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Detection of coronary artery disease with an electronic stethoscope

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Dissertation for the Degree of
Doctor of Philosophy
by
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Faculties of Medicine

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PREFACE AND ACKNOWLEDGEMENT

The idea for this thesis originates from my final semester at the Master education in Biomedical Engineering and Informatics at Aalborg University. In our Master thesis my co-student Claus Graff and I started working in the subject of detection of coronary artery disease (CAD) with an electronic stethoscope. In a small dataset which included CAD patients and fellow students we were successful in identification of CAD patients. This inspired me to continue research in the subject. The current Ph.D. work started in 2006 after successful completion of an additional preliminary study. The goal of my research was to develop a non-invasive method for diagnosis of CAD. In a recent published review the research task was outlined as:

The development of a definitive, noninvasive test for detection of coronary blockages is one of the holy grails of diagnostic cardiology.

John Semmelow 2007

The result of the current thesis is not a final solution, rather a presentation of some new results and ideas which in combination with prior knowledge may contribute to a clinical useful solution.

It is a pleasure to thank you who supported and encouraged my research, even though the goal maybe appeared unrealistic. A special thanks to my supervisor Dr. Johannes Struijk who provided admirable supervision, which guided me in the challenges of science. Thank you for the many inspiring discussions which sparked my curiosity and made me feel that I had the best job in the world. Thanks to Professor Egon Toft for the encouragements, the proficient inputs and the many times you have made use of your extensive network in the interest of the project.

I would like to thank Claus Holst-Hansen at Aalborg Hospital and Martin Græbe at Rigshospitalet Copenhagen for collecting data and for editorial feedback from a clinical view point.

In the recent years the research project expanded to include my colleges John Hansen and Henrik Zimmerman. I appreciate your enthusiastic attitude and your qualified inputs and contributions.

Thanks to the team at Coloplast A/S and Acarix A/S who was fast to realize the potential of heart sound based detection of CAD. Thank you for your support and your dedication to develop the concept beyond the scope of the current thesis.

A special thanks to my officemates Claus Graff, Mads Peter Andersen and Jonas Emborg for friendship and countless discussions about everything from personal issues to study designs and statistics.

I will thank my family and friends for their support and for reminding me of a life outside the Academic world.

Finally I express my deep appreciation to my beloved wife. I appreciate your incredible patience, your support and the warm love you show me.

Samuel Schmidt
Aalborg April 8, 2011

ENGLISH SUMMERY

Coronary artery disease (CAD) is a major health problem and accounts for approximately 20% of all death in Europe. Despite of a wide range of diagnostic tests diagnostic challenges still remains. Up to 59 % of patients submitted to the invasive and costly Coronary angiography doesn't suffer from CAD. At the same time more than 50% of people dying suddenly from CAD had no prior symptoms of CAD. The aim of the current thesis is to develop a low cost method for noninvasive diagnosis of CAD, based on analyses of heart sounds obtained with an electronic stethoscope. Signal processing algorithms for heart sound based detection of CAD was first proposed in the early eighties. It was shown that CAD was associated with weak diastolic murmurs, which increased the high frequent sound pressure. In contrast to the prototypes used in the early studies the electronic stethoscope is robust and easy to use and thereby well suited for the clinical environment.

Since CAD is associated with diastolic murmurs identification of the diastolic periods is essential. Typical solutions for heart sound segmentation use a reference signal such as ECG, but in the case of the electronic stethoscope only the heart sound signal is available. In this thesis an automatic segmentation method, based on a duration depended Markov model, was therefore developed to divide the heart sounds into systolic and diastolic periods.

To gain further insight into the CAD murmurs an analysis was conducted to examine if cardiovascular murmurs could be modeled as a chaotic process. The result of the analysis showed no significant difference between murmurs and linear stochastic models, thereby there weren't any indications of nonlinearity and low dimension chaos in the murmurs.

To improve robustness against noise, such as handling noise and ambient noise, a framework was developed to identify low noise periods in the heart sound signals. Using the framework a wide range of features were extracted to discriminate heart sounds from patients with and without CAD. The analyses of the features identified a new low frequency component which discriminates between non-CAD and CAD patients. It was found that the low frequency energy (20-40 Hz) was increased in CAD subjects.

By combination of the low frequency features and a feature from a high frequency band (250-1000 Hz) a classification system was developed. In a cross validation test the area under the receiver operating characteristic curve was 0.73, the sensitivity was 72% and the specificity was 65.2%. The results indicate that the method has a potential for detection of CAD, though further improvement is necessary to solve problems related to the application of the electronic stethoscope in a clinical environment. Such challenges include better management of ambient noise and handling noise.

DANSK RESUME

Iskæmisk hjertesygdom (IHS) er et stort sundhedsproblem og tegner sig for ca. 20% af alle dødsfald i Europa. På trods af en lang række diagnostiske tests, er der stadig diagnostiske udfordringer. Op til 59% af patienterne som undergår den invasive og dyre koronarangiografi undersøgelse lider ikke af IHS. Samtidig har mere end 50% af de mennesker som dør pludselig på grund af IHS ikke tidligere haft symptomer på IHS. Formålet med denne afhandling er at udvikle en billig ikke-invasiv metode til diagnostisering af IHS ved analyse af hjertelyde optaget med et elektronisk stetoskop. Signalbehandlingsalgoritmer til diagnose af IHS ud fra hjertelyde blev foreslået i begyndelsen af firserne. Her blev det vist at IHS var forbundet med en svag diastolisk mislyd, hvilket øger det højfrekvente lydtryk. I modsætning til prototyperne anvendt i de tidlige undersøgelser, er et elektronisk stetoskop robust og let at bruge, hvorved det er velegnet til det kliniske miljø.

Da IHS er forbundet med diastoliske mislyde, er identifikationen af de diastoliske perioder væsentlig. Typiske løsninger til segmentering af hjertelyd bygger på et referencesignal som f.eks. EKG, men i det elektroniske stetoskops tilfælde er hjertelydsignalet det eneste signal som er til rådighed. Derfor blev en automatisk segmenteringsmetode udviklet i denne afhandling. Metoden er baseret på en tidsafhængig Markov-model, som anvendes til at opdele hjertelydene i systoliske og diastoliske perioder.

For at opnå yderligere indsigt i IHS mislydene blev en analyse udført for at undersøge om hjerte-kar-mislyde kunne modelleres som en kaotisk proces. Resultatet af analysen viste ingen signifikant forskel mellem mislyde og lineære stokastiske modeller, og dermed var der ingen tegn på ikke-linæritet og lavdimensional kaos i mislydene.

For at opnå robusthed mod støj, såsom håndteringsstøj og baggrundsstøj, blev et framework udviklet til at udtrække parameter fra støjsvage perioder i hjertelydssignaler. Ved brug af frameworket blev en lang række parametre udvundet med det formål at diskriminere hjertelyden fra patienter med IHS fra hjertelyden fra patienter uden IHS. Som noget nyt viste analysen af parametrene, at energiniveauet ved lave frekvenser (20-40 Hz) var forhøjet hos IHS patinterne.

Ved at kombinere de lavfrekvente parametre med parametre fra et højfrekvent frekvensbånd (250-1000 Hz), blev et klassificeringssystem udviklet. I en krydsvalideringstest var arealet under receiver operating characteristic kurven 0.73, sensitiviteten var 72%, og specificiteten var 65,2%. Resultaterne viser, at metoden har et potentiale for diagnosticering af IHS, men yderligere forbedringer er dog nødvendige for at løse problemer relateret til anvendelsen af det elektroniske stetoskop i et klinisk miljø. Disse udfordringer omfatter bl.a. en bedre håndtering af baggrundsstøj og håndteringsstøj.

TABLE OF CONTENTS

1. Introduction

Coronary artery disease (CAD) is a result of extensive buildup of plaque deposits in the coronary arteries. The result is narrowed and hardened arteries which limits the coronary blood flow. CAD might result in myocardial infarction (MI) which is often caused by sudden ruptures of atrial plaque deposits.

1.1. Mortality and prevalence

Cardiovascular disease, which includes CAD, constitutes a major global health problem and is the leading cause of death in the world. In 2004 cardiovascular disease accounted for 29% of all death [1]. CAD is the cardiovascular disease which accounts for most deaths and CAD accounts for 12.3% of all deaths worldwide [1]. In Europe more than 20 % of all deaths were caused by CAD in 2000 [2] and the CAD prevalence in Europe was 9.9 million. Figure 1 show the US prevalence distributed according to age and gender. In 2002 the worldwide prevalence of CAD was 40 million and the total number of deaths caused by CAD was 7.2 million [1].
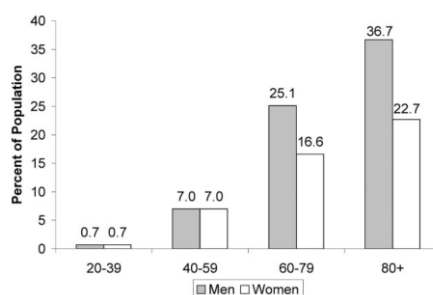
Figure 1. Prevalence of CAD in the USA by age and sex (2003-2006) [3].

In recent years CAD mortality has declined in the US and Western Europe. For example, CAD mortality decreased with 42 % in the United Kingdom from 1994 to 2004 [2]. The decrease in death rate is due to a lower rate of heart attacks and a better chance of surviving a heart attack [4]. Also the incidence rate is declining in Western and Northern Europe. Even though the mortality has been declining in Western countries a future increase in CAD mortality is expected due to the aging population [4]. The decline observed in western counties is in sharp contrast to the increases in CAD mortality in developing counties. From 1990 to 2020 CAD mortality in developing counties is expected to increase with more than 120% [4]. Already today 82% of all CAD related deaths is occurring in the developing countries [1].

1.2. Diagnostic challenge

The first manifestation of CAD is either acute (MI and unstable angina) or non-acute (typical Stable angina). The typical diagnostic process of diagnosing CAD in the non-

acute phase starts with a risk assessment based on symptoms, medical history and risk factors. Typical risk factors include family history of CAD, age, sex, smoking, abnormal blood lipid levels, hypertension, diabetes mellitus, abdominal obesity, low daily fruit and vegetable consumption and lack of Physical activity [2, 3]. Based on the risk assessment the patient might be referred further to diagnostic testing or a risk reducing treatment might be started. The choice of diagnostic test is ideally based on the patient's CAD risk, the accuracy of the test, the cost of the test and risk of the test.

Common methods for diagnosis of CAD include Coronary angiography, CT coronary angiography, ECG stress test, Stress Echocardiography and Myocardial Perfusion Imaging. Table 1 shows cost and performance of the different diagnostic methods. The cost estimates are based on the 2010B Medicare Physician Fee Schedule [5].

Table 1. Performance and cost (Medicare Physician Fee) of common methods for diagnosis of CAD.[5, 9, 10]

Diagnostic Method	Sensitivity	Specificity	Cost
Coronary angiography	Golden standard		$1,047.19
CT-Coronary angiography	97%	87%	$694.32
Echo exercise test	86%	81%	$247.05
Myocardial Perfusion Imaging (Exercise SPECT)	87%	73%	$449.48
ECG stress test	68%	77%	$94.39

The accuracy of Coronary angiography is high and Coronary angiography is considered the golden standard for the diagnosis of CAD and is used as a reference test in validation of other methods [6]. The disadvantages are that the method is invasive, costly, requires highly trained personnel, constitutes a risk of complications [7] and that the method exposes patients to radiation [8].

Computed tomography (CT) coronary angiography is under heavy development and is predicted to play an important role in the diagnosis of CAD. The advantage is that the method is noninvasive and has a relative high accuracy. A recent Meta analyses found that the sensitivity was 97% and specificity 87% [9]. Drawbacks are high cost, radiation [8] and that in case of a positive test Coronary angiography is needed for the percutaneous transluminal coronary angioplasty procedure, thereby the patient is exposed to the double amount of radiation.

The ECG stress test is the simplest CAD test. The advantages are low cost and that the test result is directly related to cardiac functionality. The disadvantage is low accuracy, sensitivity is 68% and specificity is 77% [10].

The Echo stress test is an expansion of the ECG stress test by analyses of changes in the ventricular movement under stress such as exercise. The advantage is an improved accuracy, but drawbacks are a high operator variance and that the method requires highly trained personnel.

Myocardial Perfusion Imaging is often used in combination with cardiac stress induced by exercise or pharmacologically induced. The benefits of Myocardial Perfusion Imaging are mapping of the dysfunctional myocardium. Drawbacks are radiation and high cost.

In spite of the broad range of tests, the diagnostic challenge remains. Three diagnostic challenges are outlined below:

- **A high number of referrals with negative coronary angiography results.** A recent study of American College of Cardiology National Cardiovascular Data Registry showed that only 41% patients without known history of CAD referred for coronary angiography suffered from obstructive coronary artery disease [11]. Obstructive coronary artery disease was defined as having at least one stenosis with a minimum of 50% diameter reduction. The authors of the study concluded that better strategies for risk stratification are needed to reduce the number of negative coronary angiographies [11]. This will include a better application of noninvasive tests.
- **Asymptomatic CAD is common.** Approximately 15 % of MI events in US are fatal [3] and it is estimated that worldwide 39% of the MIs are fatal [12]. It is therefore essential to diagnose CAD before the progression to the acute state [3]. However only 18-43 percent of coronary attacks are preceded by angina [3, 13]. Statistics shows that 50% of men and 64% of women who die suddenly of CAD have no previous symptoms of the disease [3]. Identification of CAD patients can thereby not be based on symptoms alone. Proposed approaches include noninvasive testing of subjects with high risk [14].
- **Low-cost diagnostic methods are needed in developing counties.** The increases in CAD prevalence in developing counties will require affordable and fast to use diagnostic tests [15].

A low-cost and low-risk test, preferably with a higher accuracy than the ECG stress test, would properly improve the risk stratification before referral to coronary angiography and thereby reduce the number of negative coronary angiography results. In addition a low-cost and low-risk diagnostic method would allow an expanded screening of patients with an intermediate to high risk of CAD. The goal of the current thesis is to develop such a low cost and easy to use CAD test using an electronic stethoscope. An electronic stethoscope based method would be low cost, low risk, easy to use and rapid. Such a method will be suited for use in the early diagnostic phase, for example in the first patient encounter with the primary care physician.

1.3. Physiology and the signature of murmurs

The rationale behind acoustic based diagnosis of CAD is that atrial constriction causes turbulent blood flow in the poststenotic region. The turbulence generates noise, the so called Murmurs or Bruits. Cardio vascular murmurs are common pathological indicators. Typical murmurs originate from the heart valves, the carotid arteries and the renal arteries. Audible CAD murmurs are rare, but reported in several case studies [16-

21]. The scope of signal processing algorithms for detection of CAD is to develop methods which identify the CAD murmurs even though they are non-audible.

Whether linear flow transitions to turbulent flow or not depends on the Reynolds[1] (Re) number and on the geometry of the channel leading the flow. Figure 2 is a model of a stenosis constricting an artery. In the figure *d* denotes the diameter of the stenosis and *D* the vessel diameter. Throughout the thesis the degree of stenosis will be defined by the percentage-wise diameter reduction 100x*(1-d/D)* caused by the stenosis. At slow flow rates the blood will be fully laminar and the blood will follow the artery boundaries immediately after the stenosis, but as the flow rate increases (Re~10) separation will occur and a jet will originate from the stenosis orifice [22]. The jet will collide with the slowly moving blood in the outer region of the artery and eddies will occur in the sides of the artery close to the stenosis orifice. As flow increases instability will occur and the post stenotic flow will become turbulent [22].
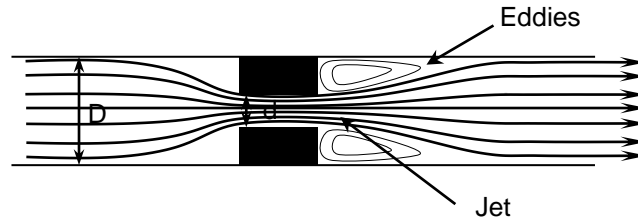
Figure 2. Illustration of flow through an obstruction.

1.3.1. The coronary anatomy

The coronary artery tree consist of three major arteries the right coronary artery (RCA), the left anterior descending (LAD) and left circumflex artery (LCX). Both the LAD and LCX originate from the left main coronary artery (LMCA). The RCA originates from the aorta. Typically, the LAD supplies the anterior parts of the left ventricle and septum, and the whole apex. The LCX supplies the left atrium, the lateral free wall and the posterior side of the left ventricle. The RCA supplies the right side of the heart, the inferior part of the left ventricle and the posterior part of the septum. In an anatomical study the outer diameters of the proximal segments of the LMCA, RCA, LAD and LCX arties in men were respectively 4.5±0.5 mm, 3.9±0.6 mm, 3.6±0.5 mm and 3.4±0.5 mm [23]. Diameters of the most distal segments of RCA, LAD and LCX were 3.1±0.5 mm, 1.7±0.5 mm and 1.6±0.6 mm. On average, in women the arteries were 14% narrower than in men.

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[1] Reynolds' number is defined as: $Re = \rho UL/\mu$ where U is fluid velocity, L is the characteristic dimension (in the current case L is the vessel diameter), ρ is the density of the fluid and μ is the dynamic viscosity of the fluid.
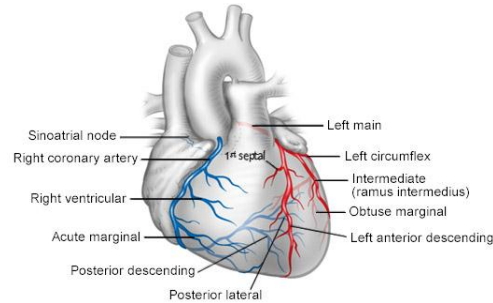
Figure 3. Illustration of the coronary anatomy (ctsnet.org)

1.3.2. Coronary flow

Due to the strong systolic myocardial contraction, the left coronary flow usually peaks in the diastolic period, see Figure 4. However in cases of severe CAD the balance between myocardial and arterial resistance is altered and the diastolic flow will decline more than the systolic flow. The flow rate varies widely from artery to artery and from subject to subject. A weighted average calculated from several studies of CAD patients showed an average coronary flow velocity in the major arteries at 20.3 cm/s and an average standard deviation at 7.8 cm/s [24-30]. There was no difference between resting flow velocities in the three major arteries [28, 31]. The peak diastolic flow was approximately 1.5 times higher than the average flow velocity [24, 27, 29]. For a 3 mm blood vessel with 20.3 cm/s blood flow the Reynolds number is 191 (the dynamic viscosity of blood =1/30 poise and density of blood 1.05 g/cm^3) this corresponds to findings by Hikita et al. who found an average Reynolds number at approximately 190 (STD: 67) in stenosed arteries. The peak diastolic Reynolds number might therefore reach to 284 in an average patient.

Figure 4. Normal coronary flow pattern recorded using a Doppler catheter [31].

The hemodynamic effect of the resistance caused by the stenosis is a pressure drop across the stenosis, but in resting conditions the pressure drop across a mild or moderate stenosis is not significant compared to the resistance in the arterioles and the myocardium [32]. Furthermore vasodilatation of the arterioles and increased blood

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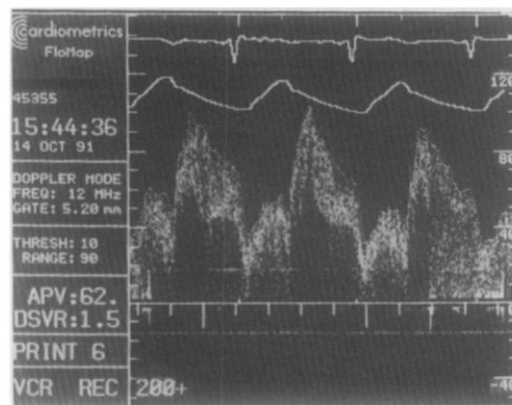pressure attempts to compensate for the increased resistance across the stenosis. Typically a 75-85% diameter reduction is necessary to influence the coronary flow rate when the patient is at rest [32], see Figure 5.
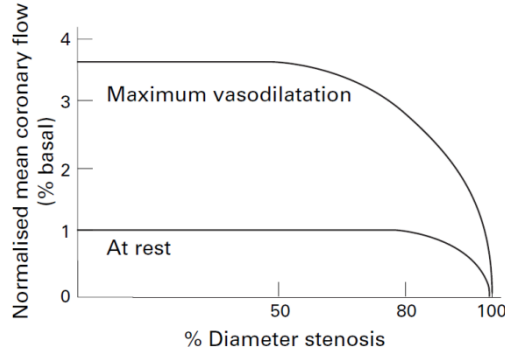
Figure 5. A typical relation between stenosis degree and coronary flow [32]

1.3.3. Onset of murmurs

The onset of murmurs is related to the geometry and the Reynolds number [33]. In a straight tube unstable flow occurs at approximately Re=2300, but when the flow is hindered by an obstruction the critical Reynolds numbers are much lower. Flow can be classified in three states: laminar, disturbed and turbulent. In the disturbed flow fluctuations occur but the fluctuations are not fully irregular [33]. Disturbed flow might cause murmurs, but the murmur intensity increases dramatically in the case of turbulent flow [33]. Sacks et al. evaluated the relationship between Reynolds number, degree of stenosis and the onset of murmurs in the aorta of dogs [34]. They found that turbulent flow was present when murmurs were observable. According to their study the Reynolds number which onsets murmurs could be estimated from the degree of the stenosis

$$Re_{Onset} = 2384\left(\frac{d}{D}\right)^2$$

where Re_{onset} is the Reynolds number in the unobstructed part of the artery which onsets the murmurs. Therefore, murmurs will occur from a 50% stenosis if the Reynolds number exceeds 596 and murmurs will occur from a 75% stenosis if the Reynolds number exceeds 149. Even slow flow with a Reynolds number at 53 will cause a murmur in the case of 85% stenosis. In the estimated average case where the peak Reynolds number was 285 a 65% stenosis will cause murmurs. However, other factors such as the degree of pulsating flow and the shape of the stenosis affect the onset of murmurs [33]. According to Young et al. an asymmetric stenosis lowers the Re_{onset} [35]. In contrast, a stenosis with a smooth transition from constriction to normal vessel diameter increases the Re_{onset} with approximately 30% as compared with a sudden

diameter change [33]. Due to the large variations in flow, Reynolds number, anatomy and pulsation it is not possible to define exact degree of stenosis which will cause CAD murmurs.

1.3.4. Murmur characteristics

As for the onset, the intensity of the murmurs is highly dependent on geometry and the Reynolds number. Two studies have used flexible tubes to study the relation between the power of the murmurs, Reynolds number and the degree of the stenosis [36, 37]. They both found a nonlinear relationship between the power of the murmurs, Reynolds number and degree of stenosis:

$$P_{mur} = K(D/d)^8 Re^{4.4}$$

where *Re* is the Reynolds number in the unobstructed part of the vessel, *K* is a constant scaling factor related to artery wall properties, properties of the surrounding tissue and recording equipment. The intensity of murmurs is thus very sensitive to changes in both flow and the degree of stenosis. Since the coronary flow only decreases slowly as the degree of the stenosis increases, see Figure 4, the power of the murmurs will likely increase until a point close to 100% obstruction. In addition to the degree of the stenosis, the shape of the stenosis effects the intensity of the murmurs [38]. Due to the large variation in physiological parameters it is difficult to estimate an absolute sound pressure for CAD murmurs, but a loose estimate can be made from experimental measurements of poststenotic wall pressure. Tobin et al. found the total poststenotic root mean square wall pressure to be 88.3 Pa, when the Reynolds number was 1500 and the stenosis degree was 68%. If this is rescaled to a Reynolds number at 285 the poststenotic root mean square wall pressure will be 1.64 Pa which correspond to a sound pressure at 98 dB (SPL).

The power spectrum of the murmurs is also related to the degree of the stenosis and the Reynolds number. The dominating component of the murmurs has a broad band character. The power spectrum of murmurs is typically characterized with a slight increase in power as frequency increases until a break frequency where the power rolls of [22], see Figure 6 which shows an experimentally obtained frequency spectrum of wall pressure in the post stenotic region.
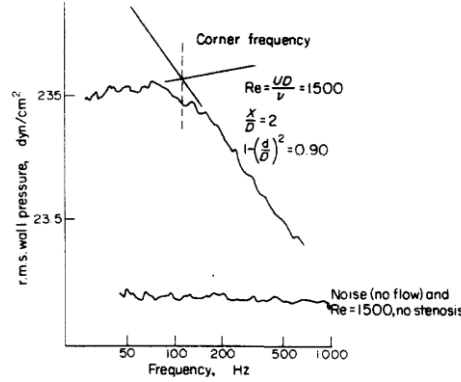
Figure 6.1/3 octave spectrum of post stenotic wall pressure in an experimental tube [39].

Several studies have found that the break frequency is related to the Strouhal number [22] which describes the relation between frequency of vortex shedding, the flow velocity and the characteristic length. The break frequency of the murmurs has been related to the average frequency of vortex shedding [22]:

$$S_2 = \frac{f_b d}{u}$$

Where f_b is the break frequency of frequency spectrum of murmur and u is the flow velocity in the stenosis. According to Jones et al. the Strouhal number can be estimated from the degree of the stenosis and the Reynolds number [40]:

$$S_2 = Re^{0.72}(d/D)^{0.26}$$

As an example, a 50% stenosis in a 3 mm artery with peak flow velocity at 30.45 m/s will generate a spectrum with a break frequency at 139 Hz. If the stenosis degree increases to 65% or 80% the break frequency will increase to respectively 375 Hz and 1738 Hz. This illustrates that the width of the murmur spectrum is strongly related to the stenosis degree.

In addition to the broad band component the power spectrum might contains narrow peaks. The peaks can be resonance frequencies of the artery wall or related to larger dominating vortices in the post stenotic region if turbulence is not fully developed [36]. Wang et al. modeled the left coronary artery tree with an electrical circuit model. He showed that a stenosis changed the resonance frequencies of the artery tree and that the turbulent flow excites these resonance frequencies [41]. According to the model two resonance frequencies changed due to the stenosis, a high frequency component (>150 Hz) increased in amplitude and shifted to higher frequencies. A second resonance frequency (<100 Hz) shifted to a lower frequency and decreased in amplitude, see Figure 7. The modeling result was compared to recordings from CAD patients. However studies of murmur from carotid arteries demonstrated that the surrounding tissue dampens the resonance frequency of the artery wall significantly [22] . The

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presence of resonance frequencies in the CAD murmurs should therefore not be taken for granted.
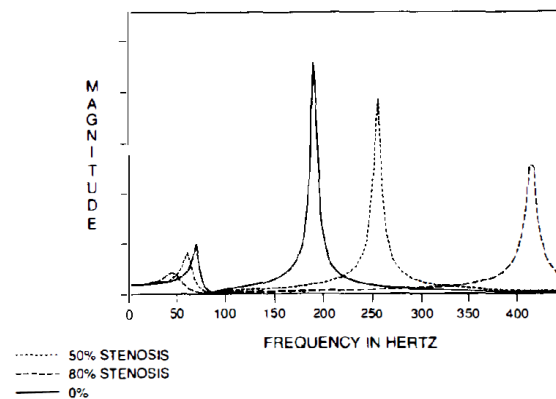
Figure 7. Model of the influence of two different degrees of stenosis on the resonance frequencies of the left coronary artery tree [41].

Murmurs from the heart will be dampened by the chest wall. By the use of pressure catheter placed in the aorta in patients with an aorta stenosis and an accelerometer placed on the chest wall, Nygaard et al. found that the damping effect of the chest wall corresponds to a low pass filter with a cutoff frequency at approximately 26±12 Hz and an attenuation slope of 29±7.9 dB per decade [42], see Figure 8. At frequencies lower than the cutoff frequency the attenuation was 36±7.7 dB. Even though the low pass filter is a simplification of the complex transfer function of the chest wall the effect of the chest wall is that the high frequency part of the murmurs is attenuated significantly. If the average attenuation across frequencies is estimated to 60 dB a loose estimate of the CAD murmur sound pressure at the chest wall is 38dB (SPL) if the poststenotic artery wall pressure corresponds to 98 dB as in the previous example where the stenosis degree was 68% and Reynolds number was 285. The detection of CAD murmurs are further complicated by the variation of the stenosis locations in the coronary artery tree, causing the distance and transfer function from the stenosis location to the recording spot to differ widely. Usually, prior studies placed the recording transducer in the 4th intercostal space at the left sternal border and a stenosis in the anterior part of the heart will thus be relatively close to the transducer.
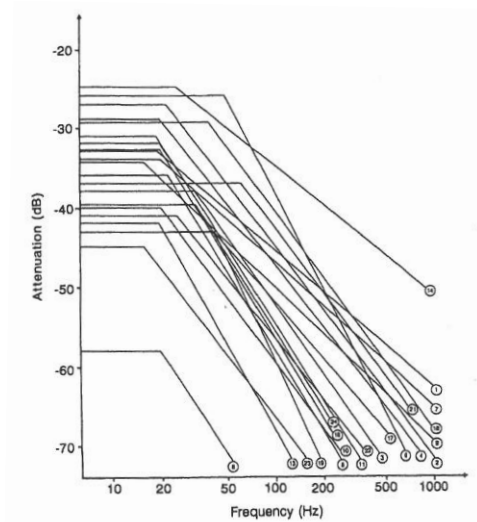
Figure 8. Estimated transfer function of the Chest wall in 24 subjects [42].

1.3.5. The normal heart sound

The normal heart sound is dominated by the first and the second heart sound (S1 and S2) which are caused by the closure of the heart valves. S1 indicates the beginning of the systole and S2 the beginning of the diastole. Usually, diastolic sounds after the S2 sound are considered to be pathological. Typical diastolic pathological sounds are heart valve murmurs, the S3 sound and the S4 sound. However the normal diastole is not completely silence. The right part of Figure 9 shows the average power spectrum of the diastoles from the illustrated recording. The diastolic spectrum in normal subjects is dominated by low frequency noise which originates from several sources including flow in the larger arteries and the heart, movement of the ventricle, ambient noise and non-cardiac physiological noise such as respiration noise and abdominal noise.
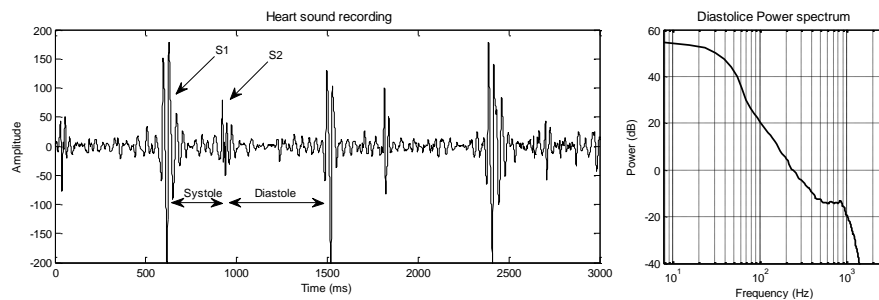
Figure 9. Typical heart sound recording from a non-CAD female and the average diastolic power spectrum.

1.3.6. Summary of physiology and the signature of murmurs

There is a large variation in the coronary flow and coronary anatomy. Typical coronary flow is likely to initiate murmurs in the case of a severe stenosis in major arteries, but

the stenosis degree which is required for the onset of murmurs varies from subject to subject. Onset of murmurs does not necessarily means that the murmurs are powerful enough to be detected at the chest wall. However the power of the murmurs increase dramatically as the degree of the stenosis increases until a point close to total obstruction, thereby the likelihood of detecting the murmur increase as the stenosis degree increase until a high stenosis degree. The frequency spectrum of the murmurs is also very sensitive to the degree of the stenosis. The upper break frequency might range from approximately 140 Hz to more than 2000 Hz depending on the degree of the stenosis and the flow rate, but the effect of the chest wall can be seen as a low pass filter which might dampen out the high frequency part of the murmurs. The combination of a wide spread in physiological variables and mechanics which is very sensitive to small changes in these physiological variables makes the exacta acoustical response of a coronary stenosis unpredictable.

1.4. Prior art

The development of algorithms for detection of CAD from heart sounds is a small sub-discipline within the area of digital signal processing of heart sounds. A literature search identified 50 publication on the subject of signal processing methods for detection of CAD from heart sounds [41, 43-78, 78-90]. In addition Semmlow et Al. publish a comprehensive review of the different methods and approaches used for heart sound based diagnosis of CAD [91].

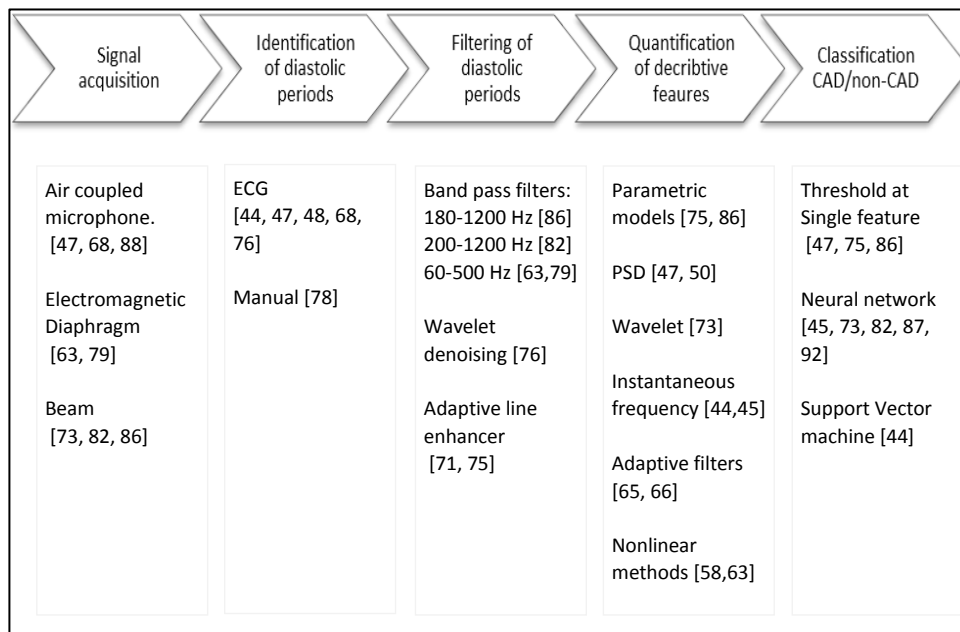| Signal acquisition	Identification of diastolic periods	Filtering of diastolic periods	Quantification of decribtive feaures	Classification CAD/non-CAD
Air coupled microphone. [47, 68, 88]	ECG [44, 47, 48, 68, 76]	Band pass filters: 180-1200 Hz [86] 200-1200 Hz [82] 60-500 Hz [63,79]	Parametric models [75, 86]	Threshold at Single feature [47, 75, 86]
Electromagnetic Diaphragm [63, 79]	Manual [78]	Wavelet denoising [76]	PSD [47, 50] Wavelet [73]	Neural network [45, 73, 82, 87, 92]
Beam [73, 82, 86]		Adaptive line enhancer [71, 75]	Instantaneous frequency [44,45] Adaptive filters [65, 66] Nonlinear methods [58,63]	Support Vector machine [44]

Figure 10. Steps in a typical signal processing method for detection of CAD and examples of different approaches applied in each step.

A typical structure of algorithms for automatic interpretation of heart sounds includes three major steps: segmentation of the recording into intervals such as systoles and

diastoles, extraction of one or more descriptive features and classification into diseases states. In CAD algorithms diastolic periods were typically identified either automatically, guided by ECG, or manually. Then characteristics were extracted from each diastolic period and averaged over several heart beats before classification into either CAD or non-CAD subjects. Figure 10 shows typical steps in algorithms for heart sound based diagnosis of CAD and summarizes different approaches from the existing literature.

1.4.1. Transducers

As described in the section "Physiology and the signature of murmurs" the CAD murmurs are weak and non-audible. Therefore, a high sensitivity and a high signal to noise ratio is required for the acoustic transducer. Two main types of sensors are often used for recordings of heart sounds: air coupled microphone and accelerometers. The air coupled setup contains a microphone situated in a coupler house and the edges of the coupler house rest at the chest wall, see Figure 11. The recorded signal is proportional to the relative displacement of the skin enclosed by the coupler house [93]. The advantage of the air coupled microphone is that the transducer's impact on the chest wall is minimal and the construction is relative simple. The drawback is that the air coupled microphones is sensitive to background noise and that air has a poor impedance match with the chest wall. The air coupled microphone was used in several studies about CAD and heart sounds [48, 48, 68, 69, 69, 88-90].
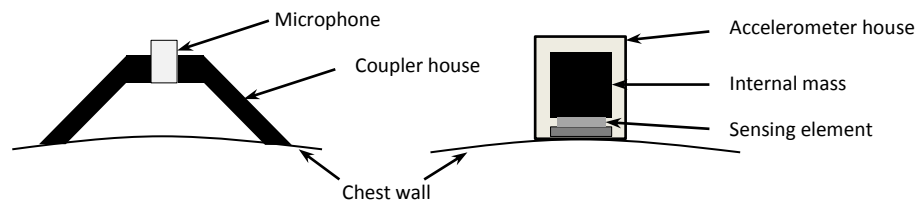
Figure 11. Illustration of the air coupled microphone and the Accelerometer

Accelerometers are often considered to be more robust against background noise [91], but the disadvantage is a mechanical load of the chest wall [94]. The weight of the accelerometer will dampen the signal, especially at higher frequencies. Therefore Padmanabhan et al. developed a lightweight accelerometer [57, 59]. Since the principle of the accelerometer was similar to the FYSPac2 accelerometer develop by Vermarien et al. the name FYSPac2 will be used as a reference to the accelerometer developed by Padmanabhan et al. The concept was a balancing beam mounted on a small stand which was attached to the chest wall, see Figure 12. Chest wall vibrations make the balancing beam bend and the deflection is collected with piezoelectric plates mounted on the beam. By adjustment of the two masses in the end of the bean the resonance frequency of the sensor is adjustable. The result was a sensitive accelerometer with a relative flat frequency response from 200-800 Hz. The FYSPac2 accelerometers

sensitivity to sound pressure[2] was approximately 100 mV/Pa in the 200-800 Hz frequency band [57]. The resonance frequency was approximately 1050 Hz. A disadvantage of the sensor is that it fragile and thereby not suitable for clinical use [95]. The FYSPac2 accelerometer was used in several studied by the research group at Rutgers University who published the majority of studies related to acoustic detection of CAD [65, 66, 70, 71, 73, 75, 82, 84, 85, 91].
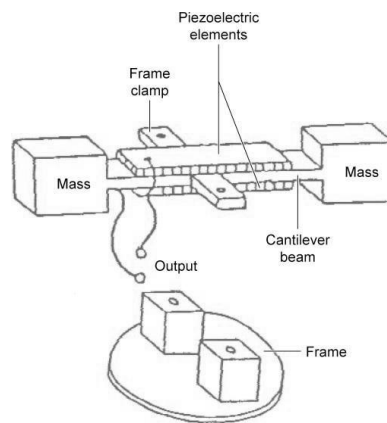
Figure 12. Illustration of the lightweight FYSPac2 accelerometer [91].

An electronic stethoscope based on Electromagnetic Diaphragm principle was marketed in 2003 by Thinklabs. The stethoscope's diaphragm is coated with a conductive surface. Behind the diaphragm a metal plate is located. The diaphragm and the plate work as a capacitor with a variable capacitance depending on the distance between them. The Thinklabs stethoscope was used in some recent studies about acoustic detection of CAD [63, 78, 79]. Other transducer principles include piezoelectric contact sensors [96] which was used by Chen et al. in studies of CAD murmurs [97].

1.4.2. Spectral analysis

Semmlow et al. publish the first signal processing study of CAD murmurs in 1983 [47]. The signal was recorded using an air-coupled microphone. By power spectral density (PSD) analysis of the diastolic segments they showed a relative increase in the spectral energy above 90 Hz in 12 CAD patient compared to 12 normal subjects.

The spectral approach was continued by Akay et al. in several studies. The power spectra were estimated using parametric models such as the autoregressive (AR) models and Eigenvector based spectral models in subjects before and after angioplasty [69, 88, 90]. Both methods showed a decrease in power above 200 Hz after removal of the stenosis with angioplasty, see Figure 13. Parametric models were chosen because of

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[2] Usually accelerometer sensitivity is not measured in pressure units. The authors of the study used a special setup to correlate the accelerometer output to sound pressure which is more comparable to microphones.

their noise robustness and their fitness for detection of spectral peaks such as the coronary artery resonance frequency.
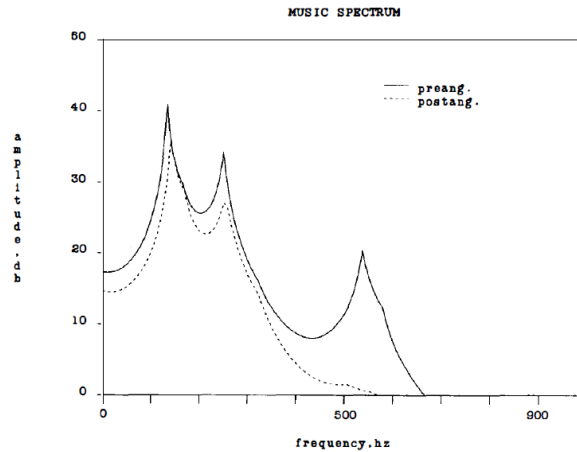

Figure 13. Power spectrum of a parametric model of diastolic sound before and after angioplasty. [69]

Later the parametric models were used to discriminate CAD subject from non-CAD subjects [68, 72, 85, 89]. A CAD related increase in energy above approximately 200-300 Hz was observed in all studies. This was observed with both the FYSPac2 sensor and the air coupled microphone. Since spectral peaks were expected in the diastolic sounds from CAD subjects the diastolic recording segments were filtered with an adaptive line enhancer before modeling [71]. The adaptive line enhancer was an adaptive filter adjusted for linear prediction, thereby enhancing the spectral peaks at the expense of the wide band part of the signal. The filter thus emphasized more distinct spectral peaks [71].

In a comparative study the classification performance of the Fast Fourier transform (FFT) and three different parametric spectral methods such as AR, Autoregressive moving average model (ARMA) and Eigenvectors were evaluated in recordings from 80 subjects obtained with the FYSPac2 accelerometer [75]. The different methods showed diverging results. The FFT analysis showed an increase in energy above 500 Hz in the CAD subjects compared to non-CAD subject, but the Eigenvector method showed that CAD was related to an increase in energy between 300-500 Hz. The AR and ARMA models showed an increase in the 400-800 Hz band. For all three parametric models the magnitude of the second pole was used as a discriminator in a classification test. The Eigenvector method was the best performing classifier. In 80 cases the sensitivity was 79.2% and specificity was 90.6% [75]. The usefulness of the Eigenvector method was further confirmed in a study including 100 patients were sensitivity was 88.8% and specificity was 78.2%

Tateishi et al. analyzed heart sounds above 400 Hz and found that the power ratio calculated as the power in the 400-700 Hz band divided by the power in the 400-1500 Hz band increased in CAD subject [50]. Recordings were made from five positions on the chest from 168 subjects. Only recordings obtained from the forth intercostal space

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showed a significant difference between CAD and non-CAD subject. The sensitivity was 71% and specificity was 65%.

Recently the Think Lab stethoscope was used in a study by Gauthier et al. [79]. Using the power spectral density they found that the power ratio between the frequency band above and below 130 Hz increased in CAD subjects compared to healthy subjects.

The different studies all showed that the diastolic power at higher frequencies was increased in CAD subjects. However the definition of higher frequencies differs widely from study to study. For example in the first study by Semmlow et al. CAD was related to an increase in power above 90 Hz, where the parametric modeling studies usually related CAD to an increase in power above 200-300 Hz. The variations are probably related to differences in the transducers, differences in the spectral analysis methods and small population sizes in some studies. An example of the influence of the transducer is that the FYSPac2 accelerometer used in several parametric modeling studies is not linear outside the 200-800 Hz frequency band. The high success rate of the parametric modeling might indicate that the spectral peaks are present in the CAD murmurs.

1.4.3. Time-frequency studies

Murmurs are non-stationary signals. Therefore, Akay et al. applied adaptive filters for tracking spectral changes over the diastolic periods [65, 66]. They monitored the magnitude of the second pole in the adaptive filter throughout the diastolic period. In one study 10 patients were monitored before and after angioplasty [66]. Using a blind protocol the authors was able to identify whether the recording was obtained before or after angioplasty in 9 out of the 10 cases. Figure 14 shows the magnitude trajectories of the second pole throughout the diastole before and after angioplasty. The pole magnitude was increased in the 200-300 ms interval before angioplasty, which was the case in 9 out of 10 cases. In a second study including 35 subjects (non-CAD and CAD subjects) the findings of increased magnitude of the second poles in the diastolic interval from 200-300 ms was confirmed [65]. Furthermore, the variance of the pole magnitude was increased in CAD patients.
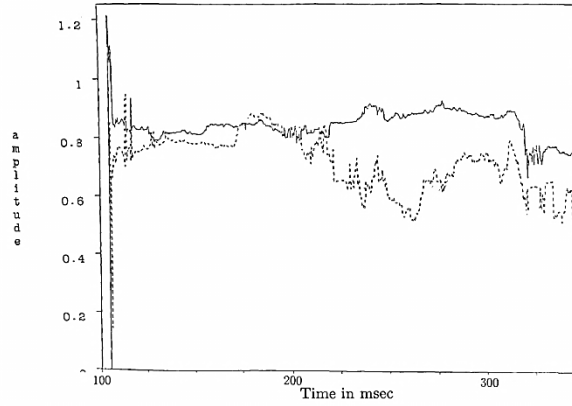
Figure 14. Magnitude trajectories of the second pole throughout the diastole. The Solid line was before angioplasty and the dotted line after angioplasty [66].

Zhao et al. calculated the instantaneous frequency throughout the diastolic period using the Hilbert Huang Transform [43]. In a case study of a CAD patient undergoing coronary angioplasty the mean weighted instantaneous frequency was 155 Hz before angioplasty and 98.3 Hz after. Similarly, the variance of the instantaneous frequency decreased from 42 Hz to 16.7 Hz after removal of the stenosis. The finding indicated that CAD increases the non-stationarity of the diastolic heart sound.

1.4.4. Nonlinear dynamics

Since murmurs originate from turbulent flow it has been argued that the murmurs reflect the non-linear and chaotic characteristic of turbulence. Padmanabhan et al. applied the Grassberger method for estimation of the correlation dimension of an underlying attractor [58]. The dimension is related to the degrees of freedom of the underlying system. The hypothesis was that if the signal is governed by a finite dimension attractor the Grassberger correlation integral will saturate even when the embedding dimension of the phase space is increased. Or explained in another way if the attractor can be described by a certain number of variables the complexity of an ideal attractor model will not increase even if a higher number of variables are available for modeling of the attractor. Opposite, if the signal is a completely stochastic process the dimension is infinite and the correlation integral will not saturate. Padmanabhan et al. found at that the Grassberger correlation integral saturated in 10 diseased subjects and that the Grassberger correlation integral didn't saturate in 5 normal subjects. This indicates that the diastolic sound recordings from normal subjects were dominated by random noise and that diastolic sound from CAD subjects were influence by a dynamical system.

Akay et al. analyzed the complexity of diastolic periods using Approximate Entropy [63]. They found that Approximate Entropy was increased in 30 CAD subjects compared to 10 normal subjects, indicating that CAD increases the complexity of the diastolic sounds.

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1.4.5. Multivariate classifiers

The parameter values from the parametric models were used as input to neural networks in a study including 100 subjects [70]. The tests showed a sensitivity of 78% and specificity of 89%. A second set of recordings from 112 subjects were analyzed with wavelets and classified with a neural network [82]. From the third wavelet band extremas of the wavelet coefficients were identified and the statistical moments Mean, Variance, Skewness and Kurtosis were calculated from the extremas. These features were combined with physiological variables such as sex, age, body weight, smoking condition, and systolic and diastolic pressure in a neural network. 82 of the recordings were reserved for the test. The result was a sensitivity of 78% and specificity of 89%. The multivariate method did therefore not perform better compared to the Eigenvector based parametric model.

Zhao et al. did several studies using multivariate classification. Based on the Hilbert Huang Transform, features such as Mean, Variance, Skewness and Kurtosis of the average instantaneous frequency were extracted. The same feature set was used in two different classifiers: a support vector machine [44] and a neural network [92]. Tested in 37 subjects the sensitivity of the support vector machine was 85% and the specificity was 100%. The neural network was tested in 40 subjects, giving a sensitivity of 95% and a specificity of 85%. In a study by Chen et al. wavelets were used for denoising of the recordings before features were extracted with parametric models [76]. The study showed a sensitivity of 87.5% and 100% specificity in 28 subjects. The weakness of those studies was a low number of subjects and that no blind protocols were used.

1.4.6. Detection of CAD using an electronic stethoscope

Two of the described studies used the electronic stethoscope for data collection [63,79]. These studies were published parallel to the current work and seem to confirm the suitability of the electronic stethoscope for detection of CAD.

1.4.7. Summary of prior art

CAD is associated with an increased energy at higher frequencies, but the specific high frequency bands which were affected by CAD diverge from study to study. Several studies were successful in application of parametric modeling for spectrum analysis and feature extraction. Other studies showed that there are indications of non-linear dynamics in diastolic heart sound. Some studies confirm that CAD increases the non-stationarity of the diastolic heart sound. Multivariate classification methods have been applied for classification. The largest multivariate classification study was tested in 82 subjects. Even though physiological variables such as sex, age, body weight, smoking condition, and systolic and diastolic pressure were combined in a neural network with four heart sound based features, the classification performance did not exceed the performance of the pole magnitudes from parametric models.

1.5. Scope of the current thesis

The aim of the current thesis is to develop an algorithm for detection of CAD with an electronic stethoscope. This includes the following challenges:

- Development of a segmentation method for automatic identification of the diastolic periods without a reference signal.
- Handling the limitations of the stethoscope such as short recording duration and that the stethoscope is handheld.
- Identification of features for detection of CAD. Based on the study of prior art this includes analyses of the reported increases in high frequency energy in CAD subjects, analysis of methods for nonlinear dynamics, analyses of non-stationary method such as Hilbert Huang Transform and exploration of new feature types.

1.6. The electronic stethoscope as data collector

The advantage of the electronic stethoscope for detection of CAD is that the stethoscope is device which is familiar to medical personnel, it is fast to use and it is a low cost device. Therefore, a digital stethoscope dedicated to diagnosis of CAD is suited for use in clinics with a limited budget for equipment, such as the office of the general practitioner.

That the stethoscope is handheld implies several challenges. Because the stethoscope is handheld the potential recording time is limited since the user will be crossing the comfort zone of the patient. A second problem with the handheld stethoscope is that friction spikes occur in recordings. The friction spikes are caused by friction between the stethoscope diaphragm and the skin because it is impossible to hold the stethoscope completely still.

1.6.1. The Littmann 3M E4000 stethoscope

The Littmann 3M E4000 stethoscope was chosen for the current studies due to its recording and storage capabilities. The stethoscope stores six recordings of 8 seconds and recordings can be transferred to a PC through an infrared data transmission. The signal resolution is 16 bit and the sample rate was 4000 sps. The sensor principle in the E4000 stethoscope is an air coupled microphone.

Figure 15. The Littmann 3M E4000 electronic stethoscope

Due to the powerful S1 and S2 sounds and the weak systolic and diastolic sounds the dynamic range of heart sounds is large. Therefore, the manufacture emphasized the high frequencies by a 1st order high pass filter with a cutoff frequency at 2000 Hz before digitalization. To remove this pre-emphasizing the recorded signals were subsequently filtered with a 1st order low pass filter with a cutoff frequency at 10 Hz to compensate for the 20 dB/decade slope introduced by the 1st order high pass filter. Figure 16 shows the average power spectrums of the diastole, systole, S1 and S2 from a normal subject before and after removal of the pre-emphasizing effect.
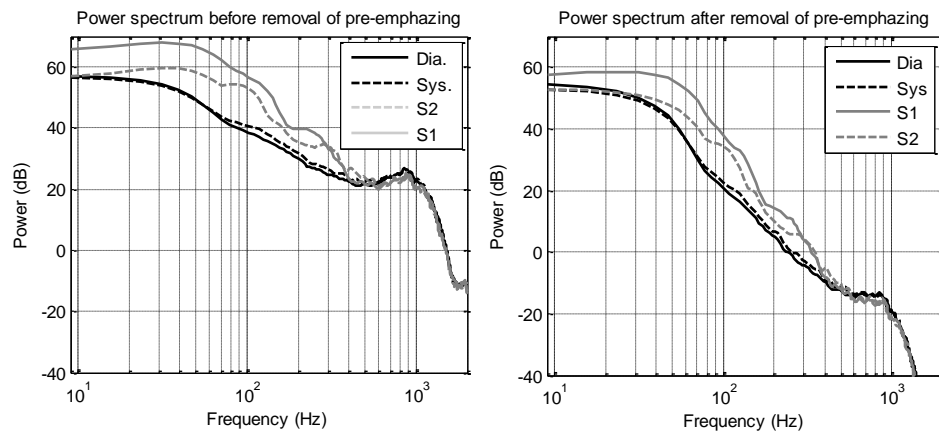
Figure 16. Example of power spectrum densities from a normal subject (Subject nr. 153) before and after removal of pre-emphasizing.

The spectra in Figure 16 show that the diastolic heart sounds roll off as the frequency increases. At approximately 500-1000 Hz a plateau occurs which corresponds to the noise floor of the stethoscope. Therefore, a reasonable signal to noise ratio can be expected below 400-500 Hz.

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1.7. Preliminary study

To test the potential of the stethoscope as a tool for detecting CAD an initial study was conducted. A multivariate classifier was trained using 39 subjects and tested in 59 subjects [98](Appendix 1 DaCRA Abstract). Only recordings with a low noise level were included in the preliminary study. The diastolic segments were filtered with a 200-800 Hz band-pass filter before two features were estimated: a power ratio between the 160 -350Hz band and the 350-750 Hz band and the pole magnitude of the 1st pole in an AR-model. The features were combined using a linear discriminant function. In the test data the sensitivity was 89% and specificity was 54%. The results indicated that the electronic stethoscope was capable of detecting differences between diastolic sound from CAD and non CAD subjects.

1.8. Introduction to the studies

The thesis is based on 5 studies:

Study 1: Segmentation of heart sound recordings by a duration-dependent hidden Markov model [99].

The first study describes a method for automatic segmentation of the heart sound recordings. The focus of the study is to develop a method which is robust and useful for segmentation of heart sounds recorded in clinical settings.

Study 2: A framework for extraction of features for detection of CAD using an electronic stethoscope [62].

The focus of the second study was to develop a framework for extraction of features from the diastolic periods. The goal was to develop methods which allowed robust estimation of features even when the recording was contaminated by friction spikes.

Study 3: No evidence of nonlinear or chaotic behavior of cardiovascular murmurs [100].

The purpose of the study 3 was to examine whether cardiovascular murmurs shows nonlinear or chaotic characteristics. Therefore, murmurs from the carotid artery were analyzed to test the hypothesis that cardiovascular murmurs are different from a linear stochastic process. Murmurs from the carotid artery were analyzed because they are powerful which ensures a good signal to noise ratio.

Study 4: Noise and the detection of coronary artery disease with an electronic stethoscope [101].

The recordings obtained for the studies were taken in a clinical environment at Aalborg hospital and the recordings were often contaminated with ambient noise. Study 4 analyzes the influence of different noise types such as ambient noise, recording noise, respiration noise and abdominal noise.

 Study 5: Acoustic features for the identification of coronary artery disease.

In study 5 a wide range of features was estimated from different frequency bands. The large number of features was validated using cross validation. The goal was to identify new features and compare the known features.

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Study 1

Segmentation of heart sound recordings by a duration-dependent hidden Markov model.

Study 2

A framework for extraction of features for detection of CAD using an electronic stethoscope

N.B. Published under the title Detection of coronary artery disease with an electronic stethoscope

Study 3

No evidence of nonlinear or chaotic behavior of cardiovascular
murmurs

Study 4

Noise and the detection of coronary artery disease with an
electronic stethoscope

Study 5

Acoustic features for the identification of coronary artery disease

7. Discussion

Five studies were conducted to develop a method for detection of CAD with an electronic stethoscope. In study one a method was developed for segmentation of the heart sounds into systolic and diastolic periods. In study two a framework was developed for robust extraction of features. Study three examined the fundamental characteristics of murmurs. The influence of noise was estimated in study 4 before the classification performance of different types of features was tested in study five. The current chapter discusses the findings in these five studies.

7.1. Segmentation

Since the CAD related murmurs are expected to peak in the diastolic periods, identification of the diastolic periods is essential. A duration dependent Markov model (DHMM) was applied for segmentation of heart sounds without the need for an additional reference signal. The concept of the DHMM fits the problem of heart sound segmentation well. The states of the repeating heart cycle can be modeled as a Markov process. As in a hidden Markov model the actual state of the heart at a given time is unknown, but the heart sounds are observable and related to the state of the heart. Since the duration of the states in the heart cycle is relatively stable over a recording period of a few heart beats, the probability of transition from the current state to the next state is related to the time spent in the current state. This aspect was modeled by the duration dependent Markov model.

The DHMM's capability to identify S1 and S2 sounds was tested in recordings from 73 patients. The sensitivity was 98.8% and positive predictivity was 98.6%, which shows that the method is robust and accurate and that the DHMM model is suited for modeling of the heart sounds. Heart valve murmurs such as murmurs from aorta stenosis did not reduce the performance significantly. The strength of the model, the duration dependency of state transitions, is also the limitation of the model since it limited the performance in highly arrhythmic patients. A potential solution to this problem is to further customize the probability distributions of the systolic and diastolic durations to the individual patient. In the current implementation probability distributions of the systolic and diastolic durations were determined by a normal distribution were only the means were determined individually from each subject. The mean durations were estimated from the autocorrelation of the signal envelope in the current implementation, but the degree of arrhythmia might also be estimated from the autocorrelation, and therefore, the duration distributions might be fitted to the degree of the arrhythmia. However no models are perfect and the perfect segmentation of heart sounds is not achievable, therefor an automatic post validation method would be needed to reduce the risk of erroneous classifications caused by incorrect segmentation. The high degree of robustness was further confirmed in study five were the diastole locations in 435 recordings were corrected if they were incorrectly placed. This happened in 3% of the diastoles.

7.2. Noise and noise reduction

In study 2 the focus was to develop a framework for extraction of diastolic heart sound features. The goal was to reduce the effect of friction spikes and other types of noise. A simple framework was developed by subdivision of the diastolic periods into sub-segments of short duration. The noise level of the sub-segmentation was estimated by the variance and the level of stationarity. Sub-segments with high variance and a high level of non-stationarity were removed before the magnitude of the 1st pole in an AR-model was extracted as a feature from the sub-segments. The final feature value was then calculated as the median of the feature values from the sub-segments. According to the study at a dataset consisting of 50 recordings the sub-segmentation improved the separation capability of the AR-pole considerably. The framework was further used for feature extraction in study 4 and 5.

Study 4 was conducted to evaluate the influence of noise on features for detection of CAD. Four types of noise were analyzed: ambient noise, recording noise, respiration noise and abdominal noise. The influence of friction spikes (friction noise of short duration) was not included in the study since these were present in nearly all recordings, but recording noise included friction noise of longer duration. 633 recordings from 140 patients were analyzed by listening and visual inspection. The degree of contamination from the four noise types was quantified according to noise intensity and duration. The magnitude of AR-poles was used as features and calculated from a low frequency band (25-250) and a high frequency band (250-1000 Hz). The classification potential of the AR-poles was evaluated by the area under the receiver operating characteristic (AUC). In 75.7% of the recordings noise contamination was identified. The AUC was first calculated in the clean recordings (recordings without observed noise) before noisy recordings were added gradually as more and more noise was tolerated. The trend in the AUC from the high frequency band was that the AUC dropped as noisier recordings were included in the analysis. Even weak noise seams to influence the performance of the feature from high frequency band. In contrast, the AUC from the low frequency band was influenced only by very extensive noise. The study clearly indicates that noise is a significant problem for analyses of the high frequency part the signal. A limitation of the study was that the estimates of the influence at specific noise levels and durations were imprecise. This was due to the fact that every time the noise tolerance was increased with one step only a few new recordings were added. For example if the tolerance for ambient noise was increased from moderate noise of maximum one second to moderate noise of maximum two seconds only few new recordings were added to the analysis.

The result of study 4 clearly indicates that, even when study 2 showed that the sub-segmentation method improved the classification performance, the noise issue isn't solved. Ambient noise and recording noise were the most common noise sources in study 4 and they both had significant effect at classification performance of the AR-poles from the high frequency bands. The effect of ambient noise might be reduced by either active or passive noise reduction. Passive noise reduction may include better shielding of the microphone or uses of other transducer types such as accelerometers, which are more robust to ambient noise. In an active noise reduction setup a reference

signal from an external microphone might be used for adaptive filtering. The problem of recording noise was typical due to scratching between the stethoscope diaphragm and the skin of the chest. In some recent versions of electronic stethoscopes, such as 3M Littmann Model 3100, the material of diaphragm was chosen to reduce the friction noise [1], but the safe solution might be to attach the transducer to the chest wall. The third most common noise source was respiration noise. Respiration noise can be limited by asking the patients to hold their breath. Therefore, the influence of three most common noise sources ambient noise, recording noise and respiration might be reduced by changes in the recording equipment and the examination protocol.

7.3. The potential of nonlinear signal processing techniques

Since the murmurs are described as broad-banded in the frequency domain, the most obvious signal model is a linear stochastic process, but as proposed by Padmanabhan et al. the murmurs might be dominated by non-linear dynamics such as chaos [2]. Clearly the murmurs cannot be described by a simple deterministic model, but maybe the murmurs might be described by more complicated nonlinear dynamics such as low dimensional chaos. Therefore, the null hypothesis that cardiovascular murmurs were from a linear stochastic process was tested using recordings of carotid artery murmurs. Even though several methods were applied for the analysis, no significant difference was observed between the murmurs and surrogates of the murmurs generated by a linear stochastic process. We concluded that there were no signs of nonlinear characteristics or low dimensional chaos in murmurs from the carotid artery. The carotid artery was chosen since the stenosis is located close to the skin which ensured a good signal to noise ratio and a simpler transfer function between the origin of the murmur and the recording spot. There might be other circumstances related to CAD murmurs which might allow more deterministic murmurs, for example if turbulence isn't fully developed the velocity fluctuations of the vortexes in post stenotic flow will be more deterministic. However study 3 underlines that careful analysis must be conducted before nonlinear dynamics is assumed. The finding in study 3 was confirmed in study 5 where the performance of spectral entropy, which doesn't handle non-linearity, exceeded sample entropy which handles nonlinear dynamics. In a supplementary study of diastolic sounds a high correlation was found between the sample entropy and features from an AR-model (see appendix).

7.4. Features for detection of CAD

Different types of feature were evaluated in a cross validation study. Since the existing literature differs in the choice of frequency bands several filter configurations were tested. Only features from lower frequency bands showed a significant difference between non-CAD and CAD subjects. A wide range of features from low frequency bands were significant, but principle component analysis of all features showed only one significant PCA component which indicates that the different features describe the same phenomena. The best feature was the pole magnitude of the 1st pole in a 6th order AR-model of the 25-250 Hz frequency band. In CAD subjects the pole magnitude was increased, which demonstrated a relative power increased at frequencies at 20-30 Hz. Similarly, an increased power was observed at lower frequencies (25-80Hz) in CAD

patients by 1/3 octave band analysis. That features from the higher frequency bands showed a poor classification performance contradict with findings in prior studies which showed a good classification performance of features from higher frequency bands such as the 180-1200 Hz band [3, 4]. Also the preliminary study conducted in the early phase of the current thesis showed a good classification performance of features from high frequency bands in low noise recordings. However the findings are not surprising since study 4, which used the same dataset as study five, found that noise influenced the performance of high frequency features dramatically. An alternative solution would have been to only analyse recordings with a low level of noise contamination, but this would have excluded approximately 60% of the recordings.

Since the features from the AR model were the best performing features, AR features were chosen for multivariate classification. By combination of the AR features from the 25-250 Hz band and the 250-1000 Hz band a CAD score was constructed. The AUC of the CAD-score was 0.73 (0.685-0.776), sensitivity was 72% and specificity was 65.2%. This was only slightly better than the performance obtained with only one AR-pole from the 25-250 Hz frequency band.

There was a clear gender difference in the CAD score. In the non-CAD subjects the females scored significantly lower compared to males. Further analysis showed a significant gender difference in low frequency features, but no significant gender difference was observed in the AR-feature from the 250-1000 Hz band. Since more males than females suffered from CAD the gender difference might explain a part of the increased CAD-score in CAD subjects, but when the CAD score was tested separately in males and females the CAD score was increased in both males and females. When the two genders was separated the AUC was 0.722 (95% CI: 0.664-0.778) for males and 0.638 (95% CI: 0.518-0.759) for females, which indicates a performance drop in the females. This is contradictory to unpublished findings referred to by Semmlow et al. [5] where a CAD detection algorithm based on high frequency features showed a poor performance in males and high performance in females. The genders differences show that further studies must take the gender difference into account.

7.5. The cause of increased low frequency power

Study 4 and 5 identify a new feature for detection of CAD from heart sounds. The studies showed a power increases at lower frequencies in subjects with CAD. Figure 1 below illustrates recordings from a non-CAD patient and a CAD patient. The recordings were filtered with a 20-50 Hz band pass filter. The recordings are from two males with approximately the same BMI. The amplitudes in both the systoles and diastoles are increased in the CAD subject. This indicates that the change also might occur in the systolic periods.
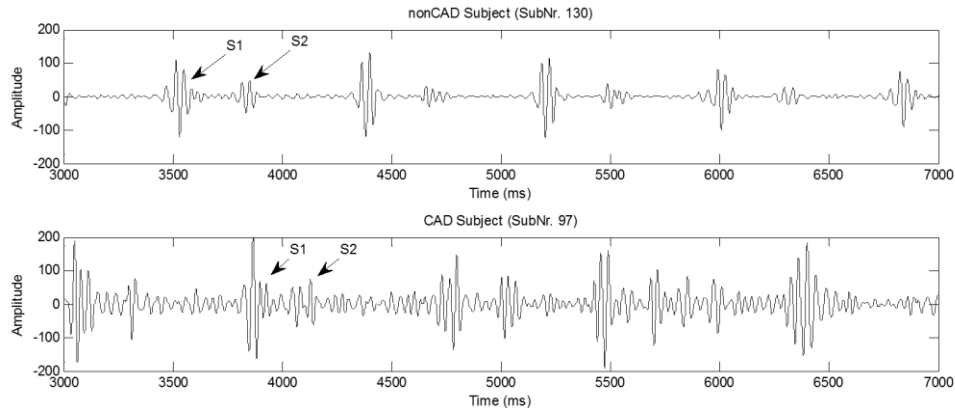
Figure 1. Two band pass filtered (20-50Hz) heart sound recordings from a CAD and a non-CAD patient.

The source of the increase in low frequency power is not known, but an increase at these frequencies is usually not related to cardiovascular murmurs. A more likely source is changes in ventricular movements caused by changes in the compliance of the left ventricle. It is known that CAD can increase ventricular stiffness, even before myocardial infarction (MI) [6]. The diastolic effect of increased ventricular stiffness is a change in filling patterns. Typically, the relation between inflow in early diastole and late diastole is altered [7]. Changes in ventricular compliance are often reflected as S3 and S4 sounds in heart sound recordings. To test if S3 and S4 sounds caused the increase in low frequency power, a small retrospective study was conducted. The S3 and S4 sounds were identified by visual screening the recordings included in study five. S3 sounds were found in 8.6% of the non-CAD patients and in 15.9 % of the CAD patients. Similarly, S4 sounds were found in 8.6% of the non-CAD patients and in 14.3 % of the CAD patients. The mean CAD score[1] was -0.21 (STD 0.44) in non-CAD subjects without S3 and S4 sounds and -0.12 (STD 0.48) in non-CAD subjects with S3 or S4 sounds. In CAD subjects the mean CAD score was 0.23 (STD 0.34) and 0.22 (STD 0.37) in respectively subjects with and without S3 and S4 sounds. Therefore, the S3 and S4 sound cannot explain the increase in low frequency power observed in CAD subjects.

Low frequency chest wall vibrations related to ventricular movements can be measured with the use of seismocardiography [8]. The typical frequency range of seismocardiography is 0.3-50 Hz [8-10], which is overlapping with the frequency range analyses in the current study. Seismocardiography is characterized by rather deterministic wave patterns which reflect cardiac events. Studies have shown that MI alters both the systolic and diastolic Seismocardiographic patterns [8-10].

Figure 2 shows heart sound recordings from a new sensor developed for future research by the current author and colleagues. The frequency response of the new sensor was flat from 0.5 Hz to 1000 Hz. The recording contains a low frequency signal with a

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[1] In study 5 a CAD score higher than zero was associated with CAD.

distinct morphology which includes landmarks known from seismocardiography. In the CAD subject the amplitude of the low frequency vibration was increased compared to the non CAD subject. When the 20-40 Hz band pass filter was applied the distinct morphology diminishes, but the amplitude difference remains. This indicates that the increase in low frequency power observed in the current study might be further understood and quantified if the frequency range of the sensor is expanded to include lower frequencies. If the power of the low frequency part of the signal is related to ventricular movements and compliance it is likely to be uncorrelated to features from higher frequency bands which is related to CAD murmurs. Therefore, if the noise problems are solved, a combination of the low frequency features and high frequency features might improve the classification performance significantly.
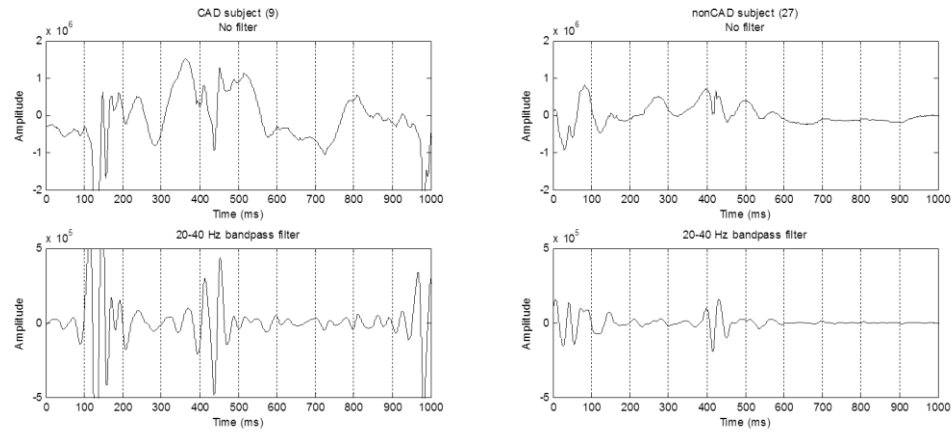

Figure 2.top figures show Heart sounds recorded with a sensor with an extended frequency range. The bottom figures show the same recordings but after band pass filtering.

To further understand the change in low frequency power, the relation to physiological variables was evaluated briefly. Unfortunately, physiological data such as blood pressure and BMI was accessible in only 66 subjects out of the 140 subjects included in study 4 and study 5. The correlation (r) between the diastolic power in the 20-40 Hz band and Age, BMI, systolic blood pressure and diastolic blood pressure was respectively 0.17, -0.27 ,-0.09 and 0.17. The most evident, but still weak, correlation was the negative correlation with BMI. This was expected since an increased BMI is likely to increase the distance from the heart to the transducer. In females the breast the increases the distance between the heart and the stethoscope which might explain the weaker low frequency power in females.
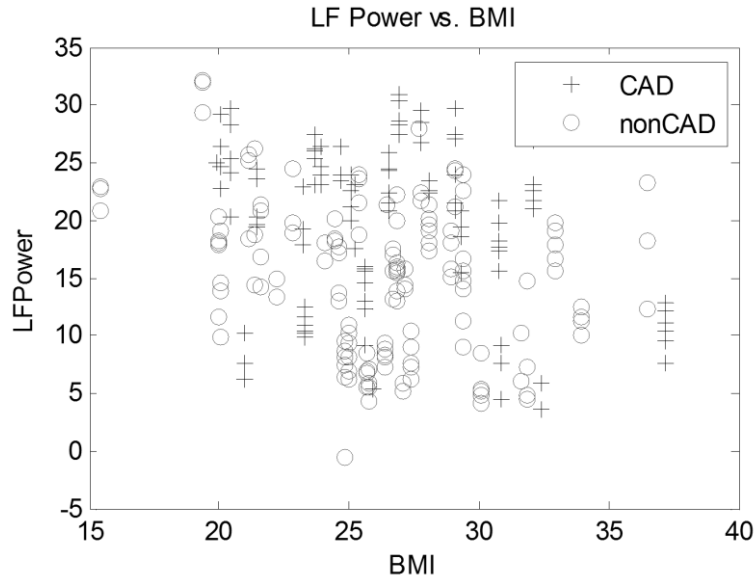
Figure 3. Scatter plot between BMI and the low frequency power of the diastolic heart sound.

7.6. Clinical implication of current findings

For sensitivities of the current method exceed the ECG stress test, but the specificity of the stethoscope based method was low. Thereby, the clinical benefits of the current method without improvements might be limited. However, despite a relative low diagnostic performance the method might provide valuable information in a broader risk estimation strategy. The Framingham risk score defines the 10 year risk for CAD in three levels: low (<10%), intermediate (10-20 %) and a high (>20%) risk. If for an illustrative purpose the 10 year risk is converted to prevalence the positive predictive value in patients with intermediate risk will be 18.6%-34% and the negative predictive value 90.3-95.4%. Therefore, nearly all patients can be reclassified to either low risk <10% or high risk >20%, which certainly has clinical value.

7.7. Recommendations for new hardware

The purpose of the current thesis was to develop a method for detection of CAD with an electronic stethoscope, but the studies revealed several weaknesses of the electronic stethoscope. Consequently, a recommendation for a new system for detection of CAD is made:

    o   **Increased recording time**. The short recording time of 8 seconds limits the possibility to reject noisy diastoles and lead to a high variance of the estimated features. Therefore, it is recommended to increase the recording time. An example could be 4 x 8 seconds where the patient is instructed to hold the breath in the 8 seconds periods.

- o **Fixed sensor.** If the sensor is attached to the skin fiction noise will be eliminated. This will reduce the noise and thereby improve the performance the features evaluated in the current studies.
- o **Increased bit resolution.** The dynamic range of heart sounds is large 60-80 dB, see figure 16 in the introduction. Therefore is the 96 dB dynamic range of a 16 bit system close to inadequate.
- o **Ambient noise reduction.** Study 4 and 5 showed that ambient noise influenced the classification performance. A passive acoustic shield will dampen ambient noise transferred through the coupler house, but an active approach might be needed to further reduce the influence of ambient noise transferred through the body.
- o **Extended frequency range.** By extending the frequency range to include frequencies down to 0.5 Hz the low frequency information usually obtained using seismocardiography might be combined with information related to the high frequency CAD murmurs.

8. Conclusion

The purpose of the current work was to develop an algorithm for detection of CAD with an electronic stethoscope. Therefore, a method was developed for automatic segmentation of the heart sounds into systolic and diastolic periods. Next a simple framework was developed for robust extraction of descriptive features. To gain further insight in the characteristics of cardiovascular murmurs, a study was conducted to evaluate whether the murmurs can be described by nonlinear dynamics. The study did not find evidence of nonlinear dynamics in cardiovascular murmurs. Instead, the murmurs might be characterized as a non-stationary linear stochastic process.

To identify features for classification between CAD and non-CAD patients a wide range of features was examined in 430 recordings from 140 patients. New efficient features were identified from lower frequency bands. The new features were related to the changes in the power distribution of the low frequency part of the signal. An advantage of these features was a high degree of robustness against noise. This was in contrast to features from higher frequency bands which were very sensitive to noise. The mechanism behind the observed change in the low frequency part of the signal is not known, but the change might be related to changes in ventricular compliance.

A cross validation test of a multivariate classification algorithm resulted in an area under the receiver operating characteristic of 0.73, the sensitivity was 72% and the specificity was 65.2%. The relative low performance reflects several weak points of the current electronic stethoscope when used in clinical settings. The limitations include friction noise, sensitivity to ambient noise and short recording time. If these limitations are handled the performance of features from the high frequency bands might improve significantly. Thereby, a system based on a combination of features related to low frequency vibrations and features suited for quantification of the high frequency CAD murmurs is likely to be a successful non-invasive test for CAD.

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Appendix

The appendix contains two publications by the current author, which are cited in the Thesis.

An abstract

S. Schmidt, C. Holst-Hansen, E. Toft and J.J. Struijk, "Detection of coronary artery disease with an electronic stethoscope: Is it possible?" in *Summer Meeting, Danish Cardiovascular Research Academy*, Sønderborg, Denmark, 2007, pp. No. 26.

A conference paper:

Samuel Schmidt, John Hansen, C. H. Hansen, Egon Toft and Johannes J. Struijk, "Comparison of sample entropy and AR-models for heart sound-based detection of coronary artery disease," *Comput. Cardiol.*, vol. 37, pp. 385-388, 2010.