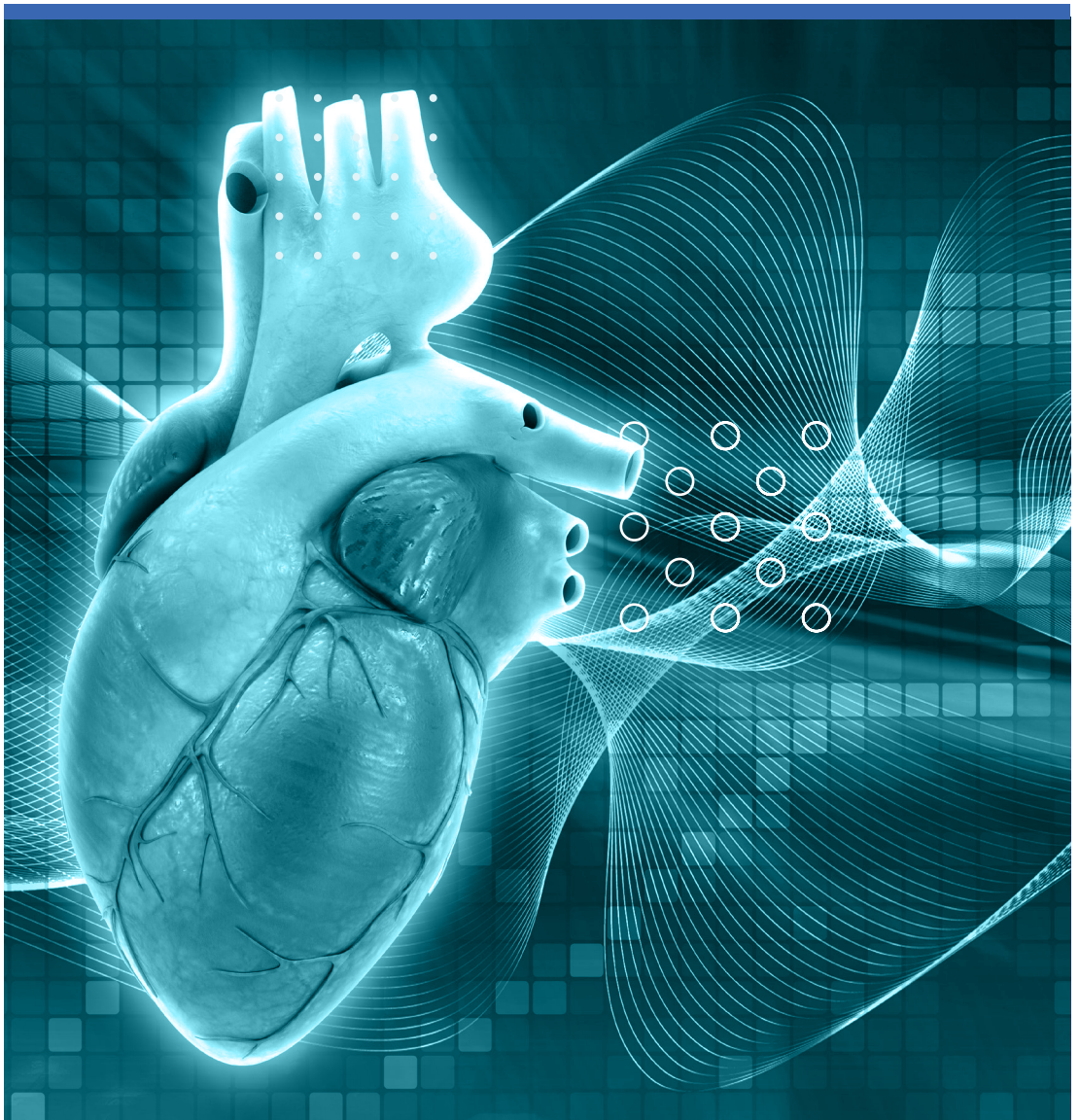Thai Anh Tuan Nguyen

Miniaturization of Circuit Packaging of an Accelerometer Heart Monitoring Device

HSN

Thai Anh Tuan Nguyen

Miniaturization of Circuit Packaging of an Accelerometer Heart Monitoring Device

A PhD dissertation in
Applied Micro- and Nanosystems

Abstract

Continuous monitoring heart activity based on implantable accelerometer devices have been demonstrated as efficient method that could provide higher sensitivity and specificity than the conventional electrocardiography (ECG) method. The method can be specified for detection of ischemia on patient who has undergone Coronary Artery Bypass Graft (CABG) surgery. The current implantable accelerometer devices are sutured to the heart surface and have to be removed before closing the patient's chest since the device dimension is not suitable for closed chest implantation. According to a surgical point of view, a heart muscle implantable accelerometer device can properly present the heart motion without interfering with surrounding organs. The device can be suitable for both intraoperative and postoperative monitoring procedures. However, the heart muscle implantation requires miniaturization of the device to provide minimal tissue trauma and simple implantation procedure.

This study focuses on development of a MEMSbased 3-axis heart muscle implantable accelerometer device. The device is to be implanted into the heart muscle, remain in place after the thorax is closed, and be pulled out though an opening in chest wall after a few days when the intensive care is no longer needed.

Five different versions of the heart muscle implantable accelerometer device were proposed and developed with regards to the prerequisites for the heart implantable medical devices including the regulatory compliances, and the clinical demands and the requirements of device components. These devices were categorised into two main groups built on two different commercial accelerometer sensors. In comparison to the earlier implantable accelerometer device, the dimensions of these five versions were significantly reduced in this study. The overall diameter of earlier device was 11 mm which was far different from the 3.2 mm diameter of the first version device and 2.0 mm diameter of the fifth version.

A novel structure of heart muscle implantable accelerometer device was first conducted in the second version device which has been able to corporate with

the pacing/sensing functionality as a temporary pacing wire. This study also suggested specific experimental set-ups for qualifying essential safety requirements (e. g. leakage current, tensile strength, flexural endurance, insulation strength) based on the standards and regulation for the implantable devices. Tests of the complete devices showed leakage currents are at least 1000 times less than the limit for heart implantable applications. This study also pointed out that the pulling strength of a device is important for accomplishing the implantation and removal of the device. Different versions of device provided different pulling strength which varied from 12N up to 100N. The muscle-implantation stability of different versions were demonstrated in this study depend on the device dimension, encapsulation structure, cable flexibility and the implantation method. The implantation procedures of different device versions and quality of the acceleration signals were verified and validated in several animal trials reported in detail in this study.

Preface

This thesis is submitted in partial fulfilment of the requirements for the degree of Philosophiae Doctor at the Buskerud and Vestfold University College (HBV), Norway.

Contents

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Abbreviation

ADC	Analogue to digital convertor
AV	Atrioventricular
BGA	Ball grid array
CABG	Coronary Artery Bypass Graft
CT	Computer tomography
ECG	Electrocardiography
FPC	Flexible Printed Circuit
GPIB	General purpose interface bus
ICA	Isotropic conductive adhesive
IEC	International Electrotechnical Commission
LA	Left atrium
LV	Right ventricle
MEMS	Microelectromechanical System
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquistion
NCA	Non conductive adhesive
PA	Pulmonary artery
PAC	Pulmonary artery catheterization
PBS	Phosphate buffered saline
PET	Position emission tomography
PI	Polyimide
RA	Right atrium
RV	Left ventricle
SA	Sinoatrial
SAC	Tin-silver-copper
SPECT	Single photon emission computed tomography
TEE	Transesophageal echocardiogram
TTE	Transthoracic echocardiogram

Chapter 1

Introduction

1.1 Research Motivation

Coronary artery bypass graft surgery (CABG) is known as a surgical treatment for severe coronary artery disease which has been established for over 50 years [1, 2]. The coronary artery disease is a narrowing or blockage of the arteries and vessels that provide oxygen-rich blood to the heart muscle [3] which is the leading cause of death [4]. CABG is the most common type of open-heart surgery in the United States with more than 150000 surgeries performed each year [5]. According to the Millennium Research Group (MRG) reports, from 2013, over 165000 CABG procedures would be performed across Europe. The International Heart Institude of Montana Foundation reported an estimated 800000 CABG surgeries are performed worldwide each year. The CABG is a reliable treatment for coronary artery disease [6] that helps relieve symptoms in most patients [7]. However, CABG surgery is not without risks. Hirsch et al. reported an estimation of transient myocardial ischemia occurring from 33% to 38% of patients post CABG [8]. Especially ischemia occuring soon after CABG surgery can be troublesome finding and can be difficult to diagnose. Besides, the postoperative myocardial infarction (MI) rate is estimated to be up to 25% with mortality rate up to 14% [8, 9]. Continuous monitoring of patients who have undergone heart surgery, e.g. coronary artery bypass grafting surgery (CAGB), is vital for early detection of complications, and has been shown to improve survival and patients outcome [10]. There is a demand for a method for continuous monitoring of cardiac function that can detect postoper-

ative complications faster and with higher sensitivity, specificity and accuracy than existing systems can [11].

1.2 Existing cardiac monitoring methods

This section presents a summary of monitoring methods which are currently and potentially used to diagnose heart deseases, especially coronary arteries desease. Three crucial properties of the methods that received considerable attention in this study are the sensitivity, specificity and continuous monitoring.

1.2.1 Computed tomography (CT)

Computed tomography (CT) images of human body cross section are produced by the attenuation data of x-rays along a large number of lines through the cross section [12]. The first CT scanner was invented by Sir Goodfrey Hounsfield in 1967 [13].
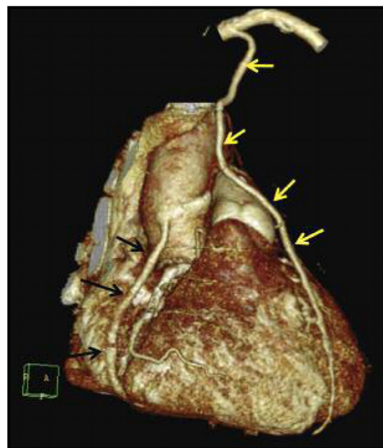
Figure 1.1: Volume-rendered view of a patient with a history of aortocoronary bypass surgery, including a left internal mammary artery implant to the left anterior descending coronary artery (yellow arrows) and a vein bypass graft to the right coronary artery (black arrows) [17]. This figure is used with permission of the American Osteopathic Association, license number 3640370573713.

Computed tomography has demonstrated accurate detection of obstructive bypass graft disease, native coronary arteries disease or the progression of coro-

nary disease with the sensitivity and specificity up to 99% and 96% respectively [14, 15]. Multi-detector computed tomography coronary angiography (CTCA) is now an established and highly effective non-invasive test in patient having coronary artery disease with excellent sensitivity [16]. However, the CT is limited by fast or irregular heart rate [16] and especially it is a non-continuous monitoring method that is run by an operator during the diagnosing procedure. The illustration of method [17] is shown in Figure 1.1.

1.2.2 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) is a medical imaging procedure that uses strong magnetic fields and radio waves to produce cross-sectional images of organs and internal structures in the body [18]. The imaging on axial MRI of a coronary artery bypass graft was first reported by Herfkens in 1983 [19].
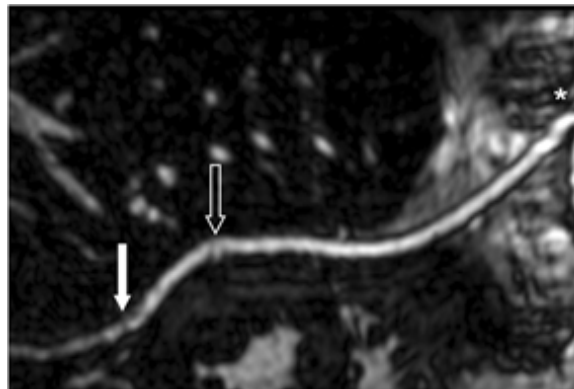
Figure 1.2: Magnetic resonance angiographic image (curved reconstruction) using intravasal contrast agent for vein bypass graft visualization [22]. This figure is reused with license number 3635840046363 - Publication: Interactive Cardiovascular and Thoracic Surgery.

On patients who undergo CABG surgery with severe compromised left ventricular function, postoperative MRI can be used to compare pre- and postoperative functional data [20]. Using magnetic resonance imaging, cardiac function can be assessed globally and regionally [21]. The magnetic resonance angiography (MRA) is the MRI test of blood vessels that can provide sensitivity and specificity up to 93% and 97% accordingly [19]. An illustration of magnetic resonance image [22] is shown in Figure 1.2

1.2.3   Electrocardiography (ECG)

Electrocardiography is a method used to measure the heart's electrical activity by placing electrodes around the heart [23]. The first prototype ECG (string galvanometer) was devised by Willem Einthoven in 1900-1903. He also pointed out the important medical value of the ECG and firstly assigned the letters P, Q, R, S and T to the ECG deflections [24, 25].   Electrocardiography has
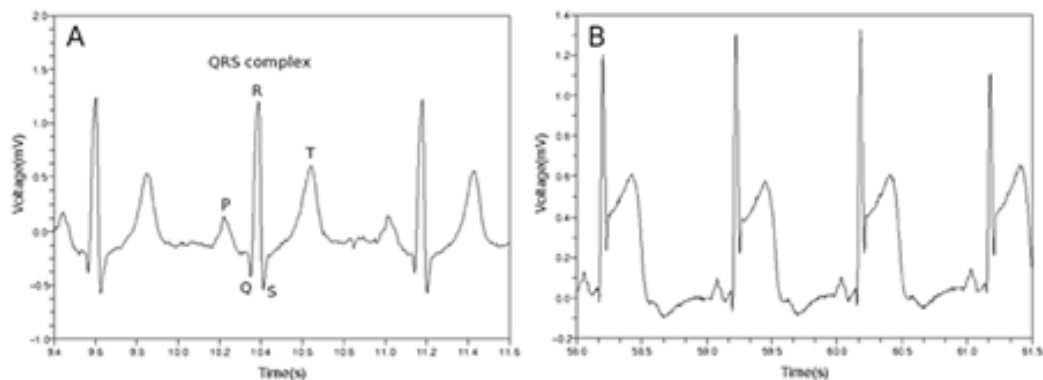
Figure 1.3: Normal ECG and ST segment elevation (ischemia). (A) Normal ECG is divided into P, Q, R, S and T parts. (B) This ECG waveform shows ST segment elevation (present of myocardial ischemia) [30]. Figure is reproduced with permission of the BioMed Central Journal, request 00571392

been used as an important and central tool in diagnosing myocardial ischemia [26, 27]. Computer-assisted ECG interpretation supports the online analysis of ischemia. It is widely available from 60% to 78% sensitivity in detection [28]. The overall specificity for detection of coronary disease is about 77% [29]. Figure 3 demonstrates the normal ECG signal (shown in Figure 3A) and the elevation of the ST segment (shown in Figure 3B) when myocardial ischemia is present [30]. However the method is reported not to be sensitive enough to diagnose myocardial ischemia and infarction for perioperative and postoperative CABG. The ECG provides fairly slow response to the existing of ischemia [31, 32, 33]. The method illustration [30] is shown in Figure 1.3

1.2.4   Echocardiography

Echocardiography uses high-frequency sound waves to create pictures of the heart. Pictures can be two-dimensional or three-dimensional. The motion of

blood through the heart can be recorded by a Doppler echocardiogram [34]. There are two echocardiogram types: the transthoracic echocardiogram (TTE) and the transesophageal echocardiogram (TEE). Sensitivity and specifity of the TTE method can be up to 78% and 86% repectively [35]. The transesophageal echocardiogram is now recognized as a sensitive tool for detection of myocardial ischemia, allowing for rapid diagnosis and treatment of perioperation ischemic left ventricular (LV) dysfunction. TEE holds out a promise of real-time, quality assessment of CABG [36]. Using TEE, the heart's wall motion abnormalities were more predictive of postoperative myocardial infarction than the ECGs [8]. However, the monitoring process is carried out serially and requires to have medical technicians and doctors present. The equipment has to be placed invasively in the esophageal.

1.2.5 Nuclear Imaging

Nuclear imaging uses low doses of radioactive substance that is injected into blood stream through a vein. The radioactive substance travels to the heart and releases energy which is used to create the picture of the heart [37]. There are three main types of nuclear imaging for heart: Single photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) and Multiple Gated Acquistion (MUGA) [38]. The sensitivity and specificity for diagnosing coronary artery disease with SPECT imaging was shown to be 86% and 89% respectively [39, 40]. SPECT cannot be used continuously throughout the postoperative follow-up period.

1.2.6 Pulmonary artery catheter (PAC)

Pulmonary artery catheterization was first introduced in 1970 by HJ Swan and W Ganz. The method used a pulmonary artery catheter (PAC) which is inserted through a central venous access into the right side of the heart and floated into the pulmonary artery. PAC is used to measure stroke volume, oxygen saturation and intracardiac pressure which help to guide diagnosis and treatment [41]. PAC can provide necessary information for myocardial ischemia diagnosis but PAC has never been shown to improve perioperative outcome [42, 43]. Use

of a PAC during CABG surgery was associated with increased mortality and higher risk of severe end-organ complications [44].

1.2.7 Cardiac Acceleration

a. Monitoring heart activity by single-axis accelerometer sensor
Initial studies used unidirectional accelerometer to investigate the heart activities in relation to contractility of the heart muscle [45]. The accelerometer was located inside the tip of standard unipolar pacing lead that was temporary inserted in the right ventricle of patient. The study featured a potential result for diagnostic applications in monitoring of myocardial function in man by using an implantable accelerometer device.

A single-axis, lead-based accelerometer positioned in the right ventricle apex were also used to detect acute myocardial ischemia in human [46]. The change in peak endocardial acceleration can be used to characterize a reduction in contractility during ischemic episodes.

b. Monitoring heart activity by triple-axis accelerometer sensor
An early study concerning continuous monitoring heart activity was carried out by using an implantable accelerometer device [11]. A triple axial accelerometer device based on two commercially available dual axial accelerometer (ADXL-202 Analog Devices Inc, USA) was implanted on the left ventricle free wall of the heart. The experimental results indicated that early recognition of regional ischemia can be achieved by real-time analysing of accelerometer data. The feasibility of a triple axial epicardial accelerometer device in detecting of myocardial ischemia in cardiac surgery patients was demonstrated by Halvorsen et al. [47]. A key finding in this study was that the significant changes of ventricle dysfunction can be observed by the processed acceleration data when occlusions were carried out. A comparable result was given by the echocardiography method while there were no significant electrocardiography and hemodynamic changes. The packaging of this device was built on a commercial MEMS based triple-axis accelerometer (KXM52-1050 Kionix Inc, USA) proposed and reported by Imenes et al. [48]. Another animal study on detection of myocardial ischemia with epicardial accelrometers (accelerometer attached on the heart surface) reported a sensitivity and specificity range of the accelerometer

from 94-100% and 92-94% respectively [49]. The technique confirmed that myocardial ischemia can be detected with epicardial triple-axis accelerometerand can be used for continuous real-time monitoring myocardial ischemia during and after surgery. Real-time automated detection of ischemia with an accelerometer device was demonstrated both in animals and in patients undergoing coronary bypass grafting was firstly documented in [50, 51]. These studies stated that accelerometers have potential to become an important sensors for detection of myocardial ischemia during and after cardiac surgery. The study used the same type of MEMS based 3-axis accelerometer device which was introduced by Imenes et al. [48].

1.2.8 Summary of above methods

Table 1.1: Basic specifications of typical heart diagnosis methods

Monitoring method	Sensitivity[1]	Specificity[2]	Continuous monitoring	References
Computer tomography (CT)	99%	96%	No	[14, 15]
Echocardiogram	78% (TTE) - 93% (TEE)	86% (TTE) - 93% (TEE)	No	[35]
Electrocardiography (ECG)	60%-78%	77%	Yes	[28, 29]
Magnetic Resonance Imaging (MRI)	93%	97%	No	[19]
Nuclear Imaging	87%	89%	No	[39, 40]
Pulmonary artery catheter (PAC)	2-25%	92-99%	Yes	[43]
Heart acceleration[3]	100%	95-100%	Yes	[51]

According to above comparison, acceleration based heart monitoring can be a promising method for diagnosis of heart activity.

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[1]Propability of a positive test among patients with disease

[2]Propability of a negative test among patients without disease [52]

[3]based on initial studies carried out by Halvorsen et al.[51]

1.3   Scope of the study

Earlier studies have shown that detection of heart activity with high sensitivity and specificity can be provided by an implantable heart accelerometer. The acceleration-based method can be used as one of the central tools for heart diagnosis [53, 48, 49]. The demand for development of existing heart accelerometer devices is a key point of interest. The main challenge that was addressed in earlier studies was the size of the implantable accelerometer devices. A new generation heart accelerometer device should be small enough to be implanted into the left ventricular muscle and to be used during open-chest surgery and after closing the thorax. Besides, the accelerometer device should be able to extract from the patient by a simple pulling procedure when the monitoring period is completed. In addition, the new generation accelerometer device should combine the functionality of the acceleration sensor with the pacing possibilities of a temporary pacing wire. This combination will allow the use of an acceleration sensor without adding procedures or number of devices beyond the present procedures using temporary pacing wires.

1.4   Overview of existing heart implantable devices

1.4.1   Epicardial pacing wires

The temporary epicardial[4] pacing wires were first introduced in 1960s. The temporary pacing wires are routinely placed in cardiac operations for therapeutic and diagnostic purposes. They are used to optimize haemodynamics by maintaining heart rate and rhythm. Both atrial and ventricular tachyarrhythmias can be suppressed by using the temporary pacing wires [54].

The epicardial suture-on pacing leads [55], shown in Figure 1.4, can only be used during open-heart surgery. The curved needle provides easy epicardial lead placement. The silicone wings with through holes may be sutured onto the epicardium to prevent dislodgement [55]. The leads have silicone outer

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[4]tissue that surrounds the heart
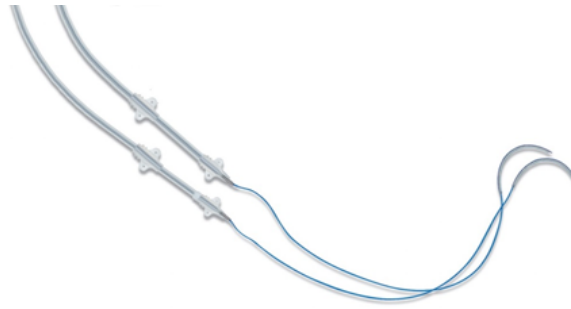
Figure 1.4: Epicardial suture-on pacing lead. The overall diameter of the lead is less than 3.2 mm. The figure is used with permission of Oscor Inc. USA. Oscor Inc. is a World-Class Developer & Manufacture of long term cardiac implantable devices.

insulation and Platinum/Iridium tip electrodes. The overall diameter of the lead is less than 3.2 mm.

1.4.2 Myocardial heart wires

Temporary myocardial[5] heart wires are used to provide consistent temporary sensing and pacing during and after cardiac surgery while providing minimal trauma to the myocardium [55]. Figure 1.5 describes temporary pacing wires from Oscor's (Oscor Inc., USA). The wires are available in either atraumatic zig-zag or tines fixation for safe and easy implantation.

Figure 1.5: Temporary myocardial heartwires. Unipolar and bipolar heartwires (upper and lower side of the photo). The overall diameter is less than 0.6 mm. The figure is used with permission of Oscor Inc. USA. Oscor Inc. is a World-Class Developer & Manufacture of long term cardiac implantable devices.

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[5]heart muscle

1.4.3   Permanent pacing leads

The pacing leads are used for pacing and sensing of the right atrium, ventricle, or both [56], see Figure 1.6. The permanent pacing leads normally contact with the endocardium or myocardium. The most important requirement of the pacing leads is to maintain the electrical performance permanently (patient lifetime). Figure 1.7 illustrates the overall structure of an active fixation pacing lead produced by Oscor.
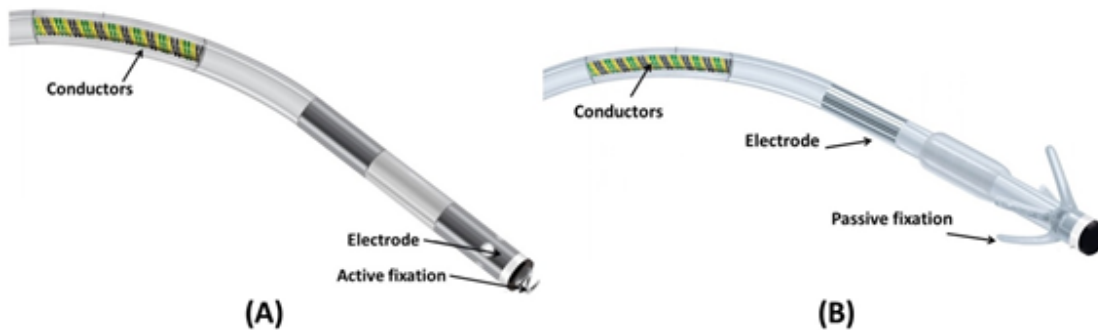
Figure 1.6: Permanent pacing leads. (A) Active fixation pacing lead; (B) Passive fixation pacing lead. The lead body diameter is 1.2 mm. The figure is used with permission of Oscor Inc. USA. Oscor Inc. is a World-Class Developer & Manufacture of long term cardiac implantable devices.
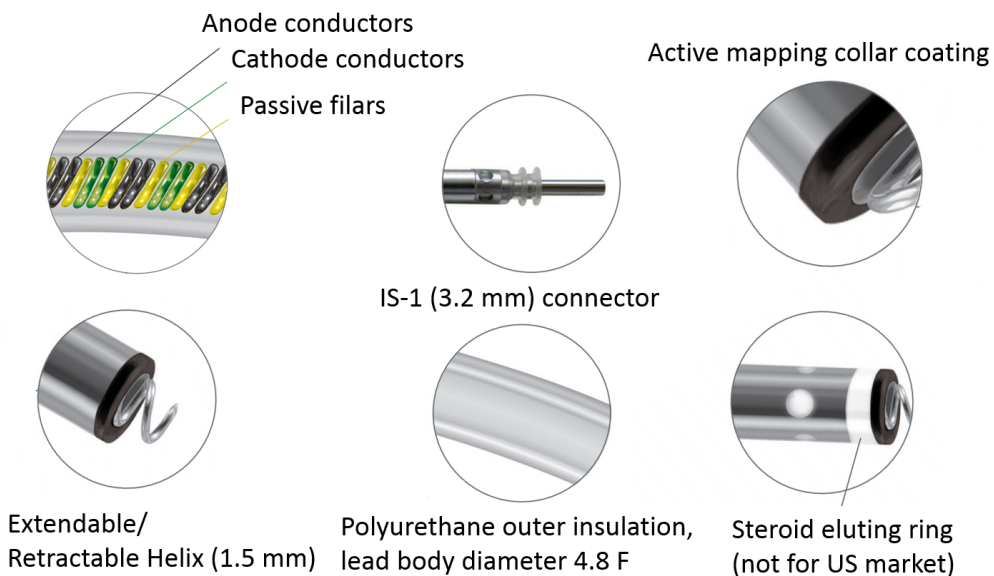
Figure 1.7: The overal structure of an active fixation pacing lead - Oscor Physique series

1.4.4   The Micra^{TM} Transcatheter Pacing System

Figure 1.8: Micra^{TM} transcatheter pacing system - This figure is used with the permission of Medtronic Inc.

The Micra transcatheter pacing system is introduced by Medtronic Inc. as the the world's smallest pacemaker. At one-tenth the size of a conventional pacemaker, the Micra is delivered directly to the heart through a catheter inserted in the femoral vein where it attaches onto endocardial tissue and provides pacing signals [57]. The device does not require a surgical incision in the chest and creation of a "pocket" under the skin [58]. The capsule weight, volume and electrode spacing are 2g, 0.8 cc and 18 mm respectively. A demonstration structure of Micra capsule is shown in Figure 1.9.
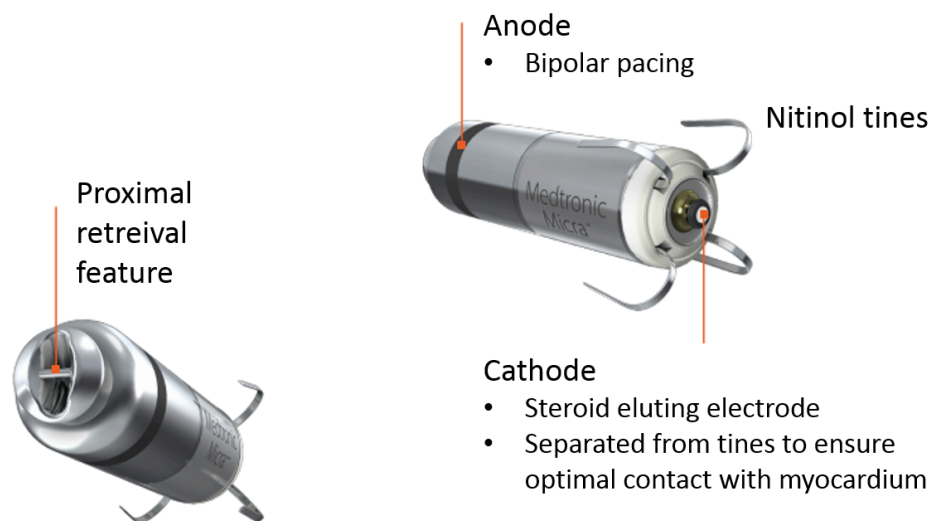
Figure 1.9: The overal structure of a Micra^{TM} capsule

1.4.5 Nanostim™ Leadless Pacemaker

Nanostim™ leadless pacemaker is introduced by St. Jude Medical Inc. This is the world's first, commercially available leadless pacemaker which is designed to eliminate the surgical lead and pacemaker pocket. Nanostim leadless pacemaker can potentially reduce conventional pacemaker complications such as infection of the pocket and lead failure, lead removal and the hemodynamic impact of the lead crossing the tricuspid valve. The Nanostim™ leadless pacemaker offers patients a minimally-invasive approach and can be repositioned and retrievable. Structure of a nanostin leadless pacemaker was described by Koruth et al. [59]. Nanostim is composed of a pulse generator with built-in battery and electrodes. A single turn helix provides the fixation mechanism with nilon tines support. The tip electrode is a titanium-nitride-coated platinum-iridium disc located at the center of fixation helix. Ring electrode is an uncoated part of the titanium pacemaker case, with a geometric surface area >500 mm^2. The overall length and outer diameter of the Nanostim leadless pacemaker are 42.3 mm and 6 mm respectively [60].

Figure 1.10: The Nanostim™ Leadless Pacemaker [62] (Overall length - Outer diameter: 42.3 mm - 6 mm). A Nanostim pacemaker stays within the right ventricle (to the right). Photos are reprinted with permission of St. Jude Medical, © 2015. All rights reserved.

1.4.6 CardioMEMS

The CardioMEMS™ HF system is introduced by St. Jude Medical [61]. The sensor system is used to measure and monitor the pulmonary artery (PA) pres-

sure and heart rate in certain heart failure patients. The implantable sensor is permanently placed in the pulmonary artery, the blood vessel that moves blood from the heart to the lungs. The sensor is implanted during a right heart catheterization procedure. The PA sensor is about the size of a small paper clip and has a thin, curved wire at each end. This sensor does not require any batteries or wires [62, 63]. Device packaging and materials are shown in Figure 1.12.
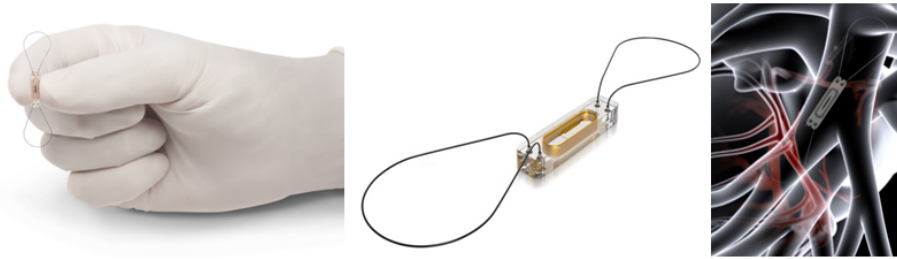
Figure 1.11: CardioMEMS^{TM} HF device in hand; photo of the CardioMEMS device and CardioMEMS^{TM} device implanted in the pulmonary artery. Reprinted with permission of St. Jude Medical, © 2015. All rights reserved.
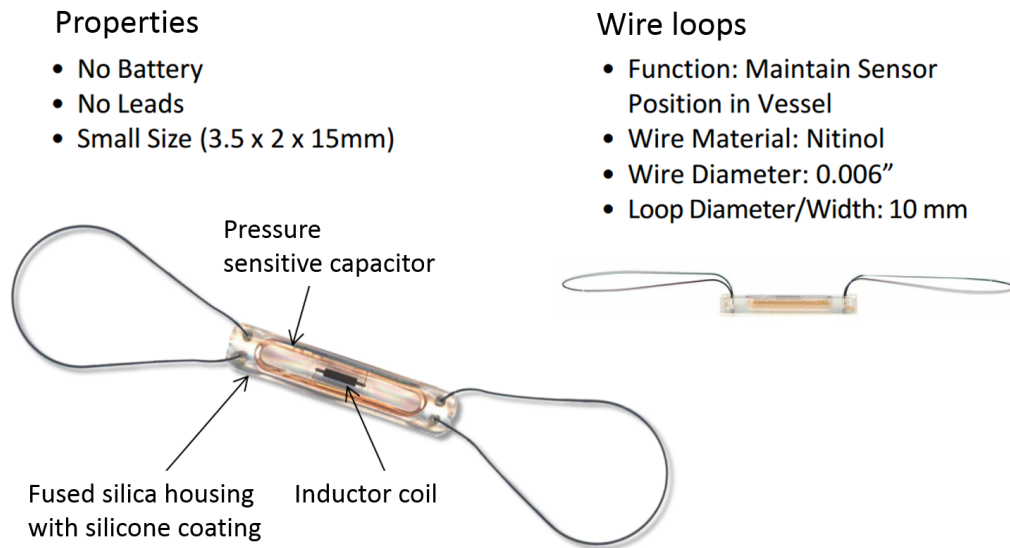
Figure 1.12: CardioMEMS^{TM} components and structure. Photo is taken from a presentation on CardioMEMS [63].

1.5 Heart implantable accelerometer device

This section demonstrates the heart implantable accelerometer devices which have been developed recently. The devices can be used to measure the vibrations correlating to heart sounds in the treatment of heart failure or to monitor the heart activities during and after heart surgeries.

1.5.1 Embedded micro-accelerometer atrial pacing lead (SonRtip)

SonRtip is developed by the Sorin Group (Italy). The SonRtip lead functions as a standard atrial lead, it also functions as a sensor to measure vibrations that correlate to heart sounds. These vibrations can be measured with an implantable microaccelerometer located inside the tip of an otherwise conventional unipolar pacing lead [45]. A key purpose of this study was to evaluate the clinical feasibility and reliability of intracavity sampling of Peak Endocardial Acceleration (PEA) of the first heart sound vibrations using an implantable tip mounted accelerometer. SonRtip accelerometer is a piezoceramic transducer loaded by a platinum/iridium seismic mass, converting flexural stress to electricity signal. A micro electric circuit is used to amplify and transmit the sensor signal to a receiver. Additional integrated micro spring can provide a shock protection and increase the sensitivity. Besides, SonRtip device can perform stable pacing thresholds and sensing amplitudes [64]. The overall structure of the SonRtip device is showed in Figure 1.13 with a 2.2 mm silicone insulation lead body features excellent flexibility and durability.
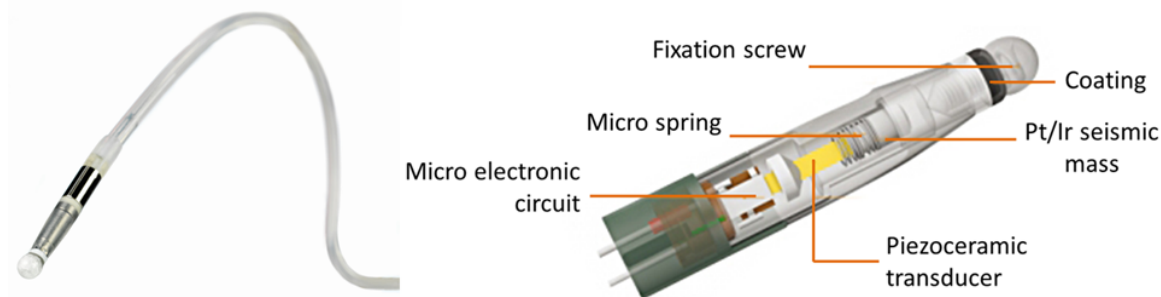
Figure 1.13: Atrial pacing lead with embedded hermetically-sealed micro-accelerometer (SonRtip)

1.5.2 Three-axis implantable heart monitoring device

Early recognition of regional cardiac ischemia using a 3-axis accelerometer sensor was demonstrated by Elle et al. in 2003 [11]. The accelerometer device was made by mounting two 2-axis accelerometers (ADXL-202, Analog Devices Inc, USA) perpendicularly on a ceramic substrate. The prototype was encapsulated by transparent silicone over-moulding and temporarily implanted onto the heart surface by a 4-point suturing.

An improvement of the implantable heart accelerometer device was introduced by Imenes et al. in 2007. The device is built on the 3.axis accelerometer sensor KXM52 (Kionix Inc, USA). The packaging of the device is based on an alumina substrate ($5.0 \times 11.5 \times 0.625$ mm^3) with thick film printed conductors. Press moulding with silicone was chosen as a suitable encapsulation method for the device since it is a well-established material for use in invasive devices and applicable for prototyping and moulding [48]. The device is shown in Figure 1.14.
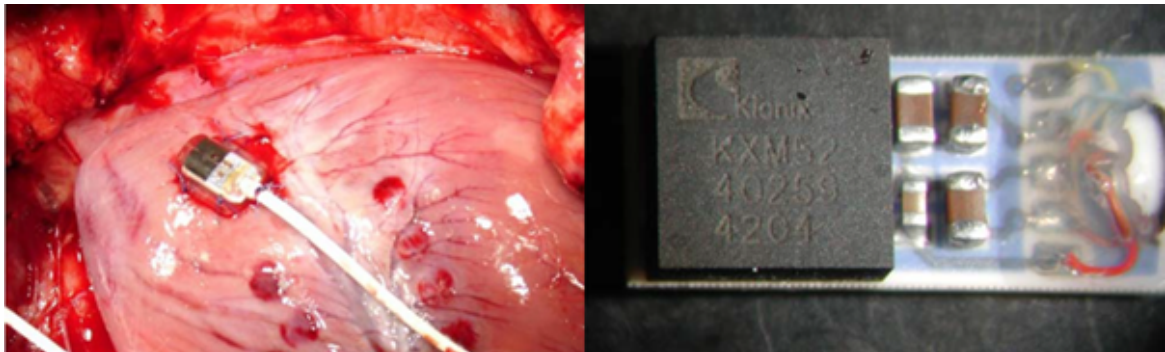
Figure 1.14: 3-axis accelerometer device sutured on the left ventricle free wall (photo on the left) and assembled sensor with capacitors and cable termination (photo on the right)

1.6 Heart anatomy and physiology

Human heart is a hollow muscular organ that rhythmically contracts and pump blood through the veins in the body. An average dimension of the heart is 13 cm x 9 cm x 6 cm. Adult heart weighs approximately 230-340g. It is enclosed by the pericardium and located two thirds to the left of the median plane, behind the

sternum [56]. Human heart has four chambers, right atrium (RA); left atrium (LA); left ventricle (LV); and right ventricle (RV), which have specific functions. The RA receives deoxygenated blood from the greater circulation and pump to the RV. The RV receives deoxygenated blood from the RA and pumps to the lungs. The LA receives oxygenated blood from the lungs and pumps to the LV. And the LV receives oxygenated blood from the LA and pumps to the rest of the body.
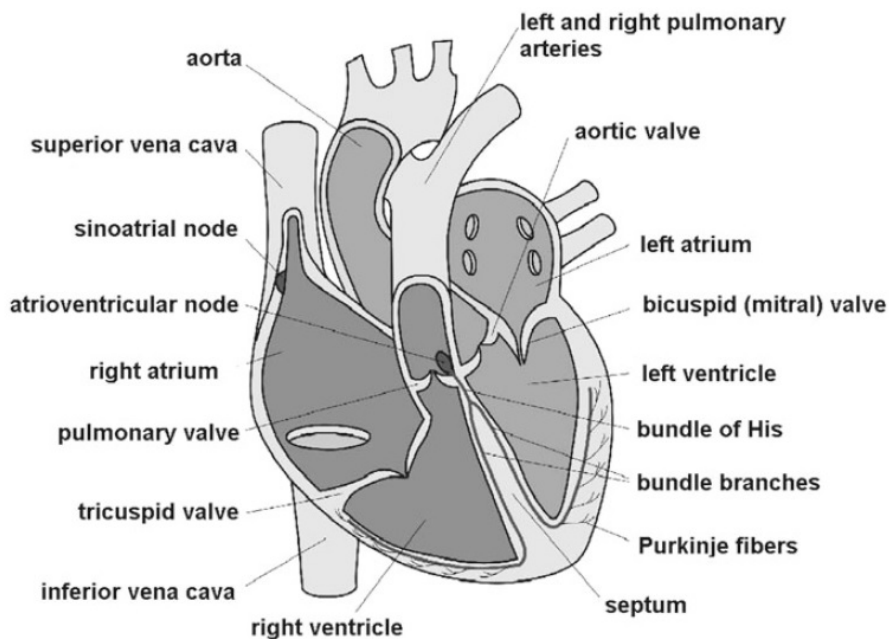
Figure 1.15: Heart cross section. Figure is reused from [56]

The heart wall consists of three layers: epicardium, myocardium and endocardium, shown in Figure 1.16. Epicardium is the outer layer of the heart wall structure which is attached to the myocardium by a thin layer of elastic fibrous tissue. Myocardium is the main component of the heart wall that contributes to the contraction of the heart. The myocardial cells consists of contractile fibers that have a structure similar to skeletal muscle fibers. The endocardium is an intracardial membrane that lines the heart cavity. Endocardium is smooth, transparent, and glistening [56]. Overall thickness of the heart wall depends on the physiological difference in their functions. The left ventricle is larger and has a thicker wall than the right ventricle. The left ventricle thickness varies from 6 mm to 16 mm [65, 66] within the age from 17 - 69.
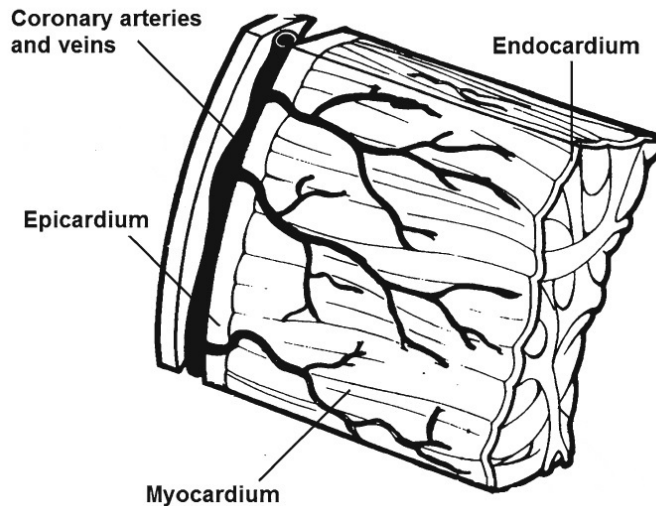
Figure 1.16: Structure of heart wall and covering. Figure is reused from [56]

1.7 Cardiac pacing and therapy

Implantation of temporary pacing wires is a conventional procedure that needs to be carried out after a heart surgery to control the heart rhythm properly [67]. A combination of acceleration and pacing function is an advantage to reduce a number of devices implanted to patient's heart. The following sections describes the basic mechanism of a heart stimulation and temporary pacing.

1.7.1 Electrophysiology of myocardial stimulation

The heart conduction system is controlled by specialized tissue which involves in the generation and conduction of electrical impulses throughout the heart. The sinoatrial (SA) node is the site of impulse generation. SA node has a key function in the heart rate regulator. The atrioventricular (AV) node allows for physiologic delay between atrial and ventricle contraction, resulting in optimal heart hemodynamic. The bundle of His (specialized fibers conduct the impulse) is divided into various bundle branches. Left and the Right bundle terminate in individual His fibers inter-digitating with heart muscle fibers [68]. The cardiac conduction system is shown in Figure 1.17, reused from [69].

According to Bunch et al. [68], stimulation of the heart muscle requires initiation of a propagating wave of depolarization from the site of initial activation,
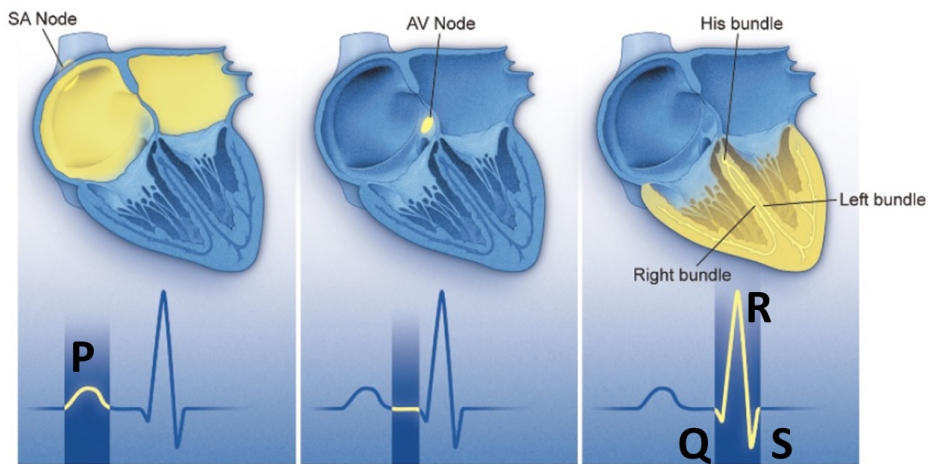
Figure 1.17: The cardiac conduction system. AV, atrioventricular; SA, sinoatrial. Conduction begins with impulse generation in the SA node. Impulse propagation through the atria gives rise to the P wave on the surface ECG. The impulse is then delayed in the AV node to allow blood to flow to the ventricles; the wavefront travel through the AV node is not seen on the surface ECG. The wavefront then pass through the His-Purkinje system, to rapidly activate the ventricular myocardium. A larger mass of the ventricles give rise a larger amplitude of QRS complex.

from SA node or from an artificial stimulus. The excitability or response to a stimulus of the heart muscle is maintained by separation of chemical charge that creates an electrical trans-membrane potential. In the heart muscle cells, the electrochemical gradient is created by the difference between intracellular and extracellular concentration of sodium (Na^+) and potassium (K^+) ions [68]. Ions movement between cells allows for the direct transmission of electric impulse through the entire network of the heart muscle [69]. The velocity of depolarization through the heart muscle depends on the cellular components of the heart muscle, arrangement and orientation of muscle cells. Factors such as myocardial ischemia, diseased tissue and drugs affect to the depolarization and depolarization velocity.

1.7.2   Stimulation threshold

A depolarization of the heart muscle can be created by an artificial pacing which delivers an electrical impulse from an electrode in contact with the heart muscle. The depolarization is then propagated to the rest of the heart muscle.

The threshold is the minimal amount of energy required to create the depolarization [68]. The stimulus energy is related to current, voltage, and pulse duration, described by the following formula [68, 70]:

$$\text{Energy}(\mu J) = \text{Voltage(V)} \times \text{Current(mA)} \times \text{Pulse Duration(PD ms)}$$
$$E = V^2 \, PD/R \quad (I = V/R \text{ Ohms Law})$$

R is the total pacing impedance. Pacing impedance includes the conductor resistance, electrode resistance, capacitance and inductance. The requirement of the pacing wire conductor is to have low resistance which helps to minimize the energy-wasting heat. The electrode is designed to have high resistance to minimize current flow and have negligible electrode polarization, resulting lower stimulation thresholds [71].

1.7.3 Temporary pacing/sensing

Temporary pacing can be indicated during intervention procedures or post-cardiac surgery. Specific electrophysiological conditions that may benefit from temporary pacing were demonstrated by Reade [72]. The temporary pacing may be performed by the application of pacing wires to the epicardium or by insertion of pacing electrode transvenously (through the veins) [73]. Temporary pulse generators are constant voltage devices, delivery a constant-voltage throughout the pulse duration [68].

Chapter 2

Device Requirements

The heart muscle implantable accelerometer devices were developed in relation to the well-established studies on the heart surface implantable devices [47, 48, 51, 74] that have been conducted in recent years. These studies set an important foundation for establising the design inputs of this study. Figure 2.1 describes the essential requirements of a heart muscle implantable accelerometer device. Three main factors directly determines the design of the heart muscle implantable accelerometer device: the regulations, the clinical requirements and the components of the device.
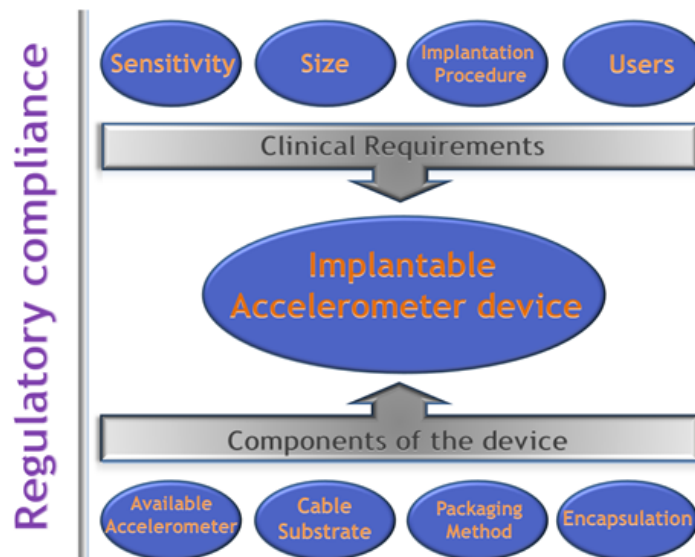
Figure 2.1: The essential requirements of a heart muscle implantable device

2.1 The regulations

EU directive 93/42/EEC and 90/385/EEC define the essential regulations concerning to the medical devices and active implantable medical devices respectively [75, 76]. In the scope of the directives, the device must not present any risk to the persons implanting them or, where applicable, to other persons. The requirements regarding the design and construction are focused on in this study. They are listed in the first annex of the directive 90/385/EEC. The following aspects are taken into account during concept development constructing the prototype devices to remoove or minimize as far as possible:

 - The risk of physical injury in connection with device physical features.

 - Risks connected with the use of energy source, insulation, leakage current and overheating of the devices.

 - Risks which may arise where maintenance and calibration are impossible, including:

   • Excessive increase of leakage currents,

   • Ageing of material used

   • Excess heat generated by the device

The device must be designed in such a way that characteristics and performances can be guaranteed, with particular attention being paid to:

 - The choice of material used, particularly regarding toxicity aspects

 - Mutual compatibility between the materials used and biological tissues, cells and body fluids

 - The quality of the connections

 - The reliability of the source energy

Regularity requirements regarding the manufacturing of the device is not in the scope of this study. These are mostly conformity requirements and the quality system requirements which are necessary for the CE mark applying routines. The heart muscle implantable accelerometer device has to comply with the general requirements for electromedical products set by the International Electrotechnical Commission (IEC), the IEC 60601-1 Part 1: General

requirements for basic safety and essential performance [76]. In this study, the following categories in the IEC 60601-1 are taken into account:

- Patient leakage current: The allowable value of patient leakage current for medical electrical equipment with type CF (cardiac floating) applied part in normal condition is 10 μA. The normal condition in which all means provided for protection against hazards are intact.

- Tensile strength: is defined as the maximum tensile stress a test piece will withstand before rupturing. The requirement is especially important in this study because the device must be pulled out the body when the monitor period is over.

- Dielectric strength: The solid electrical insulation of the medical electric equipment shall be capable of withstanding the specified test voltage which can be varried from 1000 V up to 4000 V.

- Construction of connector: the plugs for connection of patient cables shall be so designed that they cannot be connected to outlets on the same medical electric equipment intended for other functions.

The European Standard EN 45502-1: 1997 Active implantable medical devices - Part 1, subsection 23.5, attempts to practically qualify the essential requirements of implantable devices. The devices shall withstand the flexural stresses during and after implantation without fracture or cracking of any conductor.

2.2   Clinical requirements

2.2.1   Sensitivity and measurement range

Recent studies on monitoring heart activity using accelerometer have demonstrated appropriate acceleration range for detecting the heart motions which can vary in $\pm$2g [48, 49] and $\pm$5g [77]. The sensitivity of analogue accelerometer is from 174 - 660 mV/g [74, 78] with cross-sensitivity between two axes $\pm$ 2%.

2.2.2 Implantation procedure

Recent study has demonstrated an epicardial (heart surface) accelerometer device which can be sutured on the heart surface [48]. The device was used for open heart surgery only and not suitable for heart muscle implantation due to the removal method and the overall dimension. A heart muscle implantable device can enable closed chest procedure and simple removal based on a self-attachment mechanism. The device is to be implanted in the muscle and stably stay there due to the tension in the heart muscle without any suturing support. Design and construction of the implantable heart muscle accelerometer device should be compatible with available implantation-support equipment or specific tools for pacing/sensing lead placement which are conventionally used by surgeons and cadiologists.

2.2.3 Overall size

The main goal of this study is to develop an accelerometer device that can be implanted into the heart muscle. The overall dimension of the implantable device must be compatible with the average heart wall thickness. In human heart, the thickest muscle is the left ventricular one where pressure is be created to pump blood into the aorta and throughout the rest of the body [79]. The normal left ventricular thickness can vary from 6 mm to 16 mm and from 7 mm to 15 mm for women and men respectively [65, 66]. The overall size of the implantable accelerometer device must be less than the minimum ventricular myocardium thickness. Device size should be ideally comparable to the temporary myocardial heart wire (∼0.6 mm). However, there has been a challenge to achieve that small dimension. A group of experienced researchers (surgeons and cardiologists) from the Intervention Center - Oslo University Hospital has suggested a referenced value for the size of a heart muscle implantable device. An overall diameter of 3 mm is trusted to be suitable for myocardium[1] implantation. A smaller diameter can be preferred.

---

[1]Heart muscle

2.2.4 Users (surgeons, cardiologists and patients)

To be able to use in open-heart surgery, the implantable heart accelerometer device should be implanted into the heart muscle. However, the implantation method of a three-axis accelerometer device into heart muscle has not existed so far. The surgeons and cardiologists (the users) at the intervention center - Oslo University Hospital proposed a general idea of the device in term of the size, functionality, implantation position and approaches in implantable accelerometer devices. The device should have a long cable that can be used to transmit signals from accelerometer sensor to the data acquisition and processing system outside. In addition, the cable is connected through a small opening in the patients chest. The cable must be flexible enough in order not to affect the heart movement and reduce the sensor sensitivity. The crucial demand of patient is to suffer a minimally invasive operation and less trauma that enable them to recover safety and quickly [80].

2.3 Component requirements

2.3.1 Accelerometer

Recent development in MEMS-based sensors has provided smaller size and lower-cost accelerometer with enhanced performance and greater functionality [81]. Well-developed commercial MEMS-based accelerometer sensors are chosen to use in our application due to the performance, stability, reliability, and cost. The commercially available accelerometers are now sufficient small to develop an implantable heart muscle device. The smallest available accelerometer sensor was used in this study.

2.3.2 Cable/substrate

The purpose of a cable used in the implantable accelerometer device is to provide means of power supply, signals transmission and removal of the device after use. The encapsulation or other parts of the cable in contact with the body must be of biocompatible materials. The most important criteria used for

selecting a suitable cable for this application is the flexibility. A flexible cable minimizes the affect on the heart movement, the stability and sensitivity when the device is implanted in place. In addition the cable must to withstand the pulling force when the device is removed from the heart muscle through a small opening in the patients chest. A failure due to a broken cable is not acceptable for this application. The tensile strength of the cable should be higher than the pulling force needed to remove the device from the heart muscle. The tensile safety factor set by the IEC 60601-1 varies from 2.5 to 12 [82].

The additional pacing/sensing function is integrated in the device as a unipolar pacing lead. Requirement for the insulation of the cable is taken into account to avoid the interference between the stimulation signal and accelerometer output signals.

The substrate is used to hold the accelerometer sensor and discrete components (e.g. decoupling capacitors). The dimension of substrate and the cable/substrate fixation structure are also important in miniaturization of the device.

2.3.3   Encapsulation method

The purpose of encapsulation is to create a protective barrier between the implantable device and the body elements such as cells, proteins, platelets, and chemical gases. On the other hand, the the encapsulation has the functionality of protecting the inner electronics components [80]. The packaging should efficiently isolate the inner electrical, mechanical and chemical components from the environment inside human body. Encapsulation needs to be compatible with standard sterilization process (e.g. EtO[3]) applied for implantable medical device. In this study, the packaging method needs to provide simple implantation procedure, be capable of pacing/sensing function and meet the requirements of heart muscle implantable medical devices that are mentioned in this chapter.

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[3]Ethylene Oxide (EtO) Sterilization Process

Chapter 3

Summary of The Work in This Thesis

3.1 Summary

The field of study on heart implantable accelerometer device has been established for more than ten years in Norway. It started out with an innovative idea of using accelerometer in monitoring heart activity, proposed by a group of medical doctors and surgeons at the Intervention Centre, Oslo University Hospital. A research collaboration between Vestfold University College and the Intervention Centre was initiated to develop miniaturized heart accelerometer devices. From the year 2004 to 2010, technical and clinical studies on heart implantable accelerometer device were done based on two versions of accelerometer devices [48, 83, 77, 78]. They were built on available commercialized accelerometers and allowed for heart-surface fixation since the dimension was a major concern.

In 2011, a new project on miniaturization of implantable accelerometer device for heart monitoring was started. The key purpose of this project was to develop a new generation of implantable accelerometer device that can be implanted into heart muscle and specified for use on patient undergoing coronary artery bypass grafting. The device should stay in place during monitoring period and be removed by means of a cable through the chest wall after use. Researchers from the Intervention Centre took part in specifying the device shape and size

to ensure its suitability for clinical trials, testing in animal trials and implementation of accelerometer devices in medical studies. Two PhD candidates carried out technical development. The work focusing on encapsulation was carried out by Fjodors Tjulkins while miniaturization of circuit packaging was carried out by me.

I proposed and developed five different versions of circuit packaging for the heart muscle accelerometer devices. Three other concepts of fabrication of heart muscle accelerometer device were also introduced in accordance with the prototype devices. The descriptions for each version are summarized and presented as follows:

Version 1-1

This was a very first heart muscle implantable 3-axis accelerometer device that has been demonstrated. Complete prototypes were successfully developed and examined. The prototypes have proved to comply with typical regulations for the safe leakage-current of implantable devices, biocompatibility of the used materials, and mechanical durability. The accelerometer and discrete components could be encapsulated in silicone using established molding processes. The silicone encapsulation was not in scope of this study. The animal trials affirmed that the accelerometer device version 1-1 is capable of being implanted in to heart muscle with addition supporting of specific introducer. The concept of this device might be used in other application or for other types of implantable devices. The study pointed out the drawbacks of the device including the complicated implantation procedure, the flexible cable stiffness in lateral direction, the moderate sharp edge of flexible cable, and the need of implantation stability improvement.

5mm

Figure 3.1: The heart muscle accelerometer device (version 1-1) with silicone encapsulation

Version 1-2

The device version 2-1 provided significant improvements in implantation procedure, implantation stability, flexibility of the cable, safety of the flexible cable, connector for signal and power supply, and the electrical insulation. The additional pacing/sensing function was introduced in this version of implantable accelerometer device. The device was capable of pacing and sensing as a mono polar temporary pacing wire.

- **Implantation procedure:** The structure of device version 1-2 supports simple implantation procedure which is similar to that of the temporary pacing wire.

- **Implantation stability:** The combination between the new circuit packaging and the flat metal capsule enhanced the implantation stability of the device. The result was validated in an animal trial. The study on metal encapsulation was not in the scope of this work.

- **Flexibility and safety of the flexible cable:** A reduction of cable width helped to increase the flexibility in lateral direction. The additional silicone encapsulation of the cable prevented the heat tissue from being affected by moderate sharp edges of cable.

- **5-pole connector:** There is a clinical requirement for the device terminal. The connector end of the device needs to be pulled through the chest wall from the inner side. This study proposed a 5-pole round connector that was compatible with a standard introducing needle. The connector was simply inserted to the introducing needle which was used to open a small channel on the chest wall afterward.

- **Electrical insulation:** The leakage current from the device version 1-2 was 1000 times lower than that of the cable part of the device version 1-1.

The drawback of this design was the reduction of the cable pulling strength in comparison to the device version 1-1. There was a trade-off between the pulling strength and the lateral flexibility.

Version 1-3

The study has proposed method for circuit packaging of the heart muscle implantable accelerometer device version 1-3. The device was built on an approved medical grade cable which had been demonstrated by Imenes et al. [48]. The cable can provide equal flexibilities in all directions which could be
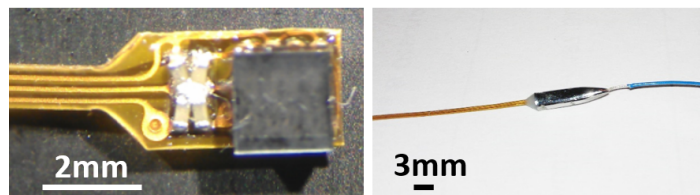
Figure 3.2: The heart muscle accelerometer device (version 1-2): the electronic assembly and packaged device with a metal capsule

a benefit for the implantable accelerometer device. The cable is constructed by several insulation layers which can provide outstanding insulation properties (observed leakage current: 10-12 Ampere).
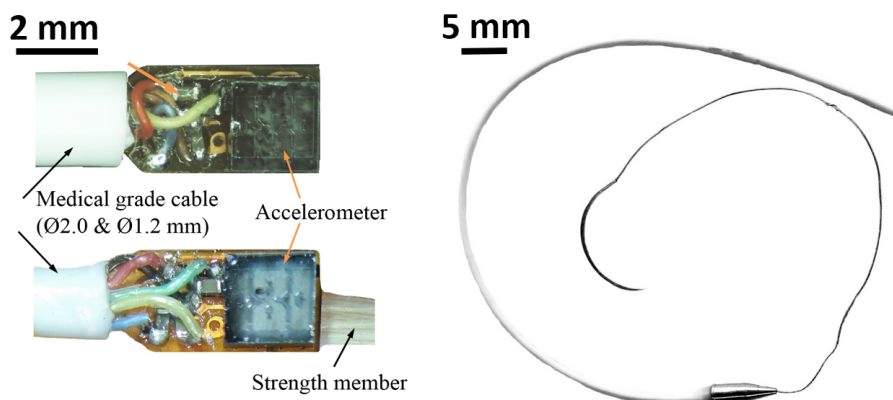
Figure 3.3: The heart muscle accelerometer device (version 1-3): the electronic assembly and packaged device with a metal capsule

The study also proposed a new medical grade cable structure which has smaller diameter than the available round cable (diameter reduction: 40%). The new round cable used the same insulation material as the previous one. The new round cable was dedicatedly designed for providing high pulling force by mean of increasing the amount of strength member in the cable core (aramid fiber). We have observed that the new round cable can withstand the pulling force 5 times higher than that of the available round cable. The smaller cable assisted implantation stability.

Version 2-1

There was a significant miniaturization approach of the heart muscle implantable accelerometer device which was carried out in this study. The overall diame-

ter of the device was 2.0 mm. The accelerometer device version 2-1 used a 3-axisMEMS accelerometer (Bosch Sensortec GmbH, Germany) which was one of the available smallest accelerometers and similar to the Bosch accelerometer BMA355. A new circuit package contains 40-60 μm layout structure that was designed to meet the miniaturization requirements of the heart muscle accelerometer device. The device version 2-1 has provided remarkable implantation stability. Two encapsulation methods of flexible cable have been introduced which can provide comparable electrical insulation and mechanical strength. The tubing encapsulation might reduce the material and manufacturing cost that suitable for disposable implantable devices. The integration of pacing/sensing function advances the benefit of this device. The accelerometer device version 2-1 can yield pacing threshold in comparable range to the original pacing wire. Nevertheless, additional studies need to be carried out to qualify the stimulation functionality of the device.
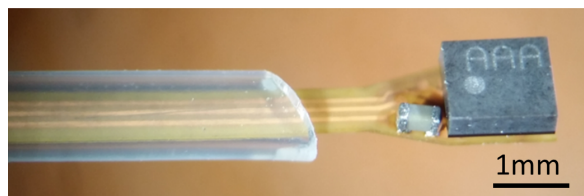
Figure 3.4: The heart muscle accelerometer device (version 2-1) without metal capsule encapsulation

Version 2-2

The structure of device version 2-1 was similar to that of device version 1-3. However there was an area reduction of flexible substrate up to 72% was obtained. Device version 2-1 and 2-2 can use identical metal capsules that yield overall diameter of 2.0 mm. The version 2-1 used the medical round cable (Ø1.2 mm) which was demonstrated in device version 1-3. The benefit of using this type of cable is to provide high pulling strength up to 100N. The pacing/sensing function was also integrated to this version. The drawback of the device version 2-1 was the challenge of the assembly procedure, especially the bonding of signal wires to flexible substrate. This was a straightforward procedure but training was required.

Besides the main contributions that were mentioned above this study has proposed and carried out essential compliance measurements and built the measurement setups. The work is described as follows:

- **Leakage current measurement:** A setup for leakage current measurement (hardware and software) has been built. The system can carried out the measurement stably at low current level (sub-femto range).

- **Tensile strength test:** The study has done several tensile strength tests for different version of devices.

- **Flexural endurance test:** A flexural tester (hardware and software) has been made to validate the performance of the devices.

- **Insulation test:** the tests were used to verify the resistance of the insulation layers.

- **Crosstalk measurement:** the test was used to define the crosstalk of signal in the flexible cable without shielding plane. The test result helped to select suitable routing structure of the flexible cable that may reduce the interference between conductors.

3.2   Publications and Contributions

This thesis is based on 3 journal papers (P1, P2, P3) and 2 conference papers (P5, P6) which are summarized and enclosed in Chapter 6. The work described in P5, P6 has been covered by the journal papers. One of the results from this study was used in a medical study on monitoring of cardiac function is described in paper P6. This is a medical paper where a developed sensor in this thesis is used. The other significant contributions of the study related to heart implantable accelerometer devices are shown in paper P7, P8, P9, P10, P11, and P12. The contribuitons are listed as follows.

3.2.1   Papers included in this thesis

Journal papers

P1: **Anh-Tuan Thai Nguyen**, F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, Miniaturization of package for an implantable heart monitoring device, Journal of Microsystem Technologies, DOI: 10.1007/s00542-014-2216-6, ISSN: 1432-1858.

Contribution*: I studied on general requirements for medical devices class III, and requirements for heart muscle implantation; made an overview of available implantable medical devices, and available data acquisition system being used with earlier heart sensors at Intervention Centre, Oslo University Hospital. I proposed, designed and packaged the device version 1-1 (except silicone encapsulation). I proposed and performed essential tests for validation of the devices based on the requirements set by standards: leakage current test, tensile strength tests, flexural endurance test, measurement setups (hardware, software). I wrote the paper.*

P2: **Anh-Tuan Thai Nguyen**; Fjodors Tjulkins; K. E. Aasmundtveit; Nils Hoivik; Lars Hoff, Ole-Johannes Grymyr, Per Steinar Halvorsen and Kristin Imenes, New Approach in Development of a Multifunctional Implantable Heart Monitoring Device, Journal of Microelectronics and Electronic Packaging, JMEP Issue 4 of 2015.

Contribution*: I proposed a new design of circuitry for the miniaturized accelerometer Bosch sensor; carried out device circuitry packaging, participated in metal encapsulation process; performed leakage current tests, tensile strength test, proposed and performed crosstalk tests. I proposed, set up and performed flexibility test of cables. I developed a galvanic isolator system for digital accelerometer with power and signal isolation. I participated in animal trials for testing of implantation stability and device functionalities. I processed of the recoded acceleration data. I wrote the paper.*

P3: **Anh-Tuan Thai Nguyen**, F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, Packaging of a Multifunctional Implantable Heart Monitoring Device, in preparation for submission.

Contribution*: I proposed a suitable packaging method for round cable and flexible substrate with pacing/sensing capability and participated in encapsulation process for device version 1-3. I proposed and carried out the measurements, performed leakage current tests in normal stressed loading conditions. I investigated the utility of a new round cable in fabrication of accelerometer device with improved tensile strength and flexibility. I participated in animal trials and analyzed the recoded acceleration data. I mainly contributed in development of a galvanic isolator system (analog isolator), which was got approval for internal use. I wrote the paper.*

Conference papers

P4: **Anh-Tuan Thai Nguyen**, F. Tjulkins, K. Aasmundtveit, H. Nils, L. Hoff, and I. Kristin, Miniaturization of package for an implantable heart monitoring device, Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP), 2013 Symposium on, p. 6, 2013, ISBN 978-2-35500-028-7.

Contribution: I proposed, designed and packaged the device version 1-1 (except silicone encapsulation). I proposed and performed essential tests for validation of the devices based on the requirements set by standards: leakage current test, tensile strength tests, flexural endurance test, measurement setups (hardware, software). I wrote the paper.

P5: **Anh-Tuan Thai Nguyen**, Knut Aasmundtveit, Nils Hoivik, Lars Hoff, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, Packaging of Multifunctional Implantable Heart Monitoring Device, Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP) 2014, ISBN 978-2-35500-028-7.

Contribution: I proposed a packaging method for round cable and flexible substrate with pacing/sensing capability. I proposed and performed all measurements, measurement setups. I participated in encapsulation process and animal trials. I analyzed the acceleration data. I wrote the paper.

3.2.2   Medical paper

Journal papers

P6: O.-J. H. Grymyr, **Anh-Tuan Thai Nguyen**, F. Tjulkins, A. Espinoza, E. W. Remme, S. Helge, E. Fosse, K. Imenes, and P. S. Halvorsen, "Continuous monitoring of cardiac function by 3D accelerometers in a closed-chest pig model," European Journal of Cardio-Thoracic Surgery, 2015, DOI:10.1093/icvts/ ivv191.

Contribution: I fabricated and tested more than 20 accelerometer devices used in specific medical studies at Intervention Centre, Oslo University Hospital.

3.2.3 Significant contributions

Journal papers

P7: Fjodors Tjulkins, **Anh-Tuan Thai Nguyen**, Erik Andreassen, Lars Hoff, Knut Aasmundtveit, Nils Hoivik, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, Fabrication and assembly of MEMS accelerometer based heart monitoring device with simplified, one step placement, Journal of Medical Engineering & Technology, DOI: 10.3109/03091902.2014.981307

Contribution: *I proposed packaging method for a medical grade round cable and flexible substrate with pacing/sensing capability for device version 1-3 (except metal capsule design). I designed and packaged devices version 1-3. I performed the leakage current measurements with combination of cycling test. I made the equipment for loading cycling tests and participated in animal trials.*

P8: Fjodors Tjulkins, **Anh-Tuan Thai Nguyen**, Erik Andreassen, Lars Hoff, Knut Aasmundtveit, Nils Hoivik, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, An Implantable Accelerometer-based Heart Monitoring Device with Improved Stability, ASME, doi: 10.1115/1.4034574, 2016.

Contribution: *I designed and carried out circuitry packaging for these devices, cable encapsulation. I built a test system for mechanical and leakage current tests, prepared samples and participated in animal tests.*

Conference papers

P9: Imenes, Kristin; Andersen, Mona Helene; **Anh-Tuan Thai Nguyen**; Tjulkins, Fjodors; Aasmundtveit, Knut E.; Hoivik, Nils; Hoff, Lars. Implantable MEMS acceleration sensor for heart monitoring: recent development and outlook; 4th Electronics System-Integration Technology Conference (ESTC 2012). IEEE conference proceedings 2012 ISBN 978-1-4673-4645-0.

Contribution: *I proposed and investigated the feasibility of a device structure based on flex cable and ceramic substrate. I designed and fabricated prototypes based on ceramic substrates.*

P10: Tjulkins, Fjodors; **Anh-Tuan Thai Nguyen**; Andersen, Mona Helene; Imenes, Kristin. MEMS Accelerometer-Based Heart Monitoring System with Myocardial Fixation. International Federation for Medical and Biological En-

gineering Proceedings 2012; Volum 38. s. 19-22.

Contribution*: I designed and fabricated prototypes based on ceramic substrates.*

P11: Tjulkins, Fjodors; **Anh-Tuan Thai Nguyen**; Hoivik, Nils; Aasmundtveit, Knut E.; Andreassen, Erik; Hoff, Lars; Imenes, Kristin. 3-Axis MEMS accelerometer based implantable heart monitoring system with novel fixation method. I: Electronic Components and Technology Conference (ECTC), 2013 IEEE 63rd, 28-31 May 2013, Las Vegas, NV. IEEE conference proceedings 2013 ISBN 978-1-4799-0233-0. s. 510-516.

Contribution*: I proposed, designed and performed circuit packaging for prototypes (except silicone encapsulation)*

P12: F. Tjulkins, **Anh-Tuan Thai Nguyen**, E. Andreassen, N. Hoivik, K. Aasmundtveit, L. Hoff, O. J. Grymyr, P. S. Halvorsen, and K. Imenes, MEMS-based implantable heart monitoring system with integrated pacing function, Electronic Components and Technology Conference (ECTC), 2014 IEEE 64th, 2014, pp. 139-144.

Contribution*: investigated and proposed a circuitry design to improve cable flexibility; carried out circuit packaging for the devices version 1-2 (except metal capsule), carried out cable encapsulation of silicone used for electrical insulation improvement, performed leakage current measurements, participated to metal capsule encapsulation (interconnection for pacing/sensing function)*

Chapter 4

Design and Fabrication

4.1 Concepts of the design

The design concepts of the heart muscle implantable acceleroemter device were mainly based on former generations [74], the requirements mentioned in chapter 2, and packaging methods used by available implantable devices. They may be devided into three groups depending on packaging techniques. The first group includes implantable heart, bladder or lung assisting devices like epicardial pacing wires, permanent pacing leads, leads neurostimulation lead, and phrenic nerve electrodes. They are shown in section 1.41, 1.42, 1.43, chapter 7 in [84], and [85] respectively. These devices are basically built on stainless steal electrodes and are encapsulated in medical grade silicone layers with different fixation structures.

I got motivation to propose the concept of device structure base on polyimide based flexible circuits in group 2. Polyimide based flexible electrodes arrays have been widely used in virsual implants [86, 87]. Seo et al. developed a rectina implant system based on flexible polyimide electrode array for electrical stimulation [88] with circuit dimension 4 × 4 mm. The micromachined polyimide-based devices for neural interfaces was presented by Lee at al. [89]. Polyimide-based chip scale packaging was also used in implantable MEMS movable microelectrodes for brain reported by Nathan et al. [90].

Group 3 consists of device-substrate or substrate-cable interconnections applied in implantable devices. Single and double gold stud bumps technique

was used to create interconnection between flexible cable and rigid substrate in a neural stimulation systems, Stieglitz et al. [91] and Yasuo [92]. Aceros at al. used silver epoxy based assembly in the development of wireless neural microsensors system [93]. These techniques can be applied in my study.

In my study, the basic suctructure of the implantable accelerometer device consists of an accelerometer sensor, a substrate for sensor mounting and a cable used for signal transmission, power supply and device removal. Three feasible concepts of the implantable heart muscle accelerometer device were proposed, developed and investigated. They are illustrated in Figure 4.1.
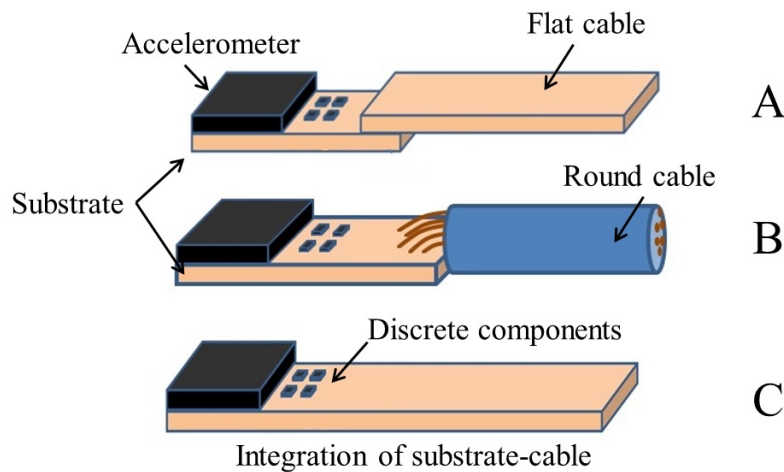
Figure 4.1: Illustration for the feasible structures of the heart muscle implantable accelerometer device.

Structure A is a combination between flexible cable and a substrate where the accelerometer and capacitors are assembled. The idea of using flexible flat cable was proposed to overcome challenges in miniaturized circuit packaging, wires soldering and cable fiaxation structure, of the earlier accelerometer device [48]. Structure B follows the concept of the implantable heart accelerometer device demonstrated in [48, 74]. The interconnection between a multi-conductor medical grade round cable and substrate is performed by solder. A fixation structure is needed to provide mechanical support and centering of cable. Structure C is an unification of substrate and cable in a flexible circuit. The idea was firstly proposed in my study. Other developed commercial implantable sensors that were built in the same manner were difficult to find since most of the available devices are conventional electrodes. These elec-

trodes do not need to have several conductors or wires to provide power and signal transmissions. A feasibility evaluation for those proposed structures are shown in Table 4.1. Criteria for selection of a structure depends on the objective evaluation on the essential properties for a heart implantable device. As regards to three structures, six different versions of the implantable heart muscle accelerometer device were developed. The versions were divided into two groups based on two types of commercial accelerometer, which have been the available smallest 3-axis accelerometers in the time of doing my PhD. Additional design ideas were proposed, evaluated and listed in the third group.

Table 4.1: Comparison of three feasible circuit structure of the heart muscle implantable accelerometer device

Essential Properties	Structure A	Structure B	Structure C
Biocompatible insulation	Yes(+)	Yes(+)	Yes(+)
Cable-Substrate interconnection	Yes: adhesive conductive film, double stud bump [80] (-)	Yes: soldering(-)	No need (++)
Flexibility	Flexibility is not equal in all direction(- -)	Round cable can provide flexibility in all direction (+)	Flexibility is not equal in all direction(- -)
Cable-Substrate fixation	Adhesive(+)	Must have (-)	No need(++)
Cable length	Limited(-)	Long(++)	Limited(-)
Sterilization	(+)	(+)	(+)
Assembly procedure	Standard (-)	Challenges (- -)	The most easiest (++)
Mass production	(-)	(- -)	(+)
Overall evaluation	(-)(3+)	(-)(5+)	(-)(9+)

4.2 Analog accelerometer-based devices:

This group includes three different versions of the implantable heart muscle accelerometer device built on the CMA3000A (Murata Electronics Oy, Vantaa, Finland) which was one of the smallest MEMS-based accelerometer devices (2 $\times$ 2 $\times$ 0.95 mm^3) in 2012. The CMA3000A was capable of providing comparable performance concerning sensitivity, acceleration range, and stability to the previous heart accelerometer devices [74]. The specification of the sensor is shown in Table 4.2. The circuit diagram for the CMA3000 is showns in Figure 4.2.

Table 4.2: Specification of the CMA3000A accelerometer

Features	CMA3000-3 axis
Dimension	2$\times$2$\times$0.95 mm
Supply voltage	1.7 - 3.6 V
Measuring range	$\pm$2 g; $\pm$8 g
Sensitivity (2g / 8g range)	0.167$\cdot$ Vdd / 0.042 $\cdot$Vdd (V/g)
Current consumption in active mode	180-200 μA
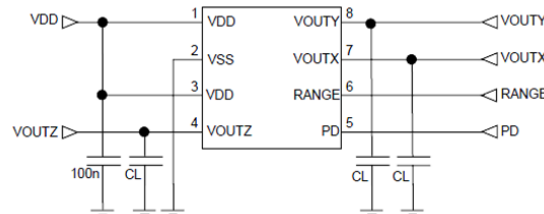
Figure 4.2: Circuit diagram for CMA3000A. CL=100nF

4.2.1 Version 1-1

4.2.1.1 Integration of substrate-cable on polyimide-based flexible circuit

Polyimide (PI) material has been used widely in electronic and electrical applications [94, 95] because of its outstanding electrical, thermal, mechanical,

physical and chemical properties [96, 97, 98]. PI can be also found in biomedical implantable device [99, 100, 101, 102], cerebral implantation [103, 90], and many other medical applications: implantable microsystem for neural prostheses [91], for neural interfaces [92], for hearing aids [104], and for EEG measurement on skull [105]. In this study, the first version of the heart muscle accelerometer device was built on a polyimide-based flexible circuit that allows an unification of substrate and cable. Circuitry design of the flexible cable/substrate is shown in Figure 4.3. The polyimide-based printed circuit includes two main parts: the substrate part and the cable part, shown in Figure 4.4. The terminal end of the integrated circuit was enlarged to adapt to a
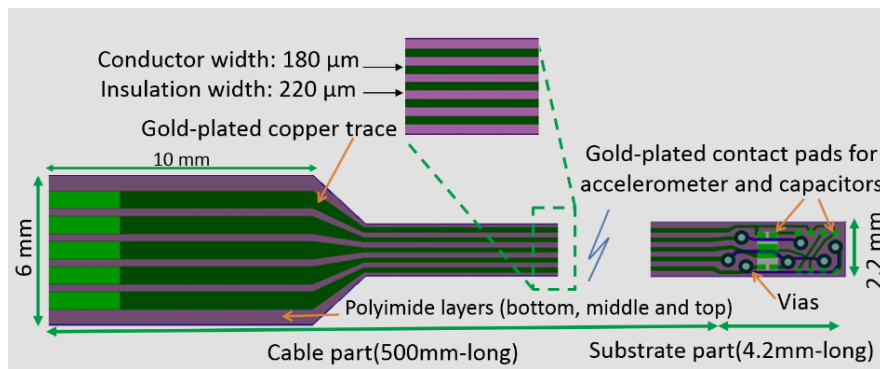
Figure 4.3: Circuitry design of the flexible cable/substrate

Figure 4.4: Flexible cable/substrate with bonded CMA3000 accelerometer and low pass filter capacitors

standard 1.0 pitch FPC connector (Molex SMT Lead Free 52207 - 0585 with 5 loaded). The size of the connector was considered to allow simple and quick coupling during implantation procedure.

4.2.1.2 Biocompatibility of materials

Polyimide material has been shown to be biocompatible and used in implanted devices like neural implant [102, 89]. The polyimide Pyralin PI 2611 was cho-

sen as substrate and cable insulation material in this study due to exellent insulation characteristics and dielectric strength as well as high material flexibility [106, 107]. Two other possibilities are polyimide PI 2566 and PI 2556. They all provide very good biocompatibility. However, the PI 2611 surpasses the others in tensile strength and water uptake coeficient [92].

The cable we chose has copper leads which are used for power and signal transmition. Copper is found naturally in the body, for instance the human enzyme systems. However, the adverse effects of copper toxicity are more consideration than copper deficiency [108]. The toxicity of copper can be prevented by an insulation layer or encapsulation, e.g. polyimide insulation. We can see that copper is available in several implantable devices. The implantable RFID glucose-monitoring sensor demonstrated in [109] used copper wire to make a coil antenna for wireless communication. Copper coil was also applied in an implantable wireless dosimeters for radiation oncology [110].

The key requirement is to protect copper from being exposed to the surrounding environment (e.g. tissues, body fluid). This is one of the most crucial requirement in this study. First, a gold based circuit structure were considered to be used since gold has biocompatibility properties [102]. However, we have been in an early state of the development process of a heart muscle accelerometer device. The copper-based design can meet the requirements related to safety, fabrication technology, prototyping development, and clinical evaluation process. The use of adhesive in fabrication of flexible cable device 1-1 described in paper 1 was one of the drawbacks we observed in this version. In later versions, this challenge was overcome by using biocompatible insulation material to cover the cable. An alternative fabrication method of flexible cable without using adhesive in multilayer structure is the use of liquid crystal polymer (LCP). LCP is biocompatible thermalplastic polymer material has been recently used as an encapsulant replacing silicone elastomers, or as a biocompatible flexible substrate for implantable active electronics [111, 112].

4.2.1.3   Encapsulation

Medical grade silicone (Elastosil 40001/40) was used to encapsulate the device by molding technique. The identical procedure has been demonstrated by Imenes et al. [74] and Donaldson et al. [113]. The silicone encapsulation covers

Figure 4.5: The heart muscle accelerometer device (version 1-1) with silicone encapsulation

the sensor-end of the device where the accelerometer and discrete components bonded. The detailed description is presented in [114, 115]. The device with silicone molding is shown in Figure 4.5.

4.2.1.4 Important compliance test

In this study, selected essential tests were carried out to ensure that the crucial compliance requirements can be met. They consist of leakage current measurement, tensile strength test, cable insulation resistance, the flexural endurance test. The experimental setups are described in detail as follows. The measurement results are shown in the next sub-section and some key results were presented in paper 1 [116].

a) Leakage current measurement:

To determine the current that may leak through the insulation layer of the accelerometer device, a measurement setup was built in this study. Figure 4.6 describes the basic components of the measurement setup: thermal chamber Heraeus T6200 used for maintaining operating temperature (37°C); a platinum electrode (5×11×0.7 mm); DC electrometer system (6430 Sub-femtoamp SourceMeter Instrument, Keithley Instruments Inc., Cleveland, OH, USA) with remote preamplifier (Keithley Remote PreAmp); beaker 100-200ml; and saline or PBS solution pH 7.4 (P3813 0.01M phosphate buffered saline Sigma-Aldrich Co. USA). Saline solution was used in initial experiments and PBS solution was used in the later ones since PBS is more realistic than saline solution in representing physiological environment (ionic concentration). The distance between platinum electrode and accelerometer device was from 2 - 3 cm. This may slightly vary with different measurements on: cable, or silicone insulation

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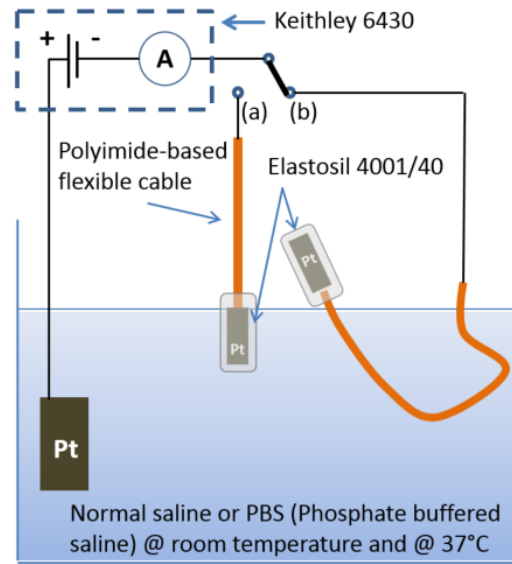
Figure 4.6: Leakage current measurement setup. (a): measurement of leakage current from the silicone encapsulation; (b): measurement of leakage current from the polyimide-based flexible cable.

part or a complete device. The thinnest silicone encapsulation thickness was about 0.37 mm. Leakage current tests were performed in either salin solution or PBS solution. However, the use of different fluids was not intendedly used to prove the relationship between leakage current and conductive fluid. In my study, I has used platinum electrode as dummy accelerometers with dimension of 2x2x1 mm. The dummy devices were used to investigate the contribution of the accelerometer output/input impedance to the measurement results due to imperfect silicone insulation and accelerometer packaging. However, the later measurement results have shown that the contribution of device impedance to the leakage measurement results was able to negligible.

b) Insulation resistance test:

Insulation resistance measurement is regulated by the IEC 60364-6 (IEC 2006), standard of verification for low-voltage electrical installations and IEC 62353. The method is used to determine current going through insulation while a high voltage is applied between two conductors. The insulation resistance between the conductors of the polyimide-based flexible cable is important for the prevention of leakage-caused short circuit or signal interferences. In this study, the insulation tests were carried out at room temperature for each pair of neighbouring conductors in the original flexible cable (without bonded accelerometer
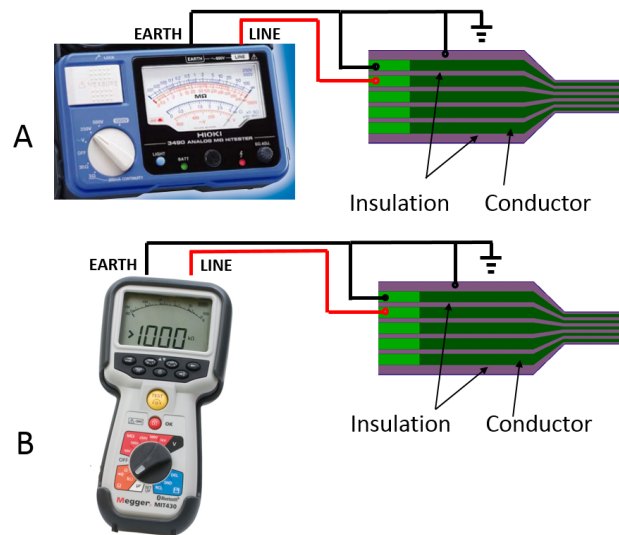
Figure 4.7: Insulation resistance measurement setup. Setup (a): performed tests presented in paper 1 with Hioki 3490 tester; Setup (b): performed additional tests in PBS solution at 37°C. The Mergger MIT430 can provide specific resistance value.

and capacitors) using a Megaohm tester (HIOKI 3490, Hioki E. E. Corporation, Japan). Two probes (line probe and earth probe) are connected to neighboring metal pads on the connector-end of the flexible cable, see Figure 4.7A. Additional insulation resistance tests performed in PBS solution at 37°C for several days were carried out with the Megger insulation tester MIT 430. This instrument can provide better measurement range than the Hioki tester used previously. Each measurement was carried out in 1 minute. The mesurement setup is shown in Figure 4.7B.

c) Tensile strength test:

In this study, there is a strict requirement for mechanical strength of the flexible cable. Because the accelerometer device removal is carried out by pulling the cable through the thorax, when the patient is ready to leave the intensive care. The European Standard EN 45502-1 (1997) (The Active implantable medical devices - Part1) specifies the requirements for implantable devices to withstand all forces that may occur during and after implantation. Tensile strength tests were carried out with a LLOYD LS100 Universal testing system (Lloyd Instruments™, Lloyd Instruments Ltd., West Sussex, UK) at room temperature. The test specimen length was 200 mm and pull speed was 50 mm/min.

d) Flexural endurance test:

In a real condition, an implanted accelerometer device has to work in a dynamic environment inside the thoracic cavity. Cable part closed to the sensor was externally fastened to the chest wall and the implanted end can move in accordance with the heart movements. A part of the device (inside the thorac wall) underwent cyclic stress condition depended on the implatation position and the heart activity. In my study, flexural endurance test was conducted to investigate different states of stress applied to the cable. The requirements were set by the the European Standard EN 45502-1 (1997) for active implantable medical devices - Part 1, subsection 23.5. A test equipment was built based on the test method IPC-TM-650 specified for the flexural endurance and flexible printed board materials. The equipment can provide harmonic motion with controlled frequencies from 1 to 10 Hz and amplitudes from 2 to 5 cm. The test reports the number of cycles to failure for the test specimen. This was measured by the data acquisition board NI-DAQ 6211 (National Instruments Inc., Austin, TX, USA). The change in resistance in each conductor is also recorded for each 9-12 thousandth cycle by the Sourcemeter Keithley 2100 (Keithley Instruments Inc., Cleveland, OH, USA). Setup of the flexural endurance test system is shown in Figure 4.8.
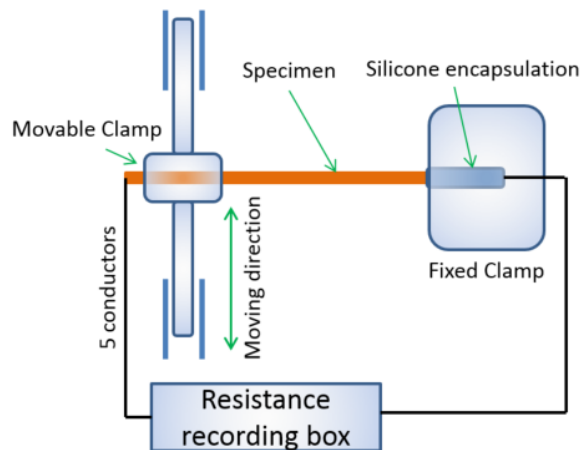
Figure 4.8: Setup for flexural endurance test

4.2.1.5 Animal trials

The implantable heart muscle accelerometer devices version 1-1 has been used and tested in thirteen animal trials. The outcomes of those trials have brought out very important technical and clinical information which support to the development of the heart muscle implantable accelerometer device [116]. The implantation procedure is straightforward but need to be carried out in several steps. A needle was used to create a channel in heart muscle. The device was inserted in a standard hollow introducer. The introducer was then pulled through that channel with a guide wire which had been placed in advanced. Figure 4.9 shows the introducer and a device used in an animal trial. The device was pulled backward to get in place underneath the heart muscle tissue. Figure 4.10 describes an accelerometer device implanted to left ventricle muscle and a size conparison with a heart surface accelerometer device. This was the first time 3-axis implantable heart muscle accelerometer devices were used in animal trials and provided promising results. The clinical studies on monitoring heart activities have now another posibility to use accelerometer device in closed chest assessments. New studies on heart activities can be carried out relied on this accelerometer device. However, there were also some challenges that have been observed in these trials. The implantation procedure was complicated and shoule be improved to provide simple handling tasks. Thr implantation stability did not meet our high expectation since fixation structure of the encapsulation was not fully functioning and the cable flexibility needed to be better.
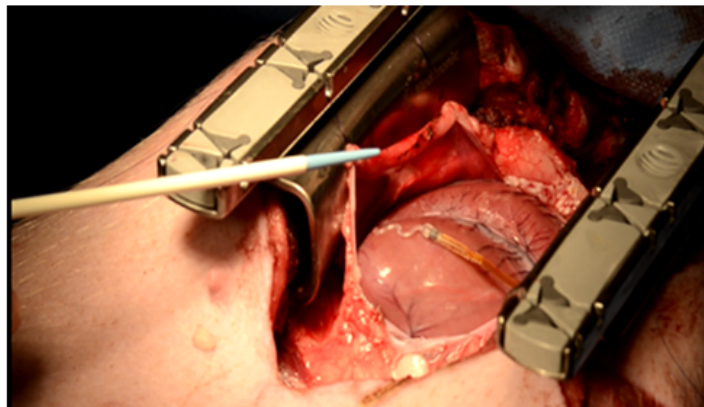
Figure 4.9: The implantation procedure is carried out with support of a standard introducer (shown in the figure with blue tip)

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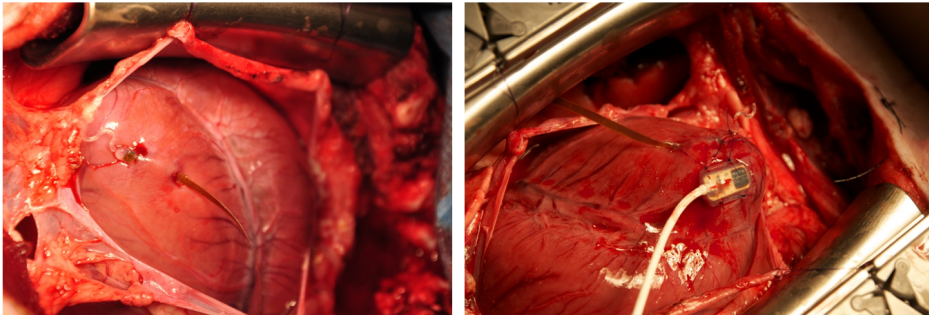
Figure 4.10: The accelerometer device (version 1-1) with silicon encapsulation (left). The device was implanted closed to a heart surface accelerometer device (to the right)

4.2.1.6 Results and Discussion

a) Leakage current test results:

The allowable leakage current threshold for different types of medical devices, (classified as B (Body), BF (Body Floating) and CF (Cardiac Floating) device, were set by the International Electrotechnical Commission (IEC-60601-1). Leakage currents from CF-type devices, devices with direct contact with the heart, are divided into "normal condition" and "single-fault condition". Under normal condition the leakage current should not exceed 0.01 mA and at single fault condition the maximum limit is 0.05 mA.

In this study, the leakage current mainly depends on the material insulation properties since the applied voltage is kept constant in all experiments. The insulation properties can be maintained or degraded by the working environment. Inside thoracic cavity, the working environment consists of blood, liquid and tissue. The insulation properties can be degraded by water absorbance, chemical reactions, physical agents (force, temperature), or minor defects in the material structure. My study has investigated the reasons that may cause leakage current from this version of accelerometer device.

The leakage current tests were performed on diferent samples: flexible cables, sensor part with silicone encapsulation and a complete device. The tests on flexible cable are shown in Figure 4.12 and Figure 4.13. The tests on insulated sensor part are shown in Figure 4.14 and Figure 4.15. Leakage current test result for a complete device is shown in Figure 4.16. The measurement results showed that leakage current from the device in all cases are far below the criti-

cal threshold (0.01 mA). This was a potential result. The leakage current from the sensor part insulated by silicone encapsulation was lower than the current from flexible cable part (1000 times). The leakage current form a complete device was in the same range with the current from the flexible cable (10^{-9}). We could assume that leakage current was mainly caused by the cable insulation. The dielectric strength of polyimide PI 2611 and silicone Elastosil R4000/40 are 2×10^5 V/mm and 2×10^4 V/mm [117, 118] respectively. A leakage current via
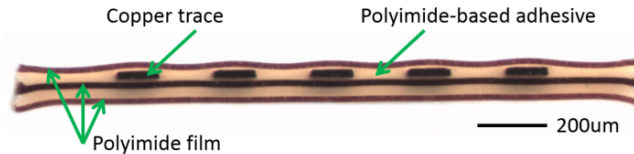
Figure 4.11: Polyimide based flexible cable cross section

polyimide film insulation may have minor posibility since the film uniformity was investigated and confirmed. The cable cross section shown in Figure 4.11 may give us a suitable answer. Minute defects in laminated structure along the flexible cable may degrade the insulation properties. The detail discussion on measurement results were reported in [117].
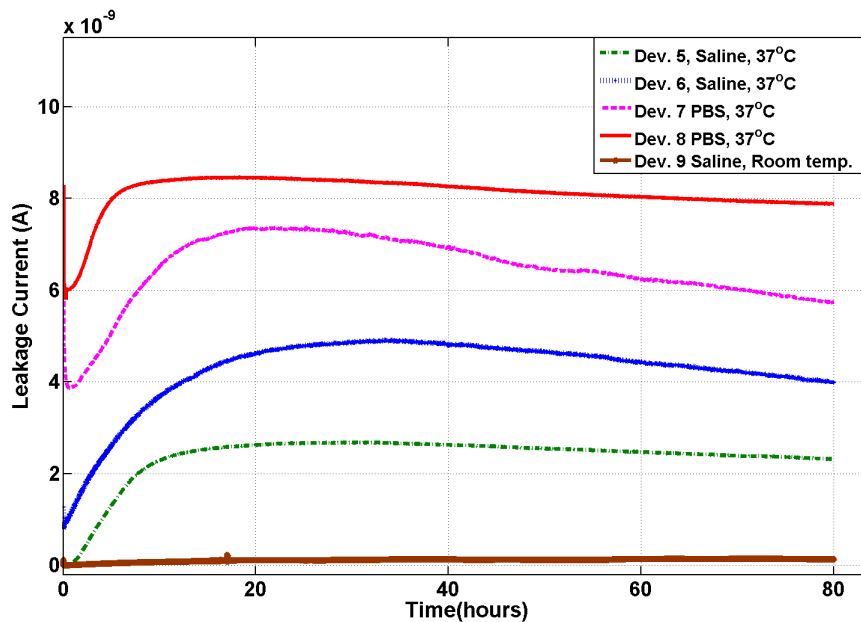
Figure 4.12: leakage current from flexible cable measured at $37°C$ in saline solution (device 5 and 6) and phosphate buffered saline (device 7 and 8), and measured at room temperature in saline solution (device 9) - Linear scale
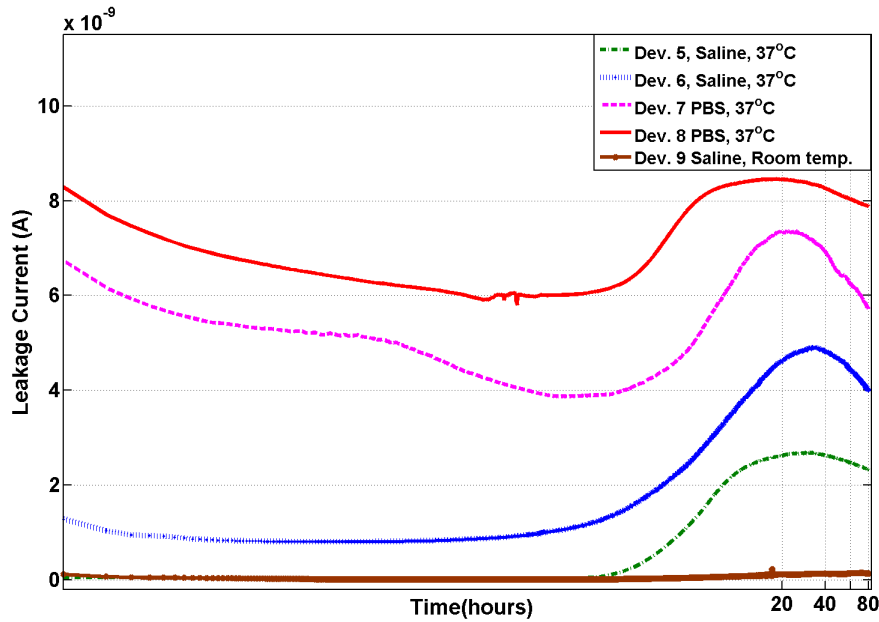
Figure 4.13: Leakage current from flexible cable measured at 37°C in saline solution (device 5 and 6) and phosphate buffered saline (device 7 and 8), and measured at room temperature in saline solution (device 9) - Log scale
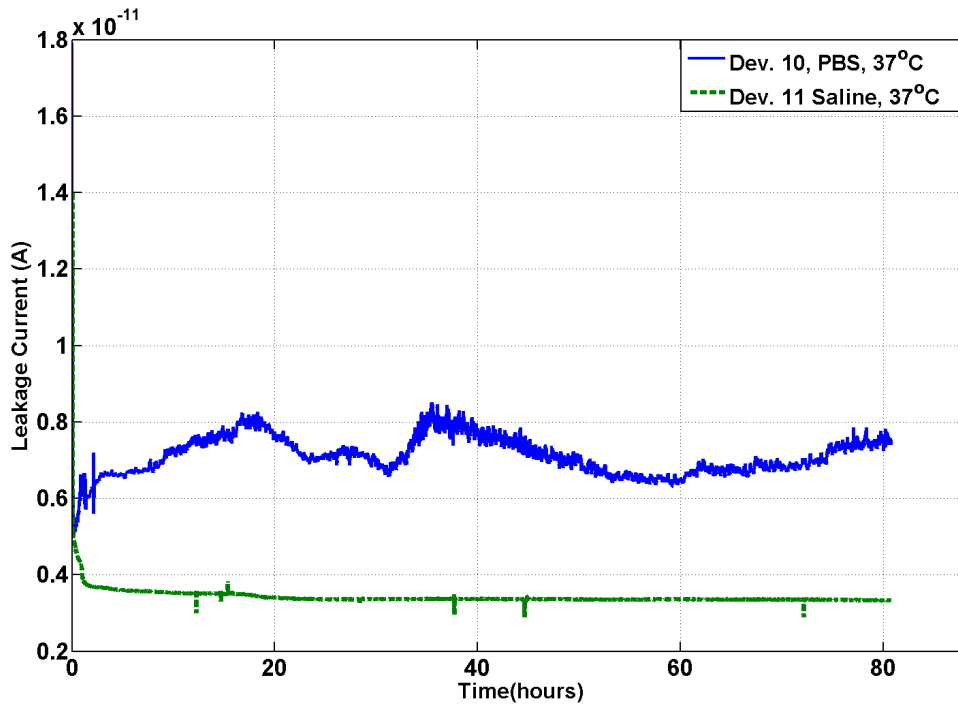
Figure 4.14: Leakage current from silicone encapsulation parts of two devices measured at 37°C in phosphate buffered saline solution and saline solution - Linear scale
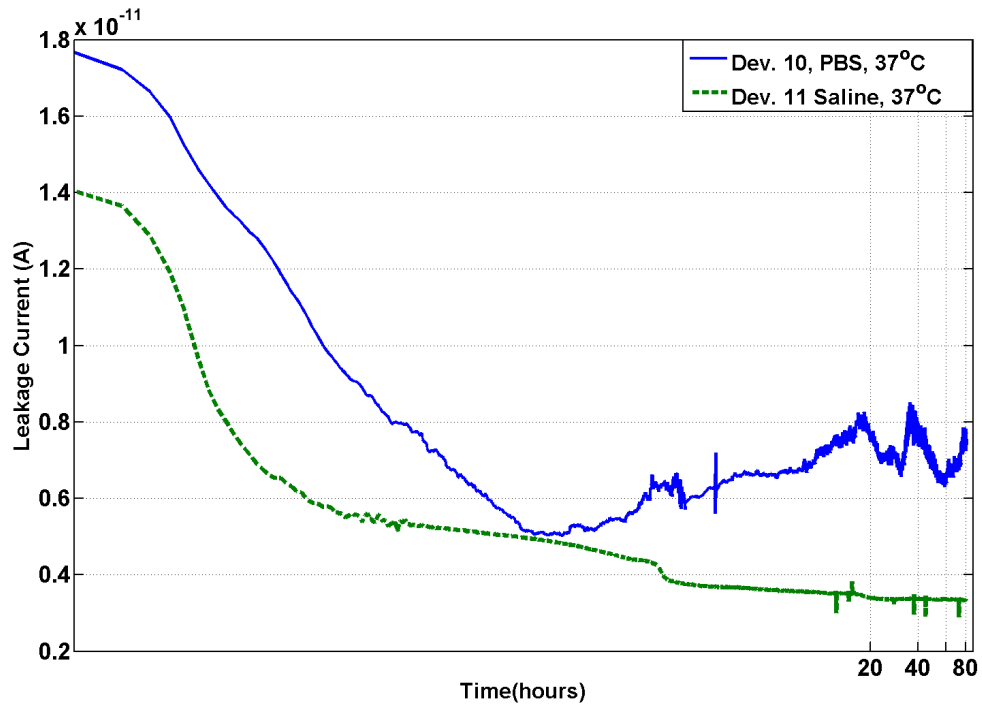
Figure 4.15: Leakage current from silicone encapsulation parts of two devices measured at $37°C$ in phosphate buffered saline solution and saline solution - Log scale
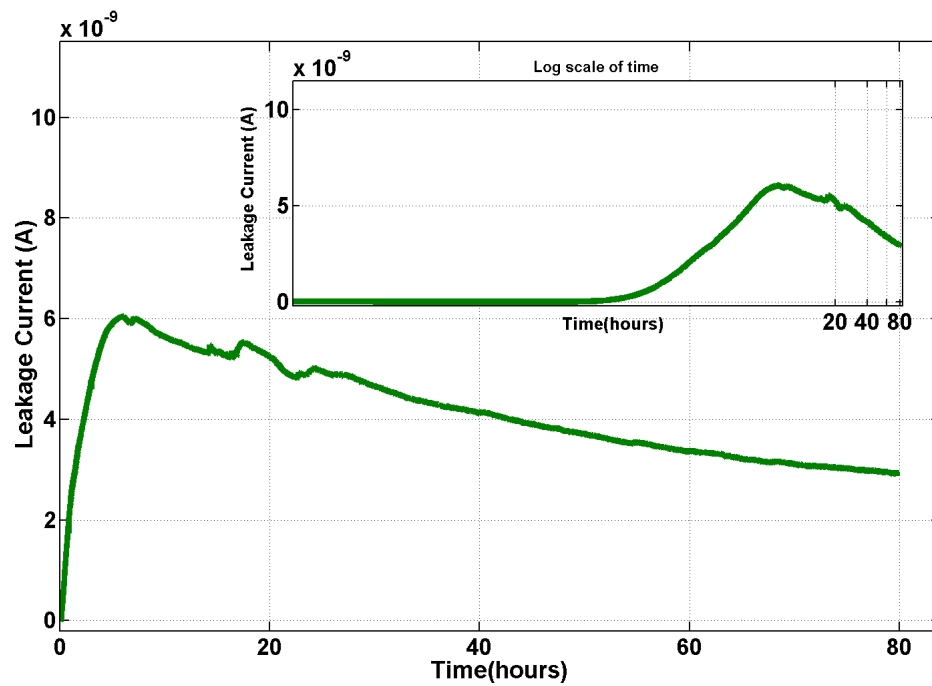
Figure 4.16: Leakage current from a complete device with silicone encapsulation. Measurement was pergormed at $37°C$ in saline solution

b) Insulation resistance test results:

A consistent result was observed in all of the insulation resistance tests performed at room condition (in air). The insulation resistance between two copper traces was higher than 4 GΩ in all cases. The insulation tests performed at 37°C in PBS solution followed the test setup in Figure 4.17. The tests were performed on two cables. Measurement results are shown in Figure 4.18.
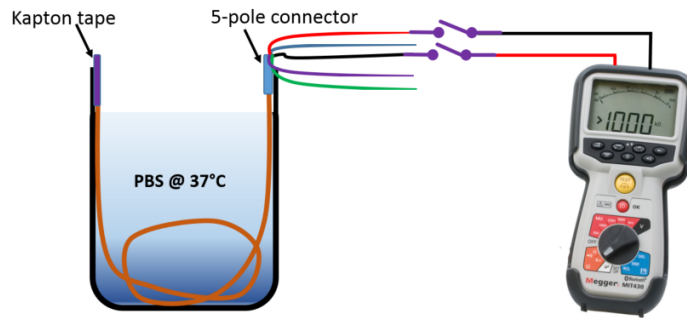
Figure 4.17: Setup for insulation resistant measurement measured at 37°C, PBS solution
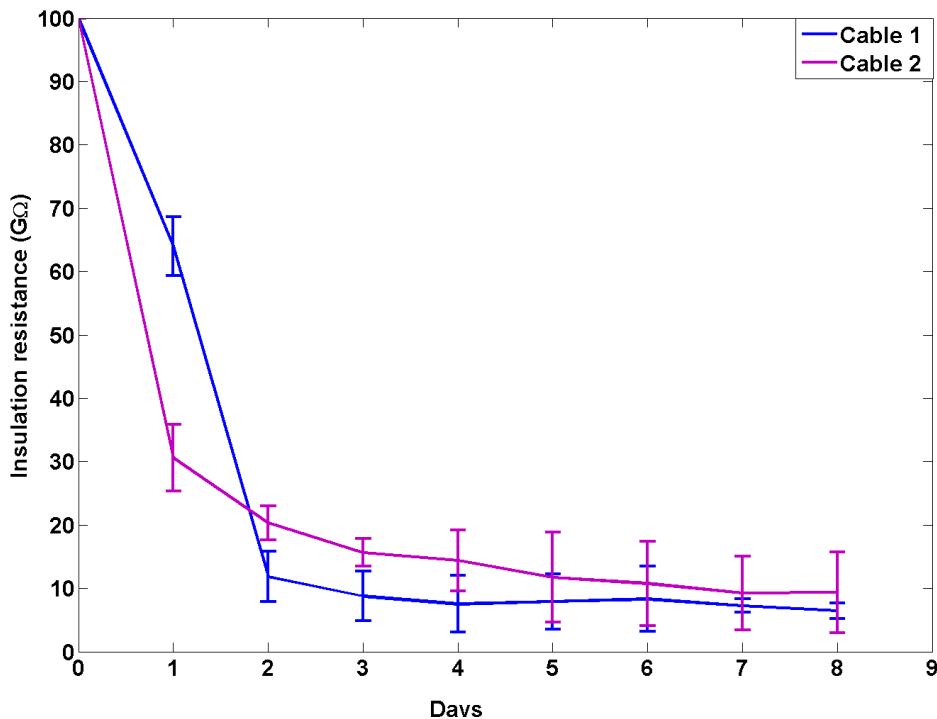
Figure 4.18: Insulation resistance test @ 37°C in PBS solution

The insulation resistances measured on both two original samples exceeded the measurement range of the instrument (>100GΩ at 500V). A significant drop of

the insulation resistance was observed after 2 first days. This may be caused by a strong absorption of water or ions in the solution taken place via minute imperfect structures of the insulation layers. The insulation quality had a tendency to be degraded in the later days. On the 4th day, the minimum trace resistance in cable 1 and 2 were 3.53 GΩ and 6.9 GΩ respectively. They were 3.52 GΩ and 1,39 GΩ respectively on the 8th day. Even though the insulation resistance was 1,39 GΩ, a leakage current between traces could be 2.4 nA at a normal working voltage of 3.3V. The device would be functioning in this case. Copper corrosion were visually inspected by optical microscope and found no corrosion on both 2 samples.

c) Tensile strength test results:
The test results and discussion were detaily presented in sub-chapter 3.3, paper 1.

d) Flexural endurance test results:
The test results and discussion were detaily presented in sub-chapter 3.4, paper 1.

4.2.1.7   Publications

Anh-Tuan Thai 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.

Anh-Tuan Thai Nguyen, F. Tjulkins, K. Aasmundtveit, H. Nils, L. Hoff, and I. Kristin, "Miniaturization of package for an implantable heart monitoring device," Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP), 2013 Symposium on, p. 6, 2013.

F. Tjulkins, **Anh-Tuan Thai Nguyen**, K. Aasmundtveit, H. Nils, A. Erik, L. Hoff, and K. Imenes, "3-Axis MEMS accelerometer-based implantable heart monitoring system with novel fixation method," Electronic Components and Technology Conference (ECTC), 2013 IEEE 63rd, 2013.

O.-J. H. H. Grymyr, **Anh-Tuan Thai Nguyen**, F. Tjulkins, A. Espinoza, E. E. Remme, S. Helge, E. Fosse, K. Imenes, and P. s. Halvorsen, "Continuous monitoring of cardiac function by 3D accelerometers in a closed-chest pig model," Eu-

ropean Journal of Cardio-Thoracic Surgery, 2015, DOI:10.1093/icvts/ ivv191.

4.2.2   Version 1-2

The second version (version 1-2) of the heart muscle accelerometer device is an improved generation of the device version 1-1 with integration of pacing/sensing function as an temporary pacing wire, device flexibility and insulation property enhancement.

4.2.2.1   Integration of pacing/sensing function

Implantation of temporary pacing wires is standard procedure after cardiac bypass surgery [119, 120]. These temporary pacing wires normally consist of an insulated wire with an electrode in one end and a connector to the stimulator device in the other end. The integration of pacing/sensing function as unipolar pacing wire reduces the need of additional invasive implantation of the wires. This chapter demonstrates a device that combines the functionality of the accelerometer device, version 1-1, with that of a temporary pacing electrode. The modern pacing wire conductors have a very low resistance of order of 5-50Ω [70].

4.2.2.2   Structure of the device

To simplify the implantation procedure of the heart muscle accelerometer device, the standard implantation routine of the temporary pacing wires was preferred to use. The device should be reconstructed to enable that simple procedure. The idea was proposed by the intervention center, Oslo University Hospital (Patent WO 03/061473 A1). The device consists of an encapsulated accelerometer sensor, a curved needle with wire attached, signal cable, and a connector. The connector should be constructed in a specific way to feature the electrical connection and be able to work as a straight needle. The connector end of the device must come out of the patient chest wall from the inner side. The overall structure of the device is shown in Figure 4.19.
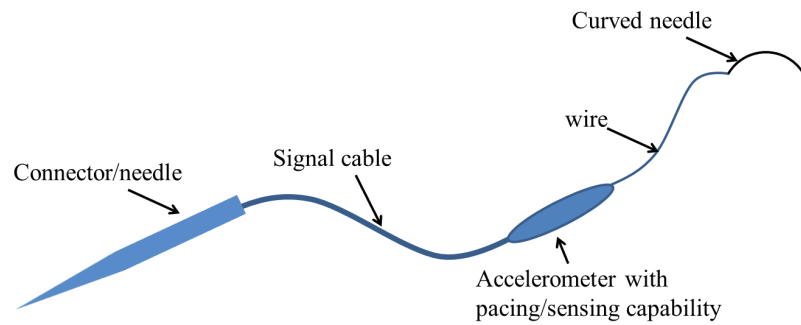
Figure 4.19: Overall structure of the implantable heart muscle accelerometer device with integration of pacing/sensing function

4.2.2.3 Circuit design
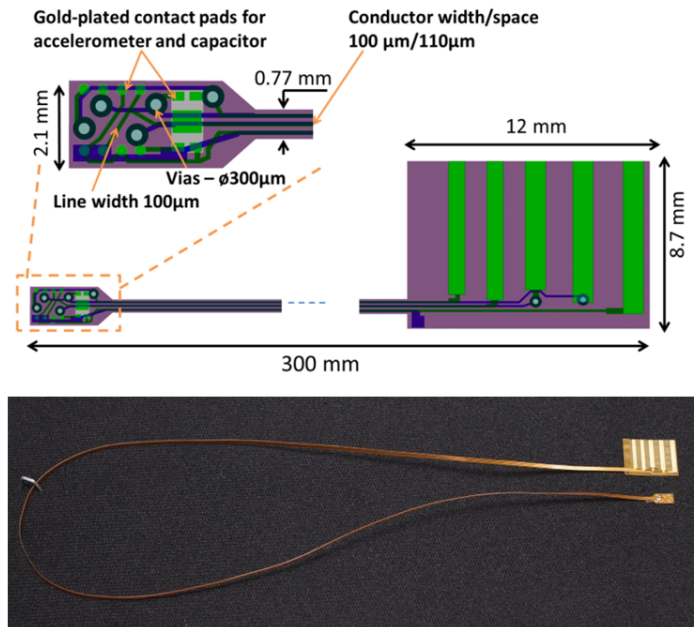
Figure 4.20: Layout of the polyimide-based printed circuit for the heart muscle accelerometer device. The connector end matches with a commercial 5-pole round connector

Polyimide-based flexible circuit was also chosen for this version of accelerometer device (version 1-2). In this design, the width of the cable was narrower (65%) than that of the device version 1-1 which might reduce the stiffness in lateral direction. An empirical study on the relation between the width of flexible cable and lateral flexibility was carried out. Several dummy flexible cables had been made for flexibility evaluations. The evaluation was carried out by

medical doctors and surgeons at Intervention Centre, Oslo University Hospital. The selected width of cable was able to provide comparable flexibility in lateral directions. The connector part was designed to match with a commercial 5-pole round connector. The design layout and the finished polyimide-based flexible circuit are shown in Figure 4.20. To use the device as a temporary pacing wire, one of the metal traces in the cable was used as a conductor for pacing. The dimension of this trace was considered to convey the overall pacing power or pacing dose. The general pacing dose provided by typical generator are reported in [70], Table 19.3. The flexible circuits were fabricated by H. K. Best FPC Co., Ltd (Hong Kong, China).

4.2.2.4 Device assembly

In this version, metal capsule is selected as encapsulation for the sensor part since conductivity is required. The design of the metal capsule was proposed by Fjodors Tjulkins. The detailed information related to the capsule are described in [121]. The cross section structure of the device is shown in Figure 4.21. The contact pad specified for pacing/sensing function is connected electri-
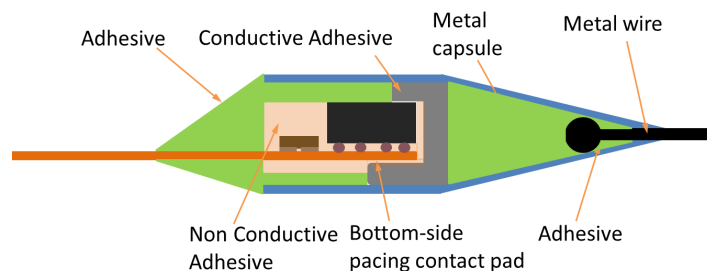
Figure 4.21: Illustration for the components inside the metal capsule. The flexible substrate and the metal capsule are electrically connected by conductive adhesive

cally to the metal capsule by isotropic conductive adhesive (ICA) (Epotek H20E, Epoxy Technology, USA). The conductive adhesive was trapped in between the tip and the rear side cyanoacrylate adhesive (Cyanolit 203TX, Panacol, Germany). The electrical insulation between the pacing contact pad, Figure 4.21, and other components (accelerometer solder balls, capacitors) was maintained by the nonconductive adhesive (NCA) layer (EPO-TEK 353ND, Epoxy Technology, USA). A drawback of the flexible circuit is the sharp edge which can be an issue in accordance with the risk analysis. The flexible cable is encapsulated by
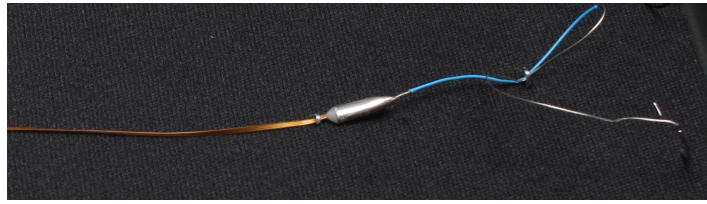
Figure 4.22: A Complete device without cable encapsulation

molding silicone (Elastosil R 4001/40, Wacker Chemie, Germany). The molding technique is identical to that described by Imenes [74] and Tjulkins [115][97] but with different mold, see in Figure 4.23. Additional cable cleaning procedure was carried out in advance by the plasma cleaner (Addax, Germany) to enhance adhesion between polyimide surface and silicone encapsulation.
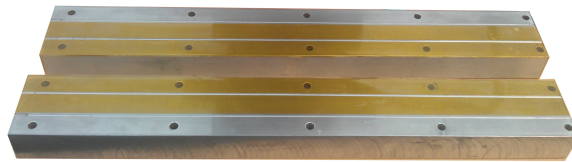
Figure 4.23: Mold used for making silicone encapsulation of flexible cable (cable length: 30 cm). The mold supports two diameter Ø1.2 mm and Ø1.0 mm.

4.2.2.5 Animal trial

The accelerometer device (version 1-2) was used in animal trial to validate the implantation performance and functionalities. The implantation stability was expectedly achieved with a simply standard procedure. The silicone encapsulated flexible cable provided sufficient flexibility in all direction which contributed to the stabilizing of the implanted device in heart muscle. Figure 29 describes the device and a temporary pacing wire implanted on the left ventricle to acquire acceleration signal and test the pacing threshold. The results were described in [121].

4.2.2.6 Important compliance tests and results

In this section, I want to investigate electrical and mechanical performances of the new flexible substrate-cable. The tests include leakage current test and
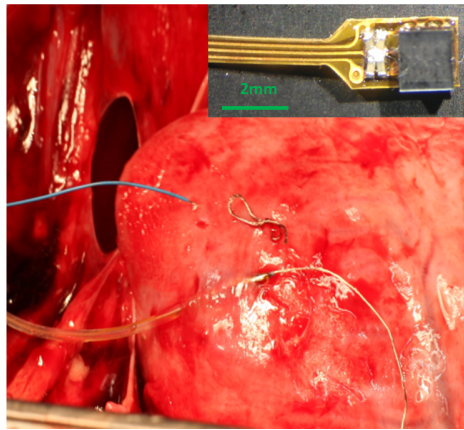
Figure 4.24: A heart muscle implantable accelerometer device - Version 1-2, used in an animal trial
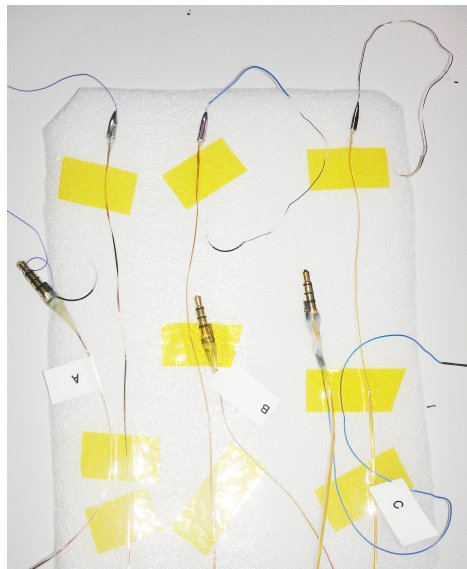
Figure 4.25: Accelerometer devices version 1-2 were used in an animal trial

tensile strength test on the complete devices. The clinical performance of the pacing/sensing function was demonstrated by real pacing tests in an animal trial. The descriptions for leakage current and tensile strength test were shown in section 4.2.1.4. The study related to this version 1-2 was reported in [121].

a) Leakage current test result

The measurement was carried out in Phosphate buffered saline (PBS) pH 7.4 (P3813 0.01M phosphate buffered saline Sigma-Aldrich Co. USA) and at 37°C. Temperature was controlled by thermal chamber Heraeus T6200. Figure 4.26 describes the components used in this setup. Electrometer system (6430 Sub-femtoamp SourceMeter Instrument) provides a DC voltage 3.3V and detects the

current. A platinum plate (5×11×0.7 mm) was used as positive electrode. The source meter negative probe was connedted to all of connector contacts (except the pacing contact since this one was directly connected to the metal capsule). The overall distance between platinum electrode and the test device was from 2 to 3 cm. Data were continuously recorded in 100 hours. Result is presented in Figure 4.27. The measurement results showed a significant improvement
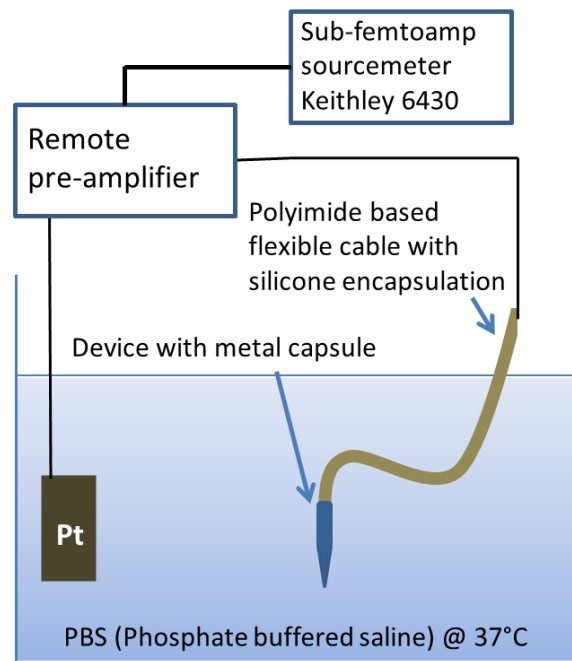
Figure 4.26: Setup used for leakage current measurement

of the device insulation resistance relied on the silicone insulation of flexible cable. The leakage current level was far below the approval leakage threshold. The most challenged step is the manual molding of cable. An automatic injection molding of liquid silicone (e.g. Nusil medical grade MED3-4013) would be a better choice for productivity.

b) Tensile strength test

The tensile strength tests provide valuable information about the maximum force that can be applied along the length of the device while implanting or extracting the device out of the body. It is especially important for closed-chest application, as the sensor is to be extracted through the chest wall using the cable when monitoring is completed. The maximum pulling force of this device was 10N. This value was two times higher than the implantation forces (pull-in and pull-out force) were investigated on an artificial tissue, shown in
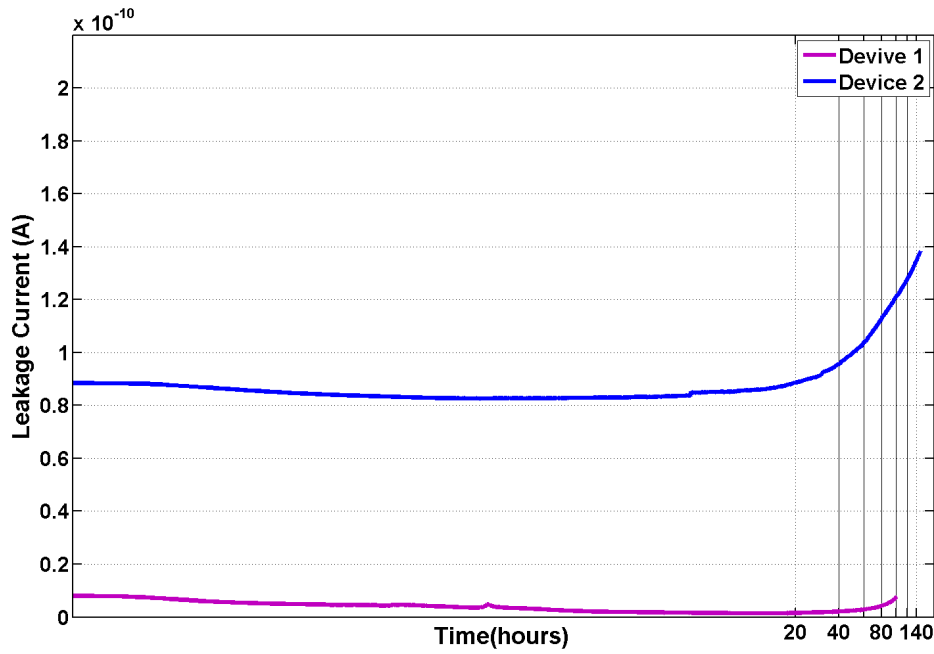
Figure 4.27: Leakage current measurement result of a complete devices, measured in 100 hours and 140 hours. The logarithmic graph is used to show the changes in the first hours.
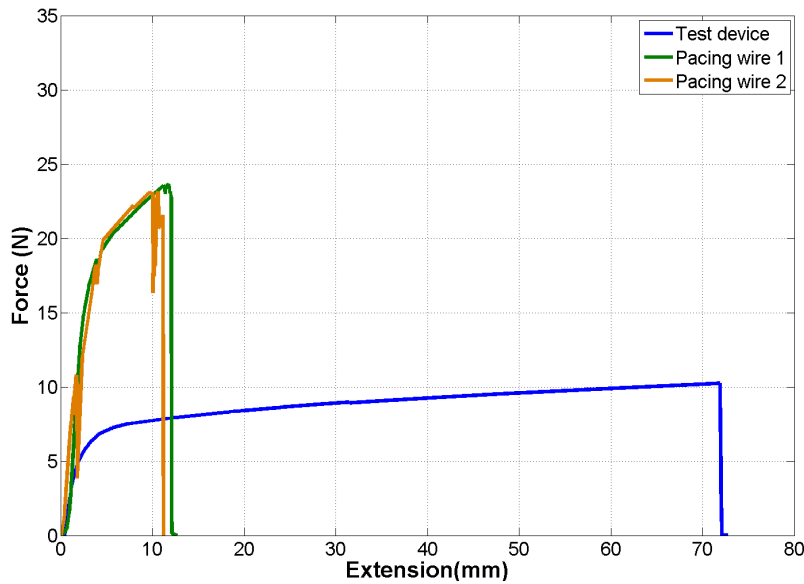
Figure 4.28: Comparison of tensile strength between the temporary pacing wire Johnson & Johnson Ethicon (Pacing wire1), Medtronic Streamline (Pacing wire 2) and the polyimide-based cable.

[121]. The tested implantation forces were in range of 4 - 6N. Another tensile strength comparison between two standard temporary pacing wires (Johnson

& Johnson Ethicon and Medtronic Streamline) and a polyimide-base flexible circuit (device version 1-2) is also presented in Figure 4.28. The specimens length were 200 mm and pacing wire specimens were in closed loop shape. The tensile strength of the device can tolerance the implantation force. However, its strength was not comparable to standard pacing wires and this posed a challenge to this study.

c) Pacing/sensing function

The epicardial temporary pacing wires are the electrical conduit between the pulse generator and the heart [68]. They transmit therapeutic energy to the heart tissue and return sensed signal to the pulse generator for monitoring purposes. The pacing threshold depends on electrical activity of the heart, tissue-electrode impedance, distance between two pacing wires (unipolar temorary pacing wires), opearation mode of the generator and the resistance of the wire. The pacing/sensing function of this device is similar to a temporary pacing wire. The important parameter is the overall resistance of pacing channel in the device (between pacing contact on the connector and the metal capsule). An average resiatance measured on five device samples was 8.6Ω. This value is lower than the resistances in some typical commercial pacing wires (e.g. Medtronic Streamline, Johnson & Johnson Ethicon, and B Braun Steelex Electrode). They were 13.8Ω, $12,2\Omega$, and $11,8\Omega$ respectively. Besides, the metal capsule can provide larger electrode-tissue contact area than a standard pacing wire. The real tests with pacing thresholds in animal trial are shown in [121]. With regard to the device structure and electrical resistance of the pacing channel, the accelerometer device can be used as a temporary pacing wire. A lower therapeutic energy provided by the generator can achieved a comparable pacing effect on the heart to standard pacing wires.

4.2.2.7 Publications

F. Tjulkins, **Anh-Tuan Thai Nguyen**, E. Andreassen, N. Hoivik, K. Aasmundtveit, L. Hoff, O. J. Grymyr, P. S. Halvorsen, and K. Imenes, MEMS-based implantable heart monitoring system with integrated pacing function, Electronic Components and Technology Conference (ECTC), 2014 IEEE 64th, 2014, pp. 139-144.

4.2.3 Version 1-3

4.2.3.1 Structure of the device

The third version of the heart muscle implantable accelerometer device (version 1-3) was built on the concept structure B presented in the section 4.1. In this study, I investigated the miniaturization posibility of circuit packaging for an accelerometer device, which consisted of challenges in making electrical interconnection and mechanical reinforcing between cable and substrate. The outer structure of the device version 1-3 was similar to the device version 1-2 which was able to provide simple implantation procedure and be capable of therapeutic pacing/sensing, see Figure 4.29. My study employed the use
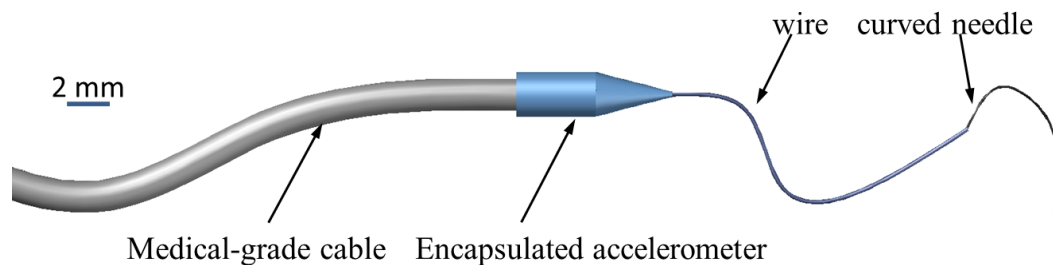
Figure 4.29: A proposed structure of the heart muscle implantable accelerometer device (version 1-3).

of an implantable medical grade cable which was validated in early studies on heart surface (epicardium) accelerometer device, demonstrated by Imenes [48] and Halvorsen [77]. The cable would be combined with a suitable substrate to form a miniaturized circuitry platform of the device. Two potential cable-substrate fixation structures are illustrated in Figure 4.30. The off-axis connection method was proposed by Imenes [48]. This structure requires a relatively large area on the substrate for fixation structure. The on-axis connection between the cable and substrate was proposed in my study that might yield the smallest substrate area with an in-cable fixation structure, see Figure 4.30b. My study also proposed a new design of the medical grade cable with smaller side, higher tensile strength, and lower cable stifness, in comparison to the available cable. Both of two medical grade cables are produced by New England Wire Technologies, Lisbon, NH, USA. Figure 4.31 and Table 4.3 show the cross sections and the main differences between those cables including the
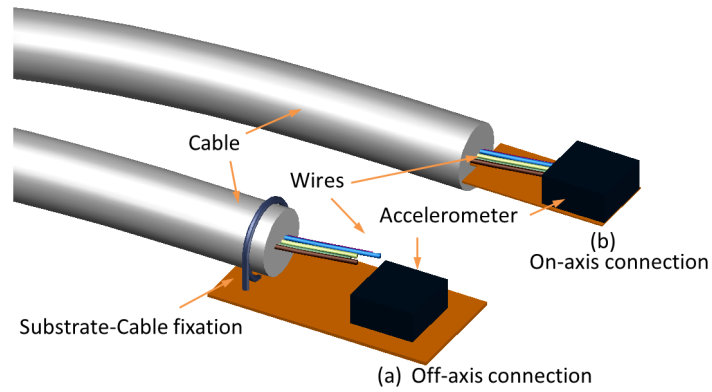
Figure 4.30: Illustration for the fixation structure between cable and substrate: (a) typical off-axis connection uses metal ring to provide fixation; (b) The substrate has an anchored part which is inserted inside the cable to get fixation by adhesive.

overall diameter and the strength member core.
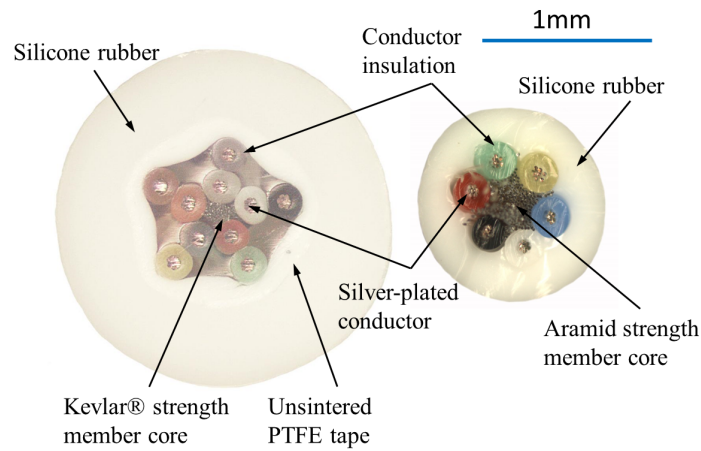
Figure 4.31: Medical grade cables used in this study. The smaller diameter cable (Ø1.2 mm) is a custom-made cable specified for this study (New England Wire Technologies, Lisbon, NH, USA)

Table 4.3: The main properties of the medical grade round cables used in this study

Properties	Availabe round cable	New round cable
Diameter	2.0 mm	1.2 mm
Conductors	10 conductors	6 conductors
Strength member	Kevlar®(Aramid)	Aramid
Tensile strength of strength member	20N	100N

4.2.3.2 Circuit design

The lumina substrate was presented in [48] may not be suitable to use in this application due to the standard thickness and brittle property of alumina material. The polyimide-base (PI 2611) flexible substrate was selected in this application. The layout of the substrate is shown in Figure 4.32. The zig-zag pattern was used to enhance the stiffness of the fixation part to get it inserted inside the cable easily. One of the cable conductors was used as pacing/sensing cable would be terminated to the pacing contact pad on the bottom side. The circuit was fabricated by H. K. Best FPC Co., Ltd (Hong Kong, China).
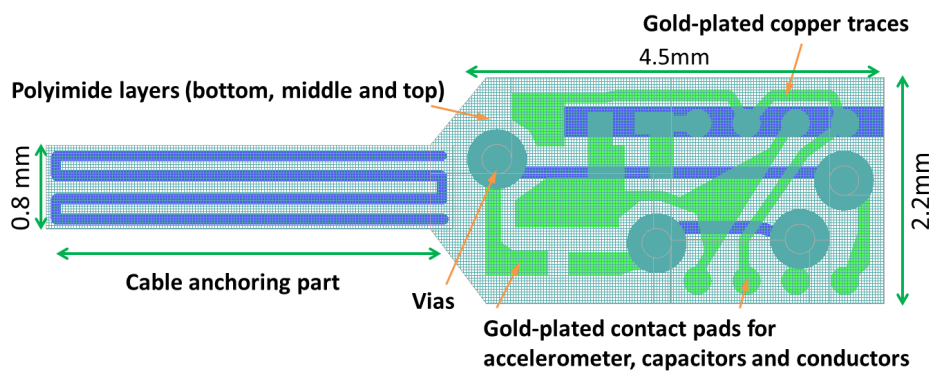
Figure 4.32: Layout of the double sided polyimide-based flexible printed circuit. Substrate dimension: 2.2×4×0.13 mm (w×l×t). A conductive layer on the fixation part is used to enhance the stiffness while inserting into a round cable.

4.2.3.3 Device assembly

The accelerometer-substrate bonding technique was carried out for the device version 1-1 and 1-2 has been also applied in this version. The procedures were described in detail in [116, 122]. The flexible substrate with bonded accelerometer and components was then axially inserted in to the round cable with pre-applied adhesive DP460 (Scotch-Weld™ Structural adhesive, 3M Oy, Finland). This adhesive was later replaced by more biocompatible adhesive (Cyanolit 203TX, Panacol, Germany or 353ND, Epotek, USA). The signal wires and the strength member are positioned on the top and bottom side of the substrate respectively. A manual soldering procedure was carried out to bond power supply conductors, signal conductors and dedicated conductor for pacing/sensing function to the substrate [122], see Figure 4.33. Lead-free solder paste SAC

(Sn96.5Ag3Cu0.5) was used in this application. Two additional layers of non-conductive adhesive (NCA) EPO-TEK 353ND (Epoxy Technology, Inc.) were applied after assembly to provide electrical insulation. The machined stain-
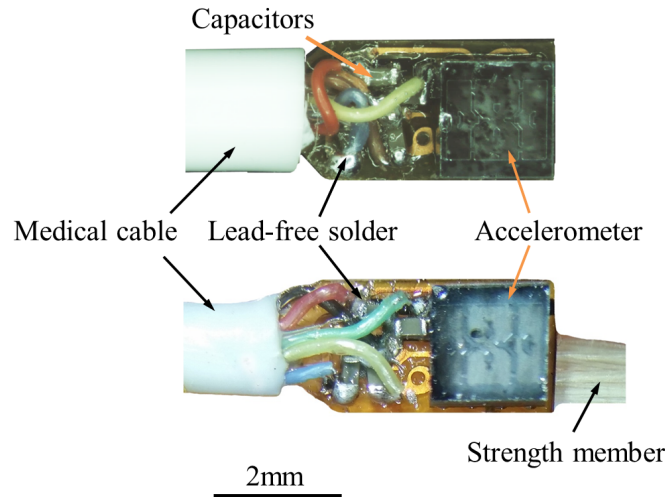
Figure 4.33: Assembly process of two accelerometer devices built on Ø2.0 mm and Ø1.2 mm medical grage cable. The accelerometer sensor and cable conductors were bonded to the gold-plated contact pads of flexible substrate.

less steel capsule (type 316L) was chosen as encapsulation due to the machinery possibility, biocompatibility, mechanical property and chemical durability [123]. Metal capsule can be used as an electrode for pacing/sensing function. The overall diameter of the capsule is 2.8 mm. The capsule assembly procedure was proposed and carried out in several steps, reported in [123]. The cross sectional assembly structure of the device are shown in Figure 4.34. The complete devices were built on Ø2.0 mm & Ø1.2 mm medical grade cable are shown in 4.35

4.2.3.4 Animal trial

This version of the heart muscle implantable accelerometer device can use a similar implantation procedure with a temporary pacing wire. The device capsule can be pulled through a tissue channel created by the curved needle. To perform this process smoothly the diameter of a metal capsule tip should be smaller than the needle diameter. In the animal trial, we investigated the implantation stability of the devices built on two type of round cable (Ø2.0 mm
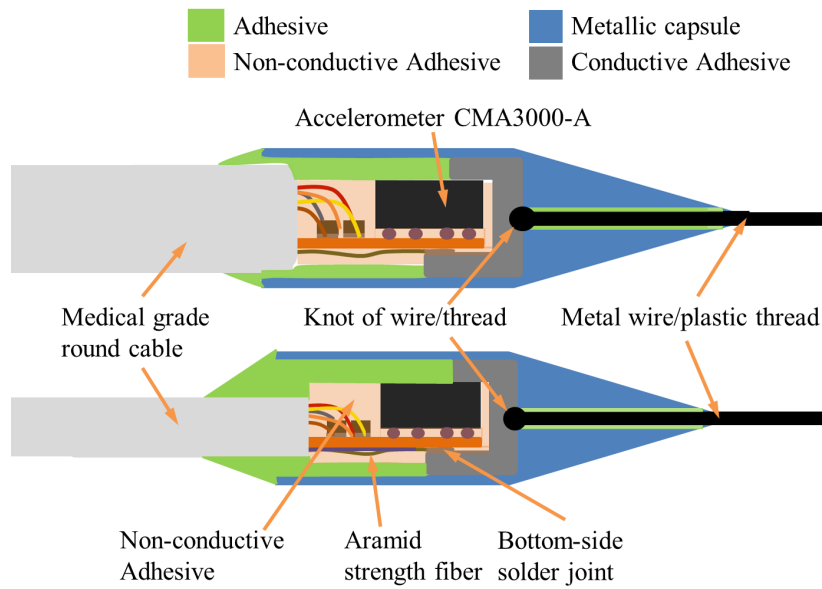
Figure 4.34: Device assembly with machined metal capsule
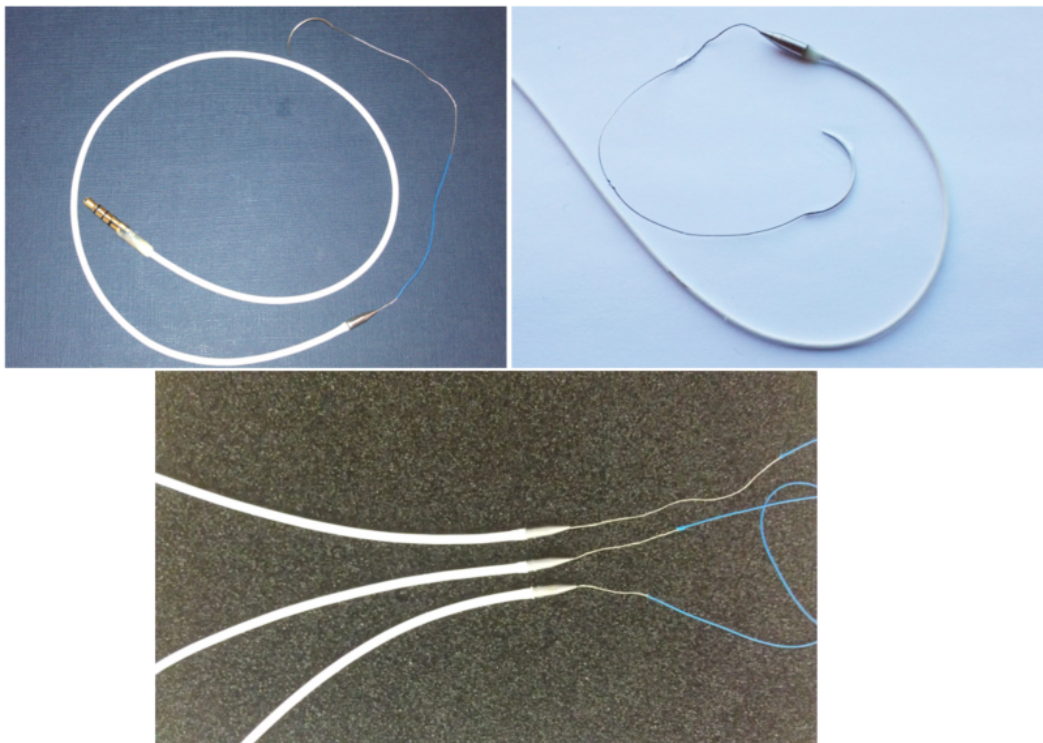
Figure 4.35: Complete devices, version 1-3. The Ø2.0 mm cable (left & bottom) and Ø1.2 mm cable (right) were used to fabricate these devices respectively.

& Ø1.2 mm). The implantation stability depends on several factors and some of them are the stiffness and diameter of the cable. A retraction of the device built on the Ø2.0 mm cable was observed. This was caused by the stiffness of

the large cable. The small cable can provide better implantation stability than the larger one due to the improved flexibility. The implantation stability aslo depends on the conical transition joint angle between cable and metal capsule. The greater joint angle is the higher implantation stability may have. However, the joint angle may be a restriction for device removal procedure. Figure 4.36 demonstrates the implantation of devices version 1-3 in an animal trial.
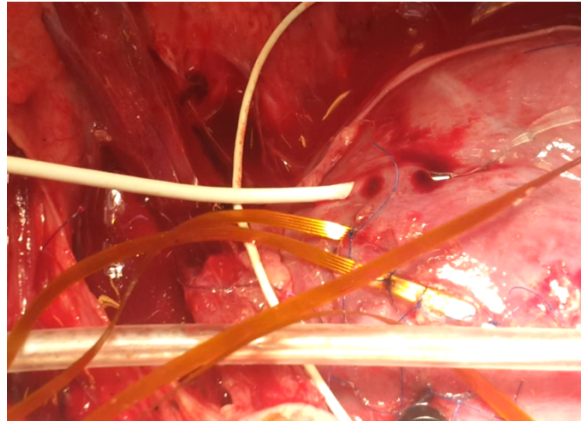
Figure 4.36: Heart muscle implantable accelerometer device (version 1-3) was used in an animal trial (white cable device). In this animal trial, devices, version 1-1, were also used to get data for clinical studies.

Signal accquisition and pacing function:

The implantation processes were performed by medical doctors and surgeons at Intervention centre - Oslo University Hospital. The recorded acceleration signals from a left ventricle implanted sensor corresponded very well to results reported for previous heart-muscle myocardial accelerometer sensors, demonstrated in [114], and the larger epicardial accelerometer sensors (implanted on the outside of the heart wall), reported by Imenes et al. [74]. Additional pacing function has been demonstrated in conjunction with an implantable accelerometer sensor. The devices can pace the heart at specific current threshold and selectable rate controlled by commercial pacing generator.

Figure 4.37 presents calibrated and synchronized acceleration signals of X, Y and Z direction over a period of 2 s. ECG and acceleration signals exhibit the same frequency. Pacing signals were sent via the device at 120 pulses/min, and they were recorded in ECG data as pacing spikes, shown in Figure 4.38.
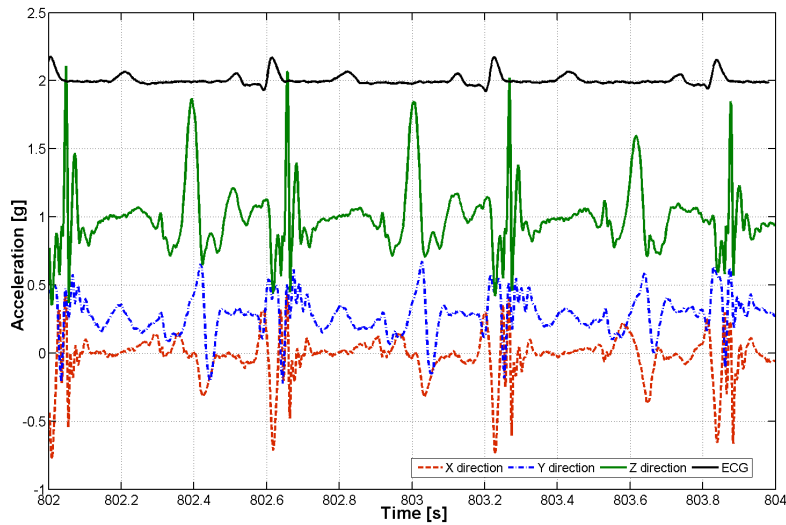
Figure 4.37: ECG and acceleration signals recorded in an animal trial. Calibrated and synchronized acceleration signals of X, Y and Z direction are plotted in red, blue and green colour correspondingly. Acceleration signals and ECG signal exhibit the same frequency
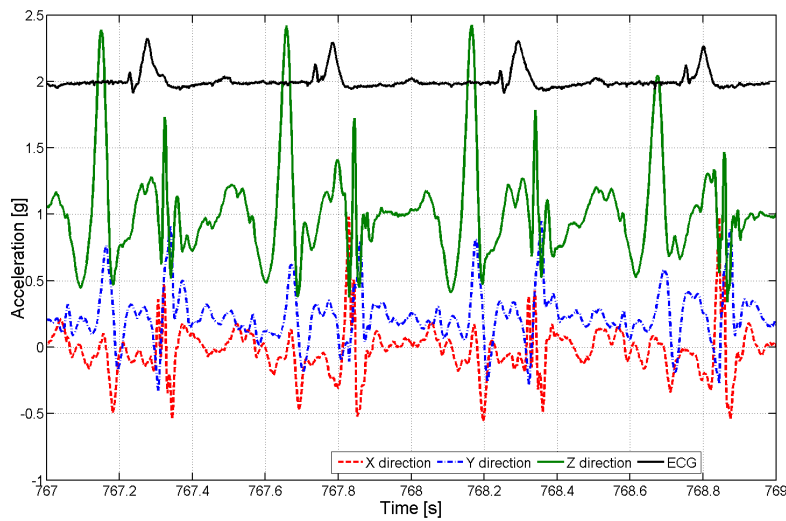
Figure 4.38: Pacing thresholds at 120 pulses/min and acceleration signals recorded in an animal trial. Calibrated and synchronized acceleration signals of X, Y and Z direction are plotted in red, blue and green color correspondingly. The pacing spikes were covered within the QSR interval.

4.2.3.5   Important measurement results

a) Leakage current measurements

Leakage current measurements were performed on complete devices with a

similar measurement setup was described in section 4.2.1.4. A comparison of leakage current between the devices version 1-3 and the flexible cable of the device version 1-1 has been carried out and shown in Figure 4.39. The leakage current recorded from devices version 1-3 was far below the leakage from flexible cable of device 1-1 [116]. No significant difference was observed in leakage current from devices were built on two types of medical grade round cable. To be more realistic, leakage current tests were combined with loading cycles
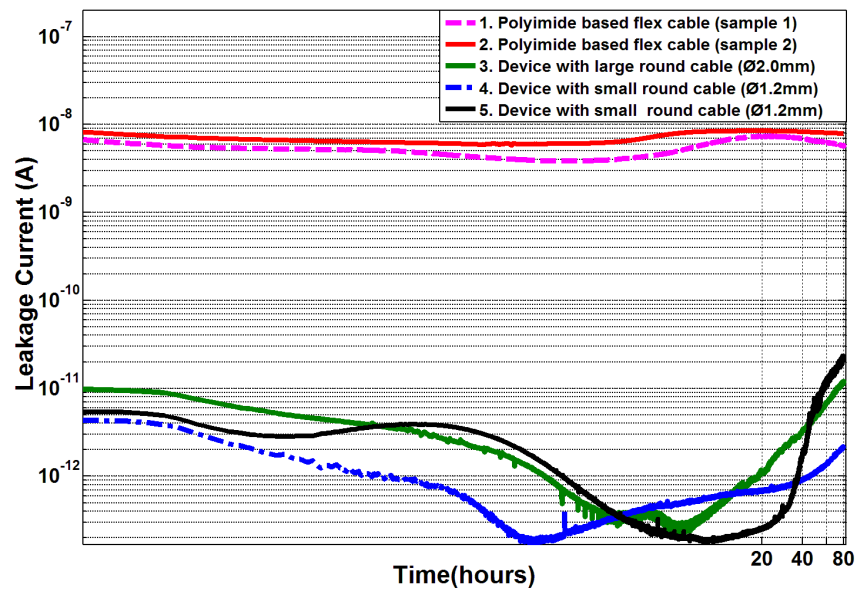
Figure 4.39: Comparison of leakage current measurements between the devices with large round cable, small round cable and flexible cable part of the device demonstrated recently in paper 1. Curves are plotted in log scale of time to see the initial transition of the leakage current.

test. The measurements were repeatedly performed in two steps: cycling test and leakage current test in 60000 cycles and 18 hours respectively. The metal capsule and the clamping stage motion was varied in range of 20 mm at 1.5 Hz-corresponding to 90 heartbeats per minute, see test setup Figure 4.40. The cable length between the movable platform and the fixed platform is 50 mm, which approximates the distance between the chest wall and the heart muscle. While moving the cable was deflected in accordance with the system motion. When the movable stage got close to the fixed platform, the distance between cable-capsule joint was around 30 mm. Measurement setups and results were presented in [124] and in Figure 4.41. The range of leakage current was far beneath the critical safety margin set by the IEC 60601-1 (0.01 mA).
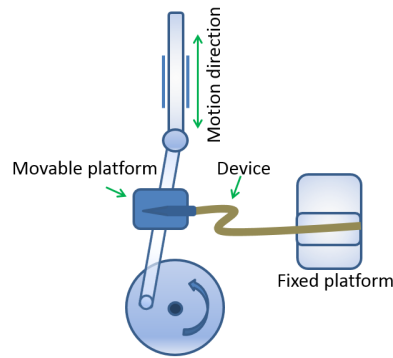
Figure 4.40: Setup for repetition of loading cycles
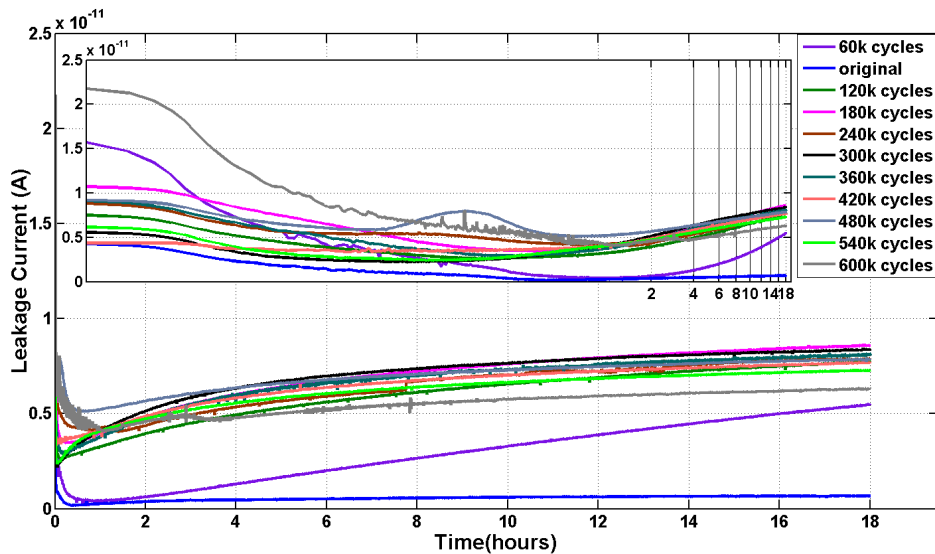
Figure 4.41: Leakage current measurements were performed in 18-hour intervals and combined with period cycling test of 60000 cycles, 600000 cycles in total.

b) Tensile strength measurement

The strength member of the cable is responsible for the tensile strength of the device. The tests were carried out for both strength members of Ø2.0 mm cable and Ø1.2 mm cable. A significant difference in tensile force which can be applied on both two types of cable was observed. The smaller cable can withstand a tensile force five times higher than that of the Ø2.0 mm cable. Results are presented in Figure 4.42. However, the overall tensile strength of a complete device depends on the adhesive joint between strength member and the capsule. A tensile force of 35N was observed when I performed pull test on a complete device. Different adhesives may provide different pulling strength of the adhesive joint. Besides, there were challenges to hold the capsule correctly

in the movable clamp. A tough clamping force may destroy the capsule. Futher investigations on optimization of tensile strength for complete devices need to be carried out.
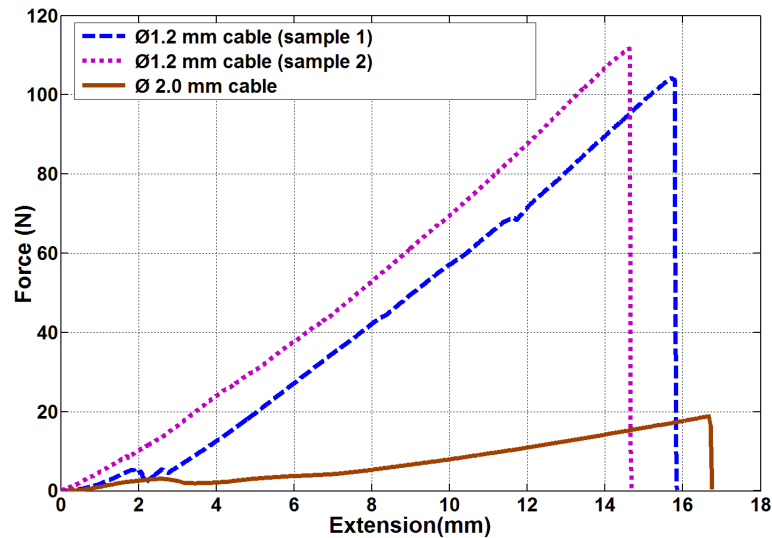
Figure 4.42: Comparison of tensile strength between two types of medical grade round cable (New England Wire): Ø2.0 mm and Ø1.2 mm

4.2.3.6 Publications

Anh-Tuan Thai Nguyen, F. Tjulkins, Knut Aasmundtveit, Nils Hoivik, Lars Hoff, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, Packaging of Multifunctional Implantable Heart Monitoring Device, Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP) 2014, ISBN 978-2-35500-028-7.

Fjodors Tjulkins, **Anh-Tuan Thai Nguyen**, Erik Andreassen, Lars Hoff, Knut Aasmundtveit, Nils Hoivik, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, Fabrication and assembly of MEMS accelerometer based heart monitoring device with simplified, one step placement, Journal of Medical Engineering & Technology, DOI: 10.3109/03091902.2014.981307

Anh-Tuan Thai Nguyen,F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, Packaging of a Multifunctional Implantable Heart Monitoring Device, in preparation for submission.

4.2.4   Analogue galvanic isolator

The International Electrotechnical Commission (IEC 60601-1) requires a galvanic isolation to ensure that the patient is isolated from the main power supply. A galvanic isolator was built to maintain an electrical isolation between Input side (patient) and output side (data acquisition equipment). The work was carried out in collaboration between the Intervention Center - Oslo University Hospital and me. The isolator got an approval for using on human with the epicardial accelerometer device [48, 125]. The isolation system is based on an isolation amplifier that utilizes optical transmission signals ACPL-C790 (Avago Technologies, Ca, USA). The isolation amplifier can provide 5000 Vrms/1 min protection rating (isolation voltage) [126]. The patient side circuit and accelerometer device are powered by a regulated voltage source delivered by a 9V battery. The isolator consists of two individual accelerometer inputs with three channels for each and two channels for the reference ECG signal. The analoge galvanic isolator is shown in Figure 4.43.

Figure 4.43: The galvanic Isolator used for analogue accelerometer devices (version 1-1, 1-2, and 1-3). The box was built in collaboration with the Intervention centre - Oslo University Hospital and got the approval for internal use. The circuit was designed by Fred-Johan Pettersen (Researcher at Oslo University Hospital HF) and advised by Prof. Lars Hoff (Buskerud and Vestfold University College).

4.3 Digital accelerometer-based devices:

In 2013, Bosch Sensortec GmbH (Germany) has introduced a 3-axis MEMS accelerometer which was one of the smallest available accelerometer. The accelerometer is similar in form, fit and function as the BMA355 (Bosch Sensortec), which has a very small size of $1.2 \times 1.5 \times 0.8$ mm^3. The new accelerometer brings challenges and opportunities to us for development of a new miniaturized heart muscle implantable accelerometer device.

4.3.1 Version 2-1

4.3.1.1 Structure of the device

Basically the structure of this version is similar to that of version 1-2 and 1-3. The device consists of a connector, medical grade cable, accelerometer with metal capsule, and a curved needle attached to a metal wire or plastic wire, shown in Figure 4.44. However the overall diameter of the device (included metal capsule) is only 2.0 mm. This is a significant improvement in miniaturization of the device. Table 4.4 describes a comparison of cross-sectional diameter reduction among this version and the other generation of accelerometer devices.

Device generation	This version (version 2-1)
Device proposed by Imenes [48]	81%
Device version 1-1	37.5%
Device version 1-2	28.5%
Device version 1-3	28.5%

Table 4.4: A comparison of the dimension reduction between this version of accelerometer device and that of previous devices
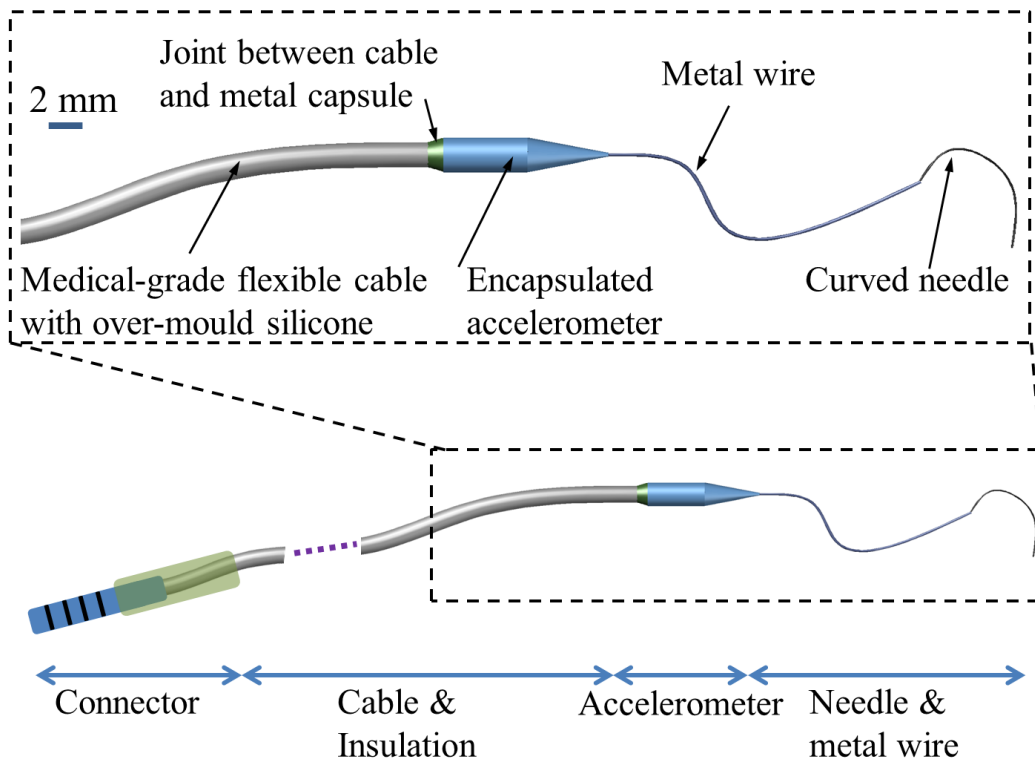
Figure 4.44: Main structure of the heart muscle implantable accelerometer device version 2-1

4.3.1.2 Accelerometer sensor

The accelerometer is similar in form, fit and function as the BMA355 (Bosch Sensortec GmbH, Stuttgart, Germany), Figure 4.45.
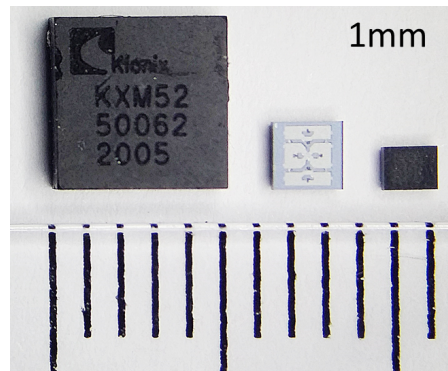
Figure 4.45: From the left hand side: the KXM52 (Kionic Inc, USA) was demonstrated by Imenes et al. [46]; the CMA3000A (Murata Electronics Oy, Finland) was presented earlier [23, 96] and the BMA (Bosch Sensortec GmbH, Germany) digital accelerometer was used in this study ($1.25 \times 1.52 \times 0.8$ mm^3).

Properties	Accelerometer (similar to BMA355)
Packaging	WLCSP 10 solder balls
Dimension	$1.25{\times}1.52{\times}0.8$ mm^3
Interface	SPI (3-wire, 4-wire), I^{2}C
Supply voltage	1.2 -3.6 V
Measuring range	±2 g; ±4 g; ±8 g; ±16 g
Sensitivity (2g / 4g range)	1024 LSB/g / 512 LSB/g
Temperature measurement range	-40 –85ºC
Current consumption in active mode	130 μA
Cross Axis Sensitivity	1%

Table 4.5: A comparison of the dimension reduction between this version of accelerometer device and that of previous devices

The main properties of the accelerometer are listed in the Table 4.5. The I^{2}C interface was selected because the I^{2}C protocol requires fewer wires than that of the SPI, hence smaller cable. The design used two wires for power supply, two wires for signal transmission (clock signal - SCL, and data signal - SDA), one dedicated wire for the interrupt signal.

4.3.1.3 Layout design

A new layout design was carried out for the digital accelerometer sensor which can support I^{2}C protocol communication, interrupt signal and one conductor for pacing/sensing function, shown in Figure 4.46. There was a challenge in miniaturization of the new flexible I proposed in this study. The company who fabricated flexible circuit for devices version 1-1 and 1-2 cannot produce the circuit with the smallest structure of 40 µm. The new polyimide-based flexible circuits were fabricated by Dyconex AG (Bassersdorf, Switzerland). They are one of the rare companies who are interested in limited order quantity for research. The multilayer structure flexible circuit was proposed in version 1-1 and 1-3 [116, 122] can be also used in this device. However there was a change in the layer structures to meet the requirement of available equipment set-up of Dyconex. A four copper layer structure was suggested to skip the need for solder mask (top and bottom polyimide layer) described in [116, 122], Figure 47. The blind vias have been used to provide interconnection between copper

layer #1 and copper layer #2 or between copper layer #4 and copper layer #3. The buried vias were used between copper layer #2 and copper layer #3.
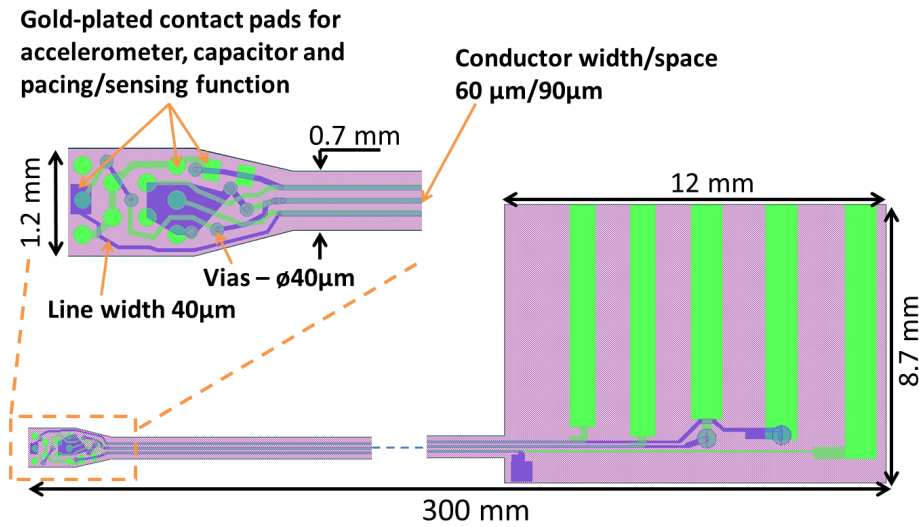
Figure 4.46: Layout of the polyimide-based flexible substrate/cable circuit

Tip and connector

Layer	Thickness (µm)
Gold	0.05
Seeding layer	5.15
Copper 1	14
Polyimide	12
Adhesive	12
Copper 2	13
Polyimide	25
Copper 3	13
Adhesive	12
Polyimide	12
Copper 4	14
Seeding layer	5.15
Gold	0.05
Overall thickness	137.4

Cable

Layer	Thickness (µm)
Polyimide	12
Adhesive	12
Copper 2	13
Polyimide	25
Copper 3	13
Adhesive	12
Polyimide	12
Overall thickness	99

Figure 4.47: Multilayer structure of the flexible circuit

4.3.1.4 Device assembly

The assembly process was carried out by using the flip chip bonder FinePlacer Pico (Finetech GmbH, Germany) which can provide a placement accuracy of 5 µm and handle components down to 0.125 x 0.125 mm^2. The accelerometer has built-in lead-free solder balls and the parameters of the flip-chip bonding
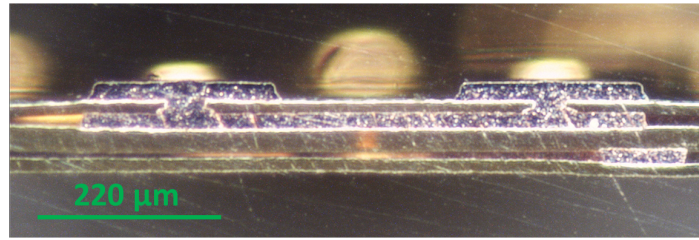
Figure 4.48: Cross section of the flexible circuit. The two blind vias are shown in this figure used to connect the BGA (Ball grid array) contact pads to the second copper layer

process are shown in Table 4.6. A small amount of no-clean flux (CW8100, ITW Chemtronics, GA, USA) was manually dispensed on each contact pad before doing pick and place of the accelerometer to improve interconnection yield. Precise alignment between the accelerometer and substrate is shown in Figure 4.49

Profile feature	Value	Duration
Preheat	40 –260ºC	70s
Applied force	2N	100s
Reflow	260ºC	30s
Cooling	260 –100ºC	200s

Table 4.6: Parameters of the flip-chip bonding process.
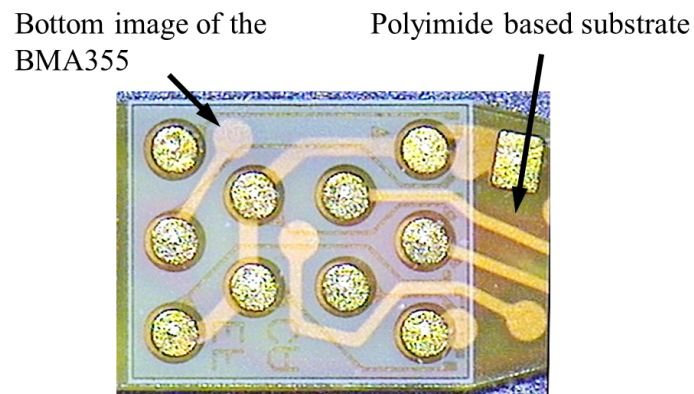
Figure 4.49: The bottom image of the BMA (1.2mm × 1.5mm) was aligned to the bonding pads on the substrate.

The assembly of the low-pass filter capacitor was done manually. Surface mounted capacitor, imperial code 0201-100nF, was connected in parallel to the power

supply terminals. The BMA accelerometer and the low pass filter capacitor got bonded to the flexible substrate, shown in Figure 4.50. Non-conductive biocompatible adhesive EPO-TEK 353ND (Epoxy Technology, Inc.) was used as underfill to improve the mechanical strength of the bonding between the accelerometer and the flexible substrate and provide additional insualtion resistant to later encapsulation steps. The curing time was set to 5 minutes at 100°C. An alternative adhesive that may use in this step is Dymax 1128 (Dymax Europe GmbH, Germany). This is an UV curved adhesive and may maintain comparable insualtion properties and water absorption to the 353ND adhesive. Dymax 1128 can provide better adhesion to polyimide substrate and less brittle than 355ND adhesive.
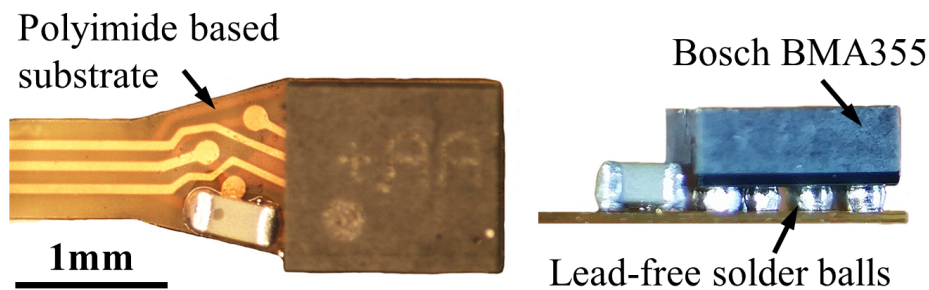
Figure 4.50: The three-axis accelerometer (similar to BMA355 Bosch Sensortec Germany) bonded to a polyimide based flexible substrate-cable

4.3.1.5   Encapsulation

a) Encapsulation of the sensor part
The device used stainless steel (316L) capsule with an outer-diameter of 2.0 mm and wall thickness 0.2 mm. The metal capsules were made by additive manufacturing (3D printing) using a Concept Laser M2 Cusing, Concept Laser GmbH, Germany. In this study, the design of the metal capsule was not in the scope. The capsule was proposed by Tjulkins[127]. The capsule assembly procedure is identical to that of the device version 1-2 which was described in section 3.2.2.4 and [121].

b) Encapsulation of the cable part using overmold-silicone
An improvement of the overmold-silicone method described in section 3.2.2.4 was performed in this study. Previous molding method can provide insufficient centralized position of the cable in the mold which makes the cable be offset
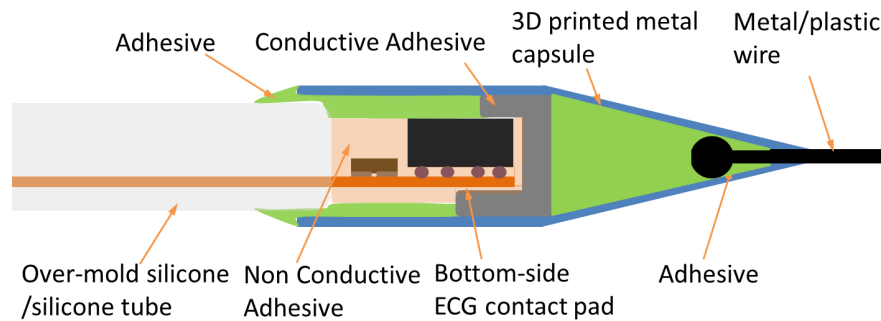
Figure 4.51: Metal capsule assembly of the implantable accelerometer device version 2-1.

against the center line. To overcome this issue, an improved overmold method was proposed. The surface of flexible substrate-cable was activated by oxygen-plasma treatment. The small end of the flexible circuit is pulled through the Ø1.5 mm silicone tube that works as a cable mould. Two components biocompatible silicone MED-4211 (Nusil Silicone Technology, USA) was mixed and filled into this tubed mould with supporting of low vacuum. In addition, low pressure may help to release air bubbles trapped in silicone. Figure 4.52 describes a handily way to have the flexible cable be in centre of the silicone filled tube.

The silicone molding-tube was placed onto a U-shaped platform with the same
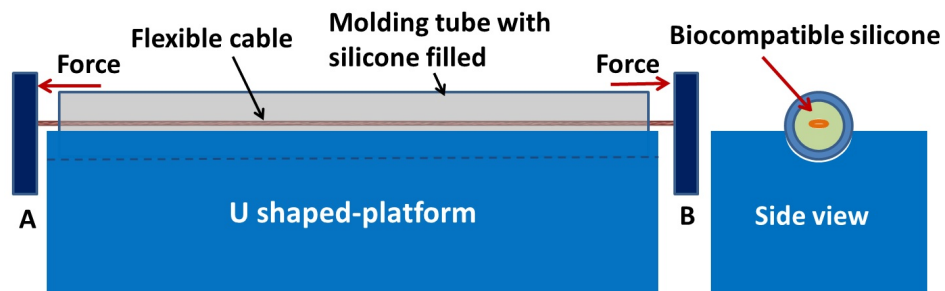
Figure 4.52: The set-up for making the overmold silicone encapsulation of the flexible cable

radius as the outer radius of silicone tube. The position of clamp A and B, see Figure 4.52, was adjusted until the cable was in the centre of the silicone tube. Sufficient force was applied to keep the flexible cable in horizontal position, as shown in Figure 4.52. Pre-curing took place at room temperature for one day followed by a post curing step at 100ºC in 3 hours.
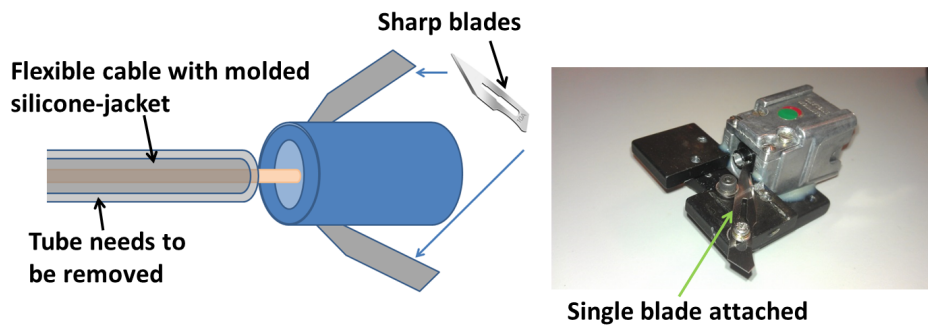
Figure 4.53: Removal mechanism of the tube remover (on the left hand side) and the real home-made tube remover with single blade attached (on the right hand side)

In order to remove the molding tube, a tube remover was used. The molding tube with molded cable inside was pulled through the tube remover which has cutting mechanism to separate the molding tube, see Figure 4.53. The two molded halves on the tube were then easily removed. Figure 4.54 demonstrates the devices were used in an animal trial.
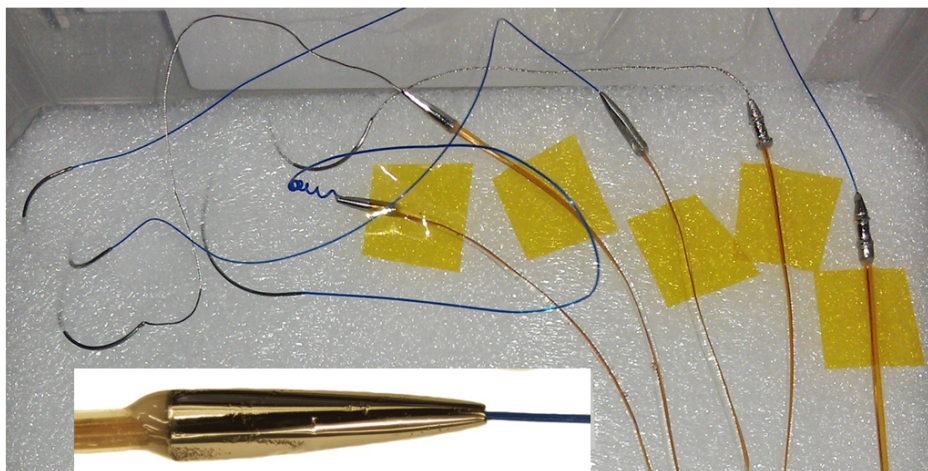
Figure 4.54: The implantable accelerometer devices with overmold silicon cable

c) Encapsulation of the cable part using medical grade silicone tube

This study proposed an productive method to encapsulate the flexible cable using a medical grade silicone tube. The method can reduce the assemply time remarkbly. The silicone tube is fabricated by Helix Medical Europe GmbH, Germany, the basic proerties is shown in Table 4.8. The flexible substrate/cable was passed through the silicone tube by a metal introducer. The accelerometer and capacitor bonding procedure were done out afterwards. Figure 4.55 shows the device with silicone tube used for cable encapsulation.

Feature	Properties
Material	Dow Corning silicone
Dimension	OD: Ø1.19mm; ID: Ø0.64mm
Type	Mono –Lumen tubing

Table 4.7: properties of the silicone tube
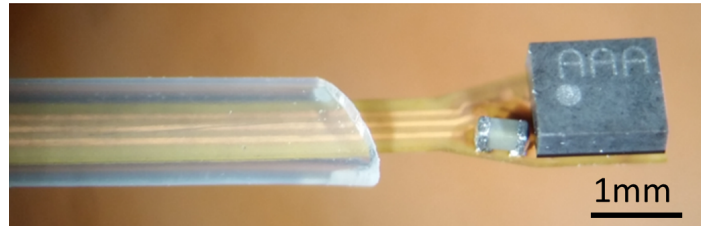
Figure 4.55: The device being assembled with silicone tube encapsulation

4.3.1.6   Important measurement results

a) Leakage current measurements

The measurement setup for leakage current tests was similar to the ones used in previous versions. The tests were performed on complete devices (at 37°C in PBS and up to 180 hours) with different types of encapsulation using silicone molding and medical grade silicone tube. Results are presented in Figure 4.56 The detail descriptions and other results were shown in [128]. The leakage
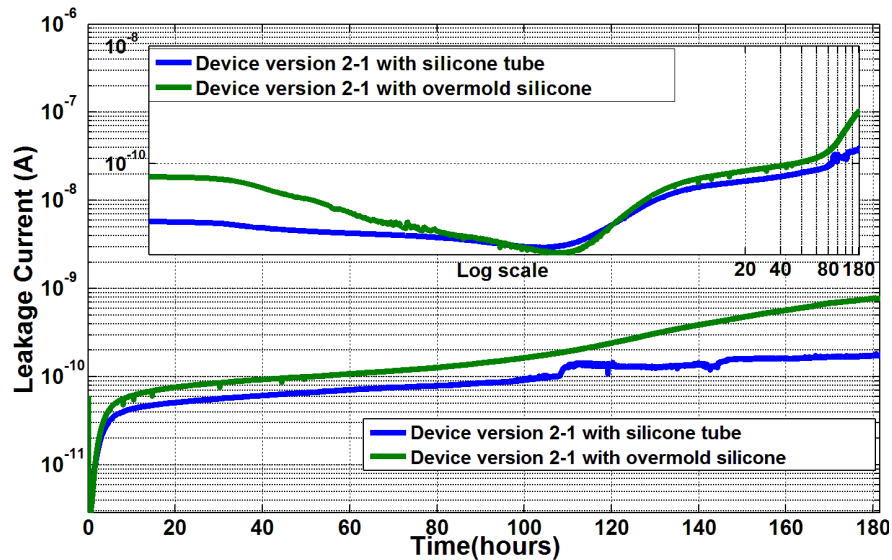
Figure 4.56: Leakage current measurements from the complete devices with different cable encapsulation; silicone molding and silicone tube.

current was observed from the device with silicone molding cable can be comparable with that of the silicone tube encapsulation. The current was varied in safe range which was 1000 times less than the requirement (10 μA) [82]. A leakage current comparison between devices version 2-1 and version 1-1 is shown in Figure 4.57.
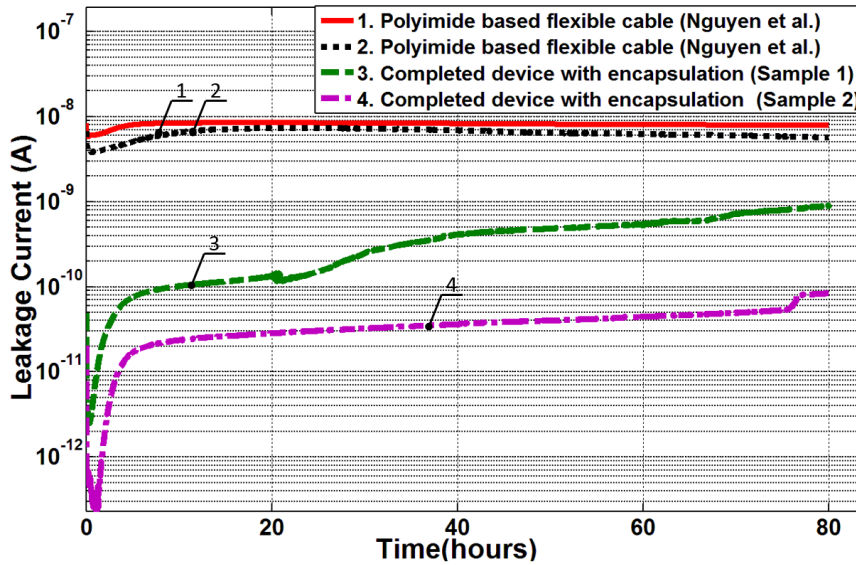
Figure 4.57: Leakage current comparison between devices version 2-1 and version 1-1, immersed in PBS solution at 37°C.

To be more realistic, the leakage current tests were combined with cycling motions which were performed in PBS at 37°C. In this test, the cycling equipment was immersed in liquid. The heart motions are really complicated. Jean
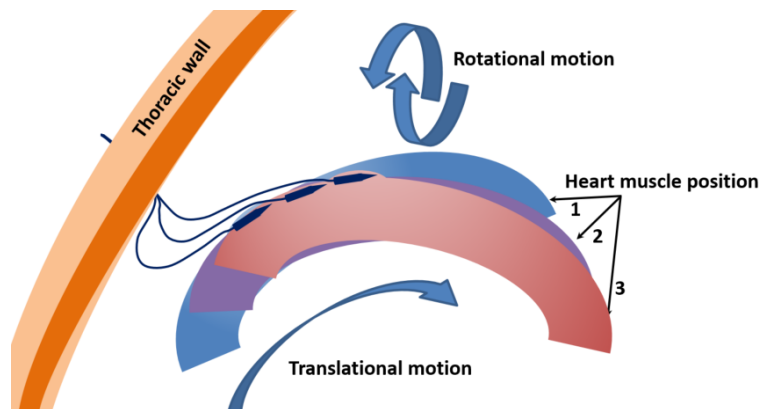
Figure 4.58: A simplified illustration for positions of an implantable accelerometer device in accordance with the heart motion.

Buithieu has reported that there are at least five identified movements in systole of a heart contraction [129] including mayocardial wall thickening, shortening, rotational motions, translation motions, and torsion. The movement
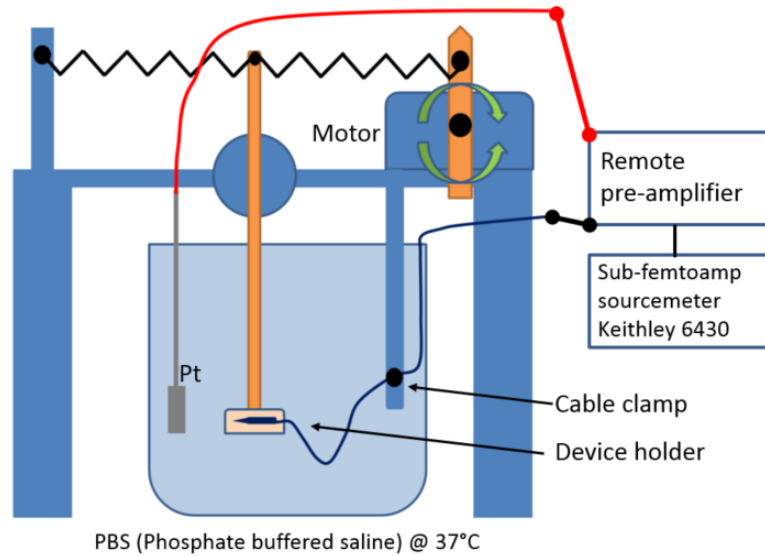
Figure 4.59: Measurement setup for combination tests of loading cycles and leakage current.
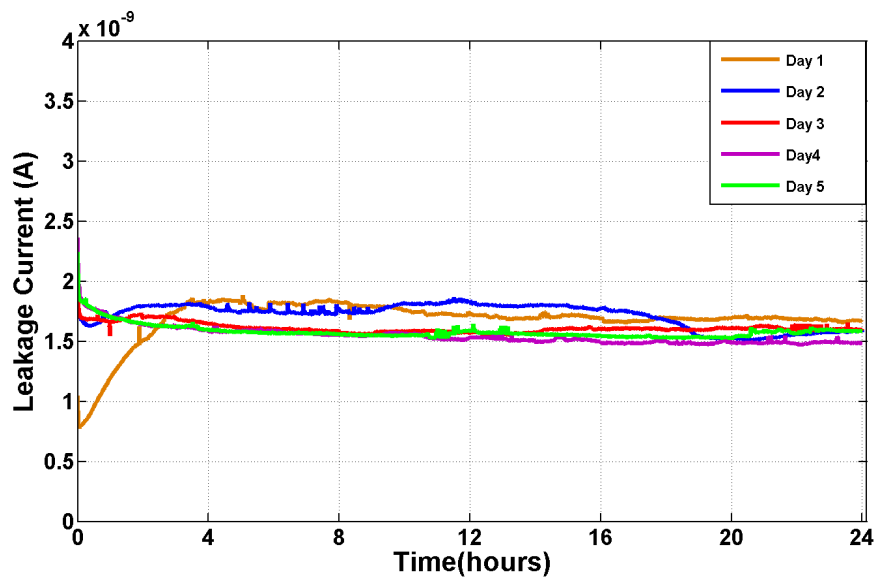
Figure 4.60: Results of leakage current measurement performed in liquid with additional cycling motion, immersed in PBS solution at 37°C.

of an implanted accelerometer device at a certain position in the heart muscle may be considered as a combination of rotational and translational motions, as

shown in Figure 4.58. To emulate a simple heart motion I have developed an equipement which can provice a harmonized motion following a curved trajectory, see Figure 4.59. The equipment performed 108000 loading cycles prior to 24 hours leakage current measurement. These processes were repeated 5 times and results are shown in Figure 4.60. The loading cyclings were performed at 1.25 Hz and an amplitude of 2 cm. Comparable leakage current results were observed in these tests. The device can withstand a tough test condition was demonstrated in this study.

b) Cross talk

The flexible cable was designed without ground shielding plane to enhance the flexibility. Hence the routing of signals in the cable should be considered to minimize the crosstalk between bus lines [130]. The study proposed a set-up for investigation of the interference between conductors in an arrangement, shown in Figure 4.61.
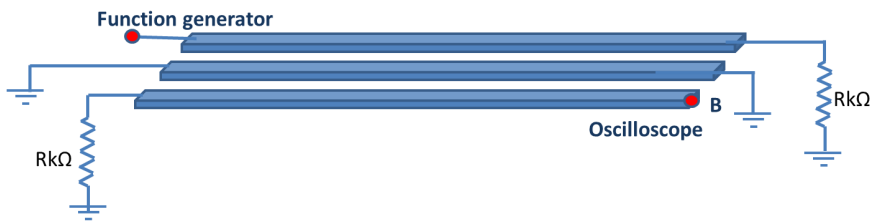
Figure 4.61: Setup for measuring interference between signals lines
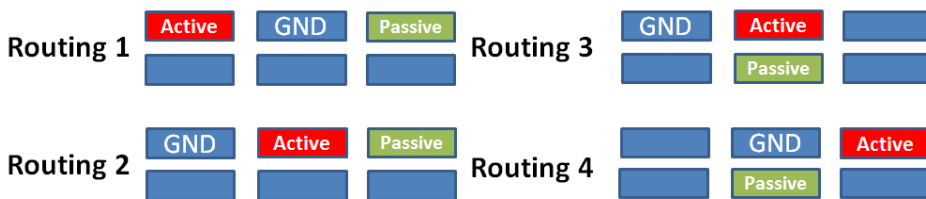
Figure 4.62: Different routing setups for crosstalk measurement of a 6 wire flexible polyimide based cable.

The cable consists of six wires including two of signal lines serial data, SDA and serial clock, SCL. The data can be transferred at rates from 100 kbit/s up to 400 kbit/s. The experiment was set up to measure crosstalk for clock frequencies in the relevant range, between 100 and 400 kHz. To investigate how the routing of the signals influenced the crosstalk, four different wiring config-

urations were tried, as illustrated in Figure 4.62. Crosstalk between the SDA and SCL lines is what should be avoided, hence, the positions of the Active and Passive wires correspond to the SCL and SDA-lines during actual data transfer. The description of the crosstalk measurement was presented in detail in [128].
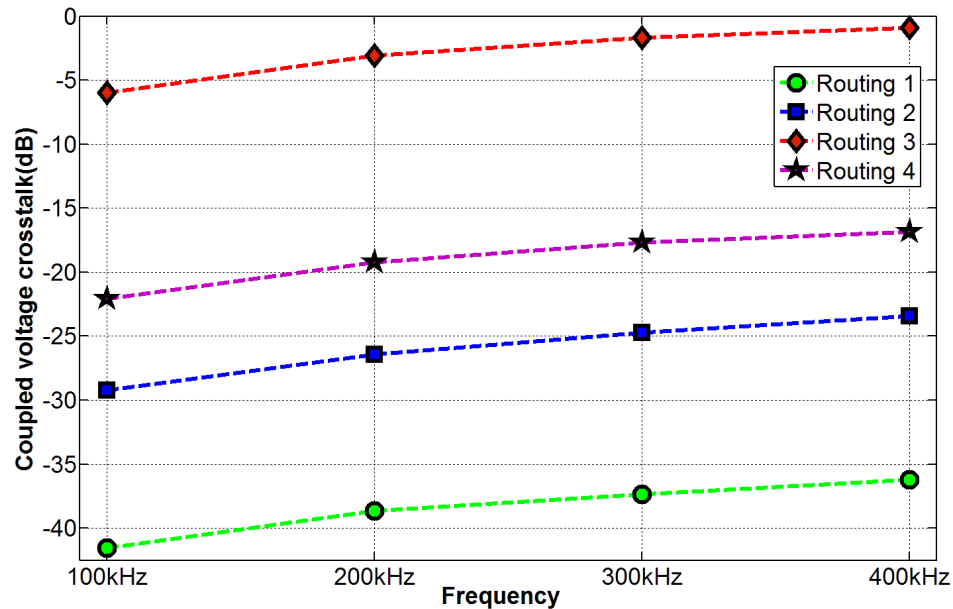
Figure 4.63: Measured crosstalk for the four routing configurations shown in Figure 62. Results measured at four frequencies corresponding to relevant transmission rates in the I^{2}C protocol. Test cables were fabricated by Best FPC, Hongkong

These results, Figure 4.63, show that the crosstalk level depends strongly on the routing of the signal lines inside the flex print cable, as the difference between the best suppression, Routing 1, and the worst, Routing 3, was approximately 40 dB. The lowest interference was found for the active and passive lines placed as far apart as possible with a ground wire between them. This result seems logical if capacitive coupling is assumed to be the main source of crosstalk. The routing configuration with the longest distance between Active and Passive lines can provide significant low crosstalk effect on signals. However, this configuaration needed to use some vias in addition and the design had no space left to tolerate them. The good routing 1 was used in the batch of flexible circuit manufactired by Dyconex AG (Bassersdorf, Switzerland). To be more realistic, additional cross-talk measurements were performed at 37°C in four days. All of test cables were used in these tests were manufactured by

Dyconex AG. The results are shown in Figure 4.64, 4.65, 4.66, 4.67, and 4.68
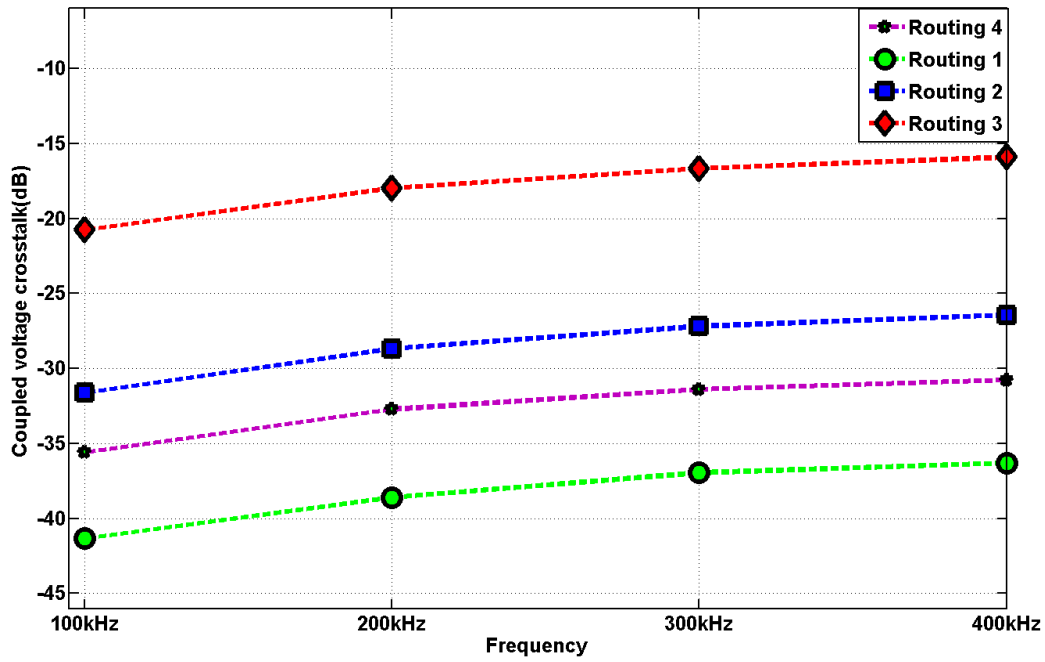
Figure 4.64: Crosstalk measurements were performed on an original cable
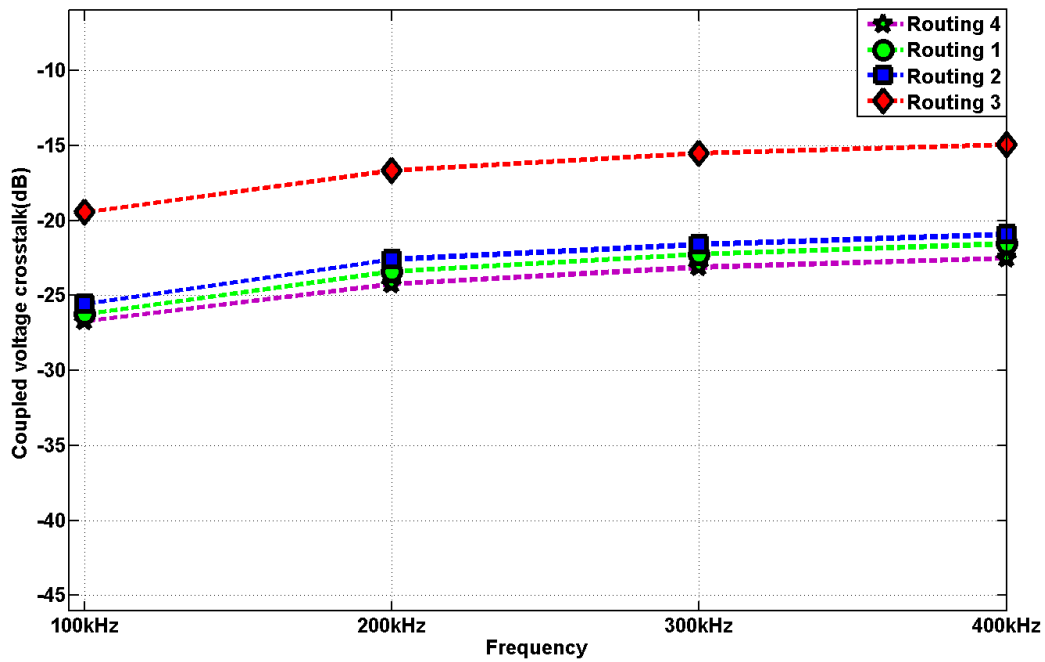
Figure 4.65: Crosstalk measurements with 1 day PBS immersion at 37°C
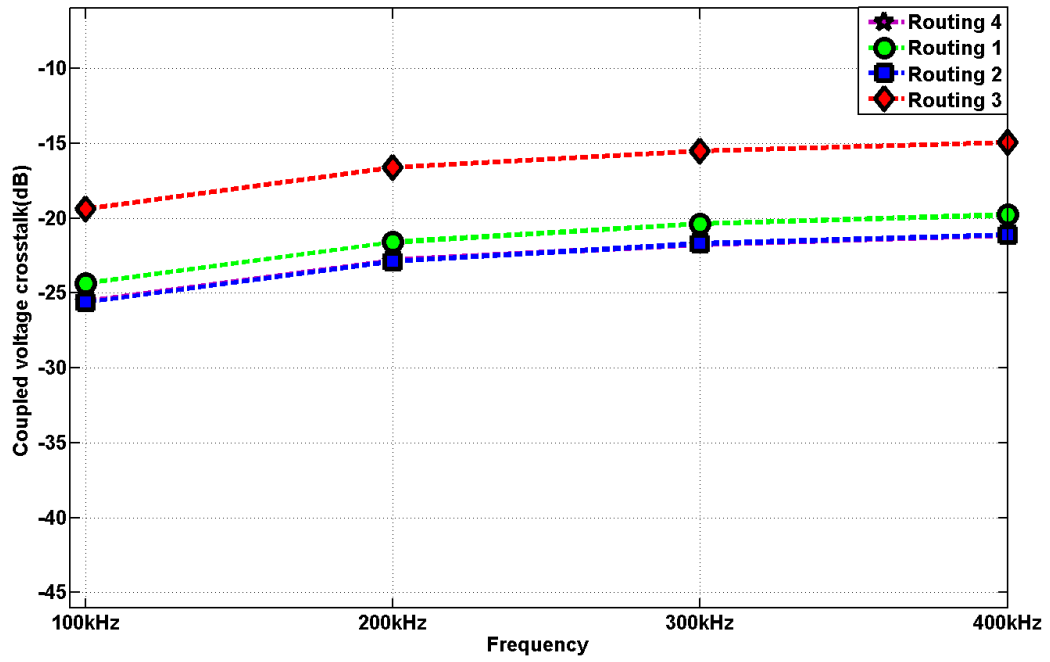
Figure 4.66: Crosstalk measurements with 2 days PBS immersion at 37°C
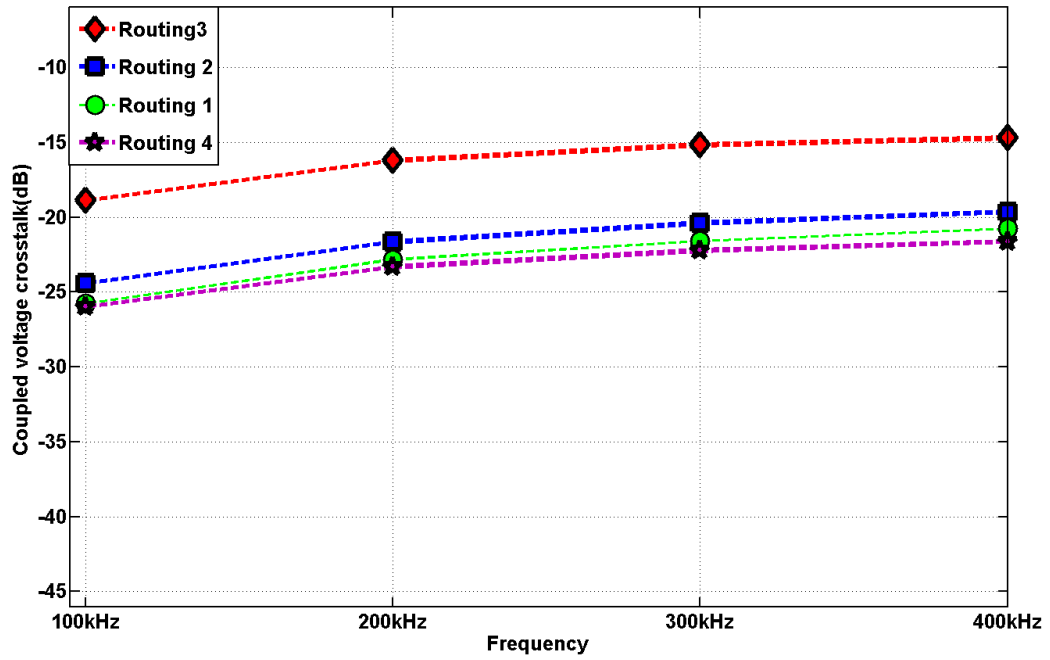
Figure 4.67: Crosstalk measurements with 3 days PBS immersion at 37°C
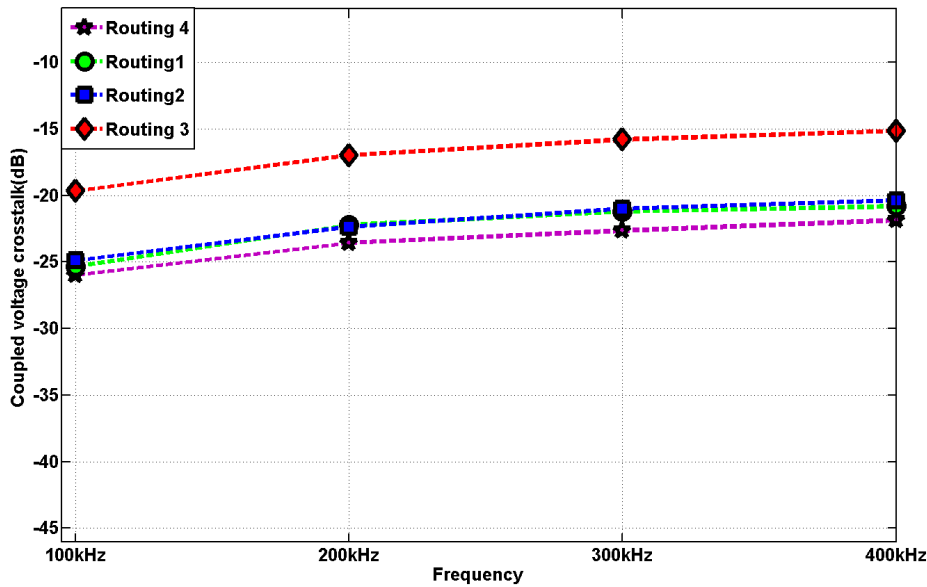
Figure 4.68: Crosstalk measurements with 4 days PBS immersion at 37°C

c) Tensile strength test

The tensile strength test was performed using a LLOYD LS100 Universal testing system (Lloyd Instruments™, Lloyd Instruments Ltd., West Sussex, UK) at room temperature. The measurement setups were shown in Figure 4.69. Figure 4.70 illustrates the result of pulling test on a complete device with metal capsule encapsulation and connector attached. The maximum pulling force and the relative extension were 12N and 37% of the device original length.

Additional tensile strength tests were performed on two flexible cable under-
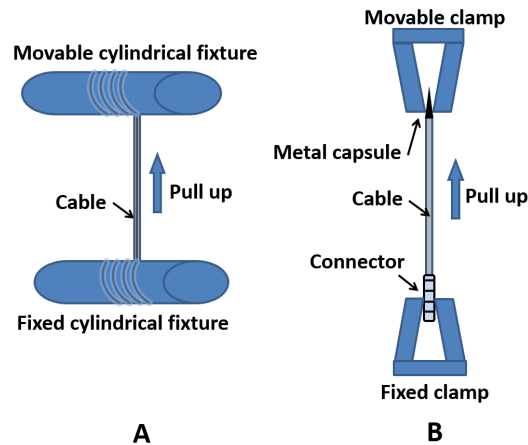
Figure 4.69: Measurement setups for tensile strength tests of complete device (B) and flexible cable (A)

went PBS immersion in 4 days at 37°C. Results are shown in Figure 4.71. The relative extension was about 34% of the test length. According to the test results were presented in Figure 4.70 and Figure 4.71, we can conclude that the test conditions (4 days, 37°C, and PBS immersion) were not susceptible of a cable degradability.
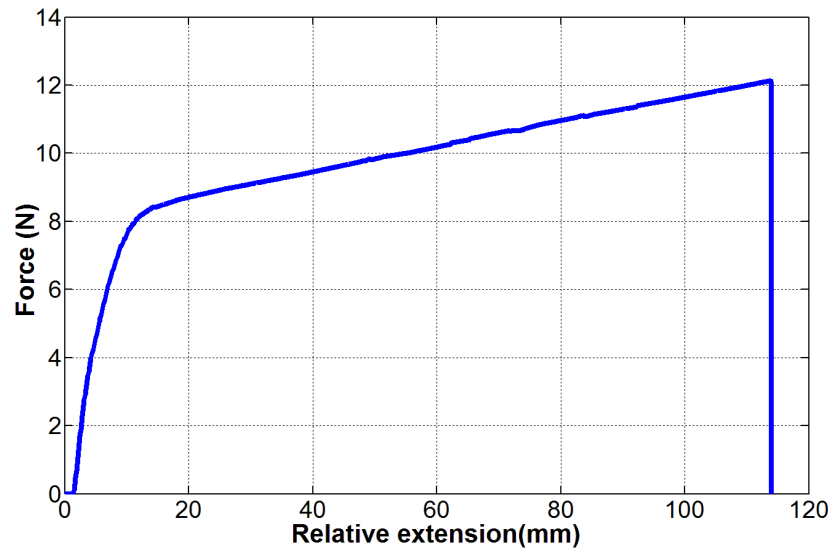
Figure 4.70: The pulling test of a complete device (cable length: 300 mm). The connector and the metal wire were clamped to the bottom and top clamp of the pull test system respectively.
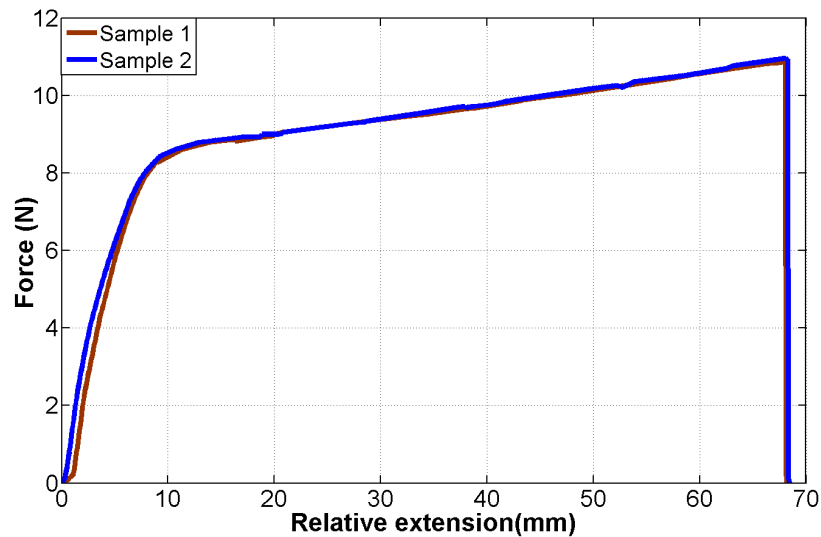
Figure 4.71: Tensile strength test results of cable underwent PBS immersion in 4 days at 37°C. The specimens length: 200 mm.

d) Insulation resistance test

Insulation resistance measurements were performed on two flexible cables without silicone insulation. The tests were carried out at 500V in 1 minute between each of 2 traces in a cable. Cables was kept in PBS at 37°C up to 8 days. The Mergger MIT430 insulation tester was used and followed the setup Figure 4.72. Measurement results are shown in Table.
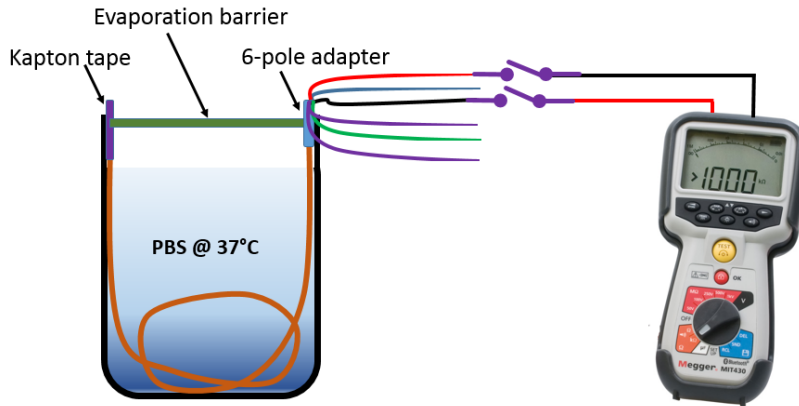
Figure 4.72: Setup for insulation resistance measurement - performed at 37°C in PBS

Table 4.8: Insulation resistance measurement results were performed on 2 flexible cable version 2-1. The tests were carried out between two traces in the cable. Measurement Unit: GΩ

Wiring #	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1-2; 1-3; 1-4; 1-5; 1-6	>100	>100	>100	>100	>100	>100	>100	>100
2-3; 2-4; 2-5; 2-6	"	"	"	"	"	"	"	"
3-4; 3-5; 3-6	"	"	"	"	"	"	"	"
4-5; 4-6	"	"	"	"	"	"	"	"
5-6	"	"	"	"	"	"	"	"

e) Device flexibility tests

The flexibility of an implantable accelerometer device is extremely important to the implantation stability, especially the heart muscle implantation. A stiff cable may push or pull the sensor out of the implanted position while the heart is moving. A flexible cable that can be bent easily, may improve implantation

stability of the device. The flexibility can be generally determined by measuring the ammount of force required to deflect the cable [131]. I have interpreted that a buckling-like force measurement of the device was mostly suitable in this application since two ends of a divice were held respectively by the heart muscle and thoracic wall. Ideally the bukling force created by the heart movement may cause cable deflection. An illustration for the test method and measurement setup are shown in Figure 4.73. The tests were performed on different
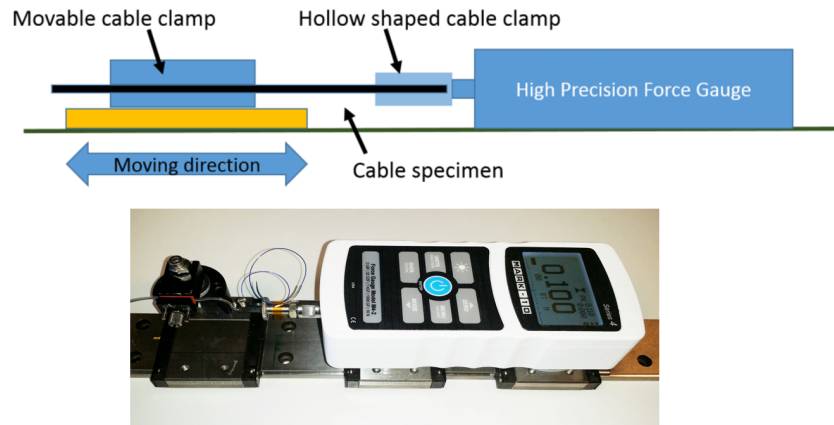
Figure 4.73: The measurement setup used to investigate axial force (buckling force) that may deflect a cable
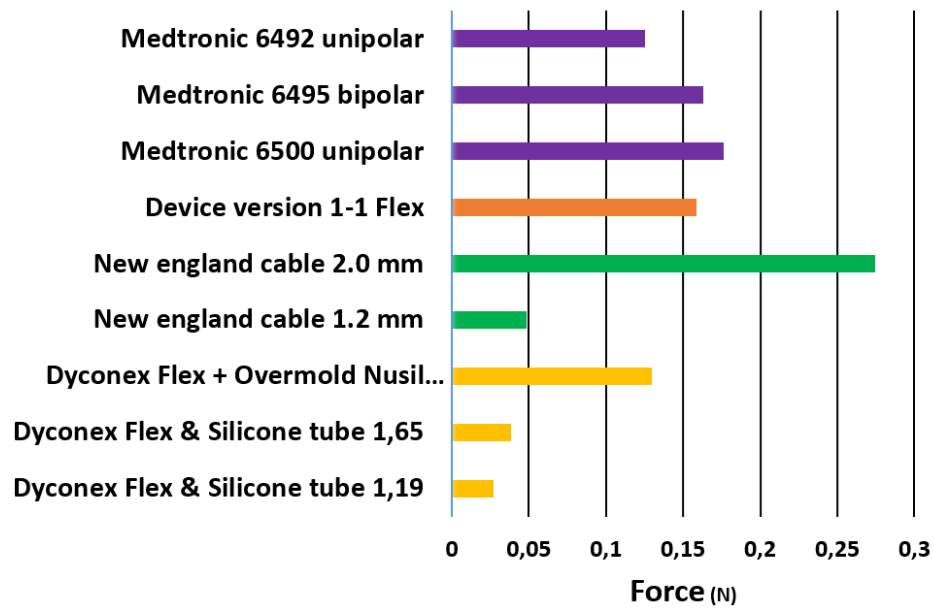
Figure 4.74: The measurement results

types of cable used in my study and the commercial temporary pacing wires.

They include three types of Medtronic temporary pacing wires, the polyimide based flexible cable demonstrated in device version 1-1; two types of round cable Ø2 mm and Ø1.2 mm were used in device version 1-3; the Dyconex flexible cable with overmolding silicone insulation presented in this study; and the Dyconex flexible cable with two types of silicone tube insulation Ø1.19 mm and Ø1.65 mm. The specimen length is 5 cm. Measurement results are shown in Figure 4.74.

4.3.1.7 Animal Trials

The animal trials were carried out in this study to demonstrate the advantages of the miniaturized heart muscle accelerometer device. The heart muscle implantable accelerometer devices, version 2-1, with two different types of cable encapsulation are demonstrated in Figure 4.75 and Figure 4.76. The structure of the device supported a simple implantation process. The devices can provide implantation stability in both open thorax and closed thorax; those assessments were done in several hours. The study also investigated the difference between closed thorax acceleration data and that of opened thorax, shown in Figure 4.77 and Figure 4.78 respectively.
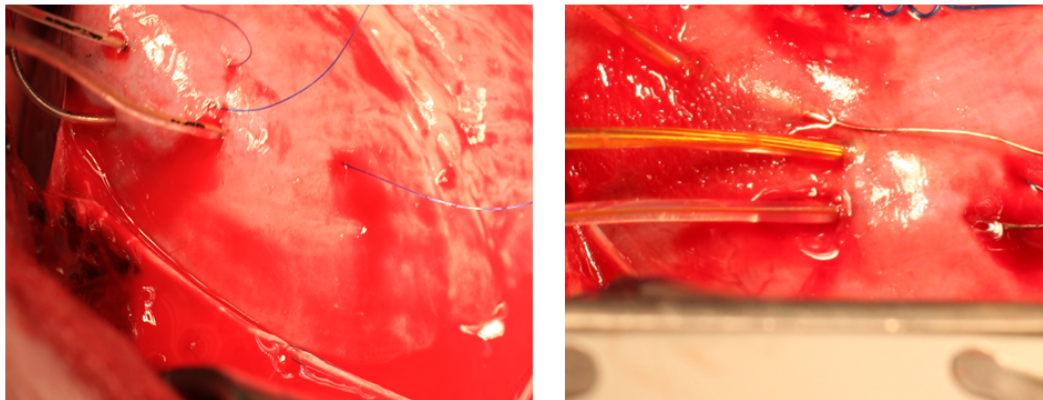
Figure 4.75: Device version 2-1 with overmold silicone encapsulation. The device was implanted and stay in place stably for both open and closed thorax assessment.

The affirmation of the additional pacing/sensing functionality was carried out. Figure 4.79 presents the recorded data when the heart was paced at 80Hz, sensing threshold was 4mV and pacing output current was 10mA. Stimulus spikes can be seen in Figure 4.79.
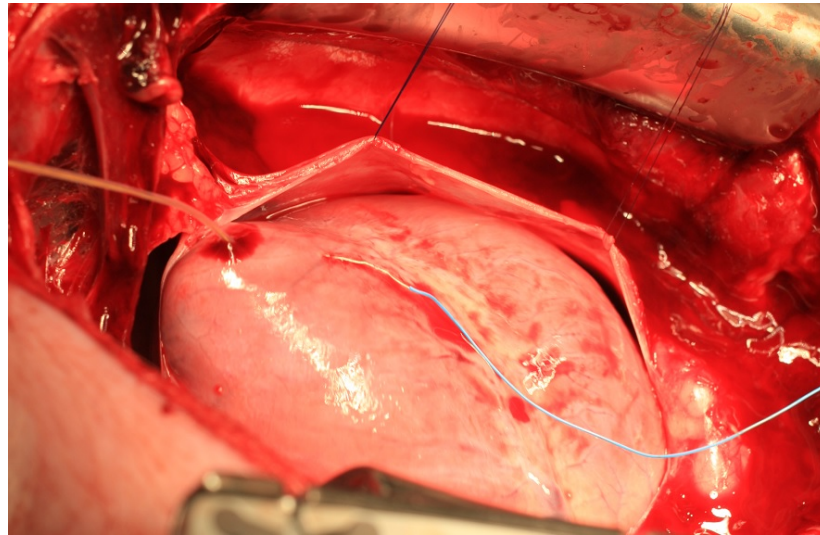
Figure 4.76: Device version 2-1 with silicone tube encapsulation. The device was implanted and stay in place stably for both open and closed thorax assessment.
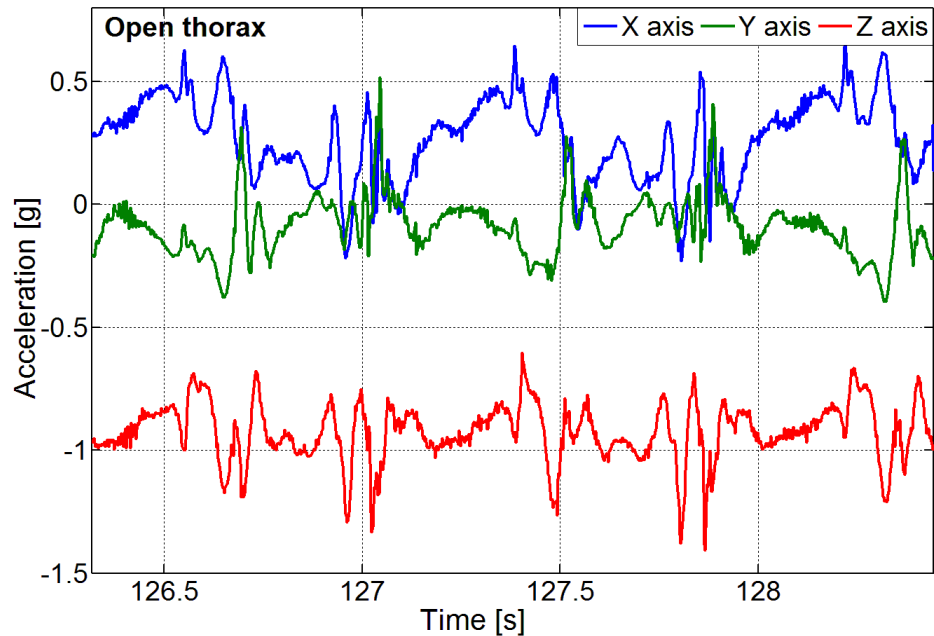
Figure 4.77: Acceleration signal recorded from myocardial implantable accelerometer device implanted on left ventricular with open thorax

Figure 4.80 presents the synchronized ECG and acceleration signals which were recorded when the heart was paced at 130Hz, sensing threshold 1mV and pacing output current 5mA. Stimulus spikes can be seen in Figure 4.80.
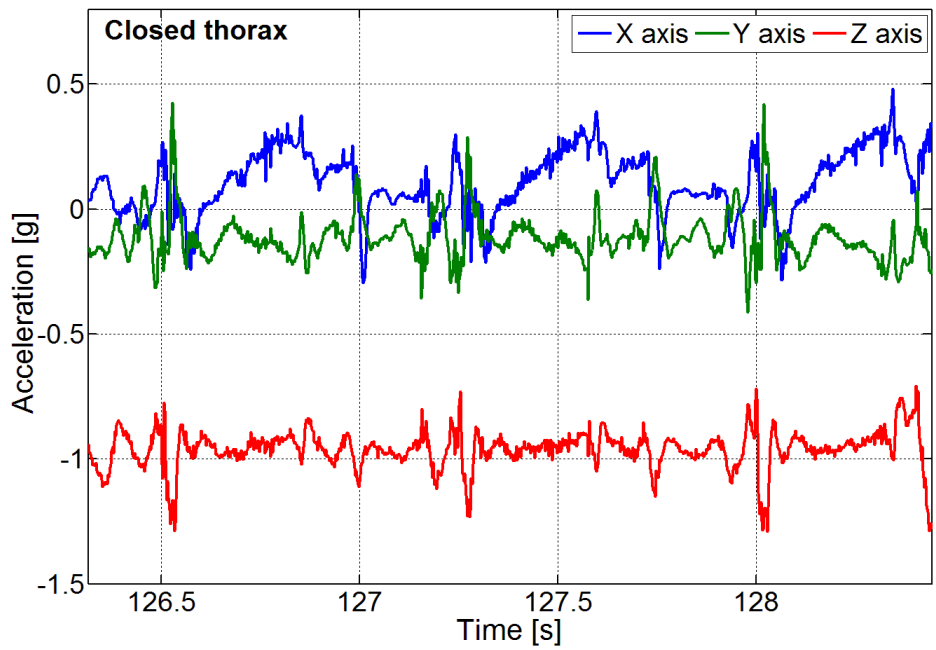
Figure 4.78: Acceleration signal recorded from myocardial implantable accelerometer device implanted on left ventricular with closed thorax
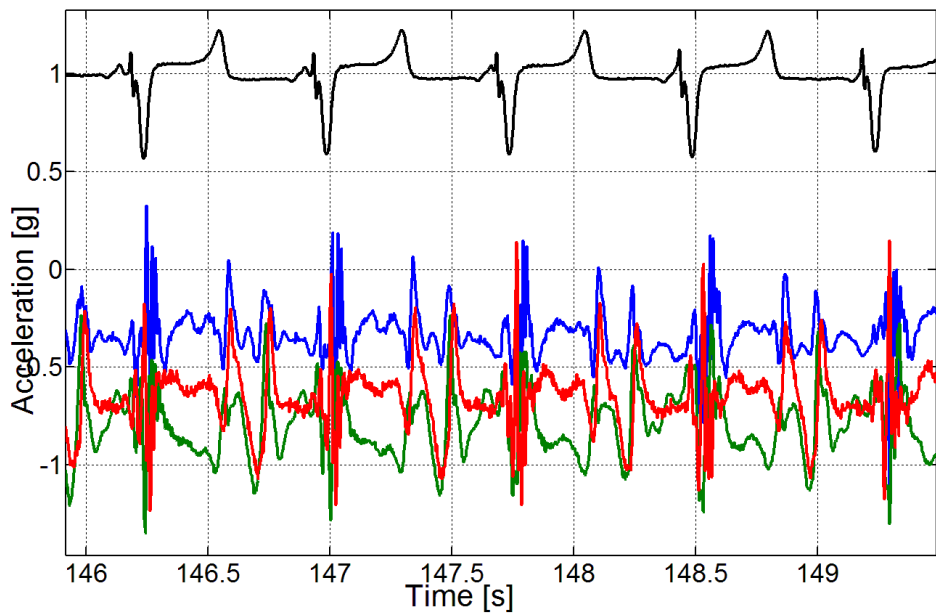
Figure 4.79: Acceleration from X, Y, Z direction and ECG are synchronized. Pacing and sensing function were carried out by two original pacing leads (Ethicon 2-0 TPW20) and pulse generator Medtronic® Model 5388 with sensing threshold 4mV, pacing current 10mA and exciting rate 80 pulses/min
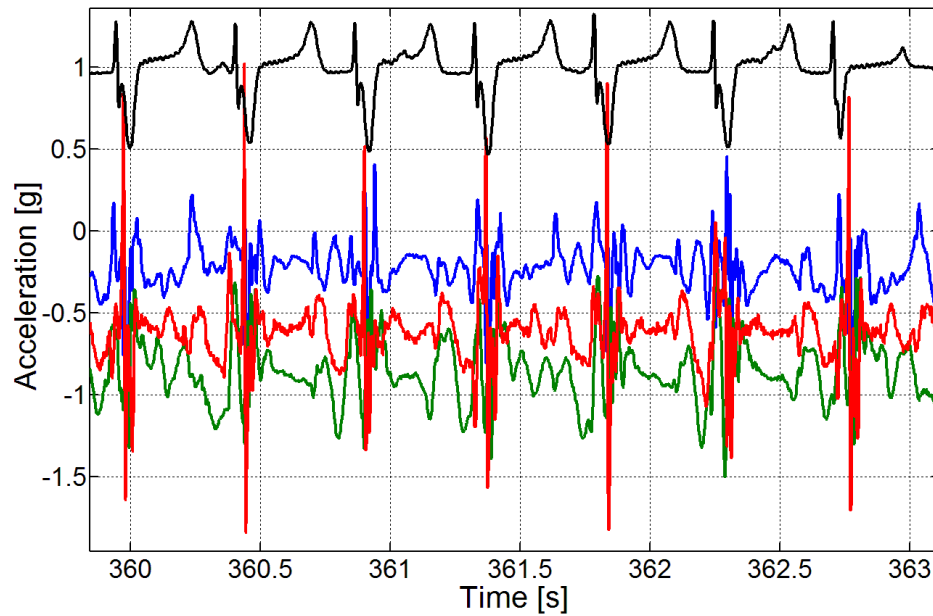
Figure 4.80: Acceleration from X, Y, Z direction and ECG are synchronized. Pacing and sensing function were carried out by one original pacing leads (Ethicon 2-0 TPW20) one accelerometer device with built-in pacing lead and pulse generator Medtronic® Model 5388 with sensing threshold 1mV, pacing current 5mA and exciting rate 130 pulses/min

4.3.1.8 Publications

Anh-Tuan Thai Nguyen, F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, O.-J. Grymyr, P. S. Halvorsen, and K. Imenes, "Development of a Multifunctional Implantable Heart Monitoring Device " Journal of Microelectronics and Electronic Packaging, JMEP Issue 4 of 2015.

F. Tjulkins, **Anh-Tuan Thai Nguyen**, A. Erik, K. Aasmundtveit, H. Nils, H. L, P. S. Halvorsen, O.-J. Grymyr, and K. Imenes, "Accelerometer-based heart monitoring device: component selection and evaluation of technology,". Journal of Medical Engineering & Physics, 2015.

4.3.2 Version 2-2

4.3.2.1 Device structure

This version of the implantable accelerometer device used the digital accelerometer which was described in section 3.3.1.2. The main structure of this version is similar to that of the device version 1-3 but with a miniaturized scale. The device structure is shown in Figure 4.81.
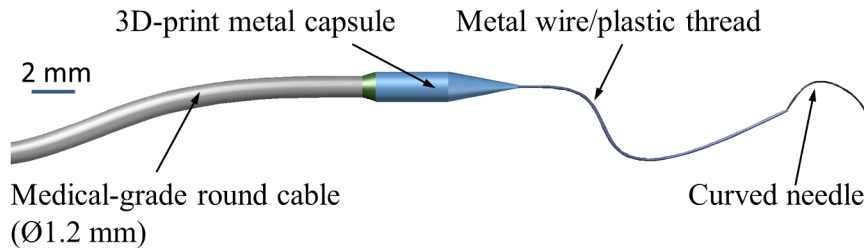
Figure 4.81: Main structure of the heart muscle implantable accelerometer device version 2-2

The overall diameter of the device is 2.0 mm and the diameter of the medical grade cable is 1.2 mm. This device would be a combination of the advantages of the medical grade round cable (Ø1.2 mm, flexibility, and high tensile strength), polyimide-based flexible substrate (biocompatible material, thin substrate, fine-pitch structure, low cost) and the metal capsule (pacing/sensing capability, rigid encapsulation, and simple implantation procedure).

4.3.2.2 Layout design

The polyimide-based flexible substrate was also chosen in this design. The substrate consists of four metal layers. The design has a narrow part that can be used as fixation structure when it is inserted inside the cable axially. The dimension of the substrate is shown in Figure 4.82.

4.3.2.3 Device assembly

The device assembly procedure was carried out firstly with the substrate anchoring. The biocompatible cyanoacrylate adhesive (Cyanolit 203TX, Panacol, Germany) can be used to provide sufficient adhesion. However the curing time
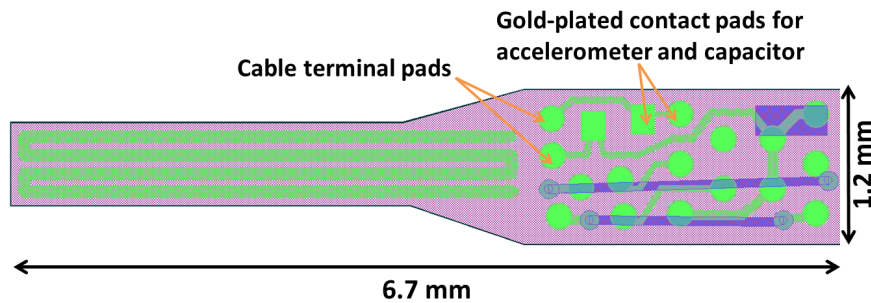
Figure 4.82: Layout of the heart muscle accelerometer device version 2-2

of this adhesive was too short to have a good cable-substrate alignment. The medical 1191-M adhesive (Dymax Europe GmbH) would be a better choice. Lead-free solder SAC (Sn96.5Ag3Cu0.5) was used to bond the wires to substrate manually; the result is shown in Figure 4.83. The cable strength member was placed beneath the substrate. The strength member is mainly responsible for the pulling strength of the device. The next step is to bond the accelerometer to the substrate manually by a hot air flow. The work was carried out at 270ºC - 290ºC, in three minutes. The manual bonding procedure requires a thin copper foil to isolate the bonded wires from the working area of hot air flow.
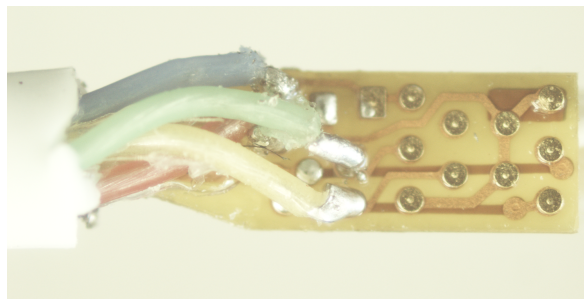
Figure 4.83: The cable is terminated to the substrate by a manual soldering procedure.

The flip chip bonding could be also used instead. The procedure consists of the following steps. The flexible substrate was positioned on the bottom heating plate of flip chip bonder FinePlacer Pico (Finetech GmbH, Germany). The accelerometer was then aligned and bonded to the substrate by the bonder. The lead-free solder ball was reflowed at 260ºC in 30 second. The substrate with bonded accelerometer was then inserted axially to the cable with a dispensed adhesive layer. The wires would be manually bonded to the substrate

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afterwards by a fine tip solder iron. Figure 4.84 illustrates a implantable accelerometer device without the metal encapsulation. Additional adhesive was applied to provide mechanical strength and enhance the electrical propertied especially electrical insulation.

1 mm

Figure 4.84: The accelerometer device version 2-2 without metal capsule.

4.3.3 Digital galvanic isolator

This study has developed a galvanic isolator for the generation of digital accelerometer devices. The work consists of defining of the overall infrastructure of the isolator, selecting suitable component, design and fabricate circuit, assembling and testing the isolator. The galvanic isolator includes the I²C data acquisition USB 2845 (National Instrument) and a high frequency digital signal isolation circuits. The requirement to ensure galvanic isolation is set by the IEC 60601-1 to ensure that the patient is isolated from the main power supply. The signal is optically transferred using a low-power bidirectional I²C isolator ISO1540 and digital isolator ISO7220 (Texas Instruments), the Insulation and safety-related specifications are listed in the Table 4.9. The bidirectional I²C signal is optically transmitted to the signal acquisition part to have two decoupled grounds for the accelerometer device and the computer system.

The reference ECG signal can also be isolated by the galvanic isolator. The 16 bits analogue to digital convertor (ADC ADS1115, Texas Instruments) was used to convert the differential input of ECG signal. The digital ECG was then optically transmitted to the data acquisition. This ADC can be used for one additional input of pressure sensor for future development. Schematic of the galvanic isolation circuit is shown in Figure 4.85. The isolated side of the isolator was powered by 9V batteries which is considered as a suitable power supply for medical applications [132] and commonly used in the pulse generator of pacing
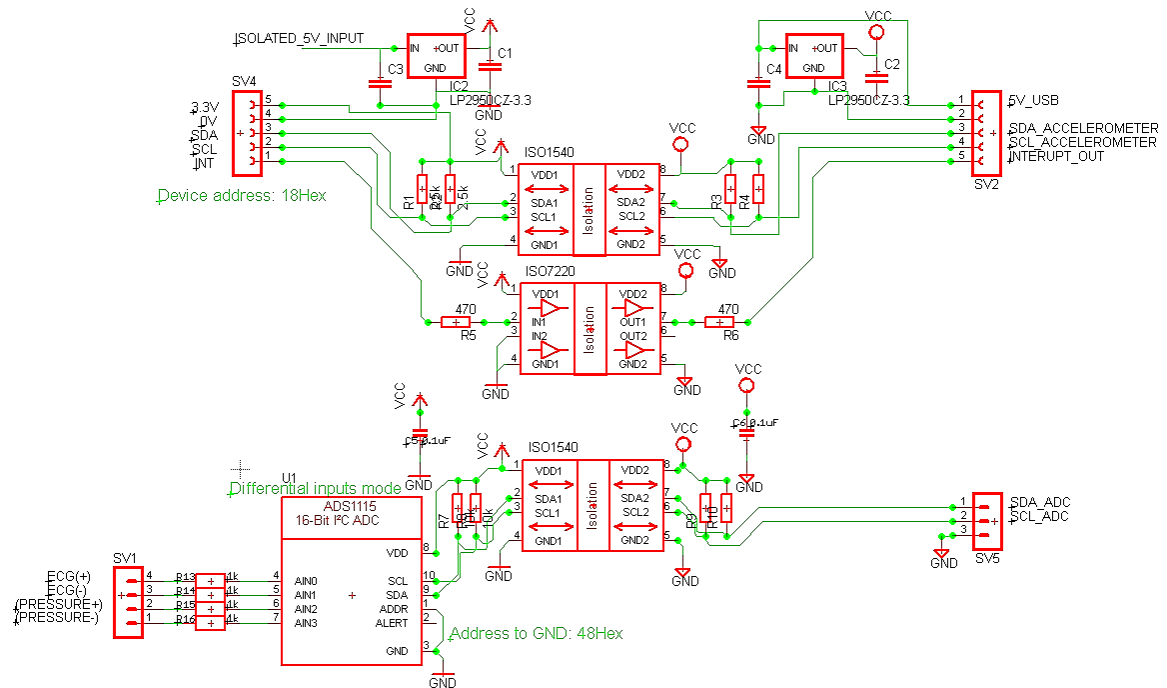
Figure 4.85: Schematic of the galvanic isolator. The isolator consists of three main groups: the accelerometer signal isolator, the interrupt signal isolator and the analogue-digital conversion isolator (for ECG and pressure signal input)

Parameter	Value	Unit	Test condition
Rated dielectric insulation voltage	4000	V	1-minute duration
Minimum air gap	4.8	mm	Shortest distance through air
Isolation	4000	V	DIN EN 60747-5-2 approved
End equipment standards			IEC 60950-1 and IEC 61010-1 approved

Table 4.9: Insulation and safety-related specifications of the low-power bidirectional I^2C isolator ISO1540 (Texas instrument)

equipment (e.g. Medtronic 5388 Dual chamber temporary pacemaker).
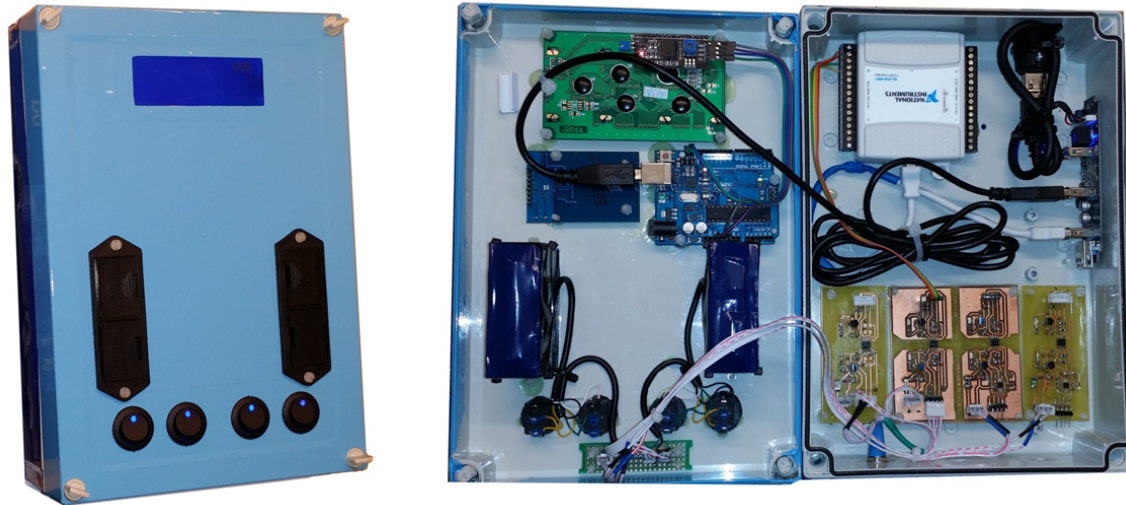
Figure 4.86: The galvanic isolator used for digital accelerometer devices. The Isolator supports two digital accelerometer devices and two ECG analogue signals input. The Isolator is powered by four 9V batteries.

4.4 Sidelined concepts: Group 3

This section introduces three different concepts of the heart muscle accelerometer device that were proposed in the project. However, it was not a feasible to develop further since one of the following crucial requirements have not been fulfilled: flexibility of the device cable, sophisticated assembly procedure, or miniaturization ability.

4.4.1 Micro-Miniature Ribbon Cable based

The device was based on the combination between the flexible substrate, mention in section 3.2.3.2, and the GORE™ Micro-Miniature Ribbon Cable (W. L. Gore & Associates, Germany). The cable cross section is shown in Figure 4.87. The cable structure was suitable for miniaturization of the accelerometer device that based on analog accelerometer CMA3000A.

The cable was encapsulated by a polyurethane tube since the polyurethane material is commonly used insulation of the permanent pacing lead [133]. This device concept was promising however we cannot have a further development. The polyurethane tube that was used could not provide sufficient flexibility for
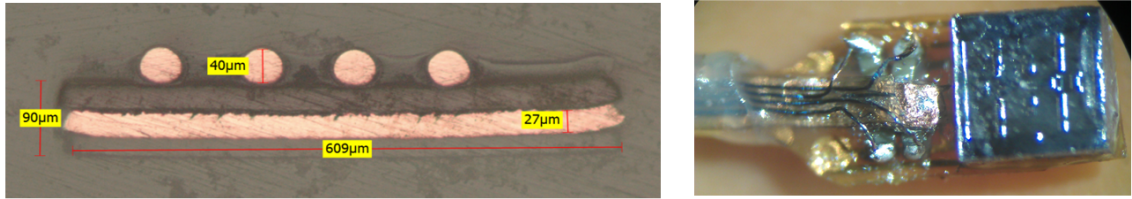
Figure 4.87: Cross section of the Gore cable (the left photo) and the interconnection between cable and flex substrate (the right photo)

heart muscle implantation. This concept has been skiped since we got dificulties in looking for a suitable material supplier. A complete device is shown in Figure 4.88.
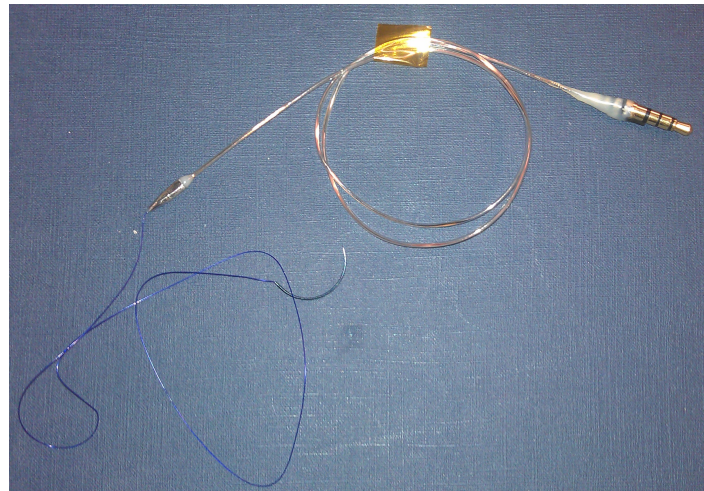
Figure 4.88: A complete prototype device with metal capsule, 5-pole round connector and polyurethane encapsulation of cable

4.4.2 Helical Micro-ribbon cable based

This concept focused on developing of the cable part of the heart muscle implantable accelerometer device which can provide a comparable tensile strength to that of the temporary pacing wire. The cable was built on a temporary pacing wire. Micro ribbon cable was demonstrated as suitable cable which can be used to develop implantable accelerometer devices [134], see dimension of the cable in Figure 4.89.

However the tensile strength of this cable was not suitable for this application.
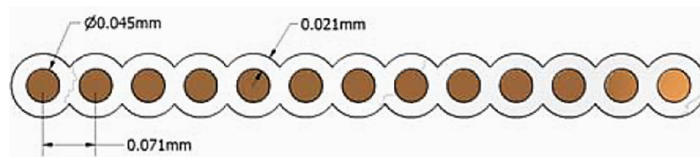
Figure 4.89: Illustration for the cross section of the micro ribbon cable, reported by Imenes et al.

To enhance the mechanical pulling strength, the micro ribbon cable was wound around a temporary pacing wire helically, see Figure 4.90. Besides, the winding with multiwound helices can provide lower mechanical stress on the cable [56].
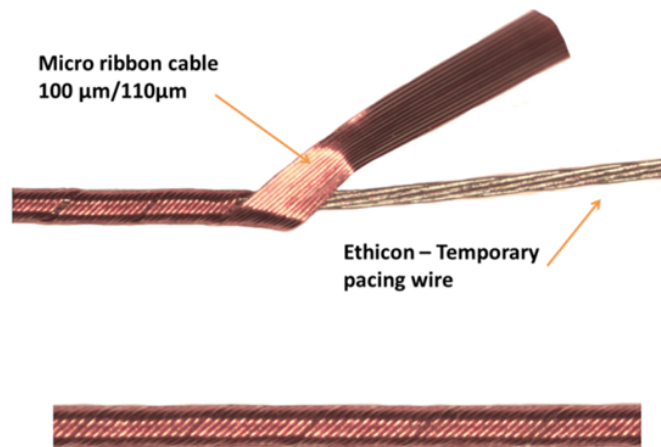
Figure 4.90: Cross section of the Gore cable (the left photo) and the interconnection between cable and flex substrate (the right photo)

The silicone molding of cable was used to provide additional insulation for the device. Figure 4.91 shows the cross section of the flexible, multi-conductor, and high tensile strength cable. Since the core of the cable is the temporary pacing wire, the integration of pacing/sensing function can be carried out straightforwardly. The device can provide identical strength to the pacing wire. However the disadvantage of the concept is the assembly procedure. This is a skill-depend and time consuming process which might not suitable for mass production of the heart muscle implantable accelerometer devices.
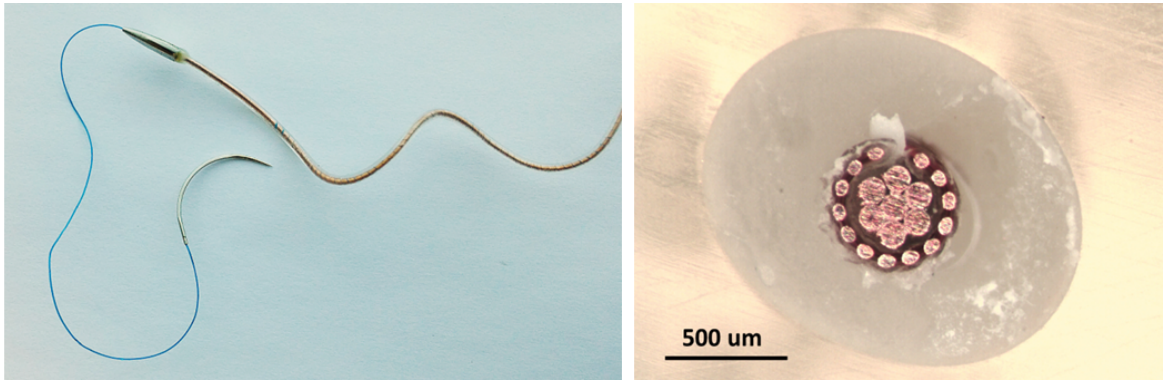
Figure 4.91: The flexible, multi-conductor, and high tensile strength cable was used in fabrication of an accelerometer device (left). The cross section of the cable (right)

4.4.3   Caramic-based substrate concept

This is the first concept was carried out in my study. The idea was simply based on the validated concept of the predecessor, the heart surface implantable accelerometer device [48]. The main structure consists of a hard substrate (alumina or silicon substrate)and a polyimide-based flexible substrate, see Figure 4.92. Both of the substrate and cable was fabricated by wet-etching processes. The work was carried out at IMST׳s lab (Buskerud and Vestfold University College). The printed-gold alumina substrate and sputtered-gold silicon wafer were used to fabricate the substrates, the properties are described in Table 4.10.The cable structure was created on the polyimide-based copper film AP7163 (DuPont USA), properties are shown in 4.11.
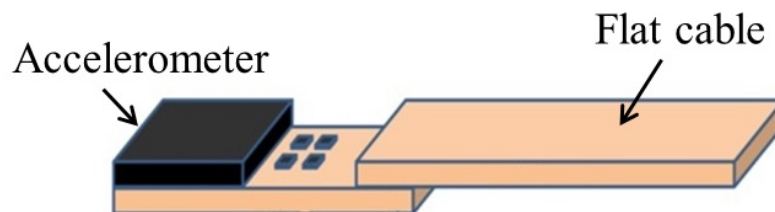
Figure 4.92: Device structure

Overall evaluations for this circuit structure
Benefit

-   Suitable for developing prototypes using IMST-lab's facilities.

-   Provide miniaturized circuit structures for this application.

Properties	Alumina substrate 99%	Silicon substrate
Substrate thickness	300 μm	500 μm
Metallization	Printed gold 2.5 μm and 5 μm	Sputtered gold 100 nm
Seeding layer	No	Ti/W

Table 4.10: Properties of the substrates

Properties	Value
Polyimide film	25 μm
Metallization	9 μm
Operating temperature	180ºC
Dielectric strength	6-7 kV/mil
Solder Float at 288ºC	Pass

Table 4.11: polyimide-based copper film property
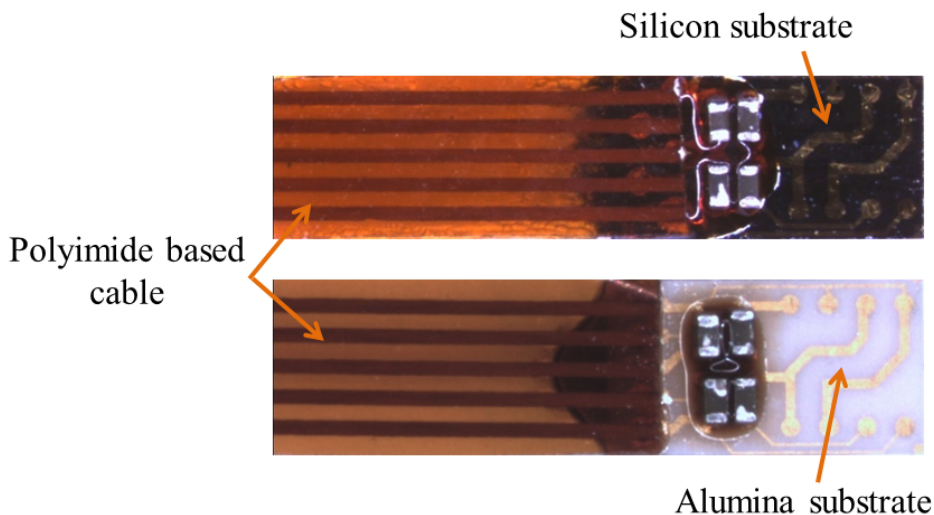
Figure 4.93: Interconnection between ceramic/silicon substrate and flexible cable were carried out by an anisotropic conductive film. The idea was reported in [103]

- Substrate has suitable properties for medical application (biocompatibility, chemical durability, low thermal expansion, rigid substrate)

- Cable has good properties (biocompatible polyimide-based material, chemical durability, popular used in biomedical field, heat resistance, dielectric strength, unaffected by radiation)
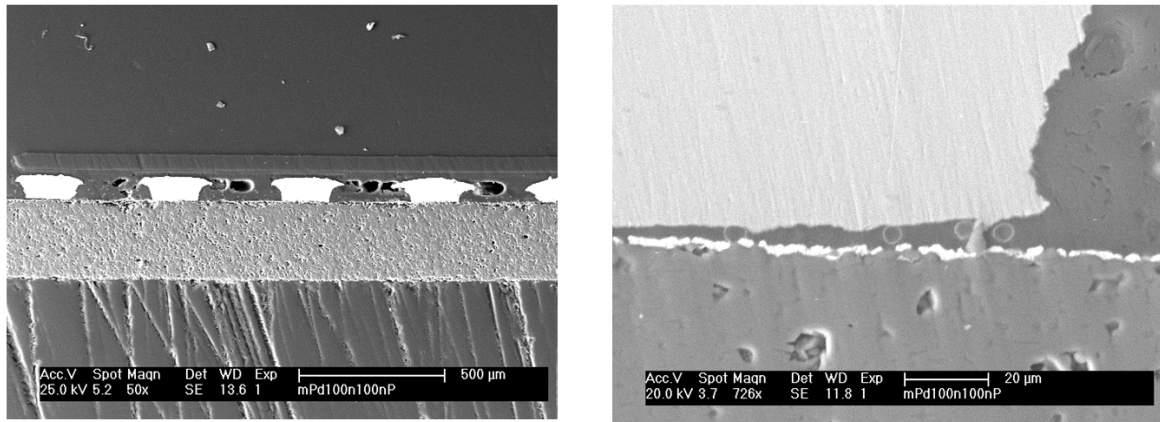
Figure 4.94: Cross section of the cable-substrate interconnection carried out by the anisotropic conductive film.

Drawback

- Expensive substrates

- Require interconnection between cable and substrate, need additional reinforcing adhesive layers.

- The device (included encapsulation) could not be smaller than 3mm in diameter due to the thickness of substrates (ceramic and silicon).

- Adhesion between printed-gold layer and alumina substrate was not good enough to withstand lead-free reflow process.

- Available facility cannot support fabrication of long cable.

4.4.3.1   Publication

K. Imenes, M. H. Andersen, **Anh-Tuan Thai Nguyen**, F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and E. Fosse, "Implantable MEMS acceleration sensor for heart monitoring : recent development and outlook," presented at the 4th Electronics System-Integration Technology Conference (ESTC 2012), Amsterdam, 2012.

Chapter 5

Conclusion

The main goal of my study was to develop circuit packaging for a short-term implantatable heart muscle accelerometer device. I has proposed and developed five versions of functioning accelerometer devices based on the literature studies on heart implantable devices , the clinical experiences from medical doctor and heart surgeons at IVS-Oslo University Hospital, the study on regulations for implantable medical devices (especially class III devices), the applicable developed circuitry in implantable bio-medical devices, and the manufacturing capability for miniaturized-biocompatible circuit. Detail properties of each version are demonstrated in Table 5. This is the first time a heart muscle implantable 3-axis accelerometer device has been studied and introduced.

The development work has been carried out by proposing ideas, fabrication of prototypes and investigation of the performances of each version. The device version 2-1 was evaluated as the most accomplished device of all devices demonstrated in my study. The device dimension is comparable to many of available transvenous pacing wires,mentioned in chapter 1 and can be implanted in right ventricular muscle. The implantation stability was very good in both open chest and closed thorax assessments (a couple of hours) that was yielded by implantation method, miniaturized dimension, capsule form, and cable flexibility. Signal recoded by the device can provide clinically meaningful information and be comparable to earlier studies on implantable accelerometer devices. The intergration of pacing/sensing function has not been thoroughly studied yet but preliminary tests proves the concept of combination between accelerometer device and pacing function with promising results. A specific characterization

study on pacing/sensing function of the device should be carried out.The study should investigate the relationship between pacing/sensing thresholds and the capsule surface area, implatation position, electrical activity of the heart, and tissue impedance.

One of the major topics in my study was standards or regulations for implantable medical devices. Much time has been spent on looking for and selecting relevant and essential requirements set by the standards. It was difficult to build a test setup or a practical measurement based on standards or regulations. My study has proposed five measurement setups in accordance with the standard requirements, some of them have, as far as I know, not ever been presented in other studies on implantable devices (e.g. leakage current test, crostalk test). Especially the leakage current test under realistic conditions with applied cyclic strain has been developed and demonstrated in the study. All the tests are valuable for both my study and other bio-medical related research.

To have a complete implantable accelerometer-based heart monitoring system, the accessor equipment have played an important role in the system development. In my study, it includes signal and power isolators that necessary for safety reasons. Two isolator modules have been developed and used for both analog and digital accelerometer devices. These galvanic isolators can provides a voltage barrier up to 4000V. Two isolated ECG feedback channels were also included for signal synchronization.

There has been an essential need to have heart muscle implantable accelerometer devices which can be used for specific clinical studied in monitoring cardiac activity. The success of this study may enable new trenches in clinical study on the heart.

My study has significantly contributed to the development of commercialized heart accelerometer sensor which has been going on with Cardiaccs AS. The knowledges with regard to the advantages and disadvantages of the developed accelerometer devices have been transfered to this company for the further production phase.

The heart muscle implantable accelerometer device is classified as medical device class III. The device can be used for short-term application up to four days. The device consists of a wire-based communication used for power and signal

transmission. Device removal can be carried out by a cable retraction. Thereby, applications concerning with similar scopes can profit from this study. For example: Study on implantable ultrasound transducers; ultrasound transducer integrated within the tip of an intravascular ultrasound catheter; study on implantable intracortical neural probe for brain implantation; study on bladder pressure implantable sensor; or implantable hearing aids sensor system. My study can be also applied to the study on implantable blood vessel pressure sensor which demands a high degree of miniatirization and flexibility.

And last but not least, the study on implantable heart sensor carried additional ethical message: "save a life".

Table 5.1: Summary of the studies

Properties	Earlier study [48]	Version 1-1	Version 1-2	Version 1-3	Version 2-1	Version 2-2
Photos						
Accelerometer dimension (mm)	5×5×1.8	2×2×0.95	2×2×0.95	2×2×0.95	1.2×1.5×0.8	1.2×1.5×0.8
Substrate material	Alumina	Polyimide	Polyimide	Polyimide	Polyimide	Polyimide
Substrate dimension (mm)	5×11.5×0.63	2.2×4.5×0.15	2.1×4.5×0.15	2.1×4.5×0.15	1.2×2.2×0.13	1.2×2.2×0.13
Cable insulation material	Silicone	Polyimide	Polyimide	Silicone	Polyimide	Polyimide
Cable cross section (mm)	Ø2.0	2.2×0.15	0.7×0.15	Ø2.0 and Ø1.2	0.7×0.13	0.7×0.13
Additional cable encapsulation	N/A	N/A	Overmolded Silicone	N/A	Overmolded Silicone or Silicone tube	No
Accelerometer encapsulation	Silicone	Silicone	Metal capsule	Metal capsule	Metal capsule	Metal capsule

Table 5.1: Summary of the studies (continued)

Properties	Earlier study [46]	Version 1-1	Version 1-2	Version 1-3	Version 2-1	Version 2-2
Maximum sensor cross section (mm)	14.5	3.2	2.8	2.8	2.0	2.0
Connector type	Lemo	Flat connector	5-pole	5-pole	5-pole	5-pole
Connector dimension (mm)	Ø14	6	Ø3.5	Ø3.5	Ø3.5	Ø3.5
Operation condition	Open thorax	Closed thorax	Closed thorax	Closed thorax	Closed thorax	Closed thorax
Implantation method	Epicardial suturing	Myocardial implantation	Myocardial implantation	Myocardial implantation	Myocardial implantation	Myocardial implantation
Implantation complexity	Standard	Complex	Fair	Fair	Simple	Simple
Implantation stability	Very good	Fair/additional supporting	Good	Fair to good	Very good	Very good
Pacing/sensing function	No	No	Yes	Yes	Yes	Yes
Temperature monitoring	N/A	N/A	N/A	N/A	Yes	Yes

Table 5.1: Summary of the studies (continued)

Properties	Earlier study [46]	Version 1-1	Version 1-2	Version 1-3	Version 2-1	Version 2-2
Device removal	Before closing chest	Pulling out after closing chest	Pulling out after closing chest	Pulling out after closing chest	Pulling out after closing chest	Pulling out after closing chest
Leakage current (μA)	<10	<10	<10	<10	<10	<10
Pulling strength (N)	20 (cable)	40	10	20/100 (Cable Ø2.0/ Ø1.2)	12	12
Flexibility (Buckling force (N))	0.28	0.16	0.13	(0.28/0.05) (Cable Ø2.0/Ø1.2))	0.027	0.05
Assembly procedure	Complex	Simple	Simple	Complex	Simple	Complex
Sterilization (suggestion)	EtO	EtO	EtO	EtO	EtO	EtO
Productivity	Fair	Good	Good	Fair	Very good	Fair
Future development	N/A	Yes	Yes	Yes	Highly recommend	Yes

Chapter 6

Summary of Papers and Outlook

6.1   Summary of enclosed papers

P1: **Anh-Tuan Thai Nguyen**, *F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, Miniaturization of package for an implantable heart monitoring device, Journal of Microsystem Technologies, DOI: 10.1007/s00542-014-2216-6, ISSN: 1432-1858.*

A heart muscle accelerometer device used for monitoring heart activity is presented in this paper. It is a device built around a commercially available MEMS accelerometer (Murata CMA-3000), packaged for use inside the body. An integration of polyimide-based substrate and cable has been proposed as a unique flexible printed circuit system with high aspect ratio of dimensions (2.2 mm/500 mm - width/length). Procedures of design, fabrication, assembly and testing of the prototypes are included in detail, obtaining a design with diameter 3 mm. This study also suggested specific experimental set-ups for qualifying essential safety requirements based on the standards and regulations for implantable devices. Several compliance tests have been done successfully and achieved very promising results: The measured leakage currents are 1000 times below the maximum allowed limit, insulation resistance between the conductors is well within the safety limits, the tensile strength is suitable for implantable devices, flexural endurance is good, and the performance was maintained after a 7-days soak test. The prototype has been used in animal trials, giving high-quality acceleration signals.

P2*: **Anh-Tuan Thai Nguyen**; Fjodors Tjulkins; K. E. Aasmundtveit; Nils Hoivik; Lars Hoff, Ole-Johannes Grymyr, Per Steinar Halvorsen and Kristin Imenes, New Approach in Development of a Multifunctional Implantable Heart Monitoring Device, Journal of Microelectronics and Electronic Packaging, JMEP Issue 4 of 2015.*

In this study, a new approach in making a heart muscle implantable accelerometer sensor is described. An overall diameter of 2 mm is achieved by encapsulating the latest miniaturized 3-axis MEMS accelerometer (similar to the BMA355) from Bosch Sensortec, Germany. The design of the sensor features a simple implantation procedure which aims to be similar to the medical procedure of temporary pacing wire attachment. The device remained in place in the heart muscle without the need for additional attachment or fixation. The essential clinical requirements for implantable devices, especially heart implantable sensors, are also taken into account in this study. Additional safety enhancement is realized by adding a galvanic isolator which ensures electrical safety.

P3*: **Anh-Tuan Thai Nguyen**, F. Tjulkins, K. E. Aasmundtveit, N. Hoivik, L. Hoff, and K. Imenes, Packaging of a Multifunctional Implantable Heart Monitoring Device, In preparation for submission*

This paper describes recent improvements of a myocardial accelerometer device, which is based on the analog acceleometer Murata CMA3000. The device is to be used for patients undergoing coronary bypass graft surgery. The improved device can reduce the complexity of implantation experienced with the former generation of device. A built-in function enabling temporary pacing was also integrated. Besides being an implantable accelerometer sensor, the device can pace the heart and sense the electrical signals when connected to an external pulse generator. The packaging method introduced in this study provides improved fixation in the heart muscle, extra functionality and flexibility. A new medical grade cable was introduced in this study, which can provide higher tensile strength and better flexibility than the accelerometer device version 1-1. Compliance tests were carried out to investigate the essential requirements set by the IEC-60601 for implantable medical devices. Compared to the earlier studies, the new device can provide lower leakage current level and higher tensile strength.

P4: **Anh-Tuan Thai Nguyen**, *F. Tjulkins, K. Aasmundtveit, H. Nils, L. Hoff, and I. Kristin, Miniaturization of package for an implantable heart monitoring device, Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP), 2013 Symposium on, p. 6, 2013, ISBN 978-2-35500-028-7.*

This study has been presented at DTIP 2013 conference. A very first myocardial (heart muscle) implantable acceleration prototype-device, using a commercial MEMS accelerometer (Murata CMA3000) is presented in this paper. Procedures of design, fabrication, assembly and testing of the prototype are included in detail. Preliminary results of tests based on the regulations for implantable devices have been done successfully. The paper concludes with directions for improving the device.

P5: **Anh-Tuan Thai Nguyen**, *Knut Aasmundtveit, Nils Hoivik, Lars Hoff, Per Steinar Halvorsen, Ole-Johannes Grymyr and Kristin Imenes, Packaging of Multifunctional Implantable Heart Monitoring Device, Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP) 2014, ISBN 978-2-35500-028-7.*

This paper was presented at DTIP 2014 conference. An improvement of a myocardial accelerometer device based on the analog accelerometer CMA3000 was described. The device package was built on a medical grade cable, flexible substrate and metal capsule encapsulation. The improved device can reduce the complexity of implantation experienced with the former generation of sensors. A built-in function enabling temporary pacing was also integrated. The device can pace the heart and sense the electrical signals when connected to an external pulse generator. Compliance tests for implantable medical device were carried out in accordance with the requirements set by the IEC-60601.

6.2   Outlook

Development of implantable medical device, especially heart implantable device, is a sophisticated process; many aspects have to be taken into account. Several approaches in development of a heart muscle implantable accelerometer device have been demonstrated in this study. The work has achieved its main goals. However, it has been so early to tell about a final product or a CE mark application perhaps. The following section proposes potential trends of

study which can be considered to improve performance of the current heart muscle implantable accelerometer devices.

(I) Device version 2-1 and 2-2 can be improved to have comparable tensile strength to a standard temporary pacing wire. Additional strength member can be a properly choice. However, the properties of the strength member have to be considered to maintain the necessary flexibility of the device.

(II) An optimization of using adhesives was not especially focused on in this study. There has been a need to characterize the performance of different adhesives used in the device with regards to the mechanical properties, insulation properties, adhesion, biocompatibility, curing time, and degradable issue.

(III) Injection molding method can be suitable for making the insulation joint between the round connector and the cable. The method is suitable for mass production of the devices since the cost can properly be reduced.

(IV) A specific study on the additional pacing/sensing function of a heart muscle implantable accelerometer device should be carried out. Quality and performance of the pacing/sensing function depend on so many variables (e. g. the surface area of the metal capsule, impedance of the system, pulse generator, implantation position, and other clinical parameters).

(V) The galvanic isolator may need additional improvement (e.g. output current threshold controller) to enhance the safety.

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P1

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P2

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P3

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