# Detection and Segmentation of Anastomoses in Epicardial Ultrasound Images for Quality Assessment of Coronary Artery Bypass Graft Surgery

Jørgensen, Alex Skovsbo

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# DETECTION AND SEGMENTATION OF ANASTOMOSES IN EPICARDIAL ULTRASOUND IMAGES FOR QUALITY ASSESSMENT OF CORONARY ARTERY BYPASS GRAFT SURGERY

BY
ALEX SKOVSBO JØRGENSEN

DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
DENMARK

# Detection and Segmentation of Anastomoses in Epicardial Ultrasound Images for Quality Assessment of Coronary Artery Bypass Graft Surgery

Ph.D. Dissertation

Alex Skovsbo Jørgensen
Medical Informatics Group
Department of Health Science and Technology
Aalborg University, Denmark

Dissertation submitted February 3, 2015

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| Thesis submitted: | February 3, 2015 |
| PhD supervisor: | Assoc. Prof. Lasse Riis Østergaard<br>Aalborg University |
| Assistant PhD supervisor: | Assoc. Prof. Samuel Emil Schmidt<br>Aalborg University |
| PhD committee: | Prof. Wiro Niessen<br>Erasmus Medical Center, Rotterdam |
| | Prof. Rasmus Larsen<br>Technical University of Denmark |
| | Prof. Johannes Struijk<br>Aalborg University |
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# Abstract

Up to 9% of coronary artery bypass graft surgery (CABG) anastomoses contain stenoses >50% post-surgery. This can cause post-operative morbidity and mortality for the patients. Intraoperative anastomosis quality assessment can be used to detect anastomotic errors to enable anastomosis revision during the primary surgery. Epicardial ultrasound (EUS) can be used to locate errors and quantify the stenotic rates within anastomoses to determine the anastomotic quality. Currently, the anastomotic quality is evaluated manually from EUS images as no objective methods are available. This can be time consuming and surgeons have to be trained in interpreting EUS images or use peer reviews by a radiologist.

The aim of this thesis was to develop medical image analysis methods to enable automatic quantification of stenotic rates from in vivo EUS sequences of CABG anastomoses made on healthy porcine vessels. For this purpose methods were developed to automatically detect and extract of the vessel lumen area of anastomotic structures within in vivo EUS sequences. The anastomosis detection was used to locate anastomotic structures within EUS images to remove human interaction in analysis of EUS sequences. To extract the vessel lumen area of anastomotic structures from in vivo EUS sequences approaches for vessel lumen segmentation, inter-frame vessel motion correction, and segmentation quality control were developed.

An area under the curve of 0.966 (95% CI: 0.951-0.984) and 0.989 (95% CI: 0.985-0.993, $p < 0.001$) of a precision-recall and receiver operator characteristic curve respectively, was obtained in detecting vessel regions extracted within EUS images in the anastomosis detection algorithm. The vessel lumen area of anastomotic structures was extracted with a mean Dice coefficient of 0.85 ($\pm$ 0.13) and a mean absolute area difference of 20.62% ($\pm$ 25.85) when compared to manual segmentations.

The developed methods were able to automatically detect and track anastomotic structures within EUS sequences without user interaction. The proposed methods have the potential to extract the vessel lumen area from EUS sequences to quantify the stenotic rates of CABG anastomoses.

# Resumé

Op til 9 % of koronar arterie bypass graft (KABG) anastomoser indeholder stenoser >50 % efter operationen. Dette kan resultere i post-operativ morbiditet og mortalitet. Intraoperativ anastomose kvalitetssikring kan bruges til at detektere fejl i anastomoser for at kunne rette disse under operationen. Epicardiel ultralyd (EU) kan bruges til at detektere anastomosefejl og kvantificere stenosegraden af disse fejl for at evaluere anastomosens kvalitet. På nuværende tidspunkt evalueres anastomosekvaliteten manuelt, da der ikke findes nogle objektive metoder til analyse af EU billeder. Dette kan være tidskrævende og samtidig skal kiruger lære at tolke EU billeder eller have en radiolog til at evaluere billederne.

Målet med denne afhandling har været at udvikle medicinske billedanalyse metoder til at gøre det muligt at automatisk kvantificere stenosegrader af KABG anastomoser lavet på raske grise ved brug af in vivo EU sekvenser. For at opnå dette blev metoder udviklet til automatisk at detektere og udtrække arealet af blodkarstrukturer i anastomoser visualiseret i in vivo EU sekvenser. Blodkardetektionen blev brugt til at finde blodkar i EU billeder for at fjerne brugerinteraktion i analysen af EU sekvenser. For at udtrække blodkararealet af anastomosestrukturer fra in vivo EU sekvenser blev der udviklet metoder til segmentering af blodkar, inter-frame bevægelseskorrigering og kvalitetskontrol af segmenteringerne.

I blodkardetektionen blev der opnået arealer under kurven på 0,966 (95 % CI: 0,951-0,984) og 0,989 (95 % CI: 0,985-0,993, $p < 0{,}001$) på hhv. en precision-recall og receiver operator characteristic kurve i at detektere blodkarregioner udtrukket i EU billederne. Arealet af anastomosestrukturer blev udtrukket med en gennemsnits Dice koefficient på 0,85 ($\pm$ 0,13) og en absolut gennemsnitsarealforskel på 20,62 % ($\pm$ 25,85) i forhold til manuelle segmenteringer.

De udviklede metoder kunne automatisk detektere og tracke anastomosestrukturer igennem EU sekvenser uden brugerinteraktion. De foreslåede metoder har potentialet til at udtrække arealet af anastomosestrukturer fra in vivo EU sekvenser med henblik på at kvantificere stenosegrader af KABG anastomoser.

# Contents

# Thesis Details

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| **Thesis Title:** | Detection and Segmentation of Anastomoses in Epicardial Ultrasound Images for Quality Assessment of Coronary Artery Bypass Graft Surgery |
| **Ph.D. Student:** | Alex Skovsbo Jørgensen |
| **Supervisors:** | Assoc. Prof. Lasse Riis Østergaard, Aalborg University<br>Assoc. Prof. Samuel Emil Schmidt, Aalborg University |

The main body of this thesis consist of the following papers.

[A] A. S. Jørgensen, S. E. Schmidt, N.-H. Staalsen, and L. R. Østergaard, Semi-Automatic Vessel Tracking and Segmentation using Epicardial Ultrasound in Bypass Surgery, *Engineering in Medicine and Biology Society (EMBC)*, vol. 34, pp. 2331–2334, 2012.

[B] A. S. Jørgensen, S. E. Schmidt, N.-H. Staalsen, and L. R. Østergaard, Automatic Vessel Tracking and Segmentation using Epicardial Ultrasound in Bypass Surgery, *Computing in Cardiology*, vol. 39, pp. 9–12, 2012.

[C] A. S. Jørgensen, S. E. Schmidt, N.-H. Staalsen, and L. R. Østergaard, Automatic Detection of Coronary Artery Anastomoses in Epicardial Ultrasound Images, *Accepted in International Journal of Computer Assisted Radiology and Surgery*, December 2014.

[D] A. S. Jørgensen, S. E. Schmidt, N.-H. Staalsen, and L. R. Østergaard, Automatic Coronary Artery Bypass Anastomosis segmentation in Epicardial Ultrasound, *Submitted to International Conference on Information Processing in Computer-Assisted Interventions*, November 2014.

This thesis has been submitted for assessment in partial fulfillment of the PhD degree. The thesis is based on the submitted or published scientific papers which are listed above. Parts of the papers are used directly or indirectly in the extended summary of the thesis. As part of the assessment, co-author statements have been made available to the assessment committee and are also available at the Faculty. The thesis is not in its present form acceptable

for open publication but only in limited and closed circulation as copyright may not be ensured.

# Preface

This PhD thesis represents three years of research at Aalborg University on development and validation of medical image analysis methods within in vivo epicardial ultrasound sequences for intraoperative quality assessment of coronary artery bypass graft surgery anastomoses. Algorithms for automatic detection and segmentation of anastomotic vessel structures within epicardial ultrasound sequences are presented. The algorithms was developed and validated based on data from anastomoses made on healthy porcine vessels. The thesis consist of three parts:

1. A chapter describing the background and objectives of the research.
2. A concluding chapter that discusses the findings and future perspectives.
3. Four papers describing and validating possible solutions for the challenges identified in the background.

**Acknowledgments**
I would like to thank my supervisors Lasse Riis Østergaard and Samuel Emil Schmidt for giving me the opportunity to make this PhD and improving my skills as a researcher by providing great feedback and helping me improve my dissemination of my research.

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Alex Skovsbo Jørgensen
Aalborg University, February 3, 2015

# Part I

# Introduction

# Introduction

Coronary artery disease (CAD) currently causes 30% of all deaths globally. [1] It creates arteriosclerotic plaque which reduces the vessel lumen of the coronary arteries. The plaque causes formation of stenoses/occlusions which affects the blood supply to the heart leading to ischemia and/or acute myocardium infarct. [2] The prevalence of CAD in the USA has been estimated to be 7.9% of all Americans above 20 years of age. [3] Approximately 785.000 Americans had a new coronary attack in 2010 and about 470.000 were diagnosed with a recurrent attack. [3]

Severe cases of CAD can be treated using coronary artery bypass graft surgery (CABG) to reestablish blood supply to the myocardium. During a CABG a bypass vessel (graft) is sutured onto the aorta and the coronary artery beyond the stenosis or occlusion by making a suture establishment (anastomosis) on the native vessels. CABG is the most common surgical procedure performed in the USA with an approximate 405.000 CABG procedures performed in 2007 [4]. The success of CABG mainly depends on the quality and patency of the anastomoses made on the coronary arteries. Mack et al. [5] has shown up to 9% of anastomoses contain stenoses above 50%. This can lead poor long term anastomosis patency or be fatal if not discovered during the primary surgery before chest closure. Intraoperative anastomosis quality assessment can disclose technical errors within the anastomosis and enable anastomosis revision during the primary surgery to improve outcome for the patient and the cost effectiveness of CABG. [6]

The gold standard for anastomosis quality assessment is coronary angiography. However, it is not normally available in the operation room and the stenosis assessment is associated with a significant inter-user variability. [7] Therefore other approaches, such as transit time flow measurement (TTFM) and intraoperative flourescence imaging (IFI), has been proposed. [8–11] However, the sensitivity and specificity of these methods are low when compared to coronary angiography. [12]

Epicardial ultrasound (EUS) can visualize the anastomotic structures and has been suggested as an alternative approach for intraoperative anastomosis quality assessment. [8, 13] It can be used to locate technical errors and quantify the stenotic rates within anastomoses for evaluation of the anastomotic quality. Ex vivo studies has shown that using EUS improved detection of surgical errors when compared to coronary angiography [14]. Recently, an ultrasound transducer positioning device, Echoclip, has been invented for visualization of anastomoses on the beating heart. [15] The Echoclip allows obtaining real-time dynamic information of the anastomotic structures for in vivo anastomosis quality assessment. Currently, EUS sequences are evaluated manually as no objective methods are available to quantify the stenotic rates of the anastomotic structures. This can limit the use of EUS in clinical practice as analysis of EUS sequences can be time consuming and users has to be trained in interpreting EUS images.

Automatic extraction of stenotic rates in anastomoses from EUS sequences may aid the surgeon in the decision to revise anastomoses during the primary surgery. This may possible by developing image analysis methods to automatically extract the vessel lumen area of anastomotic structures from EUS sequences. The extracted vessel lumen area may then be used to quantify the stenotic rates within anastomoses to obtain a quantitative and objective measurement of the anastomotic quality. The purpose of this study was to develop and test methods which may enable automated evaluation of the anastomotic quality using in vivo EUS sequences.

# 1 Coronary Artery Disease

In 2008 CAD was estimated to cause 7.3 million deaths globally, making it the most common cause of death. [1] The prevalence of CAD is increasing due to improved and more effective diagnostic methods, medicine, and invasive treatment offers. [2, 3] The mortality and incidence of CAD is decreasing, mainly due to increased knowledge of risk factors, changes in lifestyle, and a more aggressive treatment effort. [2]

CAD occurs due to buildup of arteriosclerotic plaque within the coronary arteries (Fig. 1). Plaque is mainly formed due to life style based risk factors such as unhealthy diet, physical inactivity, tobacco use, and harmful use of alcohol. These risk factors are responsible for approx. 80% of all CAD occurrences. [1] CAD is more common in low- and middle-income countries as people are more exposed to CAD risk factors and have less access to effective health care services compared to people in high-income countries. [1]

Plaque formation often occurs in clots within the vessels and in multiple coronary arteries. The main factor of plaque formation is lipids within the blood, which damages the inner walls of the blood vessels and makes the surface more rough. The rough inner surface causes substances within the blood to get stuck onto the vessel wall, which creates the arteriosclerotic plaque. The plaque build-up reduces the vessel lumen and increases the degree of stenosis within the coronary arteries. The plaque also increases the stiffness of the coronary arteries, which hinders dynamic vessel dilation when oxygen demand is increased within the myocardium e.g. during exercise. When the vessel lumen is reduced a mismatch between oxygen demand and requirement occurs. The reduced perfusion of the myocardium can trigger ischemia, which is more distinct during exercise and can cause angina pectoris. [2, 16] The plaque content is protected by a fibrotic cap, which prevents thrombosis formation which occurs when the plaque content comes into contact with the blood. [16] However, if a plaque ruptures, coagulation of the blood can occur and thromboses are formed. The thromboses can then get stuck in other stenoses within the coronary arteries creating an occlusion which causes ischemia and/or acute myocardium infarction. [2]

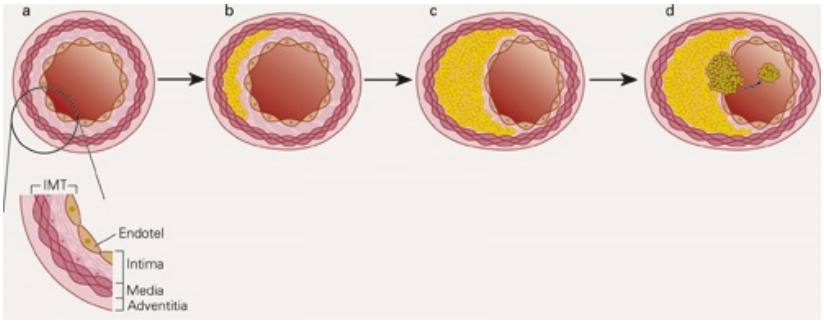



**Fig. 1:** *The process of plaque formation within an artery. (a) A normal artery. (b) The beginning of plaque formation (The yellow) within the vessel. (c) Plaque buildup has reduced the vessel lumen. (d) Plaque rupture creating thrombus formation within the vessel lumen. Modified from [16]*

The treatment of CAD can vary, ranging from medical treatment to revascularization using percutaneous coronary intervention depending on the severity of the symptoms, age, functional level, and other diseases of the patient. A CABG may be performed if medical treatment fails or if the patient has either a main stem stenosis or multiple lesions within the coronary arteries. [2]

# 2 Coronary Artery Bypass Graft Surgery

CABG is the most common surgical procedure in the United States, with approximately 405.000 CABG procedures performed in 2007. [4] The goal of CABG is to reestablish blood supply to the ischemic myocardium that lies peripheral to a stenosis or occlusion. [2] CABG has shown to releave angina pectoris, improve quality of life in high risk patients, and it has a mortality of approximately 2%. [17–19]

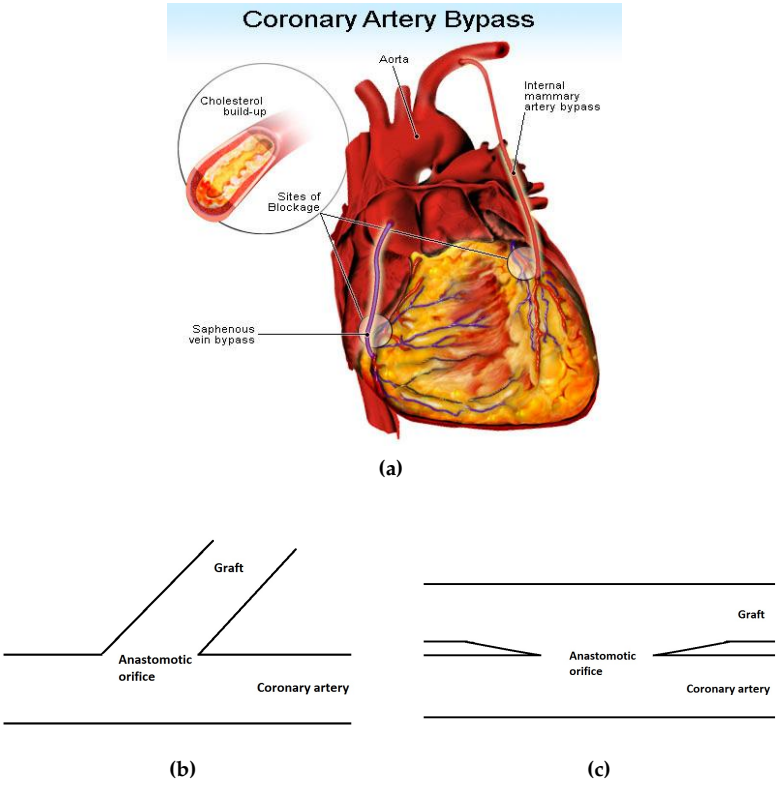



**Fig. 2:** (a) The principle of performing a CABG. The grafts (Internal mammary artery and saphenous vein) are established between the aorta and the coronary arteries beyond the stenosis or occlusion. [20] (b) A line drawing of an end-to-side anastomosis. (c) A line drawing of a side-to-side anastomosis.

CABG is mainly performed by making a median sternotomy through an incision down the middle of the chest to access the heart. A bypass is then established between the aorta or one of its major branches and the coronary artery beyond the stenosis or occlusion by suturing a graft vessel onto the native vessels (Fig. 2a). The suture establishment between the graft and the

native vessels is called an anastomosis. The vessels most frequently used for grafting are the left internal mammary artery or the saphenous vein. [2] There are two main types of anastomoses: end-to-side and side-to-side. In the end-to-side anastomosis (Fig. 2b) the end of the graft is anastomosed onto the side of the coronary artery. In the side-to-side anastomosis (Fig. 2c) the side of the graft is anastomosed parallel to the coronary artery. The side-to-side anastomoses typically provide a more stable configuration than end-to-side anastomoses. [21]

In conventional CABG a heart lung machine is used to establish a cardiopulmonary bypass to oxygenate the blood during the surgery. This enables the surgeon to stop the heart from beating during the surgery to obtain stable conditions for making the anastomoses. However, using the heart lung machine is associated with adverse effects such as systemic inflammatory response syndrome [22, 23], acute renal failure, arterial fibrillation, myocardial-, and neurological injuries. [19]

CABG can also be performed without the heart lung machine (OPCABG) to decrease the adverse effects associated with using the heart lung machine. [19, 24–29] In OPCABG the surgery is performed on the beating heart using local stabilizers on the target anastomotic area. This allows using standard suturing techniques [30] while maintaining the geometry of the heart to obtain hemodynamic stability. [31, 32] Still, only 20 - 25% of all CABG's are made using OPCABG as it is more technical demanding due to creating anastomoses on a moving target. [24, 33] This can reduce the relative benefits of OPCABG as the risk that the surgeon makes a technical error within the anastomosis is increased. A meta-analysis conducted by Parolari et al. [34] showed that the anastomosis occlusion rate within the first year was 4% higher in patients who underwent OPCABG compared to conventional CABG.

The immediate and long term patency of an anastomosis mainly depends on the construction of the anastomosis made on the coronary artery. [12, 35] A study by Mack et al. [5] demonstrated that up to 9% of anastomoses contain stenoses above 50% post-surgery. Insufficient anastomotic quality can cause refractory angina, myocardial infarction, low cardiac output, and fatal heart failure. [6, 36] It has been reported that the mortality of patients with early postoperative graft failure is above 9% after 30 days. [37] The negative impact of insufficient anastomotic quality and the potential to reduce patient morbidity using OPCABG has led to an increased interest in using intraoperative anastomosis quality assessment. [38]

# 3 Anastomosis Quality Assessment

The purpose of intraoperative anastomosis quality assessment is to confirm anastomosis patency and disclose technical errors within the anastomoses to enable revision during the primary surgery. This can reduce postoperative morbidity and mortality for the patients and improve the cost-effectiveness of CABG. [6, 14, 39, 40]

Factors causing reduced anastomotic quality can be divided into biological and technical. Biological factors include dissection, intimal flaps, atheroma, and thrombus formation. [41, 42] Technical factors consist of twisted or kinked grafts, surgical construction errors, and misplacement of the anastomotic site. [14, 43] The technical factors may be corrected if detected during the primary surgery. [6, 14, 39, 40]

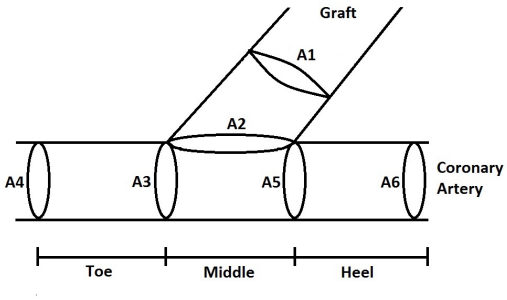



**Fig. 3:** *A schematic drawing of an end-to-side anastomosis. A1 is the graft area, A2 the anastomotic orifice area, A3 the toe site area, A4 the reference area of the coronary artery distal to the toe site, A5 heel site area, and A6 is the reference area of the coronary artery distal to the heel site. The part of the anastomosis from A3 to A4 is defined as the toe section of the anastomosis, the part from A3 to A5 is the middle section, and the part from A5 to A6 is the heel section.*

The anastomotic quality can be evaluated based on functional and anatomical analysis of the anastomosis. The functional quality can be evaluated by measuring the blood delivery from the anastomosis to the myocardium. The anatomic quality can be evaluated by visualizing the anastomotic structures to assess the morphology and locate obstructions creating stenoses within the anastomosis. An end-to-side anastomosis has distinct landmarks, which can be used to obtain anatomical measures of the anastomotic quality (Fig. 3). [21] The heel, toe, and orifice sites of the anastomosis represents locations where the graft is sutured onto the coronary artery and may therefore be subject to technical errors e.g. due to excessive tightening of the stitches by the surgeon. The patency in these anastomotic sites can be quantified by

determining the stenotic rates of the anastomosis by extracting the vessel lumen area of the graft, anastomotic orifice, heel site, toe site, native coronary artery in the heel section, and native coronary artery in the toe section of the anastomosis (Fig. 3). The stenotic rates of the anastomotic orifice can then be quantified using the ratios $\frac{A2}{A1}$, $\frac{A2}{A4}$ and $\frac{A2}{A6}$. The ratios $\frac{A3}{A4}$ and $\frac{A5}{A6}$ can quantify the stenotic rates of the outflow corner and inflow corner of the anastomosis respectively.

Currently, most surgeons uses empirical methods such as finger palpation and anastomosis probing to assess the anastomotic quality, though multiple intraoperative anastomosis quality assessment approaches has been proposed. [6, 11, 12, 44]

## 3.1 Coronary Angiography

Coronary angiography is considered the gold standard for intraoperative anastomosis quality assessment. [8–11] It visualizes the anastomotic structures in 2-D X-ray angiograms by injecting a contrast agent into the blood vessels, and allows determining the stenotic rates within the anastomoses (Fig. 4). As coronary angiography only provides 2-D images, the stenotic rates are quantified based on diameter percent stenosis, using either the smallest or mean vessel diameters of the anastomotic landmarks, obtained from different image projections.

The quality of each anastomotic landmark is classified into three categories based on the FitzGibbon grading system: excellent (grade A), fair (grade B), or occluded (O), where FitzGibbon grade B is defined as a clinical significant stenosis. The threshold separating FitzGibbon grade A and B is a vessel diameter reduction threshold of 50%. [45] However, vessel diameters may not accurately represent the stenotic rates of the anastomotic structures as the vessels may have an asymmetric shape due to surgical manipulation (Fig. 8h). Additionally, stenosis assessment using coronary angiography has been demonstrated to be subject to significant inter-user variability, especially for mid-severity stenoses. [7] Furthermore, coronary angiography is not available in many operating rooms, additional personnel are needed to perform the procedure, and it is invasive which increases the risk of complications for the patient. [6, 12] Because of the limitations of coronary angiography, other less invasive approaches has been proposed for intraoperative anastomosis quality assessment.

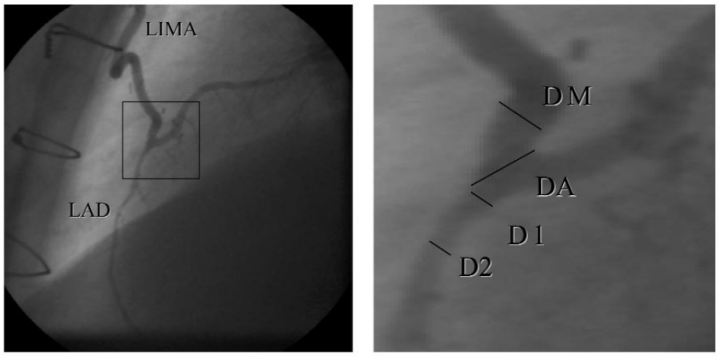



**Fig. 4:** *An X-ray image of an anastomosis using coronary angiography. The graft is the left internal mammary artery (LIMA) and the target coronary artery is the left anterior descending coronary artery (LAD). DM, DA, D1, and D2 represent diameters of the graft, anastomotic orifice, toe site, and native coronary artery in the toe of the anastomosis respectively. [46]*

## 3.2 Intraoperative Fluorescence Imaging

Intraoperative fluorescence imaging (IFI) also visualizes the anastomotic structures by injecting a contrast agent, indocyanine green dye, into the vessels. The dye binds with the plasma proteins in the blood and has fluorescent properties which emit light when illuminated with a monochromatic light source (Fig. 5). [6, 9, 11] The procedure is simple to perform and provides an immediate visual image of the anastomosis during the primary surgery. [6] However, IFI requires a direct "line-of-sight" to visualize the anastomosis, which can require that the heart has to be distracted from its native position. The anastomosis is therefore not assessed in its native state where graft kinking could be present. IFI also has a limited penetration depth (1 mm) which can prevent detailed assessment of the anastomotic quality. [6, 9, 11] The dye can also induce an allergic reaction for the patient depending on the dose. [11]

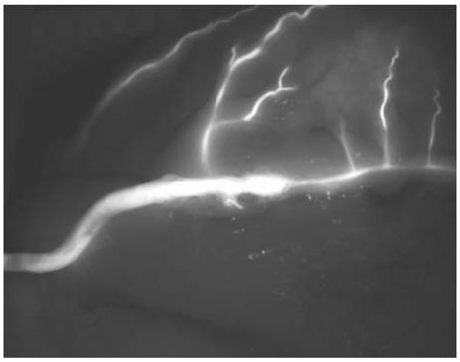


**Fig. 5:** *Coronary arteries visualized using IFI [6]*

IFI can confirm patent anastomoses and reliably detect occluded anastomoses. However, it only provides a semi-quantitative assessment of excellent, satisfactory or poor anastomosis patency and it cannot consistently identify minor, non-occlusive abnormalities. [9] Desai et al. [12] reported that the sensitivity and specificity of IFI in detecting anastomoses having clinical significant diameter stenoses (>50%) or occlusions was 83.3% and 100%, respectively when compared to coronary angiography.

## 3.3 Transit Time Flow Measurement

Transit Time Flow Measurement (TTFM) is an ultrasound-based method, which measures the flow through the anastomosis. It is simple to use, cost effective, and creates exact flow values which are reproducible independent of vessel diameter and Doppler angle. [6, 38] Currently, TTFM is recommended by the European Society of Cardiology and the European Association of Cardio-Thoracic Surgery for verification of the anastomotic quality. [47] The flow is measured by holding a flow probe perpendicular to the anastomosis and measure the time difference between the received signals from two ultrasound transducers (Fig. 6a). The measured time difference is then used to produce real-time flow waveforms, which has to be interpreted by the user (Fig. 6b). [6, 48]

The mean graft flow, in mL/min, is used as the primary determinant of the flow through the anastomosis. [6] However, no normal flow values are defined as the flow depends on multiple physiologic factors such as blood pressure, peripheral resistance, competitive flow from multiple adjacent anastomoses or septal perforators (side branches), size of the distal arterial bed, residual antegrade flow in the target vessel as well as placement of the anastomosis. [38, 49] Therefore, the reason for poor flow is not always obvious and interpretation of the waveforms depends on the experience of the sur-

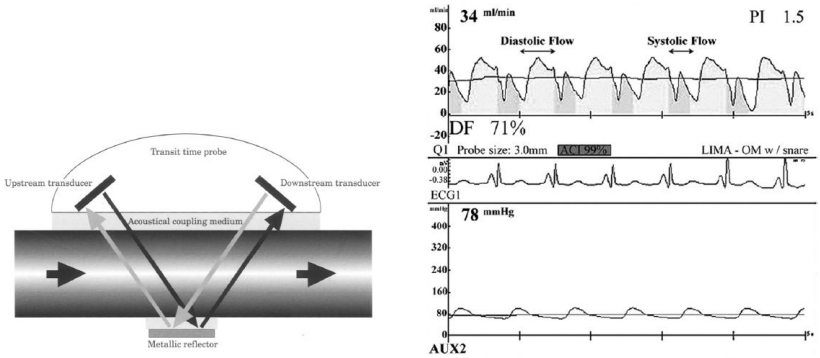



**Fig. 6:** *(a) The principle of flow measurement using TTFM. [48] (b) An example of the real-time waveforms produced by TTFM. [6]*

geon. [10, 38] Especially in low flow conditions the interpretation of the derived values may cause considerable uncertainty regarding the anastomotic quality. [10] TTFM is also operator dependent as false flow measurements can be obtained if the anastomosis is compressed or the probe is not held perpendicular to a straight, non-curved portion of the graft. Also, the probe should not be placed near stenoses or septal perforators as these structures can cause turbulent flow, which can decrease the sensitivity of the flow measurement. [50]

TTFM will confirm anastomosis patency in the majority of anastomoses with good flow. However, it is likely to over- and underestimates the need for graft revision as low flow anastomoses can be patent and high flow anastomoses can be stenotic, depending on the conditions. [9, 10, 51]. Jaber [10] showed that detectable differences in mean flow and flow morphology can only be observed in anastomoses with severe diameter stenosis (>75%) as no differences in flow was observed in anastomoses with mild (<25%) and moderate to severe (<75%) diameter senosis. Desai et al. [12] also reported that the sensitivity and specificity of TTFM in detecting anastomoses with clinical significant diameter stenoses (>50%) or occlusions was 25% and 98.4%, respectively when compared to coronary angiography. Additionally, TTFM only provides a binary assessment of the anastomotic quality as it cannot clearly define the degree and location of an obstruction within an anastomosis. [11, 38] TTFM can also lead to unnecessary revisions as it has a low positive predictive value in detecting anastomoses that needs revision. [44]

**Table 1:** Comparison of using EUS and coronary angiography to detect anastomoses with and without technical construction errors.

| Method | Accuracy [%] | Sensitivity | Specificity | Observer Agreement |
|---|---|---|---|---|
| EUS | 99 | 0.98 | 1 | 1 |
| Coronary Angiography | 78 | 0.75 | 0.81 | 0.54 |

## 3.4 Epicardial Ultrasound

Epicardial ultrasound (EUS) is another ultrasound-based method proposed for intraoperative anastomosis quality assessment. As with TTFM, EUS is non-invasive, simple to perform, and a relatively inexpensive method. [52] High frequency EUS produces images which can visualize the anastomotic structures to assess the morphology, locate obstructions within the anastomosis, and determine the stenotic rate of an obstruction (Fig. 8). EUS can obtain 2-D longitudinal and cross sectional images of the anastomotic structures, to quantify the stenotic rates within the anastomosis based on either diameter or area percent stenosis, respectively.

Multiple studies has shown great potential for using EUS for quality assessment of CABG anastomoses either using manual visual inspection or calculation of stenotic rates within the anastomotic structures from EUS images. [14, 39, 46, 53] Budde et al. [14] compared the surgeon's ability to discriminate between anastomoses with and without technical construction errors in 120 anastomoses from visual inspection of EUS images and coronary angiography. It was demonstrated that the observers obtained a higher accuracy, sensitivity, specificity, and rate of agreement between observers in detecting anastomoses containing construction errors using EUS images (Table 1). However, the study did not evaluate the accuracy in determining the stenotic rates within the anastomoses from the EUS images. Tjomsland et al. [46] showed that stenotic rates obtained in EUS images may predict the long term patency of anastomoses. They found a significant correlation between the diameter percent stenoses of the anastomotic toe site calculated from EUS images and 8 month angiographic follow-ups. A study by Di Giammarco [44] also showed that using a combination of EUS and TTFM can increase the specificity in correctly detecting anastomoses needing revision to provide a more accurate treatment of the patients.

The resolution of high-frequency EUS also allows to gain dynamic information of the vessel lumen area of the anastomotic structures during the cardiac cycle. When the oxygenated blood is pumped from the heart into the coronary arteries the elastic walls stretches due to the elevated pressure and when blood flow is reduced the arterial walls recoils. [55] The vessel lumen

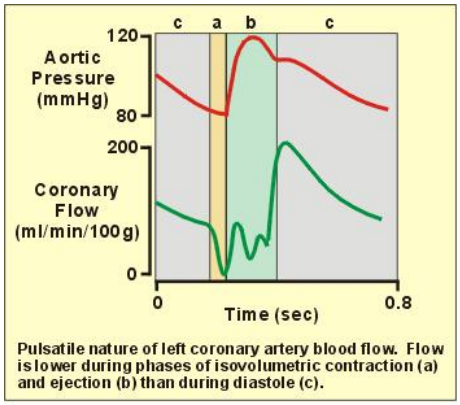



**Fig. 7:** *Flow profiles of aortic pressure and the coronary flow during a cardiac cycle. [54]*

area changes differently in the graft and coronary artery. The graft is located outside the myocardium and the vessel lumen area therefore follows the aortic pressure curve (Fig. 7). The maximum vessel lumen area of the graft therefore appears during the ventricular systole. As the coronary arteries lie within the myocardium the blood flow is affected by extravascular compression of the heart, which reduces the blood flow during the ventricular systole. Therefore, the maximum blood flow within the coronary arteries occurs during the ventricular diastole (Fig. 7). [54] Analysis of the vessel lumen area of the anastomotic structures during the cardiac cycle may provide functional information of the anastomosis post-surgery. However, to gain dynamic information of the anastomotic structures EUS sequences has to be obtained on the beating heart, which can be subject to motion artifacts such as translation of the anastomotic structures in between frames, vessels moving out of the scan plane, or loss of acoustic contrast (Fig. 9).

### Echoclip

Recently, a novel transducer positioning device, Echoclip (fig. 8a), has been developed at Aalborg University Hospital. [15] The Echoclip enables the operator to keep the transducer in a steady position without deforming the vessels to minimize frame rate variability, and motion artifacts when obtaining in vivo EUS sequences of the anastomotic structures on the beating heart. This allows obtaining real-time functional information of the anastomotic structures during the cardiac cycle.

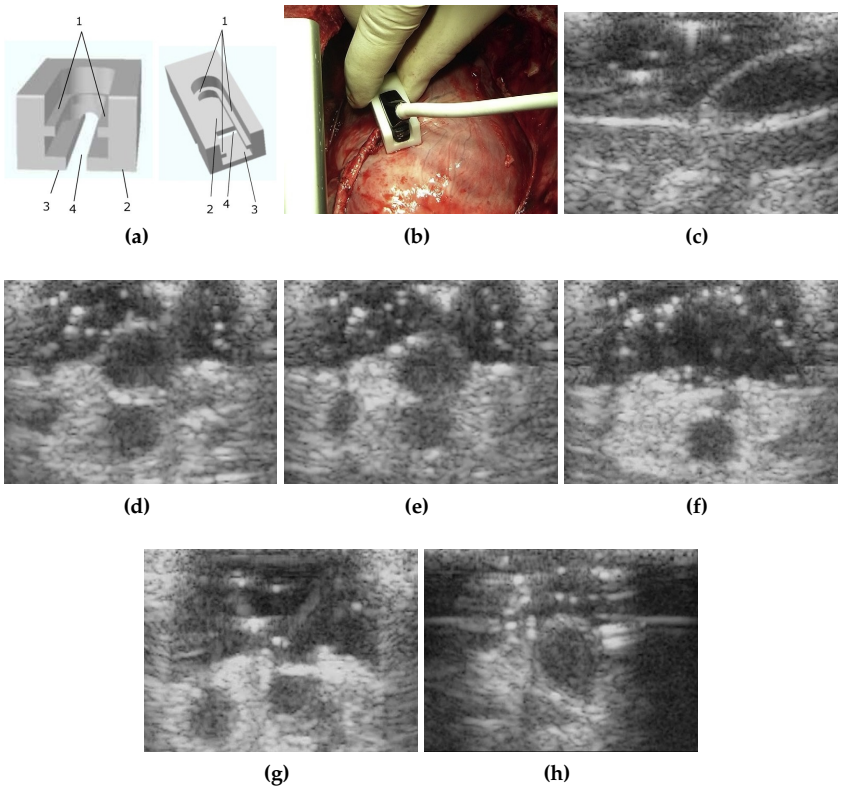



**Fig. 8:** *Obtaining in vivo EUS sequences on the beating heart using the Echoclip. (a) Two versions the Echoclip, which contains a fixing element (1) to ensure that the transducer is properly secured in the position device, two skin supports (2 and 3) to stabilize the anastomotic target site, and a cavity (4) to accommodate a bypass graft. The cavity is filled with acoustic gel to obtain optimal acoustic contact when obtaining EUS sequences on the beating heart (b). The Echoclip to the left can obtain longitudinal EUS images of the anastomosis (c). A septal perforator can be seen emanating from the coronary artery in the toe and in the heel/middle sections, respectively. The Echoclip to the right can obtain cross sectional EUS images of the heel (d), middle (e), and toe (f) sections of the anastomosis respectively. An anisotropic tissue appearance of the vessel structures can be observed in (d). (g) A large septal perforator emanates from the coronary artery creating missing tissue information. (h) A heel site with a non-circular coronary artery due to surgical manipulation. Modified from [15].*

### In Vivo Stenotic Rate Assessment

Currently, stenotic rates of anastomotic structures have to be extracted manually from EUS sequences as no quantitative and objective methods are available. Ideally, the dimensions of the anastomotic structures have to be evaluated when they are maximally distended for evaluation of the maximum flow capability of the anastomosis. This can be time consuming and surgeons has to be trained in interpreting EUS images or rely on peer reviews

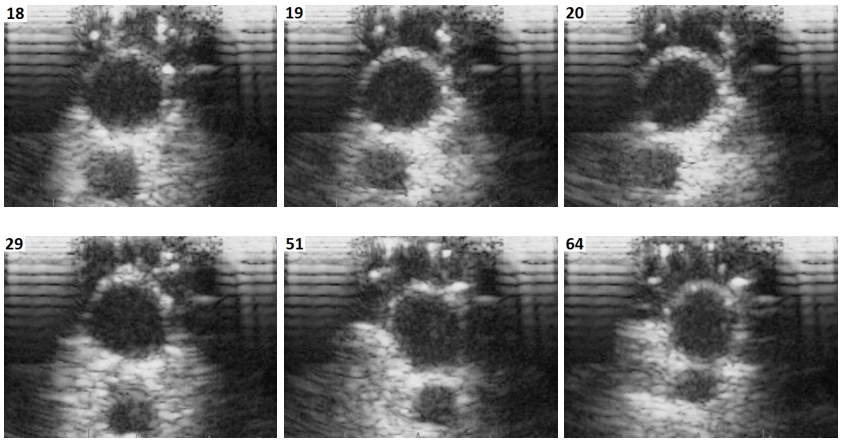



**Fig. 9:** *Six frames obtained from a EUS sequence where the vessel structures moves within the scan plane. The number in the top left corner is the frame number within the sequence. In frame 20 the coronary artery has moved out of the acoustic range of the transducer. In frame 29 the top of the vessel lumen in the coronary artery has a higher intensity due to multiple reflections within the vessel wall.*

from a radiologist post-surgery, which may limit the use of EUS in clinical practice. Additionally, real-time dynamic information of the anastomotic structures during the cardiac cycle may be lost during off line analysis of the EUS sequences, which may provide useful information in evaluating the anastomotic quality. [56] Extraction of the stenotic rates is further complicated as septal perforators emanating from the main coronary arteries are visualized when using EUS (Fig. 8), which creates missing tissue information of the target coronary artery.

Currently, studies have only calculated stenotic rates based on diameter percent stenosis of the anastomotic structures from longitudinal EUS images. However, cross sectional EUS images allows to extract the vessel lumen area of the anastomotic structures, and may provide a more accurate evaluation of the stenotic rates e.g. in anastomotic vessel structures with an asymmetric shape. Development of automated medical image analysis methods to extract the vessel lumen area of anastomotic structures from in vivo EUS sequences may enable objective evaluation of the stenotic rates within anastomoses without user interaction.

# 4 Automated Stenosis Quantification using Epicardial Ultrasound

Using medical image analysis to enable automated stenosis quantification without user interaction from in vivo EUS sequences requires three steps:

1. **Detection of anastomotic structures:** To enable automated analysis of EUS sequences, anastomotic structures have to be located within EUS image without human interaction.

2. **Vessel lumen area extraction of the anastomotic structures:** To enable automatic quantification of the stenotic rates within anastomoses, the vessel lumen area has to be extracted from different anastomotic landmarks.

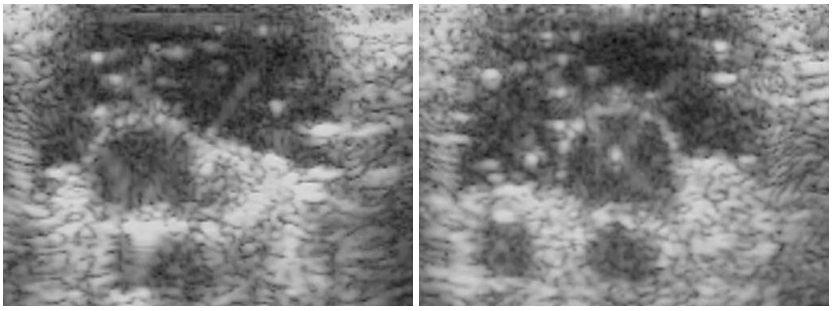
3. **Stenotic rate quantification:** To evaluate the anastomotic quality the stenotic rates within the anastomosis has to be calculated based on the extracted vessel lumen areas from the EUS sequence data.

Step 1 and 2 can be enabled by developing image analysis algorithms for automatic detection and segmentation of anastomotic structures. The output of the algorithms can then be used to quantify the stenotic rates of the anastomosis. Apart from the anatomical challenges and movement artifacts described in section 3.4 the detection and segmentation algorithms has to be robust to multiple phenomenon's related to ultrasound image acquisition e.g. speckle, reflection artifacts, and anisotropic tissue structures.

Speckle is acoustic noise which occurs due to scattering of the ultrasound beam from microscopic tissue inhomogeneities. The beam scattering violates an assumption that the ultrasound beam travels along the same path through the tissue. Speckles create a granular pattern of the anatomical structures within the EUS image. [57, 58] While speckle is often viewed as noise it can also contain useful information for image processing purposes. [59]

Multiple types of reflection artifacts can appear in EUS images e.g. reverberation (Fig. 10a). Reverberation artifacts appear when multiple reflections occur along the same path between two parallel strongly reflecting surfaces e.g. between the adventitia and intima layers of the vessels (Fig. 1). This create an inhomogeneous intensity appearance within the vessel lumen (Fig. 9d) and can misplace objects within the EUS images due to bending of the ultrasound beam, which may appear within the vessel lumen of the anastomotic structures (Fig. 10b).

Anastomotic structures in EUS images are characterized by having a dark lumen surrounded by tissue of higher intensity with an anisotropic appearance (Fig. 8d). The anisotropic tissue appearance occurs as the proportion of the reflected ultrasound signal depends on the angle between the emitted ultrasound waves and the tissue boundaries. The angle dependency causes tissue segments, which are perpendicular the ultrasound waves to reflect more of the sound waves compared to tissue segments parallel to the ultrasound beam.



**(a)** **(b)**

**Fig. 10:** *(a) A heel structure with a reverberation artifact in the top of the coronary artery. (b) A heel structure with an artifact withing the graft lumen.*

## 4.1 Automatic detection of anastomotic structures

Anastomotic structures in EUS images are characterized by having a dark lumen surrounded by tissue of higher intensity. However, EUS images contain multiple dark structures within the images. Therefore, a vessel detection algorithm has to discriminate between vessel regions and dark non-vessel regions within a EUS image.

Stoitsis et al. [60] has proposed using the Hough transform for detection of healthy carotid vessel structures in ultrasound images using the assumption that vessel structures are circular. The Hough transform is a method to detect objects within a certain class of shapes. It detects objects based on edge information within the image and the performance therefore, depends on the quality of the image data. The sensitivity in detecting anastomotic structures using the Hough transform can therefore be reduced when the anastomotic structures are corrupted by speckle, noise, and missing tissue information. Though, the robustness in detecting objects with low or missing edge information can be increased in the Hough transform, this can increase the risk of

detecting false positive vessel regions within the EUS images. Additionally, the assumption that anastomotic structures are circular is not adequate due to surgical manipulation of the vessels.

Approaches using object specific appearance information has been proposed to improve detection of objects with low contrast edge information. Liu et al. [61] proposed using template matching for detection of carotid vessel structures in ultrasound images. A trained vessel appearance template was used to find matching locations from an exhaustive scan of an image. The vessel-specific appearance information can improve the detection of vessel structures. However, when detecting objects of varying sizes and shapes, template matching is computationally expensive because multiple templates are required.

To avoid exhaustive scans, classification-based approaches have been proposed for the detection of anatomical objects in ultrasound images. [62, 63] These approaches first use a global initialization, which is sensitive in locating the object of interest but may also detect multiple false positive locations. Then, an object-specific classifier is used in the predicted locations to discriminate between object and non-object regions to remove false positive detections from the global initialization. However, these studies did not use features developed for detection of anastomotic structures.

Mori et al. [64] proposed using a combination of segmentation and classification for the simultaneous segmentation and detection of objects of interest. They analyzed superpixel combinations to make a probabilistic segmentation, using features of trained object classes for combined segmentation and detection of the objects of interest. A segmentation-based approach can allow using object-specific appearance information from within and immediately outside the object region to facilitate a more accurate classification of the objects of interest.

## 4.2 Extract vessel lumen area of anastomotic structures

To extract the vessel lumen area of anastomotic structures the vessel lumen has to be segmented within the EUS sequences. Different segmentation approaches can be used to extract the vessel lumen.

Zahalka et al. [65] and Ukwatta et al. [66] has proposed using intensity based active contour frameworks for segmentation of carotid arteries in cross sectional ultrasound images. Active contours use internal and external energies to deform a contour to an object by minimizing the energy of the contour. The internal energies impose constraints to obtain a smooth con-

tour. The external energies attract the contour to features of interest within the image e.g. based on gradient or regional information. The behavior of the active contour is controlled by weighing the different components in the energy formulation. Both these algorithms were developed for segmentation of 3-d image data sets. This requires that the image data is first recorded and then analyzed in an offline setting. However, EUS sequences have to be segmented for online evaluation of the stenotic rates during the primary surgery. Additionally, the algorithms do not utilize a priori knowledge of shape or appearance which may increase robustness in segmenting objects with uncertain object boundaries as in anastomotic structures.

Guerrero et al. [67] proposed using a modified Star-Kalman filter to segment and track vessel structures through ultrasound sequences. The Kalman filter was used to predict ellipse parameters in subsequent frames to segment the vessel structures. However, ellipse parameters are not sufficient to describe the shape variation of surgically manipulated vessel structures.

Model based approaches such as active shape models (ASM) [68] has been proposed for segmentation of structures with a characteristic appearance and shape. ASM has previously been used in other ultrasound applications e.g. for real-time tracking of the myocardium [69] and segmentation of the common carotid artery [70]. ASM uses statistical information from shape and appearance variations of objects using principal component analysis (PCA) based on training data from manual segmentations. The trained models are then used for segmentation of new images. The use of a priori statistical information from previous segmentations may make segmentation of anisotropic tissue information more robust while also constraining segmentations to known shapes. The robustness of ASM may be further improved using 2d-PCA analysis of neighboring landmarks to obtain a better global fit of the contour. [71]

Only Guerrero et al. [67] and Hansegaard et al. [69] accounted for object movement during segmentation in the mentioned algorithms. Both approaches used Kalman filters to predict object movement in subsequent images. However, the sudden movement of the vessel structures in between frames when the heart is beating can make movement of the vessel structures difficult to predict. Instead registration-based approaches using similarity metrics of the intensity information from previous frames may be used to account for inter-frame vessel movement. [72]

# 5 Background Summary and Thesis Objective

Intraoperative anastomosis quality assessment can confirm patency and disclose technical errors in CABG anastomoses. This can enable anastomosis revision during the primary surgery to improve long term anastomosis patency, clinical outcome for the patients, and the cost effectiveness of CABG.

Coronary angiography can be used to determine the stenotic rates of anastomoses and is currently considered the gold standard for intraoperative anastomosis quality assessment. However, it is invasive, not available in most operating rooms, and the stenosis assessment is subject to significant inter-user variability and is only based on evaluating diameter percent stenosis from 2-d images of the anastomotic structures. IFI also visualizes the anastomotic structures and it is simple to perform. However, IFI only provides a semi-quantitative assessment of the anastomotic quality and it is less sensitive than coronary angiography. TTFM provides a functional assessment of the anastomotic quality by measuring the blood flow through the anastomosis. It is currently recommended as the clinical standard for intraoperative anastomosis quality assessment. Still, multiple factors affect the flow measurement and the interpretation depends of the experience of the user. Additionally, it can only reliably detect diameter stenoses above 75% and it cannot define the degree and location of an obstruction within an anastomosis.

EUS can visualize the anastomotic structures and allows differentiating between gross anatomic construction errors, intimal flaps, thrombus, and spasms. It has been demonstrated to have a high accuracy in detecting technical errors when compared to coronary angiography. EUS images can be used to extract the stenotic rates within anastomoses to obtain an objective measurement of the anastomotic quality and predict the long term patency of the anastomosis. EUS also allows to evaluate area percent stenosis, which may provide a more accurate evaluation of the stenotic rates e.g. in anastomotic vessel structures with an asymmetric shape. Additionally, in vivo EUS sequences can be obtained on the beating heart to evaluate real-time dynamic information of the anastomotic structures. Currently, stenotic rates have to be quantified manually from EUS sequences as no objective methods are available. Analysis of EUS sequences can be time consuming and surgeons has to be trained in interpreting EUS images or rely on peer reviews from a radiologist post-surgery, which may limit the use of EUS in clinical practice. Additionally, to evaluate the maximum flow capability of the anastomosis the dimensions of the anastomotic structures has to be evaluated when they are maximally distended and dynamic information of the anastomotic struc-

tures can be lost during off-line analysis of the EUS sequences. Automatic evaluation of stenotic rates in anastomoses from EUS sequences may be obtained by developing automatic image analysis methods to locate and extract the vessel lumen area in the anastomotic structures.

*The aim of this thesis was to develop and test automatic image analysis methods to enable quantification of stenotic rates of CABG anastomoses from in vivo EUS sequences.*

An automatic anastomosis segmentation algorithm has to detect vessel structures within EUS images and extract the vessel lumen area of the anastomotic structures during EUS sequences without user interaction. It also has to be robust in extracting anatomical structures which is affected by noise, artifacts, has an anisotropic intensity appearance, missing tissue information, variations in shape and size. It also has to track vessel structures which are subject to inter-frame movement during the EUS sequences.

The thesis will be focused on extracting the vessel lumen area within the heel and toe section of anastomoses. These sites can be used to assess the blood flow to the myocardium in both end-to-side and side-to-side anastomoses. For the study EUS sequences from 16 end-to-side anastomoses obtained from 12 anesthetized healthy pigs that underwent CABG was available.

## 5.1 Paper Introductions

The thesis is based on four papers:

Paper A presents a generalized approach for semi-automatic tracking and segmentation of anastomotic structures of three patent anastomoses throughout an EUS sequence. An active contour model approach was used for the segmentation and a weighted centroid mean shift procedure was used to estimate inter-frame vessel movement.

Paper B presents a generalized approach for automatic vessel segmentation of EUS sequences by adding an automatic vessel detection step to the vessel segmentation algorithm in paper A. The vessel detection located patent vessel structures within EUS images based on features extracted from potential vessel regions extracted within the EUS images. A segmentation quality control step was used to detect if tracking of the vessel was lost during the sequence to reinitialize of the segmentation algorithm. Performance of the algorithms was based qualitative evaluation of EUS data obtained from 8 porcine anastomoses made on healthy vessels.

Paper C describes an automatic vessel detection algorithm based on segmentation and region classification to locate vessels of different sizes within EUS images. Features were extracted based on information of the vessel lumen and surrounding tissue to increase the accuracy of the vessel detection. Performance of the vessel detection was validated on 320 EUS images obtained from 16 anastomoses containing vessel structures with a vessel area ranging from 0.5-15 $mm^2$.

In Paper D an ASM approach was used for the vessel segmentation to incorporate statistical information of vessel shape and appearance in the vessel segmentation. Additionally, inter-frame vessel movement was estimated based on normalized cross correlation to improve tracking of small vessels and vessels with missing tissue information. The segmentation accuracy and agreement was evaluated based on manual segmentations of anastomotic structures from 16 anastomoses.

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# Part II

# Discussion

# 6 Discussion

The papers presented in this thesis described methods to automatically extract the vessel lumen area of anastomotic structures from anastomoses made on healthy porcine vessels using in vivo EUS sequences. The algorithms was developed and tested for their ability to automatically detect and extract the vessel lumen area of anastomotic structures.

## 6.1 Vessel Detection

Automated analysis of EUS sequences requires vessel structures are located within the EUS images without user interaction. For this purpose vessel detection algorithms based on region extraction and classification were proposed in paper B and C. The vessel detection in paper B located vessels by using features mainly characterizing the appearance of the vessel lumen from potential vessel regions within the EUS images. However, it was only able to detect vessel structures within a limited area range due to the preprocessing used and it was not robust in detecting vessels with noise within the vessel lumen. Additionally, multiple false positive vessel regions were detected because the features used for the vessel classification were mainly based on the appearance and shape of the vessel lumen. In paper C the detection algorithm in paper B was extended to detect vessels of different sizes and incorporate feature information of the surrounding tissue to improve the detection accuracy. Two region classifiers used region features to extract segmented estimates of the vessel lumen and the immediate surrounding tissue to detect regions that uniquely intersected with the vessel lumen of anastomotic structures. The performance of the vessel detection algorithm was tested based on 320 EUS images containing a total of 558 extracted vessel regions. M-fold cross validation of the vessel classification yielded an area under the curve of 0.966 (95% CI: 0.951-0.984) and 0.989 (95% CI: 0.985-0.993, $p < 0.001$) of a precision recall- and receiver operator characteristic-curve, respectively. The vessel detection algorithm was demonstrated to be robust in detecting vessels of different size, non-uniform vessel lumen, low tissue contrast segments, and missing vessel information due to small septal perforators.

Non-vessel regions yielding high vessel probabilities were mainly septal perforator structures located within the myocardium and non-vessel structures which had an appearance resembling vessel regions. Conversely, vessel regions containing vessel structures that were severely stenotic or had an abnormal shape due to severe construction errors were not reliably detected. This may occur because the shapes of these abnormal vessel structures were not well-represented in the training data. However, the classifiers used in the vessel detection algorithm also assume that the features used are nor-

mally distributed. Due to this assumption, the vessel detection algorithm can assign lower vessel probabilities in vessel structures which have an appearance that deviates from the average vessel structure. It may be argued that a missed detection of such vessel structures can indicate problems with the quality of the anastomosis. The vessel detection algorithm also had problems detecting coronary artery segments with large emanating septal perforators relative to the size of the coronary artery e.g. if the septal perforator is larger than 1/4 of the circumference of the vessel. This causes a significant reduction in tissue information and the vessel structures may appear as elongated dark structures. The problem in detecting such vessel structures occurs due to a trade-off between being robust, specific, and sensitive in detecting vessel structures with anisotropic tissue contrast, noise, artifacts, and missing tissue information. However, the vessel detection was only based on information obtained from a single EUS frame. The accuracy of the vessel detection may be further improved by incorporating temporal information from subsequent frames using the current vessel detection algorithm to locate likely vessel regions within the first EUS image or in multiple frames in the sequence.

A limitation to the vessel detection algorithm is that the performance can depend on the lumen-to-tissue contrast. If this contrast is low, oversegmented vessel structures may not be merged or the vessel probabilities may be reduced for the vessel regions. However, this only affected the algorithm performance when evaluating vessel structures having a combination of low tissue contrast and large noise structures within the vessel lumen. Because many of the features for the classifiers are intensity and/or contrast-based, small variations in detection performance may be observed using different ultrasound scan parameters. Therefore, the vessel detection algorithm may have to be trained under different scan settings to ensure an optimal performance regardless of scan parameters.

## 6.2 Vessel Segmentation methods

Vessel segmentation methods were presented in papers A, B, and D to extract the vessel lumen area of cross sectional anastomotic structures within in vivo EUS sequences. The proposed methods consisted of elements for vessel lumen area extraction, inter-frame vessel alignment, and segmentation quality control. The segmentation approaches were developed to extract the vessel lumen to determine vessel lumen area of the anastomotic structures. Inter frame vessel alignment procedures was used to locate the vessel structures in subsequent frames if translation of the vessel structures occurred in between frames due to cardiac motion when obtaining EUS sequences on the beating heart. The segmentation quality control was used to determine if the vessel

information was low or a poor segmentation was made during the sequence.

Paper A described a generalized approach for semi-automatic segmentation and tracking of patent anastomotic structures. A gradient based active contour approach, a weighted centroid mean shift procedure, and contour intensity analysis was used to extract the vessel lumen, estimate interframe vessel movement, and segmentation quality control respectively. It was demonstrated it was possible to segment and track vessel structures during EUS sequences. However, segmentation was not accurate in segmenting low contrast anisotropic vessel structures and tracking was easily lost due to missing tissue information, lumen contrast, and in small vessel structures. In paper B an automatic vessel detection step was added to the algorithm in paper A. The segmentation quality control was then used to discard segmentations and reinitialize the algorithm if a poor segmentation was detected to reduce the risk of using poor segmentations as initialization in subsequent frames. In paper D it was proposed to use active shape modeling (ASM) and normalized cross correlation (NCC) to improve the segmentation and inter frame vessel alignment, respectively. The ASM incorporated a priori knowledge of shape and appearance from manual vessel segmentations used as training data to improve robustness of the segmentation. NCC was used to improve the robustness in estimating vessel motion of vessels with missing tissue information, lumen noise, and small vessels.

A mean Dice coefficient of 0.85 ($\pm$ 0.13) was obtained between the vessel segmentations approved by the quality control and manual segmentations with a mean absolute area difference of 20.62% ($\pm$ 25.84). An intraclass correlation coefficient of 0.657 (95% CI 0.520-0.786) was obtained from repeated segmentations in different EUS images of the heel and toe sites in the anastomoses. The Dice coefficient indicated that a high overlap between automatic and manual segmentations of the anastomotic structures was obtained. However, the standard deviation of the absolute area difference between automatic and manual segmentations indicate that large segmentation errors occurred during the EUS sequences. Segmentation errors mainly occurred due to overestimations in coronary artery segments having large emanating septal perforators structures surrounded with high intensity information, grafts with high intensity structures located close to low intensity tissue information, or underestimation of small vessel structures due to lumen reflection artifacts. Some of the segmentation errors during the EUS sequences may be improved by using more a priori knowledge from the previous segmentations to increase the robustness of the vessel segmentation. However, segmentation errors may also occur in the first frame of the EUS sequence where a priori information is limited. In this situation the current vessel segmentation algorithm may be used in x frames and then perform a retrospective segmentation correction of previously segmented frames based on the image information from the new frames. Using more information from subsequent frames may

also improve segmentation of low contrast vessel structures which has more uncertain vessel information.

It was demonstrated that larger segmentation errors occurred in smaller vessel structures. This may be due to septal perforators and lumen artifacts have a bigger relative influence compared to large vessel structures. Larger segmentation errors in small vessel structures may induce a systematic error in determining the vessel area of vessels of different size, which may have be taken into account when determining the vessel lumen area. However, vessel structures with sizes below 3 $mm^2$ were not well represented within the porcine anastomoses made for this study. Therefore, further research has to be conducted to evaluate any potential systematic segmentation errors in segmenting anastomoses with small/ stenotic vessel structures.

The vessel segmentations had a moderate to substantial agreement between repeated segmentations of anastomotic landmarks obtained in different EUS images. The repeated segmentations in most of the anastomotic landmarks included a manual reference vessel area of the anastomotic landmark within a 95% confidence interval or had a mean value close to the reference area. The anastomotic landmarks having the largest area variations was a vessel structure which had an asymmetric shape and vessel structures with large septal perforators emanating from the coronary artery. The variation in the asymmetric vessel structure may occur as this shape was not well represented within the training data. It may also occur as the mean shape is used to deform the ASM in the coarse scale in each frame, which is used to make the segmentation more robust with regard to missing tissue information of the vessel structures during the sequence. However, this procedure may also reduce the ability to accurately segment asymmetric vessel structures creating a trade-off between segmentation flexibility and robustness. This may be resolved by using local parameter fitting or uncertainty estimation in the vessel segmentation. The area variation in vessel structures containing large septal perforators occurs as the missing tissue information creates uncertain information about location of the vessel borders, increasing the random variation in segmenting the vessel structures. Using more information from previous vessel segmentations containing more tissue information may increase the robustness in segmenting such vessel structures.

11.0% of the vessel structures with a manual segmentation did not have a vessel segmentation approved by the segmentation quality control. This mainly occurred due to not detecting vessel structures, low vessel contrast, or poor vessel segmentations. Currently, information from segmentations which are not approved is discarded from further analysis. Therefore, the current vessel segmentation algorithm setup has a tradeoff between select-

ing parameters of the quality control and loss of dynamic information of the vessel structures. Increasing the threshold of the quality control parameters can increase the accuracy of the vessel segmentation algorithm, but it also causes less segmentations to be approved. Additionally, when less segmentations are approved, the vessel segmentation algorithm has to rely more on detecting the vessel structures in during the sequence which reduces the possibility of using a priori knowledge during the sequence. It can be argued that a quality control step is not needed if the vessel segmentation algorithm is sufficiently robust. However, if vessel structures accidentally moves out of the scan plane or the acoustic contact is lost during EUS sequences false measurements may be made if vessel segmentation is continued in such frames. Therefore, it is important to assess if the vessel information is unrealistic compared to previous segmentations. The quality control may also be used to evaluate if a segmentation may benefit from using more information from previous or subsequent frames with approved segmentations.

## 6.3 Anastomosis Quality Assessment

A mean absolute area difference of 20.62% ($\pm$ 25.84) was obtained when comparing the area between the automatic and manual segmentations. Furthermore, the 95% limits of agreement in a Bland Altman plot were between $\pm$ 66.18%. These results show that the current anastomosis segmentation algorithm is subject to a large random variation in determining the vessel lumen area. The random variation of the extracted vessel lumen area may have a large influence when quantifying the stenotic rates within the anastomosis when the ratio of two vessel areas, which are both are subject to random variation, has to be compared. Therefore, the robustness of the segmentations may have to be improved to accurately determine the stenotic rates within the anastomoses. However, further studies has to be made to evaluate how much the random variation influences the stenotic rate assessment compared to the current gold standard. The effect of the random variation in the stenosis assessment also has to be compared to the inter-user variability in determining the stenotic rates using EUS images.

The anastomosis segmentation algorithm extracted the vessel lumen area more reliably in vessel structures which did not have large septal perforators emanating from the coronary artery. Stenosis assessment may therefore be more reliable in comparing vessel lumen areas of anastomotic sites which are not located close to septal perforators. To obtain the most reliable measurements of the stenotic rates, EUS may also be used to locate an optimal anastomotic target site which may also prevent placing the anastomosis near plaques within the coronary artery which can reduce the blood flow to the

myocardium. The quality of the anastomosis may also be evaluated based on analysis of the extracted vessel lumen area during the cardiac cycle. A large area variability in the extracted vessel lumen area may indicate anatomical changes of the visualized structures and can assess the validity of the extracted vessel area during the cardiac cycle. The area variation during the cardiac cycle may then be used to locate vessel segments containing e.g. emanating septal perforators or intimal flaps within the vessel lumen.

Currently, evaluation of the anastomotic quality is based on the FitzGibbon grading system, where the anastomotic landmarks are divided into patent, having clinically significant stenosis, or occluded. A clinical significant stenosis is defined by a vessel diameter reduction threshold of 50% in an anastomotic landmark. A reason for using only three categories for the anastomosis grading can be due to the significant inter-user variability using coronary angiography, especially in evaluation of anastomoses with mid-range stenoses. Additionally, TTFM and IFI only works well in confirming patent anastomoses or detect occlusions within the anastomosis. The random variation observed in current anastomosis segmentation algorithm also indicates that the current framework is better in confirming patent anastomoses or detecting occluded anastomotic landmarks. Additionally, it may be less accurate in determining stenotic rates of anastomoses containing large stenoses due to larger random variation in segmenting smaller vessel structures. However, extracting the stenotic rates from EUS sequences has great potential to add more detailed information of the patency of anastomoses compared to the current methods due to the high resolution of EUS. Accurate evaluation of the stenotic rates can provide the surgeon with a larger decision range in deciding if an anastomosis should be revised or not. Additionally, EUS is currently the only intraoperative anastomosis quality assessment which can evaluate the area percent stenosis within the anastomotic structures, which may add detail to the current anastomosis quality assessment. However, the added value of using area percent stenosis from EUS sequences during the primary surgery has to be evaluated in a clinical study.

Stenotic rates obtained from EUS images has been shown to be a good predictor of long term patency of the anastomosis. Therefore, accurate extraction of the stenotic rates may be used to improve patient outcome of CABG and the cost effectiveness of CABG. Improved anastomosis quality assessment may also increase the number of OPCABG used to further decrease adverse effects for the patients.

## 6.4 Study Limitations

The in vivo EUS data obtained for algorithm development and testing was based on 16 anastomoses made on healthy porcine vessels. While the EUS data contained a range of different vessel sizes, stenotic rates, and construction errors, more EUS data from different anastomoses are needed for training of the algorithm to fully assess performance of the anastomosis segmentation in clinical practice. Additionally, segmentation performance has yet to be evaluated on anastomoses made on diseased human vessels. Vessel structures containing plaque can have different shapes compared to healthy vessel structures and may produce shadow effects in the EUS images. However, previous ex vivo studies obtaining EUS images of human anastomoses have reported that porcine anastomoses resemble human anastomoses. [14] It was also reported that plaque and calcification did not impair anastomosis assessment in 12 anastomoses constructed in a diseased portion of the coronary artery. Even though this was concluded based on a small sample size, it is expected that the vessel segmentation algorithm can be trained to extract the vessel lumen of vessel structures containing plaque. Still, behavior with regard to motion artifacts, contrast, and vessel appearance of the EUS data used in this study is expected to resemble performance of real life clinical data. Additionally, as the vessel lumen area of the vessel structures of the anastomoses varied between 0.25-15.91 $mm^2$ based on the manual segmentations used as ground truth data it is expected that the EUS data can represent the ability to quantify various stenotic rates within anastomoses.

The anastomosis segmentation algorithm has been developed to evaluate stenotic rates in the heel and toe sections of anastomotic structures. However, technical errors can also occur in the middle or in the orifice in the anastomosis. The current framework can be adapted for segmentation of the middle of the anastomosis e.g. by detecting that a middle plane emerges and then use a specific middle plane ASM or by tracking the graft and coronary artery separately using knowledge of the segmentations made of the heel and toe sites in previous EUS frames. Stenoses in the anastomotic orifice can be difficult to estimate using only cross sectional images and may have to be further supported from information obtained from longitudinal images of the anastomosis.

## 6.5 Other Applications

The automatic vessel segmentation algorithm may be used in other applications where the lumen area of the vessels or anastomotic structures has to be evaluated in ultrasound images. For other applications only a few parame-

ters in the algorithms may have to be adjusted as many of the processes are mainly based on training data from the specific application. The vessel detection may also be used to automatically select regions of interest in the EUS images for Doppler flow measurements. The Doppler flow may then also be used to compliment the anastomosis quality assessment.

# 7 Conclusion

The thesis has presented work of developing and testing automatic image analysis methods to enable quantification of stenotic rates from in vivo EUS sequences of the heel and toe sites of porcine CABG anastomoses made on healthy vessels. The approaches was developed and tested for their ability to detect vessel structures within EUS images and extract the vessel lumen area of the anastomotic structures. The current framework is able to automatically detect and track anastomotic structures within EUS sequences without user interaction. Reliable vessel segmentations were obtained in vessel structures not containing large septal perforators. Though, further improvement may be necessary to increase the robustness of the vessel segmentations, the results indicates that the method has the potential to automatically extract the vessel lumen area of anastomotic structures in EUS sequences to enable quantification of stenotic rates in CABG anastomoses. Accurate extraction of the stenotic rates from EUS sequences may be able to predict the long term patency of anastomoses during the primary surgery to improve patient outcome of CABG.

# Part III

# Publications

# Paper A

## Semi-Automatic Vessel Tracking and Segmentation using Epicardial Ultrasound in Bypass Surgery

Alex Skovsbo Jørgensen, Samuel Emil Schmidt, Niels-Henrik Staalsen, and Lasse Riis Østergaard

The paper has been published in the
*Engineering in Medicine and Biology Society (EMBC)* Vol. 34, pp. 2331–2334, 2012.

*The layout has been revised.*

# Paper B

## Automatic Vessel Tracking and Segmentation using Epicardial Ultrasound in Bypass Surgery

Alex Skovsbo Jørgensen, Samuel Emil Schmidt, Niels-Henrik Staalsen, and Lasse Riis Østergaard

The paper has been published in the
*Computing in Cardiology* Vol. 39, pp. 9–12, 2012.

# Paper C

## Automatic Detection of Coronary Artery Anastomoses in Epicardial Ultrasound Images

Alex Skovsbo Jørgensen, Samuel Emil Schmidt, Niels-Henrik Staalsen, and Lasse Riis Østergaard

The paper has been Submitted to
*International Journal of Computer Assisted Radiology and Surgery*, October 2014.

# Paper D

## Automatic Coronary Artery Bypass Anastomosis segmentation in Epicardial Ultrasound

Alex Skovsbo Jørgensen, Samuel Emil Schmidt, Niels-Henrik Staalsen, and Lasse Riis Østergaard

The paper has been submitted to
*International Conference on Information Processing in Computer-Assisted Interventions*, November 2014.

*The layout has been revised.*

# SUMMARY

Coronary artery bypass graft surgery (CABG) is used to reestablish blood supply to the myocardium by suturing grafts onto the coronary artery, creating an anastomosis, beyond a stenosis or occlusion. Up to 9% of anastomoses contain stenoses >50% post-surgery, which can lead to poor long term outcome or be fatal for the patient. Intraoperative anastomosis quality assessment can be used to disclose anastomotic errors and enable anastomosis revision during the primary surgery.

Coronary angiography is the current gold standard for anastomosis quality assessment, but it is not available in many operating rooms. Instead, epicardial ultrasound (EUS) has been proposed to locate anastomotic errors and quantify the stenotic rates within anastomoses. Currently, the anastomotic quality is evaluated manually using EUS images as no objective methods are available to quantify the stenotic rates. This can be time consuming and surgeons have to be trained in interpreting EUS images or use peer reviews by a radiologist.

The research in this thesis has focused on developing and testing medical image analysis algorithms to enable automatic quantification of stenotic rates of CABG anastomoses from in vivo EUS sequences. Algorithms for detection and segmentation of anastomotic vessel structures to automatically extract the vessel lumen area are presented.

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