Myocardial function and 3D motion analysis using a three-axis accelerometer during cardiac surgery
© Ole-Johannes Holm Nielsen Grymyr, 2017

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List of papers

This thesis is based on the following papers, which will be referred to by their Roman numerals:


### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>3D</td>
<td>Three dimensions / three-axis</td>
</tr>
<tr>
<td>$3D \ V_{\text{ave}}$</td>
<td>Accelerometer velocity along the 3D reference vector at aortic valve closure</td>
</tr>
<tr>
<td>$3D \ V_{\text{sys}}$</td>
<td>Peak accelerometer systolic velocity along the 3D reference vector within the first 150 ms after R-peak on ECG</td>
</tr>
<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
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<tr>
<td>CX</td>
<td>Circumflex coronary artery</td>
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<tr>
<td>$dP/dt_{\text{max}}$</td>
<td>The positive time derivative of the left ventricular systolic pressure</td>
</tr>
<tr>
<td>$dP/dt_{\text{min}}$</td>
<td>The negative time derivative of the left ventricular systolic pressure</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>LAD</td>
<td>Left anterior descending artery</td>
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<td>LVSWI</td>
<td>Left ventricular stroke work index</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NYHA class</td>
<td>New York Heart Association</td>
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<tr>
<td>$S'$</td>
<td>Peak systolic longitudinal velocity by echocardiography</td>
</tr>
<tr>
<td>$V_{\text{sys}}$</td>
<td>Peak accelerometer systolic velocity within the first 150 ms after R-peak in ECG</td>
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1. Introduction

The population undergoing heart surgery in Norway has changed dramatically in the past two decades. Percutaneous coronary interventions already exceeded coronary artery bypass grafting in 1995. As coronary artery bypass grafting has declined, valve surgery has increased, and there has been a trend towards more complex surgery with combined procedures of coronary artery bypass grafting and valve repair. Surgery in patients > 80 years has increased, and there is a trend towards an increasing severity score. Transcatheter aortic valve implantation has been offered to patients who are conventionally deemed inoperable, and the number of procedures in Norway has increased from 21 in 2008 to 258 in 2014. Indications for transcatheter aortic valve implantation may change and replace open aortic valve replacement (AVR) in selected groups.

Myocardial dysfunction frequently occurs after cardiac surgery and may lead to an impaired pumping capacity and increased risk of complications. A prolonged aortic cross-clamp time and the development of intraoperative myocardial infarction are independent risk factors for postoperative heart failure after surgery for isolated aortic stenosis, and patients with low cardiac output syndrome have a high risk of postoperative heart failure and mortality. Early postoperative heart failure after AVR and coronary artery bypass grafting are associated with 5-fold and 20-fold increases in 30-day mortality, respectively. Furthermore, perioperative myocardial ischaemia is associated with high morbidity and mortality. Cardiopulmonary bypass, aortic clamping and cold cardiac arrest potentiate the risk of ischaemia, necessitating strategies for cardioprotection. Although surgery is performed in older and sicker patients and increasing age and a low ejection fraction are independent predictors for postoperative myocardial dysfunction, intraoperative haemodynamic monitoring has showed little change. During standard open-chest surgery, electrocardiogram (ECG) and invasive venous and arterial pressures represent the standard tools for haemodynamic monitoring in the perioperative period. Expanded monitoring is maintained by echocardiography, but is mainly used after valve surgery to ensure a patent valve. Moreover, the echocardiography image quality is dependent on the operator. Therefore, there is a need for continuous methods to evaluate cardiac performance.
1.1 Monitoring cardiac surgery
The majority of methods used for cardiac monitoring in heart surgery are indirect measures of myocardial function, such as invasive arterial and venous pressures, which reflect cardiac output and preload, respectively. However, as both measures are dependent on peripheral resistance and myocardial function, they are not optimal for the assessment of regional and global contractility. Expanded haemodynamic monitoring using pulmonary artery catheter- or transthoracic thermodilution/pulse contour-assessment techniques may provide additional global cardiovascular information by measuring the cardiac output. Still, impaired regional myocardial function may not be discovered.\textsuperscript{10–12}

Other techniques may be used as contractility measures, such as the positive time derivative of the left ventricular systolic pressure \((dP/dt_{\text{max}})\), although this measure is not extensively used in patients because it requires a pressure line in the ventricle and thus can be potentially harmful. ECG assesses the electrical output from the cardiac conductive system and the myocardium, and it does not reflect contractility. ST-segment analysis by multi-lead ECG is routinely used for detection of intraoperative myocardial ischaemia, but the sensitivity and specificity of this technique may be low.\textsuperscript{13,14} However, the sensitivity can be increased by the addition of precordial leads.\textsuperscript{15} The 12-lead ECG is impractical in cardiac surgery.

Imaging techniques have optimized the assessment of myocardial function. Echocardiography and magnetic resonance imaging (MRI) are both non-invasive and provide structural and functional assessments of cardiac volumes, pressures, gradients and motion. The postoperative use of echocardiography is associated with a large resource demand, and although it provides a bedside imaging technique of potentially high quality, it is impractical for continuous surveillance because the investigation is intermittent and requires skilled examiners and interpretation. Echocardiography-based analyses of myocardial velocities and deformations are complicated and must be performed off-line. MRI provides superior information on cardiac structure and function, but it is not suitable for perioperative use.

1.2 Cardiac motion
The function of the left ventricle is to supply the effector organs of the body with oxygenated blood. Function is dependent on the preload, afterload, contractility and heart
rhythm. The left ventricular myocardium consists of helical myofibres in chirality, like counterdirectional orientated fingers on superimposed human hands, where right-handed longitudinal muscle fibres in the subendocardium gradually shift into a left-handed geometry in the subepicardium. In the mid-wall, circumferential fibres predominate.16 Forming a spiral, the helix angle of the myofibres therefore continuously shifts from the endocardium to the epicardium. The mid-wall fibres that are perpendicular to the long axis thus form a sort of “equator of the heart”.17 The counterdirectional movements of the inner and outer muscle fibres produce expulsion and suction forces.16 During muscle depolarization, the right-handed oriented subendocardial fibres are first activated, initiating a brief apical clockwise movement in the isovolumic contraction phase before the left-handed subepicardial fibres with the greater load arm turns the contraction counter-clockwise during ejection.16 As illustrated in Figure 1, apical and basal contraction and rotation directions are opposite because they twist around an equatorial plane.17 Circumferential and longitudinal shortening dominate systolic contraction, pulling the base of the left ventricle towards the apex. Radial reduction, which is considered minor,18 is the result of the circumferential and longitudinal motions. The main radial effect in the transversal plane is wall thickening, which reduces the ventricular cavity volume.

The right ventricle has a thin free wall that is more or less “wrapped” around the left ventricle. Ejection of the right ventricle is dependent on longitudinal shortening, inward movement of the free wall and bulging of the interventricular septum into the right ventricle during left ventricular contraction.19 Due to few well-defined anatomical landmarks, an unfavourable location within the chest and complex motion mechanics, the use of multimodality rather than a single imaging modality is recommended for a comprehensive assessment of right ventricular function.20 However, this approach is not feasible in a perioperative setting, and there is a need for alternative methods to monitor right ventricular contractility.
1.3 Microsensors in cardiac function monitoring

The most widely used experimental method to assess cardiac function is ultrasonic crystals. Using this technique, ventricular volumes and myocardial deformation can be monitored in real-time. However, the clinical utility of the method is limited by its invasiveness because the insertion of multiple crystals into the myocardium is needed to obtain accurate measurements. An alternative is to use an epicardially attached miniaturized ultrasound transducer.\textsuperscript{21} This technique produces continuous real-time M-mode images, and wall thickening and thinning velocities can be calculated. This method can be used to detect ischaemia with high sensitivity and specificity and also allows an automated beat-to-beat analysis.\textsuperscript{22–24} One limitation of this method is that the current device must be sutured to the epicardium and is thus not suitable for postoperative use. Other technologies under clinical investigation for myocardial ischaemia detection include CO\textsubscript{2} sensors and myocardial microdialysis.\textsuperscript{25} However, these sensors cannot be used to detect global changes in cardiac function. Accelerometers, a type of motion sensor, have been used for both regional and global cardiac function assessment\textsuperscript{26} and thus provide an advantage for clinical use in comparison to other techniques. The advantages of accelerometers include their small size and minimal energy requirements. In this thesis, the use of accelerometers placed epicardially was evaluated.

1.4 Use of accelerometers in medicine

Accelerometers are motion sensors, which include a mass of piezoelectric material that changes its voltage when it moves or accelerates. These sensors were originally developed for navigation purposes in the space and aviation industry,\textsuperscript{27} but are now incorporated into a variety of consumer devices such as pedometers, cameras and smartphones. In biomechanics, their use varies from the diagnosis of sleep disorders to monitoring of daily activity in malnourished children.\textsuperscript{28,29}

In cardiac monitoring, early studies investigating accelerometer technology focused on low-level heart sounds not heard by auscultation to detect coronary artery stenosis.\textsuperscript{30,31} This technology has also been used to identify second heart sounds produced by aortic valve closure.\textsuperscript{32} Peak endocardial acceleration corresponds to the first heart sound and correlates
with ventricular contractility.\textsuperscript{33–35} Peak systolic acceleration obtained from chest accelerations measured by an accelerometer on the sternum has been shown to reflect cardiac function during dobutamine stress tests\textsuperscript{36} and during hypovolemia.\textsuperscript{37} Chest accelerations have also been used to determine the duration of systole and diastole by identifying aortic and mitral valve closures.\textsuperscript{38,39} An accelerometer placed in the right ventricle using the catheter technique has been shown to detect acute ischaemia in patients.\textsuperscript{40} The accelerometer has also been used for ballistocardiography\textsuperscript{41} and in microgravity during spaceflight.\textsuperscript{42} This technique measures the reaction forces of the body to the cardiac ejection of blood, e.g., by measuring the recoil of a person’s body on a weight, and it has been used to trend changes in cardiac output and contractility.\textsuperscript{41}

Clinically, accelerometers are most commonly used in pacemakers such as heart rate adaptors,\textsuperscript{43} to assess myocardial contractility\textsuperscript{34} and also in biventricular pacemaker systems for the treatment of heart failure.\textsuperscript{44} Our research group has focused on the use of epicardially placed accelerometers to monitor ventricular function and detect myocardial ischaemia. The ultimate goal is to develop a device that can serve as a combined temporary pacemaker electrode and accelerometer sensor for monitoring perioperative global and regional cardiac function.

1.5 Previous work with epicardial accelerometer monitoring

A three-axis (3D) accelerometer was developed in 2004 for epicardial use by combining two two-axis accelerometers.\textsuperscript{45} In experimental studies, it was demonstrated that the sensor provided detailed information for heart wall motion and function,\textsuperscript{26,46} and it could also detect myocardial ischaemia with high sensitivity and specificity.\textsuperscript{26,46–48} Combining ECG and accelerometer signals allowed the identification of ventricular motion within the different phases of the cardiac cycle,\textsuperscript{40,48} similar to ventricular function assessment with tissue Doppler imaging and strain analysis by echocardiography.\textsuperscript{49} Using the accelerometer, heart motion can be expressed by acceleration, velocity or displacement.\textsuperscript{45,50} One benefit of this technology is that it provides a real-time signal that enables automated beat-to-beat analysis. In addition, using a 3D-accelerometer, heart wall motions can be assessed in three
dimensions simultaneously. If the accelerometer axes are aligned correctly, longitudinal, circumferential and radial motions can be assessed.\textsuperscript{26,51}

In the left ventricular apical region, the greatest motion change was detected in the circumferential direction during LAD occlusion and myocardial ischaemia. The most pronounced effects of ischaemia occurred in the isovolumic phases, in which most of the pressure changes occur. An ischaemic ventricular segment behaves like a passive structure and shortens less or even stretches during early systole.\textsuperscript{52} Furthermore, systolic contraction is delayed and persists into the diastolic phase as a so-called post-systolic contraction,\textsuperscript{53} and these changes can be detected with an accelerometer.

An automated algorithm for real-time detection of ischaemia has been developed.\textsuperscript{54} This algorithm uses both the ECG and the accelerometer signal to automatically measure peak epicardial velocity in early systole (time interval of 150 ms after the R-peak in the ECG signal).

1.6 Unsolved questions with epicardial accelerometer monitoring

1.6.1 Data analysis
Previous studies using this technology have focused on single-axis analysis, in which the orientation of the sensor on the ventricular wall must be taken into account. A prerequisite for the use of single-axis analysis as an indicator of cardiac performance is extensive knowledge of the contraction patterns within different regions of the heart. However, the need for precise alignment with the cardiac contraction coordinates of the different left ventricular regions may limit potential clinical use of the accelerometer. Surgeons may also consider it impractical and cumbersome to use this technology on a daily basis, and suturing the sensor to the epicardial surface bears the risk of unintended bleeding and limits the technology to intraoperative use. However, integration of an accelerometer in a pacemaker wire, which is already routinely used, may permit postoperative use. Determination of the orientation of the individual sensor axes on such a wire is not feasible because it may rotate after implantation. One solution to these challenges may be to use the overall 3D data from the sensor to automatically determine a 3D motion vector that points in the direction of maximal systolic contraction.
1.6.2 Measurement of global cardiac function with different sensor locations
As previously noted, circumferential motion is dominant in the left ventricular apical region, whereas longitudinal motion predominates in the basal region. An apically placed accelerometer has previously demonstrated good ability to detect changes in the global left ventricular function. However, global function data from a sensor placed in the basal region have not been presented. It is likely that an accelerometer placed in a basal region may provide similarly beneficial information because longitudinal motion in the mitral annular plane is a good echocardiographic measure of global left ventricular function.

Multiple imaging modalities are recommended for a comprehensive assessment of right ventricular function. Accelerometers on the right ventricle have never been tested for functional assessment, but they may provide information on changes in load and contractility. In particular, this approach could provide valuable information for patients with ventricular assist devices.

1.6.3 Accelerometer measurements in the closed chest
All previous studies of accelerometers placed epicardially have been performed with an open chest. Sternotomy and pericardiotomy affect cardiac motion and contraction because the heart moves differently in this situation. Moreover, this technology must also be validated in closed-chest situations. Thus, a new miniaturized 3D-accelerometer has been developed that provides the possibility of subepicardial placement, which can facilitate the insertion and postoperative removal of the sensor similarly to a temporary pacemaker wire. Furthermore, the signal from a subepicardially attached sensor may be less affected by chest closure.

1.6.4 Use of an accelerometer during weaning from cardiopulmonary bypass
Weaning from cardiopulmonary bypass is a critical point in on-pump cardiac surgery, especially in patients with contractile dysfunction. Patients with aortic stenosis may suffer from reduced myocardial function due to an increased afterload, hypertrophy and fibrosis. Myocardial preservation during cardiopulmonary bypass in these patients may be challenged by left ventricular hypertrophy and cold cardiac arrest. Acute afterload reduction after AVR may alter the mutual relationship between longitudinal, circumferential and radial motions. Myocardial stunning after cardiopulmonary bypass also causes alterations in wall motions. In a normally contracting myocardium, the early-systolic velocity
is higher than the velocity at end-systole. The opposite observation indicates myocardial
contractile dysfunction, which can be observed during both myocardial stunning and
ischaemia. A normal response to acute afterload reduction after AVR is increased left
ventricular peak systolic velocity. Therefore, it is possible that the accelerometer can be
used to identify patients with left ventricular dysfunction after AVR and cardiopulmonary
bypass by measuring epicardial velocities.

A prerequisite for the implementation of accelerometer technology in clinical use is
that its implantation and use do not require any additional manoeuvres or steps in the
surgical procedure. Temporary pacemaker leads are implanted in the myocardium in almost
all cardiac surgery procedures, and they are maintained for the initial postoperative days to
allow cardiac pacing in the event of a cardiac conduction block. The ultimate goal of
accelerometer monitoring in cardiac surgery is to develop a combined pacemaker lead and
accelerometer sensor. This realization would increase the clinical applicability of the
method, but signal interpretation in open- and closed-chest situations and during
cardiopulmonary support remains to be tested.
2. Aims of the study
The aim of this study was to investigate the utility of an epicardial 3D-accelerometer for cardiac function assessment using an automated analysis of cardiac 3D motion in open- and closed-chest situations during changes in regional and global function and to assess cardiac function using the same 3D-accelerometer signal technology during weaning from cardiopulmonary bypass.

3. Hypothesis
We hypothesized the following:

1. The accelerometer 3D motion vector method was equally reliable as single-axis analysis for the assessment of left ventricular function during changes in regional and global cardiac function.
2. Global and regional left ventricular and right ventricular function could be monitored in a postoperative closed-chest situation with the 3D-accelerometer.
3. Subepicardial positioning of the sensor would increase the accuracy of the method.
4. The accelerometer 3D motion vector method could be used to detect myocardial contractile dysfunction during weaning from cardiopulmonary bypass after aortic valve replacement.
4. Materials and methods

The hypotheses were tested in two experimental studies (paper I and II) using 33 pigs and in one patient study including 23 patients (paper III). The 20 pigs in study I were included from two previously published studies by our research group.22,26 Eight of these pigs were used to generate unpublished accelerometer data.22 All 20 animals in study I were analysed with a new automated algorithm to calculate the 3D velocity and were tested against a previously developed single-axis analysis.54 Study I also included new unpublished echocardiographic and haemodynamic data. No animals were excluded in study I.

The second animal study was performed using 13 pigs. The data were derived from 11 animals because two pigs were excluded due to cardiac arrest during the surgical preparation. In the patient study (paper III), five patients were excluded, resulting in 18 patients for data assessment. The Norwegian Animal Research Authority approved the experimental studies, and the animals were treated according to the provisions of the Animal Welfare Act of 1996. The regional ethics committee approved the patient study, and informed consent was obtained from all patients.

4.1 Models

4.1.1 Experimental models

A porcine model was chosen for the experimental studies because the pig heart is very similar to the human heart in terms of anatomy and physiology and permits the precise control of coronary blood flow during ischaemia and reperfusion. This model also allows an intra-individual remote reference zone for comparison of regional changes in myocardial motion, and the heart size and surgical instrumentation are comparable.62 With minor differences, the same protocols for anaesthesia and surgery were used in studies I and II. Anaesthesia was induced by intravenous pentobarbital 2–3 mg/kg and morphine 0.5–1.0 mg/kg until the tracheotomy was completed. General anaesthesia was maintained with inhaled isoflurane (1.0–1.5%) and morphine infusion (0.15–0.2 mg/kg/h). Mechanical ventilation was performed with an inspired oxygen fraction of 0.35 and tidal volume/ventilation rate adjusted to maintain the arterial PCO₂ <5.5 kPa. Ringer’s acetate was provided at the rate of 10–15 ml/kg/h to maintain diuresis above 1 ml/kg/h. No blood transfusions were administered.
A median sternotomy was performed, and the pericardium was opened. In study I, an inflatable occluder (In Vivo Metric, CA, USA) was placed after the second diagonal branch of the LAD, and the coronary flow was measured with a 4-mm ultrasonic flow probe (Medistim, Oslo, Norway) placed distally to the occluder. In the closed-chest model (paper II), a snare was placed around the LAD to occlude the left descending coronary artery.

Invasive haemodynamic monitoring was performed by placing micromanometers (MPC-500, Millar Instruments, TX, USA) into the cavities of the aorta, left ventricle and left atrium for continuous pressure registration in study I. In addition, a 16-mm flow probe (Medistim, Oslo, Norway) was placed on the ascending aorta to monitor cardiac output. In study II, micromanometers were inserted in the left and right ventricle, in addition to a PiCCO catheter (Pulsion, Munich, Germany) in the left femoral artery and a pulmonary artery catheter (Edwards Lifesciences Corporation, Irvine, CA, USA) through the right internal jugular vein.

In study I, two accelerometers were placed epicardially, one in the anterior apical region of the left ventricle supplied by the LAD, and the other on the lateral basal region on the left ventricle supplied by the circumflex coronary artery (CX) (Figure 2A). In study II, the

![Figure 2: Illustration of sensor placement and cardiac pressure lines in A; study I, B; study II and C; study III.](image)

accelerometer sensors were placed in the same two locations, but we also included one subepicardial sensor in parallel to the epicardial sensor in the left ventricular anterior apical position and a fourth epicardial sensor in the basal anterior region of the right ventricle (Figure 2B). The accelerometers were sutured to the epicardium with two stitches (Prolene
5-0), and the subepicardial accelerometer was placed through a 9 French introducer using Seldinger’s technique.

The LAD was occluded to induce regional dysfunction similarly to previous studies testing the performance of the accelerometer for the detection of myocardial ischaemia.\textsuperscript{22,23,26,54} The data from the sensor in the CX supply area were used as a control. Ultrasound was used for reference during LAD occlusion in studies I and II.

Interventions that affect global cardiac function were also performed in both experimental studies. In study I, boluses of epinephrine (10 µg), esmolol (100 mg) and fluid (500 ml colloid) were administered to alter contractility and preload. The peak effect of each intervention was recorded. In study II, contractility was altered by infusions of esmolol and dobutamine to a target of at least a 30% change in mean arterial blood pressure to baseline values, and recordings were performed at steady state. Preload was reduced by applying positive end expiratory pressure (10 cmH\textsubscript{2}O) and increased by fluid loading (500 ml Ringer’s acetate).

After each intervention, recovery to stable haemodynamic baselines was regained before initiating new interventions. The accelerometer velocity was compared to invasive haemodynamic data in interventions that affect global cardiac function. In study I, all interventions were performed with an open chest, whereas in study II, the effect of chest closure and the effects of the interventions in a postoperative relevant setting were subjected to epicardially and subepicardially placed accelerometer testing.

\textbf{4.1.2 Clinical model}

In study III, the performance of the accelerometer during weaning from cardiopulmonary bypass was investigated in patients undergoing isolated AVR. The aim was to study myocardial function in patients with left ventricular hypertrophy but without regional dysfunction. Thus, exclusion criteria included coronary artery disease requiring concomitant bypass surgery and evolving myocardial infarction. Additional exclusion criteria were circulatory instability, bundle branch block, atrial fibrillation, and dyskinetic wall motion due to previous myocardial infarction. The patients were treated according to the standardized perioperative guidelines at Oslo University Hospital. Anaesthesia and surgical procedures are described in the methods section in paper III. In addition to standard care, an accelerometer
was placed in the left ventricular apical region (Figure 2C). For safety reasons, the accelerometer was sutured and removed during cardiopulmonary support. Recordings were performed at two time-points. The first measurements were obtained before aortic cross-clamping (time-point 1). After the haemodynamic measurements, transoesophageal echocardiogram and accelerometer readings were obtained, and full circulatory support was re-established and followed by cross-clamping of the aorta and cold antegrade cardioplegia (modified St. Thomas solution). The temperature of the heart and lung machine was set to 32°C, and AVR was performed. The second set of measurements was undertaken after valve surgery and release of the cross-clamp, rewarming and a minimum of 15 min of reperfusion (time-point 2).

At each time-point, equal preload, blood temperature and heart rate (atrial pacing of 90 beats per min) were sought. All measurements were performed after a stable 5-min “hands off” time period. Cardiac output was assessed using a pulmonary arterial catheter, whereas transoesophageal echocardiography was used as the reference method for the detection of myocardial dysfunction during weaning from cardiopulmonary bypass. In addition, the surgeon was asked to evaluate cardiac performance during weaning from cardiopulmonary bypass according to 1) “good function” or 2) “reduced function”. The sensitivity and specificity of this visual evaluation of function were tested according to the accelerometer classification (described in the next section).

4.2 Accelerometer
An accelerometer consists of a mass of piezoelectric material that reacts to changes in motion with bending of the piezoelectric material, which causes changes in the conductivity of the material and is registered as a change in voltage. These data are transformed to estimate heart motion expressed by acceleration (raw signal), velocity or displacement through a single or double mathematical integration of the raw signal. Two different silicon encapsulated 3D-accelerometers were used. In studies I and III, a 3D-accelerometer with dimensions of 5 × 5 × 2 mm was used (KXM52-1040, Kionix, Inc., NY, USA). This accelerometer had an external dimension of 11.0 × 14.5 × 5.2 mm. A smaller sensor (CMA3000-A, Murata Electronics Oy, Vantaa, Finland) with dimensions of 2.8 × 3 × 10 mm was used in study II for testing in a closed chest and for subepicardial placement.
**Figure 3:** Displacement, velocity and acceleration obtained by the 3D accelerometer for one cardiac cycle are shown in longitudinal, circumferential and radial directions together with simultaneous ECG and pressure recordings (LV cavity, left atrial and aorta) and the calculated LV \( \frac{dP}{dt} \). For each accelerometer axis, peak systolic velocity \( (V_{sys}) \) within 150 ms (blue segment) after ECG R-peak was automatically registered and used as measures of LV systolic function. LV: left ventricular; ECG: electrocardiogram; \( \frac{dP}{dt} \): the time derivative of the left ventricular pressure.

An NI USB 6009 AD converter (National Instruments, Inc., Austin, TX, USA) was used.
for data acquisition. The acceleration raw signal was sampled at 500 Hz synchronously with ECG and in experimental studies I and II together with the micromanometer pressure catheters. The accelerometer signal was high-pass-filtered to reduce the effect of gravity and breathing motion artefacts. A customized MATLAB algorithm (MathWorks, Natick, MA, USA) was used to automatically determine the onset of systole from the R-peak in ECG and to calculate the accelerometer variables by time integration (Figure 3). Acceleration samples over a 10-s interval were analysed to ensure that all heartbeats in at least one ventilator cycle were included. Because the greatest changes in left ventricular function by the accelerometer are found in early systole, the peak velocity within the first 150 ms after R-peak in ECG (V_sys) was used as the measure of left ventricular function. The x-, y- and z-axes corresponded to longitudinal, circumferential and radial left ventricular motions, respectively. In study I, the accelerometers were randomly attached, but according to a list of non-standard orientations, the algorithm could identify each accelerometer axis in relation to the cardiac coordinate system. This process made it possible to automatically calculate V_sys in the longitudinal, circumferential and radial contraction directions. Each single-axis accelerometer was compared to the new 3D method, which was obtained without information regarding the placement of the sensors. A MATLAB algorithm was developed for the 3D analysis and included five steps, which are described in detail in paper I.

1) Automatic detection of peak R on ECG and calculation of the 3D motion of the epicardial accelerometer, expressed by the 3D displacement loop (Figure 4A). The 3D displacement loop was based on the displacement in all 3 directions during one heart cycle (Figure 3). In this step, the ECG R-peak was used to determine the start and end of the 3D displacement loop (Figure 4A, left panel).

2) Determination of a 3D reference vector: The vector found from the 3D displacement loop starting at the ECG R-peak to the position furthest away in space from this point during the heart cycle was extracted (Figure 4A, left panel). This motion vector obtained at baseline (Figure 4A, bold arrow left panel) represented the accelerometer 3D reference vector. The 3D reference vector was obtained at the first baseline in study I, at the first baselines with open and closed chest in study II, and at time-point 1 in study III.

3) Calculation of displacement along the 3D reference vector, followed by calculation of the velocity by time derivation of the displacement signal (Figure 4B, left panel).
4) Automatic calculation of the peak systolic velocity within the 150-ms period after peak R on ECG along the 3D reference vector (3D \( V_{sys} \)). The 3D \( V_{sys} \) was evaluated in assessments of myocardial function in all studies.

5) The 3D motion vector (Figure 4A, bold arrow) could be influenced by the magnitude of ventricular contraction (increase or decrease in length of the 3D motion vector) and the main direction of contraction (change in the 3D motion vector angle). The subsequent recorded motion during the different interventions was then projected onto the 3D reference vector from baseline (Figure 4A, right panel). The effect of the interventions was calculated as the relative change to this reference 3D vector. In all three studies, the 3D \( V_{sys} \) was calculated using the 3D motion vector method.

In study III, in addition to 3D \( V_{sys} \), velocity at end–systole (aortic valve closure, 3D \( V_{ave} \)) was measured to determine whether myocardial dysfunction was present and accordingly to classify the patients with “normal function” or “dysfunction” during weaning from cardiopulmonary bypass. Myocardial dysfunction with the accelerometer was defined as 3D \( V_{sys} < 3D V_{ave} \) (Figure 5).
LV apical 3D motion by accelerometer

**Figure 4:** (A) Automatic calculation of accelerometer 3D $V_{sys}$. Accelerometer epicardial 3D displacement loops in LV apical region from 14 heartbeats (10 s measurement interval) during baseline and LAD occlusion. A 3D reference vector (bold arrow, left panel) was extracted at baseline from the sensors position at ECG R-peak to the furthest distance from this point, which corresponded closely to end systole (squares). The baseline 3D reference vector is also shown in the right panel, visualizing that a completely different LV motion occurred during LAD occlusion. Sensor displacement during the first 150 ms after ECG R-peak is marked with blue colour and projected onto the 3D reference vector (dashed arrow). (B) Displacement along the 3D reference vector (upper panel) and the corresponding velocity along the 3D reference vector (mid panel). 3D $V_{sys}$ (arrow) represents peak systolic velocity within the 150 ms (blue segment) along the 3D reference vector and was used as the accelerometer 3D measure of LV systolic function. The effects of LAD occlusion on 3D displacement and 3D velocity are shown in right panels. LV: left ventricular; LAD: left anterior descending artery; ECG: electrocardiogram; 3D: three-dimensional.
**Figure 5:** Accelerometer 3D velocity traces showing patients with normal myocardial function (A) and dysfunction (B) at time point 2 (after aortic valve replacement [AVR]). Systole was defined as the interval from R-peak to downslope T-wave (dashed line) on ECG. Peak 3D systolic velocity (V_{sys}) within the first 150 ms (blue) and 3D end-systolic velocity at aortic valve closure (V_{avc}) (dashed line) were measured. Myocardial dysfunction was defined as V_{sys} < V_{avc}. Time-point 1: before AVR. Time-point 2: after AVR.

### 4.3 Ultrasound

#### 4.3.1 Echocardiography

In study I, a 2.5-MHz transthoracic probe (GE Vingmed AS, Norway) was used, and the echocardiographic examination was performed using a Vivid 7 scanner (GE Vingmed AS, Norway). Conventional two-dimensional greyscale short-axis images were obtained from the left ventricular basal and apical regions, above and beneath the level of the papillary muscles, respectively. From these images, myocardial circumferential peak systolic strain in apical anterior and basal lateral segments was measured using the speckle tracking method. Myocardial strain was used as a reference method to detect regional dysfunction during occlusion of the LAD.

Systolic strain represents the change in segment length (L) during systolic contraction (ES) relative to the end-diastolic length (ED) as a percentage \(((L_{ES}-L_{ED})/L_{ED}*100\%)\). Negative strain values signify segmental shortening. A more negative value therefore represents increased contraction, whereas less negative strain represents reduced contraction. The average strain value from three consecutive heartbeats was used in the statistical calculations. EchoPAC (Version 112, GE Vingmed Ultrasound AS, Norway) was used for the off-line echocardiographic analysis.

In study III, the pre- and postoperative assessment of the patients included a standardized two-dimensional transthoracic echocardiogram according to previous
guidelines. Recordings were obtained using a Vivid E9 ultrasound scanner (GE Vingmed, Horten, Norway). The analyses were performed in the echocardiography laboratory at the Department of Cardiology, analysed by a consultant cardiologist, and included measurements of the aortic valve area, gradient and maximum velocity. Intraoperative transoesophageal two-dimensional greyscale images were obtained using a transoesophageal probe in 2- and 4-chamber views and in the short-axis view at the mid papillary level. All images were stored for off-line analysis and analysed using EchoPAC (Version 113, GE Vingmed Ultrasound AS, Norway). From the four basal segments in the 2- and 4-chamber views, the peak systolic longitudinal velocity (S’) was measured by colour tissue Doppler. The S’ from three consecutive heartbeats was measured, and the averaged S’ in the 4 basal segments was used in the statistical calculations. The annular plane moves away from the probe during systole, and the velocity becomes negative (a more negative value indicates enhanced contraction). End-diastolic and end-systolic diameters were calculated from the short-axis mid papillary level view.

4.3.2 Miniaturized epicardial sensor M-mode ultrasonography

Due to the anatomy of pig hearts, both transoesophageal and transthoracic echocardiography have image quality limitations. In study I, in which the chest was open, the ultrasound probe could be used directly on the heart. However, this was not possible in study II, in which the chest was closed. Because of poor echogenicity, we replaced echocardiography with two miniaturized ultrasonic transducers (Imasonic SA, Besancon, France) that were sutured to the epicardium. The miniaturized ultrasonic transducers, which produced high-quality M-mode images of the ventricular walls, have been validated both experimentally and clinically. These transducers are sensitive markers for regional ischaemia but are less able to detect changes in global cardiac function. The ultrasonic transducers were therefore used to confirm ischaemia during LAD occlusion. The pictures were sampled by a 14-bit digitizer board (NI-PCI 5122, National Instruments, Inc.) and analysed using LabView 8.2 software (National Instruments, Inc.). End-diastolic and end-systolic wall thicknesses were recorded, and the transmural systolic displacement was calculated by subtracting the end-diastolic from the end-systolic wall thickness. Systolic displacement was used as a reference for the detection of ischaemia.
4.4 Electrocardiogram, pressures and haemodynamic measures

ECG and hydrostatic pressures were monitored using a Siemens SC 9000XL monitor (Siemens AG, Erlangen, Germany). Mean arterial pressure and central venous pressure were measured via fluid-filled catheters. Hydrostatic pressures exhibit a delay and cannot be synchronized to the acceleration and ECG. Pressures determined using micromanometers were synchronized with the accelerometer signal and used in studies I and II. The peak systolic pressure of the left (studies I and II) and right ventricle (study II) and end-diastolic pressure were measured, and positive and negative time derivatives (dP/ dt_{max} and dP/dt_{min}) were calculated. Systole was defined from the start of the R-peak on ECG to the left ventricular dP/dt_{min} in the experimental studies and from the ECG R-peak to the downslope of the T-wave in the patient study.

Cardiac output was measured by three different techniques. In study I, a flow probe was placed on the ascending aorta; in study II, in contrast, transthoracic thermodilution with pulse contour analysis was performed using a PiCCO catheter (Pulsion, Germany). PiCCO was chosen because it offered continuous monitoring of the cardiac index during the LAD occlusions. The stroke volume index and systemic vascular resistance index were calculated from the PiCCO measurements in almost real-time. In addition, the pulmonary vascular resistance index was calculated using the cardiac index from the PiCCO monitor, left ventricular end-diastolic pressure using the micromanometer and mean pulmonary pressure according to the pulmonary artery catheter.

In study III, a pulmonary artery catheter was used to calculate the cardiac index, stroke volume index, left ventricular stroke work index (LVSWI) and pulmonary vascular resistance index. The sum of the thermodilution cardiac index and indexed cardiopulmonary bypass flow was used to calculate the systemic vascular resistance index. Haemodynamic data were sampled and stored in the ICU Pilot software programme (CMA Microdialysis AB, Solna, Sweden).

4.5 Statistics

The sample size was calculated by power analysis and has been accounted for in each study. Parametric statistical methods were used, and the data are presented as the mean ± SD unless otherwise noted. Two-tailed paired-sample t tests were used for repeated
measurements, and $P \leq 0.05$ was considered significant. Bonferroni correction was used for the comparison of multiple interventions. In study I, Bonferroni-corrected $P$ values were reported. In study II, the Bonferroni-corrected significance level was reported in addition to uncorrected $P$ values.

Calculation of 3D $V_{sys}$ with the 3D motion vector method requires a reference 3D vector. As a consequence, a single baseline is required. In study I, no differences were found between baseline values before each intervention, so the first baseline was used for comparison with interventions on left ventricular function. In study II, the open-chest baseline value was used as the baseline to assess the effect of chest closure (baseline closed chest) and the LAD occlusions performed after the chest was reopened. There were no differences between baselines performed during the period of the experiment when the chest was closed, and all interventions were compared to the first baseline after chest closure. In study II, the Bland Altman method was used to compare the measurements from subepicardial and epicardial fixed accelerometers.

Receiver-operating characteristic curves were constructed to determine cut-off values for the detection of ischaemia using an accelerometer and to assess the sensitivity and specificity to discriminate regional dysfunction from changes in global cardiac function in the two experimental studies.

The correlation coefficient was calculated to describe the association between accelerometer measurements and haemodynamic measurements in the experimental studies. In the patient study, stepwise linear regression was used to identify an association between the echocardiographic $S'$ used as the reference contractility measure and relevant measures that are considered to influence contractility. The sensitivity and specificity of the visual judgement by surgeons were calculated by 2 x 2 table cross-tab analysis.

Accelerometer variables were calculated automatically, and intra- and inter-observer analyses were not an issue. Interclass correlations and mean differences were used for reliability analysis of the peak systolic longitudinal velocity by tissue Doppler in study III. Statistical analyses were performed using SPSS version 18, 20 and 23 software (SPSS Inc., IL, USA) in studies I, II and III, respectively.
5. Summary of results

5.1 Study I: Myocardial function by 3D motion vector analysis

In study I, hypothesis 1 was tested. The aims of study I were to investigate epicardial motion patterns with the 3D-accelerometer in two different left ventricular regions and to evaluate an accelerometer 3D motion vector to quantify changes in global and regional left ventricular function induced by pharmacological interventions or coronary artery occlusion.

Interventions with epinephrine, fluid and esmolol induced typical haemodynamic changes that were detectable with the accelerometer 3D Vsys in both measured left ventricular regions. The left ventricular systolic motions assessed by single-axis analysis demonstrated domination of circumferential Vsys in the apical region and longitudinal and circumferential Vsys in the basal region. In both left ventricular regions, minor changes were found in radial Vsys. The 3D Vsys obtained from the apical and basal regions correlated, respectively, to the dominant single-axis velocities in these regions (both r=0.93, P<0.001). The circumferential and 3D Vsys in the apical region demonstrated the best correlations to left ventricular dp/dt_max and cardiac output (r=0.86 and r=0.76 for circumferential Vsys and r=0.83 and r=0.76 for 3D Vsys, all

Figure 6: Circumferential Vsys (A) and 3D Vsys (B) in the LV apical region compared with LV dp/dt_max during interventions on global and regional LV function. Solid horizontal lines indicate baseline Vsys for the accelerometer variables, whereas dashed lines indicate cut-off values obtained by ROC analysis for the accelerometer variables to discriminate regional dysfunction from changes in global function. Data reported as mean ± SD and analysed by paired sample t-tests with Bonferroni correction of P-values. *P<0.05, †P<0.01 compared with baseline and ‡P <0.01 compared with esmolol. Vsys: Peak systolic velocity; 3D: three-dimensional; ROC: receiver-operating characteristic. LV: left ventricular; dp/dt: the time derivative of the left ventricular pressure.
P<0.001).

Occlusion of the LAD induced significant reductions in accelerometer velocities in both left ventricular regions, but the changes were greatest in the intervention area. In the apical region, similar to interventions in global left ventricular function, circumferential and 3D V\textsubscript{sys} performed best, and reductions in these accelerometer variables were significantly greater during LAD occlusion than during esmolol infusion (P<0.01) (Figure 6). The cut-off values for circumferential V\textsubscript{sys} (6.6 cm/s) and 3D V\textsubscript{sys} (8.7 cm/s) were substantially different from the mean values obtained for these two variables during interventions in global left ventricular functions (Figure 6). These findings implied very good discrimination of regional dysfunction, with a similar high sensitivity and specificity (90% and 86%, 90% and 83%, respectively).

To summarize, study I demonstrated that (i) the accelerometer measures in the left ventricular apical region most precisely reflected the global left ventricular function, (ii) 3D V\textsubscript{sys} showed an effective ability similar to circumferential V\textsubscript{sys} to quantify changes in global function and to detect ischaemia, and (iii) the 3D method allowed the discrimination of regional dysfunction from changes in global left ventricular function.

5.2 Study II: Myocardial function in the closed-chest situation

In study II, hypotheses 2 and 3 were tested. The main aim of this study was to test the performance of the accelerometer in a postoperative closed-chest situation. We also aimed to investigate the effects of chest closure on the accelerometer measurements and to examine whether subepicardial positioning of the sensor would increase the reliability of the method for monitoring cardiac function.

5.2.1 Assessment of myocardial function in the closed-chest situation by epicardial accelerometers

Epicardial accelerometers were placed in the lateral basal and anterior apical position on the left ventricle and the anterior basal position on the right ventricle.
Effects of chest closure

Figure 7: Accelerometer peak systolic velocities (3D $V_{sys}$) with open and closed chest. Data reported as mean ± SD and analysed by paired sample $t$-tests. *$P<0.05$, †$P<0.01$. LV: left ventricle; RV: right ventricle; SD: standard deviation.

Effects of global interventions

Figure 8: Accelerometer peak systolic velocities (3D $V_{sys}$) in the left and right ventricle (LV and RV) under closed-chest conditions during interventions affecting global cardiac function. Data reported as mean ± SD and analysed by paired sample $t$-tests. *$P<0.05$, †$P<0.01$, ‡$P<0.05$ after Bonferroni correction for multiple comparisons. LV: left ventricular; RV: right ventricular; PEEP: positive end-expiratory pressure.

A main finding of this study was that chest closure reduced the accelerometer velocities in both ventricles. The greatest effects on accelerometer 3D $V_{sys}$ were observed in the left ventricular apical region (Figure 7). After chest closure was performed, the interventions affecting global cardiac function led to typical and significant haemodynamic changes that were also detected by the accelerometer 3D $V_{sys}$ (Figure 8).

A marked reduction in accelerometer 3D $V_{sys}$ was observed in all accelerometer sensors during LAD occlusions in both open- and closed-chest situations. Occlusion of the LAD was verified by the miniaturized ultrasonic transducer in the intervention area with a significant reduction in systolic displacement in both open- and closed-chest situations. In contrast to the right ventricular accelerometer 3D $V_{sys}$, no significant changes were observed with the ultrasonic transducer during LAD occlusion.

5.2.2 Assessment of myocardial function in the closed-chest situation by subepicardial accelerometer

The subepicardial accelerometer was placed in the anterior apical left ventricular region, aligned equivalently to the epicardial sensor in the same location. The subepicardial and epicardial sensors demonstrated similar changes during all interventions, and the 3D $V_{sys}$ for
the two sensors were highly correlated (r=0.91, P<0.001). However, the subepicardial accelerometer displayed less signal variation during the ventilation cycle, especially after chest closure. The subepicardial 3D $V_{sys}$ demonstrated the best correlation to the left ventricular $dP/dt_{max}$ and cardiac index (r=0.86 and r=0.82, respectively, both P<0.001). Receiver-operating characteristic analysis demonstrated almost identical sensitivity/specificity for the sensors to detect ischaemia (subepicardial sensor: 78%/83%; epicardial attached sensor: 78%/73%).

In summary, study II showed that (i) chest closure depressed the accelerometer signals, (ii) changes in global cardiac function with a closed chest were detected with accelerometers placed at both left and right ventricles, although the left ventricular apical sensor best reflected these changes, and (iii) the subepicardial position of the sensor improved the signal quality and performance.

5.3 Study III: Detection of myocardial dysfunction during weaning from cardiopulmonary bypass

In study III, hypothesis 4 was tested. The aim of this study was to investigate whether the accelerometer could identify patients with left ventricular dysfunction after weaning from cardiopulmonary bypass after cardiac surgery.

An accelerometer was placed epicardially at the apical anterior wall of the left ventricle. Two time-points were compared: 1) before cross-clamp while the support of cardiopulmonary bypass flow was temporarily reduced to 50% and 2) after valve surgery, rewarming and weaning to 50% cardiopulmonary bypass flow. The criterion of 3D $V_{sys}$<3D $V_{avg}$ defined left ventricular dysfunction by the accelerometer, and the patients were classified accordingly to have “normal” function or “dysfunction” during weaning from cardiopulmonary bypass (time-point 2). The accelerometer assessment showed that 56% of the patients had contractile dysfunction during weaning from cardiopulmonary bypass, compared with 11% before aortic cross-clamp (Figure 9). There were no significant differences between groups in terms of age, NYHA class or EuroSCORE, aortic cross-clamp time, reperfusion time, flow and time of cardiopulmonary bypass or use of inotropic and vasoactive drugs. The accelerometer classification and the haemodynamic and echocardiographic measures were consistent. In patients identified with left ventricular
dysfunction by the accelerometer at time-point 2, LVSWI and $S'$ remained unchanged (Figure 10). In contrast, in patients classified with “normal” left ventricular function, both LVSWI and $S'$ improved. By linear regression, changes in $S'$ could be explained by an accelerometer classification with $r=0.63$ (correlation coefficient of $1.98$, $95\%$ CI $[0.57, 3.40]$) ($P<0.01$). The surgeons were not able to distinguish “normal” function from “dysfunction” by visual judgement of cardiac performance (sensitivity and specificity of $63\%$ and $20\%$, respectively).

In summary, study III demonstrated that the accelerometer enabled the identification of a substantial proportion of patients with left ventricular contractile dysfunction after weaning from cardiopulmonary bypass.

Figure 9: Left ventricular (LV) function classified by the accelerometer during aortic valve replacement (AVR). Time-point 1 before, and time-point 2 after AVR.

Figure 10: Measures of left ventricular (LV) function. Time-point 1 before, and time-point 2 after AVR. Data: mean ± SD. Paired data: $^1P < 0.01$. Comparison between groups: $^1P < 0.05$, $^3P < 0.01$. 
6. Discussion

The main results of this thesis are as follows: 1) the accelerometer 3D velocity method performed equally as well as the best accelerometer single-axis velocity for quantifying changes in left ventricular function (paper I), 2) chest closure reduced accelerometer velocities in both the right and left ventricle, yet the accelerometer 3D method enabled the detection of changes in both regional and global ventricular function (paper II), 3) subepicardial placement of the sensor improved signal quality and allowed it to be placed and removed in a similar manner to temporary pacemaker wires (paper II), and 4) myocardial dysfunction after on-pump cardiac surgery could be detected using the accelerometer 3D method (paper III). Taken together, these results imply that the sensor can be used as a continuous, perioperative monitoring modality in cardiac surgery both for the guidance of treatment and for the detection of complications.

6.1 3D motion vector analysis

Study I was designed for quality assurance of the 3D motion method. The 3D \( V_{sys} \) calculated by the 3D motion vector method performed equally well in comparison to the best single axis in both left ventricular regions. The 3D method is more user-friendly and may enhance the clinical utility of the method because the use of single-axis analysis has disadvantages due to the need for precise alignment of the sensor to the cardiac coordinate system. To be able to interpret single-axis motions by the accelerometer, the user must have basic knowledge of the main contraction directions in the different regions of the heart. The motions obtained from the longitudinal, circumferential and radial axes are very different (Figure 3). Consequently, if a sensor axis is not perfectly aligned to the cardiac contraction coordinates, the readings will be inaccurate. For example, if the \( y \)-axis, which should be parallel to the circumferential direction (Figure 3), is oriented between the circumferential and longitudinal contraction directions, the \( V_{sys} \) along the \( y \)-axis (supposedly circumferential) will be reduced due to an increase in \( V_{sys} \) in the \( x \)-axis (supposedly oriented in the longitudinal direction). In the worst-case scenario, myocardial ischaemia may not be detected due to such misalignment.

Different indices of 3D motion from the accelerometer can be calculated. One approach would be to weigh the three individual accelerometer axes equally by projecting
the motion on a centre vector pointing 45° out from the origin in the middle of the x-, y-, and z-coordinate system. However, this method is dependent on the alignment of the sensor with the cardiac coordinate system. Alternatively, a pure Euclidian index ($\sqrt{x^2 + y^2 + z^2}$), which is alignment-independent, may seem attractive. However, an intervention or change of function may preserve the Euclidian magnitude but affect the direction of motion. Therefore, we extracted the reference 3D vector that pointed in the direction of maximal displacement during the cardiac cycle (3D displacement loop) under reference conditions, as shown in Figure 4A. As shown in the figure, circumferential motion dominated in the apical left ventricular region, and hence the calculated 3D reference vector was relatively parallel to the circumferential direction. The 3D-accelerometer displacement and velocity were projected onto this 3D vector. The resulting systolic velocity curves in this region therefore appeared similar to the circumferential systolic velocity traces during all left ventricular function interventions, even during regional dysfunction in which the greatest quantitative and qualitative changes in accelerometer velocities were observed. Equivalently, the projected velocity curve from the basal sensor would appear similar to the single-axis longitudinal velocity curve.

The same accelerometer sensor design was used in studies I and III. In study II, our aim was to investigate the subepicardial positioning of the sensor. A new prototype was developed for this purpose, which was based on a smaller accelerometer that had been available at that time (Figure 2B). One concern was that the sensor used in studies I and III was too large to be used when the thorax was closed due to the risk of mechanical disturbances of the signal. Another concern was that the positioning could not always be oriented equally in all test subjects because of confliction with coronary vessels. A third concern was that the subepicardial sensor could move around its x-axis without our knowledge when the thorax was closed. For this reason, the 3D method was used to analyse the accelerometer recordings in study II. Similarly good correlations were found between 3D $V_{sys}$ and $\frac{dP}{dt_{max}}$ and cardiac output in open and closed-chest conditions in studies I and II, indicating that the accelerometer technology and the 3D method can be used for both intraoperative and postoperative cardiac surveillance.

In study III, the changes in accelerometer 3D $V_{sys}$ diverged from the changes in the reference measures LVSWI and $S^*$ in the normal function group. This phenomenon could be explained by the observation that LVSWI represents a global index of left ventricular
function and that the echocardiographic and accelerometer recordings were performed in different left ventricular regions (the basal and apical regions, respectively). Basal tissue Doppler S' improved at time-point 2 in the “normal” function group, whereas apical accelerometer 3D $V_{sys}$ did not significantly change. In patients with aortic stenosis and concentric hypertrophy, basal longitudinal motion is reduced, whereas circumferential motion is increased at the midlevel and apex of the left ventricle. Following AVR and afterload reduction, apical motion is reduced while there is an increase in basal longitudinal motion. Using the accelerometer, circumferential motion dominated in the apex and was a major contributor to 3D $V_{sys}$ in this region (paper I). Interestingly, when we decomposed our results in study III into three individual axes, we found that circumferential and radial $V_{sys}$ were significantly reduced after AVR while longitudinal $V_{sys}$ was unaltered (data not shown). This finding corresponds to results from previous studies examining the effects of AVR on ventricular motions by echocardiography.

6.2 Myocardial function in the closed-chest situation

The results from the closed-chest model confirmed former findings during open-chest conditions in study I and in studies by Halvorsen et al. and Hyler et al. Typical and significant changes in accelerometer velocities were found in interventions affecting global and regional myocardial function both in the left and right ventricles. Importantly, for these interventions, the accelerometer measurements significantly correlated to $dP/dt_{max}$ and the cardiac index. In both open- and closed-chest situations, there was a significant reduction in accelerometer 3D $V_{sys}$ in both experimental studies and in all accelerometer sensor locations during LAD occlusion. These results imply that epicardial motions detected by the accelerometer are also affected by function in other segments (tethering effect), similar to the tissue velocity measurements obtained by echocardiography. However, an increase in the post-systolic velocity – a sensitive marker of myocardial ischaemia – was most prominent in the 3D velocity signal for the accelerometer placed in the left ventricular apical region. An increase in post-systolic velocity was observed during LAD occlusion alone but not during the interventions that affect global cardiac function.
The clinical implications of these results is that monitoring of global cardiac function can be assessed irrespective of the sensor location and that the accelerometer can detect both local ischaemia and remote ischaemia in adjoining left ventricular regions.

In general, the amplitude of the accelerometer velocity signal was suppressed by chest closure; however, only 3D $V_{sys}$ in the left ventricular apical area was significantly reduced. Circumferential motion dominates in this area$^{16}$ and provides a major contribution to 3D motion. Basal segments normally move towards the apex during systole (Figure 1). In an open-chest situation with a split pericardium and an uncovered apex, apical motion is reversed and moves towards the basis.$^{12}$ Loss of pericardial pressure and the adhesive forces between the visceral and parietal pericardium may explain this change in motion,$^{56}$ causing the apex to move more freely and magnifying the influence of gravity on the accelerometer signal.

6.2.1 Gravitational effects

Acceleration and the effects of gravity cannot be distinguished using an accelerometer. One problem with accelerometer monitoring is that rotation of the sensor in the gravitational field can induce signal artefacts. Rotation contributes to circumferential motion, and an accelerometer attached to the left ventricular apical region will move along a curved path that twists around the long axis. This rotation in the gravitational field produces an acceleration component that alternates approximately like a sinus curve with a frequency equivalent to the heart rate. Integration amplifies low-frequency and suppresses high-frequency components. This low-frequency gravity component is therefore amplified when integrating the accelerometer signal into velocity and displacement and effectively results in an overestimation of the actual velocity and displacement in the circumferential direction.$^{50}$ Longitudinal and radial motion have been found to be less affected. Chest closure may stabilize the apex of the left ventricle and reduce the effect of rotation and thus gravitation artefacts. The observed reduced velocity in this region after chest closure is therefore unlikely to be related to reduced myocardial function because no changes in accelerometer velocities were observed in other heart regions. Minor haemodynamic changes were detected during this intervention, and systolic displacement by the ultrasonic transducer was unaltered.
There is a need for a method to minimize error caused by rotation of the sensor in the gravitational field. High-pass filtering is not sufficient because it requires a cut-off frequency higher than the heart rate, which would subsequently remove a major portion of the clinical information. An algorithm has been developed to compensate for gravity in the single axis, but this method has not yet been implemented in the 3D method. It is likely that solving this problem will increase the accuracy of the method. With sensors that combine accelerometer and gyro, the effect of rotation can be isolated, potentially increasing the reliability of the method. Such a sensor is currently under investigation by our research group, but the current size of the sensor is not compatible with subepicardial placement.

6.3 Right ventricular function
Accelerometer velocities from the right ventricle corresponded to the findings obtained using the sensors on the left ventricle when global myocardial function was altered. Interestingly, right ventricular velocities were reduced during left ventricular ischaemia. In swine, collaterals from the LAD supply 28% of the right ventricle apex, and occlusion after the second diagonal branch of the left anterior descending artery resulted in biventricular apical ischaemia. Thus, it is likely that the decrease in right ventricular accelerometer 3D V_{sys} during LAD occlusion was due to an effect of tethering from a dysfunctional apical right ventricular segment. Displacement from the ultrasound transducer placed next to the accelerometer on the right anterior basal region was not affected during LAD occlusion, verifying that there was no ischaemia in this area.

6.4 Subepicardial positioning of the accelerometer
Increased signal variability due to breathing motion after chest closure was observed with the epicardial accelerometer in comparison to the signals from the sensor placed subepicardially. Temporary cessation of ventilation almost abolished this variability (data not shown), which indicates that epicardial accelerometer measurements in the left ventricular apical region were most affected by mechanical compression and decompression by the surrounding lung tissue. Furthermore, data from the subepicardial sensor correlated better with global haemodynamic measurements. Nevertheless, the epicardial accelerometer
demonstrated a robust ability to track changes in global and regional left ventricular function, which was achievable using automatic signal processing averaging peak systolic velocities over several heartbeats. The measured absolute values and significance level at each intervention were similar between the sensors. These results imply that the accelerometer does not need to be placed within the myocardium to reliably monitor left ventricular function after cardiac surgery. Furthermore, epicardial placement is less invasive and may be beneficial if the sensor is implanted for permanent use.

6.5 Detection of myocardial dysfunction during weaning from cardiopulmonary bypass

The main finding of study III was that the accelerometer 3D velocity trace could be used to detect myocardial dysfunction during weaning from cardiopulmonary bypass after isolated AVR. At this time-point, a major proportion of the patients had contractile dysfunction, as detected by the accelerometer. These patients showed no improvements in LVSWI and S’ by tissue Doppler in response to the acute afterload reduction induced by valve replacement. In contrast, the patients classified as having normal myocardial function at weaning showed enhanced left ventricular systolic function after valve replacement.

Not surprisingly, the sensitivity and specificity of the visual judgement of cardiac function were low. In the operating field, usually only the anterior wall of the right ventricle is seen, and right ventricle contraction may not reflect left ventricular function. Furthermore, it is difficult to separate normal from pathological delayed systolic contraction. The most striking effect after surgical and transcatheter AVR is increased basal longitudinal motion,\textsuperscript{72–74} whereas apical motion where the accelerometer was placed is less affected.\textsuperscript{64,72,78} Thus, our findings showing reduced accelerometer 3D $V_{sys}$ in the apical region together with unchanged basal longitudinal motion by tissue Doppler in the dysfunction group indicate the presence of global contractile dysfunction. The pathological shift from early to late systolic contraction supports the presence of myocardial dysfunction. The velocity trace appears similar when global stunning (Figure 5B) and regional ischaemia occur (Figure 4B), and it cannot be distinguished by the accelerometer. In a clinical setting, the detection of post-systolic contraction should trigger further investigations by echocardiography to determine
whether the dysfunction represents selective coronary artery hypoperfusion or global myocardial hypoperfusion due to a low perfusion pressure.

The study was not designed to determine risk factors for myocardial dysfunction after cardiopulmonary bypass. Still, an interesting observation was that those patients classified as having normal function during weaning had a thicker interventricular septum and reduced end-diastolic diameter prior to aortic cross-clamping. The left ventricular filling pressure and valve area were comparable between the groups. Altogether, these results indicate a smaller and more hypertrophic left ventricle with less volume to eject against the same afterload, potentially explaining the low $S'$ and left ventricular stroke values obtained in the normal function group prior to cross-clamping. In contrast, the left ventricle in the dysfunction group was more dilated and showed significantly more delayed systolic contraction ($V_{ave}$), even before aortic cross-clamping was performed. Therefore, it is possible that the accelerometer can detect patients with an increased risk of developing myocardial dysfunction after open-heart surgery, but larger studies are needed to confirm this conclusion.

6.6 Clinical utility

The accelerometer can provide clinically important information regarding myocardial performance that is not revealed by standard blood pressure monitoring, as there can be normal blood pressure and ventricular stroke volume despite myocardial dysfunction. Tissue Doppler $S'$ has been found to be an accurate variable of left ventricular systolic function in patients with aortic stenosis, providing more accurate results than traditional measurements such as the ejection fraction, which can be difficult to obtain using transoesophageal echocardiography. The ejection fraction poorly reflects left ventricular systolic function in severe aortic stenosis with concentric hypertrophy, and thus many patients present a normal ejection fraction despite the presence of severe left ventricular dysfunction. A previous experimental open-chest accelerometer study found that the ejection fraction poorly reflected changes in left ventricular function during alterations in load and contractility, even when it was measured using the echo probe directly on the left ventricle. In that study by Hyler et al., the accelerometer measurements correlated better
to the left ventricular stroke work than the ejection fraction during changes in global left ventricular function.

Clinical use of the accelerometer technique could allow real-time data processing and display, and if pathologic contraction is detected, an alarm could be triggered. Processing and measurement of echocardiographic tissue Doppler images must be performed post-hoc, and the recordings are obtained only intermittently, making echocardiography less suitable for bedside analysis. In contrast, the accelerometer provides a continuous output with an automated beat-to-beat analysis. This technique may therefore represent a future clinical tool for the detection of complications and for the guidance of vasoactive and inotropic treatment during cardiac surgery. We have demonstrated the usefulness of the accelerometer in closed-chest situations (paper II), and a smaller device (2.0 mm) with an incorporated bipolar pacemaker lead is being developed by Cardiaccs (Oslo, Norway) in cooperation with Ozypca AG (Rheinfelden-Herten, Germany). This multifunctional sensor will be placed and removed like ordinary pacemaker leads and thereby provide cardiac function monitoring postoperatively. This procedure will increase the practicability and clinical utility of the technology in daily routines. Clinical strategies following the demonstration of a pathological contraction by the accelerometer are described as follows. 1) In a circulatory stable patient, echocardiography should be used to determine regional coronary artery hypoperfusion. 2) If haemodynamic instability is present and global left ventricular dysfunction is verified by echocardiography, then treatment should be aimed at optimizing coronary artery perfusion pressure. 3) Myocardial stunning is the most plausible cause if global left ventricular dysfunction is present despite adequate perfusion pressure. Thus, the accelerometer must be considered a supplementary method rather than a substitute for echocardiography.

6.7 Methodological considerations

One challenge with the 3D motion vector method is that the main contraction direction may change over time, potentially representing an important change in regional or global cardiac function. During cardiac surgery, left ventricular function may be depressed initially and improve over time after surgical correction of the underlying disease, or cardiac function may be worsened due to stunning. Changes in cardiac motion measured by the
accelerometer may also represent a non-pathologic event, such as a change in patient position or chest closure after surgery. The 3D motion method therefore requires the use of representative baselines. In study II, a backward analysis was performed, although the results were not reported in the final revision of the paper. Reference 3D vectors were constructed for each intervention in terms of global and regional left ventricular function and tested against the baseline. Importantly, the 3D method also allowed the quantification of these opposite changes in left ventricular function, thus increasing the clinical utility of the method (data not shown).

The use of the technology and methodology presented in this thesis are limited for use in non-mobilized patients. As previously discussed, integration of the accelerometer signal into velocity enhances the influence of gravity, and changes in body position would cause disturbances in the signal. The detection of changes in body position may be mitigated by an external accelerometer attached to the skin or by combining the accelerometer and gyro. Such a device could discriminate changes in body position from cardiac motion. A third solution may be to process the signal differently, e.g., by frequency analysis of myocardial vibrations. This analysis may be less affected by external movement changes in body position or gravitational artefacts.

Frequency analysis by fast Fourier transform can be used to detect myocardial ischaemia, but this analysis may be difficult to interpret for clinicians. In contrast, velocity and displacement are well known measures used in echocardiography. Future clinical use of the technology may demand different signal processing techniques and the integration of all information into an easily interpretable output.

To assess myocardial function by accelerometers, at least one sensor on each ventricle is needed to cover the entire heart. As demonstrated in this thesis, an accelerometer in the left ventricular anterior apical region most precisely reflected the changes in global cardiac function in normal hearts. Furthermore, the apical anterior region is supplied by the LAD, the most frequently grafted coronary artery, which may permit detection of regional dysfunction due to insufficient LAD perfusion, changes in global left ventricular function due to stunning or vasoactive and inotropic therapy, and most likely ischaemia in the CX perfusion area due to tethering. Still, the number and placement of sensors needed to monitor the heart require further investigations.
6.8 Limitations

In the experimental studies, interventions affecting global cardiac function were always performed before interventions altering regional cardiac function because ventricular fibrillation may occur during coronary artery occlusion. The optimal study design would have been to perform all interventions on global and regional function in randomized order under both open and closed conditions. This would, however, increase the risk of circulatory instability in the pig and therefore loss of the animal early in the experiment.

The experiments were performed in healthy animals with stable circulation and normal organ function. Results from interventions that alter global cardiac function indicate that the accelerometer can be used to guide therapy by vasoactive and inotropic drugs; however, further research is needed for confirmation. A model of global myocardial dysfunction and circulatory instability is needed to test the ability of the accelerometer to guide vasoactive therapy in comparison to therapy guided by standard haemodynamic surveillance.

The detection of ischaemia has been a central topic in experimental studies. The LAD perfusion area was used as the intervention area for regional ischaemia. Occlusion of the CX coronary artery has not been investigated but would probably change the interrelationship between longitudinal, circumferential and radial motion compared with that during LAD occlusion. We would expect the 3D method to handle this effect, but it needs to be investigated further both in single vessel and multi-vessel coronary artery occlusion models. All coronary interventions were performed with total clamping of the artery, and the ability of the accelerometer to detect graded occlusions or hypoperfusion for other reasons has not been investigated. This information is important because patients in the perioperative phase may present subtotal occlusion or temporary coronary hypoperfusion due to low blood pressure. In this thesis, regional dysfunction was tested in an experimental closed-chest situation, but a clinical postoperative study with a large number of patients is needed to investigate whether accelerometer surveillance can alter the outcomes of patients undergoing open-heart surgery. The LAD occlusions were performed for 3 minutes, and large changes in motion were observed during this time interval. It is not likely that severe myocardial ischaemia was present after this short period of coronary occlusion, and the myocardium was presumably viable.\(^{83}\) It is not known whether the accelerometer can distinguish viable from non-viable myocardium, necessitating further studies.
Study III was the first study to utilize accelerometer monitoring during on-pump cardiac surgery. For safety reasons, the sensor was attached and removed while the patient was undergoing cardiopulmonary bypass. Thus, the clinical impact of our findings on postoperative outcomes was not possible to evaluate. It is likely that the mutual contribution of apical and basal motion was altered after AVR. This was not possible to investigate in this data set, but it may be achieved using one apically and one basally placed sensor. It was also not possible to obtain high quality echocardiographic measures of apical motion in study III, and thus the accelerometer velocity changes in this region could not be verified.
7. Conclusions

Epicardially attached 3D-accelerometers provided detailed information regarding myocardial motion, which could be used to precisely quantify changes in global myocardial function, both experimentally in pigs and clinically in patients undergoing aortic valve replacement. The usefulness of the 3D method to detect regional myocardial dysfunction was also documented.

1. The calculated accelerometer 3D systolic velocity revealed equally good performance as the best single-axis accelerometer systolic velocity for monitoring myocardial function. This result implied that the sensor could be attached to the ventricle without taking into account the alignment of the sensor to the cardiac contraction coordinates.

2. Miniaturized 3D-accelerometers placed on the heart enabled a precise real-time quantification of global left and right ventricular function in a closed-chest model. Regional left ventricular dysfunction was detected with high sensitivity and specificity; however, sensor measurements in remote non-ischaemic regions on the left and right ventricles were also affected due to tethering effects.

3. The subepicardial sensor performed better than the epicardial sensor placed next to it and was less influenced by the breathing motion.

4. The 3D-accelerometer identified a substantial proportion of patients with left ventricular contractile dysfunction during weaning from cardiopulmonary bypass after isolated aortic valve replacement, in accordance with the measurements obtained by echocardiography and pulmonary artery catheterization.

Accelerometer 3D motion analysis makes the technology more suitable for clinical use. The results in this thesis imply that the sensor can be used as a perioperative monitoring modality for continuous monitoring of left and right ventricular function in patients undergoing cardiac surgery, in order to guide medical treatment and detect myocardial dysfunction.
8. Future perspectives
Complex cardiac surgery is being performed in increasingly older and sicker patients,\textsuperscript{84–86} many of whom have severe biventricular failure for which continuous monitoring of the left and right ventricular function by accelerometer could be beneficial. Accelerometers may prove to be a useful monitoring modality, particularly in patients treated with a left ventricular assist device and in patients undergoing heart transplantation. This method may have the potential to improve clinical outcomes in these high-risk patients.

Due to gaming and the smartphone industry, the size of accelerometers is becoming smaller. This small size and minimal energy requirements may allow these devices to run on kinetic energy, which may be useful in heart failure patients who do not require open-heart surgery, via endoscopic implantation through a mini-thoracotomy. After hospital discharge, such a permanent sensor may provide continuous information regarding arrhythmias, ventricular performance and the occurrence of ischaemic events during daily living activities, thus offering promise for an improved diagnosis, earlier treatment of complications and enhanced guidance of interventions.

9. Literature search
A search of “((accelerometer* OR accelerometry) AND (ventricular function OR myocardial ischemia/diagnosis)) NOT physical activity” was performed in PubMed 14.10.2016 to check all relevant new references. This search included heart-related research and excluded most studies in which accelerometers were used to monitor activity in biomechanics.

10. Permissions
Figures 3-10 have been included with permission from Oxford University Press.

11. Disclosures
Ole-Johannes Holm Nielsen Grymyr is a shareholder in Cardiaccs AS.
12. References


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13. Papers