

FJODORS TJULKINS

Encapsulation of implantable microsensors

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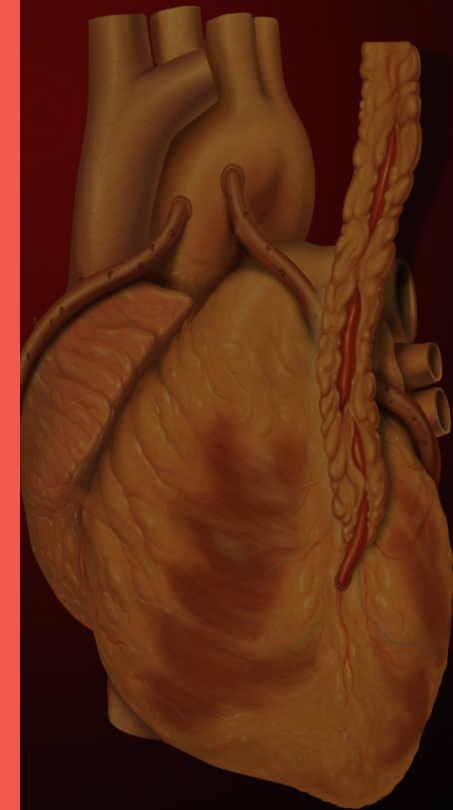


FACULTY OF TECHNOLOGY
AND MARITIME SCIENCES

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Doctoral Thesis

Fjodors Tjulkins



2015



**FACULTY OF TECHNOLOGY AND
MARITIME SCIENCES**

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Thesis submitted for the degree of Philosophiae Doctor

Fjodors Tjulkins

Department of Micro- and Nanosystem Technology (IMST)
Faculty of Technology and Maritime Sciences (TekMar)
Buskerud and Vestfold University College (HBV)
Horten, 2015

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Preface

This thesis is submitted in partial fulfillment of the requirements for the degree of Philosophiae Doctor from the Department of Micro- and Nanosystem Technology (IMST), at Buskerud and Vestfold University College (HBV).

This doctoral work has been carried out from September 2011 to December 2014, with associate professor Kristin Imenes as main supervisor and adjunct professor Erik Andreassen as co-supervisor.

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Abstract

Heart function monitoring by attaching an accelerometer directly to the heart ventricle has been established as an effective way of diagnosing ischemia. The method holds a number of advantages over conventional monitoring techniques: high specificity and accuracy surpassing that of electrocardiography, and the ability to conduct non-stop monitoring unlike x-ray imaging. To this date, the drawback has been that the accelerometer-based devices have been too large to be used in the post-operative period, when the patient's chest is closed. This period is of great interest.

The PhD project has focused on developing a heart monitoring device intended to be used on patients recovering from a Coronary Artery Bypass Graft. The device is intended to be used during surgery and for the subsequent recovery period (3-5 days). The project has employed commercial 3-axis accelerometers.

This PhD project has contributed to four different generations of devices, each one featuring incremental improvements. The first generation validated the concept, the second outlined the form factor of the device, and the third added extra functionality and revised the form of the implant. The fourth generation device also featured a newer, more compact sensor, which in turn, allowed to further miniaturize the device and evaluate different implant shapes. This evolutionary approach allowed us to formulate testing methodology for the devices. The latest generation devices underwent tests of: leakage current according to IEC60601 standard (current below 0.01 mA), including after cyclical loading of the capsule-cable joint, pull-out force measurements, implant stability evaluation that yielded tilt of no more than 4 degrees.

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List of papers

- i. **F. Tjulkins**, A. T. T. Nguyen, N. Hoivik, K. Aasmundtveit, E. Andreassen, L. Hoff, K. Imenes, "3-axis MEMS Accelerometer-based Implantable Heart Monitoring System with Novel Fixation Method," in Electronic Components & Technology Conference, Las Vegas Cosmopolitan, 2013, pp. 510 - 516
- ii. **F. Tjulkins**, A. T. T. Nguyen, N. Hoivik, K. Aasmundtveit, E. Andreassen, L. Hoff, O. J. Grymyr, P. S. Halvorsen, K. Imenes, "MEMS-Based Implantable Heart Monitoring System with Integrated Pacing Function," in Electronic Components & Technology Conference, Orlando, Florida, 2014, pp. 139-144.
- iii. **F. Tjulkins**, A. T. T. Nguyen, E. Andreassen, K. Aasmundtveit, N. Hoivik, L. Hoff, O. J. Grymyr, P. S. Halvorsen, K. Imenes, "Fabrication and assembly of MEMS accelerometer-based heart monitoring device with simplified, one step placement," *J Med Eng Technol*, vol. 39, pp. 69-74, Jan 2015
- iv. **F. Tjulkins**, A. T. T. Nguyen, E. Andreassen, L. Hoff, P. S. Halvorsen, O. J. Grymyr, K. Imenes "An Implantable Accelerometer-based Heart Monitoring Device with Improved Positional Stability" submitted to *ASME Journal of Medical Devices*

Other contributions:

F. Tjulkins, A. T. T. Nguyen., M. Andersen, and K. Imenes, "MEMS Accelerometer-Based Heart Monitoring System with Myocardial Fixation," in *International Symposium on Biomedical Engineering and Medical Physics, 10-12 October, 2012, Riga, Latvia*. vol. 38, Springer Berlin Heidelberg, 2013, pp.19-22.

Co-authorships

A. T. T. Nguyen, **F. Tjulkins**, K. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, "Miniaturization of package for an implantable heart monitoring device " presented at the Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP), 2013 Symposium on, 2013.

A. T. T. Nguyen, **F. Tjulkins**, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, "Miniaturization of package for an implantable heart monitoring device," *Microsystem Technologies*, pp. 1- 14, 2014/05/23 2014.

K. Imenes, M. H. Andersen, A. T. T. Nguyen, **F. Tjulkins**, K. Aasmundtveit, N. Hoivik, L. Hoff "Implantable MEMS acceleration sensor for heart monitoring recent development and outlook", *Electronic System-Integration Technology Conference (ESTC)*, 2012 4th 17-20 Sept. 2012, pp. 1-5

Grymyr O-JHN, Nguyen A-TT, **Tjulkins F**, Espinoza A, Remme EW, Skulstad H et al. "Continuous monitoring of cardiac function by 3-dimensional accelerometers in a closed-chest pig model." *Interact CardioVasc Thorac Surg* 2015; doi:10.1093/icvts/ivv191

The project was presented on local conferences and symposiums. In 2012, 2013 and 2014 it was presented at the NanoNetwork workshops. In autumn 2014 the project was presented at "Drammen Research days". In the summer of 2014 it won the best PhD poster award at the 2014HBVexpo.

Paper Summary

Paper I

Paper I deals with the first prototype. The paper describes the fabrication, characterization and brief animal tests. The system was able to perform its function – monitoring from a closed chest condition. Due to system limitations a conclusion is made that a revision of the design is necessary.

Paper II

The third generation prototype uses the CMA-3000A sensor, same as two previous generations, but uses capsules made by additive manufacturing. This allowed the reduction of the overall size of the device. This generation added the pacing functionality to the system.

Paper III

Paper III goes in detail describing the second generation device – a device that added the easy, one step implantation. The fabrication and testing of the device, including animal trials, are described in this paper. The characterization was far more in depth than in earlier papers.

Paper IV

Paper IV is about the latest generation device featuring a lessons learned approach and using a prototype, extra compact accelerometer provided by a partner company. The device in this paper is far more compact than even the generation three device. Along with the same tests made on previous devices, the paper includes the evaluation of rotation of the capsules inside the channel where the device is implanted.

Abbreviations

MEMS	Microelectromechanical system
CABG	Coronary Artery Bypass Graft
ECG	Electrocardiography
ALARA	As Low As Reasonably Achievable
ASIC	Application specific integrated circuit
BGA	Ball grid array
CRT	Cardiac resynchronization therapy
TTFM	Time Transit Flow Measurement
CNC	Computer numerically controlled
AM	Additive manufacturing
IEC	International Electrotechnical Commission
CAD	Computer aided design
DMLS	Direct metal laser sintering
ECP	Electro-chemical polishing
IMU	Inertial measurement unit
FEM	Finite element modelling
PEA	Peak endocardial acceleration

1 Introduction

1.1 Research context and motivation

The use of MEMS (Microelectromechanical system) accelerometers for monitoring cardiac activity has long been proposed in a number of forms. Publications on the topic can be found as early as 1993 [1]. In this project, an accelerometer is used for monitoring patients recovering from coronary artery bypass grafting (CABG). Coronary artery bypass grafting is a type of open chest surgery where arteries or veins from elsewhere in the patient's body are grafted to the coronary arteries. This is done to bypass atherosclerotic narrowings and to improve the blood supply to the myocardium (heart muscle). See Figure 1.

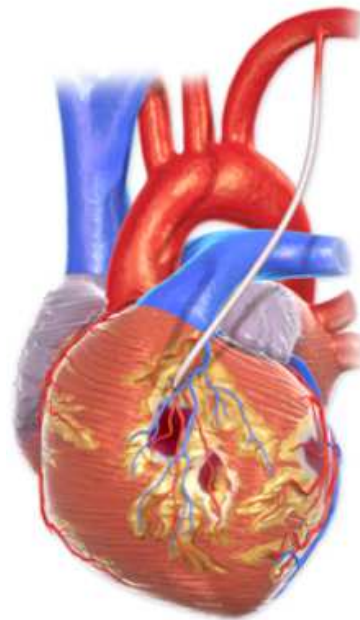


Figure 1 A typical coronary artery bypass set-up – single bypass. Graft shown in white. Figure adopted from [2].

Patients recovering from a CABG are at a risk of graft occlusion leading to cardiac ischemia. Ischemia is a condition when insufficient blood is delivered to the organ. Ischemia may lead to cardiac infarction. A study published in 2004 reported 4% of grafts occluding immediately after the chest is closed [3]. CABG is a “mass market” procedure, in 2006 in United States alone 444000 CABGs were carried out [4]. This, together with the limitations of presently available heart monitoring techniques, creates a niche for a new monitoring system.

To formulate the requirements for the new system, it is important to realize just what are the shortcomings of existing ones. ECG (electrocardiography), is an ubiquitous heart monitoring technique that is common in hospitals world-wide. ECG systems are affordable and well established in clinical practice. However, the detection of ischemia by ECG is problematic due to lack of specificity [5, 6]. Angiography, a technique where a contrast medium with high x-ray absorption is injected into the bloodstream, highlighting the vascular system in an x-ray image, is an efficient way of diagnosing the condition of the graft [3]. This technique is unsuitable for non-stop, 24-7 monitoring due to the need to inject contrast medium and ionising radiation exposure. The patient’s exposure to radiation must follow the ALARA (As Low As Reasonably Achievable) principle [7], and subjecting a living person to non-stop radiation would be a clear violation to this principle. A non-negligible problem with angiography is the cost of equipment. Somewhat similar is the issue with ultrasound imaging and characterization. High degree of accuracy is attainable with this technique [6, 8], but the limitation is the inability to conduct non-stop monitoring. This technique requires an operator to work with the patient, and it would not be reasonable to have a team of operators just for one patient, especially given the large number of CABGs performed world-wide. Other techniques exist, but these are the most commonly used. A system capable of rapid, accurate and specific ischemia detection was demonstrated previously [9]. The system consisted of two, two-axis accelerometers in an arrangement that permitted to monitor all 3 translational axis. The accelerometers were attached directly to the heart surface by sutures. A

revised design with one 3-axis accelerometer was subsequently presented [10]. The system was successful with one exception – the large size of the accelerometers available at that time made the device impossible to remove from a closed chest without surgery, making the device undesirable for post-operative monitoring. At one stage, a custom 3-axis accelerometer was fabricated with the goal of miniaturization, moving closer to the limit when the system would be small enough to facilitate extraction from the patient without having to re-operate. The manufacturing of custom MEMS is a costly and time consuming business and it became clear that a commercial, off-the-shelf device is necessary for this project to advance. Summary of technique advantages and shortcomings for post CABG monitoring is presented in Figure 2.

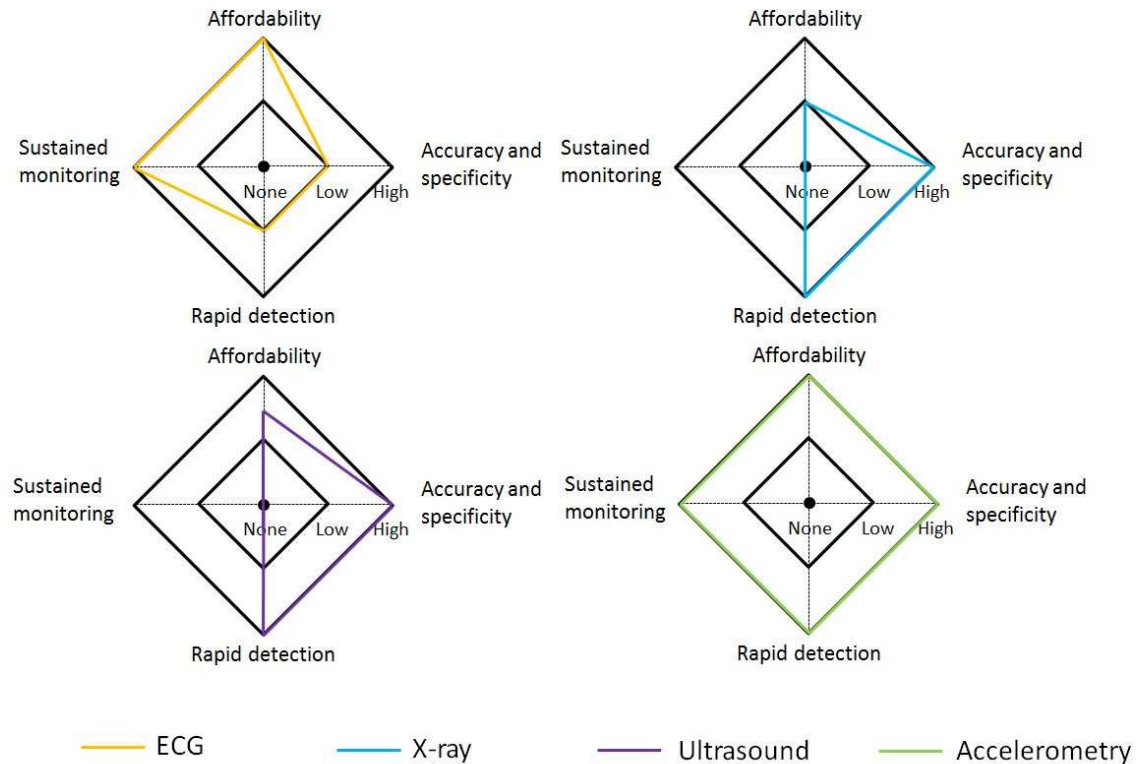


Figure 2 Diagram indicating desirable characteristics of existing systems: ECG (gold line), x-ray imaging (blue line), ultrasound (purple line) and the system under development in this project (green line).

The goal of this project is to develop a monitoring device to be used during the in-hospital stay period (4-7 days) of patients undergoing post CABG recovery. The sensing principle will be motion sensing by means of an

accelerometer, the same as in [9, 11]. The accelerometer would have to be a commercial one as developing a new sensor is too costly and takes too long. The sensors placement on the heart must be such, that removal of the accelerometer would not need a surgical procedure. The focus of this work is the encapsulation and integration of the device.

1.2 Structure of the thesis

The thesis is separated into four sections. Section 1 is the introduction where the relevance and motivation of the work is described. Section 2 deals with the background, describing the technology used in fabricating the device and a review of existing technologies that influenced the device under development. Section 3 deals with the work done in this project. Four generations of devices are described; the emphasis is placed on aspects not detailed in the papers. Section 4 contains conclusions, potential future work and “cautionary tales” – things that did not go right in the project.

2 Background

2.1 Accelerometer technology

By definition, an accelerometer is an electromechanical device used to measure acceleration forces. Acceleration forces could be static like the pull of gravity or dynamic – caused by movement or by vibrations.

MEMS accelerometers are one of the simplest and perhaps the most easily applicable MEMS devices. Such devices are widely used in many industries: automotive, gaming, telecommunications, etc. The first MEMS accelerometers appeared in 1979 at Stanford University but it took well into the 1990s for these devices to become accepted by the mainstream industry [12]. MEMS accelerometers were first used in the automotive industry, where they replaced the ball-in-tube sensors used in airbags. The demand for sensors from the automotive industry triggered development of MEMS sensors, and at the turn of the century MEMS sensors made their way into domestic electronics. They are now found in just about every laptop HDD, smartphone or gaming console controller.

MEMS accelerometers, in principle, consist of two components: the sensing die, and the ASIC (Application Specific Integrated Circuit). The sensing die is the micromechanical system where the geometry is tailored to respond to acceleration. This can be a beam or moving plates. The sensing can be based on a number of physical principles. To list some of the more common ones: piezoelectric, piezoresistive and capacitive. A piezoelectric accelerometer takes advantage of the direct piezoelectric effect: material strain produces a charge (contrary to the inverse piezoeffect, where the crystals deforms when subjected to an electric charge), the charge can then be converted into acceleration. The physical origin of the piezoelectric effect is the charge asymmetry within the crystal structure [13]. Piezoresistive accelerometers are similar, but the strain produces a change in the resistivity of the sensing element, rather than a charge. Capacitive sensors are different, a capacitive accelerometer relies on the change in capacitance of the device induced by the change in the electric field propagation media.

In its simplest form the device is a set of fixed electrodes and a set of moving electrodes or two sets of fixed electrodes with a dielectric material in between them. The relative position of the electrodes, or of the body that is between the two electrodes, leads to a change in capacitance that can be recorded and translated into acceleration. Of course, neither charge, resistivity or capacitance are measured directly. The ASICs of MEMS accelerometers vary in complexity, a good example is the Wheatstone bridge (Figure 3) set-up – a common way of measuring the signal from the sensing die in piezoresistive accelerometers. In this set-up the sensing die acts as a resistor in the bridge, and acceleration that causes the bridge to become unbalanced which is easy to interpret as electrical signals.

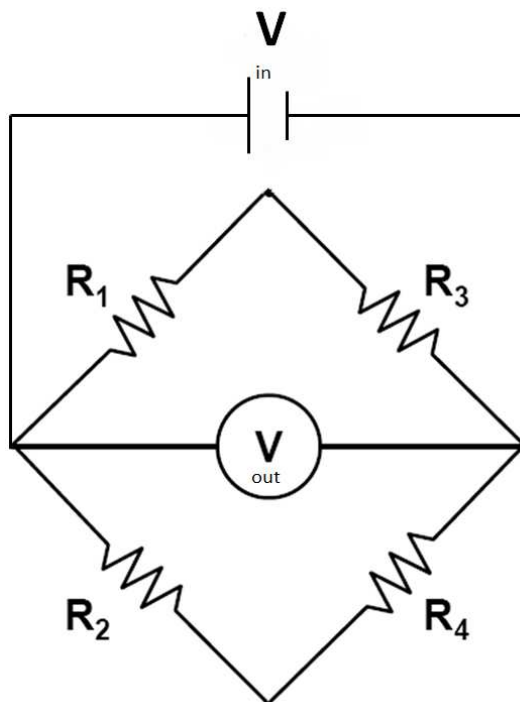


Figure 3 A typical Wheatstone bridge configuration.

Of course, MEMS accelerometers are more than just a die and an ASIC. The sensor needs an electrical interconnect system and encapsulation to protect the sensor from the environment. The process of taking the chip off a wafer and turning it into a working device is called “microsystem packaging”. This is a potential bottleneck in miniaturization and can be a costly process, reaching up to 95% of the end systems cost [14]. There is no standard, one-size-fits-all packaging solution that can be used everywhere. A common lay-

out of a modern accelerometer is a MEMS-on-chip design, when the sensing die is placed on top of the ASIC. Typically a grid of solder balls (referred to as BGA, Ball Grid Array) is placed on the bottom of the ASIC. An example of such device is shown in Figure 4.



Figure 4 CMA3000-A01 3-axis accelerometer. Left side shows the top of the sensor, right side the bottom where the ASIC and the BGA are visible. Adopted from [15]

In this project an attempt is made to leverage the industry's drive for miniaturization and develop an encapsulation for an existing device by providing additional, mission specific encapsulation.

2.2 The human heart

The human heart is a vital organ that is responsible for supplying the body with blood. The heart is located inside the chest cavity. It is contained inside the pericardium – a protective sac that also contains lubricating fluid. The heart consists of four chambers: right atrium, right ventricle, left atrium and left ventricle. The blood arrives into the heart from the body to the right atrium. From the right atrium it comes into the right ventricle and is then pumped into the pulmonary artery to the lungs. Inside the lungs blood exchanges carbon dioxide for oxygen by means of diffusion. This oxygenated blood comes into the left atrium and from there into the left ventricle. The left ventricle ejects the blood into the rest of the body through the aorta. The left ventricle is the larger one, with a significantly thicker wall: up to 15mm [16], whereas right ventricle wall thickness is about 5mm [17]. The actual heart walls consist of three layers: epicardium, myocardium and endocardium. The epicardium is the outer layer; it consists of mostly

connective tissue. Below the myocardium is the muscle that creates the contractions. The inner most layer is the endocardium, it has a function in the development of the heart [18]. A schematic drawing of the human heart is shown in Figure 5.

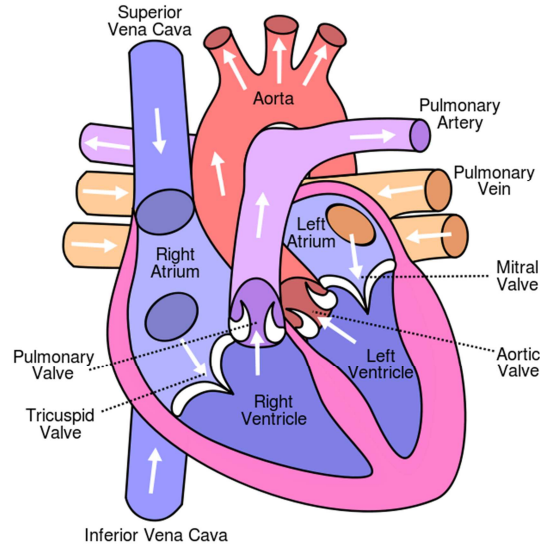


Figure 5 A schematic illustration of the human heart. Adopted from [19]

2.3 Ischemia detection: state of the art

The monitoring of the condition of patients recovering from CABG is a large research field and there is several techniques capable of detecting myocardial ischemia. The techniques varies and can conduct the monitoring under different conditions and with different accuracy. The device under development in this thesis is designed to provide accurate, specific monitoring with rapid detection and ability to provide continuous monitoring in the intraoperative and postoperative phases. The techniques in this overview will be compared to these requirements.

2.3.1 “Gold standard” for myocardial ischemia detection

Transesophageal Echocardiography and angiography are two techniques referred to as “gold standard”. These techniques have proven ability to detect ischemia; however, certain drawbacks are shared by both of the techniques.

Transesophageal Echocardiography is a technique where an ultrasound probe is inserted into the patient's throat and positioned inside the oesophagus (the passage from the throat into the stomach) corresponding to a position behind the heart. The technique is commonly used [20]. The disadvantage is that it is an uncomfortable technique for the patient and cannot be used for long term continuous monitoring.

Angiography is a technique where a contrast medium is injected into the patient's bloodstream and an x-ray machine is used to map the vascular system through which that contrast medium is coursing. This is a highly accurate way of evaluating the condition of the graft, [21]. The injection of contrast media and exposure to ionising radiation make this method unusable for long term, persistent monitoring.

2.3.2 Electrophysiological methods for ischemia diagnostic

ECG remains a commonly used technique for diagnosing ischemia. A twelve lead set-up is typically used. ECG performed on a patient that is at rest is called "resting ECG". This is the type of cardiogram that would be used to monitor a patient in the post-operative period. Resting ECG is criticised for low sensitivity (low probability of detection) to ischemia [22, 23]. ECG may be taken on a patient that is subjected to exercise, forcing the patient's heart to work harder to supply the body with blood. Exercise ECG uses 15 to 18 channel set-up [22]. It is known to have improved identification (high probability of detection) of ventricular ischemia [24]. The obvious limitation is that not all patients can exercise. A study investigating the prognostic significance of exercise testing on 6,296 patients showed that the exercise ECG examination could only be applied to 62,5% of patients [25].

Enhanced ECG techniques exist, examples include: Ventricular Late Potentials (VLP), Body Surface Potential Mapping (BSPM) and Cardiogoniometry (CGM).

VLP is a technique where the PQRST complex of the ECG is recorded and averaged. On the averaged PQRST complex, microvolt level

spikes at the end of the QRS indicate ventricular tachycardia. This technique primarily focuses on detection of patients at high risk of sudden cardiac death after myocardial infarction [22]. The technique is useful for detecting the aftermath of an infarction but not early ischemia and is criticised for having a large number of false positives [26].

BSPM is essentially a form of ECG where the number of electrodes can be from 64 to 120. The electrodes are laid out on the patient's chest, and on top of recording the standard PQRST complex the potentials can be mapped and matched with the ECG recordings. BSPM features different approaches for registering different cardiac conditions from diagnosing old myocardial infarctions to recognizing ventricular hypertrophy [22]. BSPM ability to diagnose ischemia has also been demonstrated in literature [27]. The criticism of BSPM is the complexity and the need for specially trained personnel [22].

CGM (Cardiogniometry) is a spatiotemporal electrocardiographic method utilizing computer-assisted three-dimensional data on cardiac potentials. CGM uses 4 electrodes to register the so called vector loop. The vector loop describes the polarization of the heart during every cycle. This can be used to diagnose various heart conditions. The technique is promising, but has not yet been proven in large studies [22].

2.3.3 Heart sound monitoring for ischemia detection

Listening to the heart sounds is perhaps the oldest way of studying the condition of the human heart. It has been established that a healthy adult human heart produces sounds called S1 (Sound 1) and S2. S1 is the sound of atrioventricular valves closure and the beginning of the ventricular contraction; S2 is the closing of the semilunar valve and the beginning of the diastole [28]. Additional sounds, S3 and S4, can be indicative of pathology [28]. The S3 and S4 sounds have been established to correlate well with ischemia and ventricular systolic dysfunction [29-31]. The hardware used in this type of monitoring is a stethoscope with electronics to record and store the sound.

The state of the art for these devices comes not in the hardware, but in the software. The weakness of the method is that ambient noise will interfere with the recording of heart sounds. To overcome the noise, various signal processing methods have been suggested in the literature [32-35]. The paper from Tseng et al. [35] reports promising results: over 90% accuracy in S3 and S4 detection. S3 and S4 sounds in ischemic patients appear as fast as the changes in ECG [36].

The monitoring of heart sounds to diagnose myocardial infarction is a promising technology – it is non-invasive and based on a very well-known phenomena. The technology does have certain limitations. First and foremost, the heart sound recordings used in the studies are taken from databases (cardiac auscultatory recording database of John Hopkins University in [35] and “qdheart” database for [34]). The recordings in these databases are controlled for noise they are recordings taken by physicians in clinical practice. A patient recovering from CABG will be released from intensive care after a few days, and spend the rest of the hospital stay in a general ward. The patient will be aware expecting the patient to maintain quiet (as quiet as a patient would in during a physician’s stethoscope examination) for all this time is an unrealistic expectation. Continuous, non-stop monitoring of heart sounds has not been demonstrated in literature. The second limitation is that S3 sounds can also be found in healthy people under 40 years of age [28]. This compromises the technique’s specificity.

In closing, monitoring heart sounds is a promising way of post-operative ischemia diagnostic and could be used to augment ECG and accelerometer based techniques.

2.3.4 Graft patency monitoring by means of ultrasound

Graft occlusion is a risk for patients recovering from CABG. An occluded graft is blocked and cannot supply the blood that is necessary for the muscle to survive. Therefore, monitoring the flow inside the graft would provide a picture of how well the graft is performing.

In clinical practice, ultrasound technology called Time Transit Flow Measurement (TTFM) is typically used to evaluate the graft patency [37]. A TTFM system usually consists of two ultrasound transducers that are placed on the vessel where the flow is to be measured. The transducers are positioned at a predetermined distance and angle. The transducer exchange pulses, the pulse traveling up stream will arrive later than the pulse traveling downstream. From this difference the flow velocity can be calculated. A schematic representation of TTFM is shown in Figure 6.

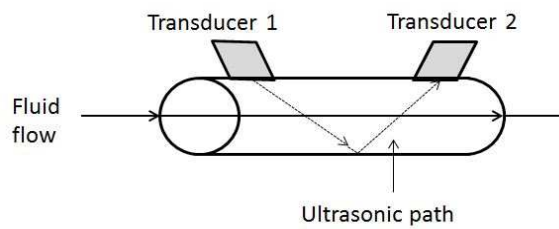


Figure 6 A schematic representation of transit time flow measurement technique

An example of a biomedical TTFM probe used for assessing graft patency is the Medistim VeriQ (Medistim, Norway). The CAD representation of VeriQ placement and a picture of the device in use are shown in Figure 7. The system's ability to predict outcomes in CABG procedures have been reported in [38].

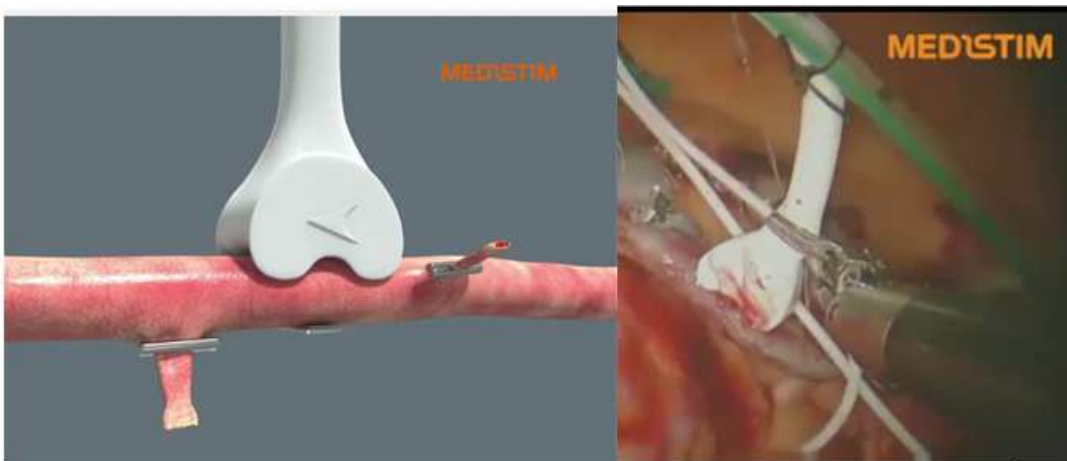


Figure 7 Left: the placement of the VeriQ probe for successful measurement. Right: use of VeriQ in actual surgery. Adopted from Medistim promotional materials [39, 40].

The technology has limitations. The promotional materials [40] point out that placement must be strictly as shown in Figure 7, if the graft is bent the flow velocity profile is asymmetric and results cannot be interpreted. The size of the device is quite large as well, meaning that it would take a significant effort to redesign the device to be an implantable post-operative monitoring aid.

2.3.5 Magnetocardiography

As the human heart beats its electrical activity produces both electric potential and magnetic fields. The measurement of electric potentials of the heart is known as ECG, the measurement of magnetic fields is referred to as Magnetocardiography (MCG).

The fact that the human body produces magnetic fields was known for a very long time, but it took into the 1960s to record a magnetocardiogram [41]. The magnetic fields produced by the human body are faint and hard to detect: 10^{-11} T – 10^{-14} T compared to earth's magnetic field of 10^{-4} T [42]. The detection of said fields was made possible by a group of devices called Superconducting Quantum Interference Device, often abbreviated as SQUID. Early SQUIDs required cooling down to 4°K (-269°C) and a shielded room to operate in [42]. In the 1990s the cost of such magnetometers was around \$2 million [42]. The advances in magnetometers as a field of study eventually enabled monitoring and detection of ischemia in an unshielded room [43]. The detection of the changes in the magnetic field of the heart caused by ischemia is both rapid and accurate [43, 44]. The cooling required for the systems of the generation used in [43, 44] made the systems rather large [45]. Further advances in magnetometers have made it possible to conduct heart monitoring at room temperature. In the new systems, SQUIDs are replaced with a device called Spin-Exchange Free Relaxation (SERF) magnetometer. SERF magnetometers are already hailed as a new era in magnetometry [46]. The key component of an atomic magnetometer is a glass cell that contains a vapour of alkali atoms. A laser is used to spin polarize the atoms via the process of optical pumping. A magnetic field perpendicular to the pump

beam rotates the spins by a small angle proportional to the field magnitude. The rotation angle can be detected and translated into magnetic field magnitude. Researchers have already demonstrated SERF based magnetocardiometers that were able to successfully map the magnetic activity of the heart [47, 48].

Magnetography appears to be an accurate, rapid, non-invasive and safe method of diagnosing heart conditions, including ischemia. Still, even the latest devices that require neither cooling nor a shielded room are fairly large [47] and have to be positioned directly over the patient's chest. For persistent monitoring for the entire duration of CABG recovery period a way of conducting the monitoring regardless of patients position must be developed. This would either require a small magnetometer placed on the chest of the patient or one that could map the heart magnetic fields regardless of the patient's position, whether that is realistic remains to be seen.

2.3.6 Conclusion on the state of the art

A large number of fundamentally different heart monitoring techniques exist and are constantly under improvement. Some of the techniques have the potential to become new industry standard, but are not at the required state of maturity yet. Each of the different techniques evaluated in this overview do not alone fulfill all the parameters that the system presented in the thesis is set to achieve: accurate, specific and continuous monitoring of a patient recovering from a CABG procedure.

2.4 Accelerometers for heart monitoring

Using an accelerometer to monitor the heart in some sort of way is not new. Plenty of scientifically sound attempts have been made to apply acceleration measurements to monitoring the cardiac cycle. Different types of techniques are good for different diagnostic purposes. It is convenient to look at these

technologies by separating them into two groups: implantable and non-implantable.

2.4.1 Non-implantable accelerometers for heart monitoring

Two key technologies can be distinguished here: ballistocardiography and seismocardiography.

Ballistocardiography is a technique, hailing from a time before MEMS [49]. In this technique a patient is lying on a bed that is suspended by springs. If the patient is lying motionless, then the recoil of heartbeat and blood being ejected from the heart will cause the bed to oscillate. Measuring the acceleration of these oscillations can be used to determine physiological parameters such as the stroke volume [50]. The drawback of this technique is the special bed or scale used to suspend the patient.

A more relevant technique is seismocardiography. Seismocardiography is the measurement of chest wall acceleration produced by myocardial movement. This is, in a way, similar to listening to heart beat, but instead of using a stethoscope an accelerometer is placed on the chest. The abundance of modern day hardware that can be used to record the acceleration and the relative simplicity of the procedure make the technique attractive. Such systems can be assembled from off-the-shelf hardware [51], or use a smartphone to achieve the same result [52]. The future of these systems is for seismocardiography devices to be integrated into fabrics of clothes allowing for monitoring of ambulatory patients [53].

2.4.2 Implantable accelerometers for heart monitoring

The use of accelerometers in pacing leads has been proposed a long time ago [54]. The parameter of interest to the cardiologists is the so-called Peak Endocardial Acceleration or PEA. The theory behind this approach is that the contractile state of the heart can be identified by the maximum velocity of the contraction. Measuring the endocardial vibration in the right ventricle during the isovolumetric contraction phase makes it possible to assess a parameter of heart contractility: the systolic isovolumetric peak acceleration or PEA [55]. The PEA is recorded by means of a single axis

accelerometer attached to the tip of a pacemaker lead [56]. Note that even if the sensor is implanted into the right ventricle, the PEA amplitude is determined by the contraction strength in the left ventricle, where systolic myocardial vibrations are generated. Even more interestingly, the sensor can detect an additional signal, designated PEA II [57]. PEA II is recorded during the isovolumetric relaxation and corresponds to the second heart sound. Experimental studies indicate that PEA II is the rate of pressure gradient rise across the aortic valve at the time of closure. Its role in measuring diastolic function has not been confirmed yet.

Leads with an in-built accelerometer sensor to monitor the vibrations corresponding to the first heart sound are a commercial product. An Italian company called Sorin Group offers the SonRtip™ – an intra-atrial pacing lead with a cleverly designed transducer that aids in monitoring the patient's heart condition. The sensor has proven to be a useful tool in Cardiac Resynchronization Therapy (CRT). In a recent study [58], a multicentre single blind study with two groups of patients was evaluated. In one group CRT was administered based on PEA based readings, and in a control group the treatment was administered based on the centres' usual practices (echocardiography etc.). After one year of treatment, 76% of the group treated with the aid of PEA was classified as improved, while in the control group 62% of the patients were classified as improved.

The other example of an implantable accelerometer for heart monitoring, is the technology that this project is based on – attaching an accelerometer to the left ventricle and processing the acceleration to approximate velocity and displacement [9-11]. The distinction from the other technology is the comparatively large range of motion characteristic to ventricle motion as opposed to the vibrations recorded by the SonRtip. The limitation of the sensor presented in [10] is that while its placement – suturing of the device to the ventricle – is an easy way to couple motion sensor to the heartbeat, it does not feature any way of removing it from a closed to chest. This forces the surgeon to either limit the sensors deployment to operative monitoring, removing the device before the chest is closed, or leave it inside and re-operate to remove the sensor. The latter

option is very undesirable. Those limitations were dictated by the size of the sensors available at that point in time. The emergence of more compact sensors that could potentially be packaged in a way that would allow surgery-free extraction was the starting point for this project.

2.5 Cardiac implant placement and fixation

An overview of existing ways of placement and fixation for cardiac implants is necessary to formulate a placement solution for the device in this project. The requirements for the device under development are: placed in or on the left ventricle (this is where the graft is located), usable in a closed chest setting, can be removed with-out the need for additional surgery. Certain existing devices provide a good reference design.

2.5.1 Endocardial placement devices

A widespread type of endocardial implant, an implant that is placed inside the heart ventricle or atrium, is the permanent pacemaker pacing lead. As the name implies this type of pacing lead is suitable for long-term implantation. Their implantation procedure can be carried out through a vein, which is minimally invasive, requires only a short recovery period and only local anaesthesia. Two types can be distinguished: passive and active fixation. Passive fixation works like an anchor, the fins getting caught on the surface irregularities of the endocardium [59]. Active fixation works like a corkscrew, burrowing into the heart muscle to achieve fixation [59]. An illustration of both of these devices is shown in Figure 8.

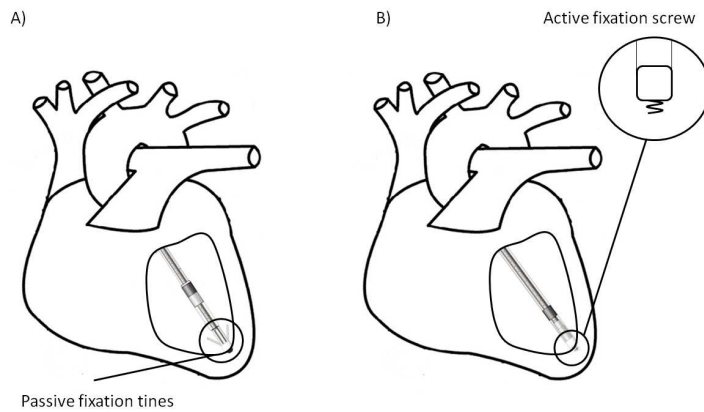


Figure 8 A) Passive fixation lead. B) Active fixation leads

The drawbacks of these devices include the simple fact that not every patient actually needs a dedicated, permanent pacing lead. CABG recipients do not need require permanent pacing, so this procedure would be excessive. The other significant drawback is the complications with lead extraction. Extraction of leads can be a dangerous procedure with complications going as far as death [60]. The active fixation could be an interesting solution for the device under development in this project, but it would complicate the design.

2.5.2 Epicardial placement devices

Epicardial placement devices are the simplest of the group. These are the devices that are placed on top of the ventricle. Normally these devices use sutures as means of fixation. The accelerometer-based heart monitoring device that was created before this project [10], is a good example of an epicardial placement. Other examples include certain types of permanent pacing leads: patients with certain complications, i.e. artificial heart valves, cannot receive transvenous placement and so the electrode is sutured on to the heart directly. These devices are uninteresting for this project because they are only meant for extraction in an open chest setting. One device, the M22 atrial pacing lead (AE Medical, USA) presents an interesting solution. The pacing lead has a loop that is put under a suture, when the lead needs to be extracted, it is pull out and the loop will compresses through the suture. This allows for both long term fixation and extraction without surgery

(sometimes called percutaneous removal). A schematic illustration is shown in Figure 9.

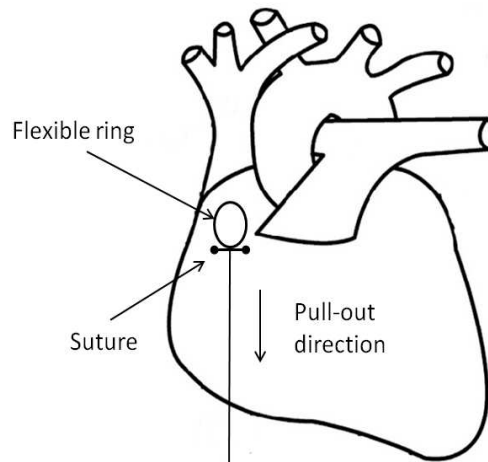


Figure 9 A schematic illustration of the M22 pacing lead placement and extraction. Adopted from [61].

This solution is the type of functionality desirable for the device in this project. However, fixing the sensor in just one point might be not enough to make the accelerometer follow the ventricle motion precisely.

2.5.3 Sub-epicardial placement devices

There is a class of devices that follow the desired operational protocol: implanted during the open chest surgery, kept inside the patient for the recovery period (closed chest) and removed by pulling out through a channel in a closed chest. This family of devices is called „temporary myocardial pacing leads“, also known as „heartwires“. Some sources refer to this as epicardial pacing [62], for the classification in this work it will be referred to as sub-epicardial due to the fact that the active part is placed below the external heart layer. Heartwires are placed within the myocardium by making a “stitch” on the outer layer of the heart wall. The tissue pressing on the wire in the stitch keeps the wire fixed. It is removed by pulling out. The leads are implanted in a way so as the pull-out direction is aligned with myocardial fibre orientation [63], minimizing the chance of tearing. Schematic illustration in Figure 10.

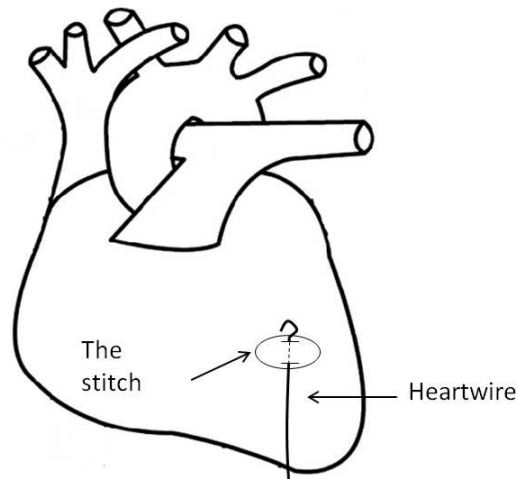


Figure 10 A schematic illustration of a heartwire placement.

This is the placement type selected for the device. The procedure is widely used in coronary patients, and integrating the system under development into clinical practice should be an easy and natural task. The fact that tissue pressure is what keeps the device in place is an advantage over having 1 point of fixation as in the M22 pacing lead described in the previous section.

2.6 Biocompatible materials

When discussing biocompatible materials it is important to clearly define “biocompatible”. Two somewhat different definitions of a “biomaterial” exist. Black, in the introduction of “Biological Performance of Materials: Fundamentals of Biocompatibility” states that: *“Biomaterials are materials of man-made or natural origin that are used to direct, supplement, or replace the functions of living tissues. When these materials evoke a minimal biological response, they have come to be termed “biocompatible”.* As it is typically used, the term *biocompatible* is inappropriate and defective of content. *Compatibility is strictly the quality of harmonious interaction. Thus, the label biocompatible suggests that the material described displays universally “good” or harmonious behavior in contact with tissue and body fluids. It is an absolute term without any referent”* [64]. The author goes on to state that the compatibility is a task-specific parameter and, due to vastly different physical parameters, no material will be universally biocompatible.

While there is no arguing against that, in this paper it is assumed that it is safe to use the term “biocompatible” or “biomaterial” as long as the application for that material is kept in mind, and there is no reason to over define materials. By contrast, Davis in the “Handbook of Materials for Medical Devices” gives a succinct definition of a biomaterial: “A *BIOMATERIAL* is a *synthetic* material that is used to replace or restore function to a body tissue and is continuously or intermittently in contact with the body fluids” [65]. The objection is that not all materials that are used in this field are synthetic, at the very least biodegradable materials are often natural in origin, silk being a prime example [66]. In this thesis bio inert materials with track records of successful implant applications will be used.

2.6.1 Types of biomaterials

Biomaterials are represented by a broad range of material types: metals, polymers, composites and ceramics. Although harvested tissues can be put into this category, they were never considered for this project, and so will not be discussed. The other classification is by the specific way of interaction with the host (other than just „harmonious“).

2.6.1.1 Classification by interaction type

These three interaction types can be singled out:

Bioinert biomaterials. The type of material to have minimal interaction with the implant recipient’s body. Little or no host response. Generally a fibrous tissue capsule will form around the implant.

Bioactive biomaterials. The type of materials to interact and cause a certain desired effect i.e. cell adhesion.

Bioresorbable biomaterials. Materials engineered to dissolve when placed inside a human body.

Of the three types listed, bioinert materials seem to be the most attractive, given the temporary nature of the device under development.

Black also gives an updated classification of biomaterials based on the concept of host response, in this approach 4 types or stages are identified: inert, interactive, viable and replant [64]. The first three are analogous to the classification listed previously, the fourth one deals with samples cultured in vitro from the cells of the patient. This type is beyond the scope of the project.

2.6.2 Classification by material group

As mentioned previously there is a broad range of biomaterials from all forms of material groups.

Metallic materials are amongst the most important biomaterials, and have been used in implantable systems for many years. Metal applications are too many to list: all sorts of artificial joints, dental implants, pacemaker casings and leads as well as many others. The three principal metallic materials are: stainless steels, titanium and alloys and cobalt-base alloys. Shape memory alloys, zirconium alloys, tantalum and precious metals are also viable options [65].

Of stainless steels, the 316L (18Cr-14Ni-2.5Mo) stainless steel, which is a vacuum-melted low carbon version of the usual 316 composition, is the one most widely used [65]. Vacuum melting improves cleanliness, and the chemical make-up is designed for maximal pitting corrosion resistance and for a ferrite-free microstructure. Type 316L can be welded. Welding and soldering can be used to joint wires [65].

Polymeric materials are, perhaps, the most versatile of all the biomaterials. To date they have been used in systems that address neurological, cardiovascular, ophthalmic and reconstructive surgery related problems. They come in form of bulk materials, adhesives or coatings.

The most telling distinction of polymers from other materials is their molecular structure. Polymer materials consist of long molecules; chains of atoms held together by covalent bonds, with carbon normally being in high

proportion. The chains can be linear or branched or chemically cross-linked. Polymer materials are commonly classified into three groups:

- **Thermoplastics:** These enter the liquid state above a certain temperature, and then solidify again upon cooling; hence they can be recycled. Thermoplastics can be (semi)crystalline or amorphous.
- **Thermosets:** These are chemically cross-linked. They degrade into "short molecules" above a certain temperature.
- **Elastomers** (also referred to as rubber). These can be thermoplastic (thermoplastic elastomers (TPE)) or thermosets (rubber).

Ceramics, glasses and glass-ceramics have had a use for a long time in the medical industry, though a lot of it was in devices that were not implantable. Two areas where ceramics are used in implants are dental prosthetics and bone reconstructive implants – the surfaces of these materials bond well with bones [65]. Ceramics are difficult to machine and process because they are hard and brittle, and sintering temperatures for ceramics are also typically high [67]. Due to this, ceramics were not considered in this PhD project.

2.7 Sterilization techniques

For an implantable device, sterilization is mandatory [68]. Sterilization is defined as complete lack of microorganisms on the object undergoing sterilization. Due to high survivability of viruses and spores, the sterilization methods can often be harsh and potentially this can damage the sensor.

2.7.1 Autoclaving

Autoclaving is the practice of sterilization by exposure to high temperature steam. Exposure of microorganisms to saturated steam achieves their destruction by the irreversible denaturation of enzymes and structural proteins [69]. The time and temperature can vary, usually 120-130°C for 2-

15 minutes [64]. Temperature is a concern for MEMS devices. Stresses induced by thermal expansion coefficients of multiple materials used in the construction can cause the device to fail [70].

2.7.2 Dry heat

The process is similar to autoclaving but there is no steam involved, only heat. Dry-heat processes takes effect by oxidation of cell constituents [69]. Temperature is 160-175°C and time is 30 minutes to 2 hours [64]. This process has the same risks as the autoclaving method.

2.7.3 Gas

Gas sterilization involves subjecting the object undergoing sterilization to ethylene oxide. The gas is flammable and potentially explosive. The World Health Organization advises to only use this method if alternatives are not available [69]. This method is low temperature: from RT (Room Temperature) to 55°C, but is time consuming: from one to 24 hours with possible 48 hour outgassing period [64].

2.7.4 Plasma

Plasma sterilization involves room low temperatures (45-55°C), moderate times (1-2 hours) and uses gas hydrogen peroxide (H₂O₂) [69]. This is an attractive method for sterilization of the device under development, but there is possible risk of promotion of unwanted bioadhesion [71] alongside the typical risk of material compatibility [72].

2.7.5 Gamma radiation

Gamma radiation and electron beams are used to effect ionization of the molecules in organisms. The process can potentially be time consuming, as some microorganisms need to build up a considerable dose – up to 24 hours. Process is room temperature [69]. Another advantage is the fact that the device can be sterilized while inside the storage container. Gamma radiation exposure is a risk for MEMS devices; radiation exposure can cause bulk lattice damage and make the die more prone to fracture [70].

2.7.6 Cold solution

Cold solution sterilization is the process of soaking in a chemical solution designed to attack microorganisms i.e. glutaraldehyde. This is a room temperature process, 1-3 hours long [69]. An attractive solution for the device in this project, providing all components will be compatible with the chemicals used for sterilization.

2.8 Animal test subject

Living organisms are highly complex and difficult to emulate. When the need arises to study an interaction involving a living organism, it is often necessary to use an animal model. Use of animals in medical experimentation and study is connected with ethical concerns and as such, care must be taken to ensure that the sacrifice of the animal is not in vain. The practice of using an animal as a model of a human body is referred to as “comparative medicine” [73].

In order to obtain the best possible results sound planning is crucial. The procedure and the organ of interest must be identified and a suitable test animal selected. Conducting experiments on animal test subjects that have notable differences from human anatomy has, on occasion, lead to false claims of efficacy. For example, when tested in humans, certain drugs did not produce the same results as those observed in canine (dog) experiments [74]. The device described in this thesis is meant for patients recovering from a CABG procedure, and the device is meant to be implanted into the left ventricle. The test subject must have a heart with anatomy closely resembling that of a human, particularly the left ventricle.

In comparative medicine, the hearts of large mammals are used as a model for human hearts [75]. Pig, sheep and dog hearts are commonly used. In human, dog, sheep and pig hearts the apex is made up of

the left ventricle [76, 77]. The main difference between the heart ventricles of these species seem to be in the way nerves conduct signals, and not in the mechanical properties of the muscle. However, dog hearts do have considerably more coronary collateralization – more fine blood vessels in the ventricle muscle [75]. In general, the hearts of pigs, dogs and sheep are interchangeable for the purpose of modelling a human heart, but the dog heart's amount of fine blood vessels make them slightly less suitable. In selecting one out of the three animals mentioned, practicality must be taken into account as well. In the modern world dogs are considered companion animals and a large number of dog breeds would be unsuitable for modelling a human heart due to small size. Sheep are bred for their fleece and it's in the interest of farmers to maintain the animal for as long as the fleece can be harvested from it. Pigs are bred for their meat and, in a way, using the animal for experimentation (as long as accepted ethical treatment standards are upheld) is no different than the animal's life cycle on a farm. This, along with their anatomical similarity, makes pigs the optimal model species for the evaluation of the device in this thesis.

3 Device Design and Fabrication

3.1 Introduction

3.1.1 The four device generations in this PhD project

The starting point of this PhD project was a device with dimensions $14,5 \times 11 \times 5,2 \text{ mm}^3$, that was tested in both animals and humans as a means of intraoperative monitoring [10]. A requirement from our partners in the project, the users at Oslo University Hospital, was to fabricate a device that could be used in the postoperative stage as well. To save development time, a commercially available sensor was used. At the time, the smallest sensor available was CMA3000 (Murata Oy, Finland), first introduced in late 2008. In 2014 an even smaller sensor was introduced on the market, the BMA355 (Bosch Sensortec, Germany). The scope of design and fabrication activities in the PhD project was to make a device capable of operating inside a closed chest and with features for easy extraction. The requirements formulated together with our partners at Oslo University Hospital are summarised in Sect. 3.1.2 The test procedures used in the PhD project are summarised in Sect. 3.1.3.

Note that one common trait shared by all four generations is that signal I/O and power was transmitted through the cable. The cable was used for extracting the device from the patient, and provided a convenient way to supply power and signal I/O.

The development of the system was an iterative, learning process. Lessons learned in early stages were carried over to the next generation design. In this project, four generations of encapsulation can be distinguished. These are summarised in Table 1. Details of the four generations are given in Sect. 3.2 to 3.5, and summaries are given below:

Generation 1 had a silicone rubber based encapsulation, as the generations developed and tested prior to this PhD project. Generation 1 was capable of monitoring, but was difficult to place in a beating heart and had no additional functionality. The fixation of the device in the tissue was

also not reliable and required sutures. More than a dozen generation 1 devices were made, and these were used in a number of experiments. The surgeons reported that the generation 1 devices needed a complicated placement procedure. Furthermore, this generation did not allow for pacing, due to the electrically insulating rubber material. A pacing functionality was desired by the surgeons. The sensor used in this design, CMA3000-A01 (Murata Electronics Oy, Finland) introduced in 2008, see data in Table 2, was also used in generation 2 and 3. It should be noted that while having a number of drawbacks, generation 1 was still a highly successful research tool. Generation 1 sensors were used to validate the closed chest monitoring in an animal model [78].

The main effort of the PhD project in the development of generation 1 was to make a proof of concept device (with fabrication techniques developed by Imenes et al. [10]).

Generation 1 of the device is described in Paper I and in several other publications [79-82]. Recently, a paper dealing with the “medical” aspects of using the sensor in a closed chest setting was published [78]. The HBV team, including the author of this thesis are co-authors of that study.

Generation 2 was a “breakthrough” device that combined the basic requirements of operating inside the human body (also fulfilled for generation 1) and an easy one-step implantation procedure. The main effort of the PhD project in the development of generation 2 was to design and fabricate the device using a steel capsule, a round cable and a needle with a thread taken from a heartwire (temporary myocardial pacing lead). The steel capsule was machined with a CNC (Computer Numericaly Controlled) machine. The general layout of this device – the sensor in a capsule with thread and needle attached – paved the way for the subsequent generations.

Generation 2 of the device is described in Paper III.

In **generation 3** we attempted to leverage the capabilities provided by additive manufacturing. The goal was to achieve size reduction by redesigning the capsule in ways that would be difficult to do with

conventional machining techniques – such as machining non rotational symmetry designs. The main effort of the PhD project in the development of generation 3 was to achieve minituarization and to introduce electric pacing and sensing.

Generation 3 is described in Paper II.

Generation 4 featured a more compact sensor than the previous three generations. This made room for implementing certain features into the capsule design. The capsules were made by additive manufacturing in stainless steel. The main effort of the PhD project in the development of generation 4 was to evaluation of the new compact device, optimal selection of components, evaluating pacing and sensing with new capsules and additional implant stability studies.

Generation 4 is described in Paper IV.

3.1.2 Requirements from the users and a summary of the main advances for the subsequent device generations

The advances from one generation to the next were guided by a set of design considerations and specifications, mostly based on input from the project partners at Oslo University Hospital. The requirements were formulated as early as the development of generation 1 device and it took until generation 3 to fit all criteria. The first two criteria, that were the most crucial, were met on all devices. Summary of the devices can be found in Table 1 and Figure 11. The criteria were as follows:

- Successful acceleration recording – the crucial parameter. A packaged device must be able to record the acceleration in vivo. Recordings from older devices developed by HBV and Oslo University Hospital prior to this PhD project [10, 83] were used for reference.
- The International Electrotechnical Commission (IEC-60601-1) regulations set the limit of leakage currents for CF-type (Cardiac Floating) devices, i.e. devices with direct contact with the heart. The leakage currents must be below 0.01 mA.

- The procedure for placing the device in the heart tissue must be easy and safe. CABG procedures are performed “off the pump” meaning that the patient’s heart is beating. This can make a multi-step procedure difficult to employ in practice and be taxing for the surgeon. A simple placement (implantation) procedure is preferred.
- The implant fixation must be such that the device stays in place during the time monitoring is necessary, and then the device should be easily removed when monitoring is no longer needed. If sutures are needed for sensor fixation, the removal will require an extra step where the sutures are cut. The alternative is to use degradable sutures, but that would mean the device can only be used until the sutures start degraded and it cannot be removed before degradation of the sutures. Hence, fixation without sutures is preferred. The effectiveness of fixation would be determined in an in vivo study. Generation 1 needed sutures, Generation 2, 3 and 4 could be secured on their own, however, spontaneous unwanted retraction was noticed in generation 2 devices.
- Two key parameters that are closely related are tissue channel dilation (expansion) and device package cross-section and volume. The device will be placed into the left ventricle. This means that a channel will be created first and the device is then positioned in that channel. A greater dilation of the channel means that the stress in the tissue will be higher. In generations 2, 3 and 4 the channel diameter was the same as the diameter of the device. In generation 1 the channel diameter was defined by the diameter of the catheter used in the placement. A smaller implanted volume is considered a plus for similar reasons: the smaller the device, the shorter is the stressed domain along the implanted device, and the less traumatic is the extraction procedure. A rounded device shape is of course also important in this respect.
- On patients recovering from CABG it is necessary to implant temporary pacing leads. Hence, it is desired to integrate the electric pacing function on the accelerometer device. This would reduce the

number of devices that would be needed to be implanted in the left ventricle.

Table 1. Summary of features of different generation devices.

Generation	Generation 1	Generation 2	Generation 3	Generation 4
Acceleration monitoring	Achieved	Achieved	Achieved	Achieved
Current leakage	<10nA	<10nA	<10nA	<10nA
Implantation procedure	Difficult	Simple	Simple	Simple
Fixation	Sutures need	Achieved	Achieved	Achieved
Channel dilation	3.2 mm	2.8 mm	2.8 mm	2.0 mm
Package volume	66 mm ³	49 mm ³	39 mm ³	26 mm ³
Pacing function integrated	No	No	Yes	Yes

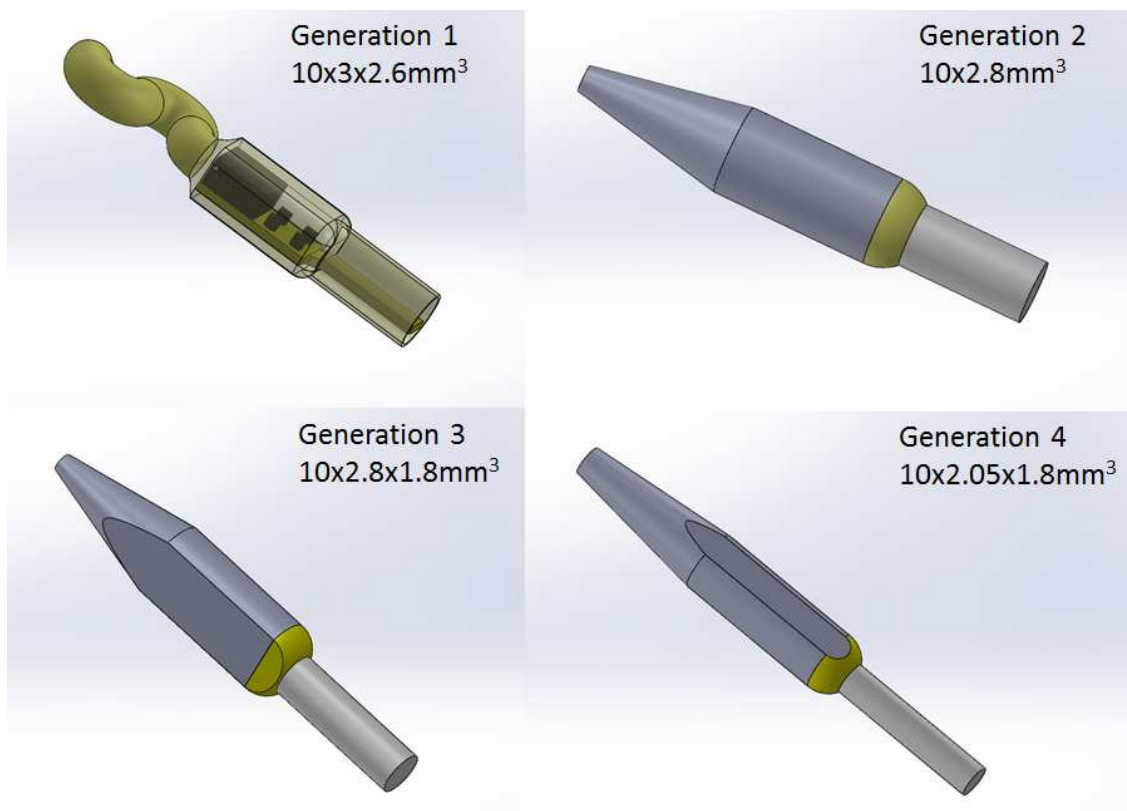


Figure 11 Four generations of devices developed in the project.

3.1.3 Test procedures used in this PhD project

Standard tests that were performed on each device generation were leakage current measurements and animal trials (implantation of the device, monitoring with the sensor, and removal of the device). Leakage current is an important design criterion – a device with excess leakage current would not be allowed on the market. The animal trials were to establish the sensors' capabilities. Some additional tests conducted with the generation 1 device were different to those conducted on subsequent generations.

A total of 12 generation 1 devices were made. The devices were tested for leakage current and then submitted to the partners at Oslo University Hospital. Additional tests as part of this PhD project were a 7-day soak test [82] and a destructive pull test. [79]. Furthermore, we tried to understand why there was flash (thin film where the mold parts separate) on the molded parts [79]. The 12 devices were used in an undisclosed number of animal trials, and the HBV team including this PhD student was present for at least six of these trials. By late 2013 all sensors were "used-up". Common

damages were unseated decoupling capacitors, severed power transmission traces and lack of response from accelerometer axes. It was theorized that the lack of response was due to damage to the accelerometer's sensing die caused by dropping the sensor.

Twelve capsules were acquired for construction of generation 2 devices. Four capsules were used for mock-ups; the rest were used to fabricate working devices. Starting with generation 2, pull tests were performed. The pull tests were used to establish the forces necessary to implant the sensor ("pull in") and remove it ("pull out") – and, hence, indirectly the stresses acting on the heart tissue. The tests conducted on generation 2 devices are detailed in section 3.3 and [84].

Only two devices of generation 3 were made. Generation 3 introduced the pacing functionality. Pull tests, leakage currents tests and animal trials are described in Paper III [85]. Capsule polishing is described in section 3.4.1.

Generation 4 underwent leakage current tests, and animal trials with more detailed examination of pacing and implants stability. The descriptions can be found in Paper IV and section 3.5.

3.2 The first generation of the device

The first generation of the device was a step into unknown territory. Key requirements were identified as: compact size – cross section less than that of a 3mm² cylinder, a biocompatible outer layer of encapsulation, smooth, rounded edges of the encapsulation. The first requirement was suggested from our medical partners based on their experience. Biocompatible materials are necessary for harmonious interaction with the host. Sharp edges might damage the organ, either by way of cutting or pressure induced necrosis. The other constraint was the interconnection technology available at that stage. The available interconnect technology at that time was a flexible cable-substrate. The cable substrate consisted of a

layered structure of Polyimide, copper traces and adhesive layers. The cable is described in more detail in [80, 81].

3.2.1 The sensor

The central part of the system was the CMA3000-A01 3-axis accelerometer (Murata Electronics Oy, Finland). It is a MEMS-on-chip device with $2 \times 2 \times 0.95 \text{ mm}^3$ dimensions, the most compact available at that time. The CMA3000-A01 is analog. The analog version was preferred for software compatibility reasons – legacy software works with analog devices. Specifications for the accelerometer can be found in Table 2.

Table 2: Performance specifications of the CMA3000 from Murata Technology Oy.

Property	Value
Acceleration range	$\pm 2 \text{ g}$ or $\pm 8 \text{ g}$ ¹
Sensitivity	450 mV/g ^{1, 2}
Supply voltage (Vdd)	1.7 - 2.7 V (2.7 - 3.6 V)
Current consumption	180 - 200 μA ³
3 dB bandwidth	0 - 120 Hz (x and z direction) 0 - 200 Hz (y direction)

¹ $\text{g} = 9.8 \text{ m/s}^2$

² at 2.7 V

³ in active mode

3.2.2 Assembly and encapsulation

A silicone compound was used to encapsulate an epicardial fixation accelerometer in a project prior to this [10]. Encapsulating the sensor in silicone was selected for the first generation in this project as well, using the same technology of molding, but with a new mold. The attractiveness of silicone is its proven track record as a biomaterial [13], as well as availability and ease of processing. The particular brand of silicone selected was Elastosil R 4001/40 (Wacker Chemie, Germany) because it exhibited good mechanical properties in the previous research [10]. The specifications for this grade of silicone rubber are given in Table 3. The curing temperature of 165 °C was deemed a risk for the sensor as it is considerably higher than

the sensor storage temperature. Increasing the curing time can allow the silicone to cure at a lower temperature. For fabricating this device, we worked out an empirical rule – for every 10°C below curing temperature the time in the oven has to be doubled. The curing schedule for fabricating generation one prototypes was 2 hours at 135°C.

Table 3. Elastosil 4001/40 properties.

Parameter	Units	Elastosil 40001/40
Appearance		Clear
Press cure	Min @ °C	15 @ 165
Cure catalyst		Platinum
Tensile strength	N/mm ²	11
Elongation at break	%	940

The encapsulation consisted of three parts: the main body that houses the sensor, a silicone tail that covers a stretch of the flex and an attachment in the front of the sensor to aid fixation. The width of the main body was 3mm, the height was 2.6mm, the edges had chamfers with the radius if 0.5mm. The length of the main body was 5mm. The cavity for the tail was 3mm wide and 2mm in height, the length was 13mm, edges were also chamfered with radius of 0.5mm. See Figure 12.

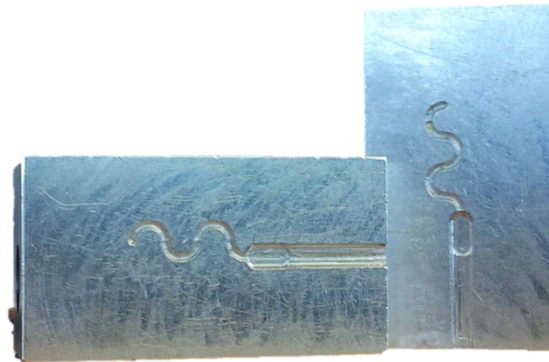


Figure 12 The mold used in the generation one device.

The mold required a coat of a mold release agent on the inner surfaces. The compound used was NanoMoldcoating™ (MouldPro, Denmark). To ensure a strong bond between the polyimide of the cable-substrate and the silicone structure of the encapsulation a primer was

applied before curing. The primer employed in this project is G 790 (Wacker Chemie, Germany). An assembled device is shown in Figure 13.

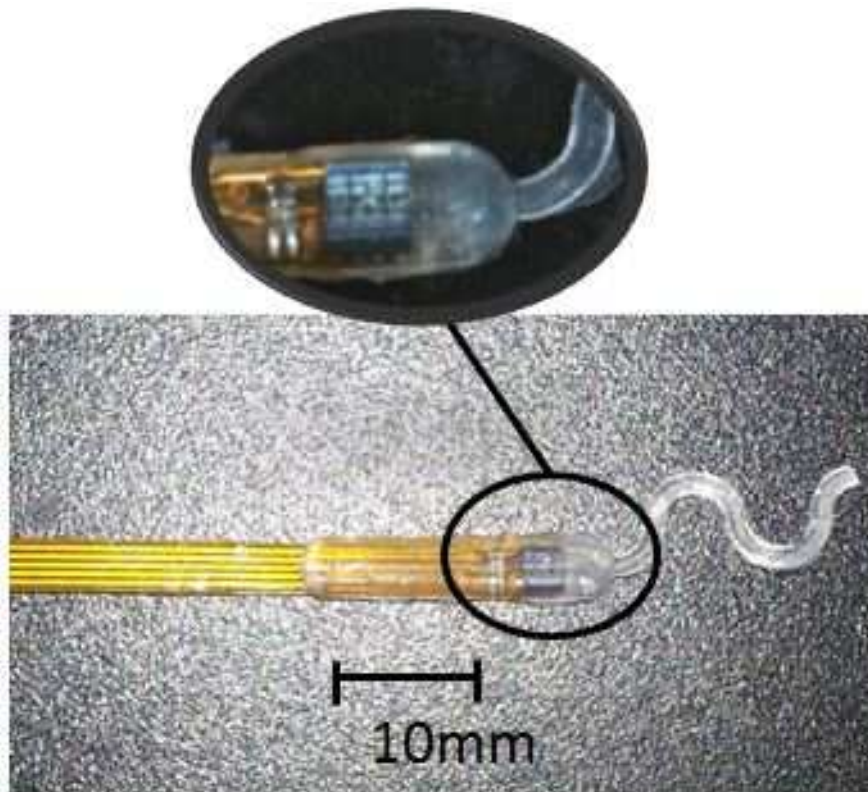


Figure 13 A generation one design.

3.2.3 Implantation procedure

The device was planned with myocardial or sub-epicardial placement on the left ventricle. The device was somewhat different from the heartwires so another implantation procedure was used. The procedure employed in this device is known as the „Seldinger technique”, it is named after a Swedish radiologist who created this technique and published it in 1953 [86].

„Seldinger technique” is a multistage implantation technique. Step one is cannulation – a channel is made in the ventricle with a cannula (large, hollow needle). Step two is guidewire insertion, the guidewire is inserted into the cannula and the cannula is removed from the channel leaving only the wire inside. Step three is catheterization; the guidewire is used to guide

the introducer catheter containing the sensor into the channel. Step four is the removal of the catheter leaving the sensor inside. See Figure 14.

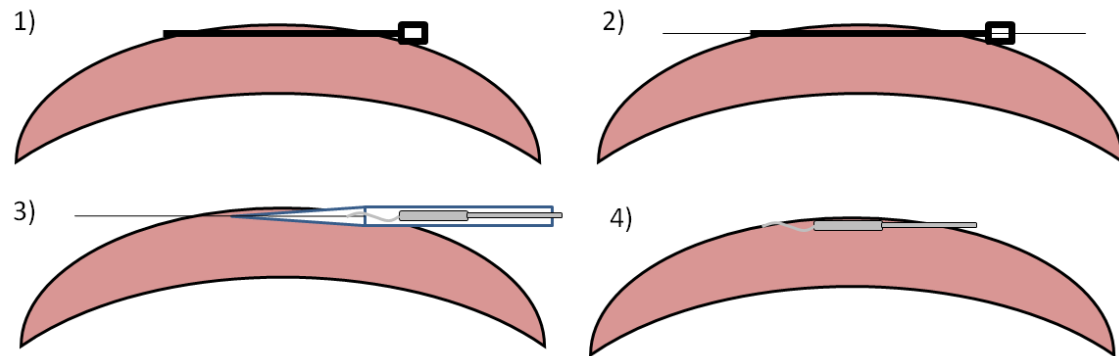


Figure 14 Schematic illustration of Seldinger technique steps. 1) Cannulation. 2) Guidewire insertion. 3) Catheterization. 4) final stage, sensor is implanted.

3.2.4 Deployment in animal trials and system tests

Generation one sensors were used in a set of animal experiments. The performance was satisfactory as a proof of concept study, but revealed a number of drawbacks. Characterization included soak testing, leakage current measurements and destructive testing. The soak test indicated sufficient insulation as the sensor was not affected by the exposure to saline solution, destructive tests indicated over 35N force necessary to forcefully strip the encapsulation from the sensor-substrate assembly and leakage current was below the threshold set by International Electrotechnical Commission's (IEC) standards. The tests and their results are detailed in [79, 82]. Sensors performed well in lab trials, but the animal experiments exposed the limitations of the design. The study, that our medical partners used generation one devices for, needed 4 sensors to be used at the same time: one sensor implanted with sub-epicardial placement on the left ventricle, one sutured on top of the ventricle close by (reference sensor), one sutured to the posterior wall (the back wall) and on the right ventricle. It was observed that the Seldinger technique creates a channel that is too dilated. This is likely due to the large diameter of the introducer used in the procedure. The zig-zag attachment in the tip of the device was not enough to ensure fixation so additional stitches had to be used. It is still possible to

pull the device out, but the stitch has to be firm enough to ensure fixation but loose enough to make the extraction possible. This makes the procedure less reliable and less predictable. The other problem was that the flexible substrate-cable is very stiff in the lateral direction, and may cut the tissues in the point of contact (the channel under the rib cage where the cable exits the body). While the results were positive, and the concept was validated, it was obvious that a redesign was necessary. An experimental set-up from one of the animal trials is shown in Figure 15.

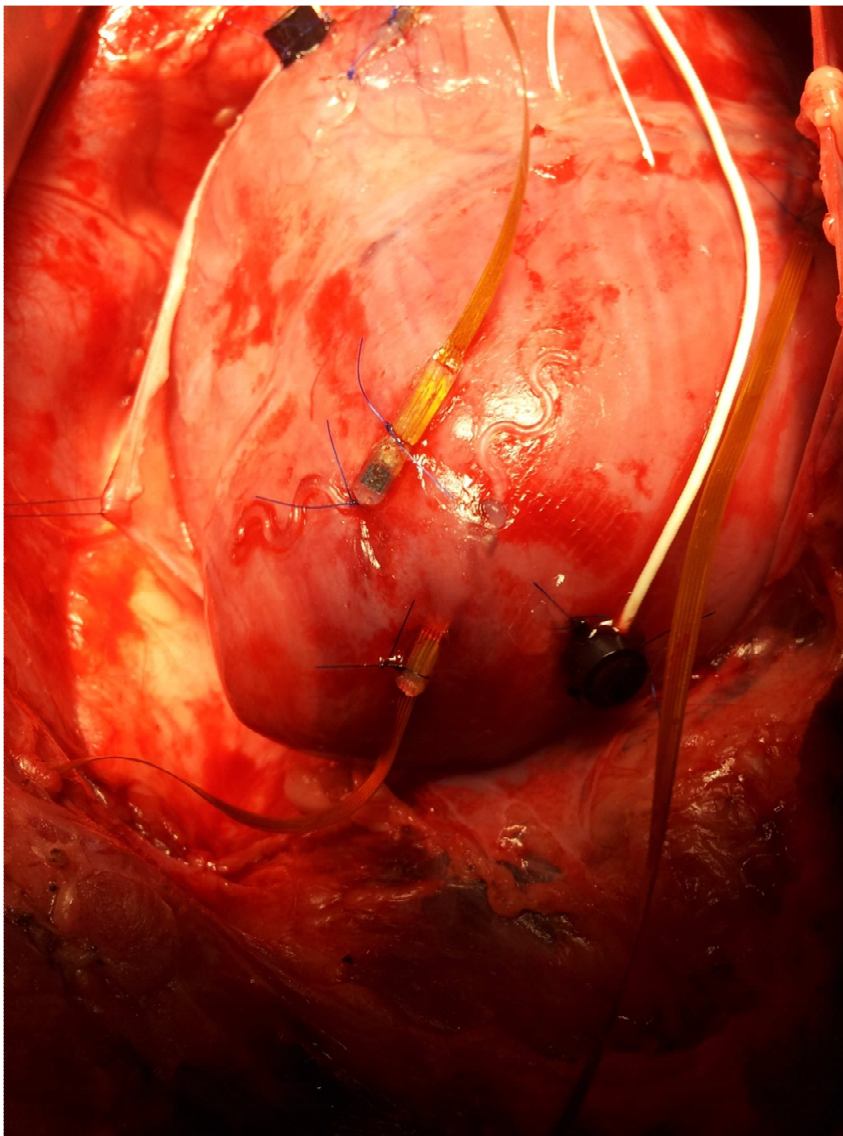


Figure 15 The set-up from one of the animal trials. In the middle a sensor is placed sub-epicardially with the reference sutured left of it. Towards the right the cable from the sensor placed on the posterior wall can be seen, top center the tip of the sensor sutured to the right ventricle can be seen.

3.3 The second generation of the device

Generation two devices were called to address the problems with the implantation method used to achieve subepicardial fixation. This device is described in Paper II or [84]. The decision was to emulate the heartwires not just in the placement but also in the layout. Generation two device consisted of a round cable, a tapered, cylindrical capsule containing the sensor, and a thread with a needle salvaged from a heartwire. The acceleration sensor was the same as in generation one (CMA3000-A01). This device was somewhat less manufacturable (requiring more manual work) than the previous generation but proved to be superior in animal trials.

3.3.1 Assembly and encapsulation

The chief component of the encapsulation of the second generation device is the capsule containing the sensor. A cylindrical shape was selected due to ease of manufacturing. 316L formulation of stainless steel was selected. 316L is a widely used biomaterial and has excellent mechanical properties [65]. The dimensions of the capsule are shown in Figure 16. The tip of the capsule is solid except a channel for the thread due to machining method limitations.

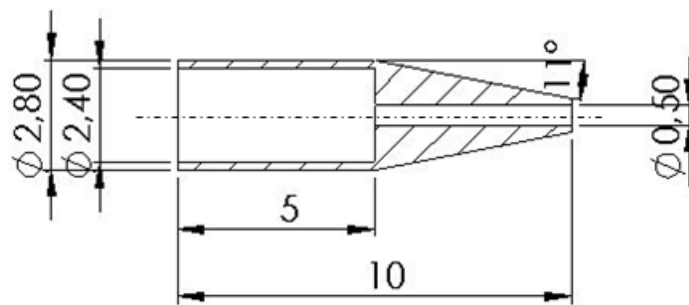


Figure 16 Dimension of the capsule used in the second generation device. All dimensions in mm unless otherwise stated.

A thread with a needle, taken from a commercial heartwire, was attached to the capsule. It was accomplished by feeding a stretch of the thread through the channel in the tip and tying a knot on the end inside the capsule. Two types of threads were used in prototype assembly: a non-

absorbable, monofilament polypropylene suture; Surgipro II V-20 (Covidien, USA) and a steel wire Ethicon MPW10 temporary myocardial pacing lead (Johnson and Johnson, USA). Both the pacing lead and the suture had the same type of needle: half circle, taperpoint, arc length 26mm. The polypropylene suture was very robust and was the preferred solution for sensors that would be re-used. However, in animal trials, the metal thread from the Ethicon lead demonstrated advantages – the metal wire could be bent or kinked for additional fixation. Figure 17 shows the package of both the suture and the heartwire used in the construction of generation two prototypes.

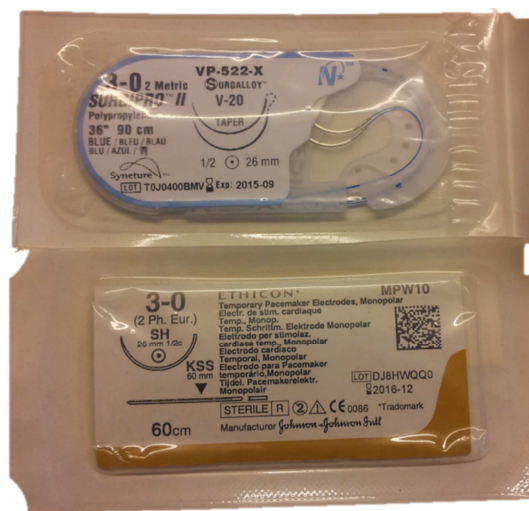


Figure 17 Surgipro II V-20 (top) and Ethicon MPW10 (bottom).

A critical part of the system is the joint between the capsule and the sensor-cable assembly. The mechanical joining techniques that was considered: crimping, threaded connection and welding. Crimping is the technique of joining two pieces of metal or other ductile material by deforming one or both of them to hold the other. This process does not have a high degree of control over joint geometry. A threaded connection would require making room for the thread inside the capsule and that would be undesirable. Welding, for example a laser welded connection between capsule and a feedthrough, is a very popular way of making hermetic connections for medical devices [87, 88]. This is a highly attractive method, but it was decided against using this technique due to lack of flexibility. Welding would require a metal feedthrough to be a part of the cable and

would have to match the capsule. It was foreseen at that point, that neither the cable, nor the capsule are final. A new feedthrough would have to be made for every change in the cable or capsule. Both the feedthrough and the laser welding would have to be outsourced. A consensus solution, one that allows for control of the joint geometry, possesses sufficient mechanical strength and is flexible enough to be applied to various geometries of capsules and cables was needed. Potting, a process of filling a complete assembly with an adhesive compound, was selected as the solution for the joint.

To create the joint, the capsule was filled with adhesive and the sensor was placed inside. The displaced excess adhesive was removed and a swab was used to shape the geometry of the transition between. In the process of manufacturing prototypes it became apparent that the “ideal” adhesive would need to have conflicting properties. Low viscosity adhesive easily fills the inside cavity of the capsule, whereas a high viscosity adhesive was difficult to get inside the cavity. A low viscosity adhesive, however, gave very little control over the transition geometry, whereas a high viscosity adhesive was easy to shape. Three adhesives were used in the fabrication of generation two prototypes: the 353ND-T Epoxy (Epotek, USA), 203TX Cyanoacrylate adhesive (Panacol, Germany) and MED-4211 two component silicone (Nusil, USA). Specifications are listed in table 4.

Table 4 Adhesive properties per specification.

	Appearance	Viscosity@ 20RPM/23°C	Curing	Post curing
Cyanolit 203TX	transparent	2,200 cPs	Dependant on conditions	24 hours at room temperature
353ND	amber	9,000- 15,000 cPs	Minimum 30 min at 80°C	n/a
MED- 4211	translucent grey	Part A: 105,000 cPs Part B: 1,500 cPs	3 min at 150°C	1 hour at 150°C

MED-4211 adhesive was eliminated from further trials when it demonstrated poor adhesion to metal. 353ND-T and 203TX adhesives both proved to be usable for fabrication of the device. A SolidWorks CAD (Computer Aided Design) model of the assembly can be seen in Figure 18 and photo of an assembled device can be seen in Figure 19.

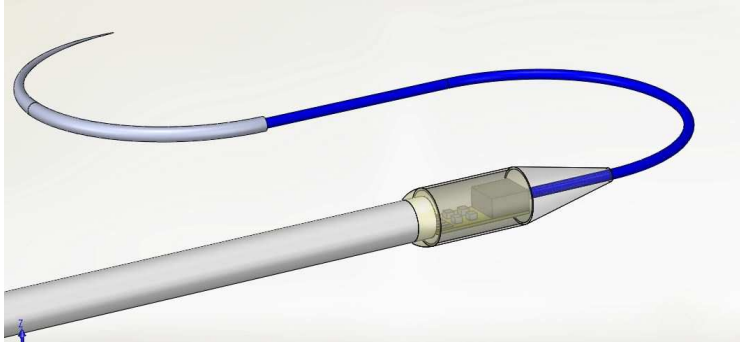


Figure 18 A CAD model of a generation two prototype. Capsule made transparent to provide a view of the inside.



Figure 19 Left, a capsule and a sensor-cable assembly prior to potting, right, an assembled device. Coin shown for scale purposes.

3.3.2 Implantation procedure

The implantation procedure for the generation two device would closely emulate that of a heartwire, not only in sub-epicardial placement but also by the procedure used to get there. The needle is used to make a channel in the tissue, and then the thread is used to pull the capsule into the channel. This technique is called “blunt dissection”. After the capsule is placed, the thread with the needle is cut. Procedure shown in Figure 20.

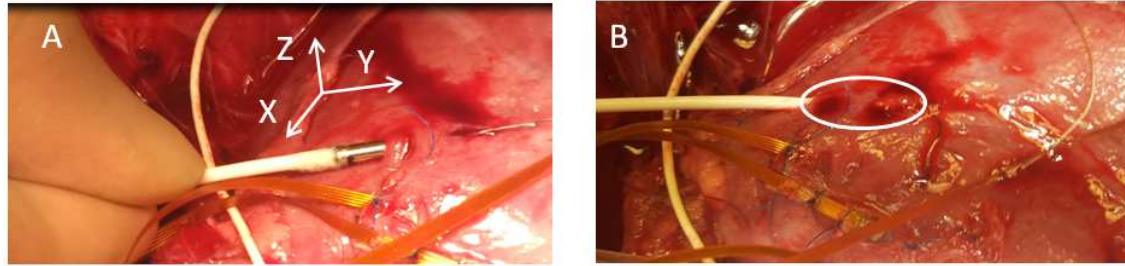


Figure 20 Placement by blunt dissection. A) Channel has been made and the sensor is pulled into the channel. B) Device placed, white oval highlights the device position.

3.3.3 Animal trials and system tests

3.3.3.1 Pull-in tests

It is important to estimate the forces acting on the device assembly and to evaluate the robustness of the adhesive joint and to evaluate the forces acting on the organ. To approximate cardiac tissue, a soft tissue phantom (Blue Phantom, USA) was used. It is to be understood that this phantom lacks a number of features present in a living heart, such as heart contractions, blood vessels and a fibrous layer. However, as it is tailored to represent soft tissue and is intended to be used in ultrasound guided biopsy training. We therefore found the soft tissue phantom suitable for carry out initial testing. However, to provide data closer to real-life scenarios, pig hearts were acquired from a butcher to be used as an alternative to the phantom. A force gauge (Model M4-2, Mark-10, USA) was used to record pull in and pull-out forces. The device sampling rate for continuous, force-over-time measurements is 10Hz, for single measurements 3000Hz. The resolution is 0.005N, accuracy is $\pm 0.2\%$ of scale (0.02N). The pulls

indicated a near linear increase of force as the capsule dissects the channel. The Blue Phantom demonstrated much higher forces than those found on the pig hearts, particularly on the pull-out. The placement procedure would also go more smoothly on the phantom. On the pig heart, initial resistance would be followed by capsule quickly entering the channel, on the phantom the capsule would enter the channel proportional to the force applied. Over a series of 15 pulls on the phantom pull in force average was 5.5N and pull-out 4N. The pig hearts displayed average 3.9N for pull in and 1N for pull-out.

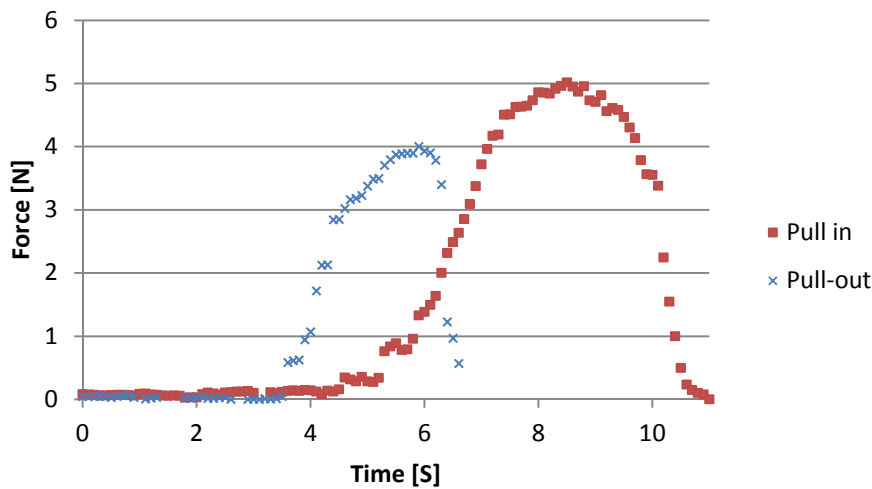


Figure 21 Pull in and pull-out force-over-time curves for one of the pulls on the phantom.

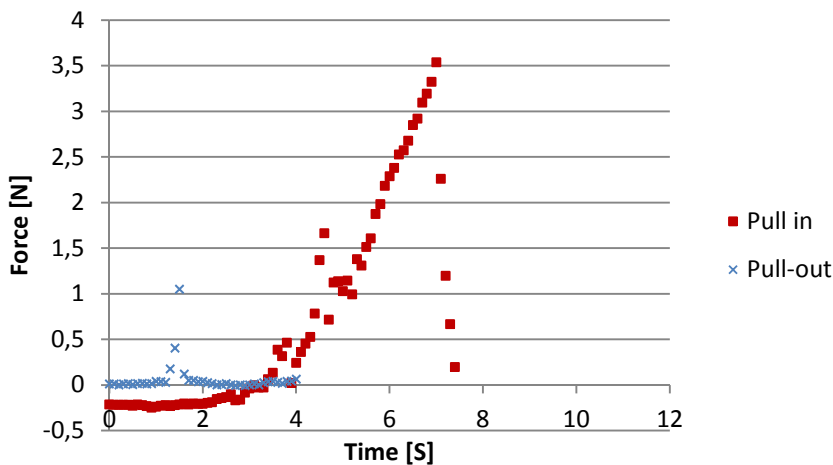


Figure 22 Pull in and pull-out force-over-time curves for one of the pulls on a pig heart.

Figure 21 and Figure 22 represent a typical force-over-time curve for a capsule being placed (pulled in) and pulled out. On both figures the peak of the pull in curve means the sensor is placed as desired, pull-out peak means the sensor started moving out of the channel at this force. More pull data is available in Paper IV. Pulls were conducted with both functioning devices and mock-ups without the sensor inside, no mechanical damage to the assembly was observed.

3.3.3.2 Animal trials

The generation two sensors were used in a number of animal trials, normally it would be deployed alongside generation one sensors that acted as a reference. The placement by blunt dissection as opposed to Seldinger technique was found to be a good solution. The new technique is less traumatic – the channel is dilated less and is simpler to execute with a less possibility for errors. On two occasions unwanted retraction from the channel, in the direction of the cable, was observed. To avoid retraction an additional stitch was made with the thread attached to the capsule. Probably the placement of the sensor is dependent on the doctor performing the operation. The retraction was observed only in two cases, the rest of the times the sensor was deployed, placement was found to be stable.

3.4 The third generation of the device

Generation three had the same general lay-out as the generation two and used the same accelerometer. The innovation was in the capsule shape and the manufacturing method of the capsule. Generation three metal capsules were made by additive manufacturing using a Concept Laser M2 Cusing (Concept Laser, Germany) machine. These capsules allowed testing geometries that are difficult to manufacture with traditional methods. However, post processing steps was necessary. The material used is the same as in the previous generation device, 316L Stainless Steel. In addition pacing and electric sensing function were integrated into this prototype. This was an important development. Heartwires are commonly used on CABG patients. If the device under development is unable to be used for pacing,

then heartwires would have to be implanted in addition to the device. Using the metal capsule as a unipolar pacing electrode allows decreasing the number of implanted devices.

3.4.1 Capsule

The generation three devices followed the generation two device assembly process, but for two distinctions: the capsule and the integrated monopolar pacing lead function. The capsules made by additive manufacturing allowed for geometries that are hard to attain by machining. The AM capsules, however, required post processing procedures (polishing) to be made suitable for use. Multiple capsule geometries were manufactured, but the selection was made in favour of the capsule that would make the smallest device. This was achieved by flattening the top and bottom of the cylindrical capsule, leaving just enough room to place the sensor and to secure it with an adhesive. The dimensions are presented in [85].

The capsules were washed prior to being sent to our laboratory. Upon visual inspection rust was observed on some of the capsules, see Figure 23. Rust on stainless steel is not an unknown phenomenon. Rusting of stainless steels is a surface effect, this can occur when a layer on the surface of the material is not sufficiently mixed with chromium and may rust. This can happen after procedures such as welding [89]. The Direct Metal Laser Sintering (DMLS) used in Cusing machines is equivalent to welding fine steel powder [90].

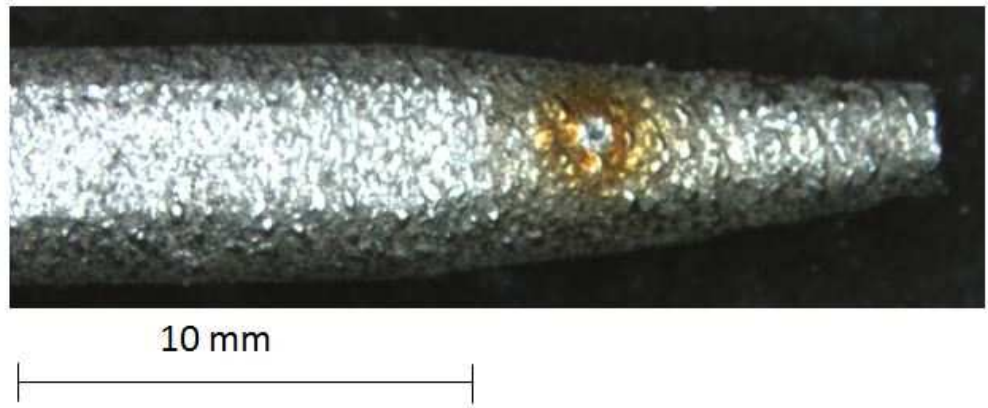


Figure 23 Capsule used in the assembly of generation three prototype before any post processing steps. Note the rust spot.

It was decided to polish the capsules to remove rust. Surface roughness was also unacceptable. Polishing was conducted by a two-step procedure. The first step was to polish the capsules on a Struers Knuth Rotor grinding station. The capsules were first polished with a P1500 grit SiC paper, then with a P2100 grit paper. The polishing cleared the rust and made the surface considerably less rough. No rusting was observed on polished capsules, even after lengthy exposure to saline solution, such as the leakage current test detailed in [85]. Abrasive polishing left a small number of “pits” on the surface of the capsule. These surface defects sensitize the metallic part to pitting corrosion [64]. The 316L formulation of stainless steel is vulnerable to pitting corrosion [91]. The risk of such corrosion was reduced by performing electrochemical polishing (ECP) [92-94]. Not only does the electrochemical polishing make the surface smoother, it also preferentially removes iron atoms compared to chromium leaving a more corrosion resistant layer on the surface [93]. The surface of the capsule is rough not just on the outside, but also the inside. Figure 24 shows the cross section of a polished capsule of the same design as in [85].



Figure 24 Cross section of a capsule used in generation three device, note the inner surface roughness.

With the idealised geometry from the CAD file, assuming 316L steel density is 8000kg/m³ the mass of the capsule after two polishing steps is still about 20% higher. See Table 5.

Table 5. Capsule mass comparison.

	Calculated	Unprocessed	Mechanical polish	ECP
Mass	0,0510	0,0990	0,0710	0,0602
(g)		0,1080	0,0740	0,0615
		0,0940	0,0699	0,0595

3.5 Assembly and encapsulation

The solution used to enable pacing functionality made the assembly process more complex. The potting would take 3 steps. First, a drop of adhesive was put into the capsule's tip. The second step would involve placing conductive adhesive on a dedicated pad on the bottom of the substrate and placing the assembly inside. The third step would be completing the potting. The schematic illustration of the device is shown in Figure 25.

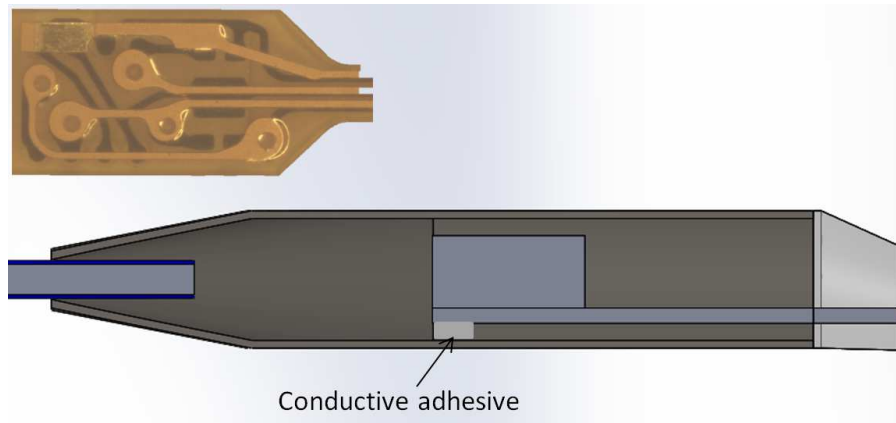


Figure 25 Schematic illustration showing the way of achieving an electrical connection to the capsule. Top – substrate with a contact pad to connect to metal capsule. Bottom – cross section of an assembled device, non-conductive adhesive not shown.

3.5.1 Animal trials and system tests

Two devices of generation three was made. The devices demonstrated good performance in both system tests and animal trials. The details of the tests can be found in [85]. Some concerns were raised as to the current density. The surface area of the capsule is larger than that of a pacing lead, which could, in theory, lead to insufficient current density and inability to pace. The pacing threshold recorded when pacing the heart was at the lower end of the scale of the pulse generator. This leads to a conclusion that current density achievable on that capsule is sufficient. Experimental set-up is shown in Figure 26.

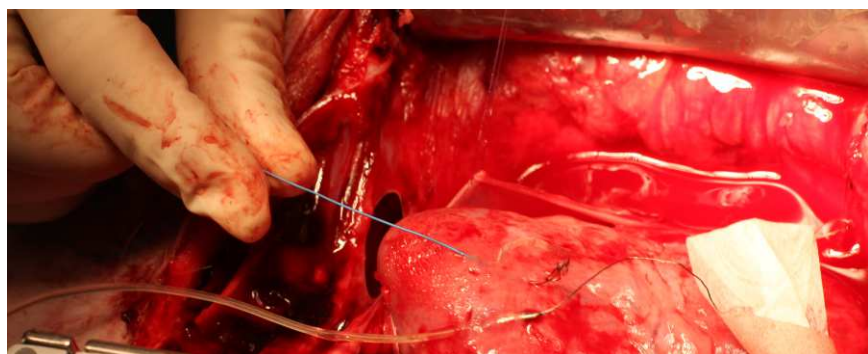


Figure 26 A generation three sensor implanted alongside a heartwire in a sensing and pacing set-up.

3.6 Generation four

The generation four devices used a new, more compact accelerometer. The sensor was provided by a partner company, the sensor is much like the Bosch BMA355. The sensor dimensions are 1.5x1.2x0.8 mm³. The other important advantage of this sensor over the CMA3000A device is the high maximum storage temperature - +150°C. This temperature is higher than the temperature used in autoclaving and should enable safe sterilization of the devices with this method. The layout was the same as the previous devices, but the capsules were more compact and had a number of distinct features. As this device was assembled late in the project, it also the best characterized device.

3.6.1 Cable flexural rigidity evaluation

Over the course of the project two approaches were used: a round cable [84] and an integrated cable and flex substrate solution [79, 80]. The cables evaluated are:

- A. A round cable that was used in early stages of the project [10] (a custom cable ordered from New England Wire Technologies, USA), outer diameter of 2.0mm. The system requires five conductors, and this cable has ten, and its outer diameter is larger than some of the capsules. This would further complicate its use with some capsules. However, it has been successfully used previously as well as being approved for clinical trials.
- B. A flex in tube design; a narrow, flat flex cable-substrate inside a polyethylene terephthalate (PET) tube, with an outer diameter of 1.2mm. The flex cable-substrate is a custom solution from Dyconex (Switzerland).
- C. A silicone overmolded flex; the same flex cable-substrate as in B, but overmolded with a two-component silicone (MED-4211 from NuSil, USA) using a custom mold.
- D. A custom made round cable manufactured by New England Wire Technologies (USA). Outer diameter of 1.2mm.

E. A flex in a silicone tube with an outer diameter of 1.2mm. The flex is the same flex cable-substrate as in B and C.

Schematic illustration of the cables cross sections are shown in Figure 27. Cables shown are to scale.

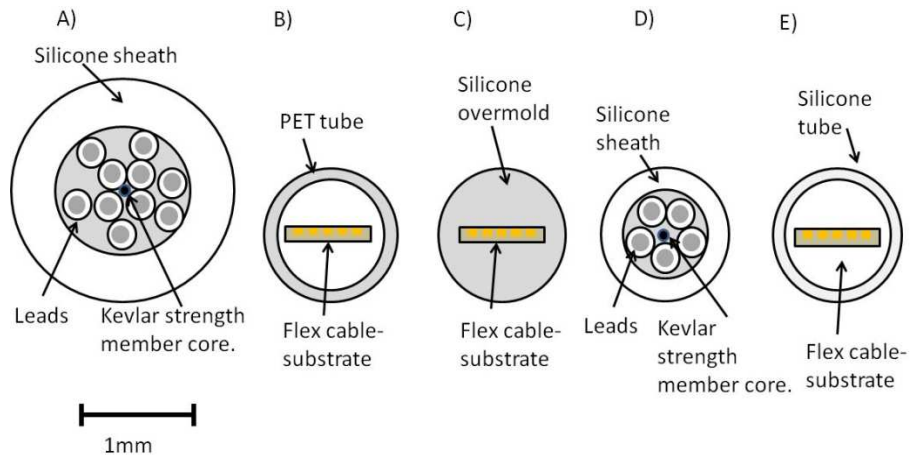


Figure 27 Cross sections of cables evaluated for flexibility.

A sensor implanted into the cardiac tissue will be subjected to a number of forces. The force the bending of the cable exerts on the implant may cause accidental retraction. A test setup was made to imitate this situation and to measure the force from the different cables. The sensor placement in a patient was approximated with a set of two fixtures: one fixture to emulate the placement in the heart and the second where the cable exits through the chest and is fixed, see Figure 28. The heart motion was approximated by motion along two axes only. The force gauge was placed on the bench and the cable was attached to the force gauge, the other end of the cable was attached to a moving stage – an orbital shaker (GFL 3005 from GFL, Germany) with 20mm circular orbit. 100mm long stretches of cable were used in the test. Two sets of experiments were conducted with varying maximum distance between the fixtures (varying slack): 95mm and 80mm. It is to be understood that the cable organization in the chest cavity will always be decided by the medical professional performing the surgery. However, the results of this experiment can help formulate guidelines on cable organization.

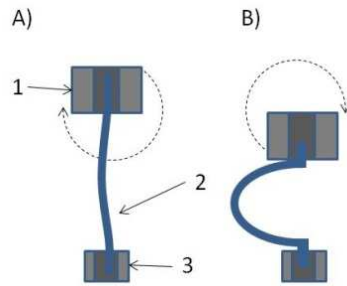


Figure 28 Schematic illustration of the flexural rigidity test. A) Start of test, platform at 12 o'clock position. 1 – clamp on the moving platform (fixture to emulate the placement in the heart), 2 – cable under test, 3 – force gauge (fixture to emulate the cable exit through the chest). B) Moving platform in 6 o'clock position.

The test revealed significant differences in cable rigidity. The A and B type cables turned out to have the greatest rigidity. With 5mm slack cable A displayed 0.035N force (in both 6 o'clock and 12 o'clock positions). Cable B recorded forces of 0.11N in the 6 o'clock position and as high as 0.26N in the 12 o'clock position. Slacking the cable greatly reduced the forces, even cable B displaying forces of 0.03N at 6 o'clock and 0.025N at 12 o'clock. The forces recorded with the thinner cables (C, D, E) were below the accuracy of the force gauge (0.02N).

3.6.2 Joint design analysis

The joint between capsule and cable could not be manufactured uniformly. As the capsules and cables got smaller, manual handling became more and more of a problem. It is relevant to know whether the inconsistencies of joint geometry can compromise the assembled system. A FEM model was created with this purpose in mind using the COMSOL platform. Three types of joint geometry were prevalent: “normal” – the transition is hemispherical or close to it, “bent” – the cable was not held upright during the curing process and the cable is off-axis to the capsule, “overflow” – too much excess adhesive resulting in a much larger joint. See Figure 29.

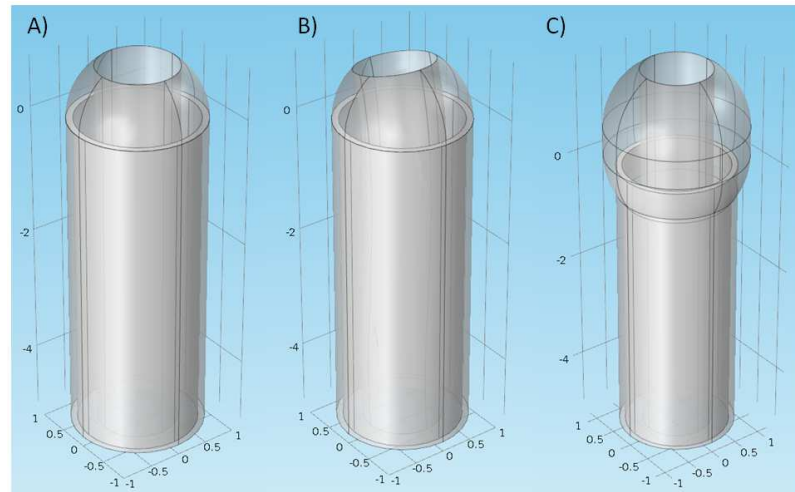


Figure 29 Joint geometris evaluated in the model. A) normal, B) bent, C) overflow.

The model consisted of the metal capsule, and the adhesive with a channel in the middle corresponding to the cable. Diameter corresponded to the type C capsule's channel found in Paper IV. Two different models were created for each geometry. One model had the forces pushing on the inner channel in the Y direction to represent the loading from the cyclical motion inside the heart. Second model with loading directed in the Z direction to represent the loads during pull-out. Force directions are indicated in Figure 30. The decision to use the 0.2N force in the lateral direction was based on the force measured in the cable stiffness test found in paper IV. Force simulating the pull-out was double the maximum pull-out force found in a living heart for C type capsule. The material properties for the 353ND-T epoxy were taken from [95]. Young's modulus – 2.1 GPa, Poisson's ratio – 0.391, density 1020 kg/m^3 , yield strength – 36 MPa ($36\,000\,000 \text{ N/m}^2$). The fixed constraints were on the outer walls of the steel capsule. The success criteria was if the von Mises stresses in the joint are below the yield strength then the design is sound. The model probes were set-up to calculate peak stress concentrations and the average for the entire joint.

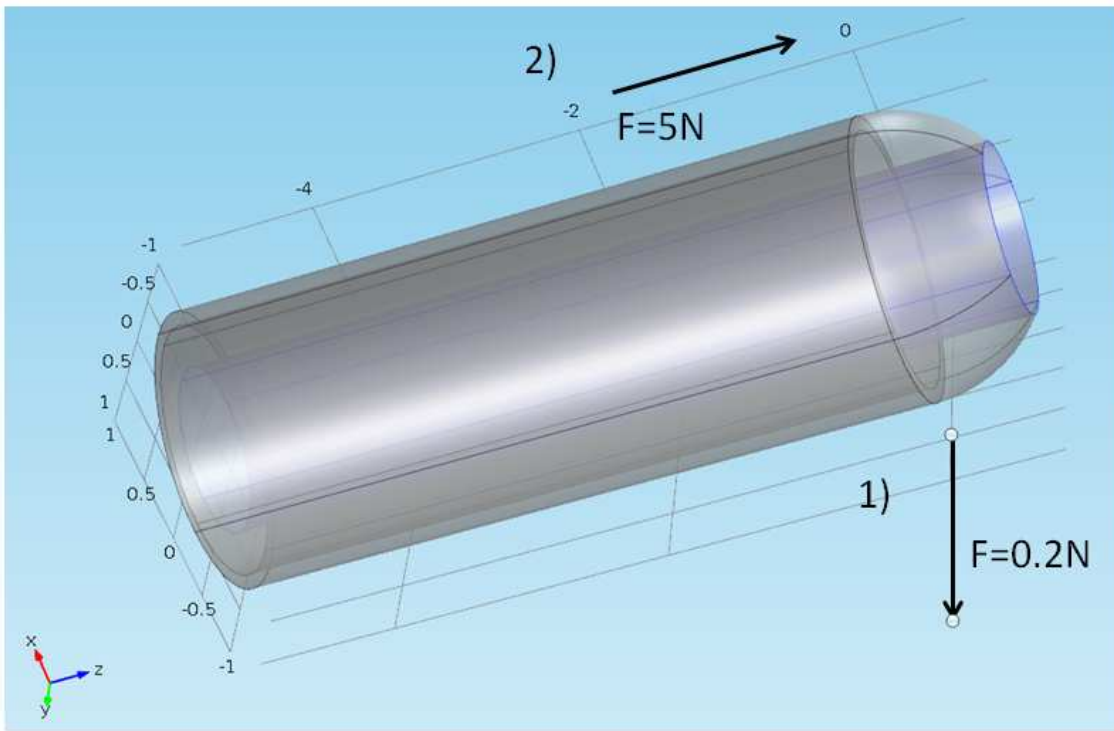


Figure 30 Forces applied in the two models for the «normal» geometry, the boundary where the force was applied is highlighted in blue.

The results indicated that all three geometries are suitable and do not compromise the mechanical integrity of the joint. Stresses are concentrated along the edges of the capsule in the direction of the sideways pressure. For the pull-out, the “bent” geometry showed stress concentrations at the edge of the transition. The calculated stress values distributions are shown in Figure 31 and the peak and average stress values are summarized in table 6.

Table 6. Von Mises stress values from the models.

Geometry	Sideways load		Pull-out load	
	Peak (N/m ²)	Average (N/m ²)	Peak (N/m ²)	Average (N/m ²)
Normal	81,736	9,096	1,297,707	343,011
Bent	89,117	9,113	1,740,252	343,220
Overflow	120,407	13,296	1,106,251	288,581

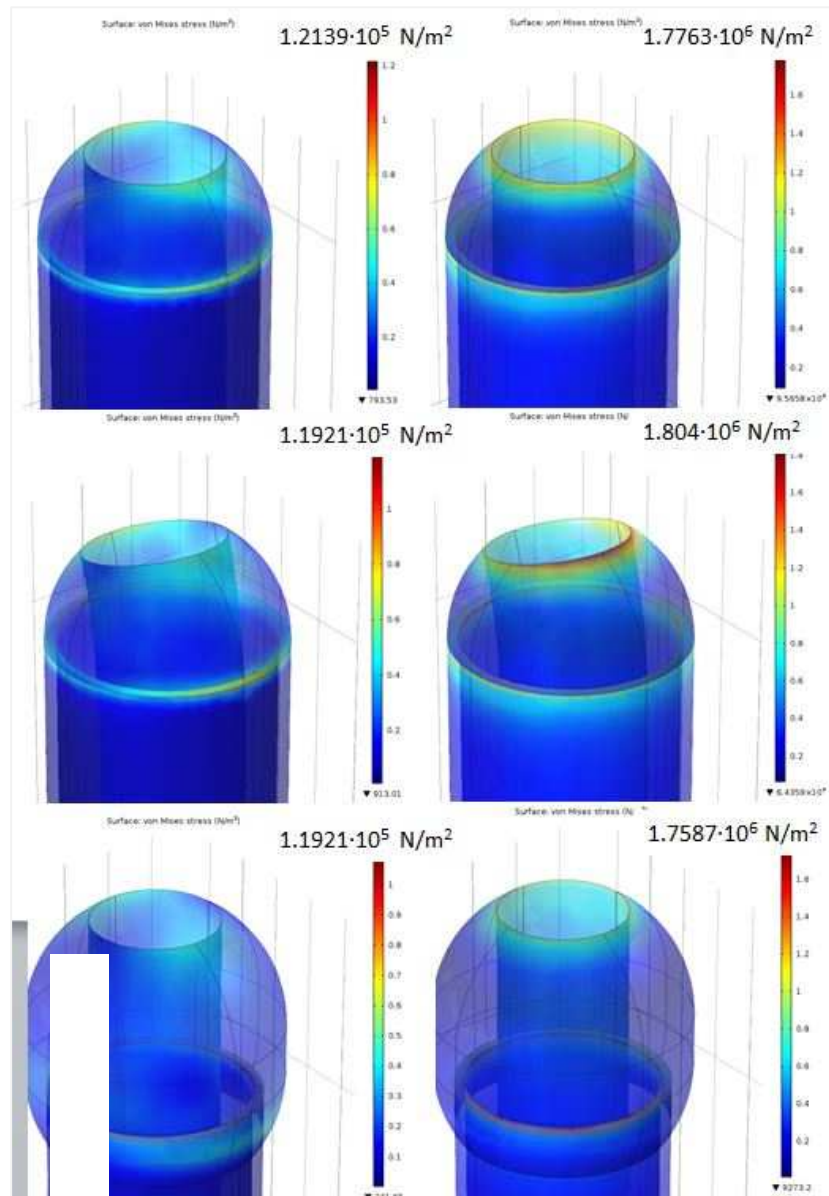


Figure 31 Left column – sideways stress distributions, right column – pull-out stress distributions.

Overflow geometry yielded high stresses for sideways load. This is due to the fact that in this type of loading, stress is concentrated on the edge on the metal capsule. The overflow joint has the adhesive on both the inner edge and the outer edge, compared to other geometries. However, the larger area over which the load is distributed reduces the pull-out stresses. The “bent” geometry, in the case of a pull-out loading has a stress concentration in the part of the joint that directly over the central axis of the capsule. The normal geometry distributes the stresses more evenly than the other geometries.

4 Concluding remarks and potential future work

The project has achieved its main goal. Heart monitoring with easy implantation and removal with additional pacing capability was demonstrated. Over the four generations of the prototypes developed, each individual generation decreased traumatism, improved usability and added functionality. System tests, such as leakage current recordings, indicated compliance to the appropriate standards. The animal model trials have verified two important aspects: traumatism level and ability to sense heart ventricle motion. The traumatism level was deemed to be acceptable. Momentary bleeding was observed, likely from the fine blood vessels in the cardiac muscle, in a minority of the implantations of generation 2 devices. Most implantations showed no signs of bleeding. Arrhythmia was never observed in any of the animal tests, including after pull-out. It can be concluded that the fixation of the implant in the tissue is sufficient to perform heart monitoring in open and closed chest conditions. This is the main achievement of the project. The fixation, however, may still be vulnerable to extraction, so organising the cable and taking care not to disturb the sensor is important.

This technology is targeted at patients recovering from CABG. It is targeted for 4-7 days inside the patient, followed by extraction. The device is not to be reused. The device developed in this project fits those conditions well. Given the limitations of time, funding and access to animal models there are still ways to improve the device. Some future work is described in the following section, roughly in the order of importance.

4.1 Device regulatory status

The devices presented in this thesis were fabricated using prototyping means, and they would have to be redesigned for manufacturing before any such certification or approval would be relevant. Clinical studies with humans do not require a CE mark – a risk assessment is sufficient. Such a risk assessment was carried out for the device presented by Imenes et

al. [10]. The devices described in this thesis only underwent the risk assessment necessary for animal trials. Subsequent human trials will be conducted after due risk assessment, with a device adopted for commercial manufacturing.

In this PhD project, prototype devices have been used in animal trials in a pre-clinical stage. The device described in this thesis is an active, implantable diagnostic device that is in direct contact with the circulatory system. This puts the device into Class III according to the 93/42/EEC directive [96].

Class III devices require extensive testing before they are allowed on the market. In Europe a certificate of conformity mark (CE mark) must be obtained. Obtaining the CE mark means going through a conformity assessment procedure, such as having a notified body conducting an audit of the device's design, based on the standard ISO 13485:2003. In the United States, the Food and Drug Administration mandates that the device must pass premarket approval – a process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

4.2 Potential future work

4.2.1 Survival trials

“Survival” in this case refers to the test subject in an animal model study. The performance of the sensor should be evaluated in a living organ for the entire duration of a 4-7 day hospital stay timeframe. The remodeling of the tissues could affect the pull-out procedure, and in vivo force recording would be interesting. However, the scar tissue formation might be incomplete and an extraction after 4 days might not be different from an extraction on the same day. Timeframe given for scar tissue encapsulation of implants is given as “weeks” [64].

4.2.2 Finite Element Model

A working Finite Element Model would simplify testing of capsule geometries. This could also greatly reduce the number of animal trials necessary to establish the preferred geometry. Models that describe the mechanical properties of the heart muscle do exist, such as [97], and could serve as a basis for a working model. In this project, some attempts were made at a model to study tissue – capsule interaction. However, due to problems with the model it was decided to focus on work with actual sensors.

4.2.3 Smaller accelerometer

Within this project an effort was made to use the smallest, commercially available accelerometers. Due to this, prototypes and custom made devices were not considered. However, MEMS Tronics, a global MEMS foundry, has a prototype 3-axis accelerometer with $1.05 \times 1.65 \text{mm}^2$ footprint (height is not specified) [98] that is in a high state of readiness. If the height is comparable to the Bosch BMA 355 then the encapsulation for this sensor could be made even more compact.

4.2.4 Reusable device

The sensor is disposable, targeted at single use. However, there might be a need for a reusable device. This could be either a device for clinical practice or a device that could be used for training. For clinical practice, the redesign would have to include measures that would ensure the device remains functioning after multiple sterilization and implantation procedures. The device would also need a reliable and simple way to re-attach the thread to the capsule after it is removed. A reusable device used for training would only need to take care of the needle re-attachment. A capsule was fabricated for such a device – the channel in the tip was replaced by a “needle eye” type of design. See Figure 32. This design was never tried out in an animal model, as priority had to be given to other devices.

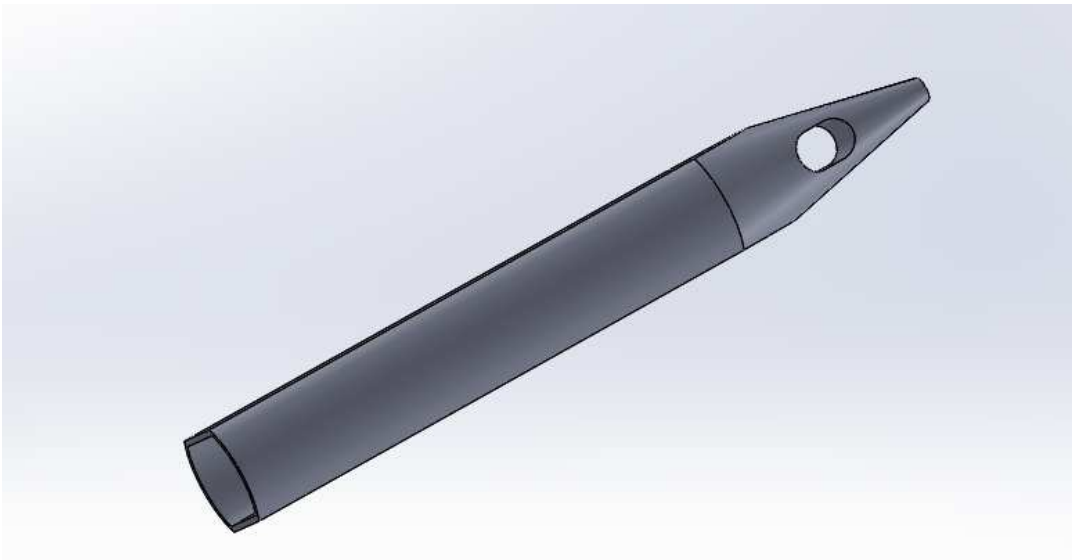


Figure 32 Capsule model with an «eye» for needle attachment.

4.2.5 6-axis sensing

The limitation of the system under development in this thesis is that it only monitors 3 translational axis. Heart motion has a rotational component to it as well. A 6-axis sensor that can monitor rotation together with translational axis would be more descriptive of the ventricle motion. To the best of author's knowledge, this work is already underway at the Intervention Centre of Oslo University Hospital. However, currently available IMUs (Inertial Measurement Units, a common name for a combined 3-axis accelerometer and 3-axis gyro) are far too large to permit sub-epicardial placement.

4.2.6 Active fixation

An active fixation, such as a retractable screw, would simplify the implantaion procedure. It could remove the subjectivism due to different techniques of blunt dissection that would be individual for any given physician. This might not be feasible for a disposable device, as this would complicate the design and make it more expensive.

4.2.7 Use in long term monitoring

Long term monitoring of the human heart is typically accomplished by pacemakers where electrodes are placed inside the ventricles and atria of

the human heart. However, in certain cases, permanent pacemaker leads are implanted directly on top of a ventricle, not inside. This type of lead, if equipped with an accelerometer, would provide the same effect as the sensor in [10]. The actual encapsulation would have to be revised to be suitable for permanent implantation and additional signal processing would be necessary to filter out non-cardiac components of the acceleration. In a long term monitoring device using a cable would not be possible so a wireless protocol would be necessary to transfer data and a battery or an energy harvester. The accelerometer used in generation 4 devices, the BMA355, has a current consumption of $130\mu\text{A}$ at full operation and $6.5\mu\text{A}$ in low power mode [99]. Whether currently available batteries are sufficient or an additional energy harvester would be necessary to ensure sufficient long term operation, is a question that needs a separate study.

4.2.8 Bipolar pacing

The device in this thesis works as a unipolar pacing lead – it needs a second electrode to form a circuit and conduct pacing or ventricle electrical activity sensing. Bipolar devices come with two electrodes and allow pacing and sensing with just one implant. Bipolar pacing is not necessarily better than unipolar, both have their uses [100]. However, there could be a situation where bipolar pacing would be preferable and this could be implemented by a slight redesign of the existing system.

4.2.9 Expanding the diagnostic application

The advantage of ventricle motion sensing over ECG will always be that it is a direct way of characterizing heart contractions. ECG effectively records what the nervous system tells the heart muscles to do, whereas ventricular motion recording tells you what the muscle is actually doing. This might be advantageous not only for ischemic patients but also for other heart conditions. To author's best knowledge, the Intervention Centre team had deployed the sensor in heart failure trials. The experimental conditions are when the function of the left ventricle is replaced by a pump and only the right heart (ventricle and atrium) remain functioning. The device was

used to sense the failures in right heart. This is a potential avenue for future work.

4.3 Cautionary tales

The project was quite successful; the design was validated both in system test and animal experiments. This is not to say that the project didn't have its fair share of failures. Among a number of things that didn't go right two in particular stand out.

4.3.1 Capsule with a collapsible ring design

A collapsible ring was an attempt to emulate the M22 pacing lead fixation solution (described in 2.5.2). Capsules made by additive manufacturing could, in principle, seamlessly integrate this flexible ring into the capsule design. A capsule was modelled with a ring on the tip. The thickness of the ring was 0.1mm. See Figure 33.

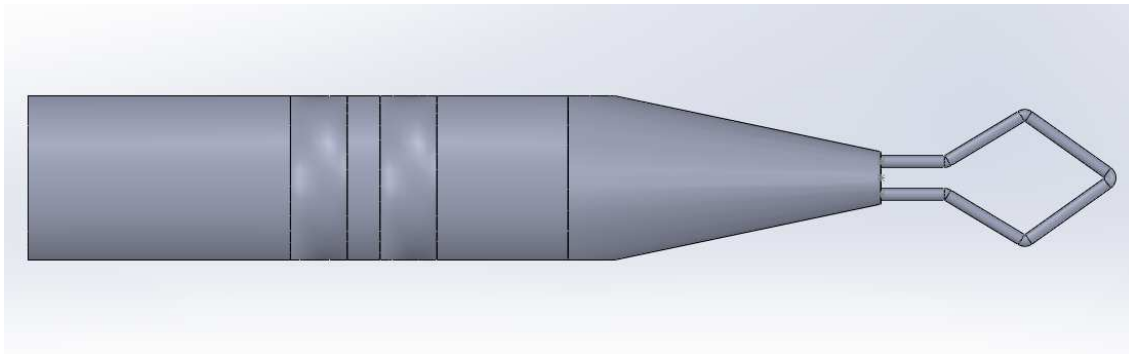


Figure 33 The capsule with a collapsible ring CAD image.

COMSOL FEM (Finite Element Modeling) suite was used to evaluate the ability of the ring to collapse under applied force. The model demonstrated that the ring would deform under 6N load. The integral von Mises stress was $0.15 \text{ N}\cdot\text{m}^2$, the maximal von Mises stress was $3.34\cdot 10^{10} \text{ N}\cdot\text{m}^2$. The maximum stress was a concern, however, the stress concentrations were only found on the edges of reference geometry used to set up boundary conditions. The cause could be the unrealistic constraint of the boundary loads. The face where the load was applied would not deform and that would cause the stress to be concentrated on the border of the loaded face

and the rest of geometry. Despite these stress concentrations concerns a batch of these capsules were included in the order sent to the company responsible for additive manufacturing. The results were a spectacular failure. The rings ended up being sharp, stiff, and prone to breaking at unpredictable loads and in unpredictable places. Figure 34 demonstrates an untouched capsule with a ring and two that failed in different ways.

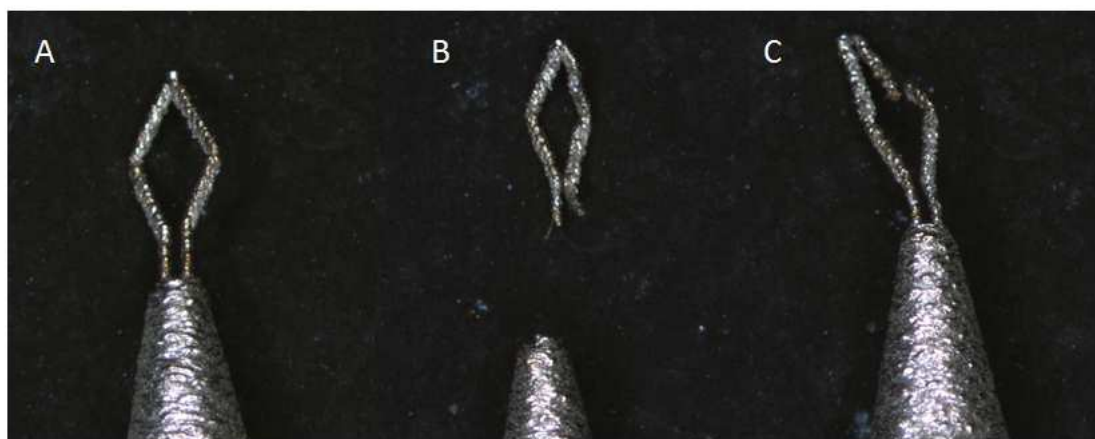


Figure 34 A) Capsule «as is». B) Ring that separated at the base. C) Ring that tore on the right hand side.

The end result was so different in geometry and material properties to the model that the results were made completely irrelevant. No further attempts at making a collapsible ring by additive manufacturing were undertaken.

4.3.2 Heat shrink encapsulation

At very early stages of the project, before the silicone based, generation one encapsulation was designed, an encapsulation based on medical grade heat shrink tubing was considered. This, in theory, would allow for very cheap and quick encapsulation for the device. The complications were finding a suitable heat shrink with appropriate diameter and stiffness. Sealing one end of the tube would also turn out to be a challenge. The idea was abandoned when it became apparent that a sufficiently tapered tip is impossible to achieve without using a long stretch of tube and that a neat welding joint is beyond the ability of the author to create. Measuring the tube stiffness using the procedure from Paper IV

indicated that the stiffness of the cables is such that the forces they create during cyclical loading are on the order of the force necessary to pull out the implant.

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Article I

F. Tjulkins, A. T. T. Nguyen, N. Hoivik, K. Aasmundtveit, E. Andreassen, L. Hoff, K. Imenes, "3-axisMEMS Accelerometer-based Implantable Heart Monitoring System with Novel Fixation Method," in Electronic Components & Technology Conference, Las Vegas Cosmopolitan, 2013, pp. 510–516.

Article II

F. Tjulkins, A. T. T. Nguyen, N. Hoivik, K. Aasmundtveit, E. Andreassen, L. Hoff, O. J. Grymyr, P. S. Halvorsen, K. Imenes, "MEMS-Based Implantable Heart Monitoring System with Integrated Pacing Function," in Electronic Components & Technology Conference, Orlando, Florida, 2014, pp. 139-144.

Article III

F. Tjulkins, A. T. T. Nguyen, E. Andreassen, K. Aasmundtveit, N. Hoivik, L. Hoff, , O. J. Grymyr, P. S. Halvorsen, K. Imenes, "Fabrication and assembly of MEMS accelerometer-based heart monitoring device with simplified, one step placement," J Med Eng Technol, vol. 39, pp. 69-74, Jan 2015.

Article IV

F. Tjulkins, A. T. T. Nguyen, E. Andreassen, L. Hoff, P. S. Halvorsen, O. J. Grymyr, K. Imenes "An Implantable Accelerometer-based Heart Monitoring Device with Improved Positional Stability" submitted to ASME Journal of Medical Devices.