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Calcium Identification and Scoring based on Echocardiography Imaging

Luís Manuel Nobre de Brito Elvas

Master's in Integrated Decision Support Systems

Supervisor:

PhD José Miguel de Oliveira Monteiro Sales Dias, Associated Professor with Habilitation,

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Resumo

Atualmente, é necessário um perito em ecocardiografia para identificar o cálcio na válvula aórtica, e é necessária uma imagem Tomográfica Computorizada (TAC) cardíaca para a quantificação do cálcio. Ao realizar uma TAC, o paciente é sujeito a radiação, pelo que o número de TACs que podem ser realizadas deve ser limitado, restringindo a monitorização do paciente. A Visão por Computador (VC) abriu novas oportunidades para uma maior eficiência na extração de conhecimentos de uma imagem. A aplicação de técnicas de VC na ecocardiografia pode reduzir a carga de trabalho médico para identificar o cálcio e quantificá-lo, ajudando os médicos a manter um melhor acompanhamento dos seus pacientes. Na nossa abordagem, desenvolvemos uma técnica simples para identificar e extrair o número de pixéis de cálcio da ecocardiografia, através da utilização de VC. Com base em ecocardiografias anónimas de doentes reais, esta abordagem permite a identificação semiautomática do cálcio. Como o brilho das imagens de ecocardiografia (com a intensidade mais elevada corresponde ao cálcio) varia consoante os parâmetros de aquisição, realizámos a binarização das ecocardiografias de forma adaptativa. Dado que o sangue mantém a mesma intensidade nas ecocardiografias - sendo sempre a região mais escura - utilizámos estruturas sanguíneas na imagem para criar um limiar adaptativo para a binarização. Após a binarização, a região de interesse (ROI) com cálcio, foi selecionada interactivamente por um especialista em ecocardiografia e extraída, permitindo-nos calcular o número de pixéis de cálcio, correspondente à quantidade espacial de cálcio. Os resultados obtidos com as nossas experiências são encorajadores. Com a nossa técnica, a partir de ecocardiografias recolhidas para o mesmo paciente com diferentes configurações de aquisição e diferentes brilhos, conseguimos obter uma contagem de pixéis de cálcio, onde os valores de pixéis mostram uma margem de erro absoluta de 3 (numa escala de 0 a 255), que se correlacionou bem com a avaliação humana perita da área de cálcio para as mesmas imagens.

Palavras-chave: Imagens de ultrassom; Ecocardiografia; Cálcio da Válvula Aórtica; Classificação da imagem; Visão por computador

Abstract

Currently, an echocardiography expert is needed to identify calcium in the aortic valve, and a cardiac CT-Scan image is needed for calcium quantification. When performing a CT-scan, the patient is subject to radiation, and therefore the number of CT-scans that can be performed should be limited, restricting the patient's monitoring. Computer Vision (CV) has opened new opportunities for improved efficiency when extracting knowledge from an image. Applying CV techniques on echocardiography imaging may reduce the medical workload for identifying the calcium and quantifying it, helping doctors to maintain a better tracking of their patients. In our approach, we developed a simple technique to identify and extract the calcium pixel count from echocardiography imaging, by using CV. Based on anonymized real patient echocardiographic images, this approach enables semi-automatic calcium identification. As the brightness of echocardiography images (with the highest intensity corresponding to calcium) vary depending on the acquisition settings, we performed echocardiographic adaptive image binarization. Given that blood maintains the same intensity on echocardiographic images – being always the darker region – we used blood structures in the image to create an adaptive threshold for binarization. After binarization, the region of interest (ROI) with calcium, was interactively selected by an echocardiography expert and extracted, allowing us to compute a calcium pixel count, corresponding to the spatial amount of calcium. The results obtained from our experiments are encouraging. With our technique, from echocardiographic images collected for the same patient with different acquisition settings and different brightness, we were able to obtain a calcium pixel count, where pixels values show an absolute pixel value margin of error of 3 (on a scale from 0 to 255), that correlated well with human expert assessment of calcium area for the same images.

Keywords: Ultrasound images; Echocardiography; Aortic Valve Calcium; Image Classification; Computer Vision.

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Glossary

CT – Computed Tomography

CV – Computer Vision

ML – Machine Learning

ROI – Region of Interest

NR - Normalization Region

CNN - Convolutional Neural Networks

IVUS - Intravascular Ultrasound

1 Introduction

Aortic valve stenosis is the most common cardiac valvular disease highly prevalent nowadays [1], affecting 7% of the population over 65 years old. It has a 60% annual mortality rate in untreated severe cases, with survival <5 years when symptoms evolve. The incidence and prevalence of the degenerative type is increasing as this segment of the population grows older [2]. It is estimated that 2 262 325 people are at risk in Portugal, accounting for 22% of the population [3]. According to the European Society of Cardiology's recommendations for diagnosing and treating aortic stenosis, echocardiography is the first-line method to make the diagnosis and monitor the patient and valve calcification is a main feature to assess severity. A standardized diagnostic tool is needed to diagnose, assess the severity of the stenosis, and follow-up this large population.

Computed tomography (CT) provides a calcium quantification method, expressed as calcium score, and when applied to aortic valve stenosis, it has been shown that valve calcification is related to disease severity. The amount of valve calcium must often be calculated because the severity of stenosis is directly related to prognosis and has impact on the decision to replace the valve. This is particularly important when assessing severity with echocardiography, which may be difficult or debatable in up to 20% of cases [4]. Previous studies have shown the value of cardiac CT-scans for determining the aortic calcium score, which is the only current imaging modality available for this purpose. Nevertheless, this approach bears costs, not only monetary but from health too, since it is an ionizing technique, that uses radiation to extract the amount of calcium [5], which may have long-term effects on the health condition of the patient.

Before performing a CT-scan to obtain a calcium score, the calcium is first identified from the early stages of the disease by echocardiography [6], non-invasive non-radiation method that uses ultrasound to scan the heart. The reliable quantification of the calcium amount has not been done, using only echocardiography data analysis.

The standard of calcium detection requires training from medical professionals, and the process is dependent on human performance and is time-consuming. Moreover, results may depend on the settings used for the image acquisition. No quantitative method was published for detecting and measuring valve calcium for clinical decisions to the authors knowledge.

There are several approaches to this problem, such as by adopting Machine Learning (ML) techniques. An example of this approach in the healthcare field can be seen in predicting the probability of lethal pneumonia to optimize costs, manage low-risk patients as outpatients, and

hospitalize high-risk patients [7]. A key ML technique, Convolutional Neural Networks (CNN), is the engine behind many of the recent advances in the field. A major drawback of CNN-based approaches is that it inherently works as a 'black box', with little visibility into the rationale and explanation of the classification decision provided by CNN [8]. As a black-box metaphor, CNN suffers from a lack of human interpretability, which is fundamental in understanding the methods' operation. Besides, implementation CNNs requires large amounts of labeled data to meet the technique training requirements [9], which we do not have access to, in this thesis, forcing us to look for alternative methods. Therefore, the we have looked to a standard Computer Vision technique, which brings the added advantage of supporting explanation. With this approach we performed the binarization of the grey-level echocardiography image input, with an adaptive image threshold technique for image segmentation, where in the end, the binary image results in white foreground (the calcium regions), with all other anatomic structures in black.

1.1 Objectives

This work aims to develop and evaluate an aortic valve stenosis Computer Vision model applicable to echocardiographic images. Our model identifies aortic valve calcification and obtains a quantification of the pixel’s intensity and area, proportional to the amount of calcium, in parallel to a CT-scan calcium scan analysis.

In this thesis, we present our Computer Vision algorithm and prototype system able to identify and quantify calcium in the aortic valve via adaptive image segmentation of echocardiography imaging. We aim at helping doctors and patients having better track of aortic valve disease, using a non-invasive and non-ionizing approach.

1.2 Methodology

Information Systems (IS) research risks losing leverage over the fields where its applicability is critical if it lacks a strong component that provides applied research solutions [10]. IS study is characterized by two major paradigms.

On one side, there's behavioral science, which tries to come up with theories that predict person or organizational conduct. On the other hand, design-science seeks to extend human and organizational capacities by developing creative artifacts [11].

In light of this, the Design Science Research Methodology (DSRM) and the six principles suggested by Peffers et al. [10] are used in this dissertation. This approach has its roots in engineering and artificial sciences, and its main goal is to create relevant artifacts that add value to the fields in which they are used. According to the authors, Figure 1.1 represents a nominal sequence of six activities that resumes the DSRM operation.

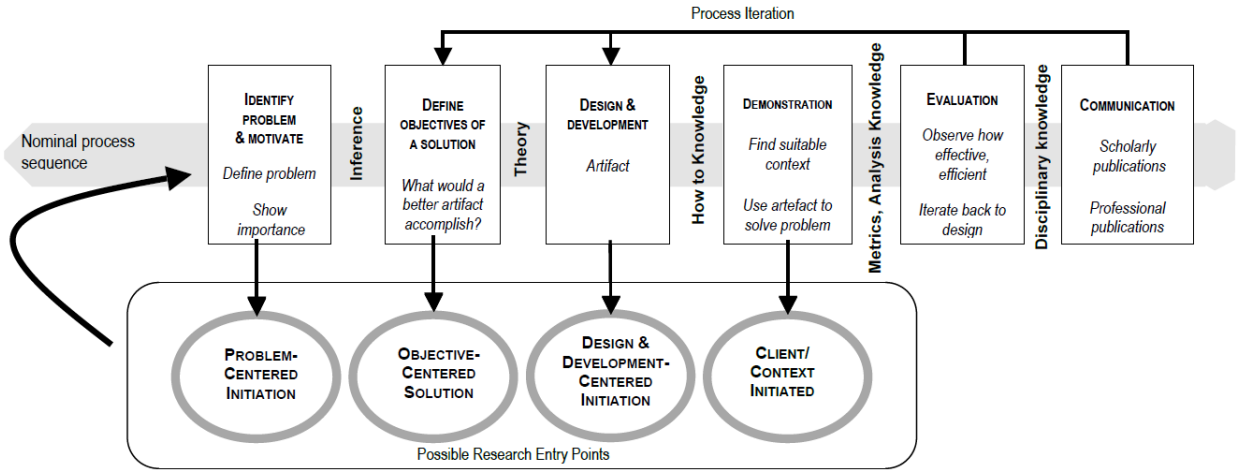

Figure 1.1 DSRM process model, Peffers et al. [10]

The DSRM has four different entry points, also known as methods, but we used the first one, Problem-Centered-Initiation, since it is, by definition, the starting point of our method.

Since DSRM takes a problem-solving approach, it's critical to evaluate the artifacts to provide feedback and a better understanding of their problems, emphasizing in the improving of both their quality and design in subsequent iterations of the process. Before the final artifact is produced, this build-and-assess loop is normally repeated several times [12].

The DSRM method was used in two iterations in our work: (1) the initial entry point to the design and construction where we have done the assessment on a controlled environment. (2) We performed a clinical evaluation of our work, in this exploratory study, where we performed a set of tests in several different echocardiographies.

According to the methodology, a single initial meeting was held to determine all of the assessment criteria, as stated in our work's objectives.

Our main goal with this project is to create a prototype that can identify and quantify calcium from echocardiographies. To perform the evaluation, we have chosen the Calcium Identification (CI) and Calcium Quantification (CQ) as the capabilities to be evaluated in our work.

Despite the fact that DSRM is a unified concept, artifact evaluation is still a topic of discussion within the DSRM community, as evaluation parameters are described in a fragmented or incomplete manner in the DSRM literature [13]. To get around this stumbling block, we agreed to use Prat et al [13] hierarchical assessment criteria for IS objects. This hierarchy is depicted in Figure 1.2, where we test our objects using the highlighted parameters having in consideration that this evaluation was performed on this exploratory study.

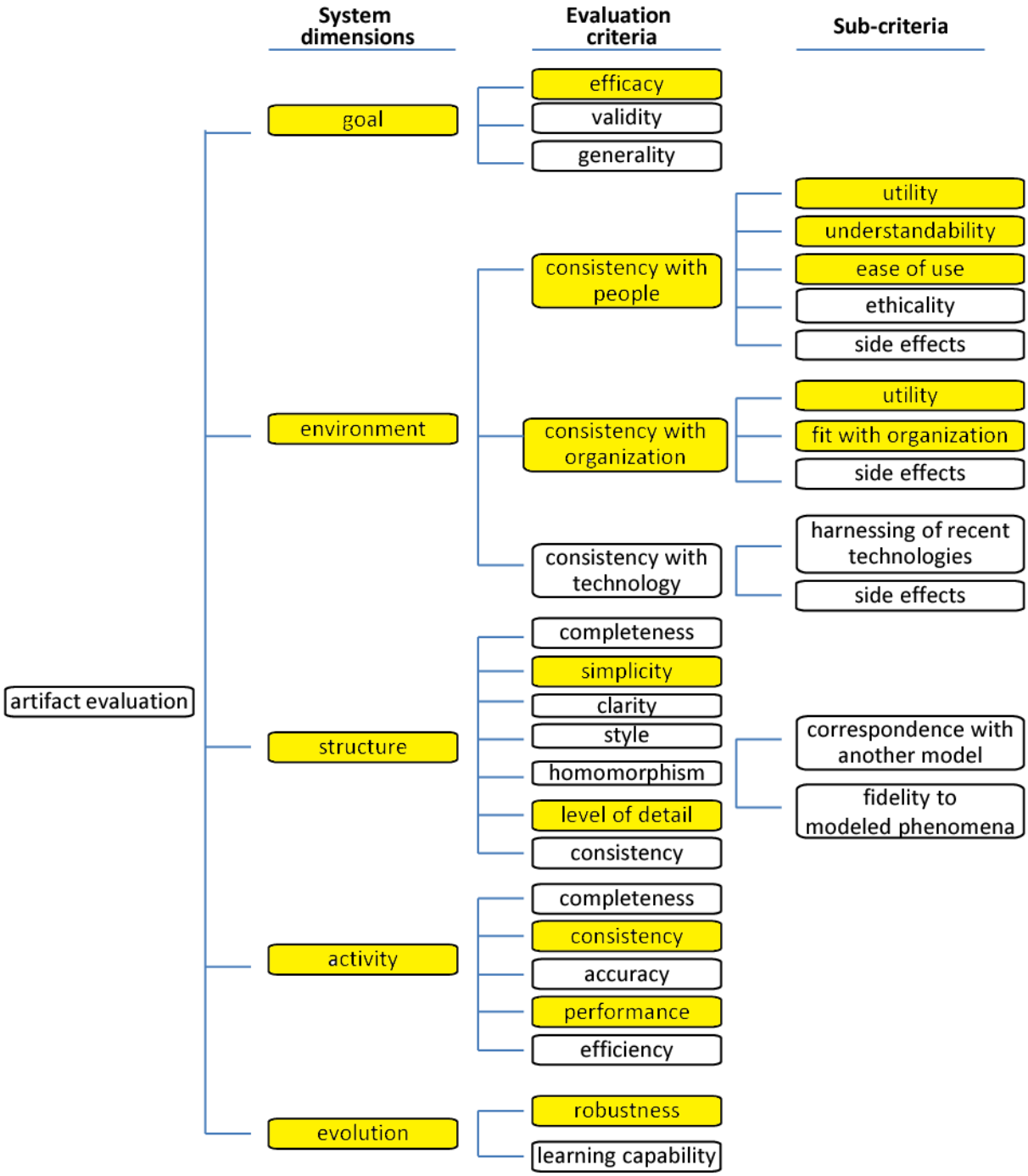

Figure 1.2 Hierarchy of criteria for IS artifact evaluation, Prat et al.[13]

Table 1.1 shows the generated objective statements, which serve as goals to be assessed in the two iterations of the DSRM method, based on both the chosen capacity and criteria (Chapter 5).

Table 1.1 Objective statements to be used in the DSRM evaluation

Capability	Dimension	Criteria	Objective statement
CI & CQ	Goal	Efficacy	To improve the doctors time on identifying and evaluating the calcium severity
CI & CQ	Environment	Consistency with people / utility	It can help doctors to save time on doing the prognostics.
CI & CQ	Environment	Consistency with people / understandability	Provides understandable results. An identification and an absolute quantification
CI & CQ	Environment	Consistency with people / ease of use	Easily understandable, and can be used with barely training
CI & CQ	Environment	Consistency with organization / utility	Provides an alternative on automatically identify and quantifying calcium
CI & CQ	Environment	Consistency with organization / fit with organization	Can keep better tracking of the patients
CI & CQ	Structure	Simplicity	Click and Run application with no extra implementation
CI & CQ	Structure	Level of detail	Provides knowledge extracted from the image
CI & CQ	Activity	Consistency	It gives consistent results despite the different image settings
CI & CQ	Activity	Performance	Has good performance on loading and interpreting the images

CI & CQ	Evolution	Robustness	Must be prepared for any usage without resulting in errors

Each evaluator assigns a score based on proof that the objective statement's added value has been achieved. With this in mind, we've chosen to use the ISO 15504 four-level NLPF scale [14], which is divided into four levels:

- Not Achieved (NA) - [0-15%]
- Partially Achieved (PA) -]15-50%]
- Largely Achieved (LA) -]50-85%]
- Totally Achieved (TA) -]85-100%]

1.3 Outline of the Dissertation

Having the objectives and methodology defined, we will have six chapters (Introduction included). The chapters are:

Chapter 2: Outlines a systematic literature review on the state-of-the-art of calcium identification and scoring from echocardiographies and CT-scans, based on computer vision, using the PRISMA method.

Chapter 3: Provides the description of the artifact as the process of image classification, covering the binarization process, the normalization of the image and ultrasound properties.

Chapter 4: Outlines the Prototype Demonstration, following Figure 1.1, covering the steps where the user is an operator and where there is image processing.

Chapter 5: Presents the evaluation of our artifacts, based on the DSRM process. Providing the validation of our study, where we performed test on echocardiographies never previously seen, in order to evaluate the robustness and capabilities of the prototype.

Chapter 6: Presents the discussion and conclusions of the work developed, where we highlight the contributions and limitations of our work.

2 State of the art

2.1 Search Strategy and Inclusion Criteria

The current European guidelines for diagnosing and treating aortic stenosis recommend echocardiography as first-line method to establish every patient's diagnosis, and repeat echocardiography every 6 months for severe cases or yearly for the moderate disease [6].

The morphology and function of cardiac valves can be assessed in vivo in patients using echocardiography, which is widely used, does not use radiation, and can therefore be repeated throughout one's life; it has a high temporal and spatial resolution that can evaluate valve morphology and mobility for every cardiac cycle in either 2D tomographic or 3D models; it can also evaluate the valve morphology and mobility for every cardiac cycle, as well in either 2D tomographic or 3D models.

We have concentrated our efforts on evaluating what the research studies are assessing regarding the score of calcium in the aortic valve and in the coronary.

Several studies have been conducted to predict cardiovascular events, being calcium presented in the aortic valve an accurate predictor of these events [15]. From our analysis, it became clear that all of our analyzed studies focused on utilizing CT-scans, since from a standard coronary artery calcium computed tomography scan, we can measure the Aortic valve calcification [16]. In terms of getting coronary score calcium, this is only possible using this resource [5]. Nevertheless, this approach bears costs, namely, monetary and health costs, since it corresponds to a very invasive scan, considering it uses radiation to extract the amount of calcium [5]. More recently, the CT-calcium score of the aortic valve has been used to identify aortic stenosis severity.

No work regarding aortic valve calcification quantification has been published from the studies found, as demonstrated in Figure 2.1. This means that there is no evaluation of the calcium score using only the echocardiography information, only detection and prevention has been studied. Figure 2.1, was created using the VOS Viewer tool using as input all the papers found, except those that use CT-Scan imaging.

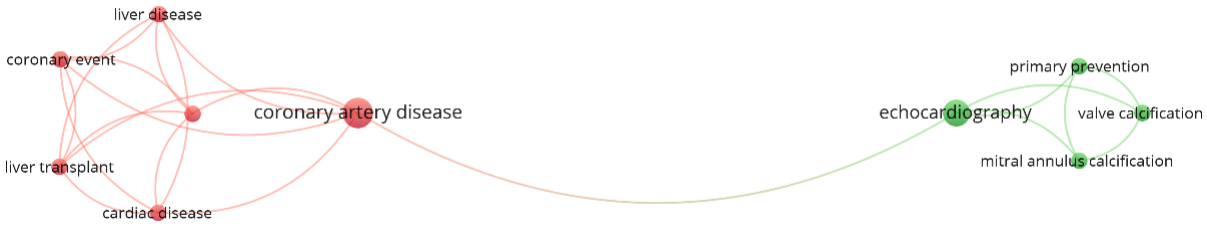

Figure 2.1 Topics relations from the literature review in echocardiography imaging

Once we add to our search CT-Scan imaging, we start obtaining published works related to quantifying the calcium in the coronaries, including some papers adopting deep learning. Figure 2.2 depicts the correlation of relevant terms in the literature with CT-scan imaging.

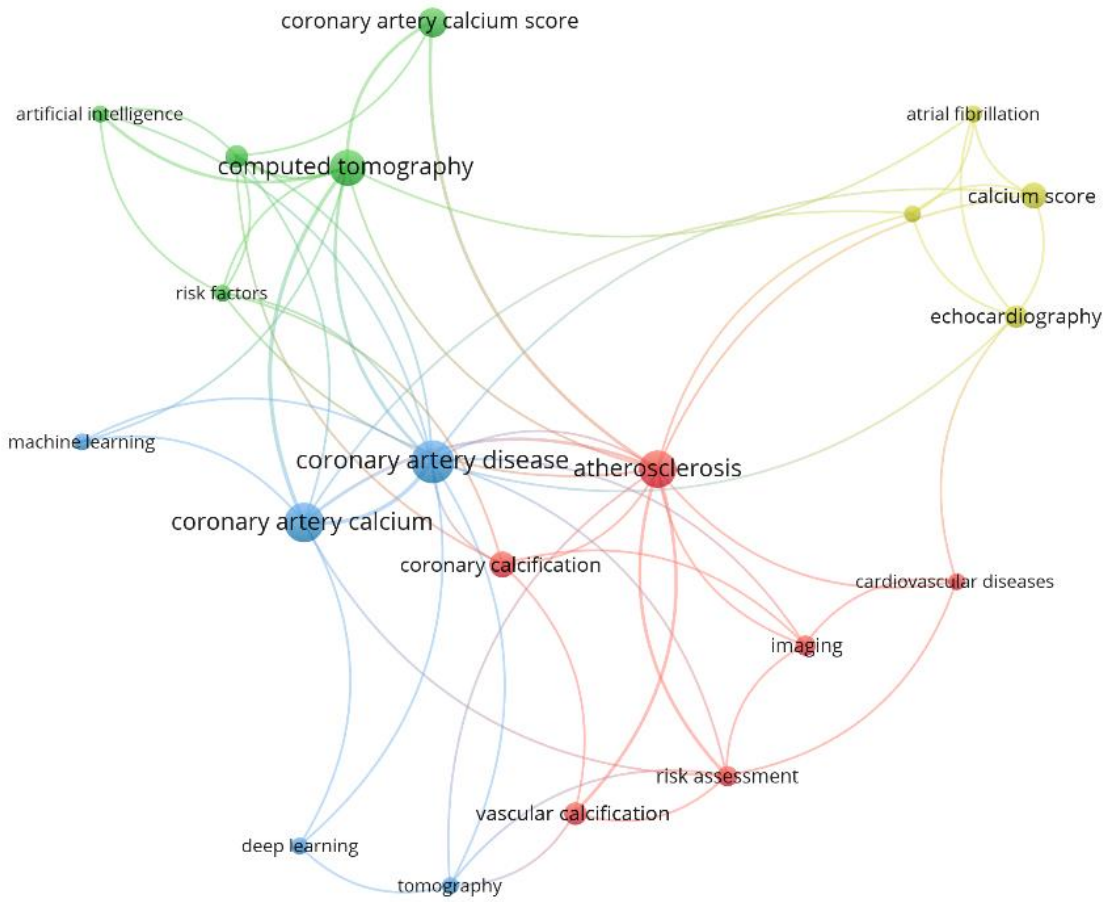

Figure 2.2 Topics relations from the literature review in echocardiography and CT-Scan imaging

A systematic literature review was made by following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Methodology [17], and with the following

research question: “What is the state of the art of analyzing Ultrasound and CT-scan imaging, to find the calcium score of the aortic valve?”.

Paper repositories searched were Scopus and Web of Science Core Collection (WoSCC), and the research was conducted through March 2021. All the results had to be journal papers, articles, or reviews published between 2016-2021 and written in English. The collected papers were only about Computer Science or Medicine. or Medicine.

From our search queries and selection regarding Coronary Artery Disease scoring using CT-Scans and Echocardiographies, we found a list of 10 papers, as shown in Table 2.1.

We can notice that there is a larger sample in terms of studies when we are dealing with CT-Scans. In fact, we can see that we have four times more papers regarding CT-Scans, than papers with echocardiography imaging analysis.

Using echocardiography, studies [18] and [19] use intravascular ultrasound (IVUS) in order to differentiate fibrous tissue and fibro-fatty tissue from the necrotic core and dense calcium, leaving behind the intention of getting the calcium score from the IVUS. In [20] researchers aim to detect a coronary artery disease, using only echocardiography automatically. However, IVUS is an invasive study not applicable for aortic valve study.

Going through the studies performed with CT-Scans, we can see that in [21] researchers try to categorize the Mitral Annular calcification and predict its valve embolization. Study [22] aims to investigate which calcium score is a predictor of the coronary artery disease recurring to CT-Scans. The validation study [23] tries to use deep learning to perform calcium quantification on CT-Scans. In the study [24], researchers automatically exclude negative CT examinations for coronary artery calcium through algorithm training. The validation study [25] evaluates the performance of deep learning for automatic calcium scoring. Study [26] proposes a computationally efficient method to automatically extract the coronary artery calcium by employing convolutional neural networks on CT-Scans. On [27], we are again presented with other deep learning methodologies to automatically get a CT-Scan coronary artery calcium score.

Table 2.1 Selected papers comparison

paper	[18]	[19]	[20]	[21]	[22]	[23]	[24]	[25]	[26]	[27]
Year	2018	2018	2018	2020	2017	2021	2020	2020	2019	2021
Echocardiography	X	X	X							
CT-Scan				X	X	X	X	X	X	X
Coronary artery disease										X
Coronary Calcium Score					X		X	X	X	
Mitral Annular Calcification				X						
Coronary artery disease characterization (plaque)	X	X	X							
Deep Learning						X	X	X	X	X
Risk Assessment										
With training	X	X	X			X	X	X	X	X
IVUS image	X	X								
coronary plaque classification	X	X								
Validation Study								X		

From our analysis, we can see that cardiac CT-scan imaging has been used for coronary calcium calcification and prognosis prediction, and some literature works adopt deep learning algorithms, while, as mentioned, there is no published work on obtaining a calcium score from echocardiography, which would avoid the disadvantages of an ionizing method such as CT-scan.

In our study, in order to avoid the use of CT-scans and the algorithm training requiring large data sets, and since no work was identified by the authors, using echocardiography imaging analysis, we aimed to assess this technique for identifying and quantifying calcium in aortic valves of patients with aortic stenosis.

2.2 Study Selection

The initial selection of papers was made using the tittle, abstract and keywords of the study, and in some cases when that information was insufficient, the full document was analyzed.

2.3 Data extraction and synthesis

The data was managed and stored using Zotero [28] and Microsoft Excel. It included title, author, year, journal, subject area, keywords and abstract.

For data analysis and synthesis, a qualitative assessment was conducted based on PRISMA. All the paper repositories – Scopus and WoSCC – were searched systematically regarding the published work related with the concepts “Ultrasound Image” or “Echocardiogram” or “CT-Scan”, the target population “aortic valve calcium” or “aortic valve” and within the context of the study “Image Binarization” or “Computer Vision” or “Calcium Score”.

2.4 Results

Our query was performed in each repository. Figure 2.3 shows our PRISMA workflow for the total of studied papers.

Our search query was “("Ultrasound image*" OR "echocardiogram*" OR "CT-scan") AND ("Coronary artery calcium" OR "coronary artery*" OR "aortic valve calcium" OR "aortic valve") AND ("Image classification" OR "computer vision" OR "calcium score")”, retrieving 100 different papers. Considering that our study is focused on echocardiography, we have excluded the studies that involve CT-scans, having only a sample of 14 papers related to echocardiography imaging what shows that this is an area yet unexplored by the community.

After performing a manual process towards identifying significant topics, research questions, and methods, identifying the outcomes, and removing the duplicates, 10 documents were obtained. Our research systematization considered year, area, RQ topic, and a small description.

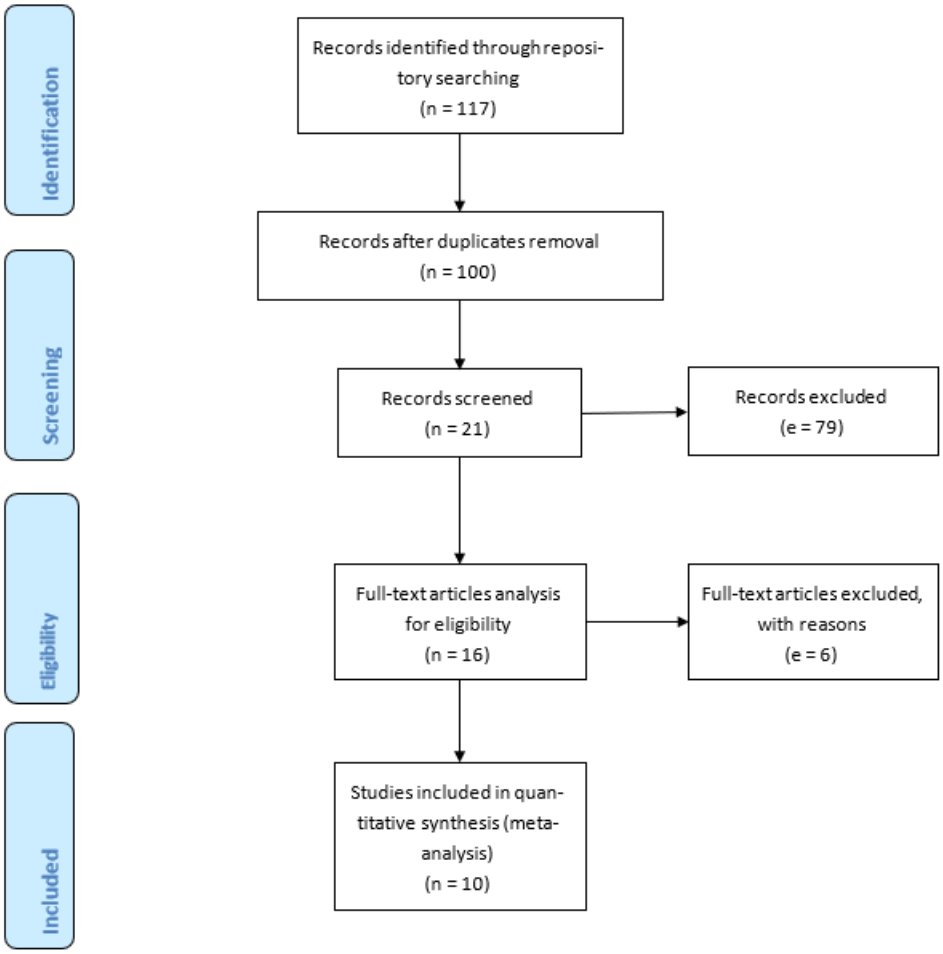

Figure 2.3 PRISMA Workflow Diagram

3 Design and Prototype Development

Our technique envisages the identification of the presence of calcium in the aortic valve. We tested several image enhancement processes aiming to highlight the areas with a high concentration of calcium, which is described in the next sections.

3.1 Echocardiography Binarization Process - Initial approaches

Our developments adopted the OpenCV library [29] – an open source library for image and video analysis [30]. In the first stage, we equalized the image histogram in order to improve the contrast of the image and stretch the intensity range, using the "equalizeHist" function. This equalization relies on the mapping of one distribution to another distribution - more uniform and wider distribution of the pixel intensity values - to spread the intensity values over the whole range. For the histogram of the input image $H_{(i)}$, its cumulative distribution $H'_{(i)}$ is:

(3.1)

$$H'_{(i)} = \sum_{0 \leq j < i} H_{(j)}$$

Where *i* is the intensity values from the given histogram and *j* the more uniform distribution of intensity values.

To use this as a remapping function, we have to normalize $H'_{(i)}$. Since the pixel grayscale intensities go from 0 to 255, the new intensity values of the equalized image can be obtained by applying the following remapping function to the source echocardiography image, $src(x, y)$:

(3.2)

$$equalized(x, y) = H'(src(x, y))$$

Subsequently, to improve the contrast of $equalized(x, y)$, a Contrast Limited Adaptive Histogram Equalization algorithm [31] was implemented that will divide the image into several non-overlapping regions of almost equal sizes, creating several histograms that will redistribute the image brightness, achieving the results in the overall image contrast depicted in Figure 3.1. To conclude the process, a thresholding technique was used, to segment the image into foreground and background, for further interpretation.

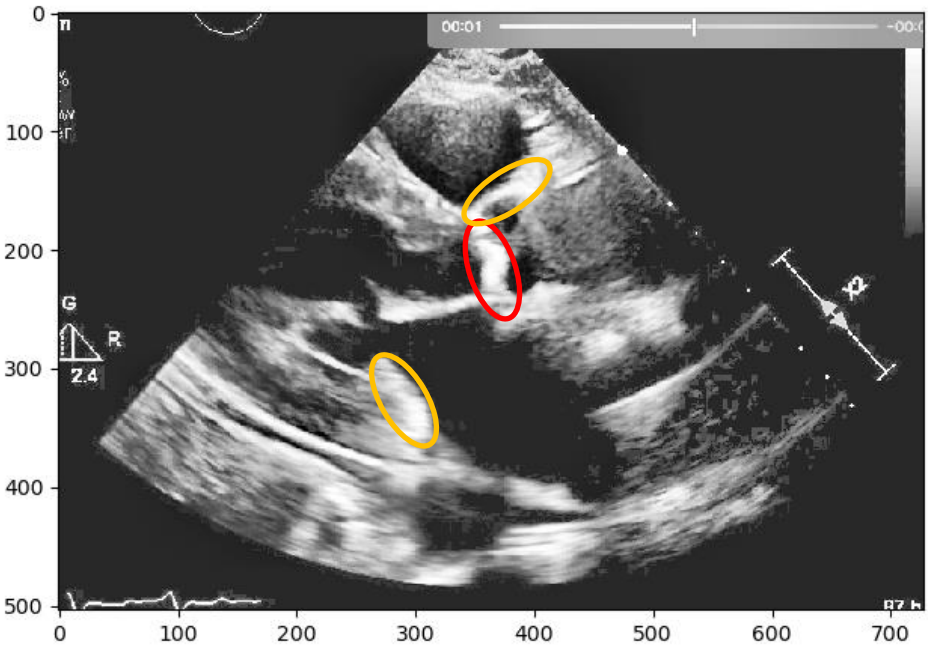

Figure 3.1 Echocardiography image with CLAHE

Nevertheless, this simple approach relying solely on histogram equalization leads to poor and inconclusive results in terms of visualizing and extracting the presence of calcium, as shown in Figure 3.1. The red circle represents where there is calcium on the aortic valve, and in yellow, other structures are marked, which are indistinguishable from each other.

In a second approach, we tried Region-based Segmentation [32], where we aimed to segment different objects (calcium/non-calcium) by analysing their pixel values. This technique classifies the pixels – based on a threshold applied to each pixel value – as an object or background. Moreover, since we may have multiple objects – given that calcium can go from severe to none in different scale values – we initially defined multiple thresholds to segment multiple objects, as represented by Figure 3.2. However, if we have an image with no significant grayscale difference, this approach will fail to get accurate segments.

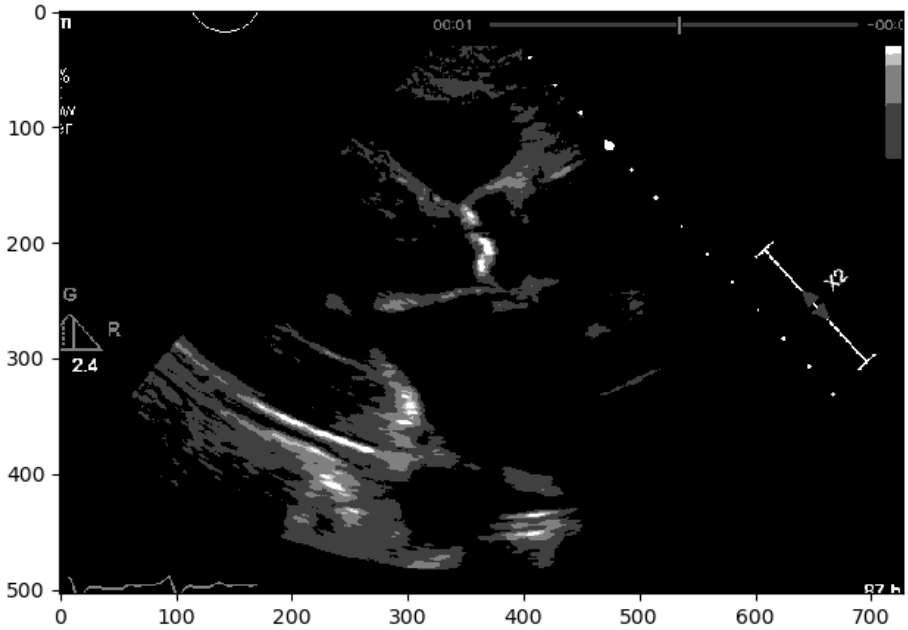

Figure 3.2 Echocardiography with Region-based Segmentation

To mitigate this issue, we tried another approach to have a more comprehensive and interpretable image. We tried an Edge Detection algorithm [33] where the pixel brightness is scaled to an embossed image, where the height of each “mountain” corresponds to the pixel brightness. Figure 3.3, shows us the application of Edge Detection on an echocardiography image of the left ventricle. This approach turned out to be redundant since it is representing the pixels values by “mountains heights”. This could be immediately calculated if the first step extracted the pixel's exact value and minimised computation time. Otherwise, after implementing this algorithm, we would need to implement another one to find each “mountain” height.

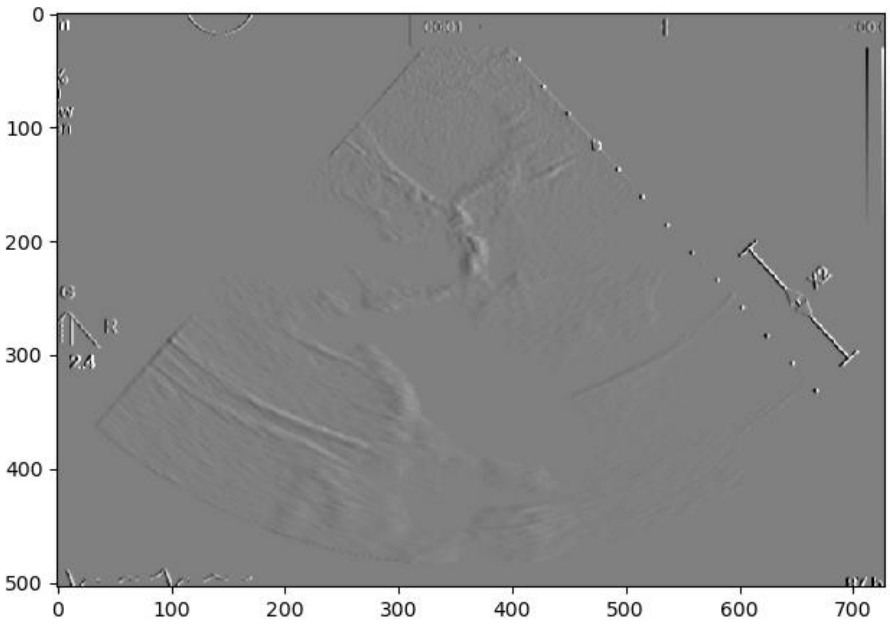

Figure 3.3 Echocardiography with Edge Detection

After the above-described initial approaches to our problem, we concluded that instead of focusing our interest in mimicking human eye comprehension of the calcium presence, we could address our challenge in a different way, by extracting the region of interest's pixel values and see how they correlate with the amount of calcium present in the aortic valve.

In a first step, we performed image binarization with a fixed threshold of 140 in the pixel grayscale value (in a scale from 0 to 255), where the pixels with an intensity above 140 were transformed in white (255), and the remaining in black (0), thus helping to identify the regions where we have the presence of calcium.

To deal with some natural constraints in terms of noise that characterize echocardiography imaging, particularly the process of sampling still images from the echocardiography video, we performed different blurring treatments to clean some of the image's noise due to the echocardiography's motion. Blurring an image will average rapid changes in the different pixel intensities, and this corresponds to a low-pass filter applied to the image [34], which removes noise while leaving the majority of the image structures still present in the image as depicted in Figure 3.4.

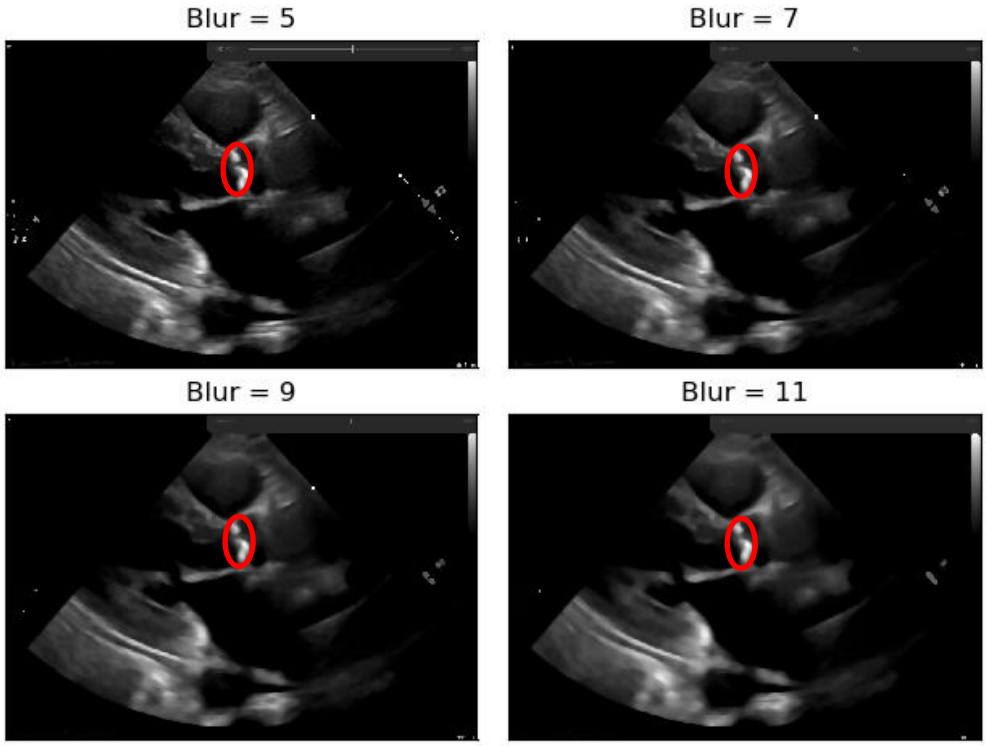

Figure 3.4 Echocardiography image with four levels of blurring applied

As we can see from Figure 3.4, when we have a Blur = 11 (experimentally adjusted with trial and error)), we can easily identify visually the regions where there is a presence of calcium (identified by the red circles). On this operation the central element of the image is replaced by the median of all the pixels in the kernel area, where the 11 means that takes into consideration a kernel of 11 by 11.

We then applied to the resulting images of this blurring phase, a binarization operation with a fixed pixel threshold value of 160, experimentally obtained by analysing 48 cases of echocardiography images, where 255 corresponds to calcium, as seen in Figure 3.5. This initial approach of a using a fixed threshold, is not sufficient for our problem at hand, since our images' brightness may vary, given different data collection conditions. To tackle this issue, we need to perform and adaptive binarization technique, which will be further explained.

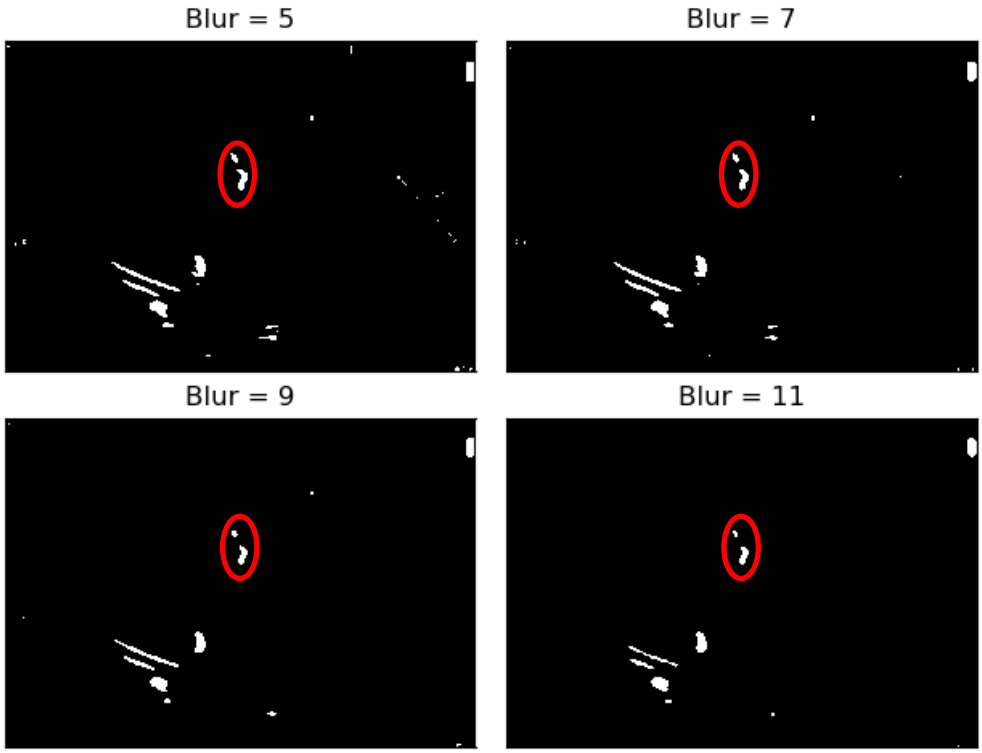

Figure 3.5 Binarization of an echocardiography image, for each size of the kernel parameter

In Figure 3.5, it is noticeable that when the blurring parameter increases from 5 to 11, we get a cleaner image (without small white dots – noise). However, we can also notice that in the region of interest (marked with red circles), when the blur increases, we lose pixels, since the region gets smaller. To mitigate this, we applied a mask dilation operator to each region of interest.

As shown in Figure 3.6, by applying the dilation mask to the regions of interest of the image, we can recover the pixels lost in the blurring phase.

The next phase is to turn our binarization adaptive and not based solely on a fixed threshold (initially set to 160), given the high variability in the imaging data collection procedures.

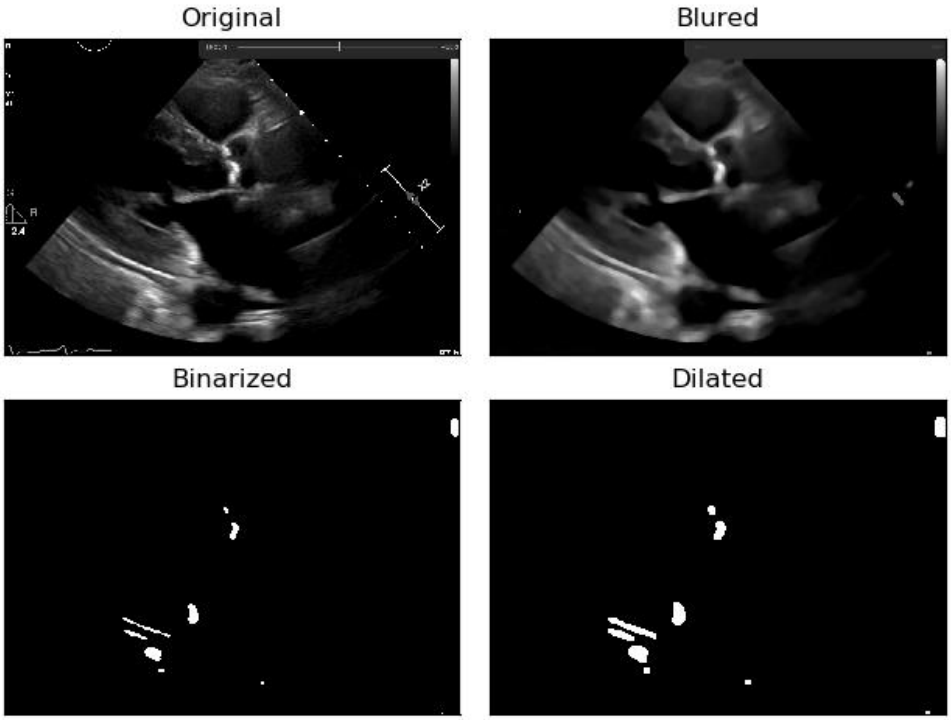

Figure 3.6 Application of the dilation mask to the regions of interest of the image in order to recover the pixels lost in the blurring phase

3.2 Adaptive Binarization Process

To achieve this adaptive binarization, starting with a fixed threshold, we need to confer it a normalization value, in order to adapt to the various images changes resulting from the settings applied to the echocardiographic image acquisition.

The echocardiographic image suffers two steps of processing: (1) a post-processing stage, where specialists introduce gains in the image, immediately after data acquisition, defined by windowing or grey-scale mapping, using the window width (WW) and level (WL) (2), and an image analysis stage performed by the specialist.

3.2.1 Post-processing Normalization

After the echocardiography raw data acquisition, specialists add gains to the image in a post-processing procedure. In our process, we need to compensate for the new brightness that the image acquires by such a process. To accomplish this, the specialist selects a region outside the ultrasound sector, that will act as a normalization boundary of “dark” regions, as represented in Figure 3.7.

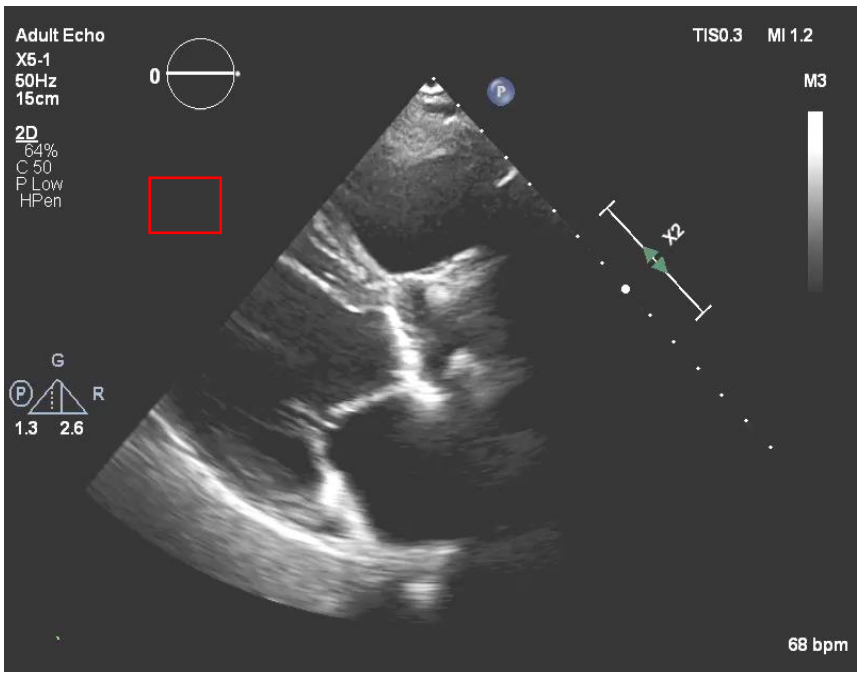

Figure 3.7 Normalization Region to mitigate the post image processing

Once we have this sub-matrix, we subtracted the mean of its values from our calcium ROI pixel values, thus compensating for the image gain of this stage.

This method was tested on several images. Figure 3.8 depicts the example of one echocardiography with 3 most used different types of gains set in a post-processing stage, with the settings Window Width fixed at 250 and Window Level (WL) permuting between 75, 100 and 125.

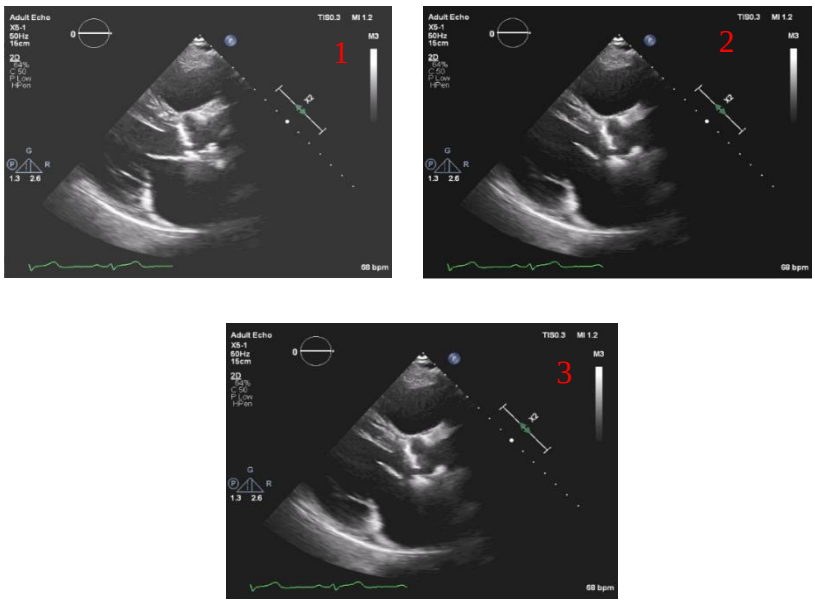

Figure 3.8 Echocardiography examples with different Window Levels (WL) and fixed Window Width of 250 (1) WL= 75, (2) WL = 100, and finally, (3) WL = 125

In Figure 3.9 we have the normalized the result of the calcium threshold obtained with these representative echocardiography cases, showing coherent results extracted from the calcium present in the aortic valve, where we have the mean and the median of the values extracted from our ROI. We can see that the values of pixels intensity extracted have a low absolute variation, suggesting the validity of our model since we have the same image with different gains.

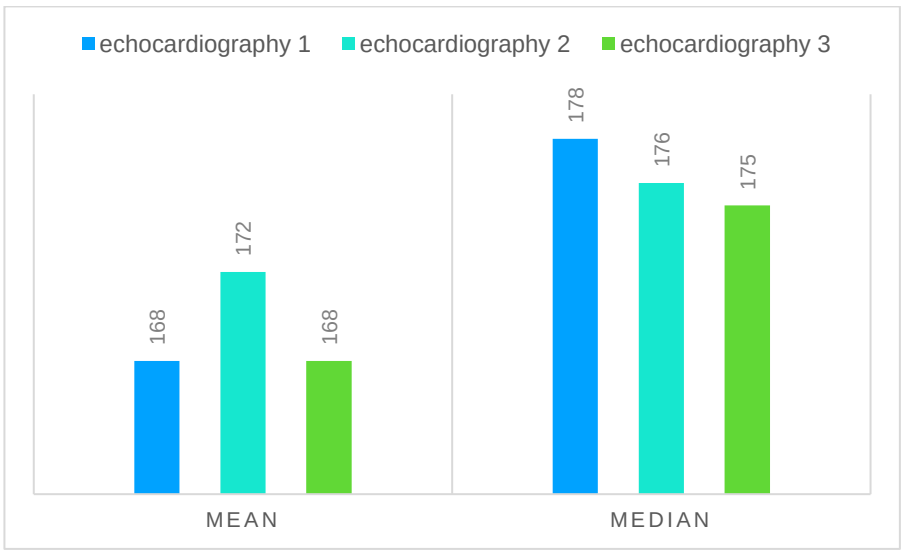

Figure 3.9 Threshold values of pixels intensity for calcium, extracted from echocardiography with different post-processing gains.

3.2.2 Ultrasound Properties Normalization

After post-processing (prior stage), we proceeded with a second normalization process that is related to the configuration of the ultrasound properties (related to acquisition settings that alter the image brightness and contrast) during the echocardiography raw data acquisition, which has direct consequences on the echocardiography brightness. To mitigate this, we needed to interactively find a darker region of the echocardiography (inside the ultrasound range) and consider the mean of the values of that region as a "black threshold", a reference area. By means of a manual step performed by a specialist, he/she interactively selects an area of the image (or of a different image belonging to the same sequence of still frames that share the same data collection tunning parameters), where a structure with very low brightness is known to exist, typically corresponding to blood flow.

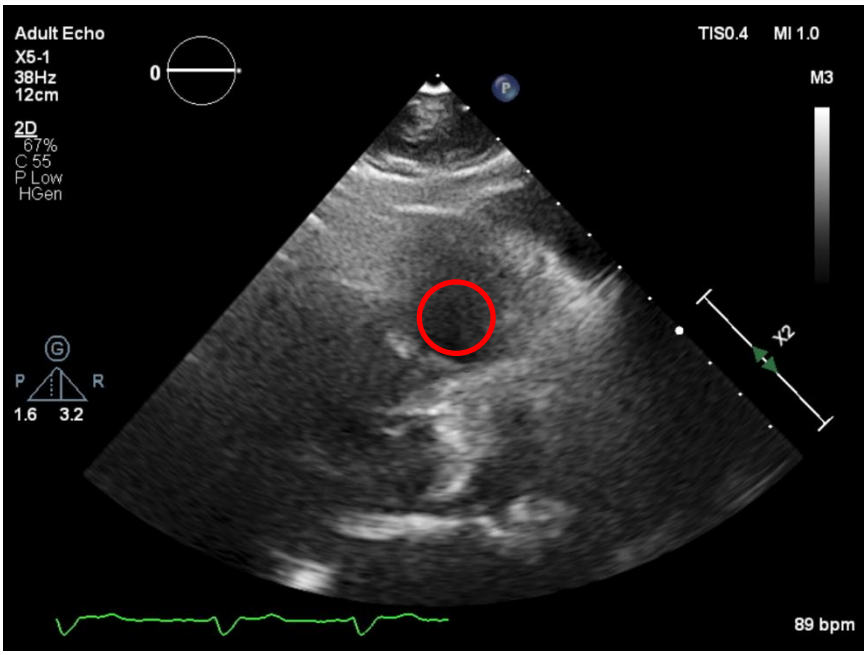

Figure 3.10 Normalization Region (right ventricle cavity)

We started to look to an image of the right ventricle cavity as a potential candidate for a reference ROI, given its substantial presence of blood and minimal signal refractions. We selected a ROI in this image (as shown in Figure 3.10), corresponding to a darker region allowing us to define the "dark" level of the image, by taking the mean of the values in that ROI and then normalized all pixel values of the image, by subtracting the "dark" value from their values. This would create a dynamic threshold, changing every time the brightness varies due to modifications on the ultrasound properties changes. We performed the same test with the ROI placed at the left atrium cavity, as shown in Figure 3.11.

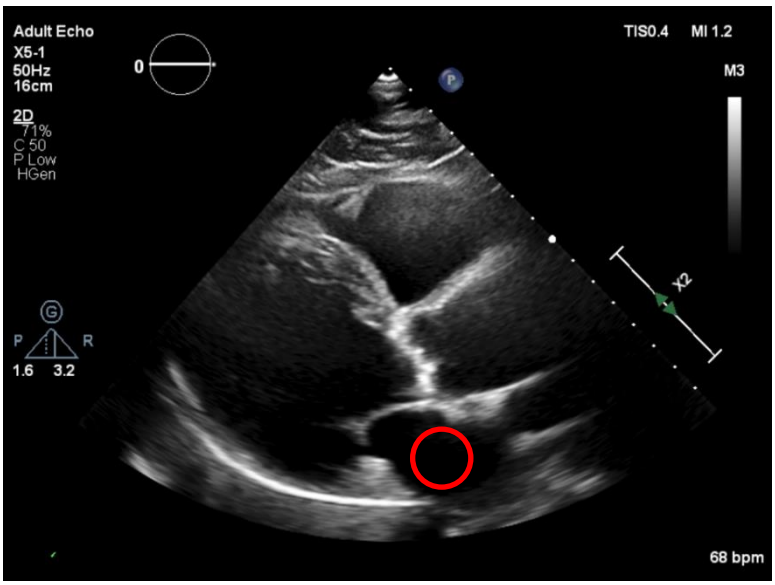

Figure 3.11 Normalization Region (left atrium cavity)

The normalization process implemented in Figure 3.10 and Figure 3.11, were applied to three different patients, and both concluded that the tests performed with the normalized ROI in the left ventricle cavity (a) were more consistent and accurate than the right ventricle cavity (b), as shown in Figure 3.12.

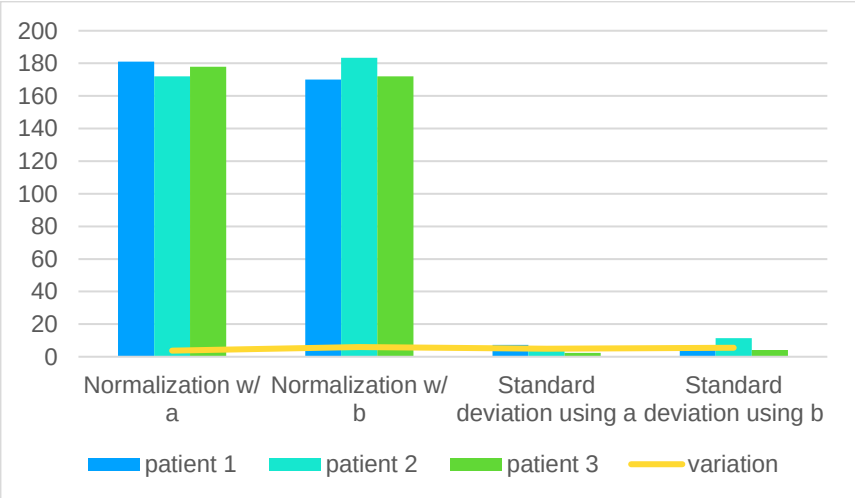

Figure 3.12 Variation between normalization regions

Our image normalization process relies on a “dark” ROI to be interactively defined in the same left ventricle cavity where we are detecting the calcium presence.

After image normalization, the final binarization result with this adaptive threshold is depicted in Figure 3.13.

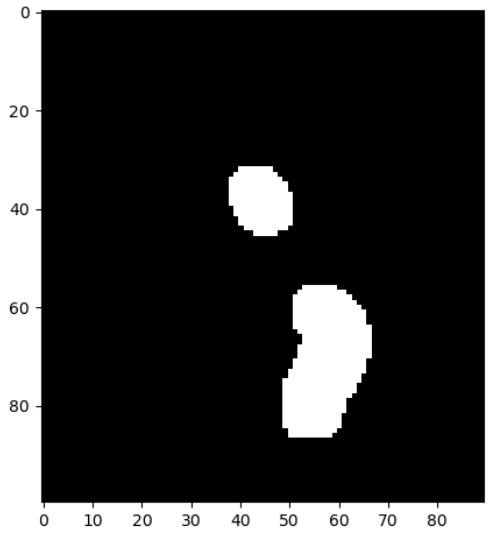

Figure 3.13 Binary image of the Aortic Valve (region of interest) where our algorithm found 2 areas with calcium.

Once we have the calcium regions (Figure 3.13), we can easily define a 2D pixel mask for each region (inspecting the ROI and keeping the 2D coordinates of the white pixels). If we apply these masks to the original image, we can extract the pixel values of each sub-image that we consider as calcium, allowing us to compute some simple descriptive statistics measures, such as mode, median, mean and standard deviation. Given that pixel values vary with the ultrasound properties, we subtracted the mean value of the normalization region from the values of the original image, to get normalized values regardless of the ultrasound properties. From the descriptive statistics analysis, we noticed that for all the different cases studied, the one with the lowest variation was the mean, as shown in Table 3.1. That said, we used this metric to validate all new cases.

Table 3.1 Descriptive statistics Variation, where Echocardiography 1 to 9 belongs to patient 1, Echocardiography 10 to 16 belongs to patient 2 and 17 to 24 belongs to patient 3

Echocardiography	Normalization by Mean	Normalization by Median
1	181	184
2	171	175
3	184	193
4	187	193
5	191	199
6	174	175
7	174	181
8	189	190
9	171	173
10	173	179
11	171	185
12	182	187
13	176	186
14	175	186
15	168	168
16	176	184
17	178	182
18	178	180
19	180	179
20	182	183
21	176	176
22	182	183
23	180	180
24	176	175
Variation	5.78	6.94

These tests were performed on three different patients, where each of them performed 9 echocardiographic acquisitions with different settings - with the most representative parameters – resulting in 27 echocardiographic images, aiming to validate the normalization method. From these echocardiographies, 3 of them had not enough quality to be analyzed, being discarded. In

Table 3.1 we can see that the mean pixel values extracted from each of these 3 different patients are coherent, having a low absolute difference between them, showing a low standard variation as well, which suggests that our normalization method is valid.

4 Prototype Demonstration

Considering the research approach performed in the previous section, our goal was to develop a prototype that uses, as input, the echocardiography and identifies calcium providing a score. considering the different acquisitions settings. The major effort is the normalization due to the different acquisition settings. The following flowchart in Figure 4.1 explains the complete process that was developed to achieve our goals.

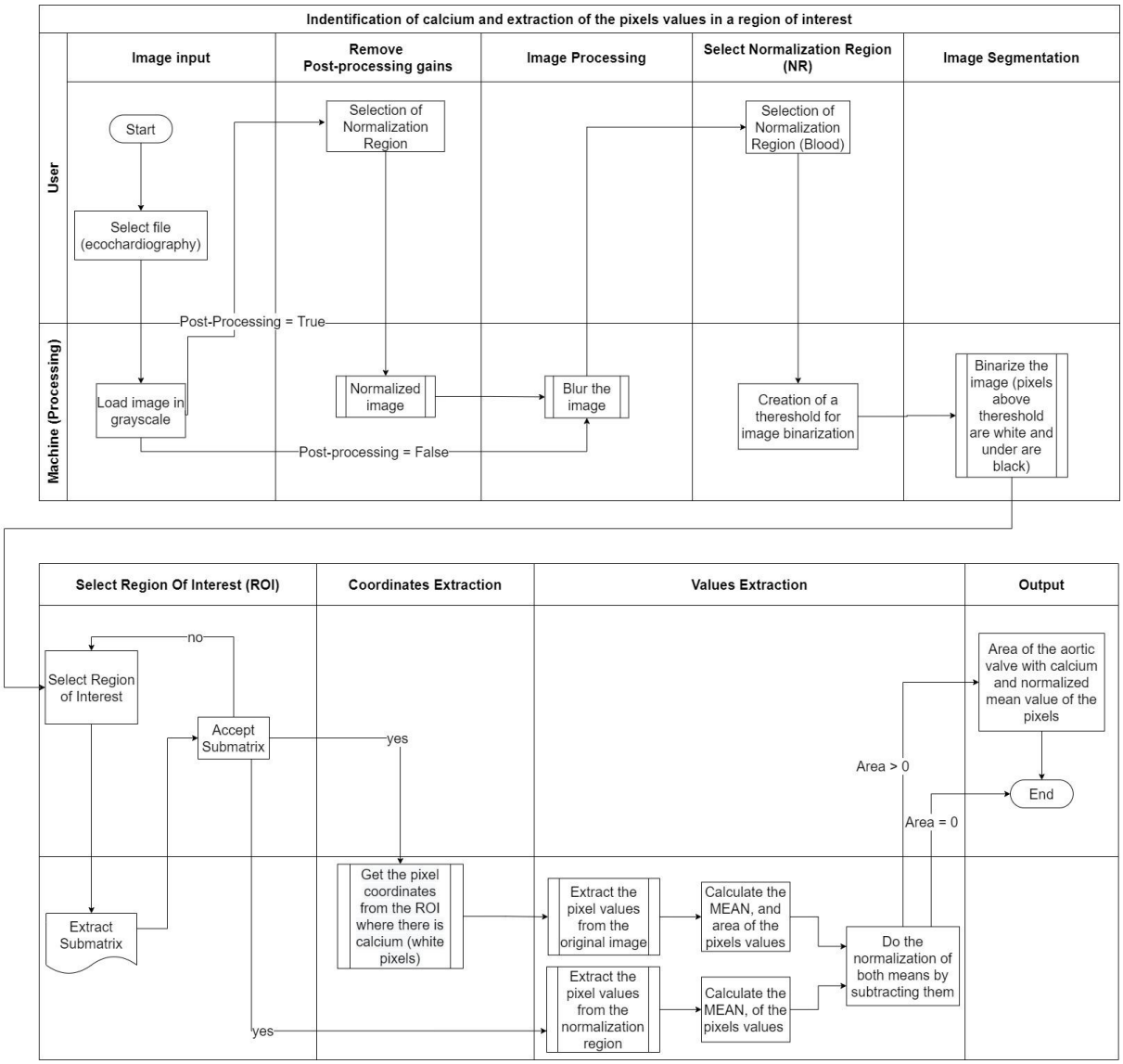

Figure 4.1 Process Description

The image processing consisted of 9 different stages with two different operators – user and machine. The stages where the user is an operator and there is image processing will be described in this chapter.

4.1 Image input

In the first stage, the user must select the image from which he intends to extract the calcium severity, allowing the machine to transform this image into grayscale and obtaining all the values scaled within the grayscale range (from 0 to 255), as shown on Figure 4.2.

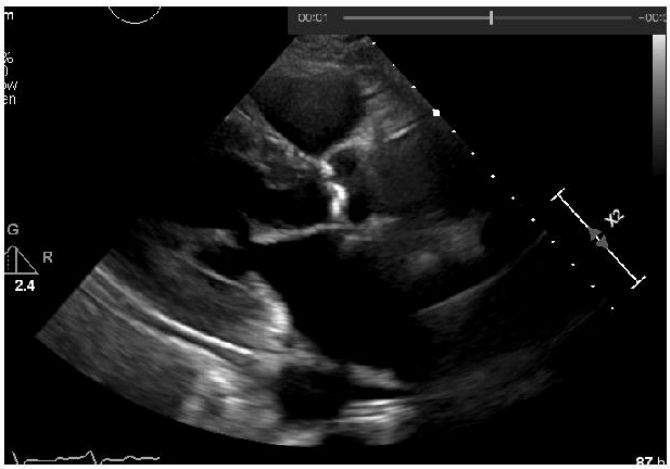

Figure 4.2 Image loaded in Grayscale

4.2 Remove Post-processing Gains

In this section, the system asks the user if the echocardiography selects has post-processing gains. If the image was subjected to such processing stage it is crucial to compensate them to get the real acquisition values and ensure a more precise result. To do this, the user needs to select a region out of the sector, as represented in Figure 4.3.

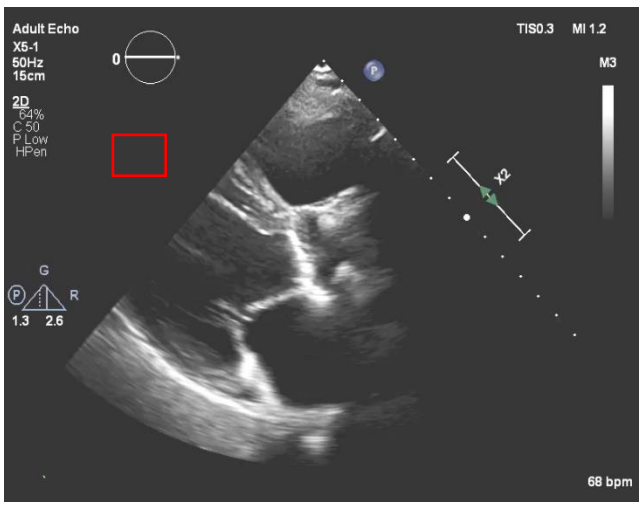

Figure 4.3 Normalization Region to mitigate the post image processing

This process will exclude the new brightness and treatment given on post-processing, achieving the original image collected by the specialist.

4.3 Image Processing

Once the image is scaled, it will be applied a blur to it, fading some of the image's noise, since this process averages out rapid changes in the different pixel intensities, as shown in Figure 4.4.

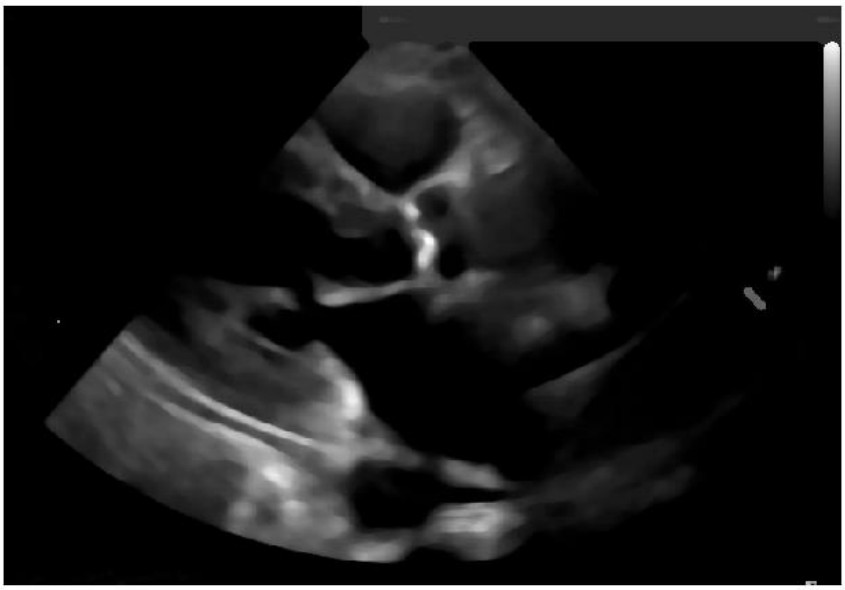

Figure 4.4 Blurred image

4.4 Select Normalization Region & Image Segmentation

To identify calcium, we need to compute a threshold for image segmentation. This means that the image will be binarized where the foreground (the calcium region) is white.

For the threshold, we started with a constant threshold for the pixels, of 160. Pixel values above such figure are considered calcium and the ones under this value are non-calcium pixels (blood, fat, muscle, or fibrous).

This initial constant threshold was weighted and defined by the experts in cardiology and echocardiography, Professor Ana Gomes de Almeida and Professor Luís Rosário with more than 20 years of experience. However, pixel intensities from echocardiographic images change with the acquisition parameters settings, such as image depth, ultrasound pulse frequency, image compressing. Moreover, the post-processing level of gain intensity also changes the

overall pixel intensity. We analysed images collected with a combination of different parameter settings, to test our normalization intensity values approach, and identify cutoffs for calcification in patients, with and without calcification, for controlling these parameters. Visual assessment by experts, was used as our reference for calcium analysis. Since after collecting the echocardiography image there is a processing stage (gains are applied to the image), we would end up with an echocardiography image with different values of brightness and setting a constant binarization threshold would not provide good image segmentation. To tackle this issue, we performed an adaptive normalization of our threshold by adding the extra-brightness. This extra-brightness is taken from a region of the echocardiography that should be completely black, the left atrium cavity, as shown in Figure 4.5:

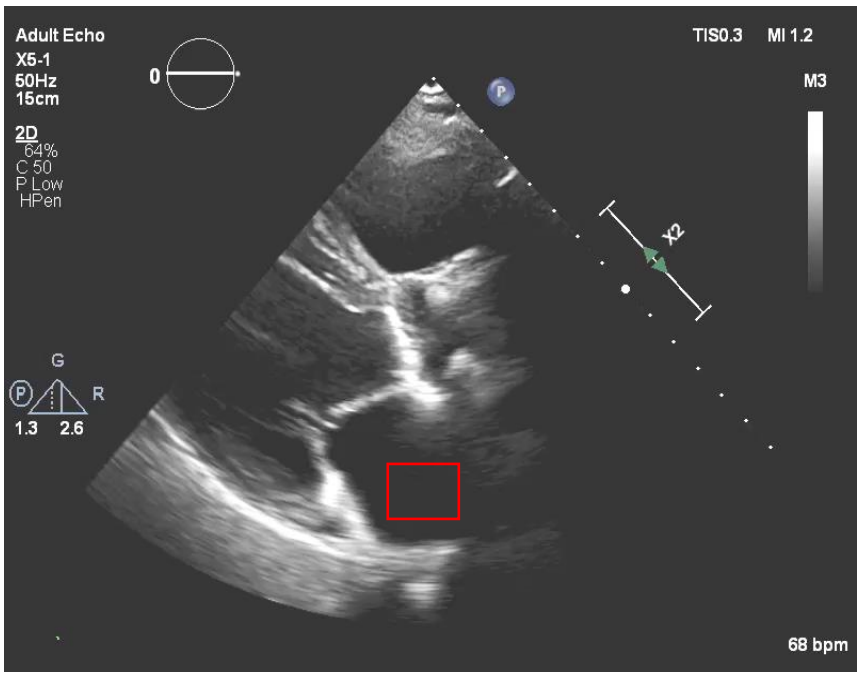

Figure 4.5 Left atrium cavity that will create a dynamic threshold for binarization

Achieving a dynamic threshold will normalize our echocardiography images allowing our model to identify the calcium in different cases with different gains. The calcium presence can be seen in Figure 4.6, marked by the red circle.

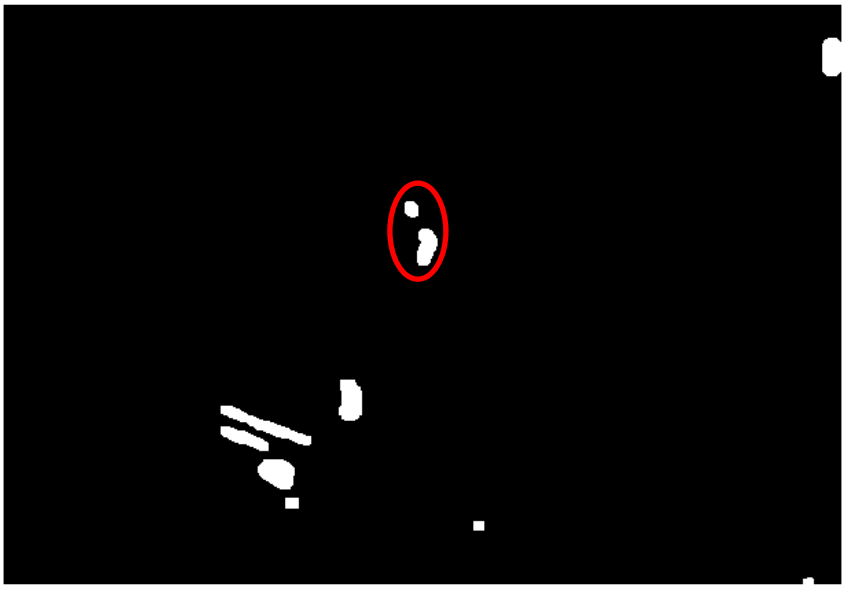

Figure 4.6 Calcium in the binarized image

4.5 Select Region of Interest

Once the image is binarized, the system asks to the user to interactively select the Region Of Interest (ROI) that should contain the aortic valve. When the ROI submatrix is retrieved, we will loop over the image to extract the coordinates of the white pixels. Figure 4.7, depicts the end result: the submatrix with the binarized ROI.

Having the exact coordinates from where the calcium is present on the aortic valve, we will go to our original images and obtain the pixel values of the region of the aortic valve with calcium, from the coordinates extracted previously. After getting such pixel values, we will calculate the mean of our matrix of pixels. In order to get these values normalized, we compute the difference between the calcium selected from the echocardiography and the normalization region selected in Figure 4.5.

Regions identified as calcium – with an intensity above the dynamic threshold – will allow, after binarization, counting the number of white pixels, a proxy to the region area, and an indication similar to the calcium score identified by a CT-scan. This approach requires validation performed by means of visual analysis conducted by echocardiography experts.

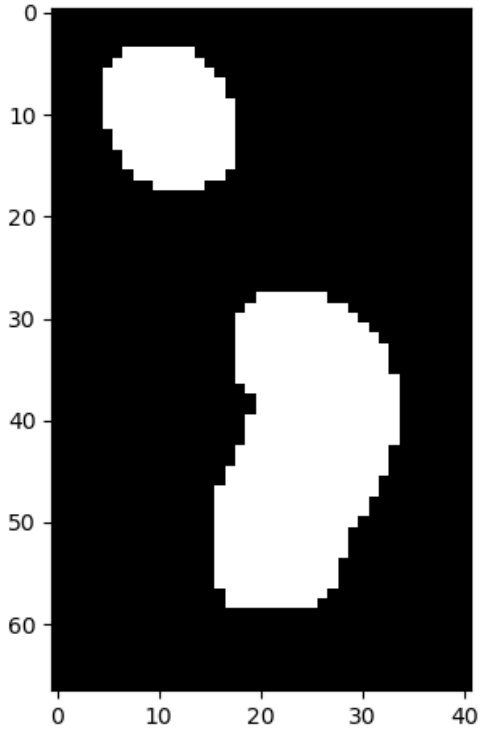

Figure 4.7 ROI binarized

5 Evaluation

We used the DSRM process model in two different iterations in our research.

Each iteration had a different entry point, which was determined by the stage of the process as well as the feedback we got after each demonstration and evaluation.

Figure 5.1 summarizes and shows all of the iterations we've gone through so far.

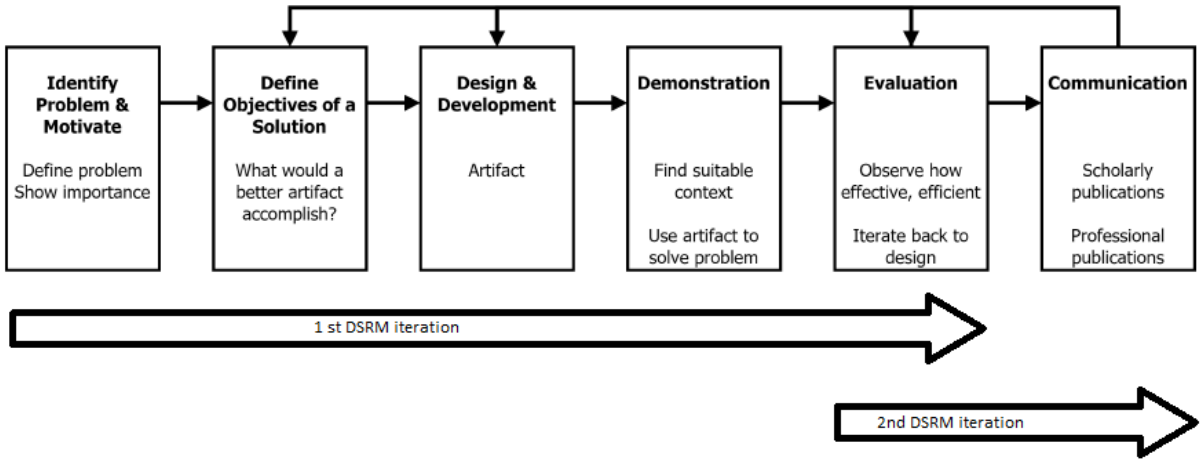

Figure 5.1 DSRM Iterative cycles scheme

5.1 First DSRM Iteration

The first iteration took the most time. It started with the initial identification of the problem and goals and ended with the creation of the first tested version of the artifacts on the demonstration, which made up the vast majority of the established work.

For this study we used Philips's ultrasound equipment, model Epiq 7 (Eindhoven, The Netherlands).

After the performed tests, we created a validation set with 12 echocardiographic studies (from 12 different patients with calcific aortic stenosis) chosen randomly from the database, where we aimed to check our model's accuracy in terms of classifying whether we have, or have not, a presence of calcium on the echocardiography image, based in the amount of calcification as assessed by CV-based calculation of the number of pixels, in comparison with the calcium area measured manually by planimetry in cm^2 [35].

In Table 5.1, we present the results extracted from the validation set composed of these 12 samples, from which we have found a high correlation between the amount of calcium based

on the number of white pixels, and the calcium area measured manually by the echocardiography experts (Professor Ana Gomes de Almeida and Professor Luís Rosário).

Table 5.1 Validation Study in a controlled patient representative – the number of white pixels (showing calcium) versus planimetry area measured manually.

	Number of white pixels	Planimetry area (cm2)	normalized mean
case 1	325	1.12	166
case 2	722	1.44	174
case 3	242	0.81	168
case 4	669	1.96	170
case 5	2251	2.67	175
case 6	2565	2.82	190
case 7	1026	1.98	188
case 8	917	1.45	174
case 9	1007	1.62	178
case 10	1315	1.77	172
case 11	206	0.72	165
case 12	1771	1.99	186

Pearson correlation between the number of white pixels and the area calculated by planimetry was 0.92, p=0.00048, as depicted in the correlation graph in Figure 5.2.

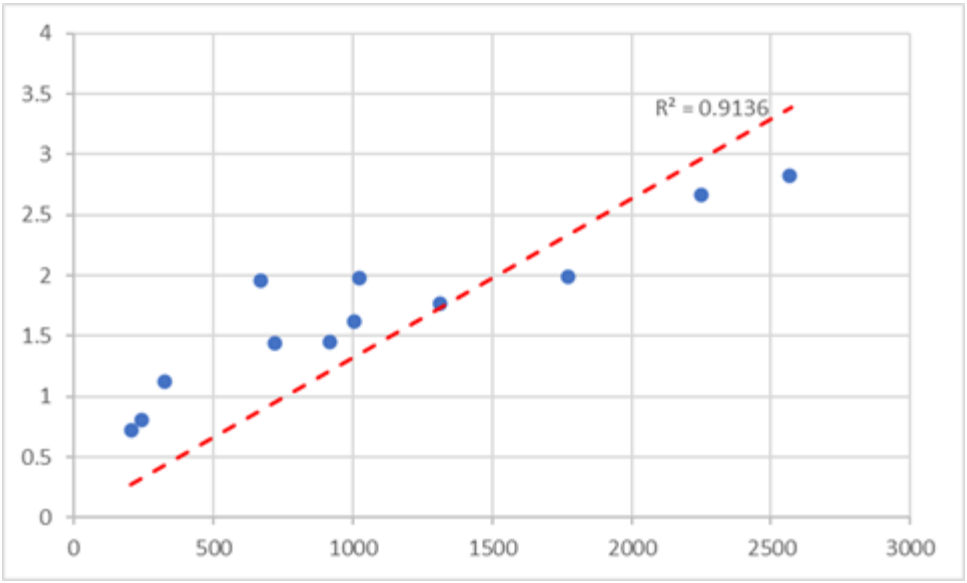

Figure 5.2 Correlation Graph, where Y-axis is planimetry and X-axis the number of white pixels taken from our approach.

5.2 Second DSRM iteration

This iteration's evaluation was carried out to ensure that our artifacts were suitable for their intended use, as described by the objective statements presented in Chapter 1.2 and defined in consultation with our experts.

For the evaluation, as stated previously we've used the standard ISO 15504 four-level NLPF scale [14], having the following levels:

- Not Achieved (NA) - [0-15%]
- Partially Achieved (PA) -]15-50%]
- Largely Achieved (LA) -]50-85%]
- Totally Achieved (TA) -]85-100%]

Table 5.2 Results of the evaluation (2nd DSRM iteration)

Criteria	Objective statement	Expert #1	Expert #2
Efficacy	To improve the doctors time on identifying and evaluating the calcium severity	TA	PA
Consistency with people / utility	It can help doctors to save time on doing the prognostics.	LA	LA

Consistency with people / understandability	Provides understandable results. An identification and an absolute quantification	LA	LA
Consistency with people / ease of use	Easily understandable, and can be used with barely training	LA	LA
Consistency with organization / utility	Provides an alternative on automatically identify and quantifying calcium	TA	PA
Consistency with organization / fit with organization	Can keep better tracking of the patients	LA	PA
Simplicity	Click and Run application with no extra implementation	TA	LA
Level of detail	Provides knowledge extracted from the image	TA	PA
Consistency	It gives consistent results despite the different image settings	LA	LA
Performance	Has good performance on loading and interpreting the images	TA	LA
Robustness	Must be prepared for any usage without resulting in errors	PA	PA

6 Discussion and Conclusions

In this exploratory study, a Computer Vision approach enabled us to identify and quantify the amount of calcium based on echocardiography imaging analysis, in calcific aortic valve stenosis. This degenerative disease evolves with ageing and is an epidemiological issue due to the high mortality, if left untreated. Literature studies performed with cardiac CT calcium score, showed that the amount of valve calcification is related to severity and may help identify high-risk patients with indication for valve replacement.

According to the Agatston method, calcium quantification by cardiac CT is usually presented as a calcium score and is validated by histopathology [36]. Although it is a reference method for calcification, CT is an ionizing method and its use in repeated studies should be avoided. On the other hand, echocardiography is a non-invasive non-ionizing technique based in ultrasound that could be used for calcium detection quantification if an automated method was available and reliable. There is a lack, so far, of a reliable quantification method for calcium by using echocardiography, although this could be a most appropriate method since it is free of negative effects on human health and is a widely available technique. However, the quantification of calcium based on echocardiography imaging is a challenge. Calcium is reliably detected visually by experts, but visual quantification is unreliable and subject to variability. In this thesis, calcification of aortic valve was used in the scope of a proof-of concept.

From echocardiographic studies of calcific aortic stenosis, we analyzed the effect of changing the post-processing windowing conditions (width and level) and found a high level of agreement of intensity pixel values after normalization (by subtracting from the values of a ROI in a dark part of the image, at flow echogenicity void). An adaptive cutoff was found for pixels intensity that ensured the presence of calcium as validated by visual inspection.

Furthermore, in additional echocardiographic studies, we analyzed the pixels values when changing the settings of acquisition that affect the brightness and contrast (ultra-sound frequency and compression) and the final values for pixels and normalized pixels at the reference ROI, just showed a small difference between exams, opening the potential for wider application in the clinical setting.

Additionally, a validation set of 12 cases of calcific aortic stenosis, chosen randomly from a database, was selected for calcium quantification in the valves by assessing pixel number counting after applying the proposed cutoff for calcium. As a proxy of the amount of valve calcification, this number, in parallel to the CT calcium-score, showed an excellent correlation

with valve calcification measured manually via planimetry by echocardiography experts. Being the entire process represented by Figure 6.1.

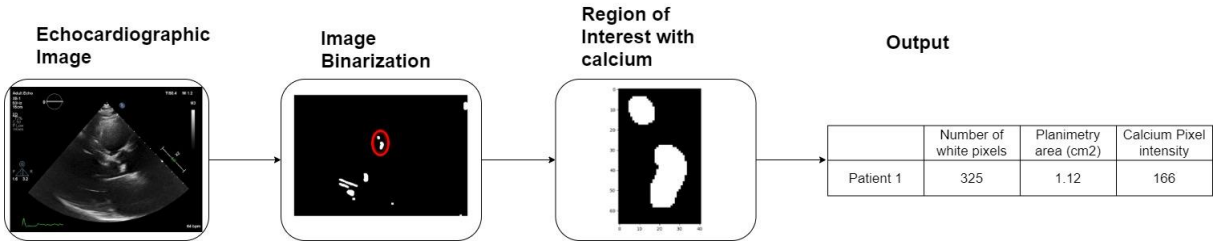

Figure 6.1. Summarized process description

A limitation for this study is the small number of cases analyzed, in accordance however to its exploratory purpose. A further study should be undertaken in the future with the inclusion of a larger number of aortic valves with a large range of calcification to validate these results. Besides expert image validation, as used in this thesis, a comparison with an additional validated method must be undertaken.

Moreover, this study was developed using a specific echocardiographic equipment. Findings must be compared in further studies using other machines that may possibly provide different kind of ultrasound images regarding pixels intensity and possibly different cutoffs need to be considered.

This work was a collaborative approach between a computer science and social sciences university with a medical university and hospital to solve and provide a real problem.

6.1 Future Work

Despite the positive findings, further iterations to the work we have done in this dissertation would be beneficial.

As pointed out in the introduction, we did not follow a ML approach, since we were lacking in data. Now, for each echocardiography that our prototype analyses, we are not only using one new echocardiography images each time we use it, but we are also annotating those images with the ROI and the normalization region, what would be fundamental for a ML approach – annotated images – therewith, we may save these images for a future ML model.

We aim in the future to apply the model to a larger number of echocardiographic images with a broad range of calcification amount, as validated by an additional method, such as CT calcium score.

Finally, performing tests in a production environment would be critical, in order to evaluate the robustness of our prototype and correct any failures that may occur in a production environment.

7 References

[1] K. Okrainec, D. K. Banerjee, and M. J. Eisenberg, "Coronary artery disease in the developing world," *Am. Heart J.*, vol. 148, no. 1, pp. 7–15, Jul. 2004, doi: 10.1016/j.ahj.2003.11.027.

[2] V. T. Nkomo, J. M. Gardin, T. N. Skelton, J. S. Gottdiener, C. G. Scott, and M. Enriquez-Sarano, "Burden of valvular heart diseases: a population-based study," *Lancet Lond. Engl.*, vol. 368, no. 9540, pp. 1005–1011, Sep. 2006, doi: 10.1016/S0140-6736(06)69208-8.

[3] "Resident population aged 65 and over, annual average: total and by age group." https://www.pordata.pt/en/Portugal/Resident+population+aged+65+and+over++annual+average+total+and+by+age+group-3508 (accessed May 01, 2021).

[4] "Computed Tomography Aortic Valve Calcium Scoring in Patients With Aortic Stenosis | Circulation: Cardiovascular Imaging." https://www.ahajournals.org/doi/full/10.1161/circimaging.117.007146 (accessed Mar. 18, 2021).

[5] D. Bos and M. J. G. Leening, "Leveraging the coronary calcium scan beyond the coronary calcium score," *Eur. Radiol.*, vol. 28, no. 7, pp. 3082–3087, Jul. 2018, doi: 10.1007/s00330-017-5264-3.

[6] A. Arjmand Shabestari, "Coronary artery calcium score: a review," *Iran. Red Crescent Med. J.*, vol. 15, no. 12, p. e16616, Dec. 2013, doi: 10.5812/ircmj.16616.

[7] R. Caruana, Y. Lou, J. Gehrke, P. Koch, M. Sturm, and N. Elhadad, "Intelligible Models for HealthCare: Predicting Pneumonia Risk and Hospital 30-day Readmission," in *Proceedings of the 21th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, Sydney NSW Australia, Aug. 2015, pp. 1721–1730. doi: 10.1145/2783258.2788613.

[8] D. T. Huff, A. J. Weisman, and R. Jeraj, "Interpretation and visualization techniques for deep learning models in medical imaging," *Phys. Med. Biol.*, vol. 66, no. 4, p. 04TR01, Feb. 2021, doi: 10.1088/1361-6560/abcd17.

[9] W. Rawat and Z. Wang, "Deep Convolutional Neural Networks for Image Classification: A Comprehensive Review," *Neural Comput.*, vol. 29, pp. 1–98, Jun. 2017, doi: 10.1162/NECO_a_00990.

[10] K. Peffers, T. Tuunanen, M. A. Rothenberger, and S. Chatterjee, "A Design Science Research Methodology for Information Systems Research," *J. Manag. Inf. Syst.*, vol. 24, no. 3, pp. 45–77, Dec. 2007, doi: 10.2753/MIS0742-1222240302.

[11] A. Hevner, A. R, S. March, S. T, Park, J. Park, Ram, and Sudha, "Design Science in Information Systems Research," *Manag. Inf. Syst. Q.*, vol. 28, p. 75, Mar. 2004.

[12] M. Markus, A. Majchrzak, and L. Gasser, "A Design Theory for Systems That Support Emergent Knowledge Processes.," *MIS Q.*, vol. 26, pp. 179–212, Sep. 2002, doi: 10.2307/4132330.

[13] N. Prat, I. Wattiau, and J. Akoka, "Artifact Evaluation in Information Systems Design Science Research ? A Holistic View," *Proc. - Pac. Asia Conf. Inf. Syst. PACIS 2014*, Jun. 2014.

[14] 14:00-17:00, "ISO/IEC 15504-2:2003," *ISO*. https://www.iso.org/cms/render/live/en/sites/isoorg/contents/data/standard/03/74/37458.html (accessed May 03, 2021).

[15] R. Zeleznik, B. Foldyna, P. Eslami, J. Weiss, I. Alexander, J. Taron, C. Parmar, R. M. Alvi, D. Banerji, M. Uno, Y. Kikuchi, J. Karady, L. Zhang, J.-E. Scholtz, T. Mayrhofer, A. Lyass, T. F. Mahoney, J. M. Massaro, R. S. Vasan, P. S. Douglas, U. Hoffmann, M. T. Lu, and H. J. W. L. Aerts, "Deep convolutional neural networks to predict cardiovascular

risk from computed tomography," *Nat. Commun.*, vol. 12, no. 1, p. 715, Dec. 2021, doi: 10.1038/s41467-021-20966-2.
[16] T. Pawade, T. Sheth, E. Guzzetti, M. R. Dweck, and M.-A. Clavel, "Why and How to Measure Aortic Valve Calcification in Patients With Aortic Stenosis," *JACC Cardiovasc. Imaging*, vol. 12, no. 9, pp. 1835–1848, Sep. 2019, doi: 10.1016/j.jcmg.2019.01.045.
[17] D. Moher, A. Liberati, J. Tetzlaff, and D. G. Altman, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *BMJ*, vol. 339, p. b2535, Jul. 2009, doi: 10.1136/bmj.b2535.
[18] G. Y. Kim, J. H. Lee, Y. N. Hwang, and S. M. Kim, "A novel intensity-based multi-level classification approach for coronary plaque characterization in intravascular ultrasound images," *Biomed. Eng. Online*, vol. 17, 2018, doi: 10.1186/s12938-018-0586-1.
[19] U. Raghavendra, H. Fujita, A. Gudigar, R. Shetty, K. Nayak, U. Pai, J. Samanth, and U. R. Acharya, "Automated technique for coronary artery disease characterization and classification using DD-DTDWT in ultrasound images," *Biomed. Signal Process. Control*, vol. 40, pp. 324–334, 2018, doi: 10.1016/j.bspc.2017.09.030.
[20] Y. N. Hwang, J. H. Lee, G. Y. Kim, E. S. Shin, and S. M. Kim, "Characterization of coronary plaque regions in intravascular ultrasound images using a hybrid ensemble classifier," *Comput. Methods Programs Biomed.*, vol. 153, pp. 83–92, 2018, doi: 10.1016/j.cmpb.2017.10.009.
[21] M. Guerrero, D. D. Wang, A. Pursnani, M. Eleid, O. Khalique, M. Urena, M. Salinger, S. Kodali, T. Kaptzan, B. Lewis, N. Kato, H. M. Cajigas, O. Wendler, D. Holzhey, A. Pershad, C. Witzke, S. Alnasser, G. H. L. Tang, K. Grubb, M. Reisman, P. Blanke, J. Leipsic, E. Williamson, P. A. Pellikka, S. Pislaru, J. Crestanello, D. Himbert, A. Vahanian, J. Webb, R. T. Hahn, M. Leon, I. George, V. Bapat, W. O'Neill, and C. Rihal, "A Cardiac Computed Tomography–Based Score to Categorize Mitral Annular Calcification Severity and Predict Valve Embolization," *JACC Cardiovasc. Imaging*, vol. 13, no. 9, pp. 1945–1957, Sep. 2020, doi: 10.1016/j.jcmg.2020.03.013.
[22] S. M. Lee, H. W. Lee, Y. K. Son, S. E. Kim, and W. S. An, "Abdominal aortic calcification score among several vascular calcification scores of plain radiograph is the most reliable predictor of severe coronary artery calcification in dialysis patients," *Ren. Fail.*, vol. 39, no. 1, pp. 729–735, 2017, doi: 10.1080/0886022X.2017.1398666.
[23] M. van Assen, S. S. Martin, A. Varga-Szemes, S. Rapaka, S. Cimen, P. Sharma, P. Sahbaee, C. N. De Cecco, R. Vliegenthart, T. J. Leonard, J. R. Burt, and U. J. Schoepf, "Automatic coronary calcium scoring in chest CT using a deep neural network in direct comparison with non-contrast cardiac CT: A validation study," *Eur. J. Radiol.*, vol. 134, 2021, doi: 10.1016/j.ejrad.2020.109428.
[24] L. B. van den Oever, L. Cornelissen, M. Vonder, C. Xia, J. N. van Bolhuis, R. Vliegenthart, R. N. J. Veldhuis, G. H. de Bock, M. Oudkerk, and P. M. A. van Ooijen, "Deep learning for automated exclusion of cardiac CT examinations negative for coronary artery calcium," *Eur. J. Radiol.*, vol. 129, 2020, doi: 10.1016/j.ejrad.2020.109114.
[25] S. G. M. van Velzen, N. Lessmann, B. K. Velthuis, I. E. M. Bank, D. H. J. G. van den Bongard, T. Leiner, P. A. de Jong, W. B. Veldhuis, A. Correa, J. G. Terry, J. J. Carr, M. A. Viergever, H. M. Verkooijen, and I. Išgum, "Deep learning for automatic calcium scoring in CT: Validation using multiple cardiac CT and chest CT protocols," *Radiology*, vol. 295, no. 1, pp. 66–79, 2020, doi: 10.1148/radiol.2020191621.
[26] B. D. de Vos, J. M. Wolterink, T. Leiner, P. A. de Jong, N. Lessmann, and I. Isgum, "Direct Automatic Coronary Calcium Scoring in Cardiac and Chest CT," *IEEE Trans. Med. Imaging*, vol. 38, no. 9, pp. 2127–2138, 2019, doi: 10.1109/TMI.2019.2899534.
[27] N. Zhang, G. Yang, W. Zhang, W. Wang, Z. Zhou, H. Zhang, L. Xu, and Y. Chen, "Fully automatic framework for comprehensive coronary artery calcium scores analysis on non-

contrast cardiac-gated CT scan: Total and vessel-specific quantifications," *Eur. J. Radiol.*, vol. 134, 2021, doi: 10.1016/j.ejrad.2020.109420.
[28] "Zotero | Your personal research assistant." https://www.zotero.org/ (accessed Apr. 16, 2021).
[29] "OpenCV," *OpenCV*. https://opencv.org/ (accessed Apr. 16, 2021).
[30] I. Culjak, D. Abram, T. Pribanic, H. Dzapo, and M. Cifrek, "A brief introduction to OpenCV," in *2012 Proceedings of the 35th International Convention MIPRO*, May 2012, pp. 1725–1730.
[31] A. M. Reza, "Realization of the Contrast Limited Adaptive Histogram Equalization (CLAHE) for Real-Time Image Enhancement," *J. VLSI Signal Process. Syst. Signal Image Video Technol.*, vol. 38, no. 1, pp. 35–44, Aug. 2004, doi: 10.1023/B:VLSI.0000028532.53893.82.
[32] H. G. Kaganami and Z. Beiji, "Region-Based Segmentation versus Edge Detection," in *2009 Fifth International Conference on Intelligent Information Hiding and Multimedia Signal Processing*, Sep. 2009, pp. 1217–1221. doi: 10.1109/IIH-MSP.2009.13.
[33] V. Torre and T. A. Poggio, "On Edge Detection," *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. PAMI-8, no. 2, pp. 147–163, Mar. 1986, doi: 10.1109/TPAMI.1986.4767769.
[34] Y. Zhu and C. Huang, "An Improved Median Filtering Algorithm for Image Noise Reduction," *Phys. Procedia*, vol. 25, pp. 609–616, Dec. 2012, doi: 10.1016/j.phpro.2012.03.133.
[35] O. Uçar, M. Vural, Z. Cetfin, S. Gökaslan, T. Gürsoy, L. Paşaoğlu, S. Koparal, and S. Aydoğlu, "Assessment of planimetric mitral valve area using 16-row multidetector computed tomography in patients with rheumatic mitral stenosis," *J. Heart Valve Dis.*, vol. 20, no. 1, pp. 13–17, Jan. 2011.
[36] C. Denzel, M. Lell, M. Maak, M. Höckl, K. Balzer, K.-M. Müller, C. Fellner, F. A. Fellner, and W. Lang, "Carotid Artery Calcium: Accuracy of a Calcium Score by Computed Tomography—An In vitro Study with Comparison to Sonography and Histology," *Eur. J. Vasc. Endovasc. Surg.*, vol. 28, no. 2, pp. 214–220, Aug. 2004, doi: 10.1016/j.ejvs.2004.05.004.