Risk Estimation of Coronary Artery Disease using Phonocardiography

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RISK ESTIMATION OF CORONARY ARTERY DISEASE USING PHONOCARDIOGRAPHY

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AALBORG UNIVERSITY
DENMARK

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ABBREVIATIONS

2D-QCA	Two-dimensional quantitative coronary angiography
A-CL	Acoustically augmented risk estimation model of the RF-CL model
A2	Sound produced by the closure of the aortic valve
ACS	Acute coronary syndrome
AHA	American Heart Association
ALE	Adaptive line enhancer
ANN	Artificial neural network
AR	Autoregressive
ARMA	Autoregressive moving average
BMI	Body mass index
CACS	Coronary artery calcium score
CAD	Coronary artery disease
CCS	Chronic coronary syndrome
CCTA	Coronary computed tomography angiography
CNN	Convolutional neural network
CPSD	Cross power spectral density
CVD	Cardiovascular Disease
EMD	Empirical mode decomposition
ESC	European Society of Cardiology
FFR	Fractional flow reserve
FFT	Fast Fourier Transform
HF	Heart failure
IC4	Fourth intercostal space
ICA	Invasive coronary angiography
M1	Sound produced by the closure of the mitral valve
MFCC	Mel Frequency Cepstral Coefficients
MLP	Multi-layer perceptron

P2	Sound produced by the closure of the pulmonary valve
PCG	Phonocardiography
PCI	Percutaneous coronary intervention
PTP	Pre-test probability
RF-CL	Advanced clinical risk estimation model developed by Winther et al.
S1	First heart sound
S2	Second heart sound
S3	Third heart sound
S4	Fourth heart sound
SCA	Sudden cardiac arrest
SST	Synchrosqueezing transform
SVM	Support vector machine
T1	Sound produced by the closure of the tricuspid valve

ENGLISH SUMMARY

Coronary artery disease (CAD) is the leading cause of death world-wide and continues to be a major health care expense also in developed countries. It is often of significant concern when patients show symptoms of the disease, and this might be one of the reasons that only 6-12% of suspected CAD patients are diagnosed with obstructive-CAD, even after general practitioners and cardiologists have evaluated the patients. This means that a large portion of patients go through expensive and sometimes invasive testing that might be avoided through more careful pre-test risk estimation.

This thesis consists of four studies, which in concert investigate the possibility to perform early risk estimation of suspected CAD patients and to safely rule-out a portion of these before proceeding to more expensive and invasive testing. The studies analyze heart sound recordings from a collection of studies performed by Acarix that in total contains more than 2500 patients. Features from heart sound analysis are used to augment an existing clinical risk model for the rule-out of healthy patients suspected of CAD.

Study I established a relationship between heart sounds and clinical parameters age, sex, and BMI. Study II documented the development of a whitening filter designed to emphasize high-frequency differences in heart sounds from CAD patients. Using knowledge and methods obtained in the previous two studies, Study III investigated the spectral differences between CAD and non-CAD patients. Finally, in Study IV, acoustic features were extracted from the heart sound, and joined to an existing high-performing clinical risk model. The addition of acoustic features to the clinical risk models significantly increased the specificity from 41.5% to 48.6% while keeping the sensitivity the same 84.9%.

The heart sound of patients with CAD carry information beyond what is contained in the parameters of modern clinical risk estimation models.

DANSK RESUME

Koronararteriesygdom (CAD) er den førende dødsårsag på verdensplan og er fortsat en stor sundhedsudgift også i udviklede lande. Det giver ofte stor bekymring, når patienter viser symptomer på sygdommen, og det kan være en af grundene til, at kun 6-12% af formodede CAD-patienter får diagnosen obstruktiv CAD, selv efter praktiserende læger og kardiologer har vurderet patienterne. Det betyder, at en stor del af patienterne gennemgår dyre og til tider invasive tests, som måske kunne være undgået med mere omhyggelig risikovurdering forud for test.

Denne afhandling består af fire studier, som i fællesskab undersøger muligheden for at udføre tidlig risikoestimering af formodede CAD-patienter og sikkert udelukke en del af disse, før man fortsætter med dyrere og invasive tests. Studierne analyserer hjertelydsoptagelser fra en samling undersøgelser udført af Acarix, der i alt indeholder mere end 2500 patienter. Funktioner fra hjertelydsanalyse bruges til at udvide en eksisterende klinisk risikomodel for udelukkelse af raske patienter, der er mistænkt for CAD.

Studie I etablerede en sammenhæng mellem hjertelyde og kliniske parametre alder, køn og BMI. Studie II dokumenterede udviklingen af et blegningsfilter designet til at understrege højfrekvente forskelle i hjertelyde fra CAD-patienter. Ved hjælp af viden og metoder opnået i de to foregående studier, undersøgte Studie III de spektrale forskelle mellem CAD- og ikke-CAD-patienter. Til sidst, i Studie IV, blev akustiske egenskaber udtrukket fra hjertelyden og tilføjet til en eksisterende højtydende klinisk risikomodel. Tilføjelsen af akustiske egenskaber til de kliniske risikomodeller øgede specificiteten signifikant fra 41,5% til 48,6 %, mens sensitiviteten forblev uændret på 84,9%.

Hjertelyden fra patienter med CAD bærer information ud over, hvad der er indeholdt i parametrene for moderne kliniske risikoestimeringsmodeller.

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Finally, I would like to thank my parents for all their support throughout my journey and of course my wife Kseniia for her support and encouragement and not least for giving birth to our beautiful son Noah.

Bjarke Skogstad Larsen

PREFACE

This PhD thesis was submitted to the Doctoral School in Medicine, Biomedical Science and Technology at Aalborg University. The research was conducted at both Acarix and Aalborg University, Denmark from February 2017 to June 2022.

The PhD was financially supported by Innovation Fund Denmark and Acarix and was supervised by associate professor Samuel Emil Schmidt and professor Mads Græsbøll Christensen from Aalborg University and Claus Bo Vöge Christensen from Acarix.

The thesis is based on four studies related to detection of coronary artery disease using phonocardiography with a focus on the fusion of clinical and acoustic parameters. The thesis consists of an introduction that goes through the basics of coronary artery disease and its influence on heart sounds. This is followed by an outline of the thesis scope and aims as well as methods and materials. Then, the four studies are summarized followed by a discussion and finally a conclusion.

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

This chapter outlines the background for thesis including a short introduction of coronary artery disease (CAD) and the link to heart sounds, a review of both technical and clinical studies on phonocardiography in CAD diagnostics, as well as the current diagnostic pathway for CAD.

1.1. CORONARY ARTERY DISEASE AND HEART SOUNDS

Coronary artery disease (CAD) is the primary cause of death worldwide and was estimated to account for 9.4 million deaths in 2016 by the World Health Organization [1]. This translates to 52.8% of deaths among cardiovascular diseases (CVD) and 16.8% of all deaths according to the same source. Though CAD has been declining as a cause of death in developed regions such as EU and USA, it has been a growing cause of death globally and especially in developing countries.

According to the 2021 Heart Disease and Stroke Statistics update from the American Heart Association (AHA), CAD declined 40% as a cause of death from 1999 to 2009, exemplifying this downward trend for developed countries [2]. However, even though there is a downward trend in deaths caused by CAD, the prevalence of the disease continues to increase. Where the 2021 AHA update [2] estimated 20.1 million (7.2%) Americans ≥20 years of age have CAD, the 2016 AHA update [3] estimated 15.5 million (6.2%) of American adults have CAD.

The 2021 AHA update [2] further reported that there were 11 million physician office visits for CAD in 2016. Two of the ten most expensive conditions treated in the US hospitals in 2013 were myocardial infarct ($12.1 billion) and CAD ($9 billion), and in 2016, the total health care spending related to ischemic heart disease was $89.3 billion.

Pathophysiology

CAD is the build-up of atherosclerotic plaque (consisting of fat, calcium, and other substances) within the coronary arteries, reducing the cross-sectional area of the lumen and thus increasing the resistance of blood flow. This progression usually spans decades

Stenoses vary in their composition of fat and calcium, with more calcified deposits generally being harder and more stable, and more fat-rich deposits having a higher risk of rupturing. Plaque rupture leads to thrombogenesis and subsequent risk of myocardial infarct.

If the stenosis is severe, the heart's demand of oxygen can exceed what is provided by the blood flow through the occluded coronary artery, leading to symptoms such as

angina. Typical angina consists of a constricting discomfort in the front of the neck, jaw, shoulder, or arm, precipitated by physical exercise, and relieved by rest or nitrates within five minutes [4]. This usually occurs during physical activity as the heart is pumping faster and has an increased demand for oxygen.

Complete blockage of a coronary artery causes ischemia of the heart and often results in myocardial infarct, leading to heart attack and sudden death. The threshold for obstructive CAD is typically set to ≥50% diameter reduction when using anatomical imaging, and stenoses with lower diameter reduction are considered non-obstructive.

The disease is strongly associated with both influenceable factors such as smoking, blood pressure, physical exercise, and diet; as well as non-influenceable factors such as age and sex.

Heart Sounds

The audible sounds of a heart cycle are dominated by the "lub-dub" of the first and second heart sounds. The first heart sound (S1) is generated by the closure of the atrio-ventricular valves at the beginning of the ventricular contraction and is typically of relative longer duration and lower frequency. The second heart sound (S2) is generated by the closure of the semilunar (pulmonary and aortic) valves at the end of ventricular systole when the pressure in the aorta and the pulmonary artery exceeds the pressure in the ventricles. This means that each of these sounds is in fact a superposition of the sounds generated by each of the two pairs of valves closing in concert. The sounds generated by the closure of each of the four valves are termed M1 for the mitral valve, T1 for the tricuspid valve, A2 for the aortic valve, and P2 for the pulmonary valve. Different conditions can change the timing of the valve closures.

Two other sounds that characterize the audible heart cycle is the third heart sound (S3) and the fourth heart sound (S4). These heart sounds are of much lower magnitude than S1 and S2, and they are not always audible by auscultation on the chest surface. S3 occurs early in the diastole and arises from the passive filling of ventricles as blood flows through the reopened atrio-ventricular valves, whereas S4 occurs late in the diastole and arises from filling of the ventricles as the atria contracts. Some conditions such as congestive heart failure can cause these two sounds to become more pronounced.

A range of other audible phenomena can be observed with auscultation of patients with various heart conditions and are generally referred to as murmurs.

CAD Related Heart Sounds

The observation of diastolic murmurs arising from stenosed coronary arteries was first reported by Dock and Zoneraich in 1967 [5]. However, it is worth mentioning that far from all coronary stenoses are clearly audible by auscultation on the chest surface.

Since then, several studies have been published associating CAD with diastolic murmurs. These diastolic murmurs are caused by turbulent blood flow following a coronary stenosis, vibrating the arterial walls. A depiction of this phenomenon is shown in Figure 1-1.

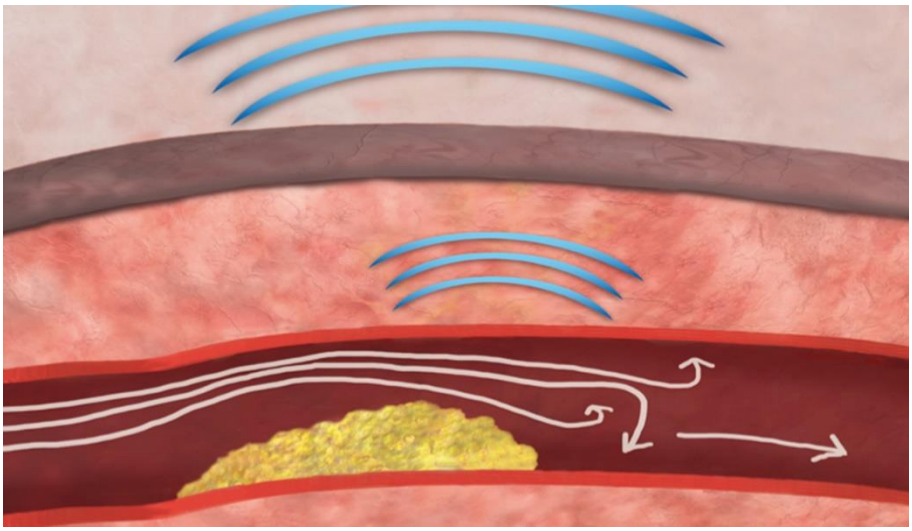

Figure 1-1 A coronary stenosis reduces the cross-sectional area and restricts the blood flow, which causes blood flow following the stenosis to become turbulent, vibrating the coronary walls and creating subtle sound patterns known as micro-bruits.

The main focus of CAD related heart sounds has been on analysis of the diastolic period, as it is during this resting period that the coronary arteries have the blood flow and therefore expectedly clearest CAD related murmurs from turbulent flow. Additionally, heart sounds of the other parts of the cardiac cycle are dominated by the two major heart sounds S1 and S2, and the weak CAD related signal would more easily be detected during the diastole.

More recently, Mansour et al. [6] reported a correlation between calcification of the coronary arteries and diastolic dysfunction. It is possible that this may cause CAD patients to have different relaxation patterns, which could influence the S1 and S2 heart sounds. This means that though diastolic murmurs arising from turbulent flow following a stenosis is the most explored and well-explained CAD related heart sound phenomenon, it may not be the only difference in heart sounds between CAD and non-CAD patients.

1.2. TECHNICAL STUDIES ON DETECTION OF CAD USING PCG

Phonocardiography (PCG) is the recording and analysis of heart sounds usually for diagnostic purposes. Using it as a method for detecting CAD was first proposed by Semmlow et al. in 1983 who established a correlation between CAD and increased relative energy in the frequency band 120-200 Hz during diastole [7]. The cause of this increased energy is explained as vibrations from turbulent blood flow following a coronary stenosis, and the findings of spectral differences have since been confirmed by several other studies referenced below.

Most of the early work on classification of CAD using PCG was done by Semmlow and Akay et al. with their highest frequency of publications on this in the 1990s. In 2007, Semmlow and Rahalkar [8] reviewed technologies, methods, and findings within the field. At the time, work had primarily involved spectral analysis and almost exclusively analysis of the diastolic period.

Modelling CAD Heart Sound Generation

In 1990, Wang et al. developed a sound generation model for healthy and stenosed coronary arteries, providing theoretical support for the observations of spectral differences between CAD and non-CAD patients. Findings were two resonant frequencies – one below 150 Hz and the other above – that were dependent on the position and degree of stenosis. There was a tendency that higher degrees of stenoses caused the lower frequency peak to be shifted toward lower frequencies, while the higher frequency peak was shifted toward higher frequencies [9].

Heart Sounds before and after Angioplasty or Stent

Following the first publication by Semmlow et al., Akay et al. analyzed the changes in diastolic heart sounds by analyzing phonocardiograms taken before and after angioplasty [10] using eigenvector methods [11], and autoregressive (AR) [12] or autoregressive moving average (ARMA) [13], [14] methods. Semmlow et al. [15] summarized these studies, and general findings were a reduction in the power levels of high-frequency peaks following angioplasty. In 2005, Zhidong [16] found that the instantaneous frequency showed obvious differences between patients before and after angioplasty, suggesting that this method should be beneficial for determining the presence of CAD. In 2016, Dragomir et al. [17] performed a similar study on the differences in heart sounds before and after stent placement. The authors found that energy above 150 Hz was reduced after stent placement, and attempted classification using two methods: power-ratio and approximate entropy. However, it is worth noting that all these studies that investigated the effects of stent or angioplasty on the PCG involved a very low number of patients, and thus the results are associated with a high degree of uncertainty. The studies generally agree that higher frequency components are decreased after angioplasty or stent, and these findings also aligned with the model produced by Wang et al. Note that all these studies were based on very small datasets of between 10 and 20 patients.

Classification of CAD vs non-CAD

In addition to the studies on changes with angioplasty, Akay et al. developed methods to distinguish between CAD and non-CAD patients. In an effort to improve the signal-to-noise ratio compared to Fast Fourier Transform (FFT), Akay et al. estimated the diastole power spectra using AR [18] and ARMA [14] methods for multiple heartbeats, and averaged the intra-subject power spectra. Akay et al. additionally used the adaptive line enhancer (ALE) method to reduce background noise of the PCG before applying the FFT, AR, ARMA, and Minimum-Norm methods to estimate the power spectra [19]–[22]. Later, they used the fast transversal filters/fast a posteriori error sequential techniques to take into account the non-stationarity of the cardiac system [23]. These studies aligned in their findings of increased high-frequency energy of heart sound recordings from CAD patients during diastole somewhere between 300-800 Hz.

Gauthier et al. [24] used FFT to perform spectral analysis of the diastole, finding that the power ratio above/below 130 Hz distinguished well between CAD and non-CAD subjects. This is in-line with findings from the authors investigating heart sounds before and after angioplasty as well as the modelled stenosed heart sounds provided by Wang et al. [9].

In 2007, Schmidt et al. [25] developed features for detection of CAD based on frequencies above 240 Hz. However, they later discovered that features based on the frequencies below 250 Hz performed better under noisy conditions in [26], [27], and in [28], the authors reported that the increase of energy related to CAD predominantly occurred in the frequency spectrum below 200 Hz.

Schmidt et al. [27] further investigated nine feature classes; including AR, IF, and sample entropy; for their capacity to detect CAD. The authors found that known higher frequency features performed relatively poorly, which was attributed to the influence of noise. Reported performance of the selected classifier was an AUC of 73%.

Khan and Ahmed [29] investigated six features for their capacity to detect CAD, identifying spectral centroid and spectral roll off as potential features. In [30], the authors used 13 features (including the previous two) to discriminate between 54 CAD and 58 non-CAD subjects, though no further information is given about the subjects. The study achieved an accuracy of 96% using band wise kurtosis of S-transform of heart sounds.

Zhang et al. [31] combined multi-modal features from ECG, PCG, echocardiography, biomarkers and Holter monitoring to create classifiers for CAD, achieving an accuracy of 97% when combining all fives modals.

In 2022, Schmidt et al. [32] focused on the low-frequency diastolic heart sounds to differentiate between CAD and non-CAD patients. The authors used the power ratio of 10-90 Hz over 90-300 Hz, and when correcting for the score for age, sex, and body mass index (BMI), they achieved a reported AUC of 77%.

Li et al. [33] combined features from the first heart sound (S1) and the diastole to classify CAD. Features from S1 included estimating the instantaneous frequencies of the mitral valve closure (M1) and the tricuspid valve closure (T1). The authors reported an accuracy of 86%.

Multi-Channel Analysis

In 2001, Tateishi [34] used spectral analysis of diastole PCGs from five positions on the chest to distinguish between 40 normal young men and 128 patients undergoing ICA. Findings indicated that recordings from the left IC4 provide the recording site for CAD detection using PCG.

Griffel et al. made a series of studies on detection of CAD from two-channel heart sound recordings coupled with recording of ambience and internal sounds as well as a fourth channel with ECG. In these studies, the authors used a support vector machine (SVM) with features from instantaneous frequency [35], auto-mutual information [36], and path length entropy [37]. However, though these studies included two-channel heart sound recordings at three different sites, there was no comparison between single-channel and multi-channel performance or the recording sites.

Pathak et al. [38] compared single-channel and multi-channel analysis using cross power spectral density (CPSD), finding that the multi-channel classifier performed better than the single-channel classifier using the same CPSD based features.

Mandala et al. [39] compared classification of CAD of PCG recordings from four positions on the chest, finding that the aortic position showed superior performance over the tricuspid, pulmonary, and mitral positions.

More recent studies [40]–[42] have combined information from multiple PCG channels to improve performance of the classifier. In [40], Pathak et al. used synchrosqueezing transform (SST) of the cardiac cycle to extract features for detection of CAD. The authors coupled this with spectral features to achieve an accuracy of 83% in a 5-fold cross validation. In [42], Liu et al. used multiple features to classify CAD and non-CAD patients, showing superior performance of the multi-channel classifier over the single-channel one, reaching 91% accuracy with the best classifier.

These latest reported accuracies are impressive, though the number of subjects is limited, and in the case of [40] and [41], the CAD subjects are very different from the non-CAD subjects with a mean age difference of about 31 years.

Nonlinearity

Padmanabhan and Semmlow [43], [44] were the first to investigate the nonlinearity of CAD related heart sounds, using the concept of correlation dimension as introduced by Grassberger and Procaccia [45].

Later, Akay et al. [46] found increased entropy of the diastolic segment of CAD patients compared to non-CAD patients using approximate entropy.

Following this, Schmidt et al. [47] compared the sample entropy with an AR method for detection of CAD, finding the two methods performing on the same level. Likewise in [48], the authors found no evidence of nonlinearity, though this time using recordings from the carotid artery instead of the coronary arteries.

Two studies by Griffel et al. [36], [37] investigated the nonlinearity of CAD related heart sounds. Again, linear and nonlinear methods performed similarly, suggesting that though CAD related sounds may contain nonlinear elements, the acoustic signal contains mostly linear information.

Classification using Artificial Neural Networks

The first studies on classification of CAD using artificial neural networks (ANN) on heart sound recordings were done by Akay et al. in the early 1990s [49]–[52]. All these studies used multilayer perceptron (MLP) networks.

In 2005, Karimi et al. [53] used features from wavelet analysis of diastolic heart sounds to train an ANN using a balanced set of 20 cardiac cycles. The classifier was then tested on balanced set of 20% of the data and tested on the remaining 80%, yielding an accuracy of 91%. However, the study only included 5 CAD and 5 non-CAD patients, with multiple cardiac cycles from each person. It is highly likely that data leakage from different cycles of the same patients occurring in both training and test sets influenced the results.

During the past 4 years there have been a higher frequency of publications within this sub-field. The trend for these more recent publications is the use of multi-channel heart sound recordings.

Samanta et al. used multi-channel heart sound recordings from a balanced dataset of 66 patients to detect CAD. In [54], the authors used spectral moments, spectral entropy, moments of PSD function, AR parameters, and IF derived features as input to an ANN classifier, achieving cross-validation accuracies of 74% and 69% for the developed multi- and single-channel classifiers respectively. In [55], the author managed to increase the accuracies to 83% and 79% respective using a similar approach.

Li et al. published three studies on detection of CAD using ANNs. The first [56] combined information from a single-lead ECG and 4-channel PCG, feeding a large number of features into a fully connected neural network. The study showed increased performance when combining the ECG and PCG over either one of them alone, achieving a cross-validation accuracy of 91% for the best classifier. The second [56] used Mel Frequency Cepstral Coefficients (MFCC) as input to a convolutional neural network (CNN) to extract features from the 4-channel PCG and combined them a number of other features in a MLP to create a classifier for CAD, achieving a cross-validation accuracy of 90%. The third [57] had a similar approach but used both ECG and PCG as input to the separate CNNs for feature extraction, achieving a cross-validation accuracy of 96.5%.

Pathak et al. [58] used transfer learning from a pretrained CNN along with a number of previously developed features to detect CAD among a group of 40 healthy young males and 40 CAD patients, achieving a 89% cross-validation accuracy.

Classification of CAD Severity

An early attempt to estimate the severity of CAD using phonocardiography was by Y. Akay et al. in 1991 using the Minimum-Norm method on the diastolic heart sound [59]. The authors reported that they were able to correctly classify 54 of 62 recordings (87%) into either CAD or non-CAD. When classifying into one of three groups of severity, they correctly classified 46 recordings (74%). This was later followed up by M. Akay [22] who used the ALE method to reduce background noise of the PCG before applying the Minimum-Norm method.

More recently (2021), Zhang et al. [60] classified patients into varying degrees of diameter reduction by combining ECG and PCG signals and calculating a number of entropy measures which were combined in a support vector machine (SVM).

Also in 2021, Khan et al. [61] along with Iqtidar et al. [62] classified patients into one of four categories: normal, single-, dual-, or triple-vessel disease, whereas Mushtaq et al. [63] only classified into diseased groups. All of these studies utilized empirical mode decomposition (EMD), MFCC and a K-nearest neighbor classifier in their approach with variations in their other methods. Reported accuracies were all close to 90% or higher.

1.3. CLINICAL STUDIES ON DETECTION OF CAD USING PCG

Technical studies on heart sounds related to CAD are sparse compared to many other fields, and this is even more so for clinical studies. Thomas et al. [64] reviewed clinical literature on detection of CAD related to acoustic detection systems available or in development. Though there have been a few new clinical studies since then, the three companies that have pursued commercialization of a device aimed toward detection of CAD using PCG to the point of clinical testing remain unchanged:

- Acarix with the CADScor®System (the CAD-score is the measure of CAD-risk calculated by the device)
- AUM Cardiovascular with the CADence system
- AusculSciences with the CAD-det System (previously SonoMedica with Cardoons)

Currently, the CADScor®System is to my knowledge the only commercially available and clinically approved device for risk assessment of CAD using heart sound analysis.

Acarix

The Acarix CADScor®System is described later in Methods and Materials section 3.2.

There have been three large clinical studies evaluating the CADScor®System. Note that the CAD-score was calculated differently for each study, and thus cannot be directly compared.

The first of these was the AdoptCAD study [65], where 255 patients referred to CCTA or ICA were included, of which 63 (28%) were diagnosed with CAD (≥50% diameter stenosis). Winther et al. reported the following performance scores for the CAD-score (which at this time was based entirely on acoustic features): 72% AUC, 76% sensitivity, 59% specificity, 87% NPV, and 42% PPV. When the CAD-score was combined with the Diamond-Forrester score, the AUC increased to 82%.

The second was the Dan-NICAD study [66], where 1675 patients with low to intermediate risks of CAD were enrolled, of which 153 (11%) were diagnosed with CAD (≥50% diameter stenosis). Winther et al. reported the following performance scores when the acoustic score was combined with clinical risk factors: 72% AUC, 80% sensitivity, 53% specificity, 95.9% NPV, and 16% PPV. The reported performance for the acoustic score alone was 63% AUC.

After a roughly 3-year follow-up on patients enrolled in the Dan-NICAD study, Winther et al. [67] investigated the prognostic value of CAD-score by evaluating the mortality and myocardial infarction hazard ratios for both the acoustic score and the CAD-score. The findings indicate that heart sound analysis carries prognostic information and may improve early risk stratification of patients with suspected CAD.

The third was the VALIDATE study [68], where 226 high-risk patients scheduled for ICA were enrolled, of which 89 (39%) were diagnosed with CAD (≥50% diameter stenosis). Renker et al. reported the following performance scores: 66% AUC, 97.6% sensitivity, 14.5% specificity, 90.5% NPV, and 42% PPV. Additionally, where the Diamond-Forrester score was unable to rule out any of the patients, the device ruled out 9.3%. This study also investigated the effects of percutaneous coronary

intervention (PCI) on the CAD-score, showing a significant drop in the CAD-score post-PCI.

In addition to these studies, Schmidt et al. [69] evaluated the reclassification capacity of the CAD-score compared to the 2013 ESC guidelines on the management of stable coronary artery disease [70]. The study showed a significant and safe reclassification of patients, indicating that the CADScor®System can be used to rule-out patients with suspected CAD and an intermediate PTP before they are referred for non-invasive testing. With the release of the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [4], the authors updated the comparison in [71] where they concluded that the relevance and effectiveness of the CADScor®System as a potential rule-out device persists after the application of the new guidelines.

Lastly, there are currently two ongoing clinical studies involving the CADScor®System: Dan-NICAD II [72] and FILTER-SCAD [73]. The Dan-NICAD II study enrolls patients in the same fashion as the Dan-NICAD study and will be used to evaluate the performance of the CAD-score. The FILTER-SCAD study will be used to evaluate the consequence of using the CAD-score in terms of safety and cost-effectiveness and includes a 1-year follow-up on all patients. Whereas the Dan-NICAD II study has finalized enrollment of patients and is expected conclude later this year, the FILTER-SCAD study is expected to conclude in 2024.

AUM Cardiovascular

CADence is a handheld wireless device which records heart sounds from the chest surface and, via a cloud service, analyses recording from four positions to evaluate the presence of CAD.

Initial data for the CADence system was obtained with a commercially available digital stethoscope in 123 patients referred for ICA of which 64 (52%) was diagnosed with CAD (≥50% diameter stenosis). Azimpour et al. [74] reported the following performance scores for detecting the presence of any stenosis ≥50%: 75% AUC, 70% sensitivity, 80% specificity, 71% NPV, and 79% PPV.

A larger trial called TURBULENCE [75] enrolled 1013 patients with chest pain referred for nuclear stress testing. Of these patients, 763 had complete angiographic and CADence data of which 111 (15%) was diagnosed with CAD (≥50% diameter stenosis). Thomas et al. reported the following performance scores: 58% AUC, 78% sensitivity, 35% specificity, and 91% NPV. PPV is calculated to 17% using reported test and diagnostic outcomes.

AusculSciences

The Cardiac Sonospectrographic Analyzer records PCG and ECG simultaneously from the chest surface, using the ECG to identify the patient's heartbeat cycle. It

combines sequential recordings from nine different placements on the chest surface to evaluate the presence of CAD.

Makaryus et al. [76] evaluated the performance of the Cardiac Sonospectrographic Analyzer (a precursor to the CardioSond) in a clinical setting. The study enrolled 161 patients with suspected CAD of which 19 (12%) was diagnosed with significant CAD (≥50% diameter stenosis). The study reported the following performance scores: 74% AUC, 89.5% sensitivity, and 58% specificity. Using reported test and diagnostic outcomes, NPV is calculated to 97.6% and PPV to 22%.

A second study (ClinicalTrials.gov Identifier: NCT03914079) to evaluate the performance of the CAD-det System was initiated in April 2019. The study planned to enroll 2000 patients with a follow-up of 1 year and was anticipated to complete in December 2020; however, recruitment was suspended in June 2020 due to COVID-19 and now has an anticipated completion date of December 2022, though recruitment has yet to resume.

1.4. DIAGNOSTIC PATHWAY

This thesis focuses on acoustic risk assessment of CAD in relation to the European guidelines to limit the scope. For this reason, other guidelines such as the AHA and the variations between guidelines will not be considered.

The 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [4] outlines the recommended approach for diagnostic management of patients with angina and suspected CAD. Throughout the guidelines, CAD is referred to as either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS). In this thesis, those terms will be referred to as either acute CAD or stable CAD respectively. The guidelines divide the diagnostic process into six steps:

The first step of investigating a patient suspected of having CAD is to assess the symptoms and perform clinical investigations. This includes patient anamnesis including risk factors (family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other lifestyle factors) as well as a physical examination. An important part of this step is to evaluate the risk of acute CAD, and rule this out before proceeding further in the diagnostic pathway for stable CAD.

The next step for patients not suffering from acute CAD, is to evaluate the patient's condition and quality of life and to consider comorbidities that could affect therapeutic decisions. Additionally, alternative causes of symptoms are considered.

If revascularization is still an option for the patient (if diagnosed with CAD) and CAD is still the primary suspicion, then the process continues to step three. Here, the patient undergoes basic testing such as blood testing, resting ECG, and echocardiography.

None of the testing modalities are used to diagnose the presence of CAD but instead used to identify possible causes of ischemia, establish cardiovascular risk factors, exclude alternative causes of chest pain, and to perform initial patient risk stratification. These tests can also reveal other conditions such as atrial fibrillation, explaining the symptoms of chest pain, or the presence of possibly concurrent cardiac diseases such as heart failure (HF).

In step four, the patient's pre-test probability (PTP) for CAD is evaluated using a clinical likelihood for CAD as shown in Table 1-1, based on Juarez-Orozco et al. [77], which uses the same three parameters as the Diamond-Forrester score [78] – though symptoms have been extended to include dyspnea. Additionally, the risk table was updated using several newer studies that showed lower prevalence of CAD. The 2019 recommendations are to proceed with diagnostic testing for all patients with PTP >15%, whereas patients with PTP 5-15% only should be considered for diagnostic testing after assessing the overall clinical likelihood based on the modifiers of PTPs (such as family history of CVD, dyslipidemia, diabetes, hypertension, and smoking). Finally, for patients with a PTP <5%, diagnostic testing should only proceed given "compelling reasons" and otherwise be assumed to not have CAD.

	Typical		**Atypical**		**Non-anginal**		**Dyspnea**	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30-39	3%	5%	4%	3%	1%	1%	0%	3%
40-49	22%	10%	10%	6%	3%	2%	12%	3%
50-59	32%	13%	17%	6%	11%	3%	20%	9%
60-69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

Table 1-1 The 2019 ESC guidelines recommended PTP table for CAD. This score is based on the clinical likelihood of CAD in patients with suspected CAD grouped by age (five groups), sex (two groups), and symptoms (four groups). Replicated from [4].

Step five introduces diagnostic testing to establish the presence of CAD using a wide range of diagnostic modalities. The guidelines have varied recommendations depending on the assessed risk of CAD. Patients with high likelihood of CAD could be investigated directly using ICA, though the guidelines recommend this is not done routinely. Recommendations for initial non-invasive testing are either functional imaging of ischemia or anatomical testing using CCTA.

Finally, step six evaluates the patient's event risk to determine the best therapeutic action. However, considerations for best therapeutic action are outside the scope of this thesis and will not be described in further details.

1.5. ADVANCED PRE-TEST PROBABILITY

Recently, Winther et al. [79] proposed a clinical risk estimation (RF-CL) model for CAD using the same clinical risk factors as the Diamond-Forrester score as well as the number of additional risk factors from 0 to 5 of family history of CAD, smoking,

dyslipidemia, hypertension, and diabetes . This new clinical risk factor model significantly and safely improves the rule-out of suspected CAD patients over the 2019 ESC guidelines. Reported performance score for the RF-CL model were 75% AUC, 88.7% sensitivity, 41.5% specificity, 14.7% PPV, and 97% NPV.

CHAPTER 2. THESIS SCOPE AND AIMS

The overall aim of this thesis was to improve acoustic detection of CAD for the purpose of early rule-out. During the thesis work, there were significant improvements to the rule-out capacity of clinical risk factors models, and this thesis aimed to further augment this performance using phonocardiography.

Among patients suspected having CAD and referred to further testing, only 6-12% require medical intervention for the disease [66], [80], [81]. Even with improvements seen in recent clinical risk factors models, early rule-out of patients with suspected CAD continue to be an issue where there is potential for improvement, which would alleviate workload on the health care system and reduce the number of non-CAD patients exposed to invasive risks.

The thesis was divided into four studies with the following prospects:

1. The first step was to investigate the influence of clinical risk factors on the heart sound. This understanding would assist exploration the phonocardiogram for acoustic features which are uncorrelated with clinical risk factors.
2. The second step was to create a filter that could emphasize spectral differences in heart sounds between CAD and non-CAD patients. This work could lead to making known spectral differences more pronounced or uncovering new spectral differences.
3. The third step was to perform a comprehensive spectral analysis of the phonocardiogram to find spectral differences between CAD and non-CAD patients which could be used to create acoustic features as addition to a clinical risk factor model.
4. The fourth and final step was to use knowledge from the previous steps to extract acoustic features from the phonocardiogram based on the spectral differences between CAD and non-CAD patients and use these features to improve the best clinical risk factor model.

CHAPTER 3. METHODS AND MATERIALS

This chapter describes the methods and materials of the four thesis studies. This includes composition of datasets, a description of Acarix studies that were used in the thesis studies as well as the Acarix CADScor®System. Study specific methods will not be described in this chapter, and readers are instead referred to the thesis articles.

3.1. DATA

Datasets used in the thesis studies were all constructed using the Acarix heart sound database, which consists of studies performed by Acarix in collaboration with various hospitals. Four of these Acarix studies were used in the thesis studies.

The datasets for the thesis studies were constructed in a similar fashion but with notable differences in patient inclusion criteria as shown in Table 3-1. Additionally, differences in methods such as size of analytical windows caused differences in which patients were included.

Studies	**AdoptCAD**	**Dan-NICAD**	**BIO-CAC**	**VALIDATE**
Study I	-	CAD Non-CAD	-	-
Study II	CAD Non-CAD	CAD Non-CAD	CAD Non-CAD	-
Study III	CAD Other	CAD Other	CAD Other	-
Study IV	CAD Other	CAD Other	CAD Other	CAD Other

Table 3-1 Overview of which Acarix studies were used for in the thesis studies as well as which types of patients were included. Diagnosis definitions are further explained in section 3.1.2.

Details about patient demographics, risk factors, and symptoms are summarized in Table 3-2, and test modalities and test outcomes are summarized in Table 3-3. Note that these tables summarize available data before further requirements were imposed by the thesis studies.

	All (n = 2698)	AdoptCAD (n = 249)	Dan-NICAD (n = 1563)	BIO-CAC (n = 661)	VALIDATE (n = 225)
Characteristics					
Male	1333 (49.4%)	132 (53%)	754 (48.2%)	312 (47.2%)	135 (60%)
Age†	59±8.72	62.1±10.6	57.2±8.76	60.3±5.02	64.5±10.6
<40	5 (0.185%)	5 (2.01%)	0 (0%)	0 (0%)	0 (0%)
40-<50	389 (14.4%)	26 (10.4%)	340 (21.8%)	0 (0%)	23 (10.2%)
50-<60	1007 (37.3%)	60 (24.1%)	577 (36.9%)	313 (47.4%)	57 (25.3%)
60-<70	1033 (38.3%)	100 (40.2%)	521 (33.3%)	348 (52.6%)	64 (28.4%)
≥70	264 (9.79%)	58 (23.3%)	125 (8%)	0 (0%)	81 (36%)
Body Mass Index, kg/m^2†	27±4.41	26.9±4.17	26.7±4.18	27.5±4.59	28.2±5.32
Risk factors and symptoms					
Family history of CAD	799 (29.6%)	NA	579 (37%)	151 (22.8%)	69 (30.7%)
Smoking					
Never	1269 (47%)	91 (36.5%)	745 (47.7%)	313 (47.4%)	120 (53.3%)
Former	952 (35.3%)	109 (43.8%)	573 (36.7%)	234 (35.4%)	36 (16%)
Active	466 (17.3%)	49 (19.7%)	245 (15.7%)	114 (17.2%)	58 (25.8%)
Dyslipidemia	1861 (69%)	195 (78.3%)	1062 (67.9%)	469 (71%)	135 (60%)
Hypertension	1652 (61.2%)	171 (68.7%)	929 (59.4%)	363 (54.9%)	189 (84%)
Diabetes	206 (7.64%)	25 (10%)	82 (5.25%)	39 (5.9%)	60 (26.7%)
Cardiac symptoms					
Typical chest pain	728 (27%)	98 (39.4%)	431 (27.6%)	6 (0.908%)	193 (85.8%)
Atypical chest pain	683 (25.3%)	105 (42.2%)	529 (33.8%)	25 (3.78%)	24 (10.7%)
Nonspecific chest pain	956 (35.4%)	40 (16.1%)	278 (17.8%)	630 (95.3%)	8 (3.56%)
Dyspnea	325 (12%)	0 (0%)	325 (20.8%)	0 (0%)	0 (0%)
CAD prevalence					
Obstructive-CAD	326 (12.1%)	68 (27.3%)	161 (10.3%)	2 (0.303%)	95 (42.2%)
Nonobstructive-CAD	1086 (40.3%)	110 (44.2%)	626 (40.1%)	344 (52%)	6 (2.67%)
Non-CAD	1085 (40.2%)	71 (28.5%)	739 (47.3%)	275 (41.6%)	0 (0%)

Table 3-2 Demographics, risk factors, and CAD prevalence for patients in the Acarix studies. Note that only patients with a heart sound recording are included in this table, and thus the number of subjects for each study could be lower than the number of enrolled patients reported in the respective studies. † denotes that values are given as statistical means ± standard deviation. Numbers in parentheses are the portion of subjects out of the total number of subjects in that study. NA means that field was not defined for that study.

	All	AdoptCAD	Dan-NICAD	BIO-CAC	VALIDATE
CACS	2454	242	1553	657	2
0	1146 (42.5%)	79 (31.7%)	791 (50.6%)	276 (41.8%)	0 (0%)
1-399	1018 (37.7%)	100 (40.2%)	606 (38.8%)	312 (47.2%)	0 (0%)
≥400	290 (10.7%)	63 (25.3%)	156 (9.98%)	69 (10.4%)	2 (0.889%)
CCTA conclusion	1731	119	1554	58	0
Non-CAD	854 (31.7%)	70 (28.1%)	739 (47.3%)	45 (6.81%)	0 (0%)
Mild-moderate	467 (17.3%)	18 (7.23%)	446 (28.5%)	3 (0.454%)	0 (0%)
Severe	410 (15.2%)	31 (12.4%)	369 (23.6%)	10 (1.51%)	0 (0%)
ICA conclusion	598	142	342	12	102
No stenosis	128 (4.74%)	48 (19.3%)	78 (4.99%)	1 (0.151%)	1 (0.444%)
Stenosis <50% diameter reduction	144 (5.34%)	26 (10.4%)	103 (6.59%)	9 (1.36%)	6 (2.67%)
Stenosis ≥50% diameter reduction	326 (12.1%)	68 (27.3%)	161 (10.3%)	2 (0.303%)	95 (42.2%)
Concluding diagnosis	2497	249	1526	621	101
Obstructive-CAD	326 (12.1%)	68 (27.3%)	161 (10.3%)	2 (0.303%)	95 (42.2%)
Nonobstructive-CAD	1086 (40.3%)	110 (44.2%)	626 (40.1%)	344 (52%)	6 (2.67%)
Non-CAD	1085 (40.2%)	71 (28.5%)	739 (47.3%)	275 (41.6%)	0 (0%)

Table 3-3 Overview of test results for patients in the four Acarix studies. Note that the number of patients that underwent each diagnostic test is listed in the rows of the test headings with the indented rows showing frequency of test results. Only patients with a heart sound recording were included in the database.

3.1.1. ACARIX STUDIES

Acarix studies were performed with different aims and patient inclusion criteria and at different points in the diagnostic pathway. Paragraphs below

AdoptCAD [65] enrolled patients with symptoms of CAD referred to either coronary computed tomographic angiography (CCTA) or invasive coronary angiography (ICA). Further details regarding inclusion and exclusion criteria are detailed in [65]. Obtained data included clinical information, heart sound recordings, CACS, and either CCTA or ICA.

Dan-NICAD [66], [82] enrolled patients who were referred to CCTA due to symptoms suggestive of CAD, and who had low to intermediate risk profiles. Obtained data included clinical information, heart sound recordings, CACS, and CCTA. Additionally, patients with suspected CAD after CCTA underwent ICA with both fractional flow reserve (FFR) and two-dimensional quantitative coronary angiography (2D-QCA).

BIO-CAC [83], [84] enrolled subjects without CAD symptoms and investigated them for a number of biomarkers as well CACS. Obtained data included clinical information and heart sound recordings, and CACS. For a subset of patients, CCTA and/or ICA were also obtained.

VALIDATE [68] enrolled patients who were scheduled for clinically indicated ICA. This study has the highest CAD prevalence of all the studies as it enrolled patients

quite late in the diagnostic pathway. Obtained data included clinical information, heart sound recordings, and ICA.

Patients in the four Acarix studies thus represent four different patient risk profiles of CAD, ranging from low-risk to high-risk: BIO-CAC, Dan-NICAD, AdoptCAD, and VALIDATE. It is worth noting that patients enrolled in the Dan-NICAD study best reflect the intended segment where early risk assessment of patients suspected of CAD using phonocardiography has a valuable contribution to the diagnostic pathway. This stage is after symptoms of CAD have been established and before any expensive testing such as CACS has been performed. At later stages, the rule-out capacity would be greatly reduced, and more expensive tests that have higher accuracies could be more relevant. Before this stage, patients would be asymptomatic, and although it is an interesting prospect to use phonocardiography as a screening tool for CAD, screening of asymptomatic patients for CAD is outside the scope of this thesis.

3.1.2. DIAGNOSTIC DEFINITIONS

A challenge to pooling data from multiple studies with different aims was that patients were included at different stages in the diagnostic pathway and underwent different diagnostic testing. Thus, diagnostic definitions necessarily differ between studies; however, the definition of significant CAD was the same for all studies. Table 1 shows an overview of rules used for the different Acarix studies in creating uniform diagnostic categories.

	Non-CAD	Nonobstructive-CAD	Obstructive-CAD
General rules	CACS=0 & CCTA=Normal	CACS>0 & CCTA Normal & no CAG or CCTA=Mild-moderate & no ICA or 2D- QCA (<50%) & (CCTA not normal or CACS>0)	2D-QCA ≥50%
AdoptCAD	CACS=0 & ICA<30% & No CCTA	-	-
Dan-NICAD	-	-	-
BIO-CAC	CACS=0	CACS>0 & CACS<400 & No CCTA & No SPECT & No ICA or (SPECT Normal & CACS>0)	-
VALIDATE	-	2D- QCA (<50%) & CACS>0	-

Table 3-4 Summarized view of how diagnoses were defined for the Acarix studies in an effort to create shared categories of diagnoses.

3.2. HEART SOUND RECORDING DEVICE

All heart sound recordings were acquired using the CADScor®System (Acarix A/S, Denmark) shown in Figure 3-1. It is a medical device with both CE and FDA approvals for risk stratification of patients with symptoms suggestive of CAD. It uses a combination of heart sound analysis and clinical risk factors to determine a risk score for patients with suspected CAD, assisting doctors in early risk stratification.

The device uses an adhesive patch to improve signal quality of the heart sound by having an air-tight fit between the microphone and the chest surface and at the same time avoiding vibrations from unsteady operator hands associated with manual auscultation.

Figure 3-1 The Acarix CADScor®System and adhesive CADScor® patch. Reprinted with permission from Acarix.

Performance of the CADScor®System as reported by the user manual [85], is as follows:

- Sensitivity: 89.4% (84.7-93.0%)
- Specificity: 42.0% (39.8-44.1%)
- NPV: 97.2% (95.9-98.2%)
- PPV: 14.9% (13.1-16.8%)

With validation data CAD-prevalence of 10.2%. Ranges in parentheses indicate 95% confidence intervals.

3.3. HEART SOUND ACQUISITION

Before recording, the CADScor®System is assembled with the patch and placed at the fourth left intercostal space as shown in Figure 3-2. The patient is in supine position during recording and for at least five minutes prior in order to attain hemodynamic equilibrium. Heart sounds are then recorded during four breath-hold periods of eight seconds each.

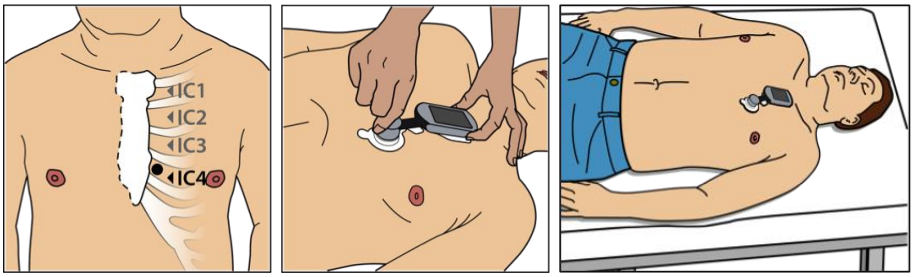

Figure 3-2 Placement of the CADScor®System at the left IC4 with the patient in supine position. Reprinted with permission from Acarix.

CHAPTER 4. THESIS ARTICLES

This PhD-thesis is based on the following four articles:

I **Correlations of First and Second Heart Sounds with Age, Sex, and Body Mass Index**
Larsen BS, Winther S, Bøttcher M, Nissen L, Struijk J, Schmidt SE.
2017 Computing in Cardiology Conference, vol. 44 (Rennes, France, 2017-09)
Doi: 10.22489/CinC.2017.141-408

II **Autoregressive Whitening Filtering of Phonocardiography Signals for Detection of Coronary Artery Disease**
Larsen BS, Winther S, Nissen L, Diederichsen A, Bøttcher M, Struijk J, Christensen MG, Schmidt SE.
2019 Computing in Cardiology Conference, vol. 46 (Singapore, 2019-09)
Doi: 10.22489/cinc.2019.354

III **Spectral analysis of heart sounds associated with coronary artery disease**
Larsen BS, Winther S, Nissen L, Diederichsen A, Bøttcher M, Struijk J, Christensen MG, Schmidt SE.
2021 Physiological Measurement 42 105013
Doi: 10.1088/1361-6579/ac2fb7

IV **Improved Pre-Test Likelihood Estimation of Coronary Artery Disease Using Phonocardiography**
Larsen BS, Winther S, Nissen L, Diederichsen A, Bøttcher M, Renker M, Struijk J, Christensen MG, Schmidt SE.
Submitted to European Heart Journal – Digital Health in April 2022
Under review

CHAPTER 5. SUMMARY OF STUDIES

5.1. STUDY I

The first study was published in September 2017 as a conference proceeding article at 2017 Computing in Cardiology Conference under the title: “Correlations of First and Second Heart Sounds with Age, Sex, and Body Mass Index.” [86]

The purpose of this study was to investigate the influence of age, gender, and body mass index (BMI) on heart sounds.

Background

The size of a normal heart varies significantly with sex, height, weight, and age [87]. It is likely that this also translates into a similar relationship between these parameters and the normal heart sound; however, this had not been investigated prior to this study. Given a thorough understanding of the relationship, future analyses of heart sounds could take these factors into account to improve feature development and selection. This especially becomes relevant when combining acoustic features with clinical and demographic parameters for risk stratification of patients suspected of having CAD.

Results

Heart sound recording from 739 subjects from the Dan-NICAD study [66], [82] who had no indication of CAD were analyzed, and the amplitudes of the first heart sound (S1) and second heart sound (S2) were investigated for correlation with age, sex, and BMI.

Whereas significant correlations were found for all three parameters with the first heart sound, only BMI showed significant correlation with the second heart sound. Among the three parameters, BMI showed by far the strongest correlation – likely because higher BMI is associated with a thicker chest wall and thus greater attenuation of heart sounds. These findings show that acoustic features may be correlated with demographic and clinical parameters, and it is therefore important to take the possible co-linearity of these factors into account when developing and selecting acoustic features for diagnosis of CAD.

Understanding this relationship is important for the application of heart sound analysis in diagnosis of CAD.

5.2. STUDY II

The second study was published in September 2019 as a conference proceeding article at the 2019 Computing in Cardiology Conference under the title: "Autoregressive Whitening Filtering of Phonocardiography Signals for Detection of Coronary Artery Disease." [88]

The purpose of this study was to develop a whitening filter for emphasizing the CAD related parts of the phonocardiogram to improve phonocardiographic diagnosis of CAD.

Background

Heart sounds have high magnitudes of low-frequency energies compared to higher frequencies. This steep roll-off causes spectral leakage which can obscure the high frequency parts of the relatively weak CAD related murmurs.

Implementation of a filter that is designed to flatten the frequency spectrum of non-CAD patients, would reduce the influence of spectral leakage, and might emphasize higher frequency spectral differences between CAD and non-CAD patients.

Results

A total of 1168 heart sound recordings from AdoptCAD [65], Dan-NICAD [66], [82], and BIO-CAC [83], [84] studies from CAD (n=213) and non-CAD (n=955) subjects were analyzed in the study. The diastolic segment of all included non-CAD patients were used to develop an autoregressive whitening filter, designed to make the mean diastolic non-CAD segment spectrally white.

A single iteration of the filtering method did not result in spectral flatness; however, repeating the filtering process increased the spectral flatness score, and a plateau near maximal flatness was achieved with an 8^{th} order whitening filter using two iterations.

Applying the developed whitening filter to both CAD and non-CAD heart sound recordings showed that higher frequency differences between the two groups were emphasized.

Though spectral differences for the low-frequency range remained largely unchanged, there were substantial changes in the high-frequency range, where differences after whitening filtering became more pronounced.

5.3. STUDY III

The third study was published in November 2021 in the journal Physiological Measurement under the title: “Spectral analysis of heart sounds associated with coronary artery disease.” [89]

The purpose of this study was to investigate spectral differences of the phonocardiogram between CAD and non-CAD patients.

Background

Previous investigations of spectral differences in heart sounds from CAD and non-CAD patients have largely focused on the diastolic period because it is during this resting period that there is maximal blood flow through the coronary arteries [8]. Therefore, this period should also be associated with the clearest murmur from turbulent flow following the coronary occlusions. However, this study aimed to make a comprehensive investigation of the spectral differences of heart sound recordings between CAD and non-CAD patients by investigating all parts of the heart sound.

Results

Heart sound recording from 1146 subjects were analyzed using a pooled dataset from three studies (AdoptCAD [65], Dan-NICAD [66], [82], and BIO-CAC [83], [84]) for each of four segments (S1, systole, S2, and diastole). Systole and diastole segments were investigated by estimating the power spectral density of the entire segment, whereas S1 and S2 were investigated by estimating the time-frequency resolution due to the dynamic nature of these segments. The average frequency and time-frequency spectra for CAD and non-CAD patients respectively were then compared to find components of statistically significant difference. In this comparison, patient risk factors (age, sex, and BMI) were adjusted for in the statistical model to identify frequency and time-frequency components from the heart sound recordings that would be able to improve a risk factor model.

Findings for the diastolic segment confirmed previous findings of increased energy for low-frequency components (<200 Hz) for CAD patients compared to non-CAD patients, and the systole segment showed similar tendency with less clear difference as the confidence interval was much wider. Analyses of both S1 and S2 segments revealed several new spectral differences between CAD and non-CAD patients.

5.4. STUDY IV

The fourth study was submitted in April 2022 to the European Heart Journal – Digital Health under the title: "Improved Pre-Test Likelihood Estimation of Coronary Artery Disease Using Phonocardiography."

The purpose of this study was to improve the currently best clinical risk factor model using acoustic features.

Background

The suggested model for evaluating patient risk of CAD in the 2019 ESC guidelines on chronic coronary syndrome (ESC2019) has a low rule-out capacity of 19-20% [90], [91], though reported as low as 11% in [79]. A recently suggested clinical risk factor weighted model (RF-CL) by Winther et al. [79] has reached a significantly higher rule-out capacity of 38% while keeping a high sensitivity by incorporating the count of risk factors present with a patient.

The improved rule-out of this risk factor model over the ESC2019 model motivated this investigation of the possibility of further improving the performance with addition of acoustic features.

Results

Using a pooled dataset of four studies (AdoptCAD [65], Dan-NICAD [66], [82], BIO-CAC [83], [84], and VALIDATE [68]), 2222 patients were included in the analysis. Using 80% of the dataset for training, three acoustic features were selected out of a feature bank of 41 acoustic features. These three features were added to RF-CL model on the basis of the improved cross-validation performance of the overall model to create the A-CL model.

Performance of the developed A-CL model was evaluated and compared with the RF-CL model on the remaining 20% of the dataset, showing significantly higher specificity (48.6%) over the RF-CL (41.5%) with the same sensitivity (84.9%). Furthermore, the addition of acoustic features showed significant improvement to the high-sensitivity part of the ROC curve compared to the already highly performing RF-CL model.

CHAPTER 6. DISCUSSION

Through four studies, this thesis investigated the addition of acoustic features to an advanced clinical risk factor model for the purpose of early rule-out of CAD.

The initial finding of correlations between age, sex, and BMI with the amplitude of the two major heart sounds suggests that it is important to take these factors into account when analyzing the heart sound signal with the purpose of finding acoustic features that can contribute to a clinical risk factor model. This study was limited to investigating the correlation of the amplitude of S1 and S2 with the three parameters. A model that included all the clinical parameters could be better suited to provide a combined evaluation of the relationship between heart sounds and the clinical parameters. Likewise, an investigation of spectral correlations with these factors would be interesting to make as well. However, for the purpose of establishing a relationship between heart sounds and the given parameters, the performed study was sufficient.

The development and application of a whitening filter emphasized higher frequency differences between CAD and non-CAD patients in the diastolic heart sound. This created the potential for development of additional features for discriminating between CAD and non-CAD patients. However, in this thesis, these high-frequency diastolic differences were not statistically significant when adjusting for age, sex, and BMI. Even so, high-frequency components with differences of statistical significance were found in both the S1 and S2 heart sounds. Spectral analysis of differences between CAD and non-CAD patients revealed several new components of interest in both the S1 and S2 heart sounds and confirmed previous findings of low-frequency differences in the diastole. However, previous findings of high-frequency differences in the diastole were not found to be of statistical significance in this thesis. Analysis of the systole showed that this segment is likely not of significant interest for diagnosing CAD; however, a separate analysis regarding stenoses of the right coronary artery could still be of interest to determine the importance of the systole for detecting RCA stenoses.

The developed risk estimation model for CAD included, in addition to clinical parameters, a previously developed entropy score and two high-frequency components of the early S1 heart sound. The existing clinical risk factor model was significantly improved and yielded substantially improved reclassification over the clinical risk factor model (RF-CL) and higher rule-out capacity.

The proposed model did not fully incorporate the clinical parameters in the model but used the weights of the existing model by Winther et al. A better performance might have been reached if each of the parameters of the RF-CL model had instead been used as the starting point of a model instead of using the aggregate score of those

parameters. However, the RF-CL model was trained using a very large dataset, and thus the weights should be considered well-trained.

Rule-in and Rule-out

A Swedish study [92] that investigated the general population of ages 50 to 64 years, excluding those with known CAD or MI, found that 5.2% of the subjects had obstructive CAD (>50% diameter reduction) as evaluated by CCTA. As an example, the prevalence of CAD among symptomatic patients referred for testing because of suspected CAD in the Dan-NICAD study was around 10%. This means that although the selection of patients for further testing done by GPs and cardiologists approximately doubles the prevalence of the testing population, the vast majority of patients sent for testing do not have obstructive CAD. Inserting the proposed model immediately before further testing would increase the CAD-prevalence of the population referred for further testing, such as CCTA, to approximately 15.5% as calculated from the sensitivity and specificity. This is a significant improvement and can likely free up substantial resources for health care services. In comparison, using the purely clinical risk factor model (RF-CL) would result in a CAD-prevalence of 13.9% in the population sent for further testing. However, there could still be improvements made to acoustic risk estimation using more advanced heart sound analysis methods. From a rule-out perspective there was substantial improvement, with the developed acoustically augmented (A-CL) model ruling out 45% over the clinical risk factor (RF-CL) model with 38%.

An acoustically augmented clinical risk estimation model (such as the one proposed) could eventually replace or supplement the PTP evaluation in step four of the 2019 ESC guidelines for the benefit of fewer patients undergoing unnecessary testing (and associated risks) as well as reducing the substantial health care costs associated with CAD. Where the classic PTP gives a risk assessment based on the observed risks in subgroups, the acoustic parts are personalized factors in the risk assessment that are independent of clinical parameters.

Future Development

Going forward, the impressive performances reported by advanced neural network algorithms warrants further investigation. Though these results were not verified on independent datasets and in some cases, the CAD and non-CAD patients were highly dissimilar, the results remain interesting. If these performances can be replicated in a clinical setting, it has the potential to transform CAD diagnostics and enable a fast, noninvasive, and low-cost method for CAD detection with high precision.

It is worth noting though, that neural networks are usually applied to solve problems that for example a doctor could perform, such as visually inspecting a tissue sample for the presence of cancer cells where the application is more of automation and consistency of evaluation. Conversely, coronary stenoses are usually not audible by human auscultation or obviously seen in a spectrogram even by trained individuals.

Another common use of neural networks is when the solution calls for the analysis of vast amounts of data that it is unfeasible for a human to perform such as DNA sequences or when complex patterns in data keys the solutions to a problem. It may be that this last application fits the problem of detecting CAD using PCG; however, to determine if this is the case, further studies using these methods in a clinical setting are required.

Potential for Screening

At least 25% of all sudden cardiac arrest (SCA) events are the first manifestation of symptoms of CAD [93]. If the potential for screening asymptomatic patients for CAD using PCG is achieved, it would unlock the possibility of early detection of CAD among these patients, allowing for treatment before the occurrence of SCA. However, this would require high model specificity in order to avoid an unmanageable influx of patients for further testing. A phonocardiographic screening tool for CAD could be implemented at a low-cost and with no invasive risk to patients, making it a viable solution, given improvements in detection performance.

As an example, a PCG screening tool could be used on a high-prevalence group such as diabetes patients or elderly, and patients estimated to have an elevated risk could subsequently be evaluated using CACS before proceeding to invasive testing.

CHAPTER 7. CONCLUSION

This thesis investigated the potential for acoustic features to improve a modern clinical risk estimation model for CAD with a high rule-out capacity.

First, a relationship between clinical parameters and heart sounds was established, and using this information, the search for acoustic features adjusted for this by decorrelating heart sound components with these parameters. Next, a whitening filter was created to emphasize the high-frequency differences between CAD and non-CAD patients previously discovered.

Acoustic features were extracted from areas showing significant differences between CAD and non-CAD patients after adjusting for age, sex, and BMI. Using a forward selection method, these features were then selected and added to the clinical risk factor model, yielding a statistically significant improvement.

In conclusion, this thesis demonstrates the contribution of acoustic components to a modern clinical risk factor model beyond what is explained by clinical parameters. This shows the potential for using phonocardiography in risk assessment of patients with suspected CAD early in the diagnostic pathway as an addition to existing clinical risk models.

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APPENDICES

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