cause focal electrical depolarization</td>
</tr>
<tr>
<td>Reference Electrode</td>
<td>Non-contacting reference electrode needs to be in close proximity to contact electrodes</td>
</tr>
<tr>
<td>Electrode Contact</td>
<td>Array must provide 10-15 grams of contact force without risk of tissue trauma</td>
</tr>
</tbody>
</table>

Pugh chart

Based on the design inputs and the customers’ needs a Pugh chart was created to determine a catheter concept to move forward with (Table 11). Based on the weighted design criteria a custom balloon catheter was selected.

Table 11. Pugh chart for a pericardial mapping catheter

<table>
<thead>
<tr>
<th>Concepts for MAP recording for identification of VT/VF substrates</th>
<th>MAPAC</th>
<th>MAP4</th>
<th>Decapolar</th>
<th>Custom Balloon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design Criteria</td>
<td>Weight</td>
<td>Design #1</td>
<td>Design #2</td>
<td>Design #3</td>
</tr>
<tr>
<td>Epicardial Conformability</td>
<td>9</td>
<td>-3</td>
<td>-1</td>
<td>3</td>
</tr>
<tr>
<td>Substrate Coverage</td>
<td>9</td>
<td>1</td>
<td>-2</td>
<td>2</td>
</tr>
<tr>
<td>Catheter Size/Maneuverability</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Electrode Array Configuration</td>
<td>6</td>
<td>2</td>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>Pericardial Accessibility</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-Contact Electrode Compatibility</td>
<td>3</td>
<td>-1</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>Sufficient structural support</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Weighted Points Total</td>
<td>3</td>
<td>3</td>
<td>63</td>
<td>75</td>
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<tr>
<td>Unweighted Points Total</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>
Initial concepts and prototypes
It was determined after an extensive patent search that no previous IP was present in this area. A patent application was filed, and approval is currently pending approval (US15441501). The illustrations shown are from this patent application.

A prototype balloon catheter was designed. The catheter was composed of 3 main parts: MAP recording electrodes, an outer pocket, and 2 inner balloons (Figure 33 and 34). The electrodes were round spheres attached to thin, but rigid, support wires. The outer balloon was sized such that the 8 electrodes could be equally spaced in two columns. Additionally, the outer pocket was made large enough to allow for 2 cylindrical balloons to fit side by side. The inner balloons, when inflated, provided the contact force between MAP electrodes and the epicardium required for MAP recordings (using counter pressure from the pericardium).

Figure 33. The prototype concept and patent renderings (US15441501) for the pericardial mapping balloon for monophasic action potential recording on the epicardial surface of the ventricles. The left two images show the balloon from the bottom (surface contacting the myocardium) and the right two images show the balloon from the top (side contacting the pericardium). The main catheter components are labeled in the patent drawings: 38 – outer structural balloon/pocket, 40 – inner balloons used for inflation and generation of contact force, and 44 – spherical electrodes for monophasic action potential recording.
Figure 34. The prototype concept and patent renderings (US15441501) for the pericardial mapping balloon for monophasic action potential recording on the epicardial surface of the ventricles. The balloon is shown from the side and the electrode can be seen protruding from the surface. The main catheter components are labeled in the patent drawings: 38 – outer structural balloon/pocket (not labeled in this drawing), 40 – inner balloons used for inflation and generation of contact force, and 44 – spherical electrodes for monophasic action potential recording.

**Preliminary testing and physician feedback**
This prototype concept was tested, and feedback was obtained from two leading electrophysiologic experts: Dr. Boaz Avitall and Dr. Michael Franz. In prototype testing only unipolar MAPs were recorded, using Wilson’s Central Terminal as a reference. A median sternotomy was performed, and the catheter was inserted into the pericardial space through a small opening. It was immediately clear that the overall size was much too large with respect to the surface of the heart (Figure 35). Additionally, the electrodes were unable to engage in a fixed location on the myocardium, moving constantly with the cardiac and respiratory cycles, and were unable to elicit MAP waveforms.
Second generation concepts and prototypes
Upon feedback from the physicians it was clear that there was a need for an epicardial mapping array, however the initial balloon prototype needed much improvement. Our second-generation concept was designed off a neurostimulation surgical paddle lead. The flat circular electrodes acted as a base on which spherical MAP electrodes could be added (Figure 36). Additionally, the flat back of the lead was modified into a rounded dome to provide the mechanical force needed for MAP recordings, provided by the inner balloons in the previous concept.
Second generation testing and physician feedback

The second pericardial mapping prototype was tested on a swine heart after a median sternotomy. The device was inserted through a small opening in the pericardium and placed on the anterior surface of the right ventricular outflow tract. A wire was placed on the proximal endo of the device (on the back of the lead) to act as a non-contact reference for bipolar MAP recordings. In comparison to the initial balloon concept, this second device was significantly smaller and easier to manipulate in the pericardial space (Figure 37). Additionally, preliminary results demonstrated the ability to record MAP waveforms with electrodes in this configuration (Figure 38). It should be noted however, that the electrodes closest to the reference (electrode 3 and 4) were the only electrodes which elicited bipolar MAP recordings.
The surgical lead based prototype was inserted into the pericardial space. The dotted outline indicates the cardiac silhouette, while the solid white outline is around the prototype.

Figure 38. A second generation pericardial mapping prototype was used on the right ventricular epicardium of an in situ swine heart. Waveforms representative of monophasic action potentials were recorded on bipolar pairs between electrodes 3 and 4 and a non-contact reference electrode.

**Conclusion**

The area of pericardial/epicardial mapping is one that is vastly underdeveloped. As more epicardial ablations for VTs, like Brugada syndrome, are being performed the need for a
tool designed specifically for epicardial mapping is increasing. While the concepts shown here are promising, there is still much that can be done to improve their ability to detect and diagnoses these arrhythmias.

One of the major hurdles in epicardial mapping and ablation is the presence of epicardial fat. These initial feasibility studies were conducted on swine hearts, which have significantly less epicardial fat than human hearts. When electrograms are recorded from regions with high epicardial fat, their amplitude is reduced, which may be misinterpreted as non-viable, or scarred tissue. The use of MAP recording capabilities would enable better distinguish between these regions.

In order for the elicitation of high-quality, focal MAP recordings, there must be a near-by non-contacting reference electrode. In these concepts bipolar MAPs were only elicited from the electrodes nearest the reference. A more central, or second reference could improve MAP recording capabilities. Additionally, the single row electrode arrangement used in the second generation concept is less conducive to activation mapping and the identification of rotors. A 2-by-2 button like array may provide added benefit in the identification of irregular ventricular substrate.

In conclusion, epicardial MAP recordings for the identification of irregular ventricular substrates may be feasible. Array size and shape will be critical inputs for the ability to record MAPs from a large range of epicardial regions, both anterior and posterior. Additionally, it will be important to optimize the electrode-tissue interface, so that stable recordings can collected. In combination with ablative energies, such as radiofrequency
and/or cryoablation, this type of system could greatly improve the efficacy of epicardial ventricular ablations.
Bibliography

Section 1.1 – The Visible Heart® project and methodologies


Section 1.2 – Reproducible cardiac action potentials


Section 2.1 – Contact force for monophasic action potential recordings


Section 2.2 – Radiofrequency lesion assessment


Section 3.1 – Circular mapping catheter


Section 3.2 – Multiarray mapping catheter


Section 3.3 – Pericardial mapping catheter


Appendices

Appendix A: Published Conference Abstracts
Recording of monophasic action potentials simultaneously from both the epicardial and endocardial surfaces of porcine hearts

Selected for poster presentation at TCT, 2014 in Washington D.C.

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³ Veteran Affairs and Georgetown University Medical Center, Washington D.C., D.C.

Objective: Monophasic Action Potentials (MAPs) are electrical signals that represent the focal depolarizations and repolarizations of cardiac myocytes. The detection of MAPs via applied catheters may aid in determining both characteristic waveforms as well as the relative viability of the underlying cardiac tissue. For example, such detection would be beneficial in cases of atrial fibrillation, where ablative therapies are used to kill the cells triggering the arrhythmia. By recording MAPs at the trigger site post-ablation, the success of the treatment can be assessed immediately, and corrected if necessary. The purpose of the present study was to collect and compare signature endocardial and epicardial MAPs from isolated swine hearts.

Methods: Hearts from swine were reanimated using previously described Visible Heart® methodologies: each heart was functioning in a normal sinus rhythm. Modified 7 Fr mapping catheters, with 4 ball electrodes and 2 ring electrodes each, were placed upon the epicardial surface while another was inserted into the heart. The catheters were arranged such that both recorded from the same approximate anatomical location. This
was verified through internal imaging with an endoscope and an overhead camera (and in some cases fluoroscopy). Endocardial and epicardial MAPs, along with the ECG, were recorded using a multichannel recorder.

Figure 1. A) Data collection from an endocardial catheter in the right atrial appendage of a reanimated swine heart. B) Endocardial and epicardial monophasic action potential recordings from the right ventricular apex.

**Results:** MAPs were recorded from both atrial and ventricular locations on the right side of the heart. Preliminary results show that the profile of MAPs when recorded in the right ventricular outflow tract (RVOT) differ for epicardial and endocardial sites. When comparing recordings taken in the right ventricle however, the profile of epicardial and endocardial MAPs were nearly identical.
Table 1. Monophasic action potential properties from endocardial and epicardial comparisons.

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>Change in Depolarization Rate (mV/s)</th>
<th>Δ APD30 (ms)</th>
<th>Δ APD60 (ms)</th>
<th>Δ APD90 (ms)</th>
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</thead>
<tbody>
<tr>
<td>Atrium</td>
<td>14</td>
<td>210.76±785.87</td>
<td>9.58±29.91</td>
<td>1.08±22.67</td>
<td>-6.74±40.94</td>
</tr>
<tr>
<td>RVOT</td>
<td>25</td>
<td>204.47±331.16*</td>
<td>2.04±36.05</td>
<td>1.04±40.59</td>
<td>-3.94±37.77</td>
</tr>
<tr>
<td>Ventricle</td>
<td>31</td>
<td>142.98±476.88</td>
<td>3.19±42.21</td>
<td>6.35±40.29</td>
<td>9.23±29.96</td>
</tr>
</tbody>
</table>

**Conclusion**: In cases of atrial fibrillation an ablation may be performed either epicardially or endocardially on the myocardium: attempting to make induced lesions transmural. The detection of Monophasic Action Potentials using a MAPs catheter can be used to determine the relative, acute, viability of cardiac tissue in a specific area, which can lead to a higher rate of success for the treatment of atrial fibrillation.
Comparison of monophasic action potentials recorded simultaneously in the right and left atrium in re-animated porcine hearts

Selected for poster presentation at ACC, 2015 in San Diego, California.

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\textsuperscript{2} Department of Surgery, University of Minnesota, Minneapolis, MN
\textsuperscript{3} Veteran Affairs and Georgetown University Medical Center, Washington D.C., D.C.

Objective: Monophasic Action Potentials (MAPs) are electrical signals that represent the focal depolarizations and repolarizations of cardiac myocytes. The detection of MAPs via applied catheters may aid in determining both characteristic waveforms as well as the electrical activity of the underlying cardiac tissue. Recording MAPs in the right and left atria simultaneously can lead to a better understand the depolarization and repolarization times. In addition, we can use this methodology to deduce these values change during arrhythmias. The purpose of the present study was to collect and compare MAPs recorded from the left and right atria in isolated swine hearts.

Methods: Hearts from swine were re-animated using previously described Visible Heart\textregistered methodologies: each heart was functioning in a normal sinus rhythm. Modified 7 Fr mapping catheters, with 4 ball electrodes and 2 ring electrodes each, were placed upon the endocardial surface of the right and left atria. The locations of the catheters were verified through internal imaging with endoscopes and fluoroscopy. Right and left atrial MAPs, along with the ECG, were recorded using a multichannel recorder.
Figure 1. The left and right atrium were divided into 6 distinct zones where the right atrium consisted of zones A-F and the left atrium consisted of zones G-L. Images are modified from the Atlas of Human Cardiac Anatomy.

**Results:** Preliminary results show the activation times (AT) for the right atrium were around 70 msec shorter than those of the left atrium (n = 10). When looking at the time taken to repolarize by 90% (APD90) the Right Atrium depolarized slightly slower, taking about 9 msec longer on average. These two results combined lead to the right atrium having shorter repolarization time than the left atrium by about 52 msec (AT + APD90). Arrhythmias were induced in both the right and left atria and the relative activation/repolarizations were recorded.
Figure 2. Comparison of half maximum duration for monophasic action potentials recorded in the left (Zones G and J) and right (Zones B, C, E, and F) atria. The half maximum duration for Zone E was significantly longer than that of Zone G when compared using ANOVA and Tukey HSD ($p < 0.05$).

**Conclusion:** The assessment of Monophasic Action Potentials simultaneously recorded from the myocardium in both the right and left atria, can lead to a better understanding of the conduction pathways and the origin of arrhythmias. Using this approach, we can begin to better understand the specifics behind the changes in right and left atrial contractions, and how they are altered during arrhythmias.
In Vitro Evaluations of Cardiac Mapping Catheters Designs and Utilities: Employing Visible Heart® Methodologies

Selected for poster presentation and publication at DMD 2016 in Minneapolis, MN

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Background
Cardiac monophasic action potentials (MAPs) are electrical signals that represent the focal depolarizations and repolarizations of the underlying cardiac myocytes [1]. These signals are typically synchronized with cardiac function, and thus can record localized waveforms that can be used to determine activation timings and patterns, conduction velocities, and/or origins of arrhythmic behaviors [2-4]. The analysis of MAPs has also been used as means of identifying catheter contact forces and lesion borders post-ablation [5].

When designing and developing medical devices the ability to study device functionality in an ex-vivo setting can be crucial. Nevertheless, it is important that the studied anatomies and functionality be as close to that of a human in-vivo as possible. For over a decade our laboratory has utilized an isolated four-chamber working large mammalian heart model (the Visible Heart® methodology) to study the device-tissue interface [6].
This experimental approach utilizes a modified Krebs-Henseleit perfusate which is clear, thus allowing for direct visualization using endoscopes.

Additionally, within our laboratory we have the unique opportunity to study device responses within a given heart both in-situ, as well as in-vitro. The purpose of the present study is to illustrate how the Visible Heart® methodologies can be best utilized to assess the design and relative functionalities of MAP recording catheters.

**Methods**
Swine weighing between 70 and 80 kg were used in these studies. Animals were initially anesthetized with 500 mg of Telazol and 500 mg of Methohexital. Animals were then intubated and maintained in a plane of deep anesthesia (1.5% isoflurane). MAPs were then recorded in-situ from both the endocardial and epicardial surfaces of the heart. To record signals endocardially on the left side a transseptal puncture had to be performed. Catheter locations were verified through either direct visualization for epicardial catheters or fluoroscopy (Ziehm Vision R) for endocardial locations, as can be seen in Figure 1.
Figure 1. Endocardial catheters were visualized with fluoroscopy (left), while epicardial catheters could be directly visualized.

These animals’ hearts were then stopped using a standard cardioplegia protocol into the aorta and then excised. Each heart was then removed and cannulated for re-animation, using previously described Visible Heart® methodologies [6]. Cardiac hemodynamic function was maintained while the various MAP recording catheters were again placed either epicardially or endocardially with using direct visualization via video endoscopes.

Various prototype MAP catheters, including modified 7 Fr mapping catheters, with four ball electrodes and two ring electrodes were used in this study (MAP4, Medtronic Inc.). Figure 2 shows the placement of MAP4 catheters on the endocardial surfaces of the right atrium (left) and the right ventricular apex (right). MAPs were recorded from the endocardial and epicardial surfaces of both the left and right sides of the heart. Other catheters, not specifically designed to elicit MAP waveforms, were also studied to assess for potential design modifications to enable the recording of MAPs.

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Results
MAPs were recorded from both in-situ and in-vitro swine hearts using a variety of catheter designs. In both the in-situ (n = 23) and in vitro (n=51) studies, MAPs or MAP–like waveforms were recorded from a variety of endocardial and epicardial locations from both the right and left sides of a given heart.

As one specific example of the utility of employing Visible Heart® methodologies for catheter assessments, with the MAP4 catheter the tip consists of four electrodes approximately .9mm apart and with direct visualization we could study the relative effect of the catheter orientation. More specifically, we were able to visualize when a given electrode was or was not in contact with the myocardial tissue and compare waveform results recorded from each of the ball electrodes. In Figure 3 the MAP4 was placed parallel to the right ventricular free wall; because two of the ball electrodes were not in contact with the tissue no MAP recordings were elicited for those two channels. On the
lower portion of the figure the catheter was placed in a pocket of tissue and MAPs were recorded on all four channels. This in turn, validates that a catheter designed with a multi-array of MAP electrodes could be used as a means of potentially evaluating the relative device-tissue interface without direct visualization: e.g., which is the case of using fluoroscopy clinically.

Figure 3. The Visible Heart® allows direct visualization of the device-tissue interface which can be used to evaluate prototype designs to record monophasic action potentials (MAPs). Shown here is a catheter with a poor device-tissue interface and MAPs only elicited on 2 of the 4 channels, in addition to a catheter with good device-tissue interface and MAPs on all 4 channels.

In addition to the utilization of MAP4 catheters, other devices, not necessarily designed to record MAPs were evaluated using Visible Heart® methodologies. In the future, as various prototype mapping catheters and systems are developed we plan to utilize the benefits of studying them using the aforementioned in-situ/in-vitro comparisons. Within our laboratory, the hearts are fully functional in-vitro, which affords us a unique platform to readily assess the endocardial device/tissue interfaces.
Direct visualization of the device-tissue interface should also provide important insights that can be incorporated into device design, such as electrode shapes, spacing, sizes and orientations. Shown in Figure 4 is an example of a MAP recording elicited from a catheter that has not been optimized for recording MAPs (left). On the right is an example of how device optimization can improve these recordings.

**Figure 4.** Seven channels of atrial signals recording using a catheter not optimized for monophasic action potential recordings (left) and a catheter that is (right, recordings from MAP4, Medtronic).

**Interpretation**
We describe here in-situ and in-vitro pre-clinical studies that were performed to gain novel insights as to cardiac catheter designs. In part, the Visible Heart® methodologies were employed as a vital tool to allowing us to evaluate the designs of various mapping catheters, specifically with the ability to record Monophasic Action Potentials. Due to benefits of directly visualizing, the device-tissue interface during catheter placements,
coupled with improved ease to access a desired anatomical location, such pre-clinical methodologies should aid in expediting the designs of future catheters. Furthermore, the obtained images should be of an educational benefit for future clinical use of these designed catheters by electrophysiologists.

**Bibliography**


Time variate comparison of in situ and in vitro monophasic action potential recordings

Selected for poster presentation and publication at DMD 2017 in Minneapolis, MN

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Background
Monophasic action potentials (MAPs) have long been used as a means to study the focal electrical activity of the myocardium \cite{1, 2}. Upon the application of adequate contact force, the signals provide important insights into focal depolarization and repolarization, activation timing, and focal arrhythmic behaviors \cite{3-6}.

Within our laboratory we have developed an isolated physiologic, four-chamber working, large mammalian heart model (the Visible Heart\textsuperscript{®} methodology) to study cardiac devices and their interactions with the myocardium \cite{7}. Through the use of a modified Krebs-Henseleit buffer, we can uniquely visualize the device-tissue interface: in this study, the placement of catheters.

The purpose of this study was two-fold. First, we demonstrated the long term stability of MAP recordings in an in situ swine model. Second, we showed the relationship between MAPs recorded from in vitro and in situ preparations of each specimen.

Methods
Swine (n=12) weighing between 70 and 80 kg were used in these studies. Animals were initially anesthetized with 500 mg of Telazol and 500 mg of Methohexital. The animals were then intubated and maintained in a plane of deep anesthesia (MAC > 1.2). A median sternotomy was performed, and a pericardial cradle was created to enable access to the epicardial surface of the heart [8]. Only specimens eliciting normal cardiac function (e.g., native sinus rhythm) were used.

For the recording of MAPs, four 7Fr MAP4 catheters, (Medtronic, PLC, Dublin, IE) were used simultaneously. First one catheter was placed endocardially in the right ventricle (RV) through an introducer in the jugular vein. A second catheter was then placed endocardially in the right atrium (RA). Next two catheters were placed on the epicardial surface of the RV and the left atrium (LA). Catheter locations were verified by direct visualization for epicardial catheters and fluoroscopy (Ziehm Vision R) for endocardial locations, as can be seen in Figure 1.

![Figure 1. Location of MAPs catheter during in situ recordings. The image on the left shows the epicardial surface of the heart with 2 MAP4 catheters recording signals from the LA and the RV. The image on the right shows a fluoroscopic view of the MAP4 catheters (arrows) recording from the RA and RV endocardium.](image-url)
MAP signals were recorded using a CardioLab Recording System (GE Healthcare, Waukesha, Wisconsin). Baseline signals were collected for 5 minutes with no disturbances of the catheters. This served as the baseline for each specimen to which all signals would be compared. Signals were then continuously collected and monitored for two hours, with only slight adjustments in catheter position to maintain constant tip pressure.

Upon completion of in situ recordings, the heart was excised using previously described Visible Heart® methodologies. The heart was then reanimated, and MAPs were collected from the same 4 locations as seen in Figure 2.

All results were analyzed in a custom MATLAB script. Significance was determined through the use of ANOVA and Tukey HSD with a p-value <0.05 considered significant.

![Figure 2. Location of MAPs catheter during in vitro recordings. The image on the left shows the epicardial surface of the reanimated heart with 2 MAP4 catheters recording signals from the LA and the RV. The images on the middle and right show the endocardial catheters in the RA and RV respectively.](image)

**Results**

All MAP recordings were normalized to the 5 minute baseline recording collected in situ from the same specimen. There were two hypotheses to be tested in this experimental
procedure. First we examined the stability of MAP action potential duration at 90% repolarization (APD90) over long periods of in situ monitoring; in this case 2 hours. Second, we examined the relationship between APD90 from MAPs recorded in vitro, on the Visible Heart® prep, and their in situ baselines. Through the combination of these results we demonstrated that this system, the Visible Heart®, provides a unique platform for studying and testing next generation catheter designs. Statistical significance was determined using ANOVA with Tukey HSD, with significance being a p-value less than 0.05.

**In situ comparisons**
The baseline recording from each catheter was compared to MAPs recorded at 30, 60, 90 and 120 minute time points. For each location, there were no significant differences in APD90 between the baseline recordings and any measured time points. Figure 3 shows the normalized APD90s for each of the four catheters in situ over the 2 hour recording period.

![Normalized APD90 for in situ MAP Recordings](image)

*Figure 3. APD90 from in situ recordings normalized to their baseline recording for catheters on the RV epicardium and endocardium, RA endocardium and LA epicardium. There were no significant differences in normalized APD90 across any in situ time points.*
**In situ – in vitro comparisons**

The in situ baseline recording from each catheter was compared to in vitro signals recorded at 0, 30, 60, 90 and 120 minute time points. The 0 minute time point represents the minute immediately following re-animation, or the restoration of full cardiac function. APD90 for all signals was normalized to the baseline in situ recording. Only endocardial RA and epicardial LA catheters showed significant differences in APD90; and only for the 0 minute time point. Both the RV endocardial and epicardial catheters showed no significant differences when compared to their relative baselines. The normalized APD90s for each catheter can be seen in Figure 4.

![Figure 4. APD90 for in vitro recordings normalized to an in situ baseline recording for catheters on the RV epicardium and endocardium, RA endocardium and LA epicardium. The stars signify a significant difference from the in situ baseline for that location and time point.](image)

**Interpretation**

The results mentioned in this paper have provided valuable insight into the recording of MAPs, both in situ and in vitro.

Over a period of 2 hours MAPs were successfully recorded in situ with only minor adjustments in catheter position/pressure. There were no significant differences in APD90 for each location when compared to their normalized baseline values. Further
analysis of the relative amplitudes, depolarization rates and repolarization at other time points are being studied.

Similarly, when looking at the in vitro recordings there were no significant differences between the endocardial and epicardial RV catheters when compared to their normalized in situ baselines. Future studies will examine these results at time points greater than 120 minutes, to determine if there is a point at which the duration of the signals differ from in situ.

The atrial MAP recordings showed a significant difference from their in situ baselines immediately after re-animation. It is hypothesized this response is due to ischemic injury that occurs during the isolation and re-perfusion processes. Interestingly, by 30 minutes into the in vitro prep there were no significant differences in APD90 for either the RA or LA MAP recordings. Further analyses will be conducted to determine how long it takes for these locations to reach non-significant values.

From these results, we have gained two important insights into the recording of MAPs. First, the long-term monitoring of MAPs is possible with only slight adjustments in the catheter tip pressure and/or location. Second, the Visible Heart® methodologies are not only a viable tool for the imaging of the device tissue interface, but also for the recordings of monophasic action potentials and other electrical signals. With this new information, the development of catheters designed specifically to record MAPs can be continued using the Visible Heart® without compromised electrical activity, or diminished MAP signals.
Bibliography


