



IONIAN UNIVERSITY
DEPARTMENT OF INFORMATICS

***“ANALYSIS OF MULTIDIMENSIONAL PATIENT DATA
WITH CARDIOVASCULAR DISEASES THROUGH MEDI-
CAL IMAGE PROCESSING, MODELING, AND MACHINE
LEARNING TECHNIQUES”***

Georgios Eleftherios Kalykakis

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Defense Committee

- 1. Themistoklis Exarchos, Associate Professor, Ionian University**
- 2. Foivos-Apostolos Mylonas, Associate Professor, University of West Attica**
- 3. Constantinos D. Anagnostopoulos, Research Director at the Center for Clinical Research, Experimental Surgery, and Translational Research, BRFAA**
- 4. Dimitrios Vlachakis, Associate Professor, Agricultural University of Athens**
- 5. Panagiotis Vlamos, Professor, Ionian University**
- 6. Theodoros Andronikos, Professor, Ionian University**
- 7. Marios Krokidis, Assistant Professor, Ionian University**

To my Parents, Brother, Friends, Enemies and Eleftheria.

*All that is gold does not glitter,
Not all those who wander are lost;
The old that is strong does not wither,
Deep roots are not reached by the frost.*

J.R.R Tolkien

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Thesis Contribution

The thesis contributes towards cardiovascular disease research by integrating computational modeling, radiomic analysis, and automated segmentation methods with advanced imaging modalities. The work advances the understanding of coronary artery disease (CAD) and systemic vascular conditions, offering innovative approaches for risk assessment and diagnostic precision.

The first key contribution is the evaluation of endothelial shear stress (ESS) through computational fluid dynamics (CFD) modeling derived from coronary computed tomography angiography (CCTA). The research systematically analyzes the relationship between ESS and plaque morphology, highlighting the influence of hemodynamic patterns on coronary vessel characteristics. By incorporating data on stenosis location and severity, the study provides a good understanding of how ESS variations contribute to myocardial perfusion changes, as assessed by non-invasive imaging techniques such as positron emission tomography (PET). These results emphasize the potential of ESS as a marker for the functional impact of coronary plaques.

The second major contribution focuses on the application of radiomic analysis to CCTA images. High-dimensional radiomic features were extracted from coronary plaques to investigate their predictive value for myocardial perfusion abnormalities. The study demonstrates that radiomic biomarkers significantly enhance the diagnostic performance of models for identifying ischemic lesions when combined with functional imaging data from PET and single-photon emission computed tomography (SPECT). This approach provides a non-invasive method for improving the characterization of functional significant regions.

Finally, the thesis addresses systemic vascular conditions by developing automated segmentation techniques for analyzing the aorta in PET/CT scans. These methods improve the precision and reproducibility of metabolic activity measurements in conditions such as large-vessel vasculitis. By optimizing segmentation workflows, the study contributes to the efficient evaluation of systemic inflammatory diseases, highlighting the adaptability of the computational techniques employed.

This research bridges computational methods, advanced imaging, and clinical relevance, offering new tools for non-invasive cardiovascular diagnostics. The integration of ESS analysis, radiomics, and automated segmentation provides a multidisciplinary

framework with significant implications for improving the understanding, diagnosis, and management of cardiovascular diseases.

Abstract

Cardiovascular diseases remain the leading cause of mortality globally, driving the need for improved diagnostic and predictive tools. This thesis integrates computational fluid dynamics (CFD), radiomic analysis, and automated segmentation techniques with advanced imaging modalities to enhance the assessment of coronary artery disease (CAD) and systemic vascular conditions.

Endothelial shear stress (ESS), calculated through CFD models based on coronary computed tomography angiography (CCTA), is evaluated in relation to stenosis severity, plaque volume and myocardial perfusion. The research explores how variations in ESS correlate with functional changes in myocardial perfusion, as measured by positron emission tomography (PET). These findings provide insights into the role of hemodynamic forces in CAD and underscore the potential of ESS as a diagnostic marker.

Radiomic analysis is applied to CCTA-derived plaque features to extract biomarkers predictive of myocardial perfusion abnormalities. The integration of these biomarkers with PET and single-photon emission computed tomography (SPECT) data significantly enhances diagnostic accuracy compared to traditional imaging metrics. This approach highlights the utility of radiomics in non-invasive CAD risk stratification.

Additionally, the thesis develops automated segmentation methods for analyzing the aorta in PET/CT imaging, enabling precise and reproducible assessment of metabolic activity in large-vessel vasculitis. These techniques improve workflow efficiency and provide new tools for evaluating systemic inflammatory conditions.

By combining ESS analysis, radiomic biomarkers, and automated segmentation, this thesis establishes a comprehensive framework for non-invasive cardiovascular diagnostics. The findings contribute to advancing patient-specific risk assessment and management strategies, with significant implications for clinical practice.

Thesis aims and outline overview

This PhD dissertation aims to explore the integration of computational techniques in order to facilitate the assessment and understanding of cardiovascular diseases, focusing on coronaries and the aortic arterial segments. The increased incidence of cardiovascular diseases is considered the main cause of mortality and morbidity worldwide. Over the past decades, advances in imaging technologies, computational methods, and machine learning techniques have opened new research fields for non-invasive diagnosis and risk assessment. By employing these advanced techniques, the study aims to improve our understanding of hemodynamic changes, in relation to plaque morphology, shear stress, imaging characteristics and metabolic markers.

The dissertation is focused on two main arteries. The coronary tree and the aorta. So, four chapters are going to be presented.

Chapter 1 is the introductory chapter. The Introduction chapter of this dissertation presents the basic biological and medical terms, imaging techniques and procedures for better understanding cardiovascular diseases, particularly coronary artery disease (CAD) and disorders of the aorta.

It begins with an overview of the cardiovascular system, presenting the heart's physiology, anatomy and the functions of the coronary network in circulating blood flow. The aorta's significance as the largest artery, along with its role in systemic circulation, is also examined, presenting conditions such as aneurysms. Following that, the study introduces atherosclerotic disease, discussing the plaque generation mechanisms as well as their connection with blood flow, and the risk of ischemic events.

Following that, the chapter transitions into imaging modalities used for assessing the coronary arteries, introducing both invasive and noninvasive techniques. The chapter also introduces functional assessment methods, such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) and their protocols to evaluate myocardial perfusion.

Additionally, the chapter explores the theory behind calculating endothelial shear stress (ESS) from CCTA and CT derived fractional flow reserve (FFR), establishing their importance in predicting hemodynamic significance.

It concludes with an overview of computational techniques, including fluid dynamics modeling, radiomics feature extraction, and machine learning methods, that can be used as a “tool” for clinical and research the cardiovascular abnormalities.

Chapter 2: Coronary Arteries – Endothelial Shear Stress

This chapter presents a series of studies focusing on the hemodynamic effects of coronary lesions, drawing on data from the EVINCI study (Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischaemic Heart Disease). The purpose of the EVINCI study was to assess the additional clinical value of hybrid imaging in analyzing coronary anatomy and myocardial perfusion using non-invasive techniques. Conducted through a collaborative network of clinical imaging centers across Europe, the study aimed to improve diagnostic accuracy for patients with stable angina and an intermediate preclinical risk of coronary artery disease (CAD). Special attention is given to the calculation of endothelial shear stress and the features derived from coronary plaques, as well as their association with plaque morphology and myocardial perfusion. This section examines hemodynamic differences according to the location (proximal or distal) and severity of stenoses. Using computational flow models, the study explores how these parameters impact the functional state of the vessels. It also emphasizes the correlation between endothelial shear stress and plaque characteristics, such as blood flow and vasodilatory capacity, as assessed through PET imaging. Finally, machine learning techniques are applied to investigate plaque characteristics and endothelial wall shear stress derived from CCTA, correlating them with myocardial perfusion imaging (PET-MPI).

Chapter 3: Coronary Arteries – Plaque Characteristics (Radiomics)

This chapter focuses on the analysis of plaque-related characteristics in coronary arteries and their association with predicting abnormal myocardial perfusion in patients who participated in the EVINCI study. The predictive power of radiomic features from CCTA is assessed for estimating the probability of abnormal myocardial perfusion, and combinatory perfusion indices from PET and radiomic data are analyzed. The chapter also discusses the potential biological and functional significance of these specific features and their link to events that induce changes in myocardial perfusion.

Chapter 4 focuses on imaging techniques for assessing the aorta, particularly in the context of Large Vessel Vasculitis (LVV) and lymphoma. The chapter examines the association of Standard Uptake Values (SUV) from ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F -FDG PET/CT) scans and metabolic profiles during active and inactive stages of LV-GCA. Additionally, the chapter discusses automated aortic segmentation in low-dose chest CT images, which enhances SUV analysis in terms of time and accuracy for vasculitis and lymphoma patients.

1. Introduction

1.1 Cardiovascular system and heart physiology

The circulatory system is an elaborate network of blood vessels that has its main purpose is to transfer the blood from and to the heart as well as oxygen and other essential components to the body [1] and to remove waste products from it like carbon dioxide Figure 1. This system is categorized into two sub systems, the cardiovascular and lymphatic systems. These components are responsible for the efficient circulation of important substances like nutrients and oxygen to every cell, by such means maintaining the functionality of the body's organs and tissues. The core piece of this network is the heart, a powerful muscle that functions as a pump. It works in a closed loop utilizing a network of blood vessels to keep the flow of blood throughout the body. The main function of this system is to transport blood full of oxygen to tissues and organs and reinstate poor-oxygen blood back to the lungs for reoxygenation [2].

Blood vessels are divided into two main circulatory systems: systemic and pulmonary. Systemic circulation begins when the left ventricle feeds blood full of oxygen to the aorta [1]. There, the blood flows through an elaborate network of smaller and smaller in diameter arteries until the capillaries. In the capillaries it pushes oxygenated blood and other essential nutrients to heart tissues. It is also where it removes unwanted blood products like carbon dioxide [3]. This exchange is essential for preserve the metabolic health of tissues and the human in general. The deoxygenated blood is then accumulated in the veins, which send it back to the right atrium and into the right ventricle, preparing it for reoxygenation [1]. Pulmonary circulation begins when the right side of the heart pushes deoxygenated blood into the pulmonary artery. Pulmonary artery is spliced into smaller vessels called capillaries. There carbon dioxide leaves the blood and goes into the air inside the lungs, while fresh oxygen enters the blood. Then carbon dioxide is expelled from the lungs as we breathe out. The full of oxygen blood then follows the pulmonary veins and ends up into the left atrium and descends into the left ventricle, preparing for the next pulse [4]. The circulatory system's efficiency and health are essential to an individual's overall health. Conditions such as hypertension as well as coronary artery disease, severely impact health, highlighting the importance of preventive measures like regular physical activity, a nutritious diet, and avoidance of smoking.

Furthermore, the lymphatic part of the circulatory system is crucial for immune responses and maintaining fluid equilibrium within the body, emphasizing the system's complexity as well as vital role [5].

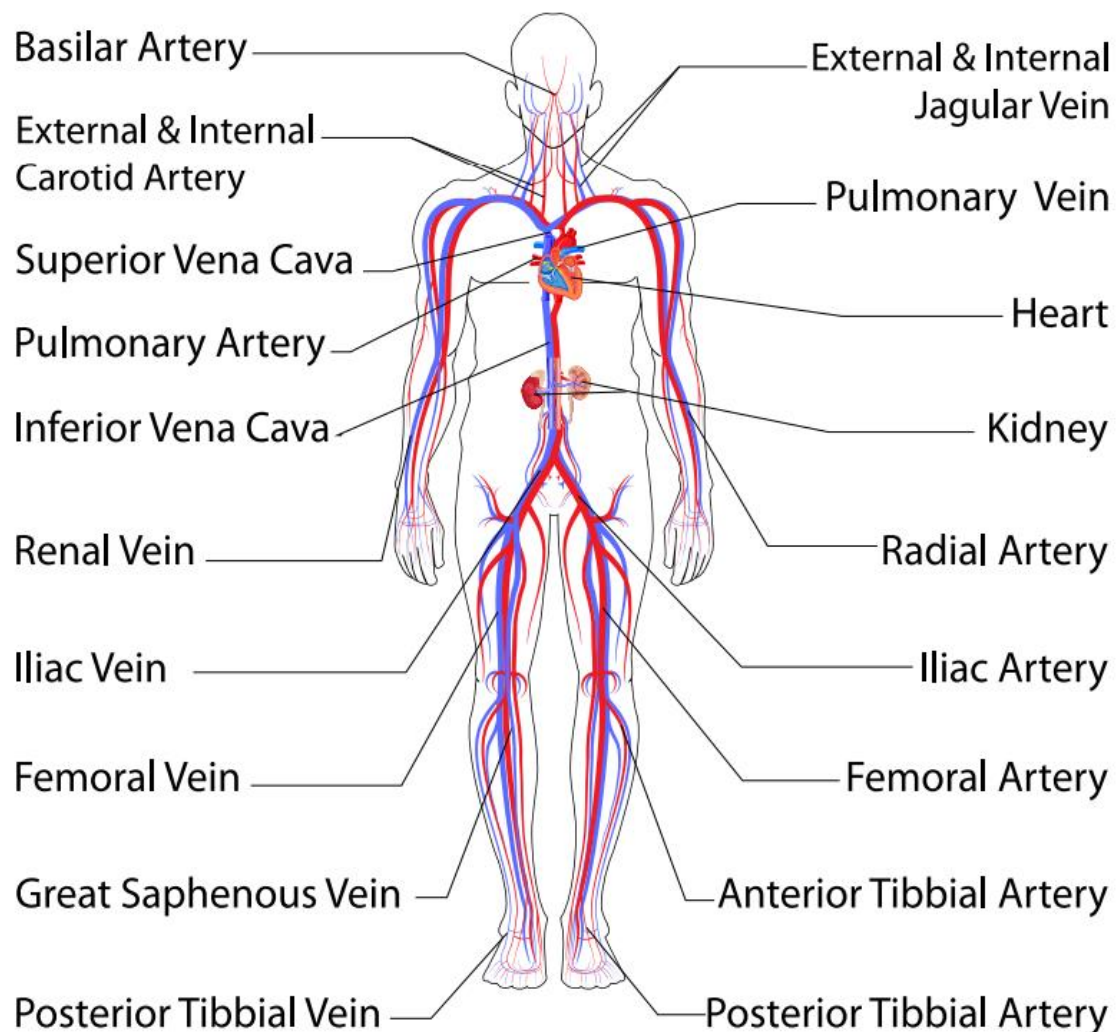


Figure 1 Human circulatory system, including the arteries and the veins that pushes oxygenated and deoxygenated blood throughout the body (Peate et al. ,2018) [6]

The human heart, a muscular organ consists of four chambers ^{Figure 2}, is roughly the size of an apple, and the majority of its mass located to the left side of the body. It is located inside the thoracic cavity, between the lungs [7], [8]. The heart is encapsulated within a pericardial sac, consisting of the pericardium's outer layer, a tissue sac surrounding the heart. Inside this sac, the inner surface is lined with layers of a smooth, slippery membrane [9]. Adjacent to this, the visceral layer of the membrane creates the epicardium. The heart wall consistency can be described in three separable segments:

1. Epicardium: The outer layer.
2. Myocardium: The middle muscular layer.
3. Endocardium: The innermost layer.

The innermost layer, lining the surrounding of the heart, is called the endocardium. The pericardium surrounds the pericardial cavity. It serves as both a mechanical and immunological protection and it constrains the heart's expansion, preserving a maximum volume of the heart [10]. The myocardium constitutes the central layer of the heart wall, and is located between the inner endocardium and the outer epicardial layer, which is part of the pericardium. This layer consists of various sheets of muscle fibers oriented in multiple directions, effectively encapsulate the heart [11]. The endocardium, which is the last heart layer of the wall, covers the interior chambers and heart valves. It contains capillaries that “feed” the heart muscles, along with nerve fibers and cells that help conduct the heart's electrical impulses [12].

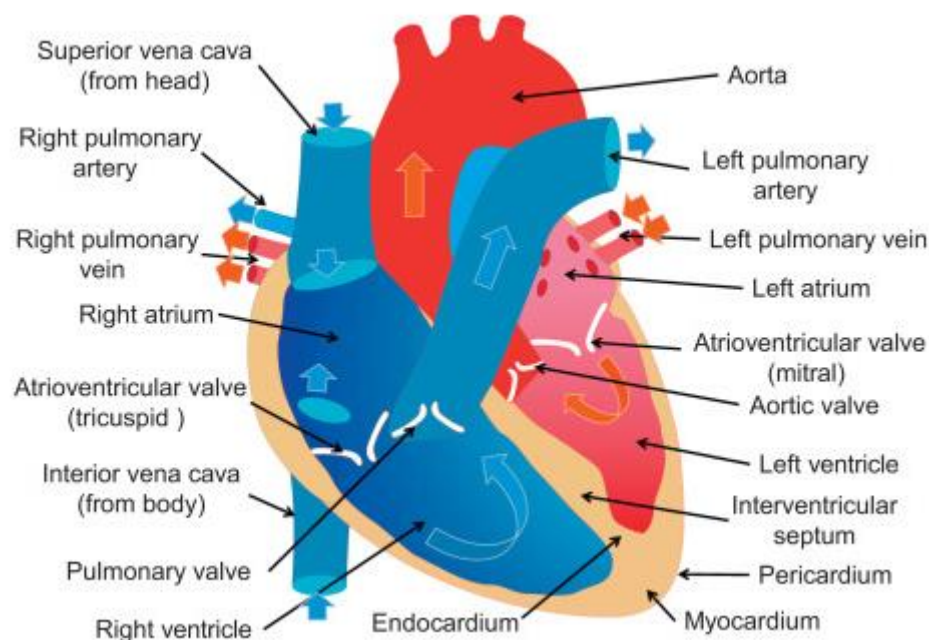


Figure 2 Anatomy of the human heart (Athanasidou et al., 2017)[13]

1.1.1 Functions of the Heart and Coronary network

The heart as we have already mentioned is organized into four primary chambers: the atria at the upper section of the mass and the lower ventricles located at the end part, designed to optimize the blood flow ^{Figure 3}. The atria function as intake regions for returning blood, while the ventricles push the blood throughout the organism. A vital component, the septum, separates the heart into left and right halves, ensuring that oxygen-rich and oxygen-poor blood do not mix. The tricuspid valve pushes blood from the atrium to the ventricles, while the mitral valve pushed the blood from the left atrium to the left ventricle. With the opening of the aortic valve the blood goes through the aorta distributing blood full of oxygen throughout the tissues. From the right atrium,

the blood follows a path to the tricuspid valve and then goes into the right ventricle. The right ventricle then pushes the poor oxygenated blood through the lungs in order to fill it with the essential oxygen. After that the blood goes back to the left atrium and into the left ventricle. There, the mitral valve prevents the backflow, securing the blood exit through the aorta. Moreover, the coronary arteries, branching out from the aorta, are essential for pushing oxygenated blood to the heart tissue. The left coronary artery, shortly after its origin, bifurcates into two branches: the left anterior descending (LAD) artery and the left circumflex (LCx) artery [14]. The LAD artery follows the heart's surface, providing blood to the ventricular septum and anterior myocardial wall. At the same time, the LCx artery goes along the atrioventricular groove [15]. Opposed to that, the right coronary artery (RCA) is responsible for perfusing the right side of the heart [16], [17]. This cycle presents the heart's activity, which is vital for supporting life [1], [7].

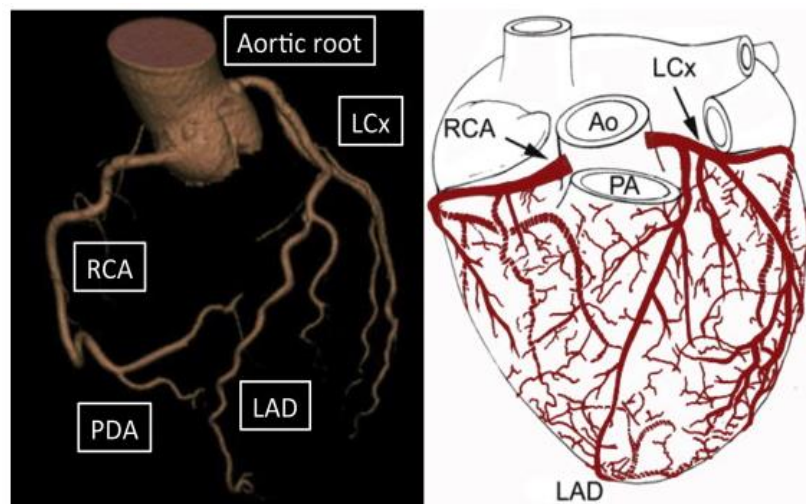


Figure 3 Anatomy of the coronary arteries in 3D and 2D representations (Pena-Duque et al., 2015) [18]

1.1.2 Aorta

The aorta is considered the largest artery in the human vascular system ^{Figure 4}. The aorta, emerging from the left ventricle, and its purpose is to provide blood full of oxygen to tissues and body regions in general. It begins with the ascending aorta, which extends upwards, moving posteriorly to the right of the pulmonary trunk. Following the ascending aorta is the aortic arch. From this arch area, several arteries branch off, including subclavian arteries, that is fissure into the right carotid and right subclavian arteries, as well as the left carotid. These arteries are vital for supplying blood to the head and the neck. Following the aortic arch, the aorta proceeds downward as the descending aorta,

which is subdivided into the thoracic aorta [19], and the abdominal aorta. The abdominal aorta bifurcates into the common iliac arteries at the lower abdomen, completing the aorta's path and the blood distribution [20].

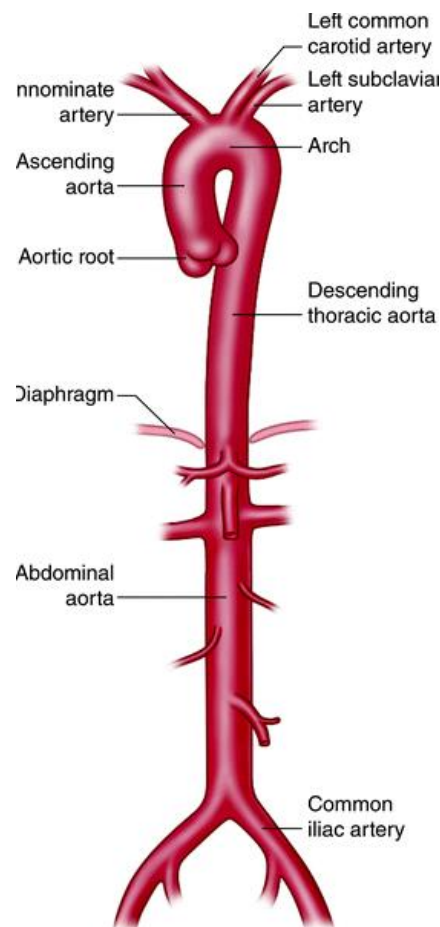


Figure 4 Anatomical illustration of the aorta (Maus et al., 2016)[21]

1.1.3 Atherosclerotic Disease

Atherosclerosis disease the most common occurrence of cardiovascular disease (CVD) and because of that it is also the most common cause of mortality in the world [22]. It is a disease that has been characterized by the presence of intimal plaques throughout the vascular system. The primary cause for atherosclerosis is the increased formation of cholesterol ^{Figure 5}, in particular the low-density lipoprotein (LDL) cholesterol, that has been transported through the blood circulation [23], in the inner layer of the artery as well as the underlying smooth muscle [24][25]–[28].

There is plenty of evidences that lipid oxidation in LDLs is responsible for inflammation in the vessel wall [29]. Specifically, LDLs with the addition of factors that promote atherogenesis, are having an important role in the stimulation of activity in the endothelial cell, encouraging the appearance of monocytes in the intima. Monocytes interact with the LDLs and that interaction is creating foam cells [30]. In addition to that, several

pathways of inflammatory signal transduction are engaged in fatty streak formation, one of the early components of atherosclerosis [31]. These factors are considered the starting point for atherosclerotic plaque initiation and further development.

Plaque creation and accumulation in the endothelium can be very dangerous because it can reduce significantly the lumen diameter of the artery, limiting blood flow, that is crucial for organs like the heart and the brain. Limiting flow scenarios because of stenosis can also lead to thrombotic episodes or vessel rupture [32].

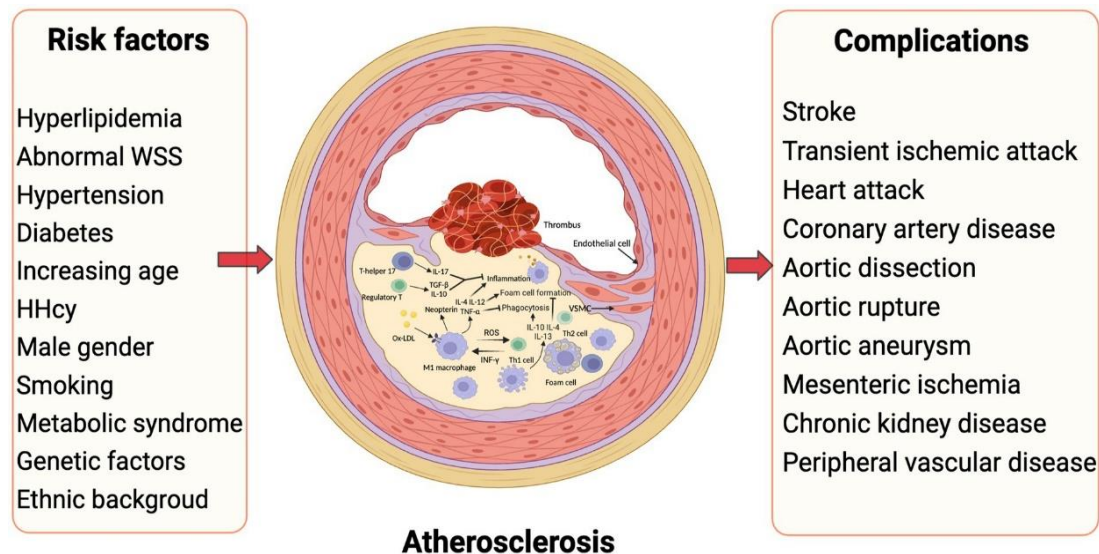


Figure 5 Inflammatory atherosclerosis ,risk factors complications (He et al,2023) [33]

Plaque composition is important for the assessment of a lesion and its evaluation ^{Figure 6}. Plaque phenotype can be described in 4 categories. Fibrofatty, fibrous, necrotic core and calcified. Fibrofatty plaque can be characterized as a plaque composition that goes from fatty streak composition to fibrous tissue. Fibrous plaques are characterized by a combination of a large volume of lipids and smooth muscle cells [34]. Necrotic core consists of a lipid hypocellular region and increased his size because of macrophage death. Calcified plaque is considered a stable plaque and the process initiates with small matrix vesicles produced by apoptotic smooth muscle cells and macrophages. These vesicles gradually coalesce into larger formations, usually near the necrotic core, and eventually evolve into calcified plates [29]. The progression of atherosclerotic lesions into symptomatic cardiovascular disease often involves plaque growth, rupture, and subsequent clot formation (thrombosis) [35]. Plaque vulnerability to rupture is highly dependent on its composition, with plaques containing a substantial lipid core and a thin fibrous cap is considered high risk plaque and are prone of rupture [36][37]. Such

ruptures can trigger serious cardiovascular events, such as myocardial infarction and possible stroke [38].

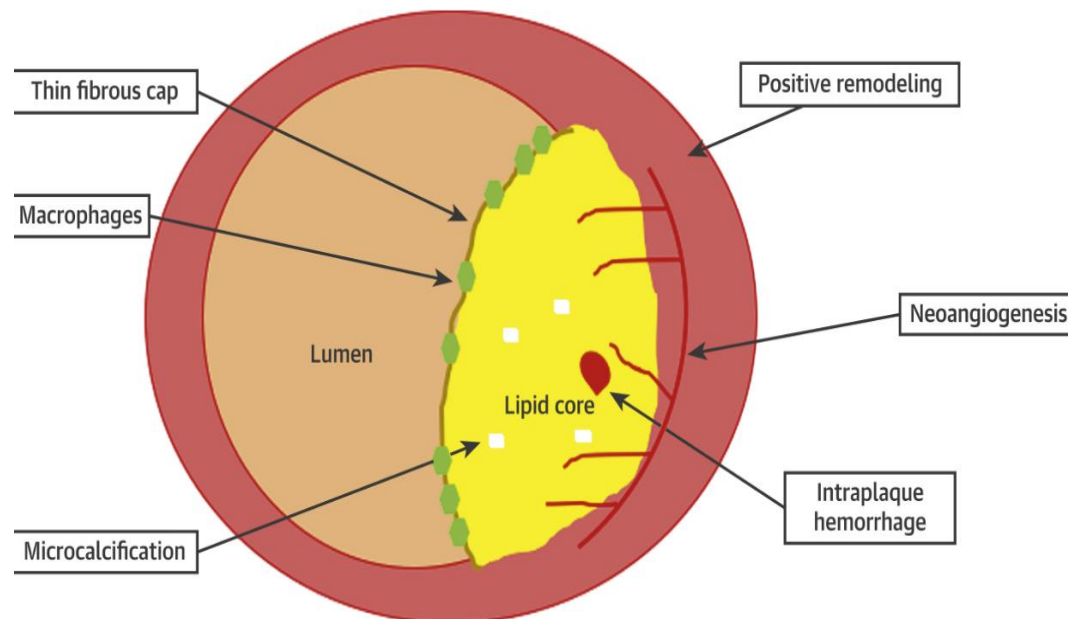


Figure 6 Lumen depiction with plaque anatomy (Daghem et al.,2020) ^[37]

Another important reason that has linked to plaque formation is the endothelial cell wall and blood patterns interaction [39]. The endothelium can act as a detector and converter of signals through the generation of biologically active compounds [31]. Changes in blood circulation can be captured by the endothelium [31]. Blood flow act as a force in the endothelium and can have an important role in activate and deactivate the expres-
 sion of genes that has an impact in plaque formation [31]. One of the forces that acts in the endothelia wall is the wall shear stress. Wall shear stress is a frictional force that derived by the blood flow patterns across the endothelial layer, and is vital for control-
 ling the expression of genes within the endothelium, fostering the development of ath-
 erosclerotic plaques by encouraging an atherogenic phenotype in the endothelial cells. Wall shear stress patterns ^{Figure 7} in the endothelium appear to promote or downregulate plaque formation [40]. Specifically, low wall shear stress in the endothelium seems to initiate plaque formation. On the other hand, there are indications that high shear stress with oscillatory movement, is responsible for plaque growth and rupture emphasizing the importance of the interaction between vascular wall biology and local hemodynamic forces in the progression of atherosclerosis [41]. Endothelial cell geometry can be also altered by the wall shear stress patterns. Multiple studies have found that their align-
 ment and shape is correlated with the direction of the shear stress patterns. In areas without turbulence, endothelial cells are presenting a flattened and elongated shape, in

contrast in areas with high and turbulent shear stress, that presents a more polygonal cell endothelial shape [42].

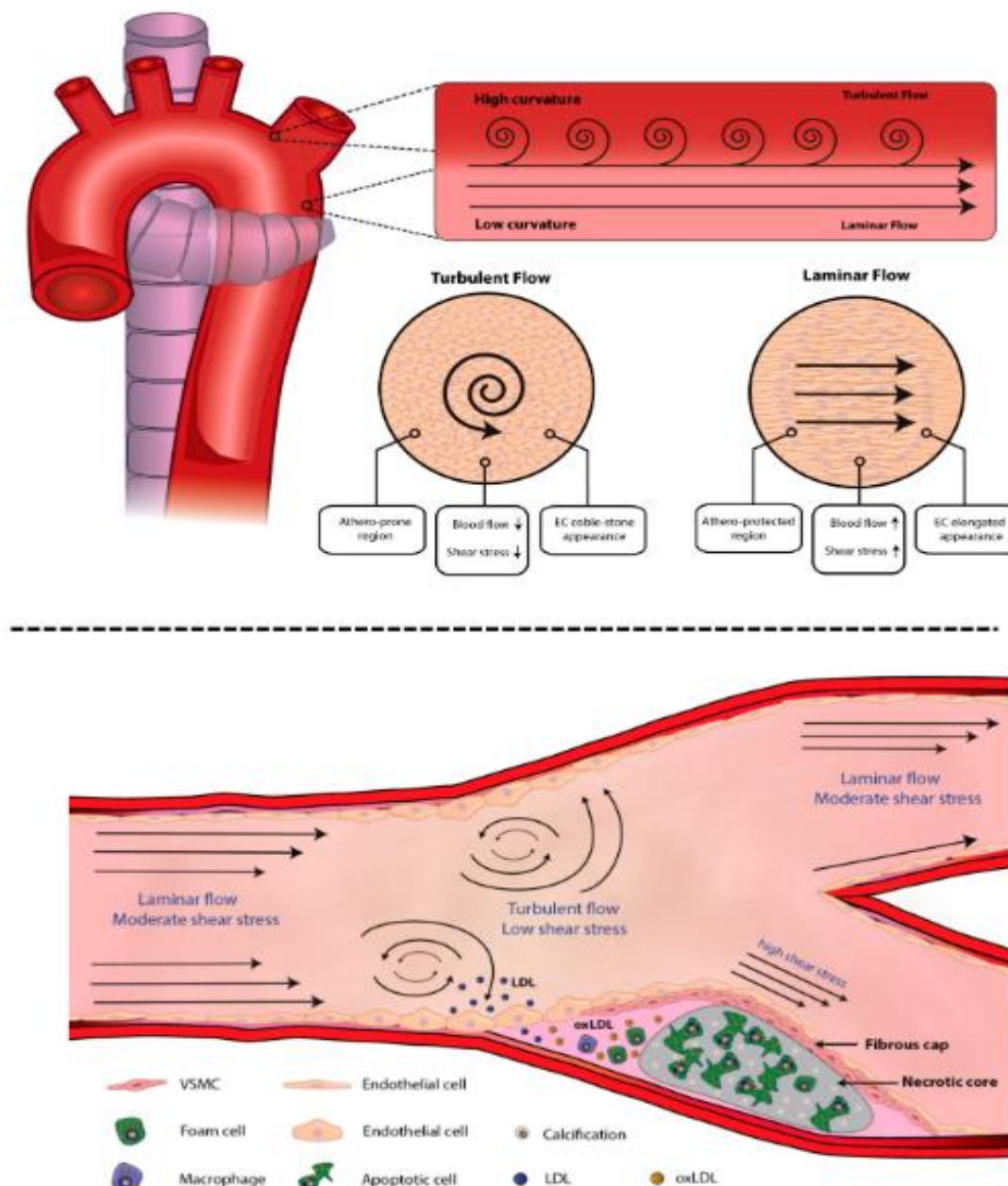


Figure 7 Impact of flow dynamics and wall shear stress (WSS) inside a vessel (Jebari-Benslaiman et al, 2022) [31]

In order to mitigate atherosclerosis successfully and to lower the risk of cardiovascular events like myocardial infarction, stroke or death, lifestyle modifications such as changes of nutrition, increasing physical activity, and completely discontinuing tobacco use [43], complemented by pharmacological treatments like statins to reduce cholesterol levels are essential. Emerging research on advanced imaging modalities and biomarkers aims to enhance the prediction of plaque vulnerability and cardiovascular

event risk, seeking to tailor prevention and treatment approaches for individuals at increased risk.

1.1.4 Arterial Revascularization

Significant blood flow restriction due to narrowing caused by atherosclerotic plaque typically occurs in the advanced stages of atherosclerotic disease. In the early stages of atherogenesis, atheromatic is not associated with malignant symptoms because of a mitigating mechanism known as arterial remodeling. Initially, the plaque tends to expand with outward direction, away from the lumen, causing an expand in the diameter of the vessels [44]. The growing atheroma does not limit the diameter of the arterial lumen until the plaque burden exceeds almost 40% of the original lumen [45]. Therefore, during the early atheromatic progression, the atheroma does not cause stenosis that limits tissue perfusion [46][47].

In patients with stenotic plaques but normal blood flow at rest, blood flow issues can happen after a stress test because the heart's backup mechanisms become exhausted under pressure. Any additional increase in oxygen demand can cause ischemia, as the compensatory mechanisms have already reached their limit [48]. Stress testing and pharmacologic stress tests, combined with myocardial blood flow scintigraphy (MBF) or assessment of myocardial perfusion with Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT), can effectively highlight myocardial ischemia in clinical practice [49][50]. The administered radiopharmaceutical visualizes the myocardium in proportion to its blood supply. During a stress test, myocardial blood flow increases in areas supplied by normal coronary arteries but not in areas supplied by vessels with stenosis [51]. Thus, the uptake of the radiopharmaceutical in ischemic areas is reduced compared to the uptake in areas with normal perfusion[49][48][52].

The evaluation of cardiac ischemia is essential for the diagnosis of CAD and for quantified its severity. Imaging techniques such as PET and SPECT offer two-fold information. Both the quantitative and qualitative indications for the myocardial perfusion, helping substantially the identification of areas at risk of ischemia under stress conditions [53]. These diagnostic procedures are essential for treatment decisions, including revascularization procedures like angioplasty or grafting, helping to restore the blood flow. Additionally, they play a crucial role in assessing risk and predicting outcomes in patients with coronary artery disease. This facilitates the customization of therapeutic approaches to each patient's specific needs, thus improving clinical results [54].

1.2 Imaging modalities of the coronary circulation

To explore the changes in the atherosclerotic plaque burden and enhance the detection of coronary artery disease, anatomical or functional imaging tests (invasive or non-invasive) are employed in everyday clinical practice [55].

1.2.1 Invasive assessment of the coronary circulation

Invasive Coronary Angiography (ICA) is considered as the golden standard technique [56] for identifying lesions within the coronary arteries ^{Figure 8}. It offers critical insights into the severity of arterial stenosis and facilitates the understanding of plaque composition[57], although, it faces challenges in presenting much detail for effectively quantification of stenosis severity and depiction of the atherosclerotic plaque's composition [58].

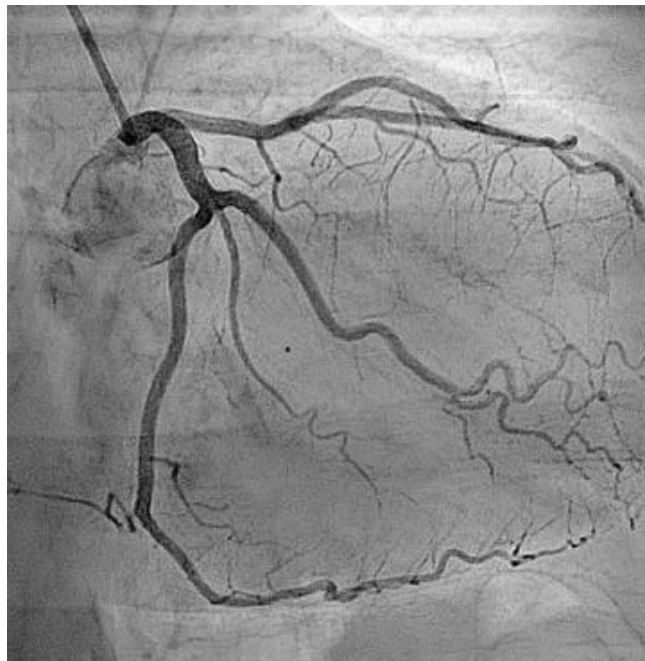


Figure 8 Example of invasive coronary angiography (ICA) (Kocka et al., 2015)[59]

To mitigate these drawbacks, new advanced invasive imaging techniques have been introduced. Most prominent are Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT) ^{Figure 9}. IVUS stands out for its ability to quantify the volumetric presence of atherosclerotic plaque and explain effectively its composition, thus enabling an exhaustive evaluation of plaque burden [60][61]. OCT distinguishes itself by delivering images with high resolution, offering great detail of the plaque's structural anatomy, although it cannot penetrate too deeply, affecting its capability to evaluate the vessel wall's deeper layers effectively [62].

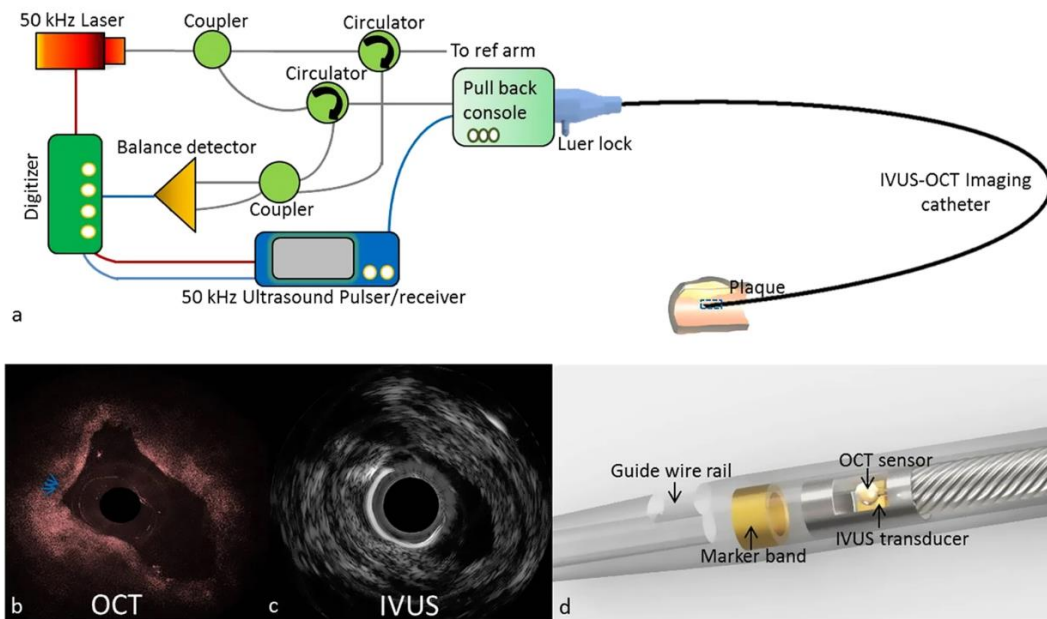


Figure 9 The diagram illustrates the IVUS-OCT imaging system (Li et al., 2015) [63]

1.2.2 Advances in Non-Invasive Cardiovascular Imaging

The domain of non-invasive imaging has also experienced a significant leap forward over the years, expanding the diagnostic capabilities for arterial and plaque characterization and evaluation. Computed Tomography (CT) has emerged as a decisive instrument in this field, helping the evaluation of the thoracic aorta's status, the degree of coronary artery calcification, plaque composition and stenosis severity [64]. Despite its sensitivity to motion artifacts due to cardiac movement, CT remains invaluable for specific diagnostic contexts. Positron Emission Tomography (PET), especially when integrated with CT (PET/CT) ^{Figure 10}, provides comprehensive anatomical, morphological, and biological information of the coronary tree.

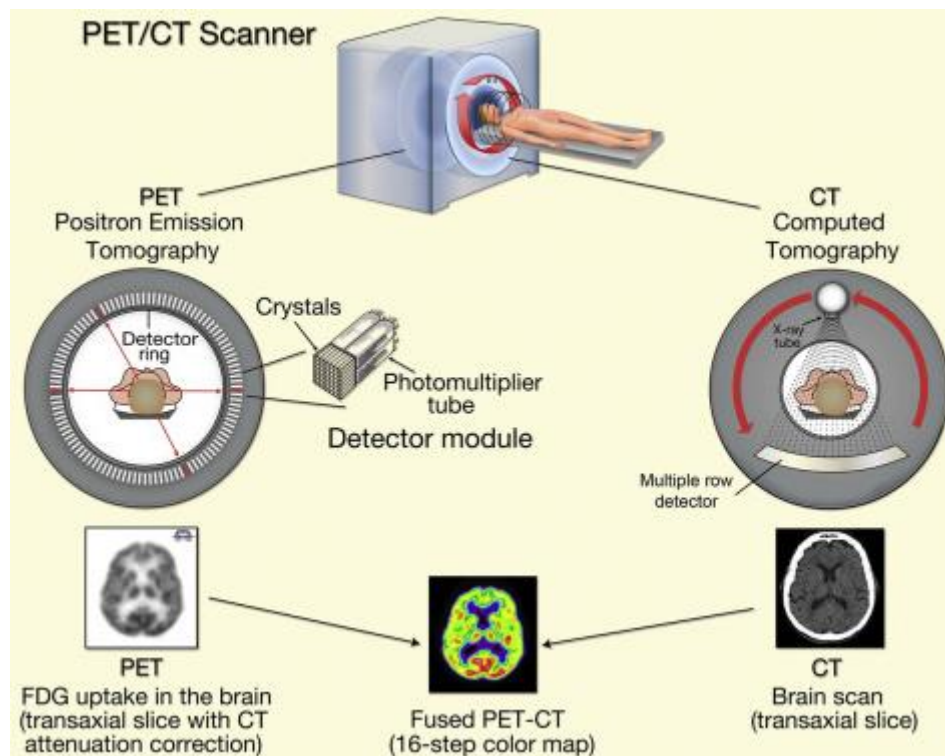


Figure 10 PET/CT scanner components (Lameka et al., 2016)[65]

The incorporation of Single Photon Emission Computed Tomography with CT (SPECT/CT) further facilitates the diagnostic insights of myocardial blood flow, plaque stability, and anatomical specificity, thus epitomizing a comprehensive approach to non-invasive coronary evaluation [66][67].

1.2.3 Functional Assessment of Coronary Arteries

The quantification of the coronary lesions is essential for guiding the treatment strategies, especially in noncritical settings. Fractional Flow Reserve (FFR) ^{Figure 11} has become the most used method for evaluating the hemodynamic significance of specific stenoses [68], using a ratio of pressures across lesions under induced hyperemia [69][70][71]. FFR is a highly valued metric in cardiology particularly in guiding decisions around the need for revascularization procedures like percutaneous coronary intervention (PCI). FFR compares the blood pressure before and after a stenosis under conditions of induced maximal blood flow (hyperemia)[68]. This comparison is presented as a ratio, where a value of 1 presents normal blood flow and values less than 0.75 typically signify a hemodynamically significant stenosis that may benefit from intervention [72][73].

FFR has the power to improve the diagnostic accuracy compared to ICA alone, which can sometimes overestimate or underestimate the severity of arterial stenosis. By directly measuring the physiological impact of a lesion, FFR can lead to more appropriate

patient selection for stenting, potentially avoiding unnecessary procedures in cases where stenosis does not significantly impair coronary blood flow.

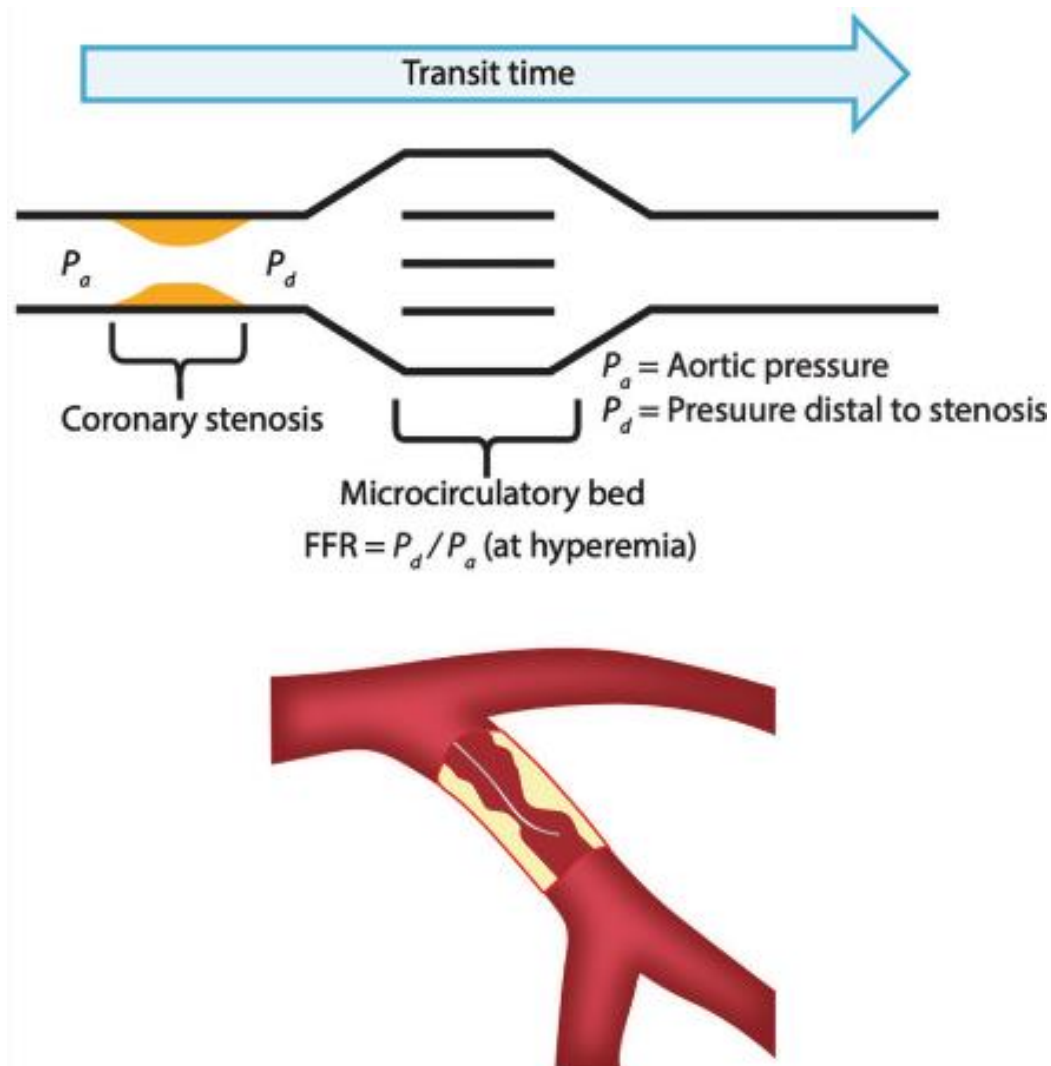


Figure 11 FFR calculation diagram (Jyotsna,2020)[74]

However, this technique is not without its downside. The necessity for prompting hyperemia to measure FFR can introduce patient discomfort and carry risks associated with the use of vasodilators. Also, the invasive nature of FFR, requiring a pressure wire and additional procedural time, might not be suitable for all patients. Alternative techniques like the instantaneous wave-free ratio (iFR) offer simplified assessments without the need for vasodilators, maintaining the diagnostic integrity while reduce some of FFR's challenges [75]. However, the necessity for a dedicated pressure wire remains a common weakness across these methods. The landscape of coronary imaging and functional assessment continues to evolve, driven by technological advancements and a deeper understanding of coronary artery disease pathophysiology. While invasive methods offer unparalleled detail, the trend towards non-invasive approaches reflects a

growing preference for patient safety and convenience. Integrating imaging results with functional assessments is fundamental in contemporary cardiovascular care. This approach aims to personalize interventions for each patient and enhance outcomes in the management of coronary artery disease [76].

1.3 Positron Emission Tomography (PET)

PET imaging stands as a foundation technique within the domain of Nuclear Medicine, presenting functional and molecular visualization through the use of radiopharmaceuticals enhanced with radioactive isotopes. It is a powerful technique that can map the distribution of radio-tracer molecules, as they undergo metabolic processes inside the body, making it a crucial technique for quantifying the metabolic activities. Positron Emission Tomography (PET) can capture and quantify the differences in blood flow, metabolism, tissue abnormalities, detect abnormal proteins, and quantitatively measure receptors and transporter proteins on cell membranes [77][78][79]. PET has evolved into a preferred imaging modality for diagnosing, staging, and monitoring various diseases, playing a substantial role in the personalized treatment of cancer and heart diseases, particularly for detecting inflammation in atherosclerotic disease due to its ability to measure biological and physiological processes in vivo, offering valuable data complementary to CT and MRI images.

1.3.1 Fundamental Principles of PET Imaging

PET imaging operates on two fundamental physical phenomena: positron emission and the annihilation of positron-electron pairs. Positron emission occurs when an unstable atomic nucleus, which has an imbalance of neutrons and protons, releases a positron. Annihilation happens when this positron encounters an electron, and they both are transformed into high-energy light particles called photons [80][81]. After the injection, the radiopharmaceutical goes through the bloodstream to the targeted area, concentrating in the tissue or organ under study. Detection relies on capturing two photons moving in opposite directions, recorded by detectors positioned diametrically across from one another. This detection method, known as annihilation coincidence detection (ACD), significantly increases the system's sensitivity compared to other tomographic techniques, like SPECT. However, it's noted that noise in the image may be present possible from scattered photons from unrelated annihilation events, with the path length of positrons and deviation from their 180-degree trajectory being key factors in imaging accuracy [80].

1.3.2 PET/CT Imaging

The PET/CT ^{Figure 12} is a high-tech, modern imaging method combining PET and CT scans in a single device, providing simultaneous functional and anatomical information [82]. CT measurements are utilized primarily for two reasons: to correct the produced PET data from scattered radiation that produces “noise” within the body and to enhance the accuracy of the final image through correct localization of CT and PET images. CT scans can provide high detailed images of anatomical structures, but they only show lesions clearly when the lesions are large enough or there is a massive difference compared to the surrounding tissues. On the other hand, PET can detect functional changes before any visible changes in the tissues. However, using sole the PET scan presents the difficulty to point the exact location of a lesion. Combining PET with CT solves this problem, making PET/CT a powerful tool in molecular imaging for studying processes inside the body.

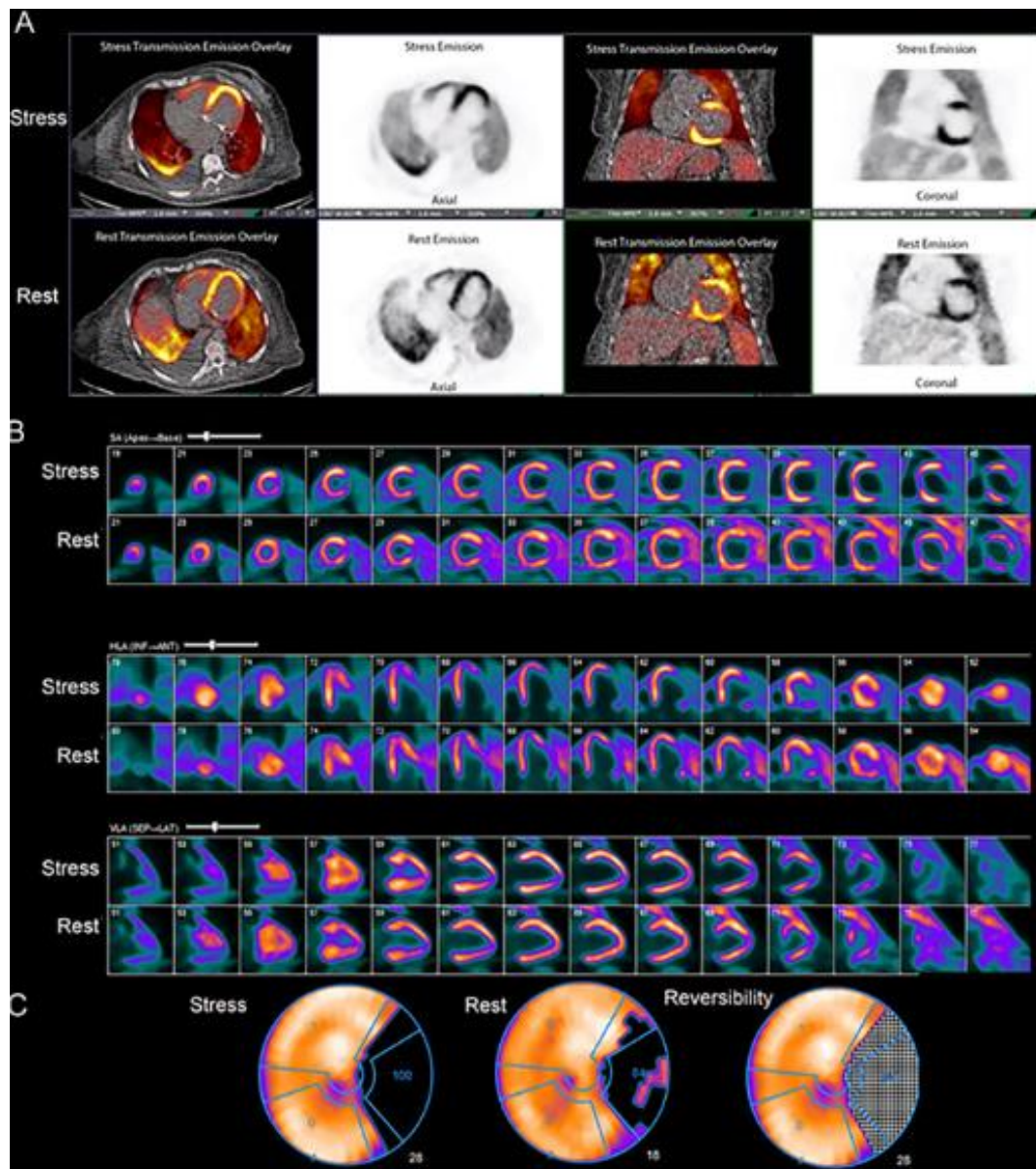


Figure 12 PET/CT Imaging at rest and stress (Singh et al.,2021)[83]

1.3.3 Positron-Emitting Radiopharmaceuticals in Cardiac Flow Studies

Several tracers are commonly used to assess myocardial blood flow, with the most widely used being Oxygen-15 labeled water ($^{15}\text{O-H}_2\text{O}$) Rubidium-82 (^{82}Rb) and Nitrogen-13 labeled ammonia ($^{13}\text{N-NH}_3$) [84][85][51]. Rubidium-82, a potassium analog, offers a brief half-life of 76 seconds but benefits from generation via a specialized commercially available generator, extending its utility for up to 4-5 weeks. This characteristic makes possible myocardial blood flow examinations in centers without a cyclotron. Once administered intravenously, ^{82}Rb is absorbed into myocardial cells by the Na^+/K^+ ATPase pump [86], though less efficiently compared to $^{13}\text{N-NH}_3$ or $^{15}\text{O-H}_2\text{O}$. $^{13}\text{N-NH}_3$ ammonia enters myocardial cells and is metabolically trapped, highlighting a significant disadvantage of requiring a cyclotron for production [87].

1.3.4 Imaging Protocols and Image Interpretation

The imaging process has two parts: one when the patient is at rest and another after a vasodilator is given. A CT scan is performed before and after the stress phase to adjust for any changes in radiation levels [88]. The total examination time for $^{13}\text{N-NH}_3$ is a bit longer, allowing for the administration of a lower activity at rest followed by a higher dose during stress, thus shortening the overall duration. Alternatively, the same activity can be administered for both rest and stress phases, with sufficient time in between to allow the background radiation to diminish before the second dose is given. A normal myocardial blood flow exam is characterized by uniform tracer uptake across the left ventricular walls, except possibly for the lateral wall in $^{13}\text{N-NH}_3$ studies, which may show lower uptake. Ischemia is identified by reversible deficits in blood flow, while infarctions are indicated by stable deficits. Right ventricular imaging suggests pulmonary hypertension, and transient dilation of the left ventricle is seen as a negative prognostic indicator. Lastly, blood flow shortage can be categorized into 3 ranks, mild, moderate and severe and can be semi quantified using scoring systems based on the American Heart Association's 17-segment model [89][14][90][91].

1.3.6 Quantification Techniques

PET imaging is the method of choice in clinical practice for quantifying myocardial blood flow (MBF) at rest and during stress ^{Figure 13}, as well as for assessing myocardial coronary flow reserve (MFR) [50], [92] [93][94]. This is possible because PET scans are highly sensitive and have excellent temporal resolution, allowing for dynamic imaging of how radiopharmaceuticals move within the body [95]. $^{15}\text{O-H}_2\text{O}$ is one of the most preferred tracer for quantification, freely diffusing across membranes and showing a linear correlation between uptake and flow rates at high blood flow levels [96]. However, other radiopharmaceuticals used in PET also provide satisfactory quantification results.

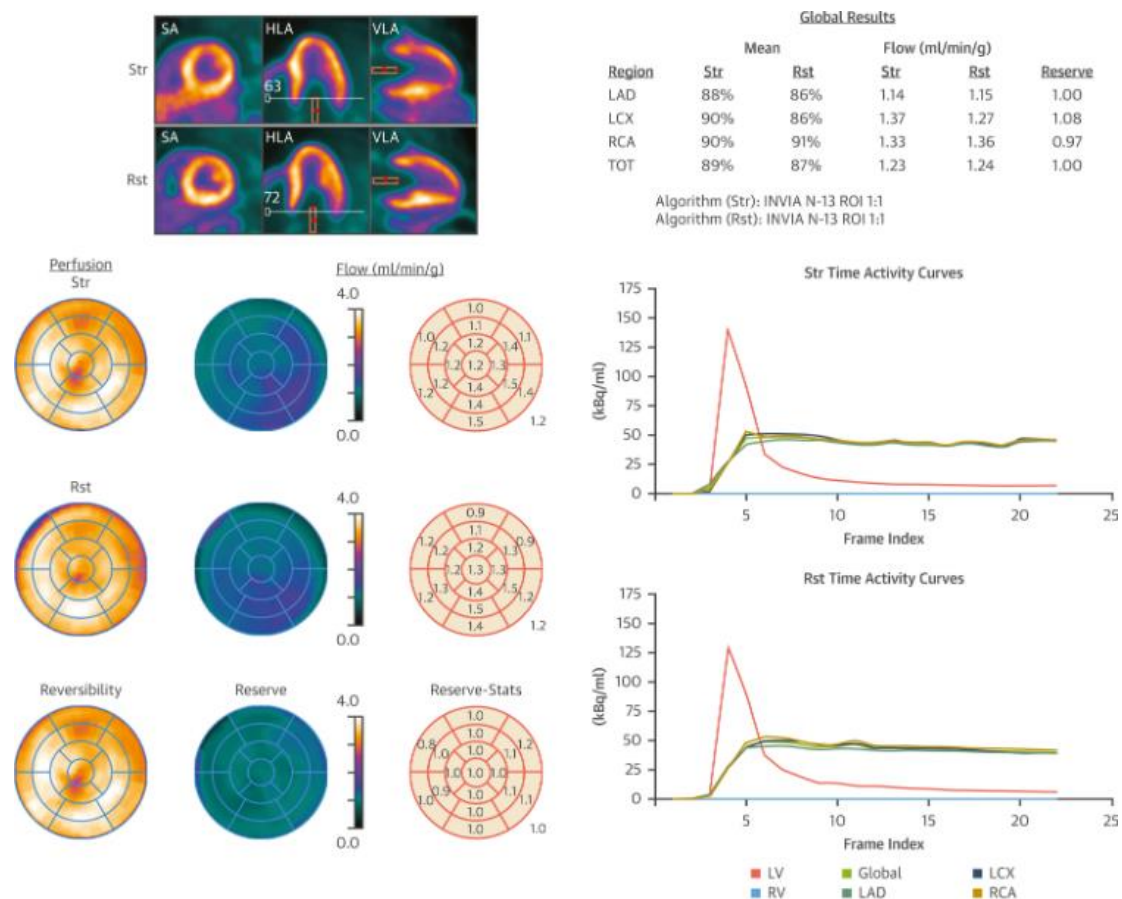


Figure 13 The scan showed normal blood flow at rest but revealed a significant decrease in global hyperemic myocardial blood flow and myocardial flow reserve. These results indicate severe dysfunction in the coronary microvasculature (Schindler et al., 2023) [97]

1.3.7 ^{18}F -Fluorodeoxyglucose (^{18}F -FDG) as a Tracer

^{18}F -FDG, a type of glucose with a fluorine atom, has become one of the most commonly used tracers. It highlights metabolic activity, shows increased glucose absorption in cancer cells, helps assess glucose metabolism in different tissues [98][99]. As the first approved tracer for imaging atherosclerotic plaques, ^{18}F -FDG can exhibit focal mild or no uptake in atherosclerotic lesions, with histological analysis revealing that accumulation in atherosclerotic areas highly correlates with macrophage infiltration levels[100]. The higher the ^{18}F -FDG uptake, indicates a higher chance of underlying plaque severity [101].

1.3.8 Quantifying ^{18}F -FDG Uptake (SUVs, TBR)

The widespread application of ^{18}F -FDG PET imaging for therapeutic and diagnostic purposes has made important task the effective quantification of results. The main technique for that is calculating standardized uptake values (SUVs) which relate the detected activity in the area of interest to the administered dose and the weight of the

patient's body [102] ^{Figure 14.} Another semi-quantitative measure is the target to background ratio (TBR), which compares SUVs of the artery to that of a corresponding vein [103][104][105]. These measurements, despite their effectiveness, are influenced by various factors such as radiopharmaceutical circulation time, attenuation and scatter correction, body movement and measurement methods. Nonetheless, they have proven to be quite stable with high repeatability in detecting vascular inflammation, and in cross variation observation analysis.

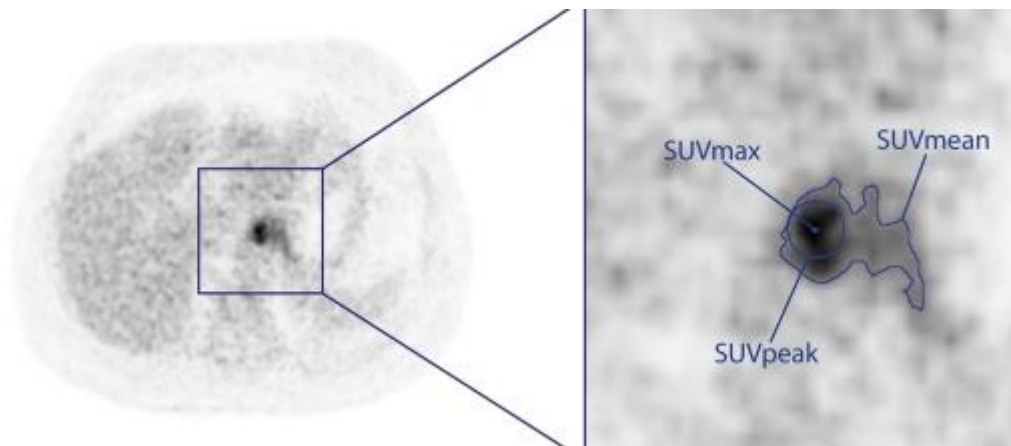


Figure 14 Example of SUV calculation in Region of interest in a PET study (Brendle et al.,2015) [106]

1.4 Single-Photon Emission Computed Tomography (SPECT)

Single-Photon Emission Computed Tomography (SPECT), introduced in the 1960s, is now a fundamental imaging technique in nuclear medicine worldwide. Its capability to provide functional insights into physiological processes makes it highly useful across various fields, including cardiology, neurology, and oncology [107].

1.4.1 Basic Principles of SPECT Imaging

SPECT imaging works by detecting gamma photons emitted from radiotracers introduced into the patient's body. In contrast to PET, which detects pairs of photons from positron annihilation, SPECT captures single gamma photons emitted directly by radionuclides such as Technetium-99m and Iodine-123 [108]. A gamma camera with collimators rotates around the patient, collecting multiple two-dimensional images from different angles [109]. These images are then reconstructed into a three-dimensional map of radiotracer distribution using computational techniques like filtered back projection or iterative reconstruction [110]. While collimators are essential for spatial resolution, they also limit the number of photons reaching the detector, which reduces sensitivity [111].

1.4.2 SPECT/CT Hybrid Imaging

SPECT/CT combines effectively the functional imaging capabilities of SPECT with the anatomical detail of CT. This combination enables the acquisition of precise anatomical information combined with functional data, enhancing the overall diagnostic accuracy of the imaging process. The CT component delivers high-resolution images of body structures and assists in attenuation correction of SPECT data, which enhances image quality and quantitative accuracy [112]. Attenuation correction accounts for gamma photons that are absorbed or scattered within the body, which could otherwise result in image artifacts and misinterpretations [113].

1.4.3 Radiopharmaceuticals for SPECT-MPI

A range of radiopharmaceuticals is selected in SPECT-MPI, chosen based on their physical properties and clinical applications[114]. As we already said, the most commonly used radionuclide is Technetium-99m because of its favorable characteristics, such as a 6-hour half-life and suitable gamma emission energy for detection by gamma cameras [115]. Thallium-201 was historically used in cardiac imaging but has largely been replaced by Technetium-99m agents due to their superior image quality and reduced radiation dose [116]. Other tracers include Iodine-123 for thyroid and neuroendocrine tumor imaging, and Indium-111 for labeling white blood cells in infection imaging [117].

1.4.4 Assessment of Myocardial Perfusion by SPECT

Myocardial perfusion imaging (MPI) with SPECT is a method for evaluating coronary artery disease (CAD) by utilizing heart images both at rest and hyperemia, following pharmacological agents like adenosine or by common exercise. Clinician doctor can identify segments of the heart with reduced blood flow [118]. These images help detect ischemic regions (reversible perfusion defects) and infarctions (irreversible defects), as well as assess left ventricular function [119].

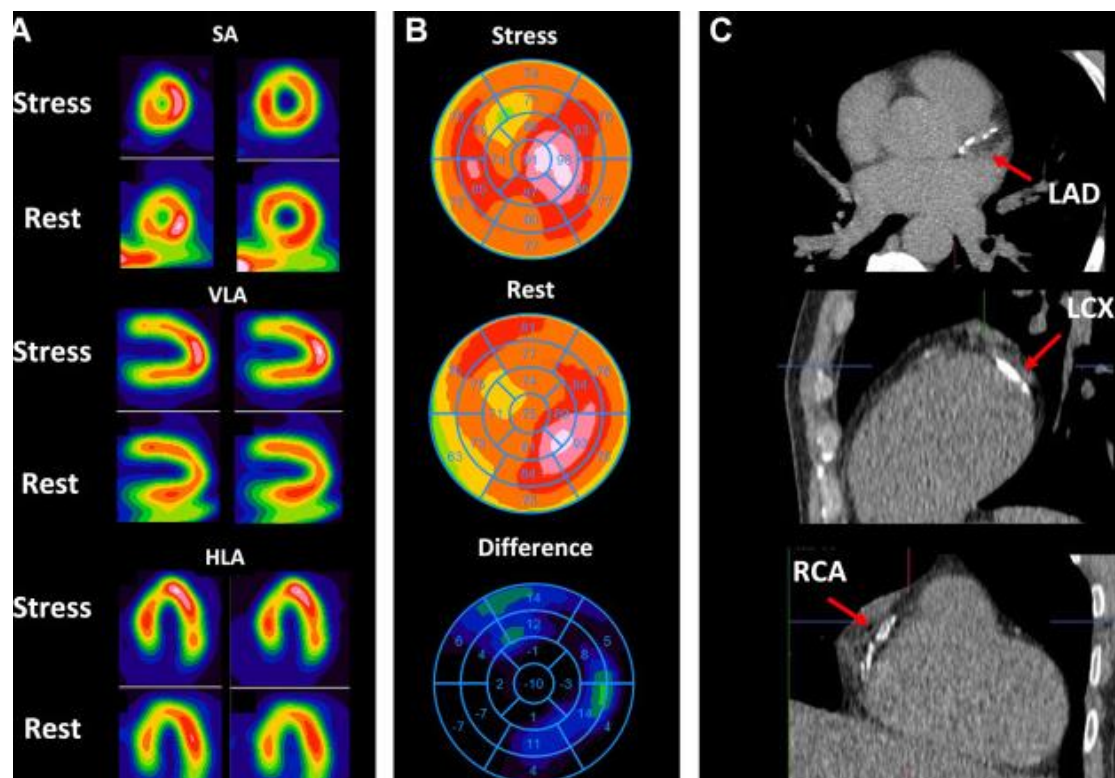
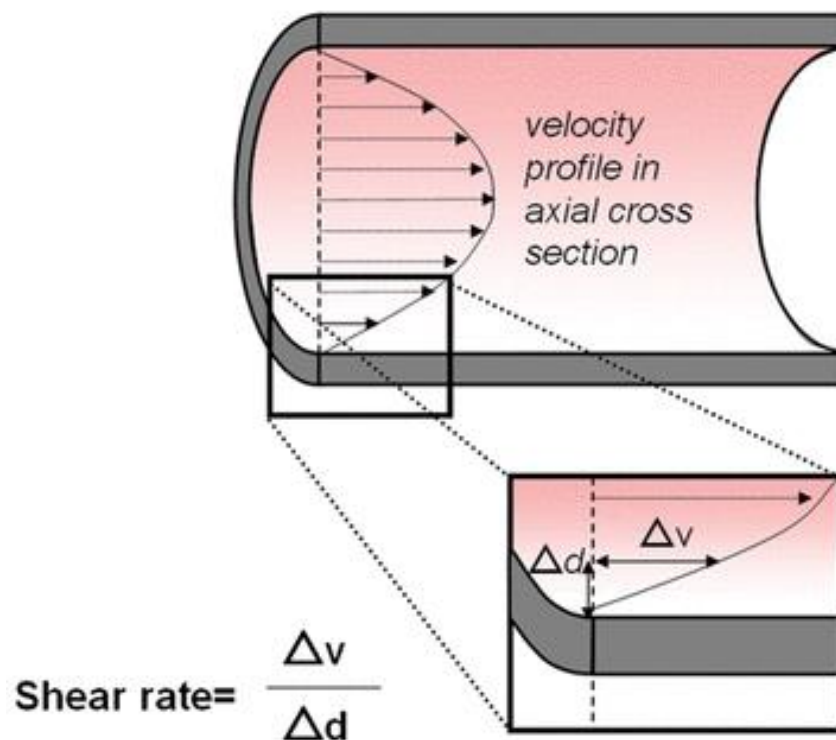


Figure 15 SPECT/CT depiction of a patient with a heavily calcified LAD coronary artery on low-dose 99m-tetrofosmin stress MPI (Ruddy et al., 2023)[120]

1.5 CCTA derived Endothelial Shear Stress (ESS)

Endothelial shear stress presented as the sideways force that flowing blood applies to the endothelium and accumulated in the inner area of arterial walls [121] ^{Figure 16}. This

force is measured as force per unit area most notably in Pascals (Pa).



Endothelial Shear Stress (ESS)= Shear rate * viscosity

Figure 16 Endothelial shear stress (ESS) generated by blood flow is calculated by multiplying the velocity gradient at the vessel wall, also known as the shear rate, by the blood's viscosity (Wentzel et al., 2012) [122]

Blood flow patterns are having a crucial role in the ESS patterns and eventually his impact on the endothelium. Blood flow can appear as undisturbed laminar flow, characterized by smooth and orderly movement along parallel lines, or as disturbed laminar flow, where this smooth pattern is affected [123]. Disturbed laminar flow is marked by regions where flow reversal occurs, leading to a non-uniform motion that disrupts the streamlined nature of blood movement. Such disturbances in laminar flow are particularly significant as they promote the initiation and progression of atheroma by affecting the endothelial cell regulation and subsequently endothelial shear stress [124] [125]. Endothelial cells respond to shear stress and regulate its magnitude through a feedback mechanism by adjusting arterial dimensions according to blood flow. However, in areas where arterial geometry changes, such as at bifurcations, this control of shear stress is altered to maintain levels close to zero ^{Figure 18}. Endothelial shear stress (ESS) is a dynamic variable influenced by both plaque formation or geometry in general and vascular remodeling. Endothelial Shear Stress (ESS) is characterized by variations in both direction and magnitude, spanning a spectrum from low, physiological, moderate and

high [123]. The severity of systemic risk factors [123], such as hypercholesterolemia, significantly influences the local hemodynamic conditions. Additionally, the progression of atherosclerosis, the vascular wall's remodeling response to plaque buildup, and regional variations in structure and stiffness are crucial in determining the local ESS conditions. These factors together influence the progression and individual outcomes of atherosclerotic lesions [126][127].

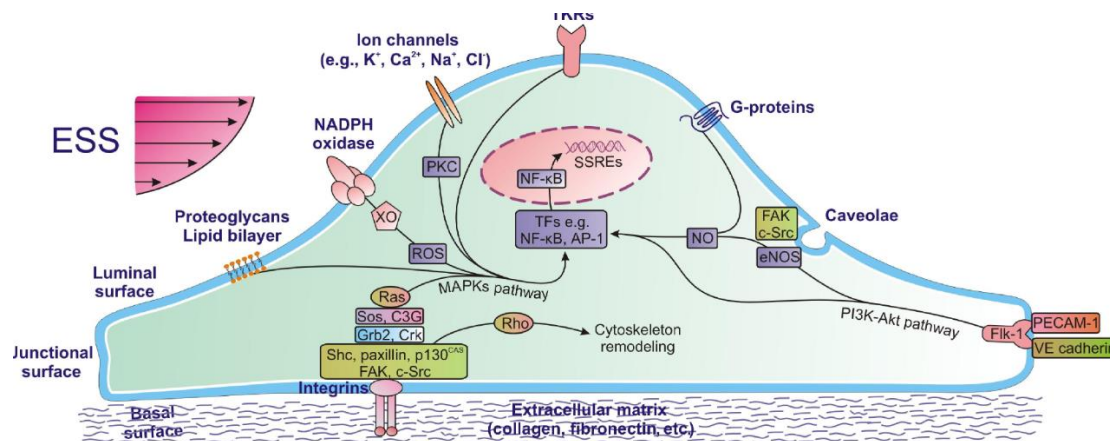


Figure 17 Local endothelial shear stress (ESS) is detected by various mechanoreceptors in endothelial cells, including ion channels, G-proteins, TKRs, NADPH oxidase, and the plasma membrane's lipid bilayer. These ESS signals are transmitted through the cytoskeleton, activating integrins and mechanosensory complexes like PECAM-1 and Flk-1. This activation triggers a signaling cascade involving non-receptor tyrosine kinases, Ras GTPase, and MAPKs function. (Chatzizisis et al, 2007) [45]

Low shear stress, enhances endothelial dysfunction and the formation of eccentric plaques. Conversely, normal to high shear stress tends to protect against atherosclerosis. Initially, the narrowing of the arterial lumen is counteracted by outward remodeling of the vessel [128]. However, maintaining a normal lumen size preserves low shear stress conditions locally, worsening the growth of eccentric plaques. As these plaques expand, they experience increased tensile stress at their base, increasing their possibility of fracturing and leading to thrombosis. This expansion can eventually cover healthy areas of the arterial wall, disrupting the shear-stress-regulated preservation of the lumen and leading to higher shear stress. This increase in shear stress may then accelerate the transformation of the plaque into a rupture-prone vulnerable plaque [129][130] ^{Figure 17}. In experiments with cultured endothelial cells, a shear stress of 0 ± 0.5 Pascal (Pa) is typically employed to replicate conditions conducive to atherosclerosis, while a range of 1.2 to 1.5 Pa is considered normal or high arterial shear stress. This hypothesis is supported by replicating conditions in vivo, where a low, oscillatory shear stress of approximately 0.05 ± 0.5 Pa has been observed in areas of the internal carotid artery

susceptible to disease, and an average wall shear stress of around 1.4 Pa has been recorded in healthy human coronary arteries. In arteries with atherosclerosis, shear stress varies depending on changes in arterial geometry and can rise above 7 Pa at plaque narrowing. For experimental purposes, a shear stress of 7.5 Pa is often applied in vitro to simulate these elevated conditions. [131][132][133][134].

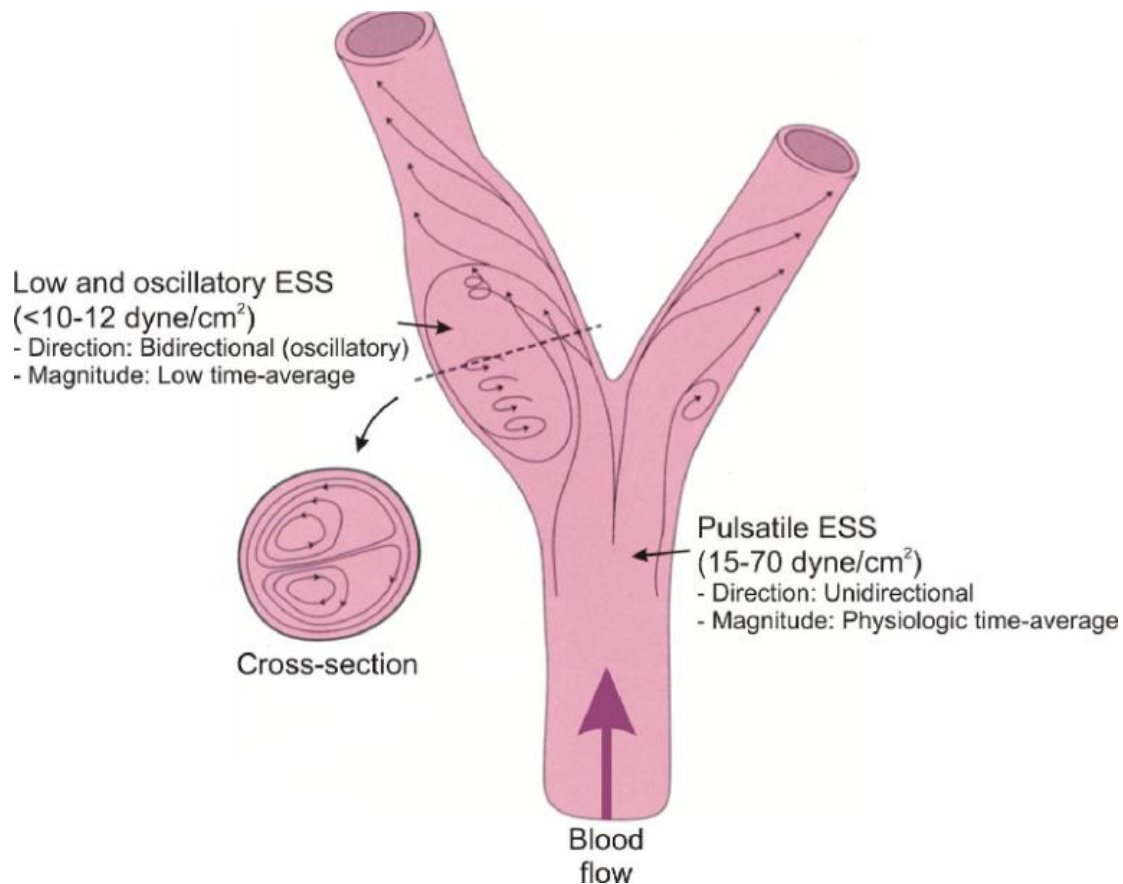


Figure 18 Example of Pulsatile, Low, and Oscillatory flow leading to different types of ESS inside a vessel
(Chatzizisis et al, 2007) [45]

Endothelial shear stress in human coronary arteries can be evaluated using computational fluid dynamics (CFD). This method uses three-dimensional arterial models combined with patient-specific blood flow data [123]. The foundational work by Zarins et al. explored how computational techniques, particularly those integrating CCTA data, could be employed to assess the relationship of plaque position with different fluid dynamics parameters and endothelial stress in carotid bifurcations [22][133]. Using CCTA, the study managed to find that different variations in shear stress are related with the specific locations of plaque accumulation [133]. Expanding on this, the research by Ku et al. (1985), examined the impact of pulsatile flow and shear stress on atherosclerosis development within the human carotid bifurcation, utilizing CCTA for enhanced visualization of the vascular structure. This study underscored the importance

of CCTA in identifying regions of low and oscillating shear stress that are susceptible to initiate atherosclerosis, thereby highlighting CCTA's role in predicting atherosclerotic risk [134].

Schultz et al. used CCTA to measure ESS in normal coronary arteries. Their goal was to investigate how different biological affect ESS values [135]. Analyzing CCTA images from 168 patients, the study found that ESS report the highest values in the left anterior descending artery and varied with lumen diameter, also showing elevated values in smaller segments. The results highlighted a strong correlation between ESS and the position of segments to the coronary ostium, particularly in the left anterior descending artery.

Lastly, Wentzel et al. (2003) used CCTA to explore how the wall thickness of a vessel, increased with atherosclerosis can be extended into endothelium areas that present high shear stress can affect the vascular remodeling. Through CCTA, the study effectively mapped the regions of altered shear stress and their relation to atherosclerotic progression [132].

1.6 CCTA derived computational FFR assessment

The integration of Computational Fluid Dynamics (CFD) with three-dimensional arterial models derived from CCTA is increasingly popular for assessing Fractional Flow Reserve (FFR) [125] ^{Figure 19}. This method employs lumped parameter models to estimate variables such as cardiac output, coronary microcirculatory resistance, and systemic circulation pressure. These elements are integrated into the artery flow dynamics to compute FFR values within a time frame of 1 to 4 hours. Several pivotal studies have support the effectiveness of computational FFR against directly measured FFR, showing promising results and its utility as a clinical tool [136][137][138]. PLATFORM study compared the outcomes of CCTA-guided FFR strategies against conventional care in individuals suspected of coronary artery disease (CAD), shedding light on the practical uses of FFR-CT [139]. However, the accuracy of FFR-CT can be compromised by CCTA's limited spatial resolution, which affects the assessment of lumen stenosis severity. A meta-analysis highlighted that combining CCTA with fractional flow reserve derived from computed tomography (FFR-CT) can reduce the frequency of false positive diagnoses by creating an ensemble scheme where both tests must confirm the presence of pathology [140]. Moreover, factors such as heavy calcifications,

arrhythmias, and tachycardia also impact the precision of both CCTA and FFR-CT results [141].

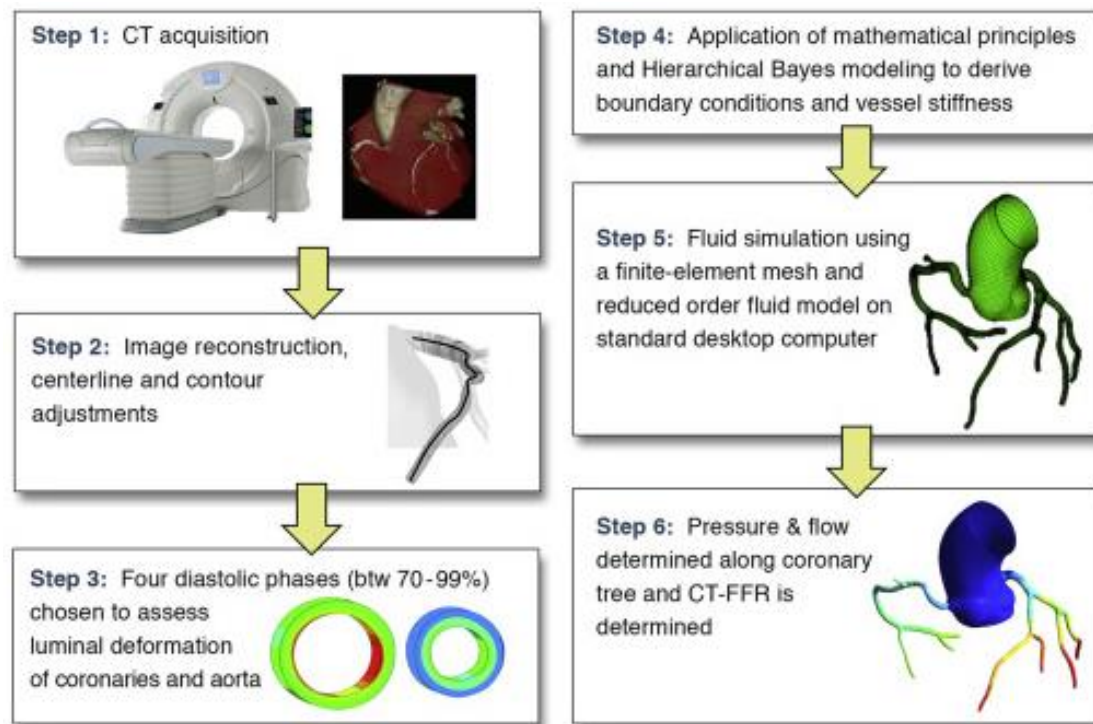


Figure 19 The CT-FFR method starts by creating a detailed model of the coronary artery shape from coronary CTA images (Steps 1 and 2). Using the changes seen in the arteries and aorta during diastole, boundary conditions are set with hierarchical Bayesian modeling (Steps 3 and 4). Then, fluid dynamics simulations are run on a regular computer to measure pressure, blood flow, and CT-FFR along the coronary arteries (Steps 5 and 6) [142]

The adoption of the virtual functional assessment index (vFAI), also known as Smart-FFR, has already been suggested as a viable alternative for FFR evaluations during invasive coronary angiography (ICA) [143][144][145][146].

This method employs three-dimensional (3D) coronary models alongside the assumption of steady-flow computational fluid dynamics (CFD) [147] to calculate the pressure of the lesion (P_{dist}/P_{prox}). The ratios are computed for flow rates ranging from 0-4 ml/s and are normalized against a reference value derived from a normal artery. This approach provides a quantitative assessment of the hemodynamic significance of coronary artery disease (CAD) and matches the mean of the calculated pressure ratios across the specified flow range ^{Figure 20}. The vFAI – SmartFFR demonstrated greater efficacy than 3D quantitative coronary angiography (QCA) in determining the physiological relevance of lesions [145]. Moreover, it showed high accuracy (88%), sensitivity (90%), and specificity (86%) in predicting FFR values ≤ 0.80 . Further smaller-scale investigations employing intravascular imaging or invasive angiography have reinforced

the capability of virtual hemodynamic assessments to accurately assess coronary stenoses. These studies have demonstrated a robust correlation and consistency, evaluating the predictive power of these methodologies [143].

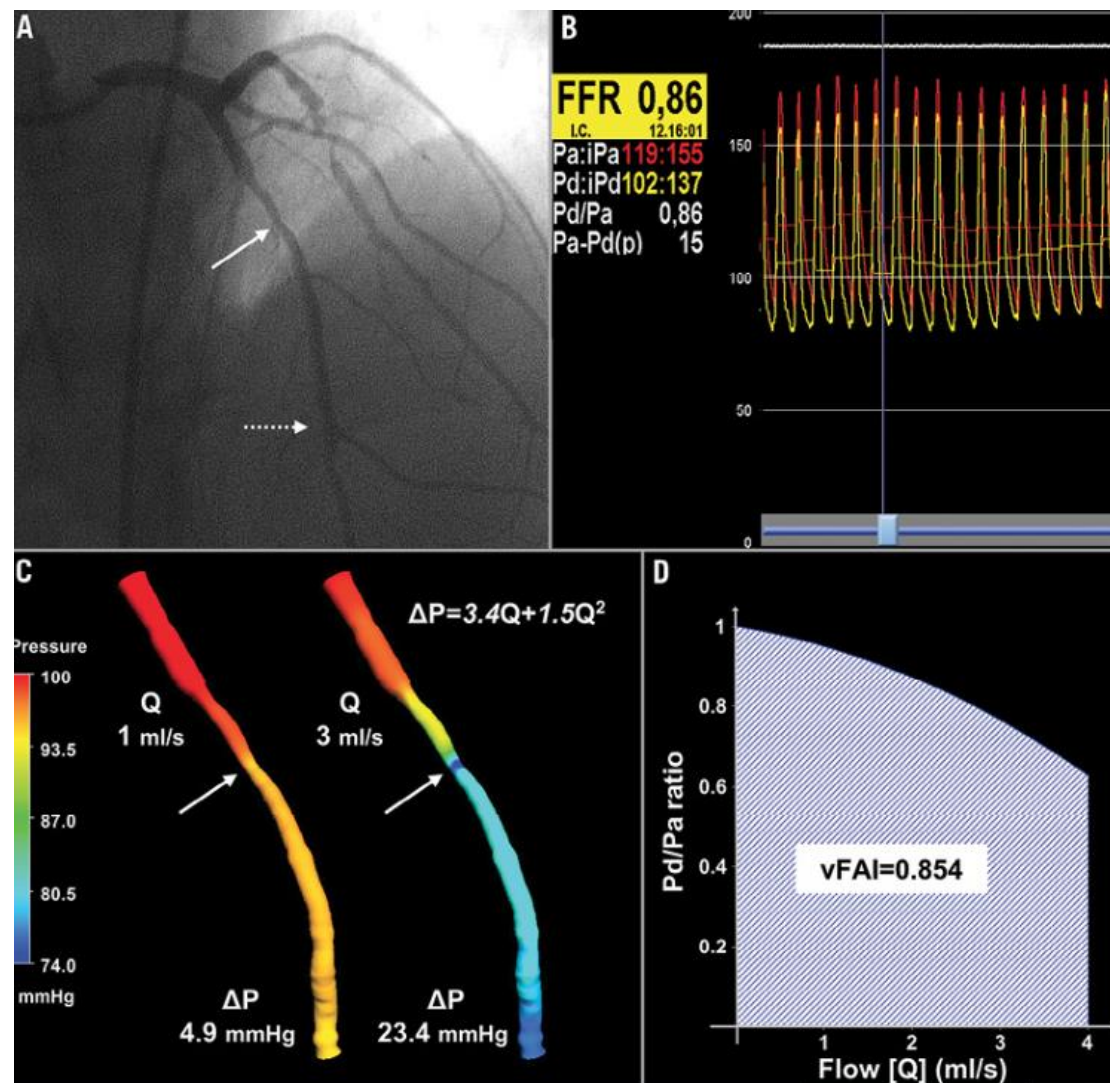


Figure 20 A moderate LAD lesion (51% stenosis by 3D-QCA) showed a high FFR (0.86) measured distally using a pressure wire, indicating no significant hemodynamic impact. The vFAI (0.85) correlated well with FFR, further confirming the assessment (Papafaklis et al., 2014)[146]

1.7 Fluid dynamics modeling

Research in the dynamics of blood flow has been an increasingly expanding field of study, with numerous reports focusing on its various aspects. The finite element method is a preferred computational tool for modeling arterial blood flow. Early studies made the assumption to model blood as an incompressible, laminar flow derived Newtonian fluid, using very simple modes of arteries emulate them as cylindrical 3D shape models. These studies involve solving the three-dimensional transient Navier-Stokes equations.

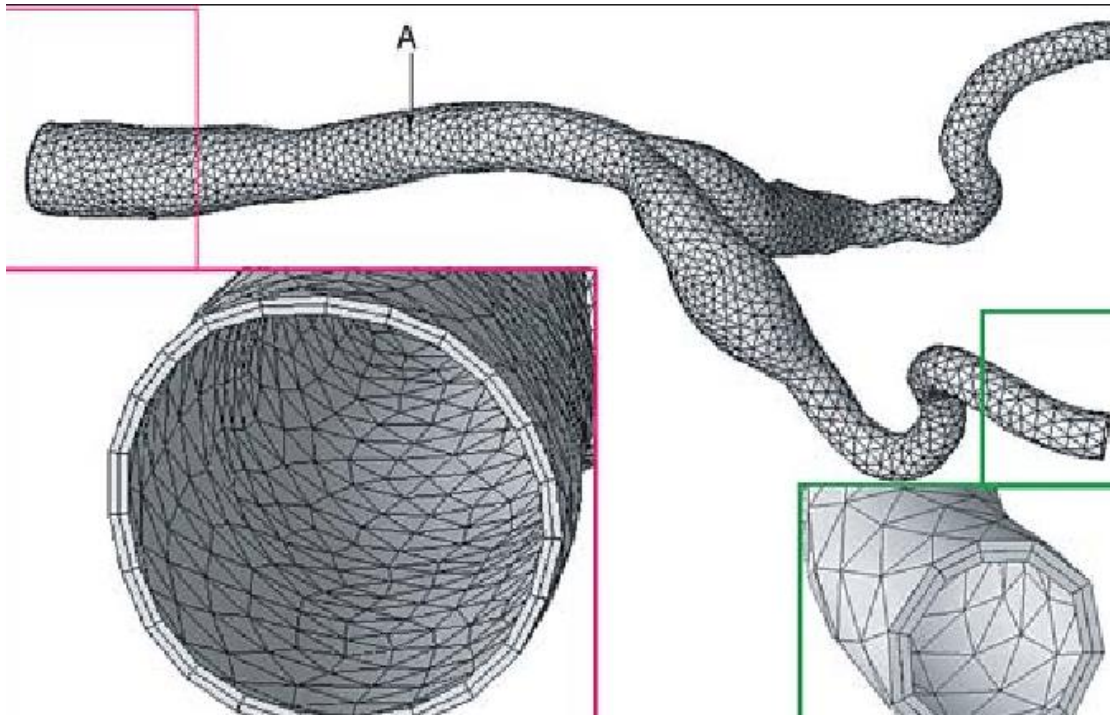


Figure 21 Mesh of a coronary artery bifurcation (Luo et al.) [148]

In one study, fluid dynamics derived blood modeling of aorta and a graft-artery anastomosis was simulated using finite element methods [149]. Similarly, additional studies used the finite element methods to analyze the hemodynamic effects of coronary stenosis, comparing pressure drop calculations from experimental and computational simulations to assess the significance of stenosis in clinical settings [150][151]. Additionally, multiple other studies have modeled pulsatile blood flow in an idealized aorta, adjusting the model for hypotension and hypertension scenarios, assuming a rigid aortic wall to simplify the analysis [152][153][154]. Modern advancements in medical imaging have facilitated the generation of highly detailed, individualized three-dimensional representations of coronary vessels ^{Figure 22}.

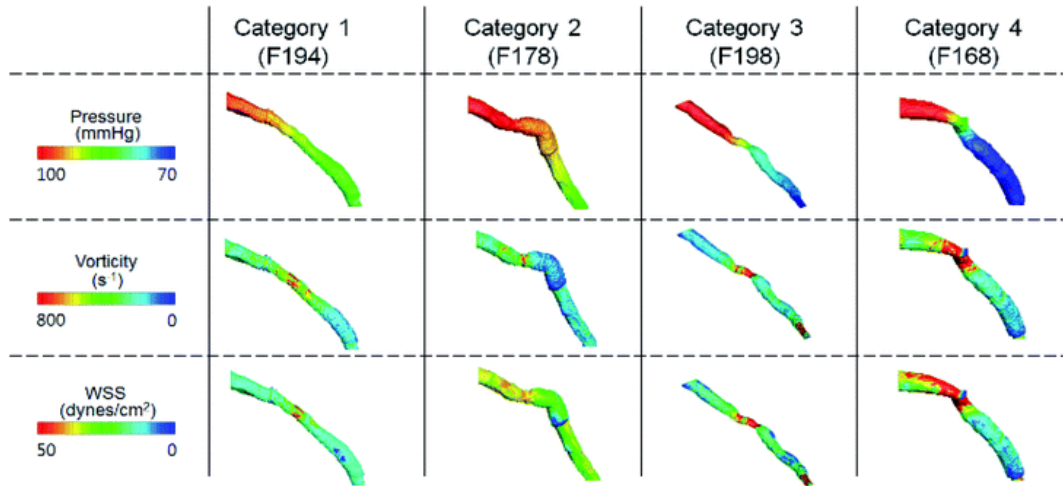


Figure 22 Different fluid dynamics parameters on a coronary artery (Woo Kim et al.,2020) [155]

1.8 Texture Analysis – Radiomics

Texture analysis is a computer vision and pattern recognition utilized method and has been proven especially useful for studying biological images[156]. It helps recognize patterns that may indicate differentiations between normal and diseased states. This technique is especially useful for detecting and classifying cancers, diagnosing autoimmune diseases, studying how the body functions, and measuring substances in PET scans. With the growing complexity of medical needs, there's been more research into developing texture analysis systems for biological images, particularly in radiology, using tools like CT and MRIs. Through texture analysis, features called radiomics are extracted from medical images potentially revealing important differentiative information that we can't see with our naked eyes ^{Figure 23}. The base of texture analysis lies in how tiny units called pixels, if we are analyzing 2D images or voxels for 3D images, are arranged in a specific area of interest in the scans. For PET scans, texture analysis

helps measure how a drug spreads in the body and provides information about tissue differences.

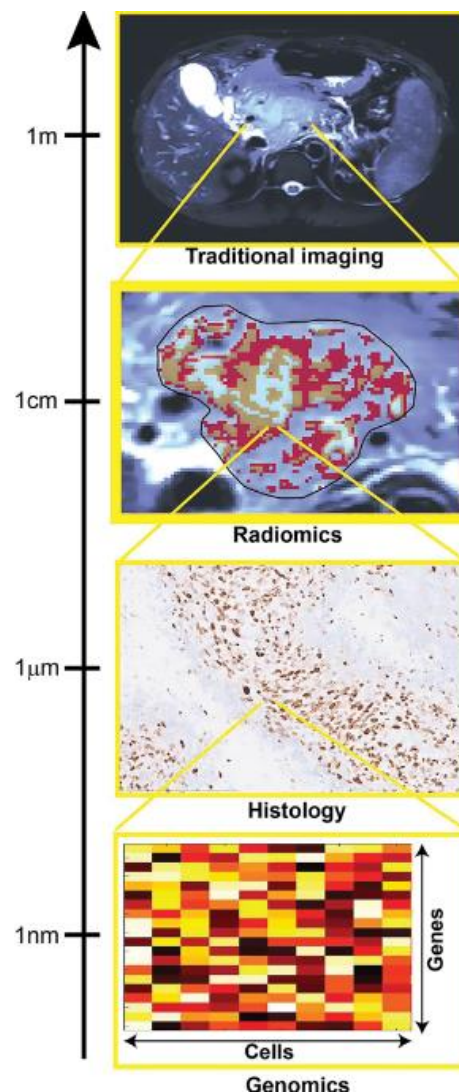


Figure 23 The image illustrates how multiscale quantification offers additional insights into tumors. Detailed histological and genomic analyses provide small-scale information that helps validate radiomic findings (Tomaszewski et al,2021) [157]

This can be crucial for understanding how treatments work in cancer patients and predicting outcomes. While there are promising results, some studies show that there are limits to what texture analysis can tell us. For example, previous studies have been using texture analysis to analyze the possibility of infections in artery grafts [158], but similar studies have not been done extensively on artery plaque derived radiomics from CCTA.

1.8.1 Image Preprocessing

For texture features to be reliable and consistent, the images go through several preparation steps. One of the first steps is adjusting the image so that all the voxels are evenly spaced, which makes it easier to compare images from different sources. The image can

either have details added (which might add noise) or have details reduced (which can lose information). Making sure the image's intensity is measured correctly is key for extracting useful features. Typically, intensity is categorized into fixed groups or bins, which helps in comparing different patients' images. This step is particularly useful in methods like PET. How the image is categorized greatly impacts the features that can be drawn from it, affecting the reliability of those features. Normalizing the image's intensity also helps ensure results are comparable across different machines and testing protocols. Other common steps include smoothing the image to reduce noise and sampling the image.

1.8.2 Potential Biomarkers from Textural Features

Textural features ^{Figure 25} are grouped into two main categories:

First-Order Statistics (Histogram-Based Features):

First-order statistics are presenting the voxel intensity distribution without taking into account the relationship between the pixels within the region of interest (ROI).

- **Mean Intensity:** The average value of voxels intensity within the ROI.
- **Variance:** Measures the dispersion of intensity values.
- **Skewness:** Indicates the asymmetry of the intensity distribution.
- **Kurtosis:** Reflects how “sharp” or “elongated” is the distribution.
- **Entropy:** Represents the randomness or complexity of the intensity distribution.
- **Median, Mode, Minimum, Maximum:** Basic statistical measures of intensity values.

Second-Order Statistics (Textural Features):

Second-Order Statistics include methods that analyze the spatial relationship between pairs of pixels or voxels, capturing how gray levels co-occur within a certain spatial configuration. The power of radiomics comes in hand from the features that can derive from these matrices.

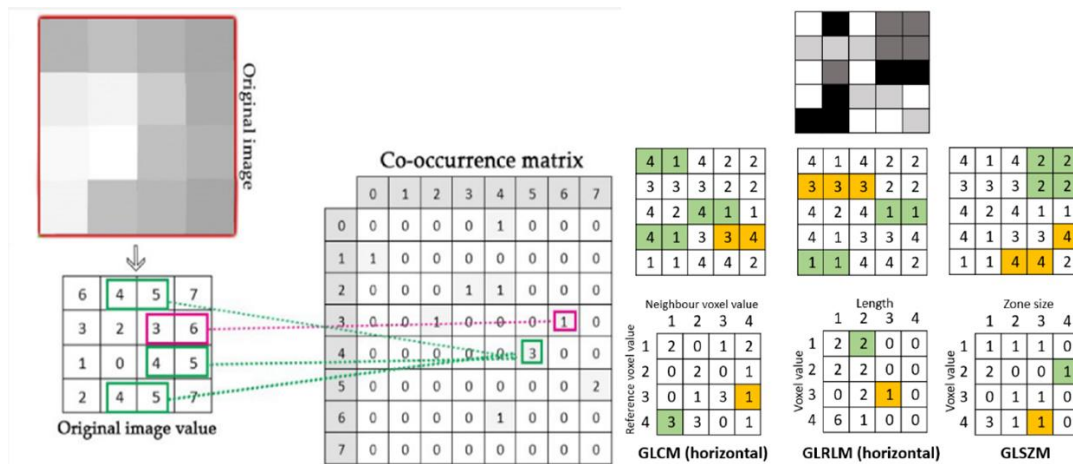


Figure 24 Left) Depiction of a Co-Occurrence matrix based on a ROI; Right) Examples of different Gray Level matrices. Matrices like that can be created assessing different rules for modeling the pixel's relationships (Hajeb et al.,2020, Cheng et al.,2021)[159],[160]

The **Gray Level Co-occurrence Matrix (GLCM)** assesses spatial relationships between pairs of pixels or voxels. It evaluates the frequency of appearance of specific pixel levels occur at a certain distance and orientation, capturing textural patterns based on gray level variations.

- **Contrast:** Evaluates the intensity difference comparing pixels with their neighbors across the total image [161].
- **Correlation:** Examines the linear relationship between each image pixel compared to their neighbors.
- **Energy:** Is the sum of squared values in the Gray-Level Co-occurrence Matrix (GLCM), indicating how uniform the texture is.
- **Homogeneity:** Quantifies how closely the elements in the GLCM are distributed around the diagonal, reflecting similarity within the image texture.
- **Dissimilarity:** Captures the degree of variation between gray levels of pixel pairs, highlighting differences in texture.

The **Gray Level Dependence Matrix (GLDM)** qualifies the gray level pixel or voxel correlations within a predefined distance. It measures how many neighboring voxels are within a certain gray level difference from the center voxel.

- **Small Dependence Emphasis (SDE):** Highlights fine textures with many small dependencies.
- **Large Dependence Emphasis (LDE):** Emphasizes coarse textures with large dependencies.

- **Gray Level Non-Uniformity (GLN):** Assesses the similarity of gray-level intensity values within an image. Low GLN values are a sign of more similar intensity values.
- **Dependence Count Energy (DCE):** Indicates the uniformity of dependence lengths.

The Neighborhood Gray-Tone Difference Matrix (NGTDM) measures the difference between a pixels or voxel's value and the neighbors' average values within a specified distance. This approach captures local intensity variations, allowing it to identify textural features based on the contrast between each voxel and its immediate neighborhood.

- **Coarseness:** Reflects the fineness or coarseness of the texture.
- **Contrast:** Measures the amount of local intensity variation.
- **Busyness:** Indicates the rate of change of gray levels in the image.
- **Complexity:** Assesses the intricacy of texture patterns.
- **Strength:** Represents the perceptual strength of structural patterns.

The Gray Level Run Length Matrix (GLRLM) quantifies how many consecutive pixels with the same pixel value appeared in a specific length.

- **Short Run Emphasis (SRE):** Highlights short runs textures.
- **Long Run Emphasis (LRE):** Highlights long runs textures.
- **Gray Level Non-Uniformity (GLN):** Measures the variability of pixel levels.
- **Run Length Non-Uniformity (RLN):** Assesses the variability of run lengths.

The Gray Level Size Zone Matrix (GLSZM) quantifies regions within an image that consist of connected voxels with identical gray level intensities, defining each such region as a "gray level zone." This matrix captures texture by analyzing the distribution and size of these homogeneous zones.

- **Small Zone Emphasis (SZE):** Focuses on fine textures with many small zones.
- **Large Zone Emphasis (LZE):** Highlights coarse textures with large zones.
- **Zone Percentage (ZP):** Indicates the distribution of zone sizes.

There are also transform based features that are extracted after applying mathematical transformations to the image. These transformations highlight specific image characteristics, such as edges, textures, or patterns, and capture frequency and scale information. After a transformation we can also extract first and second order statistics features. Common transformations in radiomics include:

- **Wavelet Transform Features:** They decompose the image into different frequency components, analyzing textures at multiple scales and orientations.
- **Laplacian of Gaussian (LoG):** This 2-step filter enhances edge detection by first smoothing using Gaussian blur filter to reduce noise, and then applying the Laplacian operator to identify ROI with high intensity changes to the image.
- **Square Transformation:** Amplifies higher intensity values more than lower ones, enhancing bright regions.
- **Square Root Transformation:** Compresses the dynamic range of high-intensity values, reducing the impact of extreme intensities and enhancing darker regions.
- **Logarithmic Transformation:** modifies image intensity by compressing high values and expanding low values, enhancing details in darker regions.
- **Exponential Transformation:** Expands high-intensity values and compresses low-intensity values, emphasizing brighter regions.
- **Gradient Filters** calculate the change in intensity in the image, emphasizing edges and transitions. They are useful for edge detection and highlighting boundaries within the ROI.

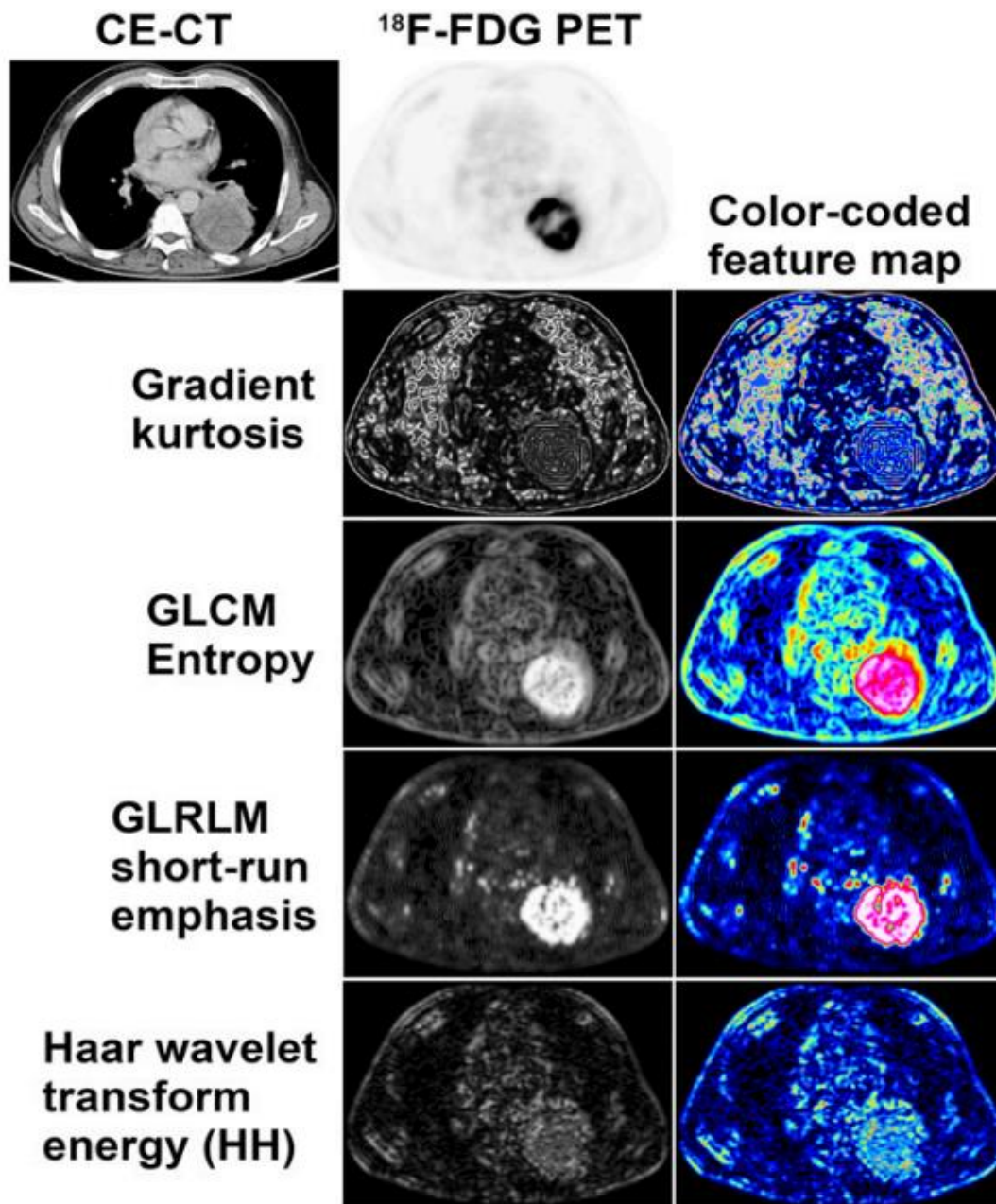


Figure 25 Example of different radiomics signatures on PET/CT slides (Mayerhoefer et al., 2020)[162]

1.9 Machine Learning

Machine Learning (ML) is a subdomain of Artificial Intelligence (AI) ^{Figure 26}. The purpose of this field is to create models that can map relationships between the data with the aim of extracting useful predictions or conclusions using automated optimization parameter techniques [163]. As the quality and the quantity of available training samples increases, the algorithms' performance improves adaptively. These algorithms are detecting patterns within the data, generating insights that facilitate the decision-making and predictive capabilities. They are utilized for critical decision-making in areas such as medical diagnosis, stock market analysis, energy load forecasting, and other

complex tasks involving numerous data points and variables, all without relying on predefined equations. While machine learning represents a subdomain of artificial intelligence, deep learning can be interpreted as a specialized branch within it. Recent reductions in hardware costs and advancements in consumer-grade GPUs have propelled deep learning techniques into a broader range of scientific domains, facilitating the extraction of valuable insights from highly dimensional and volumetric datasets. The machine learning process is typically stepwise, requiring human intervention for feature extraction, whereas classification occurs automatically and with relatively small datasets. Deep learning, on the other hand, is an entirely automated process that necessitates a substantial amount of data, allowing the data to "train" the neurons, with any errors providing feedback for model adjustment.

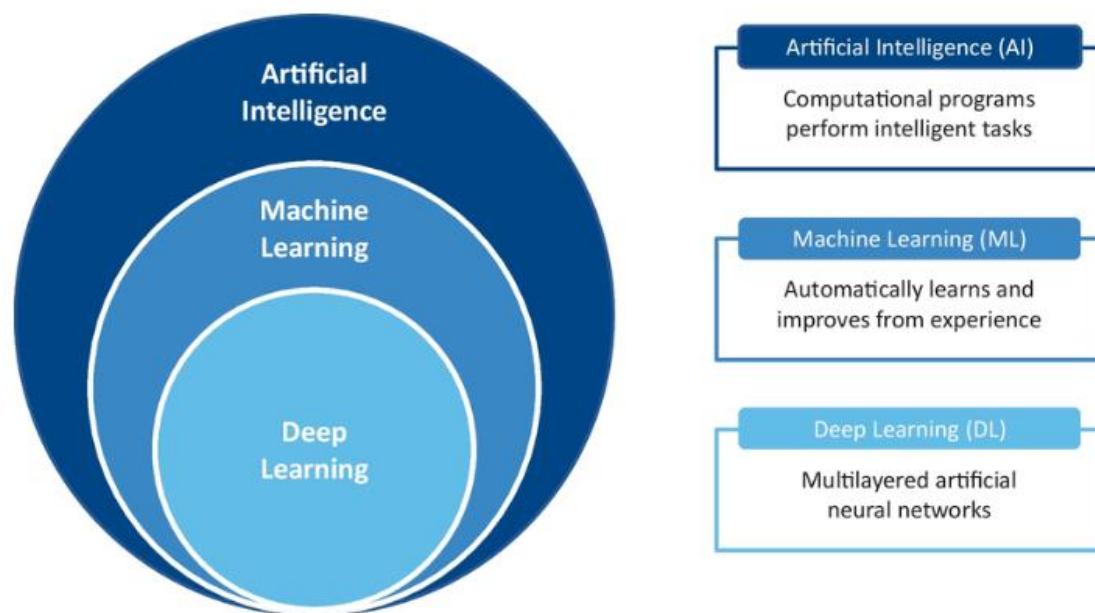


Figure 26 Artificial intelligence (AI) is a general terms that encapsulates machine learning (ML) and deep learning (DL) (Joshi et al., 2023) [164]

1.9.1 Machine Learning Methods

Machine Learning primarily works through two approaches: supervised learning and unsupervised learning. In supervised learning a model is created based on data with specific labels. In unsupervised learning, the model analyzes data to uncover underlying patterns or structures [165] [54] ^{Figure 27}. Moreover, the choice between using supervised or unsupervised learning should be based on the pool of data that we have, the information that we are looking to be extracted from it, as well as where and how it will be applied.

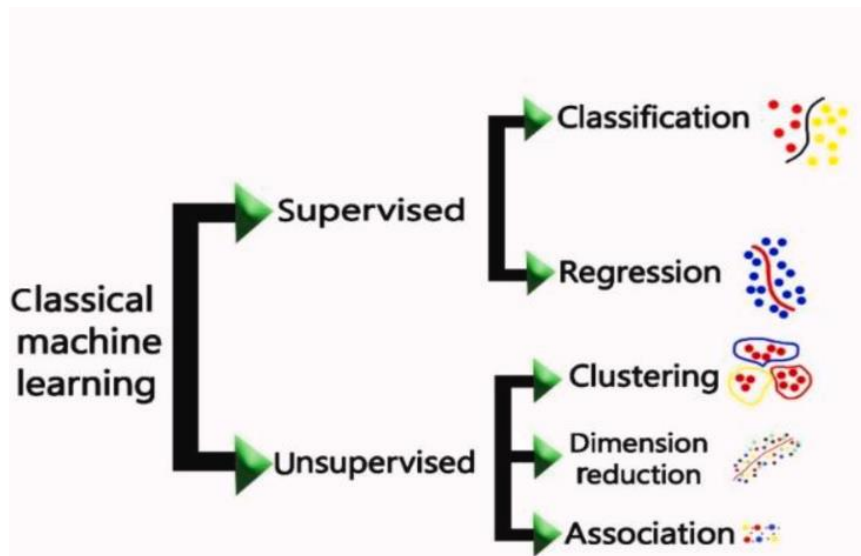


Figure 27 Examples of supervised and unsupervised algorithms (Abbas et al.,2023)[166]

1.9.2 Supervised Machine Learning Algorithms

A supervised learning algorithm uses a known dataset as input, along with corresponding known outputs, to train a model capable of generating predictions for new, unseen data. This learning process employs classification and regression techniques to build predictive models [119]. Regression techniques focus on predicting continuous outcomes [119][54]. In contrast, classification techniques aim to predict discrete outcomes by categorizing input data into distinct classes. Typical applications of classification include medical diagnosis, sentiment analysis, spam filtering etc. [54].

1.9.3 Regression

Regression algorithms are utilized for data characterized by continuous outcomes. The scope of regression analysis is to map the input to the output variables. Linear regression is the most fundamental regression technique. It works doing the assumption that the input and output variables have a linear connection, so a straight line can be modeled to effectively represent the input-output outcome. This relationship can be established by the equation:

$$y = \beta x + \alpha$$

where y is the dependent variable and x is the independent variable. β was called the slope of the line and α is called the intercept [167].

In higher dimensions, the line is called a plane or a hyper-plane. This relationship can be represented by the equation:

$$y = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n + \alpha$$

The goal is to estimate the values of β and α that minimize a loss function.

1.9.4 Logistic regression

Logistic regression despite the name regression, is a classification technique. It effectively addresses binary and linear classification problems by applying logistic function at the end of the outcome in order to predict the binary class. The logistic regression can be established by the equation:

$$p(x) = \frac{1}{1 + e^{-x(b_0 + b_1 x)}}$$

Where $b_0 = -\mu/s$ and is known as intercept of the line $y = b_0 + b_1 x$ and $b_1 = 1/s$ that presents the slope of the line. A fundamental difference between logistic regression and linear regression is in the output range of the former, which is bound to values between 0 and 1. Logistic regression does not require for the dependent and independent variables to have a linear relation.

1.9.5 Classification

Classification algorithms are used when the data outputs are discrete, i.e., the data are separated into classes. Multiple “flavors” of models are existing based on their architecture and type of operations.

Linear models construct an equation that best distinguishes between classes by forming a decision boundary through a weighted combination of data features:

$$y = f \left(\sum_j w_j x_j \right)$$

where x_j is the value of feature j , w_j is the weight of feature j , and f is a threshold function that assigns the dot product $\vec{w} \cdot \vec{x}$ in a specific class, for example a sign function. The weight vector $\vec{w}$ is optimized based on the training set. Optionally, another parameter b , called bias, is also summed but it is omitted herein for simplicity. For binary classification, the problem is a weight optimization task:

$$\min f(\mathbf{w}) \equiv r(\mathbf{w}) + C \sum_i L(\mathbf{w}^T \mathbf{x}_i, y_i),$$

where $\mathbf{x}_i$ presents the vector of features of i samples, y_i is the label of the class, $\mathbf{w}$ the weight vector, L presents the cost function to calculate the distance between the predictions and the real values, $r(\cdot)$ is a regularization term, and $C(\cdot)$ is a constant that balances the regularization term and the sum of the losses.

ML classifiers can also be generative, meaning that they try to learn to predict the probability density function of the feature data. Instead of calculating the joint distribution $p(y, \mathbf{x})$ from:

$$p(y, \mathbf{x}) = P(y|\mathbf{x})p(\mathbf{x})$$

in generative learning the joint distribution $p(y, \mathbf{x})$ is calculated from:

$$p(y, \mathbf{x}) = p(\mathbf{x}|y)P(y)$$

where $\mathbf{x}$ is the feature vector of a sample, y its class, $P(y)$ is the predictive probability of class and $p(\mathbf{x}|y)$ is the conditional distribution of the input given the class label. In Bayesian classification, the Bayes' theorem is applied:

$$P(A, B) = P(A|B)P(B) = P(B|A)P(A)$$

where $P(A|B)$ is the probability of event A occurring given B , $P(B|A)$ is the opposite, and $P(A)$ and $P(B)$ are the probabilities of A and B , respectively. Resulting in the a-posteriori probability:

$$P(y|\mathbf{x}) = \frac{p(y, \mathbf{x})}{p(\mathbf{x})} = \frac{p(\mathbf{x}|y) P(y)}{p(\mathbf{x})}$$

Then, the error is minimized by partitioning the feature space so that an unknown pattern, represented by the feature vector $\mathbf{x}$, is assigned to a specific class.

$$P(y = i|\mathbf{x}) > P(y = j|\mathbf{x}) \quad \forall i \neq j$$

Linear Discriminant Analysis (LDA) is a classification method that creates a linear combination of features to best distinguish between multiple data classes. In the context of LDA, it works under the assumption that the classes are of normal distribution. The LDA classifier operates under the assumption that the conditional density $p(\mathbf{x}|y)$ follows a multivariate Gaussian distribution and that all classes have a common covariance matrix, denoted as Σ :

$$P(\mathbf{x}|y) = \frac{1}{\sqrt{(2\pi)^d |\Sigma|}} \exp\left(-\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_k)^T \Sigma^{-1}(\mathbf{x} - \boldsymbol{\mu}_k)\right)$$

where d denotes the features number and $\boldsymbol{\mu}_k$ is the mean vector of class k .

Quadratic discriminant analysis (QDA) is obtained by following the same steps as LDA addressing one major difference. QDA does not make the assumption that the covariance matrix is shared across classes. Each class y has a different covariance matrix Σ_y calculated using:

$$\Sigma(y) = \frac{1}{N_y - 1} \sum_k (x_i - \mu_k)(x_i - \mu_k)^T$$

For binary classification, we have:

$$P(\mathbf{x}|y) = \frac{1}{\sqrt{(2\pi)^d |\boldsymbol{\Sigma}|}} \exp\left(-\frac{1}{2}(\mathbf{x} - \boldsymbol{\mu}_k)^T \boldsymbol{\Sigma}^{-1}(\mathbf{x} - \boldsymbol{\mu}_k)\right)$$

The conditional density $p(\mathbf{x}|y)$ cannot be solved easily and the previous ML algorithms suffer from the curse of dimensionality.

This issue is addressed in the naive Bayes algorithm which assumes that all features $\mathbf{x}$ is mutually independent given the class label, resulting in:

$$p(\mathbf{x}|y) = \prod_j p(x_j|y)$$

$$P(y|\mathbf{x}) = \frac{\prod_j p(x_j|y)P(y)}{p(\mathbf{x})}$$

The $p(\mathbf{x})$ does not depend on y and can be omitted and the resulting formula can be rewritten and solved using the maximum a-posteriori rule:

$$\hat{y} = \operatorname{argmax}_k P(y = k|\mathbf{x}) = \operatorname{argmax}_k \prod_j p(x_j | y)P(y)$$

The decision tree (DT) classifier ^{Figure 28} is a set of if/else decision rules that continuously splits the training set according to a criterion that maximizes the separation of the data. The result is a tree-like structure where branches represent the data split and leaves represent the outcomes. A DT is developed through the iterative process of partitioning the data into progressively smaller subsets, utilizing one or more input attributes as the basis for this split of the branches [120]. The algorithm chooses the feature that gives the best "information gain," which is the difference between the impurity of the original group and the combined impurity of the new groups. The lower the impurity in the new groups, the higher the information gain. This splitting continues until the data is fully separated, or a certain stopping point is reached [121].

A DT with a greater maximum depth or a smaller minimum sample size in a leaf node will typically result in a higher number of leaf nodes, which can lead to overfitting. A DT characterized by a smaller maximum depth or a larger minimum sample size in a leaf node may result in underfitting the training data.

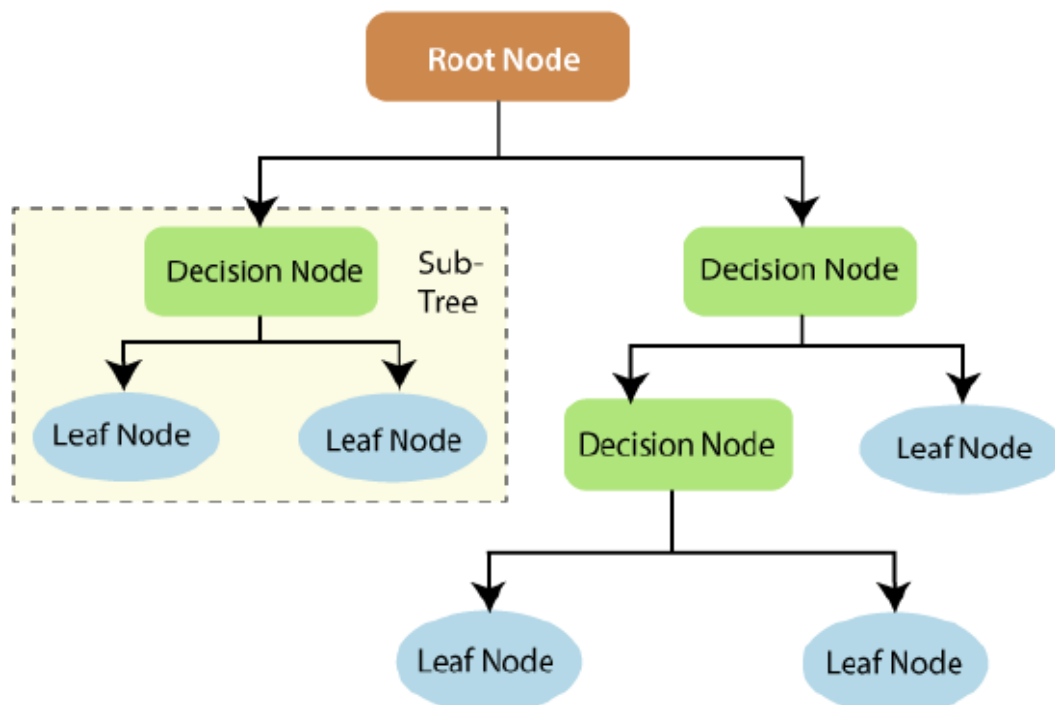


Figure 28 Decision Tree Classification Algorithm (Charbuty 2021)[168]

Neighbor-based algorithms such as k-nearest neighbors (k-NN) classify a data point by take into consideration the category that appeared in higher frequency among a predefined number of nearest neighbors ^{Figure 29}. In k-NN, the "k" is the count of nearest neighbors that is taken into consideration for classifying any new data sample. It identifies the "k" closest neighbors based on a distance metric. "k"-NN append the class of a new data sample by aggregating the class labels of its "k" closest neighbors [169].

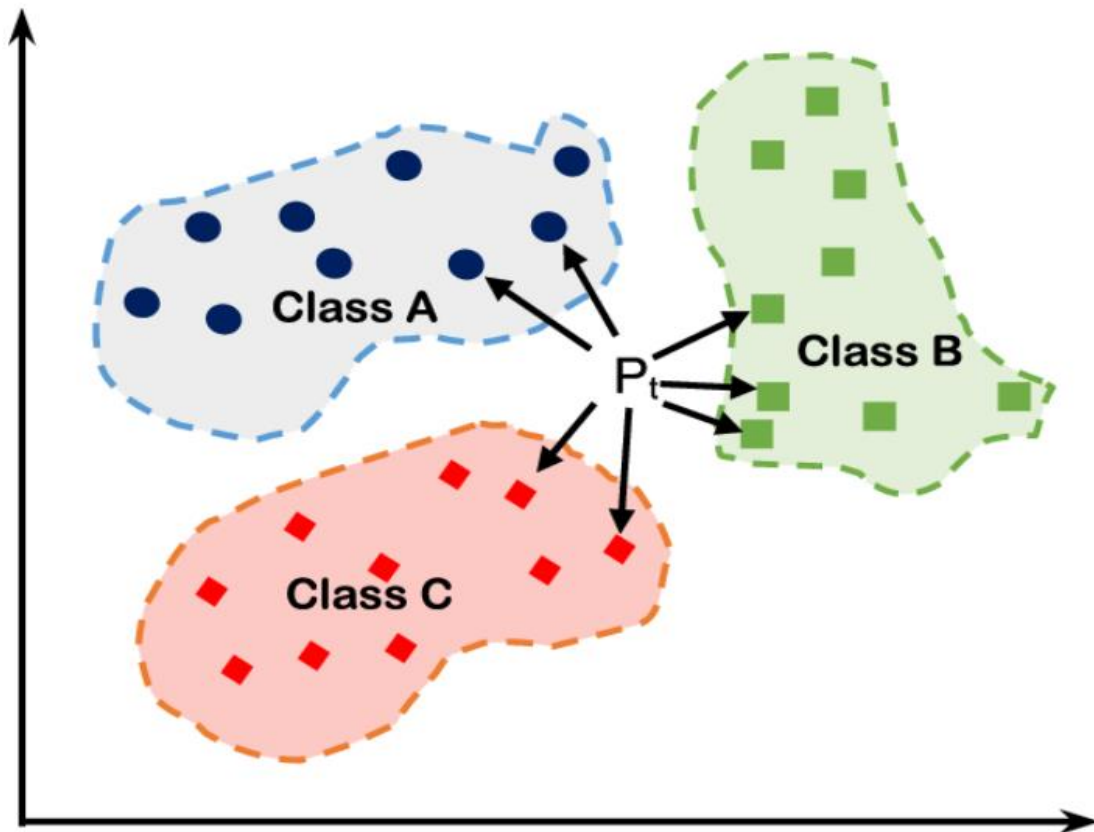


Figure 29 Example on KNN classifier (Atallah, 2019)[170]

Support Vector machines (SVM)

Introduced by Vapnik in 2000, SVM ^{Figure 30} functions by determining the ideal boundary to separate data points within a transformed, higher-dimensional space. This optimal hyperplane helps clearly distinguish between different classes [171]. It was then solving a linear separation problem in this space.

SVM classification is defined by the hyperplane given by:

$$y = f(x) = w^T + b$$

where w^T and b represent the weight vectors and the term bias. These parameters are estimated by minimizing a regularized cost function. Support vectors are considered points that are very close to the separation plane. SVM takes into account these points in order to better differentiate the classes, using the best possible maximal distance between them. When dealing with data that isn't linearly separable, SVM can apply a kernel function to augment the data into a higher-dimensional space, where a higher order classification may become fusible [172].

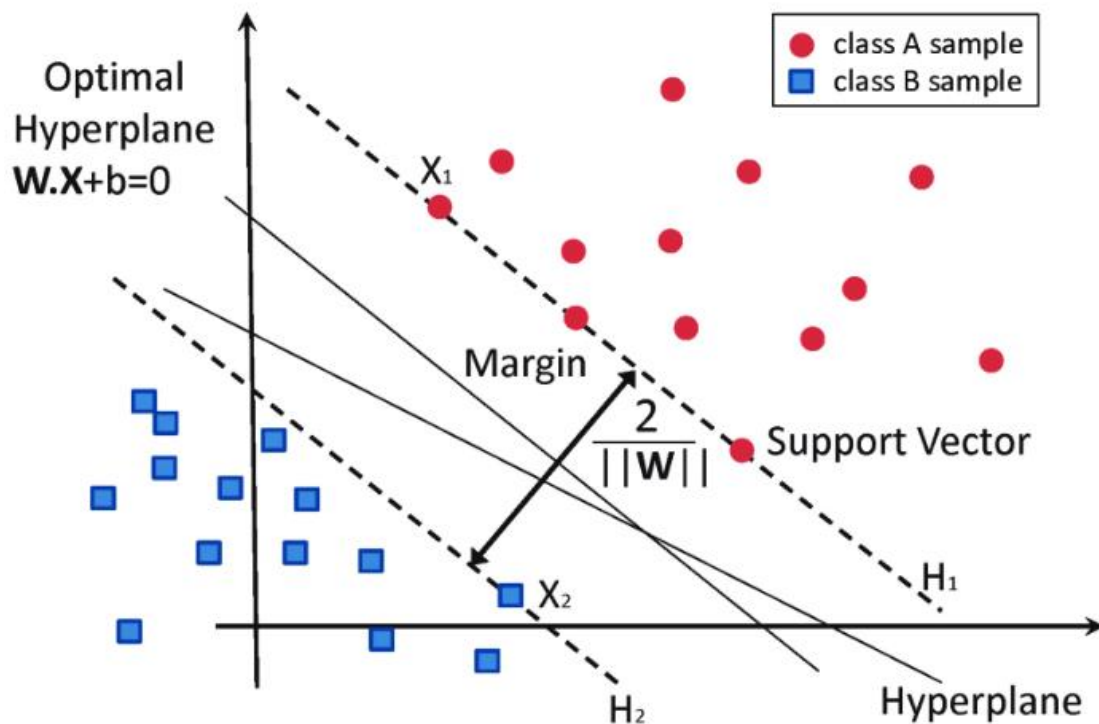


Figure 30 Classification example of data using support vector machine (SVM) (García-Gonzalo, 2016)[173]

1.9.6 Unsupervised Machine Learning

Unsupervised learning aims to reveal hidden patterns within datasets without relying on labeled outputs. This approach is selected in order to “mine” useful information from the dataset without relying in labels. The most used group of algorithms that is used in unsupervised learning as a technique are the clustering algorithms. Clustering algorithms are exploring the feature space, trying to identify common patterns between groups of data and their use is s proven to be effective in multiple applications, including computer vision, object recognition and biological and economical systems [174]. Also, it serves as a technique for reducing the dimensions of the data with prominent example the principal component analysis (PCA) algorithm [175] .

1.9.7 Machine learning Explainability

Machine learning explainability is an area of research in artificial intelligence having the mission of making the decisions and predictions of machine learning models easier to understand. This is important not only for building trust in the models but also for identifying and correcting biases or errors to improve model performance.

One key technique for improving both interpretability and performance is Sequential Feature Selection (SFS). This method works by selecting the most useful features from a dataset, which helps reduce the complexity of the model, lowers computational costs,

and prevents overfitting as well as, gain information about marker/features that are responsible for the specific task. SFS works by iteratively evaluating the “power” of each feature to the model’s performance, selecting the best subset based on selected metric criteria that the user wants. There are two main types:

Sequential Forward Selection (SFS): Starts with no features and iteratively adds them one by one, selecting those that improve performance the most [176].

Sequential Backward Selection (SBS): Starts with all possible features and removes the least important one’s step by step [176].

Following that, at the end we can investigate the selected features, their impact on the task and their downstream importance in the research field.

1.10 Deep Learning

Despite the existence of deep learning algorithms from the 80’s, today, following advancements in the hardware, and the “technological boom” of computational power, deep learning has emerged as an indistinguishable part of our everyday life.

1.10.1 Origins and the Perceptron Model

Deep learning traces its origins to the mid-20th century with the creation of the perceptron algorithm in the 1940s and 1950s [177]. This early model of neural networks aimed to mimic human thinking processes and decision-making. Although “ahead of their time”, the perceptron was limited to solving problems that were linearly separable. The limitations of the perceptron were critiqued by Minsky et al, in their famous now book "Perceptrons," which argued for more complex architectures to address nonlinear problems [178].

A feedforward neural network (FNN) is a type of NN that the connections between input and output neurons are unidirectional, flowing exclusively from the input layer passing multiple hidden layers to the final layer, without forming closed loops ^{Figure 31}. The term "feedforward" indicates that data moves strictly in one direction, from inputs to outputs, without any recursive connections like recurrent neural network (RNN) models. FNNs are employed to find a function that describes the input to an output. In their simplest form of one layer, can be considered as utilizing the simplest regression, or classifications algorithms.

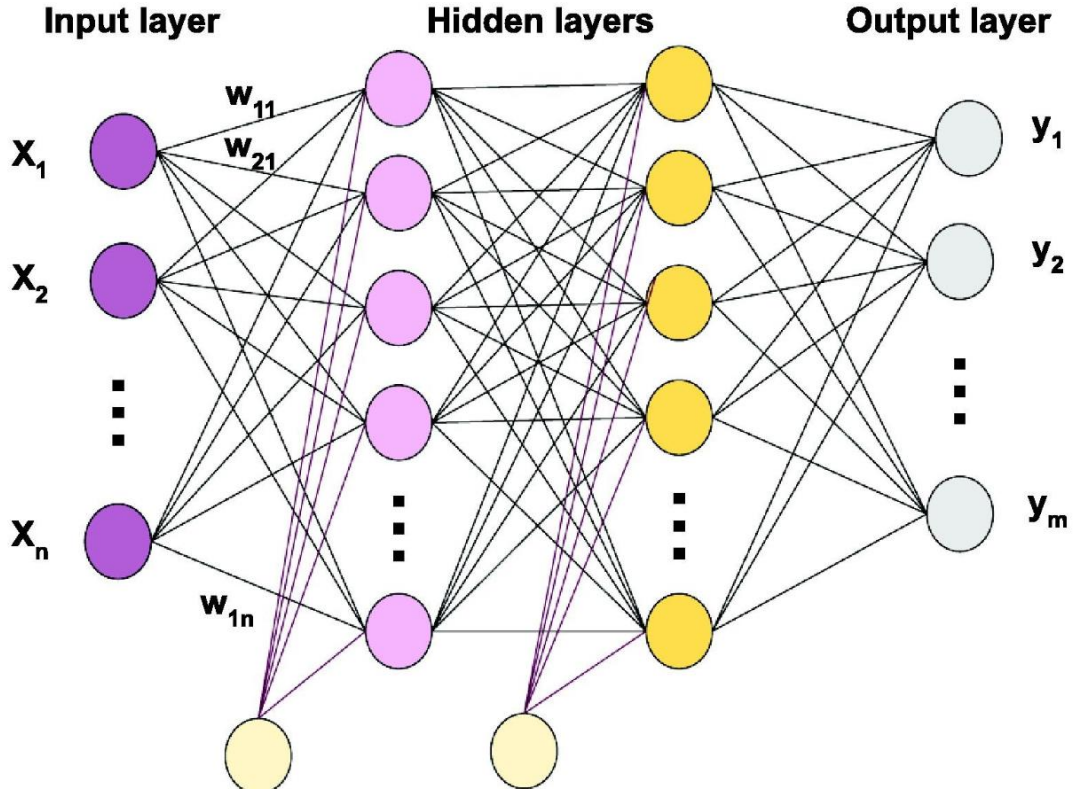


Figure 31 Example of a FF-Neural Network (2 Layer MLP, Chan, 2023)[179]

The perceptron, which is the most basic form of a FNN, utilizes an input layer and a classification or regression layer only. The output is computed as the weighted sum of the inputs plus a bias term, on top of an activation function. Traditionally, perceptrons produces binary outputs, either 0 or 1, achieved by employing a step activation function $H(x)$, defined as (equation 4):

$$H(x) = \begin{cases} 1 & \text{if } x \geq 0 \\ 0 & \text{if } x < 0 \end{cases} \quad (4)$$

For an input vector x of dimension n , a weight vector w of the same dimension, and a bias b , the perceptron's output o is given by (equation 5):

$$o = \begin{cases} 1 & \text{if } w * x + b \geq 0 \\ 0 & \text{if } w * x + b < 0 \end{cases}$$

As the perceptron splits the input space into two distinct classes (0 or 1), it functions as a linear classifier. The boundary separating these two classes is referred to as the decision boundary or classification boundary. In 2D feature vector space, this boundary is

a line, while in higher-dimensional spaces, it becomes a hyperplane. In more generalized single-layer perceptrons, other activation functions can be used instead of the step function like:

the identity function:

$$f(x) = x$$

the sigmoid function:

$$\sigma(x) = \frac{1}{1 + e^{-x}}$$

or the hyperbolic tangent function:

$$\tanh(x) = \frac{e^x - e^{-x}}{e^x + e^{-x}}$$

Utilizing these functions we can produce continuous outputs, in contrast to the binary output of the step function, and because of that they can produce nonlinear classification boundaries [179]. In general, for a perceptron using an arbitrary activation function $g(x)$, the output is computed as:

$$o = g(x * w + b)$$

1.10.2 Advancements in Neural Networks: Backpropagation

In the 1980s, neural network research hits a major breakthrough utilizing the backpropagation algorithm by Hinton et al. [180]. Backpropagation algorithm was pivotal for enabling the efficient calculation of error gradients across multiple layers of a neural network, a process crucial for updating the network weights during training. Using the chain rule the backpropagation algorithm calculates the error of the total network, allowed for the systematic updating of weights calculating the gradient of loss in respect to the weights of the loss function. This advancement made it possible to train deeper in terms of layers neural networks effectively, opening the way for more complex architectures.

1.10.3 Convolutional Neural Networks (CNN) Advancements

Yann LeCun developed the first CNNs during the 90's [181] represented another major milestone. LeCun's LeNet-5 model was very successful in recognizing handwritten digits from the MNIST dataset, showcasing CNNs' power in computer vision tasks. CNNs utilize spatial patterns in the images in order to extract meaningful information, making them particularly suited for image processing.

1.10.4 The Evolution of Deep Learning

Deep learning saw a “reinvention” and eventually took the world by storm in the 21st century because of several factors: The availability of powerful and affordable GPUs enabled the training of large-scale neural networks. The creation of extensive datasets, like ImageNet, provided a high volume of data required for training complex models. Improved training techniques, such as new initialization methods and regularization strategies like dropout, batch normalization etc., helped mitigate overfitting issues. A pivotal moment was the introduction of AlexNet by Alex Krizhevsky et al. in 2012 [182] ^{Figure 32}, which significantly outperformed other networks in the ImageNet challenge, proving that deep learning systems are capable of performing very complex tasks effectively.

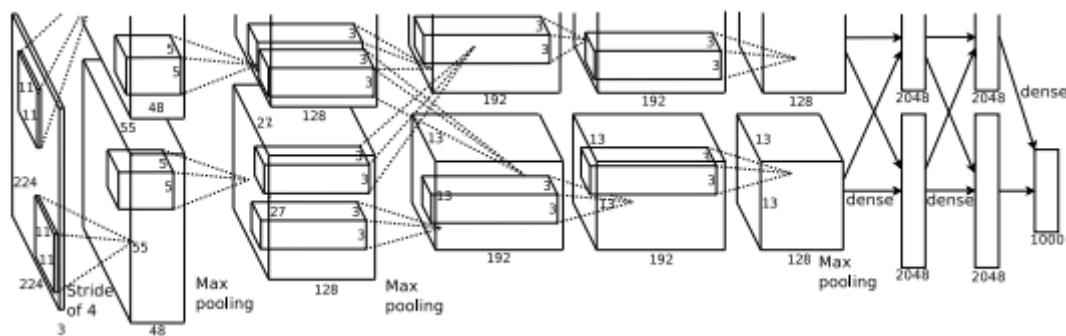


Figure 32 Original AlexNet Model architecture (Krizhevsky, 2012)[182]

1.11 Segmentation Algorithms

1.11.1 Basic Segmentation Techniques

Image segmentation is the technique of dividing the pixel values into well-defined clusters that share common properties, such as color, value, or statistical properties in general [183]. The goal is to cluster the image pixels in order to uncover patterns and segments in the image and analyze them for specific tasks. For example, segmentation in medical imaging helps identify anatomical structures facilitating better diagnostics and treatment planning.

Thresholding is considered the most basic form of image segmentation [184]. It separates an image into regions by applying a threshold value to the image pixels. This method is particularly effective for high-contrast images. Otsu's method, is an automated technique in order to find the optimal threshold for maximize the variance between classes, enhancing adaptability across varying lighting conditions. Edge Detection algorithms, such as the Sobel, Prewitt, and Canny detectors, identify object boundaries by detecting brightness intervals ^{Figure 33}. These methods are crucial for outlining

object shapes but typically require extensive post processing techniques in order to classify the pixels within the identified boundaries.

Region Growing is another segmentation technique that begins with specific seed points into the image and “grows” by taking into account neighboring pixels with similar properties like intensity or texture. This technique is more adaptable than thresholding but is computationally demanding for large images.

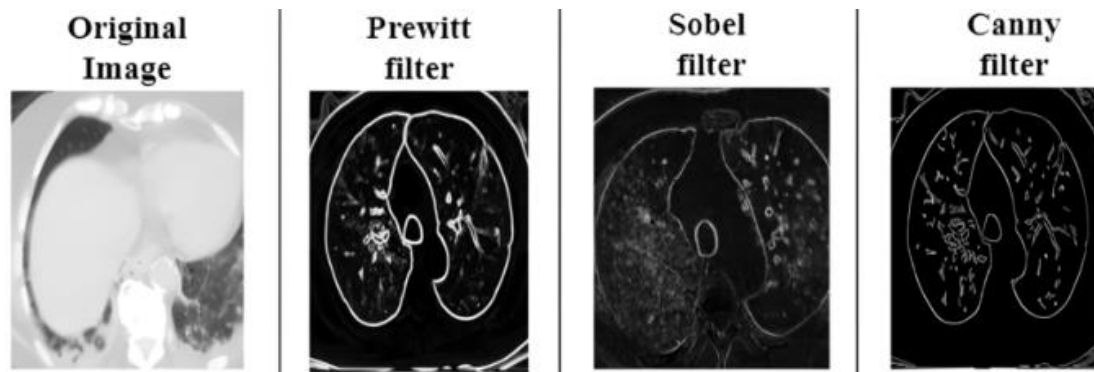


Figure 33 Example of a CT scan and the corresponding Prewitt, Sobel and Canny filtering algorithms (Bagwan et al., 2023)[185]

1.11.2 Advanced Segmentation in Medical Imaging

Convolutional Neural Networks (CNNs) have greatly improved image segmentation by automatically learning which parts of an image are important. The U-Net architecture, in 2015 [186], has been proven as crucial step forward in medical image segmentation. To effectively perform image segmentation, the U-Net architecture was designed with an encoder path that progressively captures contextual information by down sampling, and a symmetrical decoder path that accurately restores spatial details through up sampling, ensuring that the network learned their asked feature space and precise localization [187]. Fully Convolutional Networks (FCNs), introduced by Long et al. in 2015 [188], allow for segmentation across whole images in a single operation, speeding up the process and increasing computational efficiency.

1.11.3 Images as Input in Neural Networks

In medical imaging, such as CT scans, images are treated as volumetric data in a three-dimensional array. Unlike standard RGB images, the pixel values in CT images represent different tissue densities, measured in Hounsfield units, which are crucial for identifying various tissue types.

1.11.4 U-Net Architecture

The U-Net architecture has been characterized as a "U" shape network ^{Figure 34}, which effectively captures both feature space and localization context necessary for precise segmentation tasks [186]. The architecture consists of a down sampling path that captures context through repeated convolutions and an up-sampling path that reconstructs the image and provides the effective feature space for the segmentation task.

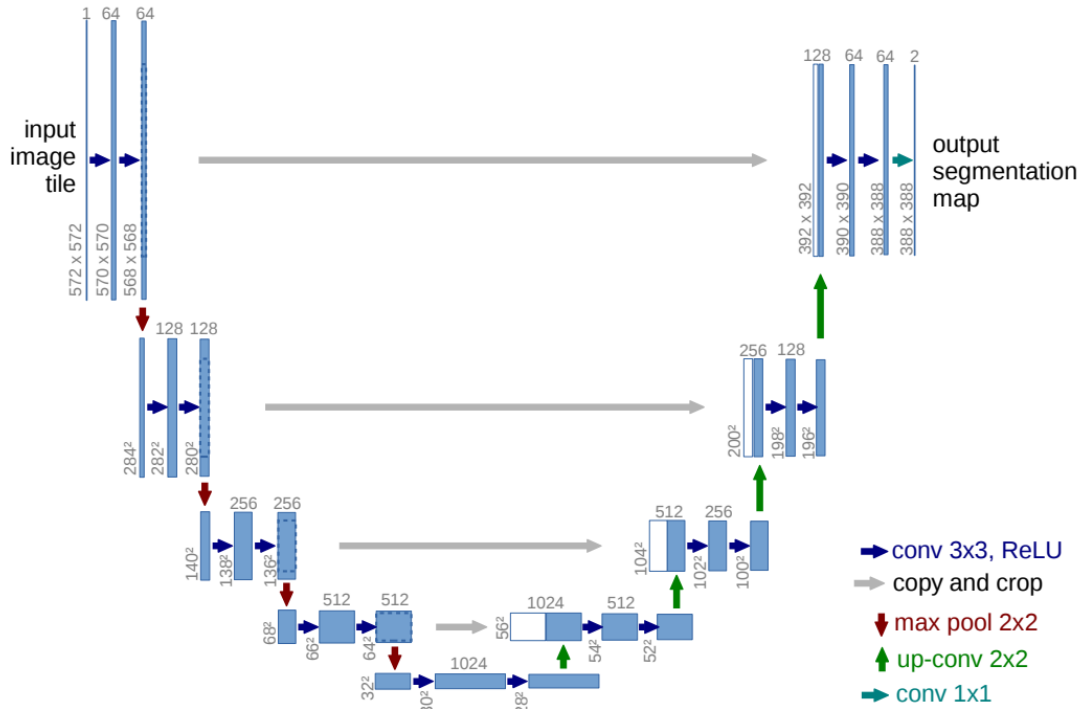


Figure 34 The U-Net architecture consists of a down sampling path on the left and an up-sampling path on the right (Ronneberger, 2015)[186]

ResUNet architectures utilize the deep latent space exploration capabilities of ResNets combined with the precise segmentation abilities of U-Net [189][190]. The combination is achieved convolutional blocks in the original U-Net architecture with residual blocks ^{Figure 35}.

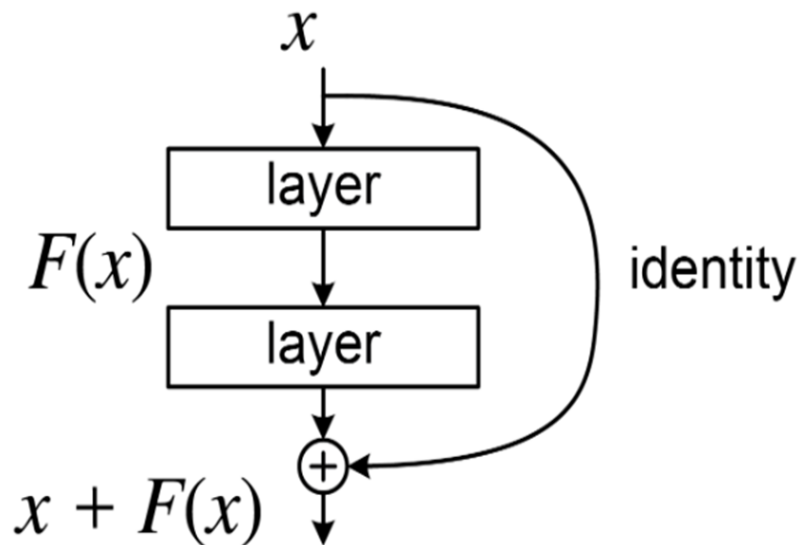


Figure 35 Residual Block Architecture (Zhu, 2019) [191]

This modification allows ResUNet to learn more complex representations making it highly effective for segmenting medical images where high precision is important[192]Figure 36

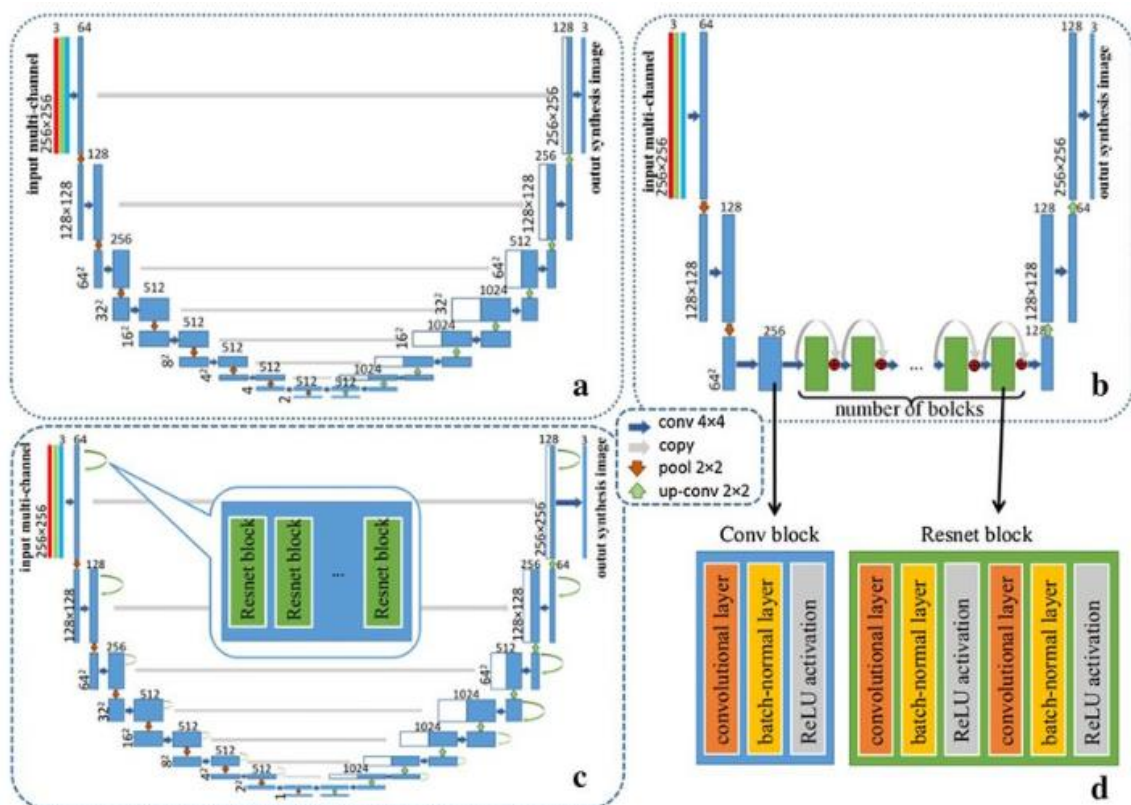


Figure 36 Example of A) U-Net; B) Residual-UNET; C) Convolutional and ResNet Blocks (Yu, 2019)[190]

1.11.5 Activation Functions

In order to teach the model non-linear relationships, specific functions, called activation functions are applied. This allows the network to learn and perform complex tasks that

linear models cannot achieve. These functions are applied to the output of each neuron or layer and act as a gate guard that decides whether it should be activated or not, changing the numerical way that information passes through the network. Choosing the right activation function affects how well the neural network performs and how effectively it learns from the data during training. Common activation functions, are the Sigmoid, Tanh, SoftMax and ReLU functions.

Sigmoid Function: The sigmoid function translates the output value from the final network layer into 0 to 1 range, making it easily interpretable as a probability [193]. Sigmoid function is no longer used in between the hidden layers thought due to issues like vanishing gradients, where gradients become very small, essentially disturbs the weight update process.

Tanh (Hyperbolic Tangent) Function: Tanh function outputs values ranging from -1 to 1. The tanh function centers the data between the 0, leading to higher efficiency in learning in certain cases [194]. Like the sigmoid, it also suffers from the vanishing gradient problem, making it less favored for layers deep within the network.

ReLU (Rectified Linear Unit): ReLU has become a “golden standard” function because it helps neural networks train faster and more effectively by partially solving the vanishing gradient problem [195]. It outputs the input as is if it is greater than 0 or zero otherwise. Despite its simplicity, ReLU has been shown to improve neural network training significantly.

SoftMax: SoftMax Function is used in tasks involving multi-class classification, the SoftMax function maps the initial output scores from the network into probabilities between 0 and 1, enabling their interpretation as probabilities for various classes [196].

1.11.6 Optimization algorithms

Optimization algorithms are essential in order to train NN by tuning the model’s weights in order to minimize a loss function, which quantifies the distance between the true values and the predictive values.

Gradient Descent

Gradient Descent is a well-established optimization technique. In gradient descent we calculate the impact that every weight has, in respect to the loss. It determines both the direction and magnitude of weight adjustments needed in order to minimize a loss function.

Update Rule:

$$weight_{new} = weight_{current} - \eta * \nabla_{weight} * J(weight)$$

where η is the learning rate and $\nabla_{weight} * J(weight)$ is the gradient of the loss function J with respect to the weights. The drawback of this method is that for big datasets, it is very expensive in calculations.

Stochastic Gradient Descent (SGD)

SDG is similar with GD with the main difference be that it updates the weights of the network utilizing the same principles of GD but it is computed for a batch of samples every time instead for all the dataset. The stochastic in the name is because it introduces noise not utilizing at the same time the total dataset, which can help the optimization process to not “stuck” in local minima areas.

Update Rule:

$$weight_{new} = weight_{current} - \eta * \nabla_{weight} * J(weight: Batch)$$

where the gradient $\nabla_{weight} * J(weight: Batch)$ is computed for a small batch of data.

Adam (Adaptive Moment Estimation)

Adam is a combination of Momentum and RMSProp and is working by keeping the mean and the standard deviation of the past gradients in order to update the weights. This method adjusts the learning rate for each parameter dynamically, facilitating faster convergence.

Update Rule: Adam’s update rule involves two steps:

1. Compute the moving averages:

$$m_t = \beta_1 * m_{t-1} + (1 - \beta_1) * \nabla_{weight} * J(weight)$$

$$u_t = \beta_2 * u_{t-1} + (1 - \beta_2) * \nabla_{weight} * J(weight)^2$$

2. Correct the bias:

$$\bar{m}_t = \frac{m_t}{1 - \beta_1^t}$$

$$\bar{u}_t = \frac{u_t}{1 - \beta_2^t}$$

3. The final weight update is:

$$weight_{new} = weight_{current} - \frac{\eta * \bar{m}_t}{\sqrt{\bar{u}_t + \varepsilon}} * \nabla_{weight} * J(weight)$$

where η is the learning rate, $\nabla_{weight} * J(weight)$ is the gradient of the loss function J with respect to the weights and ε is a constant that helps with algorithm stability.

1.11.7 Loss Functions

In machine learning and deep learning, loss functions help quantify the error between real values and predicted data, guiding the model to adjust the weights in order to minimize that error [197]. Loss functions differ based on the type of problem: regression (predicting continuous values) and classification (assigning labels to categories).

Regression Losses:

Mean Squared Error (MSE):

$$MSE = \frac{1}{N} \sum_{i=1}^N (x_i - \hat{y}_i)^2$$

This function computes the average of the squared differences between predicted and real labels. When the error is really large, it penalizes more significantly the model, making it highly sensitive to larger discrepancies.

Mean Absolute Error (MAE):

$$MAE = \frac{1}{N} \sum_{i=1}^N |y_i - \hat{y}_i|$$

MAE quantifies the average absolute differences between predicted and real labels. Unlike MSE, it penalizes errors linearly, making it more robust to outliers by treating all errors with equal weight, regardless of size.

Huber Loss:

$$L_{\delta} = \begin{cases} \frac{1}{2} (y_i - \hat{y}_i)^2 & \text{for } |y_i - \hat{y}_i| < \delta \\ \delta * |y_i - \hat{y}_i| - \frac{\delta^2}{2} & \text{otherwise} \end{cases}$$

Huber Loss merges characteristics of MSE and MAE, using a threshold δ . For small errors, it acts like MSE, while for large errors, it resembles MAE, enhancing robustness to outliers.

Classification Losses

Cross Entropy Loss (CE) or Log Loss (Multi Class):

$$CE\ Loss = - \sum_{i=1}^N y_i \log(\hat{y}_i)$$

CE loss calculates the difference between the predicted probability distribution $\hat{y}_i$ and the real distribution y_i . Commonly applied in multi-class classification tasks, it penalizes inaccuracies and motivates the model to boost certainty in correct predictions.

Binary Cross Entropy Loss (BCE):

$$BCE\ Loss = - \frac{1}{N} \sum_{i=1}^N y_i \log(\hat{y}_i) + (1 - y_i) \log(1 - \hat{y}_i)$$

BCE loss is preferred when the problem has binary labels, where it calculates the cross-entropy between the predicted and actual binary classes.

Jaccard Loss (Intersection over Union):

$$Jaccard\ Loss = 1 - \frac{|Y \cap \hat{Y}|}{|Y \cup \hat{Y}|}$$

Jaccard Loss, also known as IoU Loss, is widely applied in image segmentation tasks to evaluate the similarity between predicted and actual segmentations. The Jaccard index (or IoU) ranges from 0 to 1, where 1 represents a perfect match. Jaccard Loss is defined as 1 minus the Jaccard index, meaning that minimizing this loss promotes greater alignment between the predicted and ground truth segments.

Hinge Loss:

$$Hinge\ Loss = - \frac{1}{N} \sum_{i=1}^N \max(0, 1 - y_i \cdot \hat{y}_i)$$

Hinge Loss is mainly utilized in support vector machines (SVMs) for binary classification, penalizing predictions that fall on the incorrect side of the margin. This loss encourages the model to make more confident, margin-separated predictions.

1.12 Machine Learning-Deep Learning Pipelines

Machine learning does not follow a concrete method for utilizing data. Instead, it involves ongoing iteration and testing of various ideas and approaches, with many challenges centered around data handling and model selection.

Data Loading

At this stage, labeled input data are stored in a file. Machine learning algorithms cannot inherently differentiate between noise and useful information, so a thorough check for data cleanliness and completeness is conducted before the data is used for training.

Data Preprocessing

Following data loading, preprocessing takes place, where:

Outliers, which are data points that are “outside” of the range of the distribution, compared to the other data from the dataset, are identified to determine whether they should be excluded or if they hold significance for the model.

The presence of missing data is checked. Depending on the situation, missing values may either be disregarded—shrinking the dataset—or filled in using interpolation or similar data from another sample.

The data is split into two parts: a test set is reserved for evaluating the model, and a training set is used for building the model. This process, known as holdout, facilitates cross-validation by assessing the model’s performance on previously unseen data.

Feature Reduction

As datasets grow, the complexity increases, often necessitating a reduction in the volume of data to enhance the algorithm’s accuracy, interpretability, and performance on high-dimensional datasets, while also preventing overfitting.

Model Creation and Training

Initially, a simple algorithm is selected for its speed and ease of interpretation. Various algorithms are tested until an optimal one is identified that provides reliable classification. If an effective classifier is not found, improvements to the model must be considered. Model performance is evaluated using clearly defined metrics, with the confusion matrix—a chart comparing predicted values against actual values—serving as a critical tool. Key performance indicators might include accuracy, sensitivity, specificity, and the area under the curve (AUC) from ROC analysis.

2. Coronary Arteries-Shear stress

2.1 Introduction

The cases of deaths caused by cardiovascular diseases increase every year, mainly due to the westernized way of living which embodies many risk factors like the absence of exercise, high-fat diets, overconsumption of red meat and elevated levels of everyday stress [198]. Numerous imaging techniques for coronary arteries are used every day in clinical practice. Two main categories of techniques are presented:

Invasive techniques like Invasive Coronary Angiography (ICA), Intra Vascular Ultra Sound (IVUS) or Optical Coherence Tomography (OCT) and non-invasive techniques like Computed Tomography Coronary Angiography (CCTA), Magnetic Resonance Angiography (MRA). Each modality has an advantage that the others do not but also suffer from several cons. For example, IVUS provides the most information on the arterial wall morphology, as well as, the composition of the atheromatic plaques but suffers from low spatial resolution, several artifacts and the fact that the procedure is invasive. The traditional ICA provides a great view of the arterial lumen and is the most well-used modality worldwide but it also has several disadvantages such as the inability to view the arterial wall or any atheromatic plaques, the fact that a contrast agent is mandatory for the exam to be taken and the fact that it is also an invasive technique.

CCTA keeps gaining ground over the years because it has the ability to provide information about both the lumen and the outer wall as well as the composition of the atheromatic plaques and has the main advantage that it is non-invasive [199]. However, it also has some disadvantages such as the higher radiation than other techniques, the presence of artifacts which can distort the image that the clinician receives etc.

Fractional Flow Reserve (FFR), the prevailing imaging technique to assess the functional status of a major coronary vessel [200], is often chosen when a clinician is unable to acquire a sufficient image of the vessel or when there are doubts regarding the choice of the most proper treatment for a case [201]–[204]. In FFR intravascular pressure is assessed after inducing hyperemia with medication, utilizing a specialized pressure-sensing wire. FFR is defined as the ratio of distal pressure beyond the stenosis to the mean aortic pressure [68]. Patients presenting with an FFR of 0.80 or less are generally recommended for percutaneous coronary intervention (PCI).

In recent years, the rapidly progressing computer science has offered the ability to reconstruct the entire coronary vasculature in a three-dimensional (3D) scale. Several 3D

reconstruction techniques have been described in the literature, some of which use only one imaging modality, while others take advantage of a fusion of two distinct imaging techniques. For example, IVUS and ICA or OCT and ICA have been used extensively in the literature for the accurate 3D reconstruction of the major coronary vessels [205]–[207]. More recently, single imaging modalities such as CCTA or ICA were more than enough to create either the lumen (ICA) or every component of the coronary tree (CCTA) [208].

The reliable and accurate calculation of very important hemodynamic factors such as the Endothelial Shear Stress (ESS) and intracoronary pressures has become feasible by utilizing a combination of 3D modeling and Computational Fluid Dynamics (CFD) on the coronary vasculature. A less commonly explored option is evaluating biomechanical forces on the vessel wall using CCTA (coronary CT angiography) [209]. A key focus is the assessment of endothelial shear stress (ESS), which is calculated as the product of blood viscosity and the gradient of the velocity near the arterial wall in respect to the center of the vessel. ESS is a sensitive hemodynamic parameter, strongly affected by geometric changes in the vessel, such as those caused by plaque buildup or stenosis. The high sensitivity of ESS as a marker is of great use for the evaluation of a coronary lesion. Endothelial shear stress (ESS) is a prominent factor in the formation and progression of coronary plaque by disrupting the physiological equilibrium of the vessel wall [125], [210]–[212]. Studies have shown that increased blood flow during peak coronary vasodilation leads to locally elevated ESS levels, especially at sites with atherosclerotic lesions. This suggests a complex interaction between coronary atherosclerosis, the vessel's ability to dilate, and the biomechanical forces at play [213].

The relationship between ESS and CCTA-derived plaque phenotype, as well as coronary ischemia assessed by FFR, has been previously investigated [214] however, the complex relationship between anatomic-morphological and biomechanical data with myocardial blood flow (MBF) has not been examined yet [200]. Myocardial blood flow (MBF) can be accurately assessed using Positron Emission Tomography (PET), which is considered the gold standard for estimating functional biomarkers. Previous studies attempted to determine the degree and location of coronary stenosis and the impact that they have on blood flow [215], [216]. They concluded that stenotic lesions situated closer to the origin of the coronary arterial system –as compared to equivalent, but more remote lesions- can decrease blood flow across a more extended area of the myocardium and thus result in more intense ischemic reactions during exercise. It has also been

stated that plaques causing stenosis of the vessel diameter at a percentage of 30-50% often followed segments of higher-grade stenosis.

A study that investigates wall shear stress into four idealized coronary artery models suggested that for cases where coronary stenosis exceeds 50%, more turbulent fluid dynamics are noted beyond the point of narrowing. This turbulence could contribute to the stenosis's advancement and potentially heighten the risk of atherosclerosis and plaque accumulation in areas affected by the disrupted flow[217]. Several studies already have validated that the calculations of FFR derived from CCTA simulations align closely with the FFR measurements taken invasively, offering a dependable marker for identifying myocardial ischemia and the necessity for hemodynamic intervention in coronary artery disease patients[218][219][220][221].

Utilizing CT-FFR not only aids in making clinical decisions but also helps in monitoring plaque progression and forecasting potential significant cardiovascular incidents in the future. Research conducted [222] on patients undergoing statin therapy in a forward-looking study revealed that for non-calcified plaques, the changes in CT-FFR values diminished alongside reductions in plaque volume. It was observed that the prevalence of high-risk plaques escalated with decreasing FFR values. Moreover, the study established a notable correlation between the presence of high-risk plaque features, FFR metrics, and adverse outcomes over a five-year period [223], [224]. Multiple coronary stenosis has also an effect on ESS and FFR calculation and line of action and the presence of one severe stenosis can restrict blood flow to such an extent that it conceals the gradient across another stenosis or throughout the artery in cases of diffuse disease [225], [226] As we have already mention, Computed Tomography Coronary Angiography (CCTA) has emerged as a potent non-invasive imaging modality for the comprehensive assessment of coronary artery disease (CAD) [227], providing both anatomical and functional insights. Leveraging the power of Machine Learning (ML) algorithms and explainability techniques, it's now possible to extract and process valuable information from multidimensional datasets, aiding in the evaluation of coronary lesions. Previous studies have already presented the feasibility of using machine learning algorithms for ischemia prediction using only CCTA derived features such as plaque and geometric lumen characteristics and presenting the most important features that took place in the classification [228]–[231]. The additional information on top of the classification results can help the practitioners to quantified the magnitude of the lesion as well as to give insights for the decision features that are responsible for the results.

In pursuit of understanding the complex relationship between the blood flow product in relationship with plaque content and lumen geometry and their results in cardiac functionality assessed by PET-MPI, four pivotal studies are presented in this chapter.

1. The effect of the degree and location of coronary stenosis on the hemodynamic status of a coronary vessel

In this work, we perform a multi-parametric study on a coronary vessel to investigate the effect of parameters such as the degree of stenosis, the number of lesions and the location of the lesions on the hemodynamic status of the vessel and to assess the functional status of the stenoses in comparison to the location of the lesions using a control environment of artificial stenotic segments.

2. Coronary atherosclerosis and its consequences to the vessel wall and the myocardium: a new anatomical, functional, morphological and bio-mechanical approach

The objective of this study is to investigate and compare lesion specific endothelial shear stress (ESS) and the already validated smartFFR values, for the entire vessel, and investigate the relationship between ESS and smartFFR in addition to MBF stress (myocardial blood flow) and MFR (myocardial flow reserve).

3. Relationship of endothelial shear stress with plaque features with coronary CT angiography and vasodilating capability with PET

This study aimed to evaluate the relationship between endothelial shear stress (ESS), stenosis severity, lesion-specific plaque volume and phenotype, and their relative effectiveness in predicting reduced coronary vasodilatory capacity, as measured by PET myocardial perfusion imaging (MPI).

4. Coronary CT angiography derived features for predicting myocardial perfusion changes by PET myocardial perfusion imaging: a machine learning approach

This study aims to explore the potential of combining machine learning and explainability techniques in integrating computational fluid dynamics (CFD) derived parameters with quantitative plaque burden, plaque morphology, and anatomical characteristics to predict impaired myocardial flow reserve (MFR) as detected by PET myocardial perfusion imaging (MPI).

2.2 The Effect of The Degree And Location Of Coronary Stenosis On The Hemodynamic Status Of A Coronary Vessel

2.2.1 Study Aim:

The aim of this project is to investigate the hemodynamic impact of coronary artery lesions, specifically focusing on whether lesions located at proximal or distal segments of the coronary arteries are more likely to cause ischemia. By utilizing advanced three-dimensional coronary artery models reconstructed from Computed Tomography Coronary Angiography (CCTA) images and incorporating sophisticated computational fluid dynamics (CFD) algorithms, the study seeks to simulate blood flow and assess the hemodynamic significance of different lesion severities.

2.2.2 Methods

Dataset

One subject who underwent a Computed Tomography Coronary Angiography (CCTA) was used in the present study (64-slice General Electric Medical Systems Discovery PET/CT 690® scanner).

3D Reconstruction

The 3D reconstruction of the eight arterial segments was performed using an appropriate 3D reconstruction algorithm [232]. Briefly, the algorithm is based on the following approach: a) the CCTA images are pre-processed and the image distortion caused by intense calcified objects, is removed. b) A minimum cost path approach is used to extract the 3D centerline of the artery of interest. c) Using a function of the distance from the centerline and the Hounsfield Units (HU) values, an estimation of the weight function for the lumen is made. A final refinement of an active contour model for the lumen is implemented. d) Finally, the 3D surfaces for the lumen are created. From the initial healthy Right Coronary Artery (RCA) that was reconstructed, we used the point-cloud contours that were generated in order to create the artificial stenoses, using an inhouse developed algorithm. In order to investigate the influence of the stenosis location and stenosis degree, we created eight models that contained either one or two stenoses of varying degrees (i.e. 50% and 70% lumen diameter reduction). These lumen diameter reduction values are considered to represent the majority cohort of patients with low to intermediate CAD [233]. The locations of the stenoses were identical (i.e. one proximal and one distal with a distance of 25 mm between them). All possible combinations were used in the tandem lesion's cases, whereas, for the single stenosis cases, all combinations regarding the location of the stenosis (i.e. proximal or distal) were used ^{Figure 37}.

Blood Flow Simulations

To assess the impact of stenosis degree and location, we conducted blood flow simulations utilizing the finite element method. The specifics of these simulations are provided in detail below:

Rigid Wall Assumption

Blood flow modeling was conducted using the Navier-Stokes and continuity equations, treating blood as a Newtonian fluid with a density of 1050 kg/m^3 and a dynamic viscosity of $0.0035 \text{ Pa}\cdot\text{s}$. Flow characteristics were assumed to be laminar and incompressible, with Reynolds numbers spanning from 450 to 1870.

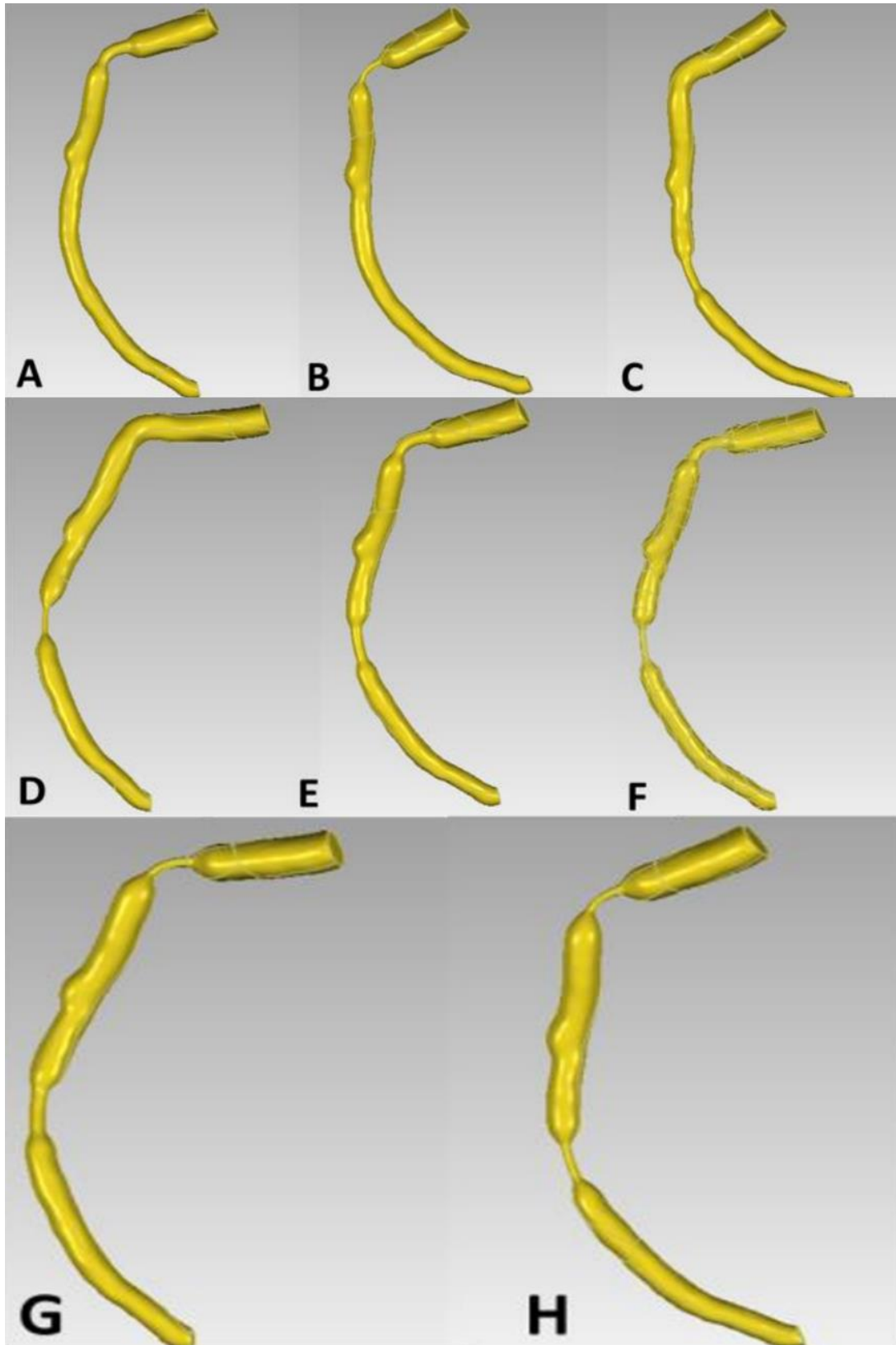


Figure 37 3D reconstructed cases. A) Proximal=50%. B) Proximal=70%. C) Distal=50%, D) Distal=70%, E) Proximal=Distal=50%, F) Proximal=50%, Distal=70%, G) Proximal=70%, Distal=50% and H) Proximal=Distal=70%.

Boundary Conditions

To determine the smartFFR index, a transient simulation was run for each case. A mean aortic pressure of 100 mmHg was set as the inlet boundary condition. For the outlet, a flow profile with 5-time steps (each 0.25 seconds) was used, applying volumetric flow rates of 0, 1, 2, 3, and 4 ml/s as boundary conditions. The vessel wall was defined as impermeable with a no-penetration condition, and a no-slip condition was imposed on the wall surface. To construct a patient-specific Pd/Pa curve, Pd/Pa values were calculated at each time step, then plotted and smoothed with a 100-point spline. The area under this curve (AUC) was then normalized by dividing it by the AUC of a corresponding healthy artery segment with no pressure drop. This normalized value represents the smartFFR. Wall shear stress (WSS) was calculated using the flow data from the 1 ml/s rate, reflecting an approximation of average resting flow.

Mesh

All eight arterial models were discretized into tetrahedral elements using the same meshing parameters. The element face size ranged between 0.12 and 0.14 mm, resulting to a total mesh size of around one million elements. A mesh sensitivity analysis was performed in order to determine the optimal mesh size. The limit of iterations for the convergence of the analysis was 50 and the convergence criterion was 10⁻⁴.

2.2.3 Results

We chose cross-sections that were equidistant (i.e. the average distance between cross-sections was 0.5 mm) and measured the WSS values to calculate how the extent of the stenoses impacts the WSS ^{Figure 40}. A similar trend is observed for the WSS waveforms, which however deviates in terms of peak WSS values and WSS right after the throat of the stenosis ^{Figure 38}. Initially, we can see that the distal stenoses give increased peak WSS values when compared to their respective proximal ones. Moreover, the case of the single distal 70% stenosis produces higher peak WSS value in comparison with the tandem lesion case of the two 70% stenoses ^{Table 1, Figure 38}.

Table 1 ESS results for proximal and distal segments of different stenotic cases

A/A	Proximal	Distal	ESS
Case 1	-	-	0.9
Case 2	50%	-	4.5
Case 3		50%	6.9
Case 4	70%	-	18.9
Case 5	-	70%	28.1

Case 6	50%	50%	4.5 - 6.7
Case 7	50%	70%	4.6 – 26.2
Case 8	70%	50%	19.5 – 6.9
Case 9	70%	70%	21.3 – 25.8

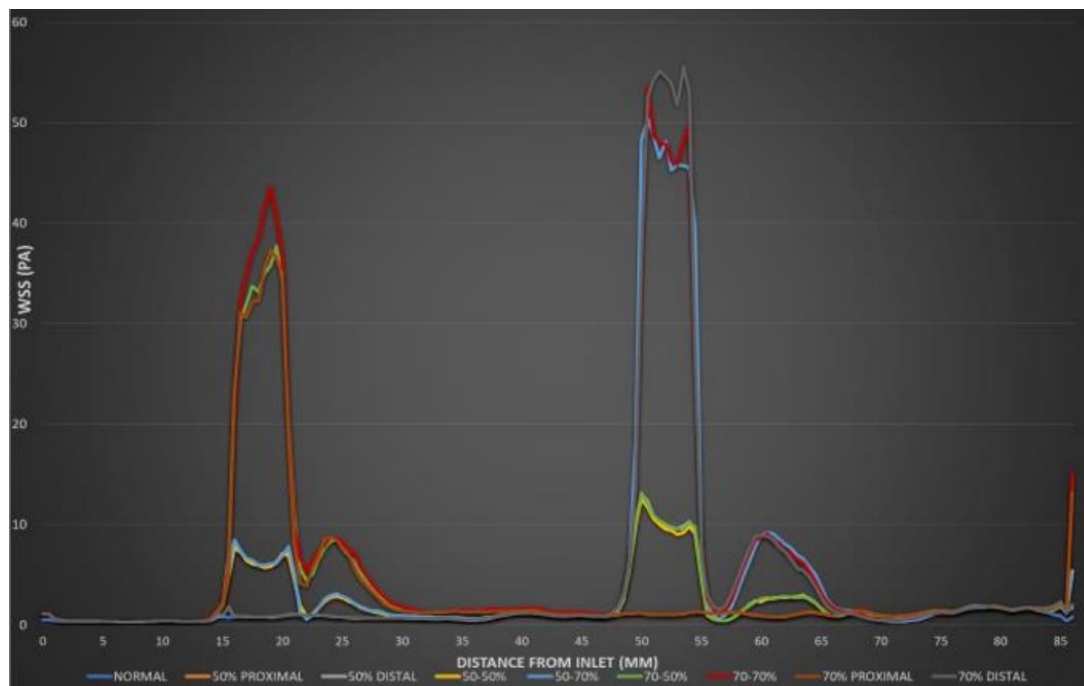


Figure 38 WSS throughout the LCx branch for all three cases

Furthermore, we calculated the smartFFR values for all the examined cases -including the healthy initial patient-specific model- and we saw that the distal stenoses have a more significant functional role compared to their respective proximal ones ^{Table 2}.

Table 2 Smart FFR results for proximal and distal segments of different stenotic cases

A/A	Proximal	Distal	SmartFFR
Case 1	-	-	0.95
Case 2	50%	-	0.93
Case 3	-	50%	0.91
Case 4	70%	-	0.70
Case 5	-	70%	0.58
Case 6	50%	50%	0.87
Case 7	50%	70%	0.50

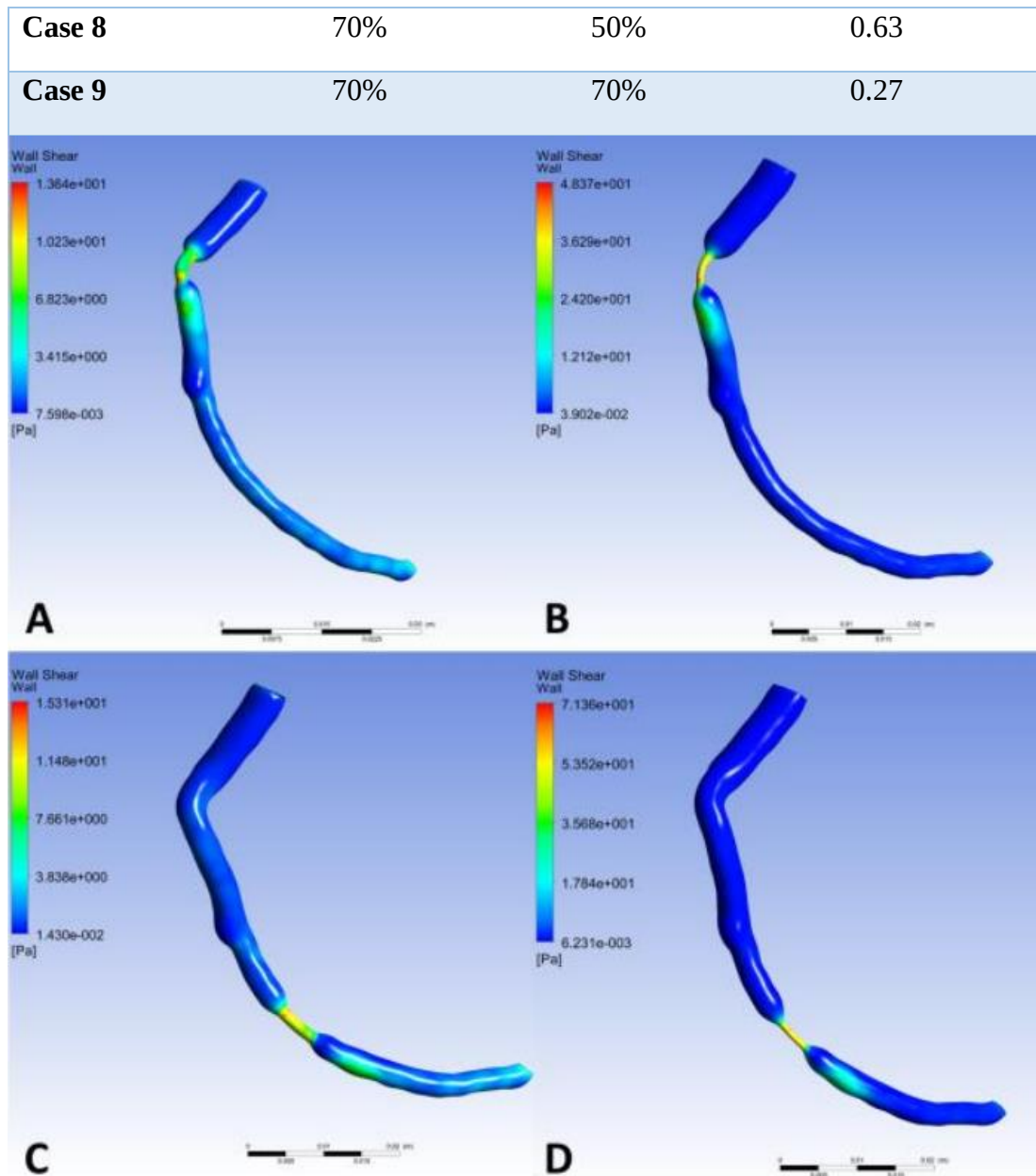


Figure 39 WSS distribution for A) Case 2, B) Case 4, C) Case 3 and D) Case 5

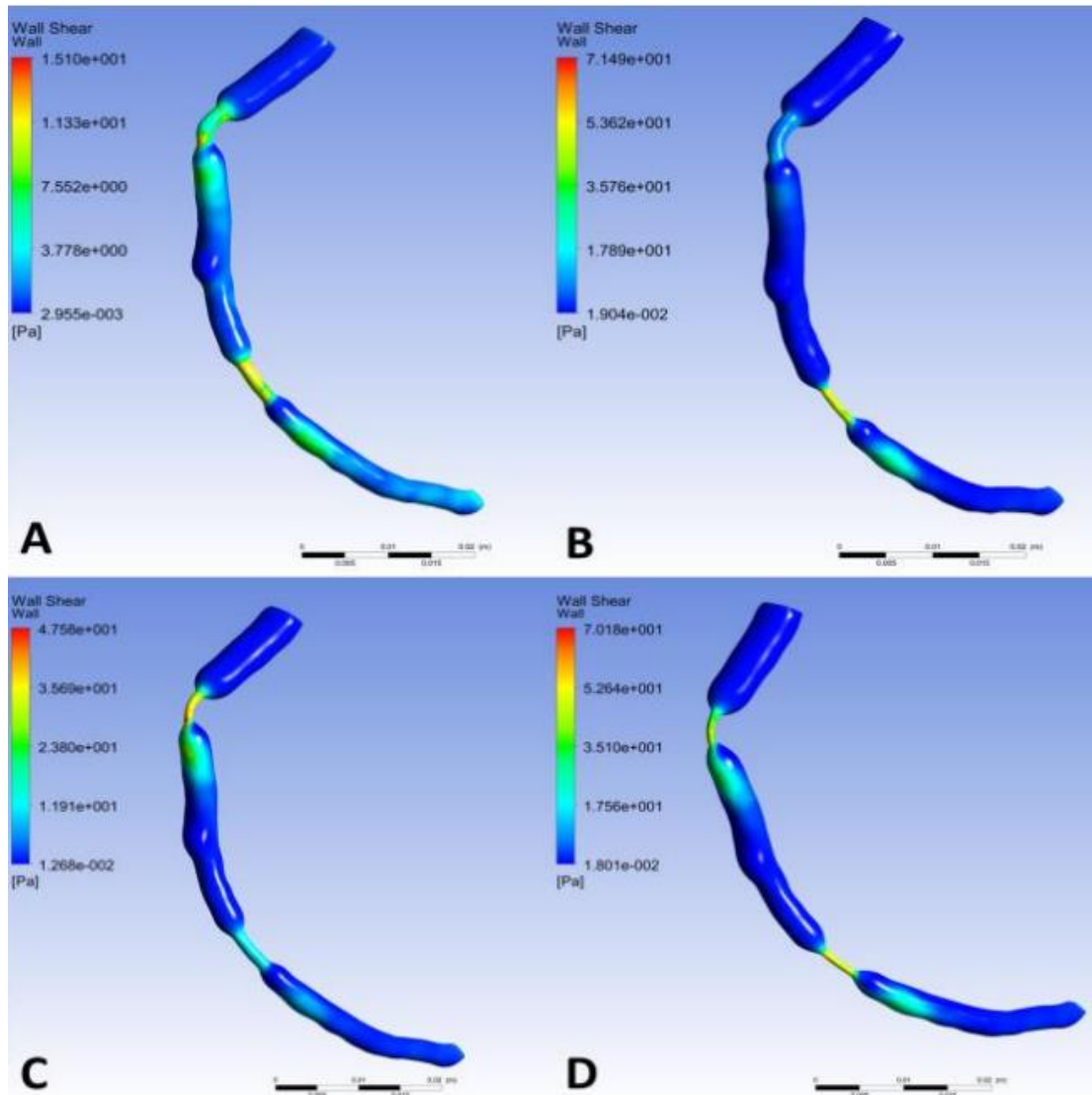


Figure 40 WSS distribution for A) Case 6, B) Case 7, C) Case 8 and D) Case 9, respectively

2.2.4 Discussion

In this study, we performed a multi-parametric analysis in order to investigate how the functional significance of a stenosis and the hemodynamic status of the examined artery are affected by the degree of the particular coronary stenosis and its location in single or tandem-lesion cases. For our study we used data from a healthy subject that underwent a typical CCTA exam. The CCTA sequence from the particular individual was used to create a 3D base healthy model upon which we then built eight distinct diseased models with a single or a couple of stenoses each. The particular healthy RCA segment was chosen for our analysis because it bore the general features of a normal vessel and could be effectively reconstructed and modified to imitate the different types of CAD-related lesions.

Based on the WSS distributions we showed that the site of the stenosis has an influence on the hemodynamic condition of the vessel. In particular, the observed WSS was higher at the distal stenoses rather than at the proximal ones. This means that distal stenoses are more likely to cause a plaque rupture. Additionally, we observed that the site that resides right after the throat of a stenosis is characterized by a drop at the WSS values followed by a small rise. This increase of the WSS can be attributed to the recirculating flow which often develops at this particular area. Furthermore, the distal 70% stenosis in all the examined combinations produces much higher peak WSS values in comparison with their respective proximal ones (i.e. 55 Pa vs. 37 Pa). As far as the functional significance of the stenoses is concerned, the smartFFR values show lower levels at the distal lesions, thus indicating a more severe phenotype in hemodynamic terms. Moreover, even a single lesion of 70%, results in an ischemic vessel and requires a percutaneous coronary intervention (PCI). On the contrary, the presence of two 50% tandem stenoses was not enough to produce an ischemic smartFFR value, which remained well above the threshold (at 0.87).

2.2.5 Conclusions

The hemodynamic status of a coronary vessel is highly affected by the degree, the number, and the location of the stenoses. WSS and smartFFR –obtained solely by non-invasive methods such as CFD- could serve as markers for the hemodynamic functional significance of a vessel.

2.3 Coronary Atherosclerosis and Its Consequences to The Vessel Wall and The Myocardium: A New Anatomical, Functional, Morphological and Bio-Mechanical Approach

2.3.1 Study Aim:

This study aims to evaluate and compare lesion-specific and total vessel smartFFR values with corresponding ESS values and to investigate the relationships between smart-FFR, ESS, stress myocardial blood flow (MBF), and myocardial flow reserve (MFR). By analyzing 21 coronary vessels from 10 patients using Computed Tomography Coronary Angiography (CCTA) and PET-MPI imaging, this study aims to assess the functional significance of coronary artery lesions and their effects on stress MBF and MFR.

2.3.2 Methods

2.3.2.1 Study population

The study included ten patients with an intermediate pre-test likelihood of coronary artery disease (CAD), who had participated in the EVINCI and SMARTool projects [55], [232] and had undergone CCTA and PET-MPI using either 15O-water or 13N-ammonia, were included in the study. Detailed descriptions of the study population characteristics, imaging procedures, and protocols have been provided elsewhere [234]. Ethical approval for the main EVINCI study was granted from all participants [234].

2.3.2.2 3D coronary artery reconstruction

The algorithm is based on the following approach: a) the CCTA images are pre-processed and the image distortion caused by intense calcified objects, is removed. b) A minimum cost path approach is used to extract the 3D centerline of the artery of interest. c) Using a function of the distance from the centerline and the Hounsfield Units (HU) values, an estimation of the weight function for the lumen is made. A final refinement of an active contour model for the lumen is implemented. d) Finally, the 3D surfaces for the lumen are created [235].

2.3.2.3 Computational fluid dynamics and boundary conditions

For each vessel, a tetrahedral mesh was constructed, and steady-state flow simulations were conducted using the incompressible Navier-Stokes equations. Blood was modeled as a Newtonian fluid with a density of 1050 kg/m^3 and a dynamic viscosity of 0.0035

Pa·s. Flow was assumed to be laminar and incompressible, with vessel walls modeled as rigid and subjected to no-slip and no-penetration boundary conditions [236]. At the inlet, a pressure boundary condition of 100 mmHg, representing the mean human aortic pressure, was applied. Steady-state simulations were performed across all cases, with two different scenarios at the outlet: one using flow values derived from ICA images and another using a flow rate of 1 ml/sec, which is a universally accepted coronary flow benchmark. [237] ^{Figure 41.}

Assessment of endothelial shear stress

Endothelial shear stress (ESS) at the luminal surface of the artery was determined by multiplying blood viscosity with the velocity gradient near the vessel wall. ESS was evaluated both at the most stenotic segment and across the entire vessel.

Calculation of smartFFR

To calculate the smartFFR, a transient simulation was performed for each case. At the inlet, a boundary condition of 100 mmHg, representing average human aortic pressure, was applied. The outlet boundary was defined by a flow profile with 5-time steps, each 0.25 seconds long, featuring volumetric flow rates of 0, 1, 2, 3, and 4 ml/s. The vessel wall was assumed to be impermeable (no-penetration) and subjected to a no-slip condition. To generate the patient-specific Pd/Pa curve, Pd/Pa values were computed at each time step, plotted, and then smoothed with a 100-point spline. The area under this curve (AUC) was then normalized by dividing it by the AUC of a theoretical healthy artery segment (with no pressure drop). This resulting ratio defines the smartFFR value, with a pathological threshold of 0.85, as established by prior studies [237].

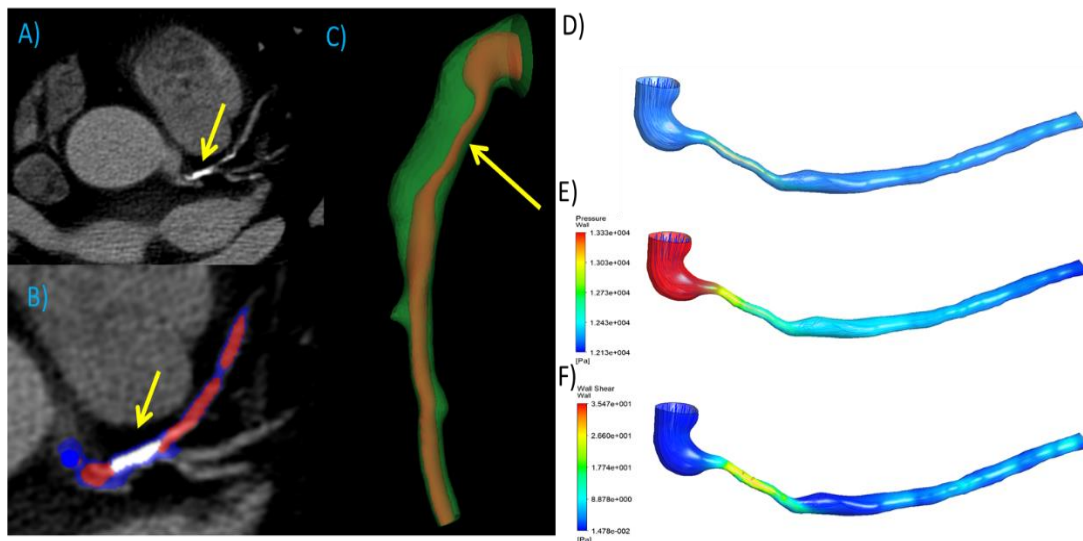


Figure 41 A) CT Coronary Angiography showing the LAD segment with stenosis severity exceeding 70% due to a high calcified volume; B) Zoomed-in view of the segment with lumen (red) and wall (blue) segmented; C) 3D model displaying the lumen (red) and wall (green); D) CFD flow analysis within the 3D reconstructed model, including SmartFFR and ESS calculations.

PET imaging and data analysis

PET/CT imaging was conducted according to international guidelines and the EVINCI study protocol [9] using ^{15}O -water or ^{13}N -ammonia. PET was classified as abnormal if more than one contiguous segment demonstrated both a stress Myocardial Blood Flow (MBF) ≤ 2.3 mL/g/min and a Cardiac Flow Reserve (CFR) ≤ 2.5 for ^{15}O -water, or an MBF < 1.79 mL/g/min and CFR ≤ 2.0 for ^{13}N -ammonia, respectively [238].

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or as median with interquartile range (IQR), while categorical variables are shown as absolute and relative frequencies. For continuous data, two-sided p-values were obtained using either the t-test or Mann–Whitney U test. Comparisons across multiple groups were made using ANOVA or Kruskal–Wallis tests. Agreement between the two ESS calculation methods were evaluated with Bland–Altman plots. A p-value of < 0.05 was considered statistically significant.

2.3.3 Results

Patient and vessel characteristics

In Table 3 we can see the demographics, the clinical and coronary lesion characteristics of the whole population used in the present study. We chose twenty-one (21) vessels

for our analysis, based on the degree of the stenosis (30%-70%) and the PET-MPI result. Of the above vessels fifteen (15) showed both normal MBF stress and CFR results, while six (6) had abnormal values.

Table 3 Baseline patients characteristics

PATIENT CHARACTERISTICS	
Patient (n=10)	N (%)
Age (years)	64.6 ± 4.5
Gender (male)	8 (80)
Vessel	
LAD	10 (48)
LCx	4 (19)
RCA	7 (33)
Lesion location	
Proximal	10 (48)
Middle	8 (38)
Distal	3 (15)

Comparison of ICA derived flow and 1 ml/sec for endothelial shear stress calculation

The 21 examined vessels had an average ICA-derived flow of 0.8 ml/sec. Additionally, segments with stenosis of 30%-50% and 51-70% showed no statistical difference between their flow values (median: 0.80 ml/sec vs 0.75 ml/sec, $p=0.36$, Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.). Regarding the lesion-specific ESS, we observed a significant difference between the two methods (1.96 vs 2.4, $p=0.006$, Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε. , Figure 43), therefore we selected the ICA flow for the rest of our analysis to calculate the ESS value.

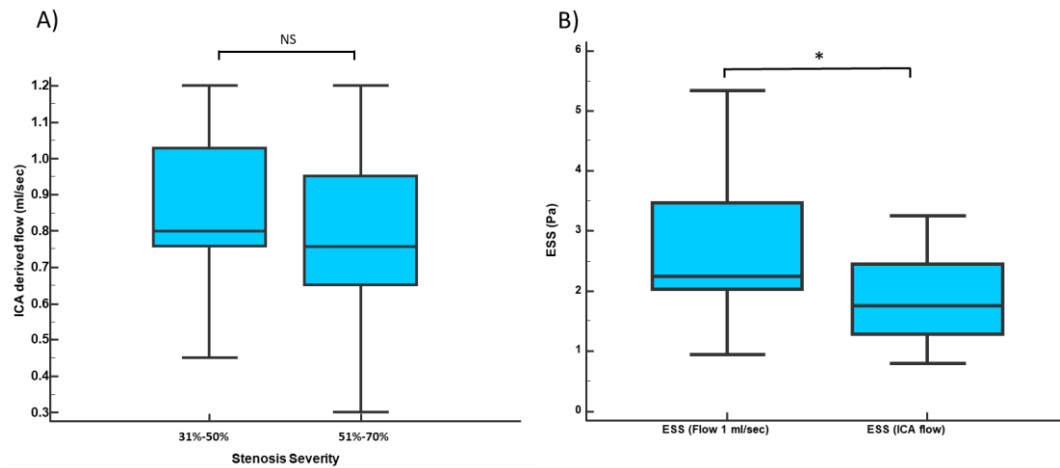


Figure 42 A) Flow distribution in the ICA for segments with CT-determined stenosis of 31-50% and 51-70%; B) ESS (Pa) distribution for ICA and at a flow rate of 1 ml/s.

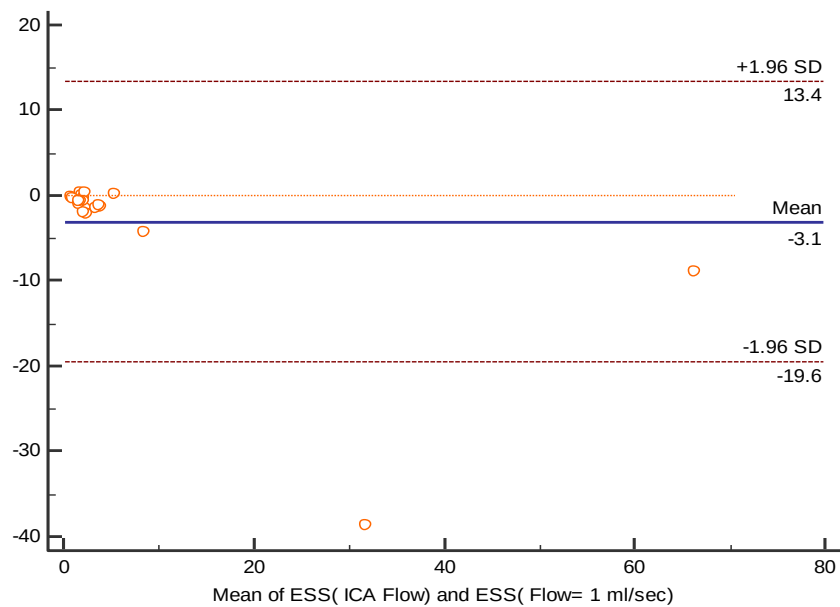


Figure 43 Bland-Altman plot for ESS derived from ICA flow compared to a flow rate of 1 ml/s.

Lesion specific vs total vessel length for ESS and smartFFR

The smartFFR values are significantly different when calculated for the whole vessel as compared to the site of the lesion (0.88 vs 0.96, $p=0.001$,

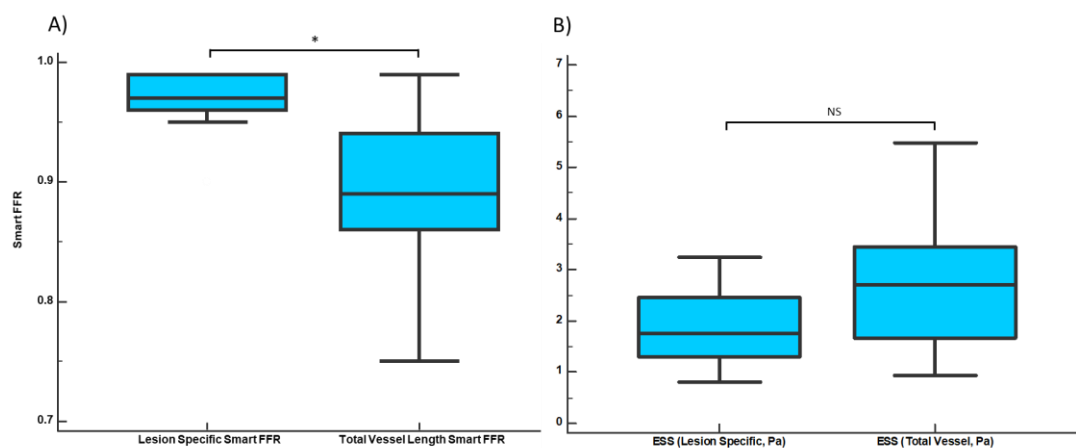


Figure 44). On the contrary, the ESS shows no such difference (1.96 vs 2.81, $p=0.61$, Figure 44). Therefore, for the rest of the analysis we chose to use the lesion-specific ESS as a representative marker for total ESS. We found out that both the lesion specific and the total vessel smartFFR are moderately and negatively correlated with the ESS ($r = -0.531$, $p = 0.01$, and $r = -0.585$, $p = 0.005$, Figure 45A, Figure 45B). Furthermore, vessels with abnormal total smartFFR showed higher ESS values (1.67 vs 6.28, $p=0.0001$, Figure 47A), as was the case for the lesion smartFFR (1.78 vs 34.1, $p=0.03$, Figure 47B). However, only 2 vessels presented abnormal lesion smartFFR.

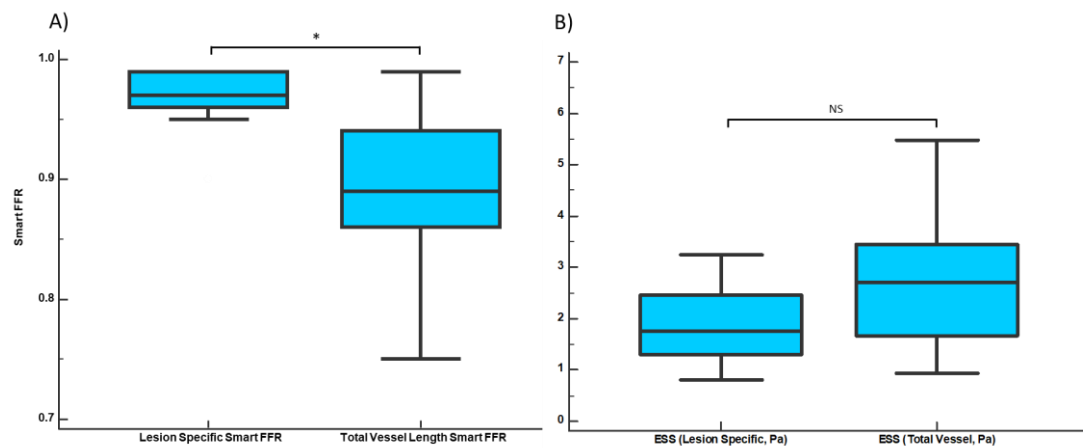


Figure 44 A) Comparison of SmartFFR values between lesion-specific areas and the total vessel area; B) Comparison of ESS values between lesion-specific areas and the total vessel area.

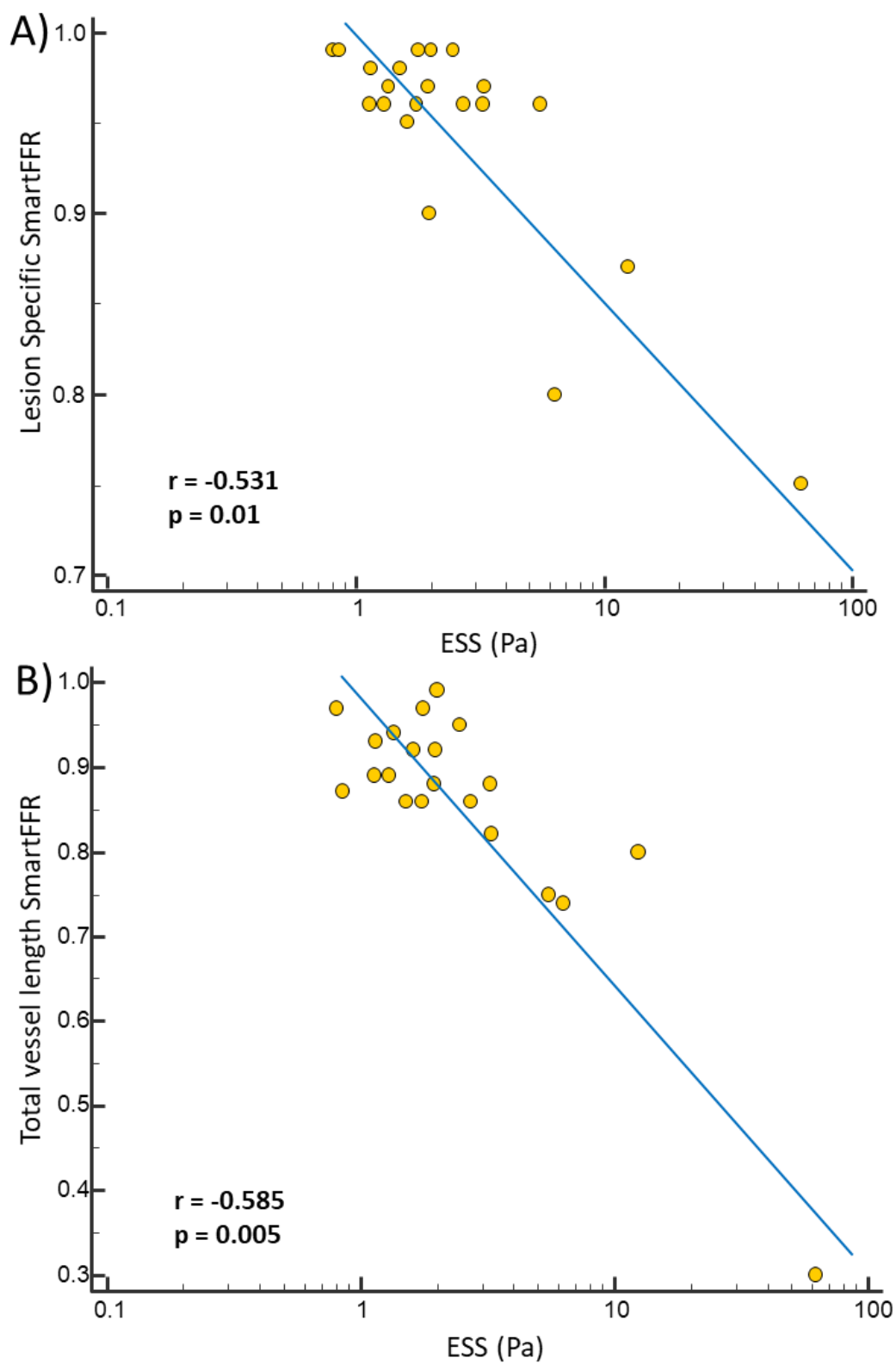


Figure 45 A) Correlation plot of ESS and lesion specific SmartFFR; B) and of ESS and total vessel SmartFFR

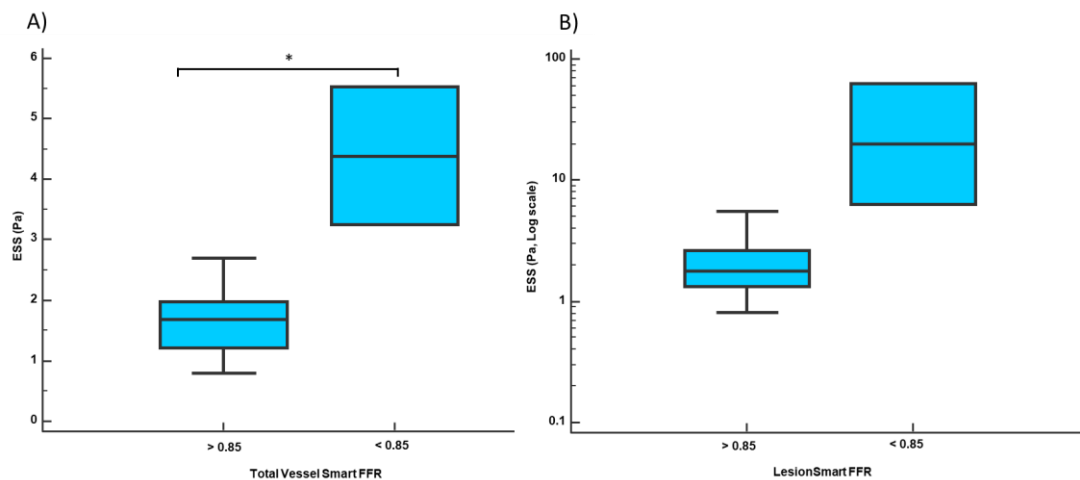


Figure 48 A) ESS values in vessels with total SmartFFR and B) Lesion greater than and less than 0.85., $p < 0.05$

Stenosis severity, smartFFR and ESS

Segments with stenosis of 30%-50% showed higher lesion and total vessel length smartFFR compared to segments with 51%-70% stenosis, but the observed difference was not statistically significant ($p = 0.17$, $p = 0.19$, Figure 49). Accordingly, the ESS values show a similar trend (1.61 vs 2.34, $p = 0.12$, **Σφάλμα! Το αρχείο προέλευσης της αναφοράς δεν βρέθηκε.**).

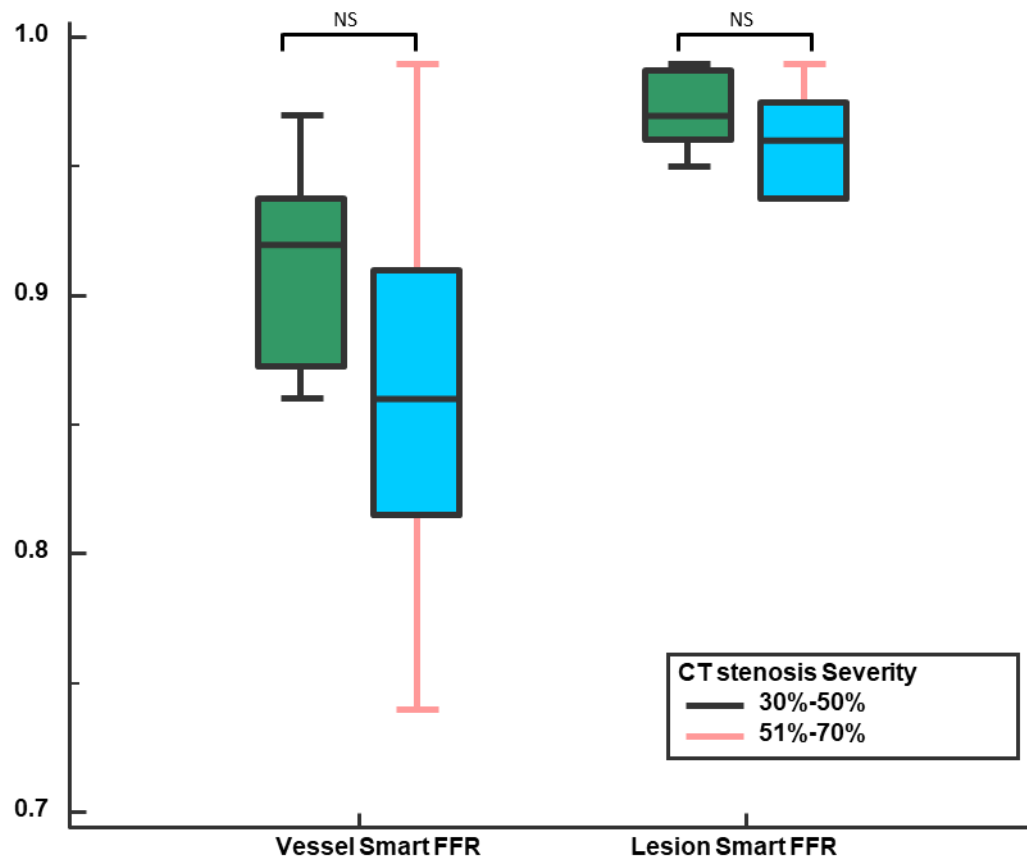


Figure 49 Total vessel and lesion-specific SmartFFR values for CT stenosis severity ranges of 31-50% and 51-70%.

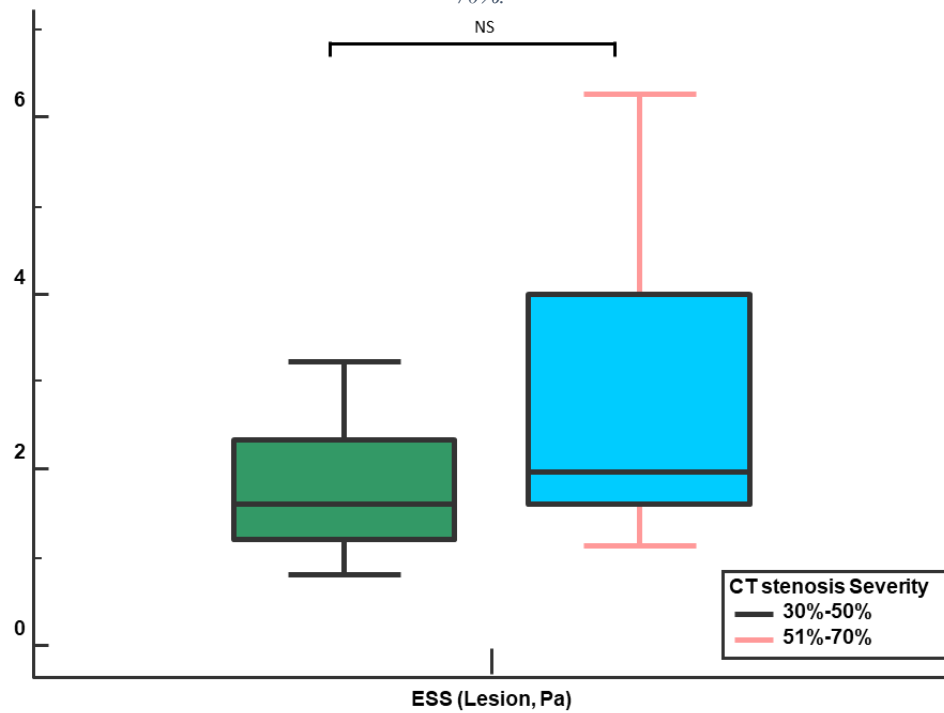


Figure 50 ESS (Pa) values for CT stenosis severity ranges of 31-50% and 51-70%.

MBF stress and CFR relationship with smartFFR and ESS

Vessels with abnormal PET-MPI showed lower total vessel length and lesion specific smartFFR in comparison with the normal vessels (0.78 vs 0.92, $p=0.001$ and 0.92 vs 0.97, $p=0.02$, respectively, Figure 51). ESS values are higher in vessels with pathological MBF stress and CFR (5.9 vs 1.61, $p=0.001$, Figure 52). When the PET-MPI results are considered in every vessel, the total vessel length smartFFR and ESS in lesion appears to represent in more detail the functional significance of the vessel ^{Figure 53}.

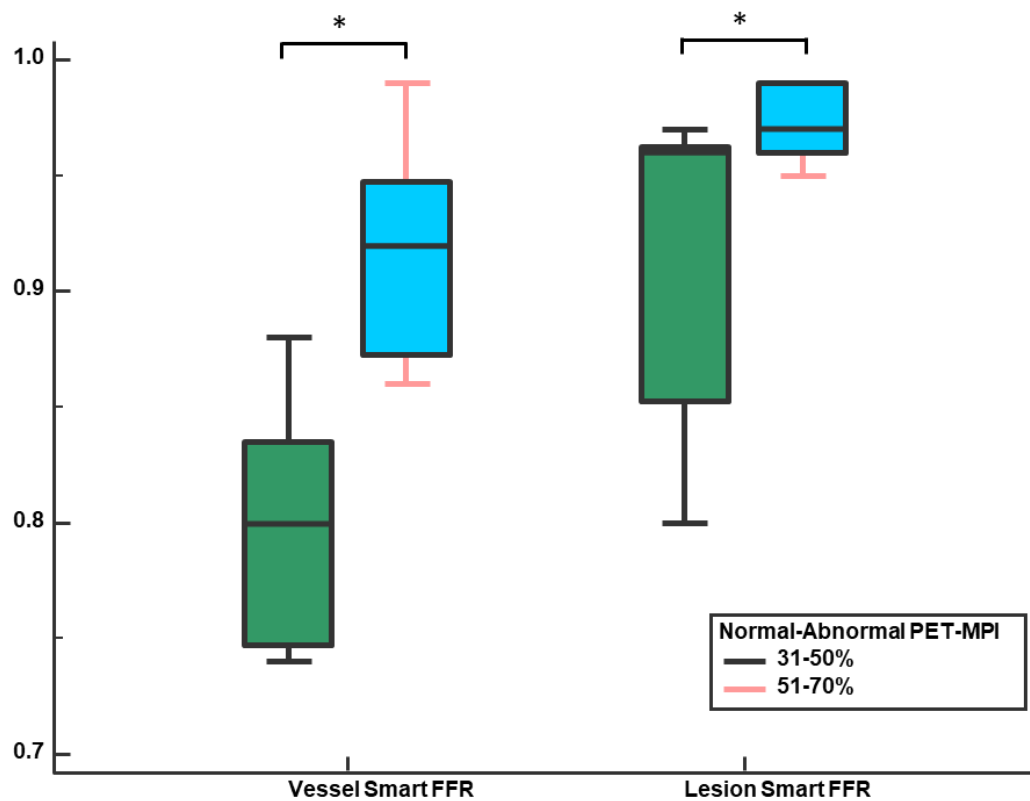


Figure 51 Total vessel and lesion-specific SmartFFR values in vessels with normal and abnormal PET-MPI.

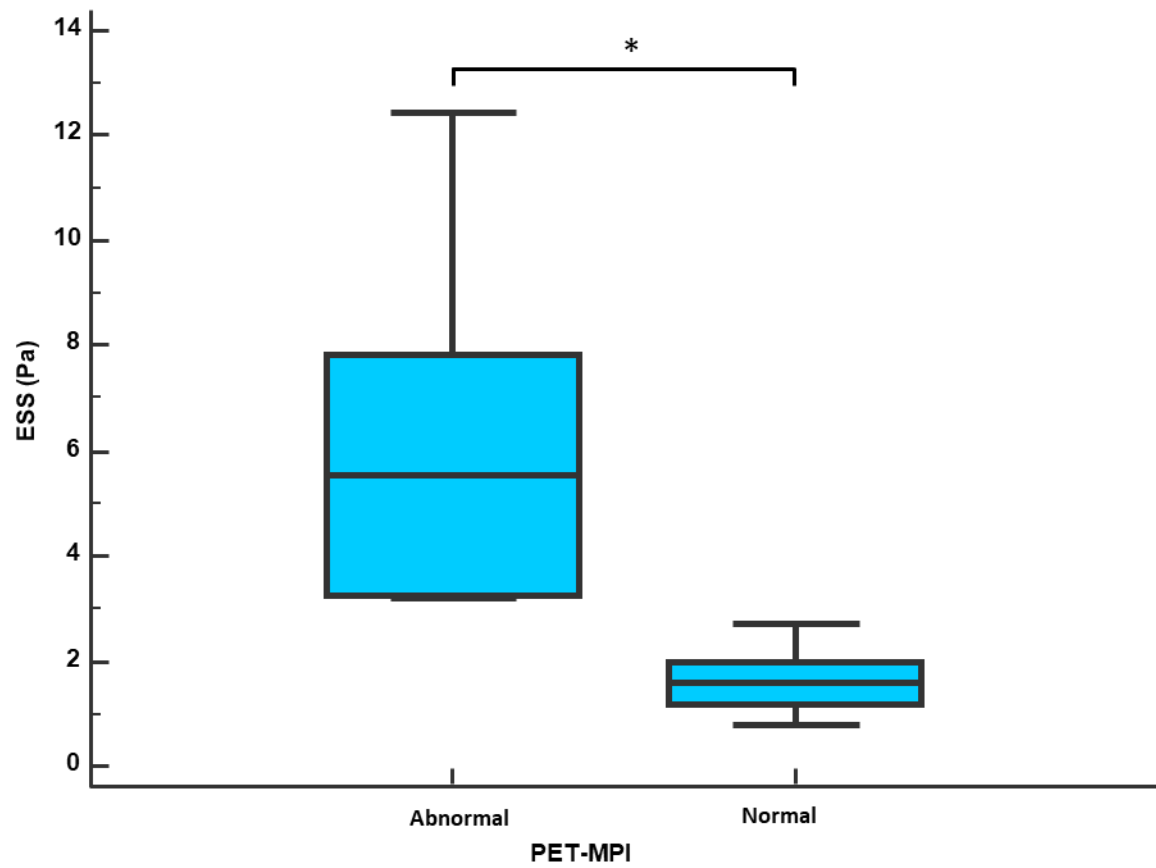


Figure 52 Lesion-specific ESS (Pa) in vessels with normal and abnormal PET-MPI.

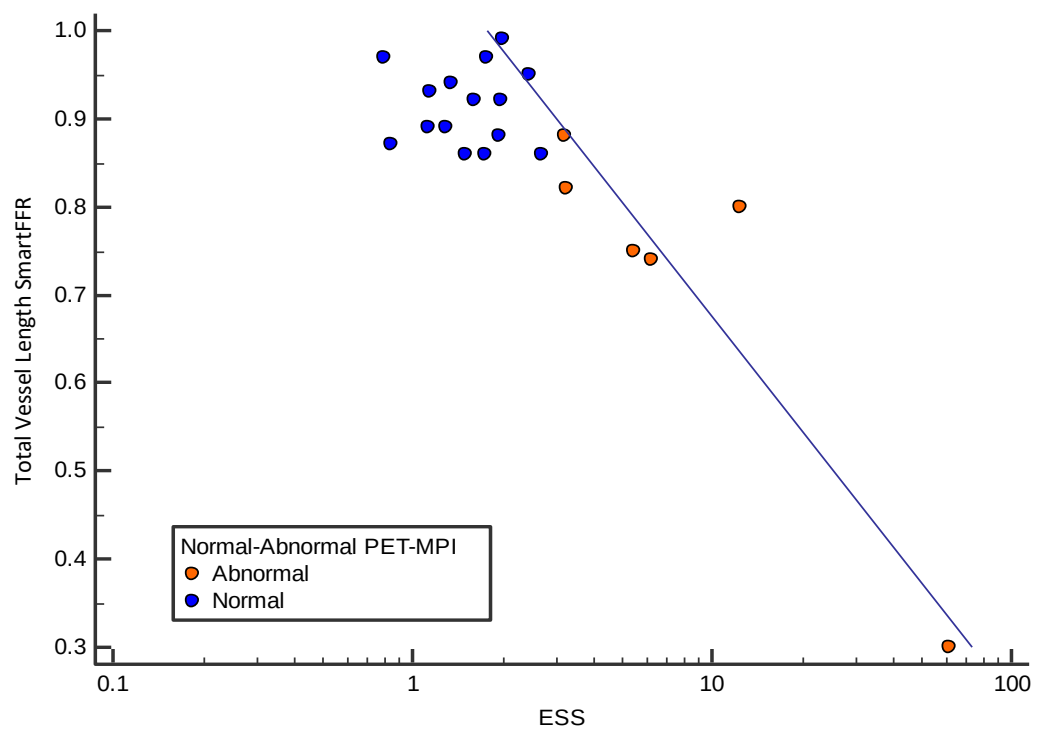


Figure 53 Relationship plot between ESS and SmartFFR.

2.3.4 Discussion

Thanks to the ongoing progress in the field of biomedical engineering we are now able to calculate quickly and accurately important hemodynamic factors for the coronary vasculature, such as ESS or other functionality markers. In the present study we primarily examined the efficiency of such metrics and their combination (ESS and smartFFR) -as measured by PET-MPI analyses- in distinguishing coronary segments with impaired flow from normal ones. Our most standout findings were the following: a) vessel smartFFR was significantly lower in cases with abnormal stress MBF and CFR (0.78 vs. 0.92), while ESS was significantly elevated (5.9 Pa vs. 1.61 Pa, respectively). The aforementioned findings indicate that it is feasible to use solely smartFFR as a marker for the functional assessment of coronary flow impairment, since, using the already established smartFFR threshold of 0.85, it showed significantly high accuracy, sensitivity, specificity, positive predictive (PPV) and negative predictive values (NPV) (95.2%, 83.3%, 100%, 93.75% and 95.24%, respectively).

Furthermore, diseased vessels showed substantially increased ESS values compared to healthy ones; thus, ESS alone could also be used for the identification of vessels with impaired flow.

The detection of diseased vessels is anticipated to improve further by the utilization of a combination of the two aforementioned markers, which will possibly lead to the minimization of the false positive or false negative results. Nevertheless, our study has certain limitations. First, we analyzed exclusively single coronary segments and did not take into consideration any side branches. Second, the limited size of our dataset prevented us from establishing an ESS threshold for the identification of impaired vessel flow, therefore we were unable to produce quantitative results for the combination of the two examined metrics. The establishment of an ESS threshold is imperative for the development of a combined functional index which will be used for the assessment of coronary lesions. However, our initial findings present a clear trend where lower ESS values correspond to cases with normal stress MBF and CFR, thus making the concept quite promising. In general, considering that this is a proof-of-concept study, the results presented are encouraging.

2.3.5 Conclusions

Concluding, ESS as well smartFFR present discriminative power in identifying vessels of impaired flow compared with PET-MPI measured stress MBF and CFR. Both metrics are geometry-based and combining them is expected to improve their discriminative power and establish them as a useful CAD assessment tool.

2.4 Relationship of Endothelial Shear Stress with Plaque Features with Coronary CT Angiography and Vasodilating Capability with PET

2.4.1 Study Aim:

This study aims to examine the relationship between computational fluid dynamics (CFD) metrics derived from coronary CT angiography (CCTA) and the anatomical and morphological features of coronary lesions. Specifically, it seeks to evaluate the performance of these metrics, including endothelial shear stress (ESS), in predicting reduced coronary vasodilatory capacity as measured by PET myocardial perfusion imaging (MPI). Additionally, the study aims to determine whether combining ESS with CCTA-derived stenosis severity enhances the prediction of functionally significant coronary lesions.

2.4.2 Methods

Study population

The study cohort comprised 53 patients (31 male, mean age 64.7 ± 7.1 years) with an intermediate pre-test probability of coronary artery disease (CAD), all of whom were participants in the EVINCI and SMARTool projects [55], [239]. Each patient underwent both CCTA and PET-MPI using either ^{15}O -water or ^{13}N -ammonia tracers. Exclusion criteria included a recent history of acute coronary syndrome, established CAD, a left ventricular ejection fraction under 35%, more than moderate valvular disease, and any cardiomyopathy. Comprehensive details regarding the study cohort, imaging techniques, and procedural protocols are provided in prior publications[55]. Following SMARTool selection standards, only CCTA scans rated as fair to excellent in quality were included, focusing on patients exhibiting stenosis levels between <30% and 90%. From the initial pool of 98 EVINCI patients who had completed both CCTA and PET/CT scans, 30 were excluded due to suboptimal imaging quality that precluded analysis. Additionally, 15 patients without detectable coronary lesions on CCTA were omitted. The resulting sample of 53 patients included individuals with at least one vessel free of significant noise, pronounced calcification, or motion-related artifacts. Ethical approval for the EVINCI project was secured from each institution involved, and informed consent was obtained from all study participants [55].

CCTA imaging and data analysis

CCTA imaging was performed using CT scanners with a minimum of 64 slices, adhering to the EVINCI study protocol [55]. To ensure high-quality images, sublingual nitrates and intravenous beta-blockers were administered to reduce heart rate. Iodinated contrast medium (100 ± 46 ml) was delivered at a rate of 5-8 ml/sec, followed by a saline flush (84 ± 14 ml) at 5 ml/sec. Scanning parameters included detector collimation set to 64×0.625 mm, a gantry rotation speed of 350 msec, and a tube voltage of 120 kV. The arterial segments targeted for analysis were reconstructed during mid- to end-diastole, corresponding to 70%-80% of the R-R interval.

3D coronary artery reconstruction

A comprehensive description of the 3D CCTA reconstruction protocol is provided elsewhere [57]. This study specifically targeted analysis of the three primary epicardial coronary arteries—namely, the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA)—while excluding side branches. The CCTA-based 3D reconstruction process proceeded as follows: a) preprocessing with the Frangi Vesselness filter to identify potential vessel regions; b) derivation of each vessel's 3D centerline using a minimum-cost path technique; c) computation of a weighting function for the lumen, outer wall, and calcified plaque regions, leveraging Hounsfield Unit (HU) values and distances from the established 3D centerline; d) segmentation of the lumen and outer wall boundaries through an active contour model; e) utilization of a level set method to isolate significant calcified regions for plaque segmentation; and f) creation of 3D surface models for both the lumen and outer wall.

Outlet flow calculation from Intracoronary Angiography (ICA)

Coronary blood flow for each arterial segment of interest was calculated using the method proposed by Stone et al. [240]. Briefly, for each segment we chose a section with no side branches along its length because the presence of side-branches could potentially alter the calculated flow. Flow was calculated by the actual time required for the volume of blood of this particular section to be shifted by the contrast agent that was injected to the artery. The 3D volume of the segment was calculated from the respective reconstructed model and the number of cine frames that were required for the aforementioned shift was counted [240]. The artery-specific flow rate was calculated using the following equation:

$$\text{Flow rate} = \frac{3D \text{ volume} \times \text{frame rate}}{\text{frame count}}$$

where 3D volume is the volume of the examined segment, frame rate the frame rate of the angiography (i.e. 15, 25 or 30 frames/second) and frame count the number of frames needed for the radio-opaque agent to reach the end of the examined segment, respectively. The average outlet flow results according to stenosis severity are the following:

Table 4 ICA average flow results for different stenosis severity

Stenosis severity				
		<30%	31-50%	51-90%
Outlet	Flow, (ml/sec)	0.94 (0.12)	0.78 (0.20)	0.70 (0.19)
(SD)				

SD: standard deviation

Computational fluid dynamics and boundary conditions

Each vessel was represented by a tetrahedral mesh, with steady-state flow simulations performed according to the incompressible Navier-Stokes equations. A mesh sensitivity analysis established a face size range of 0.095 to 0.120 mm. Blood was simulated as a Newtonian fluid, with properties defined by a density of 1050 kg/m³ and a dynamic viscosity of 0.0035 Pa·s. Flow conditions were set as laminar and incompressible, while rigid vessel walls were modeled with no-slip and no-penetration boundary conditions. To manage computational demands, a fixed inlet pressure of 100 mmHg was applied to mimic resting myocardial blood flow [204], [241], [242]. Individual vessel flow rates (ml/sec) were calculated from corresponding intra-coronary angiography (ICA) data and implemented in the simulation, which was conducted using ANSYS CFX 15 (Canonsburg, PA, USA).

Assessment of endothelial shear stress

Lesion start and end points were identified on CCTA images by an experienced, independent reader (A.A), using SMARTool software [232]. For analysis, the total lesion (TL) length was subdivided into three sections: proximal (ESSprox), minimum lumen area (ESSMLA, covering a segment ≤ 3 mm), and distal (ESSdist). Each segment, along with the entire TL, was assessed independently for ESS. ESS at the luminal surface was

calculated by multiplying blood viscosity by the velocity gradient near the vessel wall, with results averaged every 0.5 mm along the TL and within each segment (proximal, MLA, and distal) along the coronary centerline ^{Figure 55}. The analysis included only vessels with at least one coronary lesion, and the mean (SD) total time required for ESS calculations was 20 ± 10 minutes.

Plaque analysis

An expert in CCTA analysis, blinded to PET-MPI results, conducted the CCTA plaque assessment using multiplanar reformatted images with an average slice thickness and increment of 0.6 mm. To quantify total plaque volume and its individual components, as well as to allow direct comparison with ESS changes, the analysis was limited to the TL segment rather than the full vessel length. Semiautomated software (Aquarius Workstation, TeraRecon Inc., Foster City, CA, USA, Figure 56) was used, with manual adjustments for vessel and wall boundaries where needed. Plaque volume (PV) in each lesion was categorized by Hounsfield units (HU) into non-calcified PV (-30 to 350 HU) and calcified PV (> 350 HU). Non-calcified PV was further classified into necrotic core (-30 to 30 HU), fibrofatty plaque (31 to 130 HU), and fibrous plaque (131 to 350 HU) [243]–[245]. The percentage composition of each plaque type within the total plaque was determined by the ratio of each component's volume to the total PV. The intra-observer coefficient of variation for total PV and non-calcified PV, calculated from 32 patients and 40 randomly selected vessels (43%), was 8.6% and 9.4%, respectively.

PET imaging and data analysis

The PET core lab center specified acquisition protocols, and data processing was conducted using the cardiac PET modeling software (PCARDP) within PMOD (version 3.5, PMOD Technologies, Zurich, Switzerland, [246]). Myocardial blood flow (MBF) at rest and under stress was calculated through model fitting of the arterial input function and tissue time-activity curve [246], following established tracer-specific methods (Hermanssen et al for ^{15}O -water, Grado et al. for ^{13}N -ammonia). The left ventricular wall was segmented into 17 regions.

PET/CT imaging conformed to international standards and the EVINCI study protocol [246] employing ^{15}O -water or ^{13}N -ammonia. Supplementary details on PET imaging procedures are provided in the Supplementary Material. To match myocardial segments with their respective coronary regions, fusion of CCTA and PET images was performed

on the Advantage Workstation (4.4, GE Healthcare) using the CardIQ Fusion software package (GE Healthcare) [247]. PET was marked as abnormal if more than one contiguous segment displayed both a stress MBF ≤ 2.3 mL/g/min and an MFR ≤ 2.5 for 15O-water, or an MBF < 1.79 mL/g/min and an MFR ≤ 2.0 for 13N-ammonia [235], [244].[238], [246].

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) or as median with interquartile range (IQR), while qualitative variables are shown as absolute and relative frequencies. The normality of data distributions was assessed via the Kolmogorov-Smirnov test. Two-sided p-values were computed using the t-test or Mann–Whitney U test for continuous variables, and for multi-group comparisons, ANOVA or Kruskal-Wallis tests were applied. Statistical significance was defined by a p-value threshold of <0.05 . Relationships between ESS and plaque characteristics were examined using the Spearman rank correlation coefficient. The intra-observer coefficient of variation was calculated by dividing the SD of the measurements by their mean, presented as a percentage (%). Angiographic stenosis severity was categorized into three ranges: $<30\%$, $31\text{--}50\%$, and $51\text{--}90\%$. An ESS threshold of 3.67 Pa, selected based on the median ESS value at the minimum lumen area (MLA) for this study population and aligning with typical values in the literature [248] was employed to delineate “low” versus “high” ESS subgroups. A stenosis severity threshold of $\geq 50\%$ on CCTA was used to indicate angiographically significant coronary artery stenosis. In vessels with multiple stenoses, the most severe narrowing was selected for ESS and plaque characteristic calculations. To assess the added predictive value of ESS alongside stenosis severity and total plaque volume (PV) or non-calcified PV for abnormal PET-MPI findings, logistic regression models and corresponding c-index (AUC) values were calculated, with bootstrapping (1000 iterations) performed using SPSS software (version 13, Ostend, Belgium) and the R statistical software package (version 3.6.3).

2.4.3 Results

Patient and vessel characteristics

Table 6 presents the demographics, clinical data, and coronary lesion characteristics of the study population. Among the 159 coronary arteries in the dataset, 28 (2 LAD, 13 LCx, and 13 RCA) were healthy, 10 showed diffuse disease (1 LAD, 2 LCx, and 7 RCA), and 22 were excluded due to low image quality (6 LAD, 10 LCx, and 6 RCA). In 4 cases (RCAs), hybrid imaging analysis indicated that perfusion of the inferior wall was supplied by a posterior descending artery originating from the LCx. Additionally, 3 arteries (2 LAD, 1 RCA) exhibited stenosis severity >90%. These arteries were excluded from further analysis. For the remaining 92 vessels (including 72 with a single lesion), stenosis severity, plaque characteristics, and ESS values were assessed Figure 54.

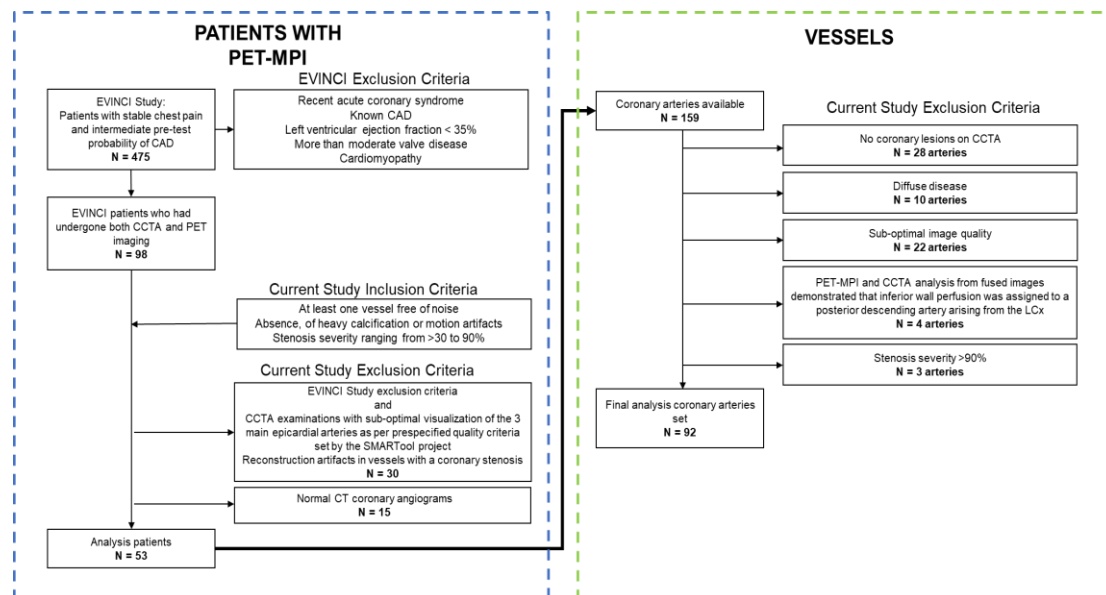


Figure 54 Study flow diagram of patients and vessels. CAD = Coronary Artery Disease, CCTA = Coronary CT Angiography, EVINCI = Evaluation of Integrated Cardiac.

Endothelial shear stress distribution across coronary lesions and relationship with stenosis severity

For our analysis the ESS at MLA was used as a marker for lesion-related ESS, since all ESS indices were highly positively inter-correlated ($\rho > 0.78$ for all comparisons, Figure 58). ESS at MLA was significantly higher compared to ESS_{prox} and ESS_{dist} Figure 57. ESS presented higher values in regions with > 50% stenosis, in comparison with segments with stenosis < 50% (Figure 59, Table 2).

Table 5 Distribution of ESS and plaque burden across subgroups of stenosis severity

Stenosis severity

	<30%	31-50%	51-90%	P-value
ESS (TL), Pa (SD)	1.99 (1.52)	2.49 (1.67)	6.80 (11.7) *	0.0122
ESS (Prox), Pa (SD)	1.74 (1.18)	2.11 (1.15)	5.36 (8.47) *	0.0203
ESS (MLA), Pa (SD)	3.30 (2.96)	4.63 (3.99)	15.1 (29.8) *, #	0.0037
ESS (Dist), Pa (SD)	1.41 (0.96)	1.67 (0.86)	4.78 (7.84) *	0.0216

Dist: distal lesion segment; ESS: endothelial shear stress; MLA: minimum lumen area; Prox: proximal lesion segment; SD: standard deviation; TL: total lesion

***p<0.05 vs SS<30%, #p<0.05 vs. SS 31-50%.**

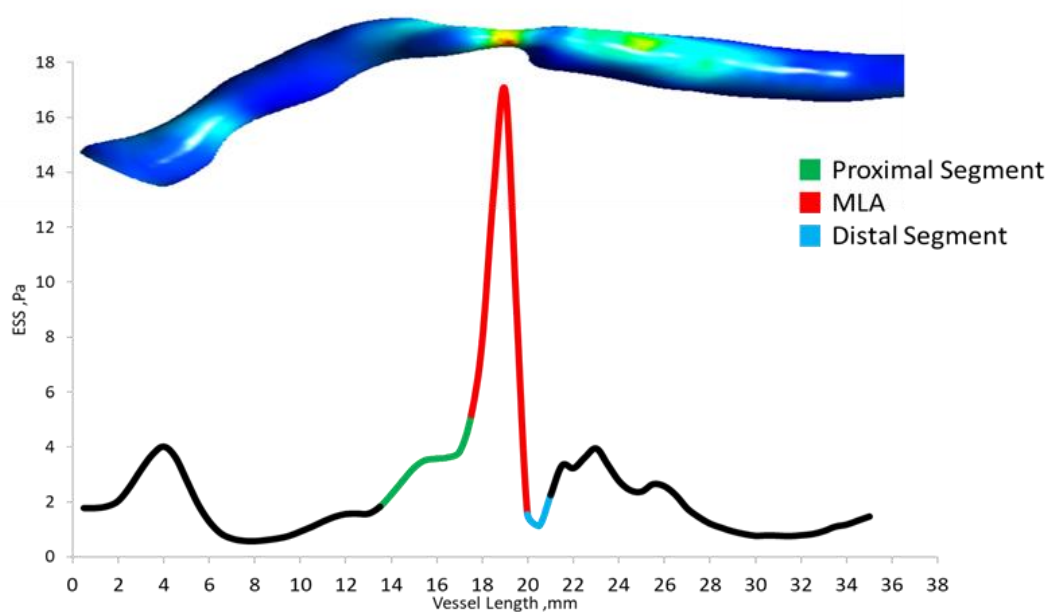


Figure 55 ESS values in stenotic segments, plaque attributes, and stenosis severity. (A) Right coronary artery segment displaying calculated mean ESS values measured at 0.5 mm intervals along the vessel's length. The minimum lumen area (MLA) demonstrates elevated mean ESS values in comparison to proximal and distal sections (10 Pa vs. 3.6 Pa vs. 1.9 Pa).

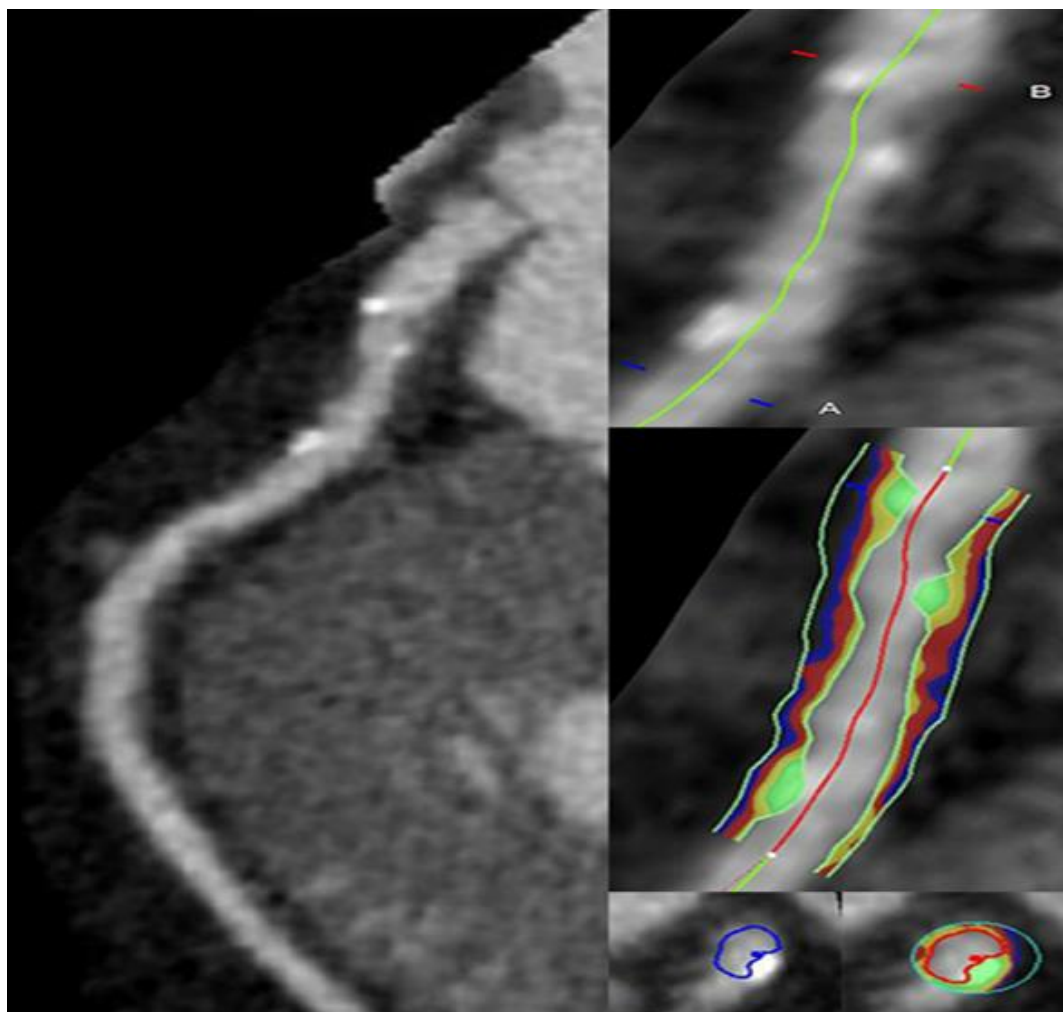


Figure 56 Identification of plaque in the left anterior descending artery on CCTA (left panel) and in curved planar reformat (upper right panel); detailed view of the targeted volume with color overlays indicating plaque components (middle right panel: blue for necrotic core, red for fibrofatty tissue, yellow for fibrous tissue, and green for dense calcium). The cross-sectional image (lower right panel) highlights lumen boundaries with color-coded plaque components.

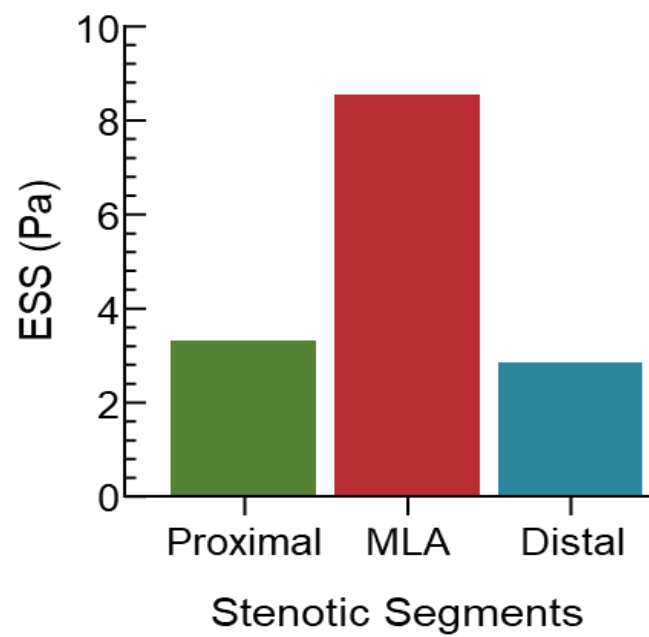


Figure 57 Mean ESS value distribution across segmented lesions. ESS is higher in proximal segments compared to distal ones, with the minimum lumen area showing the highest ESS among the three calculated stenotic segments.



Figure 58 Correlogram showing correlations between ESS in the total lesion, proximal, MLA, and distal segments.

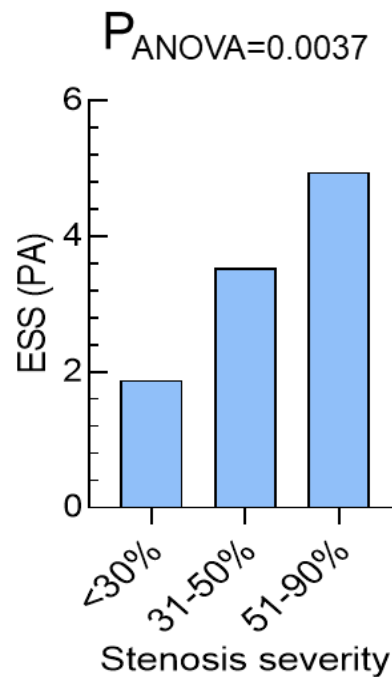


Figure 59 Mean ESS_{MLA} distribution across stenosis severity levels. * $p < 0.05$ compared to proximal and distal segments, * $p < 0.05$ vs. SS <30%, # $p < 0.05$ vs. SS 31-50%.

Relationship between endothelial shear stress, plaque volumes and plaque composition

We observed that ESS and total PV ($\rho = 0.281$, $p = 0.0068$), as well as ESS and non-calcified PV ($\rho = 0.266$, $p = 0.01$, Figure 60) were weakly positively correlated. Next, we saw that ESS showed a weak positive correlation with plaque phenotype features i.e. individual components of non-calcified PV: necrotic core, fibrous and fibrofatty plaque volume^{Figure 61}. Arteries with high ESS showed significantly higher non-calcified PV^{Table}

⁸, while no difference was observed regarding plaque composition (necrotic core, fibrous, fibrofatty and calcified plaque, Figure 62).

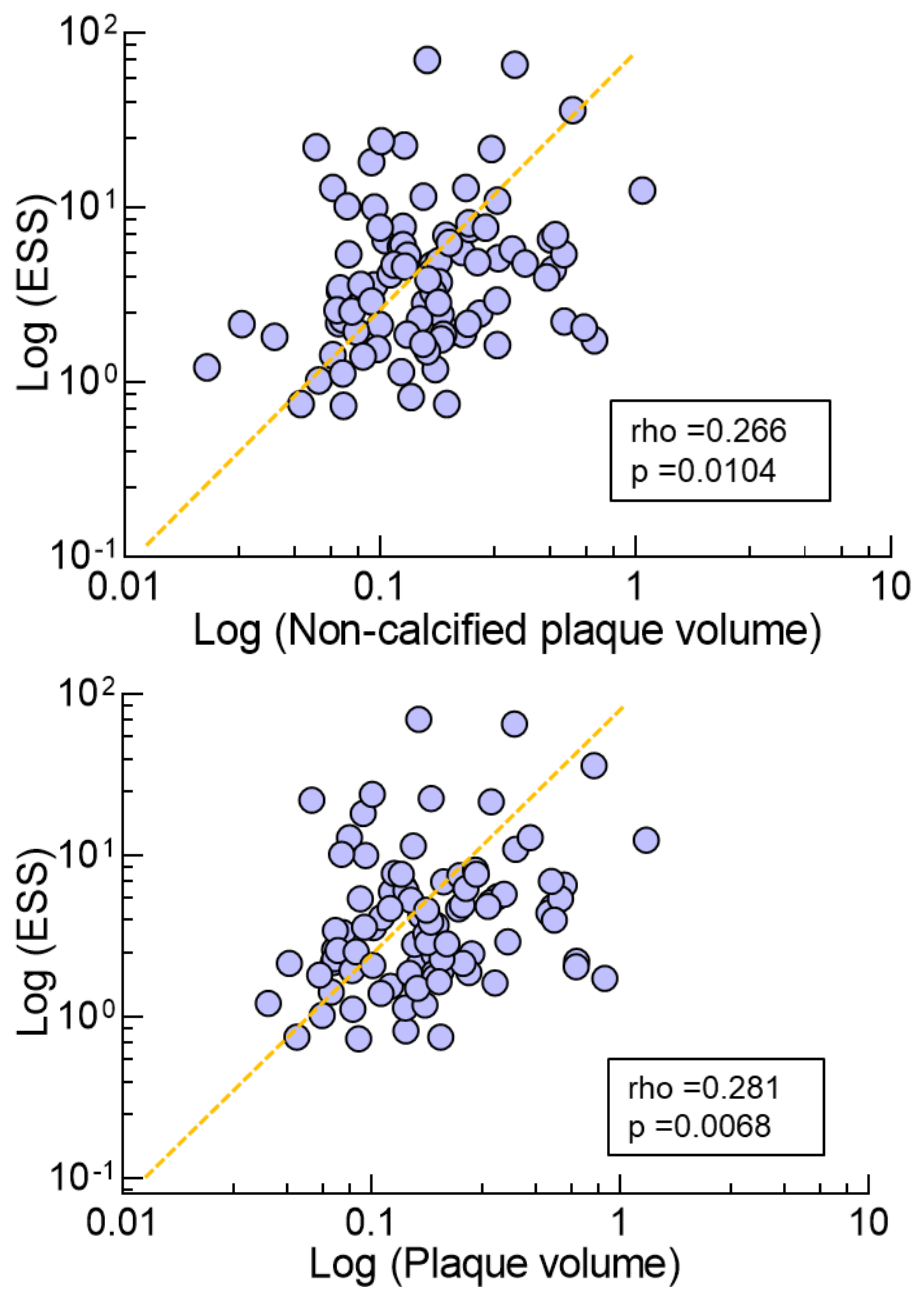


Figure 60 Correlations between ESS and plaque characteristics. Scatterplots presenting Scatterplots presenting Spearman's rho correlation between ESS and plaque volume as well as ESS and non-calcified plaque volume

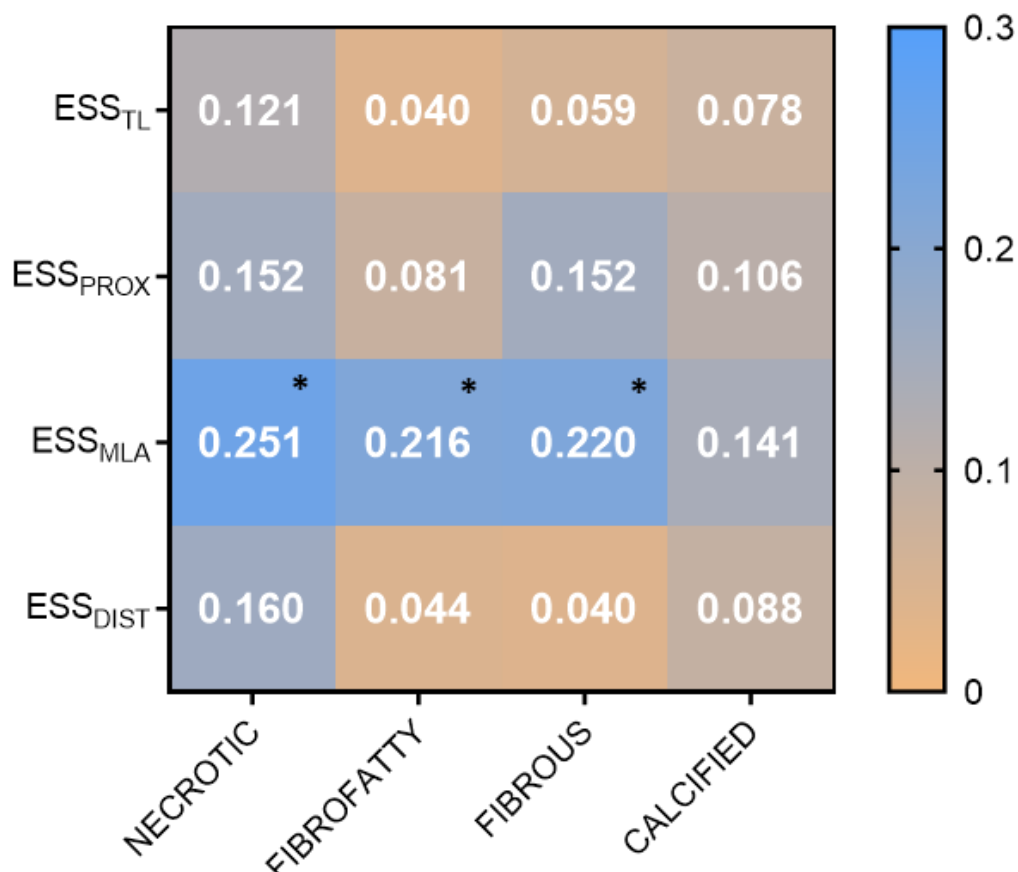


Figure 61 Correlogram showing correlations between ESS and plaque characteristics, * $p < 0.05$.

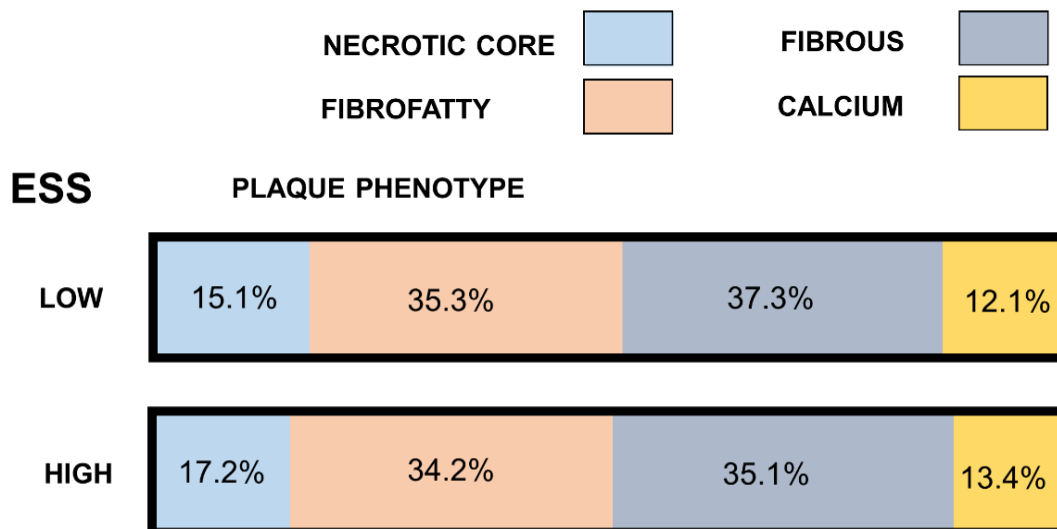


Figure 62 Mean percentage of plaque phenotype across ESS subgroups.

Table 6 Study population and lesion characteristics

Patients (n=53)		Lesion characteristics (n=92)	
Age, years (SD)	64.7 (7.1)	LAD (%)	44 (48)
Male sex (%)	31 (58)	LCx (%)	26 (28)
Symptoms		RCA (%)	22 (24)
		Focal lesion vessels (%)	72 (78)
		>1 vessel Patients (%)	31 (58)
Typical angina (%)	8 (15)	Stenosis Severity, %	
Atypical angina (%)	29 (55)	<30 (%)	17 (18)
Non-anginal chest pain (%)	16 (30)	31-50 (%)	38 (41)
		51-90 (%)	37 (40)
Risk factors		Lesion length (SD)	14.1 (9.7)
Arterial hypertension (%)	28 (53)		
Diabetes mellitus (%)	9 (17)	Plaque characteristics	
Obesity (%)	9 (17)	Total plaque volume, cm ³ (SD)	0.22 (0.20)
BMI, kg/m ² (SD)	26.7 (4.1)	Necrotic core, cm ³ (SD)	0.04 (0.04)
		Fibrofatty tissue, cm ³ (SD)	0.08 (0.07)
Medications		Fibrous tissue, cm ³ (SD)	0.08 (0.07)
Oral antidiabetics (%)	7 (13)	Calcified plaque, cm ³ (SD)	0.03 (0.05)
Insulin (%)	3 (6)	Non-calcified plaque, cm ³ (SD)	0.19 (0.17)
Statins (%)	37 (70)	Outer wall volume, cm ³ (SD)	0.37 (0.33)
ACEi (%)	20 (38)	Lumen volume, cm ³ (SD)	0.11 (0.10)
Diuretics (%)	8 (15)		
ARBs (%)	8 (15)	ESS segments	
b-blockers (%)	30 (57)	ESS TL, Pa (SD)	4.1 (7.8)
Calcium antagonists (%)	8 (15)	ESS Prox, Pa (SD)	3.3 (5.6)
ASA (%)	43 (81)	ESS MLA, Pa (SD)	8.6 (19.7)
Nitrates (%)	9 (17)	ESS Dist, Pa (SD)	2.9 (5.2)
Dist: distal ; ESS: endothelial shear stress; ACEi: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; ASA: acetylsalicylic acid; BMI: body			

Mass Index; LAD: left anterior descending; LCX: left circumflex; MLA: minimum lumen area; Pa: Pascal units; Prox: proximal; RCA: right coronary artery; SD: standard deviation; TL: total lesion

Relationship between endothelial shear stress, stenosis severity, plaque volume and quantitative PET perfusion

Among the 92 vessels examined in this study, 46 (50%) showed normal stress MBF and MFR, while 23 (25%) had abnormal values for both parameters. Additionally, ESS values were higher in arteries with abnormal MBF and MFR ^{Table 7, Figure 64}.

Table 7 Categorization of ESS according to normal or abnormal PET-MPI

	Abnormal stress MBF+MFR	Normal stress MBF+MFR	P-value
ESS (TL), Pa	4.1 [2.23-9.28]	1.7 [1.20-2.69]	0.0004
ESS (Prox), Pa	3.1 [2.06-8.38]	1.4 [0.99-2.81]	0.0005
ESS (MLA), Pa	6.9 [4.96-22.6]	2.5 [1.82-4.94]	0.0001
ESS (Dist), Pa	2.6 [1.16-7.63]	1.4 [0.79-2.16]	0.0055

Vessel's classification using stenosis severity (below or above 50%) and ESS (high vs. low), resulted in a total of 21.7% arteries with stenosis severity < 50% and high ESS

which showed an abnormal PET-MPI result ^{Figure 63, Table 9}.

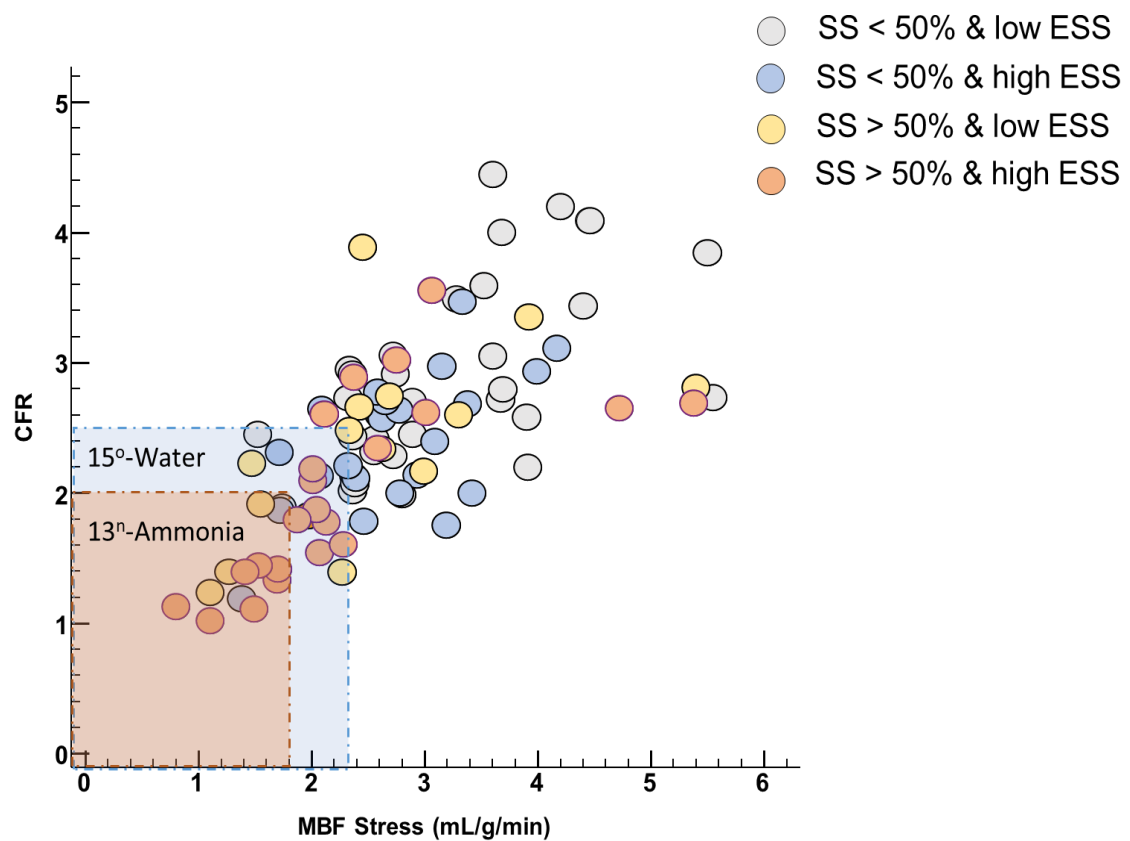


Figure 63 Scatter plot of stress myocardial blood flow (MBF) and myocardial flow reserve (MFR) values. Colored dots indicate ESS strata in MLA (low vs. high) and stenosis severity (StSev). Shaded areas with dotted lines mark abnormal limits for stress MBF and MFR using water and ammonia PET tracers.

Table 8 Comparison of NCPV and CPV with corresponding high and low ESS values.

	High ESS		Low ESS	P-value
Non-Calcified Plaque Volume, cm³	0.17	[0.120-0.287]	0.11 [0.071-0.173]	0.002

Lesion-specific PV, non-calcified PV, and plaque characteristics (e.g., calcium and fibrotic content) were insufficient predictors of an abnormal PET-MPI result. However, there was a trend toward significance for necrotic core and fibrofatty plaque volumes (p=0.08 and 0.09, respectively). Adding these features to stenosis severity did not provide incremental value to the predictive model. ^{Table 9}.

Table 9 Diagnostic value of plaque volume, non-calcified plaque volume and individual plaque characteristics for an abnormal PET-MPI

	AUC (95% CI)	p-value	Δ[AUC] (95% CI)	p-value
Plaque volume	0.594 [0.469-0.710]	0.22	0.135 [-0.050-0.329] ^a	0.17 ^a
Non-calcified plaque volume	0.594 [0.469-0.711]	0.21	0.134 [-0.050-0.322] ^a	0.16 ^a
Necrotic core	0.623 [0.498-0.737]	0.09		
+StSev	0.772 [0.655-0.865]	<0.001	0.044 [-0.027-0.115] ^a	0.22 ^a
Fibrofatty	0.626 [0.501-0.740]	0.08		
+StSev	0.769 [0.652-0.862]	<0.001	0.041 [-0.029-0.112] ^a	0.25 ^a
Fibrous	0.552 [0.427-0.672]	0.50		
+StSev	0.745 [0.626-0.842]	<0.001	0.016 [-0.057-0.090] ^a	0.66 ^a
Calcium	0.542 [0.418-0.663]	0.63		
+StSev	0.744 [0.625-0.841]	<0.001	0.015 [-0.059-0.091] ^a	0.68 ^a

On the contrary, both stenosis severity and ESS proved to efficiently predict impaired vasodilating capability. The threshold for ESS was set at 5.42 Pa, a cut-off giving the

most optimal sensitivity and specificity values (73.9% and 80.4%, respectively). Importantly, adding the ESS marker on top of the CCTA stenosis severity alone, or the CCTA-derived anatomical models too (i.e. stenosis severity + plaque volumetrics - total PV) resulted in incremental value and improved reclassification in predicting an abnormal PET-MPI result ^{Table 10}

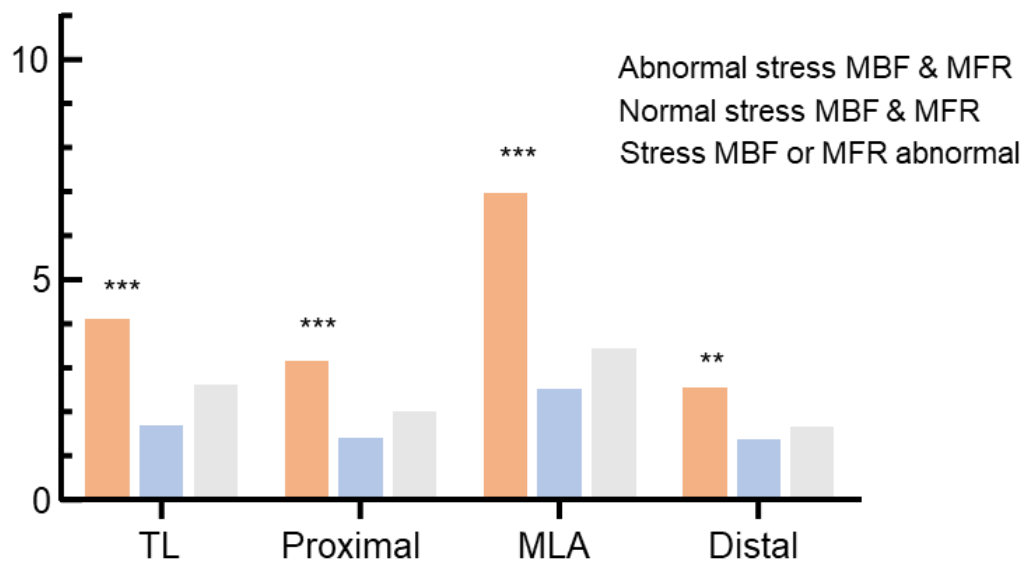


Figure 64 ESS distribution in vessels showing normal versus abnormal results on PET myocardial perfusion imaging (PET-MPI). (A) Median endothelial shear stress (ESS) across the entire lesion and within each specific stenotic segment for vessels categorized by normal and abnormal PET-MPI findings.

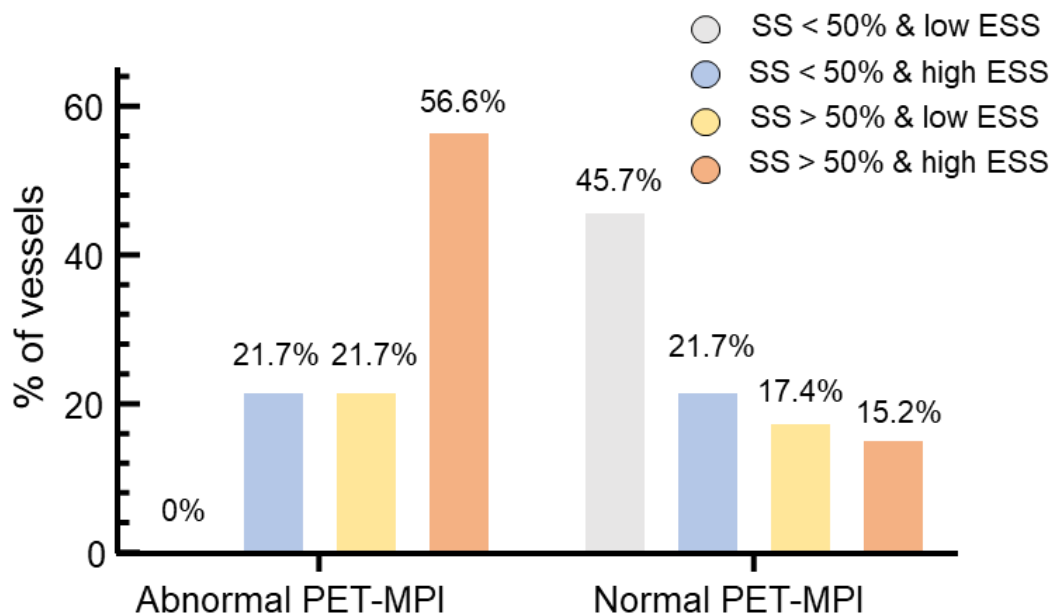


Figure 65 Percentage of vessels with normal vs. abnormal PET-MPI across different strata of ESS and stenosis severity (SS) * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 10 Diagnostic value of endothelial shear stress combined with CCTA anatomical information for identifying abnormal PET-MPI.

	AUC (95% CI)	Δ [AUC] (95% CI)	p-value
StSev >50%	0.728 (0.608 to 0.828)		<0.001
ESS	0.792 (0.677 to 0.880)		<0.001
StSev >50%+ESS	0.831 (0.721 to 0.910)	0.103 ^a (0.037 to 0.168)	0.002 ^a
StSev >50%+TPV	0.762 (0.644 to 0.856)	0.034 ^a (-0.041 to 0.109)	0.38 ^a
StSev >50%+TPV+ESS	0.831 (0.720 to 0.911)	0.069 ^b (-0.001 to 0.139)	0.054 ^b

2.4.4 Discussion

To the best of our knowledge, this study is the first to explore the association between lesion-specific ESS derived from CCTA and myocardial blood flow (MBF) measured via quantitative PET-MPI. Key findings include: a) ESS derived from CCTA is elevated in both proximal and minimum lumen area (MLA) segments of coronary lesions; b) there is a weak positive correlation between ESS and individual non-calcified plaque volume (PV) components; and c) ESS, when combined with stenosis severity, provides additional value for identifying functionally significant lesions as evaluated by PET-MPI.

Relationship between endothelial shear stress and coronary lumen anatomy

The regions with the highest and lowest ESS values were proven to be the MLA of a coronary lesion and the distal plaque segment, respectively. This came as no surprise, since plaque anatomy affects the blood flow and forms downstream flow recirculation zones with low ESS [242][249]–[251]. We found that ESS rises in segments with stenosis severity >50%, a result which comes to an agreement with previous studies [250][214].

Endothelial shear stress and plaque volume-phenotype

Previous studies have linked low ESS to a more vulnerable plaque phenotype [252]–[254] and an increase in necrotic core volume [255]. Simultaneously, high ESS has been associated with high-risk plaques in coronary arteries [233], [250]. These conflicting findings may be due to differences in the high/low ESS threshold values used across studies [250], [255] a possible U-shaped relationship between ESS and plaque vulnerability [250] the lack of established physiological ESS values for human coronary circulation, [212][256][257][258][259] and variability in study populations, such as whether healthy or atherosclerotic arteries were examined. In our study, ESS showed a positive correlation with total PV and non-calcified PV. Changes in ESS may partly result from altered endothelial mechanotransduction, which then influences plaque biology and vulnerability, leading to increased non-calcified plaque volume.

Prediction of functionally significant lesions by endothelial shear stress vs. lesion anatomy and characteristics

Arteries with abnormal stress MBF and MFR showed significantly higher ESS values. Further, we showed that stenosis severity and lesion specific ESS were both capable of predicting cases of impaired vasodilation. We hypothesize that the ability of ESS to function as a marker relies on the fact that at regions with non-calcific plaques the mechano-transduction is impaired, thus leading to increasing ESS values as the degree of the stenosis increases itself, and this likely results in reduced capability of dilation. Another possible explanation is that a chronic increase in ESS, and the subsequent rise in vasodilatory stimulus, may push the already impaired endothelial-mediated flow reserve to its limits [260]. Unlike ESS, total plaque volume (PV), non-calcified PV, and specific plaque components (such as calcium and fibrotic tissue) showed no correlation with impaired vasodilation. Our findings are consistent with certain previous studies [261] but diverge from others [262][263]. These inconsistencies may arise from methodological variations, such as differences in the vessel segments analyzed and the reference standards employed (e.g., FFR or PET/SPECT). Our analysis indicates that ESS carries hemodynamic relevance, potentially offering insight into how coronary plaque anatomy and geometry within the lumen affect function. For example, the functional significance of non-obstructive coronary lesions appears to be influenced by plaque geometry and structure, factors encapsulated in the ESS measurement.

Study limitations

This study has several limitations that warrant mention. Firstly, the influence of side branches on ESS was not assessed, nor was ESS analyzed under hyperemic conditions, which might yield further insights into its relationship with PET-MPI; however, steady-state ESS simulations are likely sufficient as surrogate markers. As in previous studies, we focused on the most prominent lesion in cases where multiple stenoses were present within the same artery [251][264]. Furthermore, our sample contained a limited number of vessels with significant stenosis (>50%). Lastly, in line with prior research [255] our analysis was confined to plaque phenotype, excluding other vessel features (such as positive remodeling, napkin-ring sign, and spotty calcification) as they fell outside this study's scope.

Clinical implications

Our study indicates that ESS is associated with coronary lesion hemodynamics and plaque characteristics. Unlike plaque volume quantification, which adds limited information beyond stenosis severity in assessing functional significance, ESS provides a more comprehensive view of plaque-induced changes in blood flow, possibly capturing indirect information about plaque characteristics as well. Further investigation into ESS could enhance our understanding of persistent angina in patients with non-obstructive lesions, such as long lesions with high plaque volume but minimal luminal narrowing. Additionally, consistently high ESS, influenced by vessel, lumen, or plaque anatomy, may increase the likelihood of forming non-calcified plaques with larger necrotic cores, which are more susceptible to rupture and the onset of acute coronary syndromes. However, these findings warrant additional studies for confirmation.

2.4.5 Conclusions

ESS can be calculated from CCTA datasets and shows a positive correlation with coronary plaque volume and luminal stenosis severity. Our study suggests that high ESS is associated with increased non-calcified plaque volume and a greater amount of low-attenuation plaque. Additionally, the functional significance of a coronary lesion can be assessed through plaque anatomy and its impact on fluid dynamics, as indicated by the ESS value. Lastly, ESS offers incremental value beyond stenosis severity alone, enhancing the prediction of impaired vasodilatory capacity as measured by PET-MPI.

2.5 Coronary CT Angiography Derived Features For Predicting Myocardial Perfusion Changes By Pet Myocardial Perfusion Imaging: A Machine Learning Approach

2.5.1 Study Aim:

The objective of this study is to evaluate the predictive capability of machine learning (ML) algorithms for detecting impaired myocardial flow reserve (MFR). This is achieved by integrating computational fluid dynamics (CFD)-derived metrics with quantitative measures of plaque burden, plaque morphology, and anatomical features obtained from coronary CT angiography (CCTA). Through testing multiple ML classifiers, the study aims to determine the most effective feature combinations for accurately predicting abnormal MFR, as established by PET myocardial perfusion imaging (MPI).

2.5.2 Methods:

This study involved a cohort of 49 patients with an intermediate pre-test probability of CAD, all of whom had undergone both CCTA and PET-MPI. A positive PET-MPI outcome was defined as positive findings in both myocardial blood flow (MBF) and myocardial flow reserve (MFR) ^{Table 11}. Several CFD-derived metrics were evaluated, including a CT-FFR surrogate, the virtual functional assessment index (SMART FFR), segmental endothelial shear stress (ESS), along with anatomical and plaque characteristics. Various machine learning models were applied, including k-Nearest Neighbors (k-NN), Support Vector Machine (SVM), Logistic Regression, Linear and Quadratic Discriminant Analysis, Naïve Bayes, and Decision Trees. Internal validation employed 5-fold cross-validation repeated 100 times. Sequential forward selection (SFS) was used for feature selection, with a single-layer Perceptron ^{Figure 66} tracking the frequency of features achieving the highest AUC in each fold. An exhaustive search (ES) was subsequently conducted on the top three most frequently selected features to pinpoint optimal feature combinations. Classifier performance was assessed through area-under-the-curve (AUC) analysis for the receiver-operating-characteristic curve.

Table 11 Patients and Vessel characteristics

Characteristics	Vessel (n = 92)
LAD	44 (48)
LCx	26 (28)
RCA	22 (24)

Focal lesion vessels	72 (78)
<i>Stenosis Severity</i>	
<30	17 (18)
31-50	38 (41)
51-90	37 (40)
Lesion length *	14.1 (9.7)
<i>Plaque characteristics</i>	
Total plaque volume, cm3 *	0.22 (0.20)
Necrotic core, cm3 *	0.04 (0.04)
Fibrofatty tissue, cm3 *	0.08 (0.07)
Fibrous tissue, cm3 *	0.08 (0.07)
Calcified plaque, cm3 *	0.03 (0.05)
Non-calcified plaque, cm3 *	0.19 (0.17)
Outer wall volume, cm3 *	0.37 (0.33)
Lumen volume, cm3 *	0.11 (0.10)
<i>ESS segments</i>	
ESS TL, Pa *	4.1 (7.8)
ESS Prox, Pa *	3.3 (5.6)
ESS MLA, Pa *	8.6 (19.7)
ESS Dist, Pa *	2.9 (5.2)

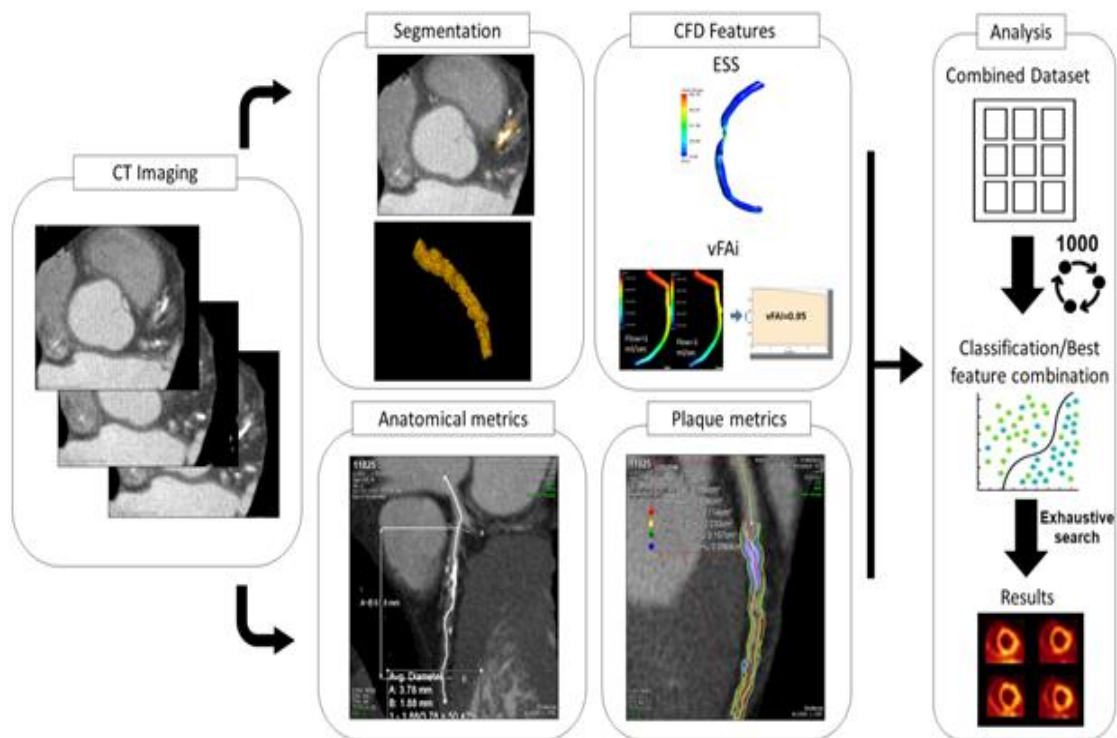


Figure 66 Pipeline for feature extraction and results interpretation

2.5.3 Results:

In the present study we analyzed 92 coronary segments in total, and we ended up with 28 features which were extracted from CCTA. The best performing classifier was found to be the K-NN($n=3$), which produced an AUCmean of 0.80 ($\text{SENS}_{\text{mean}}=0.77$, $\text{SPEC}_{\text{mean}}=0.71$, $p<0.05$, Table 12). The features and their frequency of appearance are depicted in Figure 67. We saw that the most common feature appearance in top AUC score was SMART FFR followed by ESS in the proximal position and Fibrofatty Tissue Volume. The exhaustive search results are illustrated in Table 13. Specifically, the most predictive indicators were shown to be the ESS and SMART FFR combination ($\text{AUC}_{\text{mean}} = 0.806$, $\text{SENS}_{\text{mean}}=0.72$, $\text{SPEC}_{\text{mean}}=0.76$, $p<0.05$) followed by the Fibrofatty Tissue Volume and ESS combination ($\text{AUC}_{\text{mean}}=0.803$, $\text{SENS}_{\text{mean}}=0.75$, $\text{SPEC}_{\text{mean}}=0.72$, $p<0.05$), and finally all three together ($\text{AUC}_{\text{mean}}=0.802$, $\text{SENS}_{\text{mean}}=0.76$, $\text{SPEC}_{\text{mean}}=0.72$, $p<0.05$).

Table 12 Performance of classifiers

Classifier	AUC	SENSITIVITY	SPECIFICITY
<i>k</i> -NN ($k=3$)	0.80	0.77	0.71
Logistic Regression	0.77	0.71	0.77

<i>LDA</i>	0.77	0.69	0.68
<i>QDA</i>	0.73	0.65	0.71
<i>SVM (LINEAR)</i>	0.72	0.55	0.77
<i>Naïve Bayes</i>	0.68	0.5	0.76
<i>Decision Trees</i>	0.65	0.4	0.75

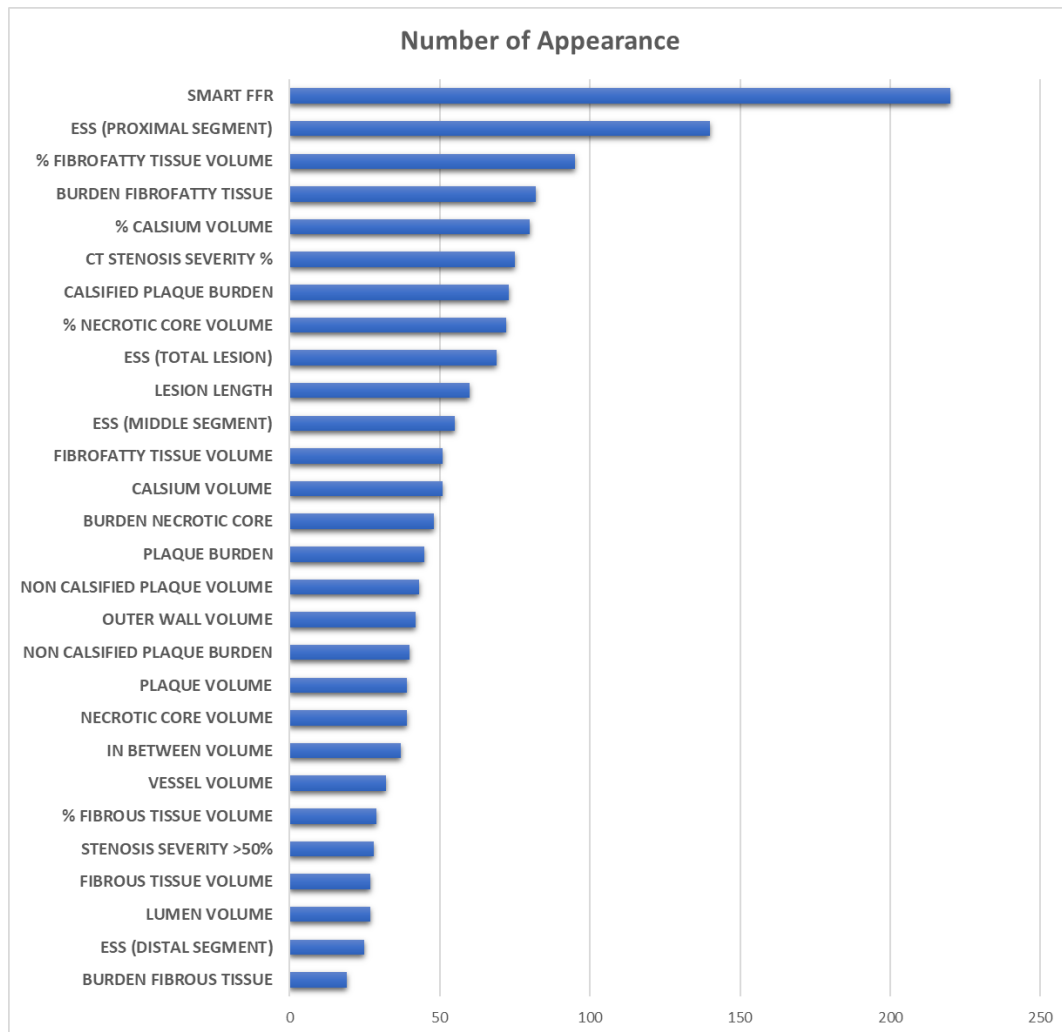


Figure 67 No of Appearance of features in SFS of best AUC score

Table 13 Best Feature Combination ES results

Feature	AUC	SENSITIVITY	SPECIFICITY
<i>ESS (Proximal Segment) + Smart FFR</i>	0.806	0.720	0.760
<i>% Fibrofatty Tissue + ESS (Proximal Segment)</i>	0.803	0.750	0.720

<i>% Fibrofatty Tissue + ESS (Proximal Segment) + Smart FFR</i>	0.802	0.760	0.720
<i>% Fibrofatty Tissue Volume + Smart FFR</i>	0.801	0.690	0.730
<i>Smart FFR</i>	0.791	0.720	0.790
<i>ESS (Proximal Segment)</i>	0.782	0.700	0.730
<i>% Fibrofatty Tissue</i>	0.764	0.690	0.740

2.5.4 Conclusions:

Our study demonstrates that machine learning (ML) analysis can effectively predict abnormal PET-MPI results by incorporating a combination of CFD-derived parameters, anatomical, and morphological features. Notably, among the feature combinations evaluated, ESS and SmartFFR consistently emerged as strong predictors. Integrating ESS with plaque characteristics and other CFD-derived features significantly improved sensitivity and specificity for detecting impaired MFR, underscoring ML's potential in enhancing CAD patient risk classification. Finally, the exploratory analysis highlights the key features and their combinations that contribute to the algorithm's performance.

3. Coronary Arteries-Radiomics

3.1 Introduction

Coronary heart disease (CHD) is a leading cause of mortality and disability worldwide, with its prevalence continuing to increase globally [46]. Myocardial ischemia resulting from CHD serves as an independent predictor of future cardiovascular events in both chronic and acute clinical settings [265][266]. Consequently, accurate assessment of inducible myocardial ischemia—primarily through non-invasive imaging techniques—is recommended for risk stratification in patients with suspected CHD and for identifying those who may benefit most from revascularization [267]. Myocardial perfusion imaging (MPI) methods, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET), facilitate the non-invasive assessment of regional myocardial ischemic burden. Additionally, with dynamic imaging, these techniques provide quantitative measurements of myocardial blood flow (MBF) and myocardial flow reserve (MFR). Additionally, advancements in computed tomography coronary angiography (CCTA) offer anatomical visualization of the coronary arteries, plaque identification, and plaque phenotyping, all of which provide independent prognostic information regarding future adverse outcomes [224], [268].

CT radiomic textures could further enhance plaque phenotyping by allowing identification of plaque features not visible to the human eye. The use of a coronary CT angiography (CCTA)-based radiomic signature to identify vulnerable coronary artery plaques and predict major adverse cardiac events have already been presenting promising results [269]. CCTA-derived radiomic signature effectively identifies vulnerable plaques and holds significant predictive value for future adverse cardiac events, highlighting its potential utility in clinical risk stratification [270]. Previous studies have compared the effectiveness of radiomics characteristics and conventional parameters such as stenosis severity, both derived from coronary CT angiography (CCTA), in detecting hemodynamically significant coronary artery stenosis, using invasive fractional flow reserve (FFR) as the gold standard benchmark [271]. Recent studies have established a correlation between vascular inflammation and the geometrical and biological alterations in perivascular adipose tissue. The Perivascular Fat Attenuation Index (FAI) quantifies the inflammation-driven rise in CT attenuation values and serves as a robust predictor of major adverse cardiovascular events (MACE). Additionally, the fat radiomics profile (FRP) has demonstrated significant enhancement in the prediction of MACE when compared to

conventional risk factors, including coronary calcium scores, coronary stenosis, and features of high-risk plaques [272], [273].

Expanding further this work, we hypothesized that CCTA- based plaque radiomic analysis that provides a more detailed description of coronary lesions has an additive impact of over conventional CCTA assessment in predicting the presence of regional myocardial ischemia on patients with normal or abnormal results based on PET and SPECT-MPI. Additionally, an analysis pipeline was introduced, taking into consideration the already mentioned problems of non-standardized feature extraction processes, utilizing simple feature reduction and explainability techniques [274].

3.2 Relationship Between Radiomic CCTA Derived Characteristics, Plaque Characteristics and Their Predictive Power for PET And SPECT-MPI.

3.2.1 Study Aim:

The aim of the study is to evaluate whether the integration of machine learning (ML) and radiomics techniques can enhance the characterization of functionally significant coronary lesions identified in Coronary CT Angiography (CCTA) data. Specifically, the study seeks to determine if incorporating radiomic features alongside anatomical data such as stenosis severity (SS) and plaque characteristics (PL) can improve the identification of flow-limiting coronary lesions. Ultimately, the study endeavors to highlight the potential of radiomics as a complementary tool in the assessment and prognosis of coronary artery disease (CAD).

3.2.2 Methods

Study Population

The Evaluation of Integrated Cardiac Imaging in Ischemic Heart Disease (EVINCI) trial was a prospective, multicenter study conducted across Europe to compare the diagnostic accuracy of widely-used imaging modalities in detecting significant CAD [209]. Between March 23, 2009, and June 15, 2012, a total of 475 patients underwent coronary anatomy evaluation via CCTA along with at least one functional imaging test [55]. A subsequent EVINCI and Simulation Modeling of Coronary Artery Disease (SMARTool) sub-study was performed to assess the effectiveness of a CCTA-based FFR surrogate index for identifying impaired coronary vasodilatory capacity [239]. Further analyses also indicated that CCTA-derived endothelial shear stress could offer valuable predictive information regarding impaired vasodilatory capacity as assessed by PET MPI [209]. This current sub-analysis sought to evaluate the predictive value of stenosis severity, plaque volume, and plaque radiomic features in identifying abnormal PET or SPECT-MPI outcomes. Patients with stable chest pain and an intermediate pre-test probability of CAD were included in the study [209]. Exclusion criteria encompassed recent acute coronary syndrome, pre-existing CAD, left ventricular ejection fraction below 35%, more than moderate valve disease, and cardiomyopathy. Further details on the inclusion and exclusion criteria are shown in Figure 68 [209].

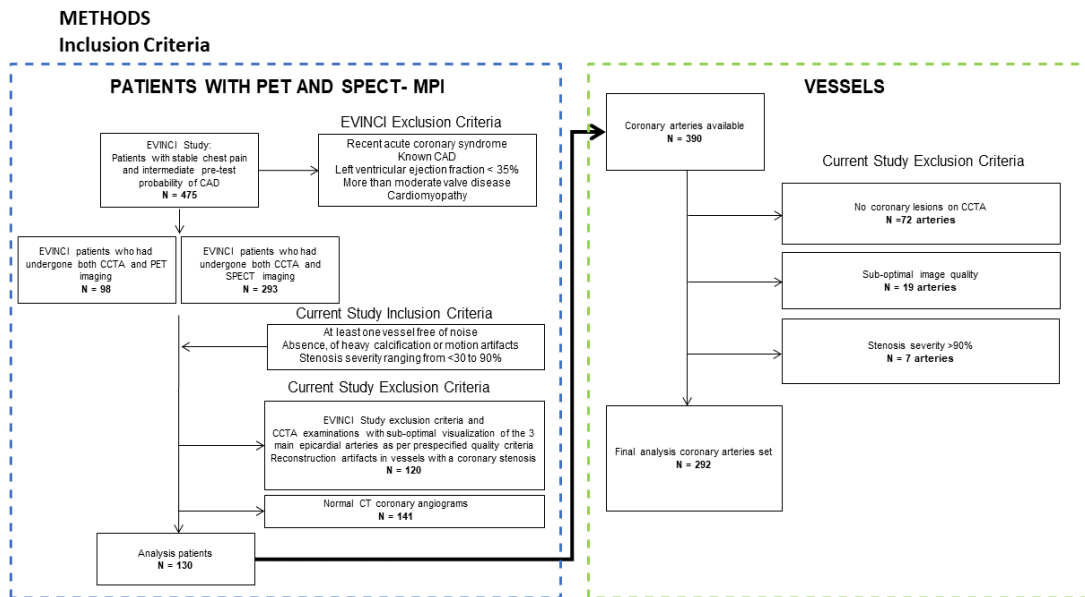


Figure 68 Flow diagram represents the inclusion and the exclusion criteria for patients' selection based on the EVINCI and SMARTool project studies. Patients with heavy artifacts, noise and heavy stenosis were excluded as well as patients with normal CCTA.

CCTA imaging and data analysis

CCTA images were obtained using CT scanners with at least 64 slices, in accordance with the EVINCI study protocol, utilizing iodine-based contrast agents. For most CCTA studies, axial images were reconstructed with a slice width of less than 1.0 mm, with minimum slice thicknesses ranging from 0.5 to 0.6 mm. The ideal reconstruction phase was chosen during diastole, at 70–80% of the R-R interval, to capture the most favorable point in the cardiac cycle [234].

PET, SPECT imaging and data analysis

SPECT/CT and PET/CT imaging followed both international guidelines and the EVINCI study protocol. Detailed methodologies for PET and SPECT imaging protocols, as well as hybrid imaging analysis, are documented in prior publications [55], [246], [247]. PET was deemed abnormal when more than one contiguous segment showed both stress MBF ≤ 2.3 mL/g/min and Myocardial Flow Reserve (MFR) ≤ 2.5 for ^{15}O -water, or <1.79 mL/g/min and MFR ≤ 2.0 for ^{13}N -ammonia, respectively [238], [246]. SPECT was considered abnormal if defect reversibility (DR) was evidenced by a summed difference score (SDS) of ≥ 2 between stress and rest images.

Plaque analysis

Plaque analysis was conducted on multiplanar reformatted images (average slice thickness 0.6 mm, increment 0.6 mm) along the entire vessel length down to a diameter of 2 mm. An independent reader with over 5 years of experience in cardiac CT performed the analysis, with prior knowledge of lesion start and end points but blinded to PET-MPI and SPECT-MPI results. The readout sessions were separated by a 6-month interval, and intra-observer coefficient of variation (ICV) in 55 randomly selected vessels (~20% of the total vessel population) for total plaque, vessel, and lumen volume was <3%. Total plaque volume and its individual components were assessed over the entire lesion length. Analysis utilized semi-automated segmentation software (Q-Angio CT RE (LKEB) 3.1.5.1), with minimal manual corrections as needed for wall and vessel boundaries. Lesion-specific total plaque volume (PV) was classified by Hounsfield Units (HU) into non-calcified PV (-30 to 350 HU) and calcified PV (>350 HU) [243], [245].

Radiomic Plaque analysis

Plaque regions identified in CT images were segmented and converted into 3D NRRD models. Radiomic feature extraction was performed using PyRadiomics 2.2.0 [275]. Each original plaque volume was subjected to a series of transformation filters designed to enhance feature diversity. These transformations included:

- **Wavelet Transform:** Separates spatial frequency components across multiple scales.
- **Laplacian of Gaussian (LoG):** Highlights regions with significant intensity changes by emphasizing edges.
- **Square and Square Root:** Non-linear intensity adjustments that emphasize mid-to-high and low-intensity ranges, respectively.
- **Logarithmic and Exponential:** Adjust intensity scaling to emphasize low (logarithmic) and high (exponential) HU values.
- **Gradient:** Captures intensity change between neighboring voxels to accentuate transitions.

Each transformation generated a separate 3D plaque model, resulting in 18 transformed models in addition to the original volume. From each model, 1,743 radiomic features were extracted, classified as follows:

- **First-order Metrics** (18 features): Statistical descriptors of HU distribution within the plaque like mean, median, range and entropy.
- **Second Order Metrics - Gray Level-Textural Parameters** (73 features): Quantifies voxel and intensity variations based on different rules of pixel or voxel spatial relationships like contrast, energy, variance etc.
- **Geometric Parameters** (14 features): Shape and spatial characteristics of the plaque, such as volume and surface area.
-

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) or as median with interquartile range (IQR), while qualitative variables are reported as absolute and relative frequencies. Normality was assessed using the Kolmogorov-Smirnov test. Two-sided probability values were derived using either the t-test or Mann–Whitney U test for continuous data, with ANOVA or Kruskal-Wallis tests applied for comparisons across multiple groups. A p-value of <0.05 was set as the threshold for statistical significance. The Spearman rank correlation coefficient was utilized to examine associations between radiomic features and plaque characteristics. The percentage composition of each plaque characteristic was defined as the ratio of plaque component volume to total plaque volume.

Feature reduction pipeline and model building

Due to the high number of extracted features and the complexity of the dimensional space that they create, a feature reduction and model creation pipeline was constructed ^{Figure 69}. The steps were the following: 1) Remove features with high cross variation $> 20\%$ 3) Discard features with Spearman correlation coefficient > 0.8 ; 4) Further reduction using Sequential forward feature selection using 5-fold Cross validation (CV) with a maximum threshold of 15 selected features; 5) Final multivariate model after applying bootstrapping method for 1000 iterations with out of bag (OOB) test predictions. For the above pipeline, Support Vector Machine (SVM, Polynomial kernel), Naïve Bayes and k-NN (k=5) classifiers were deployed. Final models comparisons between AUC and PR-AUC metrics were performed using Kruskal-Wallis for the multi-model comparisons and Dunn test for the pairwise comparisons.

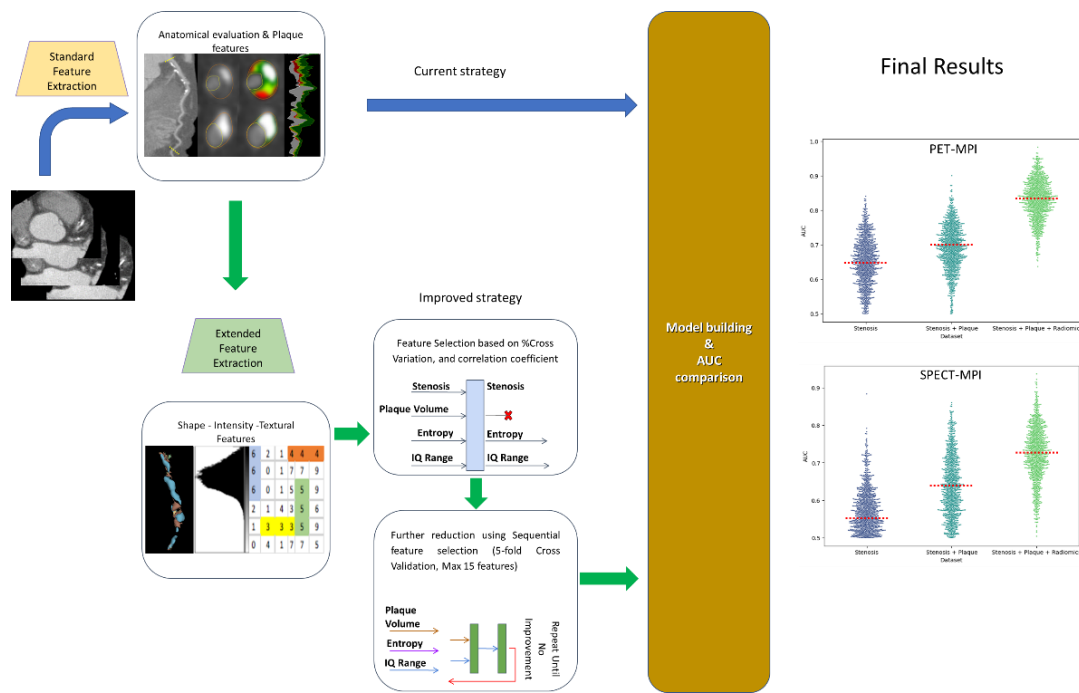


Figure 69 This flow diagram presents the radiomics study's methodology in CAD assessment, featuring four principal steps: A) High-resolution CTA scans undergo feature extraction to identify coronary plaques and anatomical details. B) First feature reduction step removing high correlated features and features with low predictive value. C) A sequential feature selection with classifier cross-validation method pinpoints critical features. D) These features are then integrated into classifiers models, predicting abnormal PET or SPECT-MPI outcomes.

3.2.3 Results

Patient and vessel characteristics

Our dataset consisted of 475 individuals belonging to the EVINCI and SMARTool projects study, which underwent PET and SPECT-MPI. In Table 14 are presented the demographics, clinical and coronary lesion characteristics of the whole study sample. We excluded 120 patients due to sub-optimal image quality or reconstruction artifacts based on the EVINCI and SMARTool study protocol and another 141 because they showed normal CCTA. The remaining 130 individuals' data (Mean age: 62.8 ± 7 years, [standard deviation], 42-75 [age range], 80 Male, Male group: 61 ± 8 years, Female group: 65.8 ± 5 years, $p = .21$) were assessed for stenosis severity, plaque characteristics and radiomics features. Out of the total 390 coronary arteries of the study sample, we excluded 32 due to lack of coronary lesions on CCTA, another 8 due to sub-optimal image quality and 3 because they showed a stenosis severity $> 90\%$. For PET-MPI a total of 141 vessels were extracted (39 positive PET-MPI) and for SPECT-MPI a total of 151 vessels (26 positive SPECT-MPI)

Table 14 Demographic and clinical study sample characteristics

Characteristics	Total (n = 130)	PET-MPI (n = 66)	SPECT-MPI (n = 64)
-----------------	-----------------	------------------	--------------------

Age (y)*	62.8 (7) [42-75]	63 (7) [42-75]	
Men	80 (58)	37	43
Age (y)*	61 (8) [42-75]	62	63
Women	50 (42)	27	23
Age (y)*	65.8 (5) [59-73]	65	68
Symptoms			
Typical angina	35 (15)	10	25
Atypical angina	70 (55)	35	35
Non-anginal chest pain	25 (30)	19	6
Risk factors			
Arterial hypertension	76 (53)	33	43
Diabetes mellitus	29 (17)	13	16
Obesity	23 (17)	12	11
BMI, kg/m2 *	27.5 (4)	27.8	27.4
Medications			
Oral antidiabetics	25 (13)	10	15
Insulin	8 (6)	4	4
Statins	78 (70)	43	35
ACEi	43 (38)	24	19
Diuretics	20 (15)	9	11
ARBs	21 (15)	11	10
b-blockers	61 (57)	34	27
Calcium antagonists	12 (15)	9	3
ASA	97 (81)	51	46
Nitrates	16 (17)	9	7
Note. - Except where indicated, data are numbers of participants, with percentages in parentheses; ACEi: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; ASA: acetylsalicylic acid; BMI: body Mass Index; *Numbers are means $\pm$ standard deviations. Numbers in brackets are range			

Plaque characteristics distribution across coronary lesions

Vessels in patients with a normal PET-MPI show lower Calcium Volume, Percent atheroma volume (PAV), Plaque Burden, and Plaque Volume, in comparison with vessels associated with an abnormal PET-MPI result (all $p < 0.05$, Table 15).

On the contrary, vessels with a normal SPECT-MPI, showed no statistical difference regarding Calcium Volume, Percent atheroma volume (PAV), Plaque Burden, and Plaque Volume to vessels with abnormal SPECT-MPI ^{Table 15}.

Table 15 Plaque characteristics distribution across coronary lesions for Normal and Abnormal PET and SPECT

	Normal PET		Abnormal PET			Normal SPECT		Abnormal SPECT		
	Mean	SD	Mean	SD	P value	Mean	SD	Mean	SD	P value
Dense Calcium Volume,mm³	49.5	79.5	102.7	97.7	<0.01	85.7	35.1	99.9	34.9	0.07
Percent atheroma volume,mm³	35	10.1	41.8	9.1	<0.01	264.7	137.1	339.4	201.9	0.10
Plaque Burden Mean	33.8	9	39.5	8.3	<0.01	38.5	52.8	78.4	147	0.18
Plaque Volume,mm³	333.9	187.9	439.6	225.8	0.01	215.6	128.6	279.5	206.8	0.32
Non calcified plaque volume, mm³	281.6	128.5	334.9	159.9	0.12	313.2	106.7	364.8	189.4	0.40
Region Length, mm	89.7	32.4	90.5	36.2	0.99	29.8	6.3	29.5	6.5	0.99
Note. - SD: Standard Deviation; PET: Positron Emission Tomography; SPECT: Single Photon Emission Computed Tomography										

Prediction of abnormal perfusion by stenosis severity, plaque volumes and radiomics features

Regarding PET-MPI population, k-NN classifier using only stenosis severity feature performed an AUCmedian = 0.623 (95% CI: 0.618 to 0.629) with a PR-AUCmedian= 0.532 (95% CI: 0.522 to 0.540). The combination of stenosis severity and Plaque characteristics gave an AUC = 0.672 (95% CI: 0.667 to 0.679) that was statistically different from the stenosis severity model alone (p-diff < 0.05). PR-AUC was no different (p > 0.05). The combination of stenosis severity, plaque and radiomics features ^{Table 16} was also different

from the model of stenosis, and stenosis + plaque (AUC= 0.775, 95%CI: 0.769 to 0.779, p-diff < 0.01 for both comparisons, Figure 70). PR-AUC there was higher compared to stenosis and plaque model (AUC=0.652, 95% CI: 0.646 to 0.660 vs 0.535, 95%CI: 0.526 to 0.543, p<0.05)

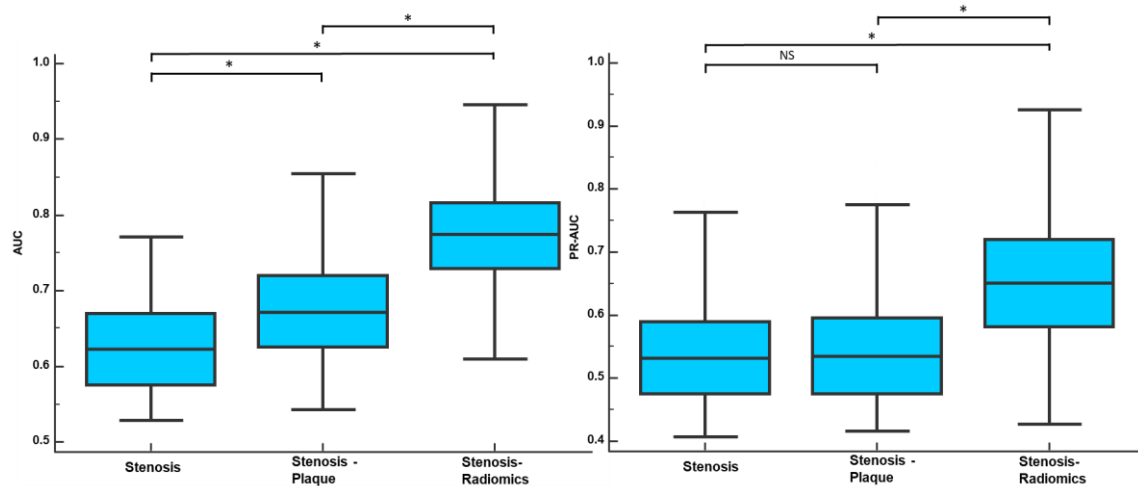


Figure 70 k-NN results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in PET-MPI population. * < 0.05

Table 16 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal PET-MPI using k-NN

Image Type	Description	Feature
original	shape	Maximum Diameter Column
original	shape	Maximum Diameter Row
original	First Order	Skewness
wavelet-LHH	First Order	Entropy
wavelet-HLL	glcm	Joint Energy
LoG ($\sigma=1$)	glcm	Cluster Prominence
LoG ($\sigma=1$)	glrlm	Long Run Emphasis
LoG ($\sigma=1$)	First Order	90 Percentile
LoG ($\sigma=1$)	First Order	Entropy
LoG ($\sigma=2$)	First Order	Kurtosis
LoG ($\sigma=3$)	glcm	Autocorrelation
LoG ($\sigma=4$)	glcm	Cluster Prominence
-	Plaque	Region Length
-	Plaque	Fibrous Fatty Volume %
-	-	Stenosis Severity

Regarding Naïve Bayes classifier stenosis severity model performed an AUCmedian = 0.703 (95% CI: 0.698 to 0.709) with a PR-AUCmedian= 0.588 (95% CI: 0.581 to 0.594). The combination of stenosis severity and Plaque characteristics gave an AUC = 0.755 (95% CI: 0.750 to 0.760) and the comparison between that and stenosis severity alone

was statistically significant ($p\text{-diff} < 0.05$). PR-AUC was different compared to the stenosis model alone ($p < 0.05$) although without actual meaning because it is smaller than stenosis alone. The combination of stenosis severity and radiomics features was also different from the model of stenosis, and stenosis + plaque (AUC= 0.810, 95%CI: 0.806 to 0.816, $p\text{-diff} < 0.01$ for both comparisons). PR-AUC was also higher compared to stenosis, and stenosis + plaque model (PR-AUC = 0.677, 95%CI:0.669 to 0.685, $p\text{-diff} < 0.01$ for both comparisons, Figure 71).

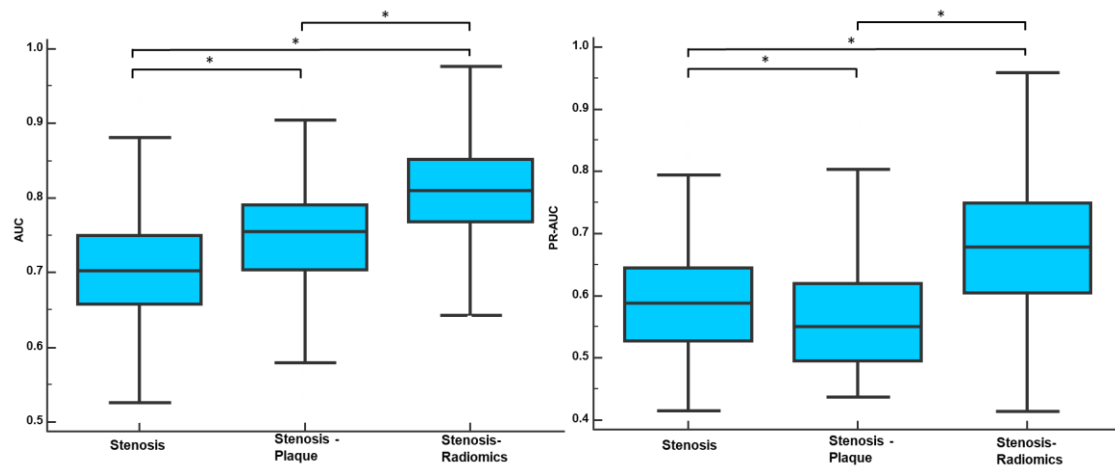


Figure 71 Naïve Bayes results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in PET-MPI population. * < 0.05

Table 17 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal PET-MPI using Naïve Bayes

Image Type	Description	Feature
original	shape	Maximum Diameter Column
original	shape	Maximum Diameter Row
original	First Order	90 Percentile
wavelet-HLH	First Order	Kurtosis
wavelet-LHL	First Order	Entropy
wavelet-LHL	glcm	Joint Energy
wavelet-LHL	glcm	Idm
wavelet-HLL	First Order	Minimum
LoG ($\sigma=1$)	glcm	Cluster Prominence
LoG ($\sigma=2$)	glcm	Autocorrelation
-	Plaque	Fibrous FattyVolume %
-	Plaque	Necrotic CoreVolume
-	-	Stenosis Severity

Finally for SVM classifier, stenosis severity as a sole feature model performed an AUC_{median} = 0.642 (95% CI: 0.637 to 0.649) with a PR-AUC_{median}= 0.500 (95% CI: 0.489 to 0.506). The combination of stenosis severity and Plaque characteristics gave an AUC

= 0.692 (95% CI: 0.687 to 0.697) and the comparison between that and stenosis severity alone was statistically significant ($p\text{-diff} < 0.05$) although the PR-AUC was not different ($p > 0.05$). The combination of stenosis severity and radiomics features was also different from the model of stenosis, and stenosis + plaque (AUC= 0.820, 95%CI: 0.816 to 0.825, $p\text{-diff} < 0.01$ for both comparisons, Figure 77). PR-AUC was also different from stenosis + plaque (PR-AUC=0.708, 95%CI: 0.700 to 0.717 vs 0.500, 95% CI: 0.490 to 0.503, $p < 0.01$ for comparisons)

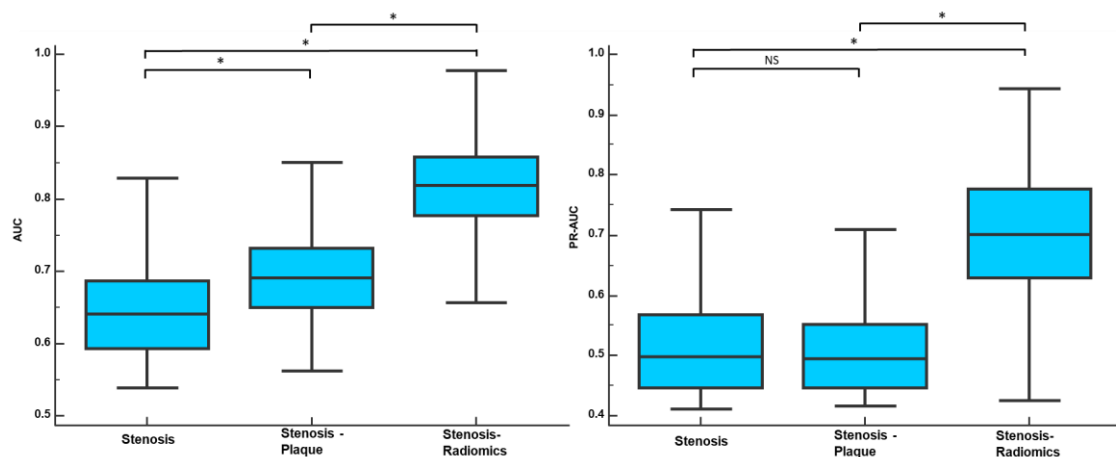


Figure 72 SVM results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in PET-MPI population. * < 0.05

Table 18 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal PET-MPI using SVM

Image Type	Description	Feature
original	shape	Maximum Diameter Column
original	shape	Maximum Diameter Row
original	First Order	10 Percentile
original	First Order	Skewness
original	glcm	Joint Energy
original	glrlm	Long Run Emphasis
wavelet-LLH	First Order	90 Percentile
wavelet-LLH	First Order	Median
wavelet-LHL	First Order	Mean
wavelet-LHH	First Order	Entropy
wavelet-HLL	First Order	Kurtosis
LoG ($\sigma=3$)	glcm	Cluster Prominence
LoG ($\sigma=4$)	First Order	Skewness
-	Plaque	Fibrous Fatty Volume %

-	-	Stenosis Severity
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Regarding SPECT-MPI population, k-NN classifier using only stenosis severity performed an AUCmedian = 0.571 (95% CI: 0.565 to 0.576) with a PR-AUCmedian= 0.442 (95% CI: 0.430 to 0.455). The combination of stenosis severity and plaque characteristics gave an AUC = 0.585 (95% CI: 0.580 to 0.592) and was different from the stenosis severity model alone (p-diff < 0.05). PR-AUC was no different also (p > 0.05). The combination of stenosis severity and radiomics features performed better compared to the model of stenosis, and stenosis + plaque (AUC= 0.736, 95%CI: 0.729 to 0.741, p-diff < 0.01 for both comparisons, Figure 70). PR-AUC was also higher compared to stenosis and stenosis + plaque (PR-AUC = 0.499, 95%CI: 0.486 to 0.506, p< 0.01 for both comparisons, Figure 73).

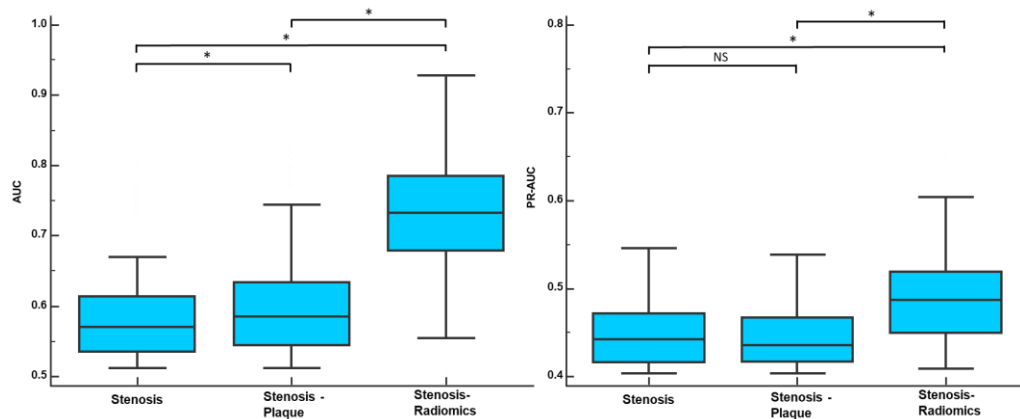


Figure 73 k-NN results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in SPECT-MPI population. * < 0.05

Table 19 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal SPECT-MPI using k-NN

Image Type	Description	Feature
original	shape	Maximum Diameter Column
original	shape	Elongation
original	glcm	Cluster Shade
LoG ($\sigma = 4$)	glcm	Idm
LoG ($\sigma = 5$)	glrlm	Short Run Low Gray Level Emphasis
wavelet-LLH	First Order	Skewness
wavelet-LHL	glcm	Difference Variance
wavelet-LHH	First Order	Minimum
wavelet-LHH	glcm	ClusterTendency
wavelet-HLH	First Order	10 Percentile
-	-	Stenosis Severity

For Naïve Bayes classifier stenosis severity model performed an AUCmedian = 0.601 (95% CI: 0.597 to 0.607) with a PR-AUCmedian= 0.446 (95% CI: 0.439 to 0.458). The

combination of stenosis severity and Plaque characteristics gave an AUC = 0.668 (95% CI: 0.659 to 0.674) and the comparison between that and stenosis severity alone was statistically significant ($p\text{-diff} < 0.05$). PR-AUC was no different compared to the stenosis model alone ($p > 0.05$). The combination of stenosis severity and radiomics features was also different from the model of stenosis, and stenosis + plaque (AUC= 0.720, 95%CI:0.711 to 0.727, $p\text{-diff} < 0.01$ for both comparisons). PR-AUC was also higher compared to stenosis, and stenosis + plaque model (PR-AUC = 0.473, 95% CI:0.463 to 0.480, $p\text{-diff} < 0.01$ for both comparisons, Figure 74).

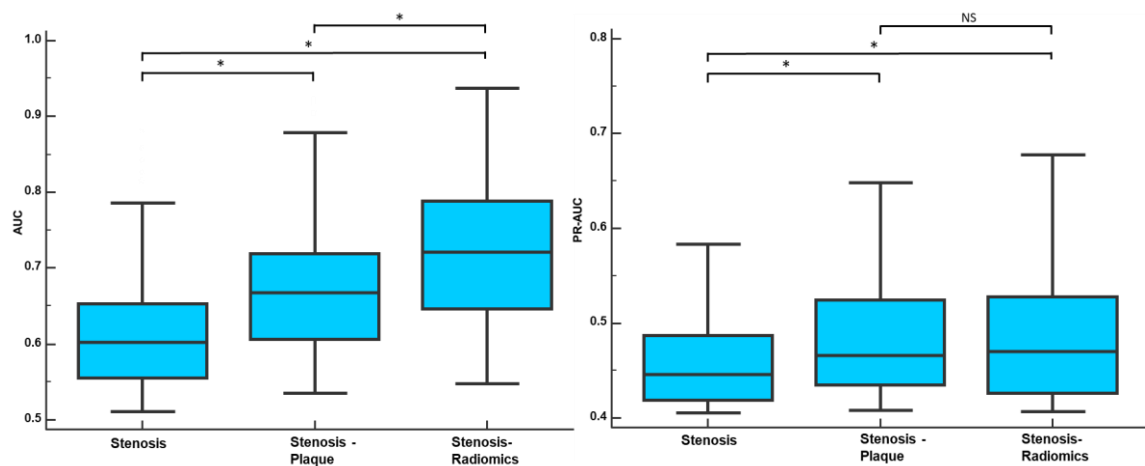


Figure 74 Naive Bayes results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in SPECT-MPI population. * < 0.05

Table 20 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal SPECT-MPI using Naive Bayes

Image Type	Description	Feature
original	shape	Elongation
LoG ($\sigma = 1$)	ngtdm	Complexity
LoG ($\sigma = 2$)	glcm	Autocorrelation
LoG ($\sigma = 2$)	glcm	Cluster Prominence
LoG ($\sigma = 5$)	glrlm	Short Run Low Gray Level Emphasis
wavelet-LHL	First Order	Mean
wavelet-LHL	glcm	Correlation
wavelet-HLL	firstorder	Skewness
wavelet-HHL	ngtdm	Busyness
square	glcm	Correlation
exponential	ngtdm	Busyness
gradient	glcm	Cluster Tendency
-	Plaque	% FIBROUS
-	-	Stenosis Severity

Finally for SVM classifier, stenosis severity as a sole feature model performed an AUC-median = 0.567 (95% CI: 0.559 to 0.574) with a PR-AUCmedian= 0.435 (95% CI: 0.424 to 0.455). The combination of stenosis severity and Plaque characteristics gave an AUC

= 0.633 (95% CI: 0.625 to 0.644) and the comparison between that and stenosis severity alone was statistically significant ($p\text{-diff} < 0.05$). PR-AUC was also different compared to the stenosis model alone (0.451, 95% CI: 0.443 to 0.457, $p\text{-diff} < 0.05$). The combination of stenosis severity and radiomics features was also different from the model of stenosis, and stenosis + plaque (AUC= 0.702, 95%CI:0.697 to 0.709, $p\text{-diff} < 0.01$ for both comparisons). PR-AUC was also higher compared to stenosis model only (PR-AUC = 0.469, 95%CI:0.456 to 0.485, $p\text{-diff} < 0.01$ for both comparisons, Figure 75).

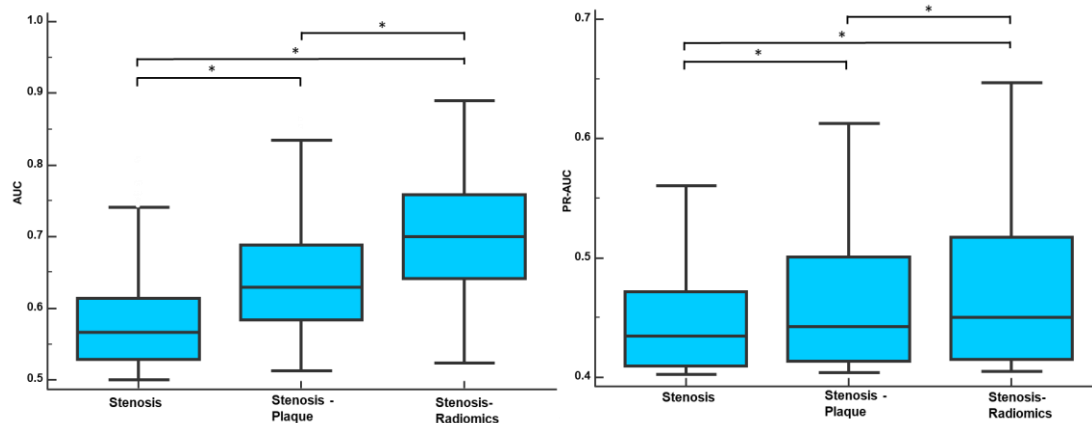


Figure 75 SVM classifier results of AUC (left) and PR-AUC (right) for stenosis, stenosis + plaque and stenosis + radiomics models in SPECT-MPI population. * $p < 0.05$

Table 21 Combination of Radiomics and plaque features on top of stenosis severity for predicting an abnormal SPECT-MPI using SVM

Image Type	Description	Feature
original	glrlm	Long Run Emphasis
LoG (s=1)	glrlm	Short Run Low Gray Level Emphasis
LoG (s=2)	First Order	Maximum
LoG (s=4)	glcm	Imc2
wavelet-LHL	ngtdm	Busyness
wavelet-LHH	glcm	Cluster Prominence
wavelet-HHL	First Order	90 Percentile
square	glcm	Imc2
square	glcm	Correlation
exponential	glcm	ClusterTendency
	Plaque	% FIBROUS
-	-	Stenosis Severity

3.2.4 Discussion

In the present study we wished to examine the additive value of radiomic analysis over conventional CCTA evaluation for the prediction of regional myocardial ischemia on MPI. We resulted in two main findings. First, we showed that specific radiomic features are correlated with the presence of significant regional myocardial ischemia, offering

increased accuracy over conventional CCTA characteristics (i.e. stenosis severity and plaque volume). Second, our analysis showed that particular radiomic features of CCTA datasets were able to identify cases of myocardial ischemia at either PET or SPECT MPI, underlying the value of radiomic analysis to distinguish between specific coronary perfusion patterns revealed by individual imaging techniques. CCTA has been established as a reference standard for the non-invasive examination of patients with low to moderate likelihood of CAD. People with negative scan results usually do not undergo other diagnostic controls and are classified as low risk of future cardiac events.

New developments of the CCTA technology have made it possible to perform a simultaneous evaluation of the anatomy and function of a coronary vessel, giving reliable measures of CAD hemodynamic relevance [137]. Estimations of fractional flow reserve (FFR) assessed using computational fluid dynamics (CFD) on CCTA datasets are in line with the accepted gold-standards [147], [239] and this method has been adopted by most recent guideline statements. Nevertheless, it is not widely used in the clinical practice [276]. Additionally, the 3D representation of the vessel volume used in CFD models usually does not take into consideration the effect of individual plaque components – features with probably more diagnostic value than mere stenosis severity- on coronary flow dynamics [277], [278].

Radiomics contributes to the accurate phenotyping of pathological findings identified in radiological imaging, likely offering a higher diagnostic potential than the conventional CCTA analysis [279]. In more detail, radiomic analysis is the process of creating big-data information from CCTA multidimensional data sets, where each vessel lesion is described by a vast group of hundreds of features that are not identifiable via simple visual examination [280]. Previous studies have shown that stable and unstable plaques exhibit significantly different radiomics [281]. Until now, there has been no sufficient proof regarding the value of plaque radiomics for the prediction of an abnormal perfusion.

We have managed to show that, in patients with intermediate coronary artery lesions, there was a strong correlation between radiomic plaque features and the existence of downstream myocardial ischemia on MPI. Based on the 3 classification pipelines, we observed a common feature selection cluster pattern for both the PET-MPI and SPECT-MPI population. For the PET-MPI population, two geometric features (Maximum Diameter in axial plane, And Maximum diameter in Coronal plane) as well as two first order characteristics (Entropy, Kurtosis) and two of second order (GLCM Cluster Prominence,

GLCM_{Joint Energy}) in addition to Fibro-Fatty plaque volume we present as common selected features.

Common geometric characteristics such as plaque length was been proven as predictors of ischemia when measured by FFR or by CCTA characteristics [282] [262]. Driessen et al., prove that non-calcified plaques with large diameters and complex geometries, like those at bifurcations, have been associated with increased vulnerability, leading to future coronary events. These characteristics are crucial for identifying high-risk patients in coronary CT angiography studies (CCTA). In addition to that Rizvi et al. observe the impact of the percentage of the plaque diffusion, an present that the more diffused plaque we have in a vessel, there are higher probabilities of having a pathological FFR result [283]. Finally, the same study, showed that positive remodeling is also a factor that has a role in the FFR result. Based on these studies we can assume that Maximum Diameter in axial plane and Coronal plane have the potential to also capture and translate the flow abnormalities measured by PET-MPI.

Entropy quantifies the complexity or randomness in voxel intensity values. In cardiovascular imaging, it is commonly used to assess the texture of plaques, with higher entropy values indicating more disorganized and unstable plaque structures. Zhang et al., and Badesha et al, has present that higher entropy in CT scans is often associated with vulnerable plaques, which are more prone to rupture and can lead to acute coronary events. It is frequently used in combination with other radiomic features to improve risk prediction models in coronary artery disease [284], [285].

Kurtosis in cardiovascular radiomics is considered a significant feature in evaluating the shape and "peakedness" of intensity distributions within plaques. Huang et al., analyzing CT coronary angiography (CCTA) emphasize that higher kurtosis values are linked to plaque compactness, which correlates with adverse outcomes, including higher risk of cardiovascular events [286]. This feature is particularly useful in detecting more rigid, but vulnerable calcified plaques that have limited deformability and greater potential for causing ischemic events [284] [285].

GLCM derive Cluster Prominence and Joint Energy are two second order characteristics that have been associated in multiple studies as plaque prominent differentiable features. Cluster Prominence quantifies the asymmetry and heaviness of the tails of the GLCM derived pixel distribution. It is sensitive to the presence of texture patterns that are far from the mean value. Joint Energy measures the uniformity of the GLCM distribution. High values indicate homogeneity in the texture. Kolossváry et al. has present that

GLCM derived Energy and Prominence were good predictors of identifying napkin ring signature inside plaques [281]. The napkin-ring sign is recognized as a feature of plaque, characterized by a cross-sectional appearance where a central zone of low CT attenuation directly contacts the vessel lumen and is encircled by a ring-shaped area of higher attenuation plaque tissue. Otsuka et al., colleagues found that the presence of the napkin-ring sign on coronary CCTA is highly associated with future acute coronary syndromes. This association persists independently of other high-risk plaque features detectable by coronary CCTA [287][288].

Regarding the one common plaque characteristic, Fibrous Fatty volume, it has been shown as a prominent characteristic of vulnerable plaque prone to rupture. Vulnerable plaque are characterized by a thin fibrous cap with excessive lipid core and macrocalcifications [289]. Treatments aiming to stabilize plaques focus on reducing lipid content and inflammation, thereby increasing fibrous tissue content and cap thickness [290].

In addition to that for SPECT-MPI population, one geometric feature (Elongation) as well as one first order characteristic (Skewness) and three of second order (GLCM Cluster Tendency, GLCM Correlation, GLRLM Short run low gray level Emphasis) in addition to % FIBROUS tissue were present as common selected features between the three classifiers.

Elongation is the geometric descriptor that quantifies how "elongated" or stretched a shape is. A study presents that lower elongation values (more irregular peri coronary adipose tissue shapes) are correlated with rapid plaque progression in coronary arteries. This suggests that as plaque progresses, the surrounding adipose tissue may undergo structural changes, such as becoming less uniformly distributed or more irregular in shape. These changes could reflect underlying biological processes like inflammation or remodeling of the fat tissue[291].

Skewness measures the degree of asymmetry in the distribution of pixel intensities in an image. A positive skew indicates that most pixel intensities are concentrated at lower values, with a long tail toward higher values. A negative skew indicates that most pixel intensities are concentrated at higher values, with a long tail toward lower values. A study by HUO et al., proposed that skewness can reflect the nature of the tissue's composition and changes due to disease processes. They found that in Rapid plaque progression negative skewness is prominent. A possible explanation is that Inflammation leads to increased water content, cell density, and other factors that raise pixel intensity in imaging. Therefore, the higher concentration of bright (high intensity) pixels reflected in the negative skewness can be associated with the heterogeneous nature of inflammation [291].

Cluster Tendency, Correlation and Short Run Low Gray Level Emphasis are a second-order statistical texture features derived from the Gray-Level Co-occurrence Matrix (GLCM) and Gray-Level Run-Length Matrix (GLRLM). Cluster Tendency measures the tendency of gray-level values to form clusters, meaning how often similar pixel intensities occur together in a given region of interest (ROI). GLCM Correlation assesses the linear dependency of gray levels between neighboring pixels. GLRLM Short run low gray level Emphasis quantifies the texture of an image by examining the occurrence of consecutive runs of pixels with the same intensity specifically focused on sequences of pixels with the same gray level that appear over a short distance in a specific direction in the image. High values means that there are a lot of small-scale artifacts of low intensity in the image. Cluster Tendency, Correlation and Short run low gray level Emphasis were found to differ between patients with healthy versus unhealthy coronary segments. This suggests that patients with more advanced CAD have different clustering patterns and lower correlation as well as lower Short run low gray level Emphasis patterns of PCAT segments around the coronary arteries [292][293]. PCAT can influence coronary artery function by exerting mechanical pressure on the vessels. This could lead to alterations in the local hemodynamics (blood flow patterns), potentially affecting the wall shear stress and thereby contributing to plaque development and progression [294].

As before with fibrofatty, fibrous tissue is also a prominent characteristic in atherosclerosis and more importantly it is considered a indication of high risk plaque composition [287][288].

Previous studies examining the putative correlation between radiomic parameters and inducible ischemia have not come to a definite conclusion, since they show, at the most, only a moderate additive value of radiomics over traditional CCTA evaluation in detecting significant CAD at ICA + FFR [202]. Lin et al., have recently verified that radiomic analysis has a moderate additive value over conventional CCTA evaluation in predicting hemodynamically significant CAD on invasive assessment [271]. Our analysis -despite producing a similar accuracy for conventional CCTA assessment with previous studies (AUC ranging from 0.62 to 0.74) [202], [271] – exhibited a significantly improved performance of radiomic analysis in the detection of inducible ischemia at either PET (AUC 0.85; $P < 0.05$ vs conventional CCTA) or SPECT MPI (AUC 0.82; $P < 0.05$ vs conventional CCTA). The observed difference of our results compared to previous reports could be due to the usage of different method for the identification of ischemia, namely MPI vs FFR. Even though invasive FFR has been established as the reference standard for the

assessment of inducible ischemia, it has some limitations: it measures the hemodynamic relevance of focal coronary lesions, while it does not consider the putative negative effect of diffuse CAD on myocardial perfusion data. Conversely, MPI offers a global functional evaluation of CAD burden, especially in the case of quantitative PET imaging [278]. This could explain the observed modest correlation between inducible ischemia and either CAD severity or visual plaque features [55], [262]. Our analysis showed that radiomic features reflecting the spatial distribution of voxels (higher-order radiomic metrics like GLCM) could efficiently identify an abnormal MPI, outperforming the traditional CCTA markers. Additionally, particular sets of radiomic features –fingerprints- could predict inducible ischemia at either SPECT or PET MPI, underlying the intrinsic differences between the two imaging techniques’ diagnostic potential. Our study offers mechanistic insights into the determinants of myocardial ischemia. Radiomic analysis is able to provide an improved prediction of downstream inducible ischemia on MPI -compared to traditional CCTA estimation- in patients with CAD lesions of intermediate severity and can identify the functionally significant lesions, especially when performed for the whole coronary vessel.

We have to acknowledge certain limitations to our study. Our radiomics analysis, just like all previous related reports, did not take into consideration the effect of coronary side branches. Moreover, the discrepancies originating from the distinct image acquisition systems and reconstruction algorithms were not accounted for. There have been developed various methods for the elimination of such heterogeneity effects and the harmonization of features in radiomics analysis and we believe that the use of such strategies could improve the significance of our results and the robustness of the proposed models [295]. Finally, we were forced to exclude some patients and vessels due to insufficient image quality, a fact which underlies the need of well-powered comparative studies between traditional and radiomic-based CCTA assessment.

3.2.5 Conclusions

Specific sets of radiomic features –fingerprints- were found to be correlated with cases of significant regional myocardial ischemia in patients with an intermediate probability of CAD. Furthermore, the combination of stenosis severity and plaque volume with specific radiomics features results in incremental value in the classification of lesions with impaired flow, as assessed by MPI.

4. Aorta

The increasing mortality rates associated with cardiovascular diseases highlight the need for effective diagnostic and therapeutic strategies, particularly for conditions affecting the aorta. Large vessel vasculitis (LVV), including Giant Cell Arteritis (GCA), primarily target the aorta and its branches [296], necessitating robust imaging tools for accurate assessment. 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) has become an essential tool for detecting vascular inflammation and measuring immune cell metabolic activity within diseased vessels [297]. This technique not only distinguishes between vasculitis and atherosclerotic lesions but also provides insights into soluble macrophage-related inflammatory markers in the serum of LVV-GCA patients [298]. Investigating these associations can enhance our understanding of the inflammatory milieu in different disease states and lead to improved patient stratification.

Additionally, the current research explores the feasibility of developing an end-to-end automated system for segmenting the aorta using low-dose PET/CT scans. This study employs advanced deep learning algorithms to facilitate the accurate and efficient measurement of tracer uptake in the aorta, replacing the manual, time-consuming process of region-of-interest (ROI) selection. The integration of these automated techniques promises to enhance diagnostic precision in assessing vascular inflammation and improving treatment monitoring for patients with aortic conditions.

Initially, we conducted a preliminary study focusing on LV-GCA patients during both active and inactive disease stages. This study was the first to employ a detailed ROI-to-ROI manual analysis to quantify 18F-FDG uptake in the aorta and its branches, linking PET/CT findings to serum markers such as inflammatory mediators and metabolic profiles. The manual process, though informative, posed significant challenges, including being labor-intensive and subject to operator variability. This highlighted the need for new, automated techniques to enhance accuracy and reduce the time and variability involved in image analysis.

Recognizing these challenges, we undertook a second study to address the critical need for automation in PET/CT analysis. In this phase, we aimed to develop a fully automated system for aortic segmentation and tracer uptake calculation using advanced deep learning algorithms. These algorithms were applied to low-dose CT images, significantly improving the speed and accuracy of PET/CT data analysis. The automated

process was designed to replace the manual slice-by-slice ROI selection, minimizing operator bias and providing reproducible results for assessing disease activity in both vasculitis and lymphoma patients. This approach has the potential to standardize image analysis, making it more efficient and scalable for clinical and research applications.

Therefore, the two studies we implemented and present are as follows:

1. Association of 18F-FDG PET/CT Findings with Metabolic Profile in LV-GCA During Active and Inactive Disease Stages: An Integrated Analysis

This study employed a manual ROI-to-ROI analysis to assess PET/CT imaging in LV-GCA patients. It explored the correlation between metabolic activity and disease state, identifying key associations between PET/CT findings and metabolic profiles but not with macrophage-related cytokines.

2. Automated Aortic Segmentation in Low-Dose Chest CT Images with PET-Based Standard Uptake Value (SUV) Analysis for Vasculitis and Lymphoma Patients.

This study focused on developing a fully automated method for aortic segmentation and SUV analysis using deep learning. The goal was to replace manual ROI selection, enhancing the reproducibility and efficiency of PET/CT analysis in vasculitis and lymphoma patients, thereby addressing the need for standardized and automated tools in clinical practice.

4.1 18F-FDG PET/CT In LV-GCA During Active and Inactive Disease Stages Is Associated with The Metabolic Profile.

4.1.1 Introduction

Large vessel vasculitis (LVV) is a group of autoimmune and autoinflammatory disorders that primarily affect large arteries, such as the aorta and its major branches [299]. Among these, Giant Cell Arteritis (GCA) is the most common, predominantly affecting individuals over 50 years of age [300]. GCA presents with two main clinical phenotypes: cranial-GCA, which involves the temporal arteries, and large vessel GCA (LV-GCA), which affects the thoracic aorta and its branches. If untreated, LV-GCA can lead to severe complications, including aortic aneurysms and dissections, ischemic stroke, and blindness [301]. The pathogenesis of GCA involves an immune response, where macrophages, T-helper and B cells, are accumulated to the arterial walls. Traditional diagnosis of GCA has relied heavily on clinical findings and temporal artery biopsy [302], but newer imaging techniques have emerged as essential tools. PET/CT using 18F-FDG has become a valuable method for diagnosing and assessing disease activity in LV-GCA by detecting metabolic activity in inflamed vessels [303]. New guidelines now recommend PET/CT as a key diagnostic tool, alongside vascular ultrasound and magnetic resonance imaging [304]. While PET/CT is widely used, its correlation with soluble inflammatory markers remains under investigation. Markers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may occasionally lack reliability in differentiating between active and inactive disease states [305]. To address this, researchers have turned to metabolomics, which offers insight into systemic metabolic changes that may reflect disease activity more accurately than traditional markers [306]. Specifically, a group of metabolites have been associated with increased cardiovascular risk and systemic inflammation [307]. This proof-of concept study aims to integrate 18F-FDG PET/CT imaging with serum metabolomic profiling to establish a more accurate method for assessing disease activity in LV-GCA. Our approach centers on metabolites to create composite indices that integrate imaging and biochemical data, with the goal of enhancing disease progression monitoring and evaluating treatment response.

4.1.2 Methods

Study Cohort

Between 2021 and 2023, we prospectively enrolled 41 patients diagnosed with Giant Cell Arteritis (GCA) and Polymyalgia Rheumatica (PMR) from the Rheumatology outpatient clinic at the Department of Pathophysiology, Laiko General Hospital. Patients were classified as having large vessel GCA (LV-GCA) based on findings from PET/CT vascular reports. All LV-GCA patients (n=13) underwent two PET/CT scans: the first at the time of diagnosis (active phase) and the second six months after initiating treatment (inactive phase). Blood samples were collected from all participants at both time points to assess acute-phase reactants. Active disease was defined by the presence of clinical symptoms alongside elevated erythrocyte sedimentation rate (ESR >20 mm/h) and C-reactive protein (CRP >5 mg/L) [308],[309]. Remission was characterized by the absence of these markers. Six months after the treatment all patients were classified to the inactive phase.

¹⁸F-FDG PET/CT Imaging Protocol

Participants fasted for at least six hours prior to the PET/CT scan, and blood glucose levels were ensured to be under 180 mg/dL before the radiotracer injection [310]. ¹⁸F-FDG (3.7 MBq/kg body weight) was administered intravenously, followed by PET/CT imaging (Biograph, Siemens, Forchheim) 90 minutes later [311]. Attenuation correction and co-registration were performed using a low-dose non-gated, non-contrast CT scan (120 kV, 30–70 mAs). PET images were reconstructed with an iterative ordered-subset expectation maximization algorithm, applying 4 iterations and 5 subsets within a 440 x 440 matrix [312].

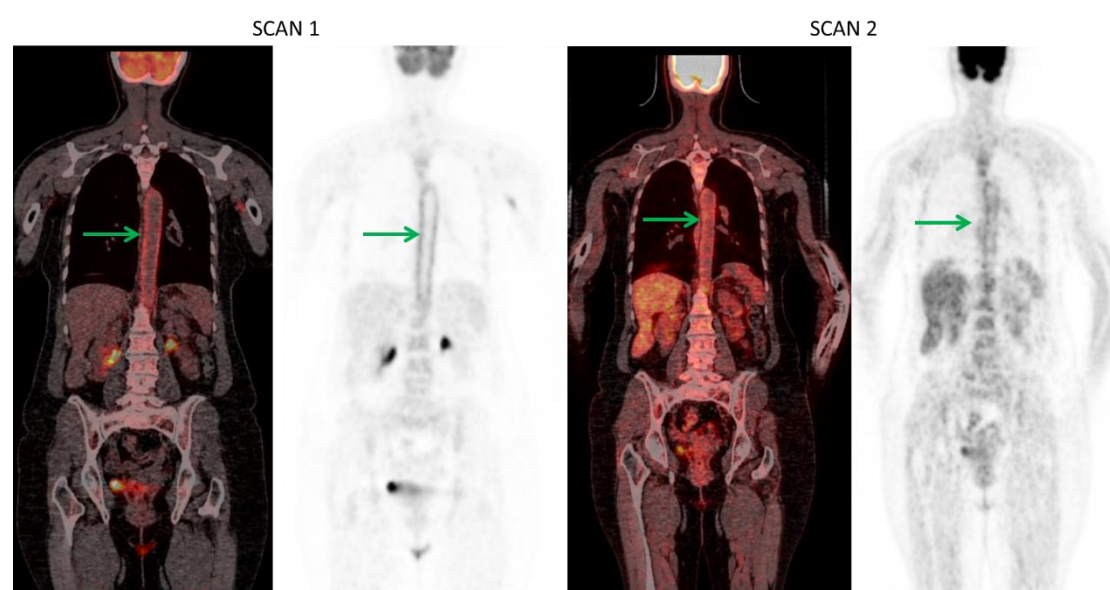


Figure 76 A female patient (60 y.o) at the first PET/CT scan and the second one. Arrows present the disease activity distribution in the descending aorta.

¹⁸F-FDG PET/CT Measurements

PET/CT images were anonymized and assessed both qualitatively and semi-quantitatively by an experienced reader blinded to patient data. The PETVAS score was used to evaluate large vessel involvement by comparing FDG uptake in seven vascular regions (carotid, iliac, subclavian, axillary, femoral arteries, and thoracic and abdominal aorta) relative to liver uptake. Vessels were scored on a 0–3 scale: 0 (no uptake), 1 (uptake less than liver), 2 (equal to liver), and 3 (greater than liver) [303]. Patients with a score of 0–1 were classified as PET/CT negative, while those with scores of 2–3 were positive. The target-to-background ratio (TBR) was calculated by dividing the arterial maximum standardized uptake value (SUV_{MAX}) by the mean venous SUV from the superior vena cava (SVC). Specific TBR values were computed for the abdominal aorta (TBR_{ABD}), the global aorta (TBR_{GLOBAL}), and the most diseased segment (TBR_{MDS}), the latter being derived from the highest SUV_{MAX} and its neighboring slices. These values were later used to create composite indices.

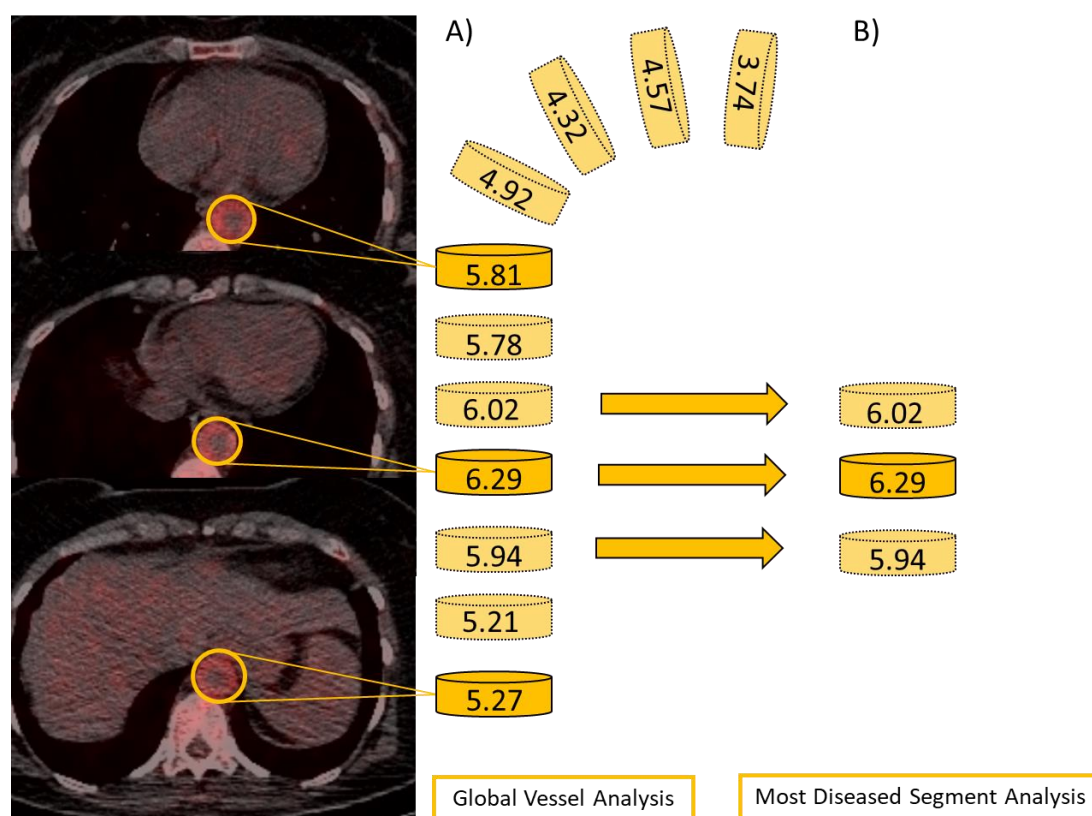


Figure 77 Calculations of SUV_{max} in the aorta segments A) Is the Global Vessel SUV analysis; B) Calculation of Most Disease Segment (MDS).

Metabolomics Data

This study utilized serum NMR metabolomics data that have been previously published [313]. 21 metabolites (3-Hydroxybutyric acid, Acetic acid, Acetone, Alanine, Choline

Smoothed, Citric acid, Creatine, Creatinine Smoothed, Dimethyl sulfone, Formic acid, Glucose, Glutamine, Glycine, Histidine Smoothed, Lactic acid, Leucine, Lysine, Phenylalanine Smoothed, Tyrosine Smoothed, Valine and Isoleucine) were assessed using the SMolESY platform and 1D-NOESY NMR spectra.

Composite Index Generation

Three composite indices were created by combining PET/CT results with CRP, ESR, and metabolite levels. Each variable (TBR_{MDS}, CRP, ESR, and choline) was converted into categorical values ^{Table 22} to ensure uniform scaling. Composite index 1 comprised TBR_{MDS}, CRP, and ESR. Composite index 2 added choline to the first index, while composite index 3 included CRP, ESR, and choline without TBR_{MDS}.

Table 22 Transformation of CRP, ESR and choline levels into categorical scale for composite index generation. CRP and ESR levels are increased during active disease resulting to an increased categorical value. Choline levels are decreased during active disease compared to inactive disease resulting to reversed categorical values.

CRP SCALE	CRP CATEGORY	ESR SCALE	ESR CATEGORY	CHOLINE SCALE	CHOLINE CATEGORY
≤ 5	1	≤ 20	1	≤ 6000	9
>5 to ≤ 20	2	> 20 to ≤ 35	2	> 6000 to ≤ 9000	8
> 20 to ≤ 40	3	> 35 to ≤ 50	3	> 9000 to ≤ 12000	7
> 40 to ≤ 50	4	> 50 to ≤ 60	4	> 12000 to ≤ 15000	6
> 50 to ≤ 60	5	> 60 to ≤ 70	5	> 15000 to ≤ 18000	5
> 60 to ≤ 70	6	> 70 to ≤ 80	6	> 18000 to ≤ 21000	4
> 70 to ≤ 80	7	> 80 to ≤ 90	7	> 21000 to ≤ 24000	3
> 80 to ≤ 90	8	> 90 to ≤ 100	8	> 24000 to ≤ 28000	2
> 90	9	> 100	9	> 28000	1

Statistical Analysis

Quantitative data were reported as medians with interquartile ranges (IQR), while qualitative data were presented as absolute and relative frequencies. The Wilcoxon signed-rank test was used to compare non-parametric continuous variables after the Shapiro-Wilk test for normality. Spearman's correlation coefficient assessed associations between variables, and multiple group comparisons were conducted using the Kruskal-Wallis test with Dunn's post-hoc correction.

Table 23 Baseline characteristics of all LV-GCA patients included in the study. In the parenthesis the interquartile range (IQR) is shown.

	LV-GCA (13)
Age (median, years)	64 (60-75)

Gender (Female%, N)	70%
Positive temporal artery biopsy	44,4%
ESR active phase (median) (<20mm/h)	50 (34,25 - 111,5)
ESR inactive phase (median) (<20mm/h)	5 (3-12)
CRP active phase (median) (0-5mg/l)	42,8 (37,5 - 146,5)
CRP inactive phase (median) (0-5mg/l)	0,5 (0,3-1,82)
Hct active phase (median) (%)	35,4 (33,05-36,45)
Hct inactive phase (median) (%)	39,4 (37,45-41,8)
PLTs active phase (median)	392000 (292000-489500)
PLTs inactive phase (median)	201000 (173000-238000)
Median time to inactive disease (months)	6
Arterial Hypertension (% , N)	44,4%
Diabetes Mellitus (% , N)	11,1%
Dyslipidemia (% , N)	55,6%
BP lowering drugs	33,3%

4.1.3 Results

PET/CT imaging differentiates between active and inactive phase in LV-GCA patients

During the active phase, patients exhibited significantly higher TBR values in the ascending aorta (TBR_{ASC}), aortic arch (TBR_{ARC}), abdominal aorta (TBR_{ABD}), descending aorta (TBR_{DSC}), and global aortic (TBR_{GLOBAL}) measurements compared to the inactive phase ($p < 0.05$ for all comparisons, Table 24). Both TBR_{MDS} and TBR_{GLOBAL} significantly decreased from the active to inactive phase [(3.32 vs. 2.65, $p = 0.006$) and (2.71 vs. 2.44, $p = 0.048$) respectively, Figure 78]. Similarly, PETVAS scores showed a significant reduction between the active and inactive phases (12.5 vs. 8, $p = 0.011$, Figure 78). The inflammatory markers of CRP and ESR present a statistically significant reduction observed from the active phase to remission ^{Figure 79}.

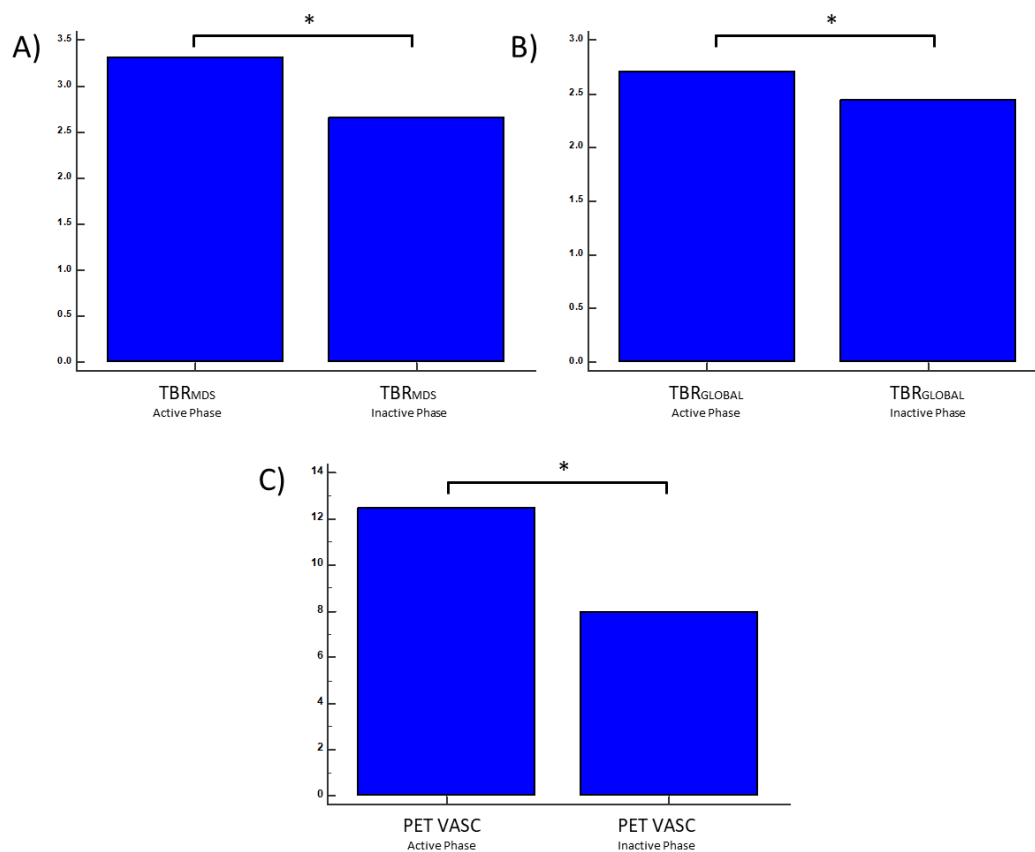


Figure 78 A) TBR of most disease segment during activity and inactivity; B) TBR Global during activity and inactivity; C) PET VASC during activity and inactivity. * $p < 0.05$

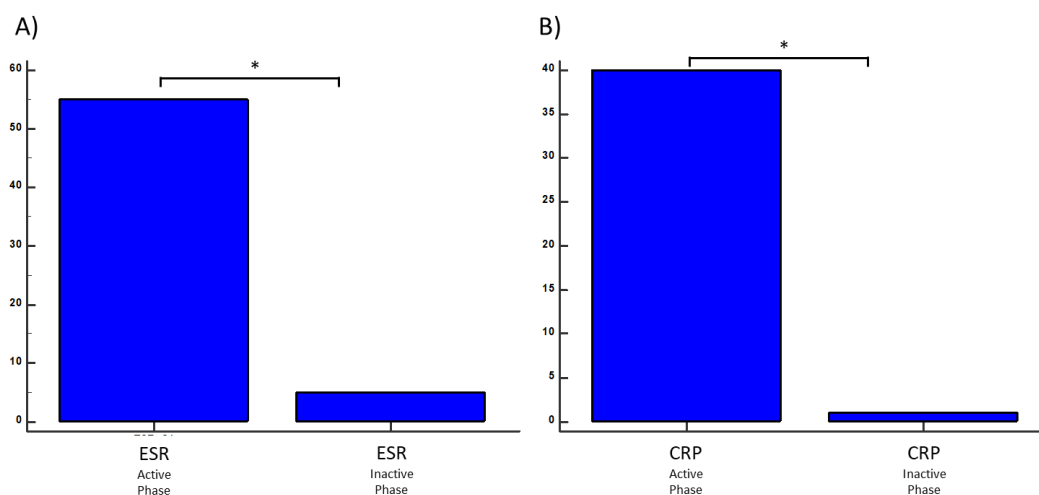


Figure 79 Comparison of A) ESR and B) CRP during active and inactive phase. * $p < 0.05$

Significant changes in serum metabolites, between active and inactive phases in LV-GCA

To further identify systemic inflammation markers associated with the active phase of LV-GCA, metabolites were analyzed and compared between the active and inactive phases of the disease. Interestingly, there were significant changes in metabolites serum level such as, Alanine, Choline and dimethyl sulfone ($p < 0.05$ for all comparisons).

There was no statistically significant correlation between metabolites and CRP or ESR Figure 81, Figure 82 even though there is a moderate correlation “trend”, between Choline and MDS_{TBR} both in active and inactive phase Figure 80^{Figure 81, Figure 82}.

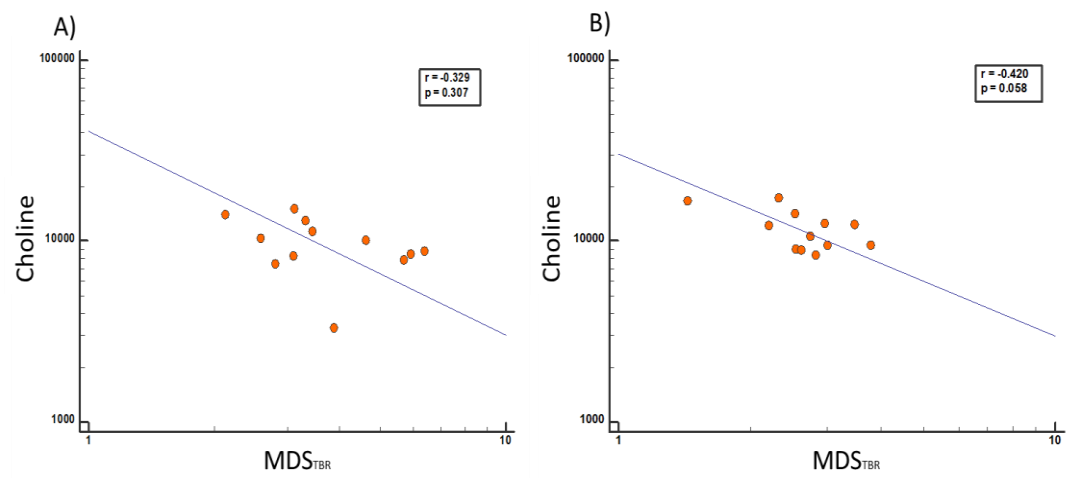


Figure 80 Correlation between Choline and TBR_{MDS} in A) Active and B) inactive phase. Scale is Logarithmic

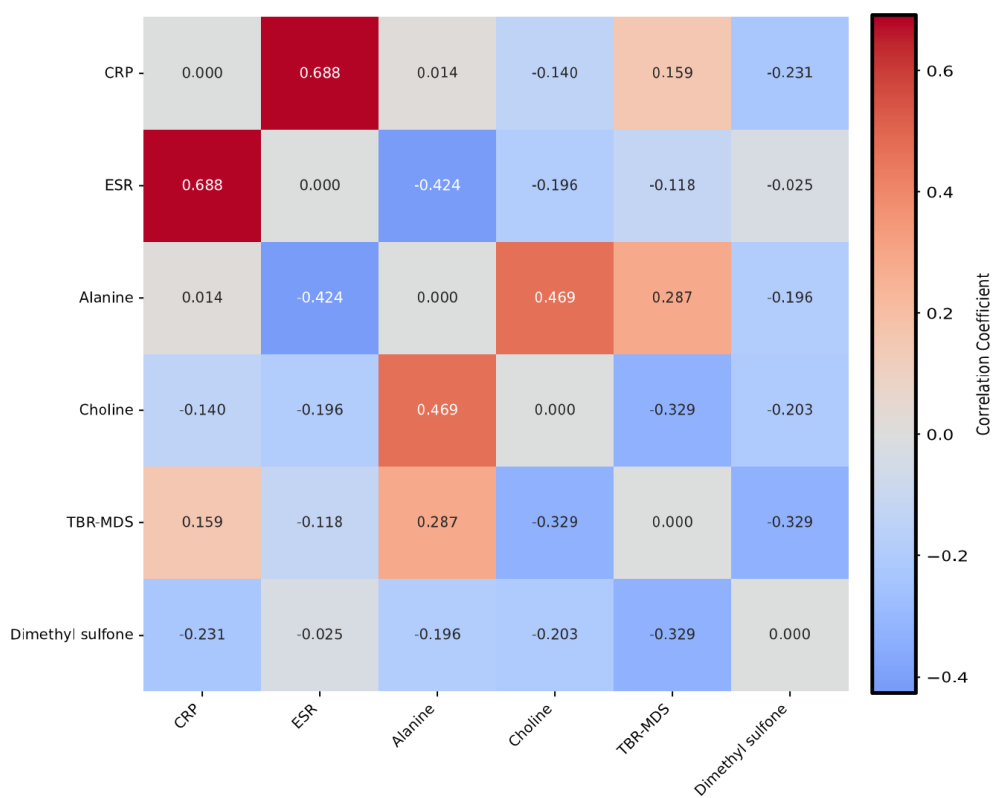


Figure 81 Correlation Coefficient table between PET, CRP, ESR and metabolites in active phase. All combinations $p > 0.05$.

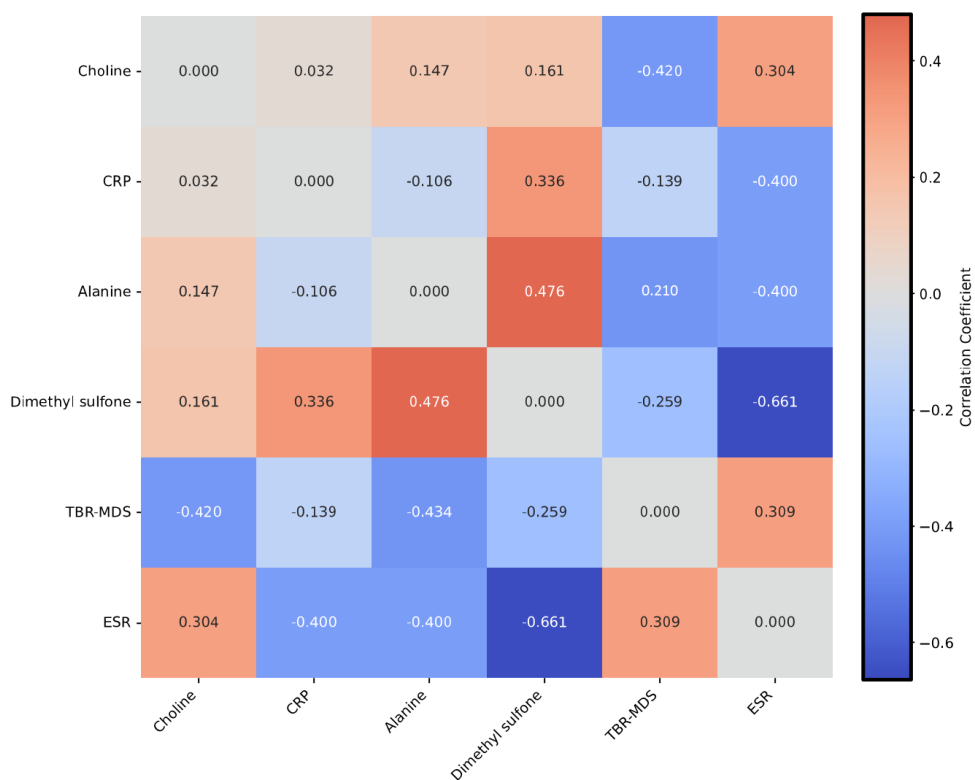


Figure 82 Correlation Coefficient table between PET, CRP, ESR and metabolites in inactive phase. All combinations $p > 0.05$.

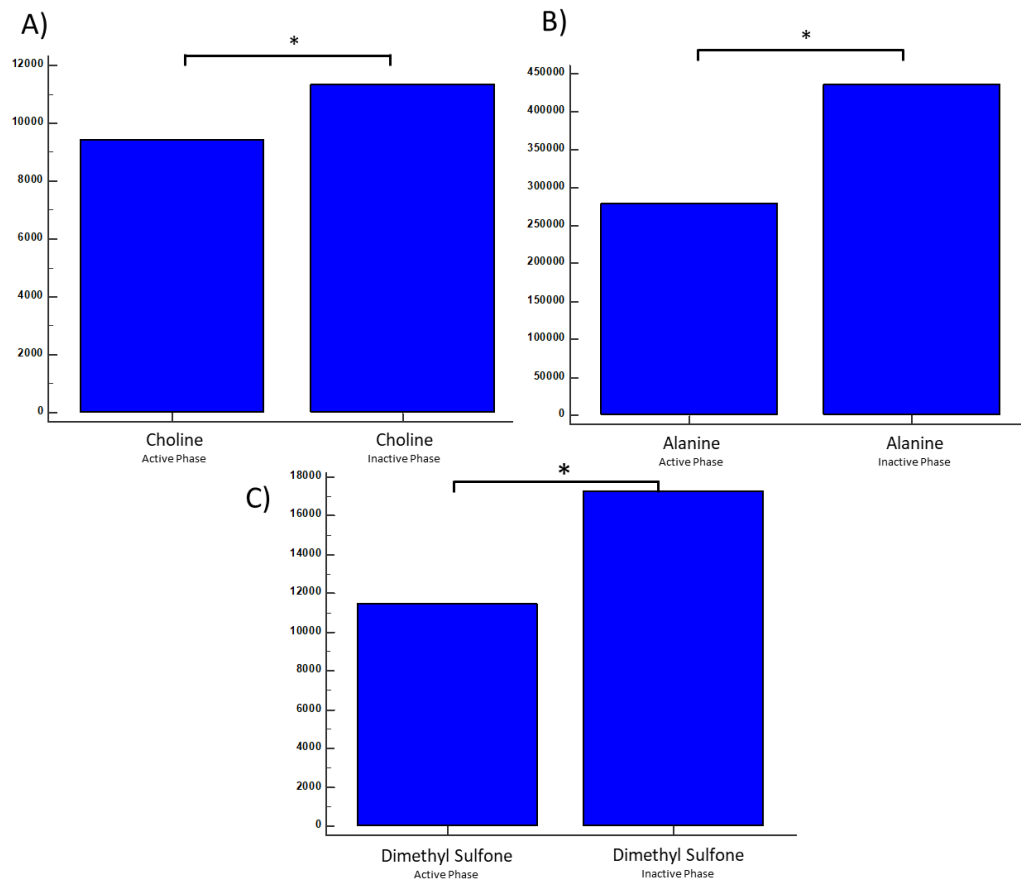


Figure 83 A) Choline during activity and inactivity; B) Alanine during activity and inactivity; C) Dimethyl Sulfone during activity and inactivity. * $p < 0.05$

Table 24 Comparison of metabolic activity assessed by 18-fluorodeoxyglucose (18F-FDG) positron emission tomography / computed tomography (PET/CT) and quantified by TBR, metabolites, and lipid moieties on different aortic segments. In the parenthesis the interquartile range (IQR) is shown.

Pair	Activity	Inactivity	P value
	Median	Median	
TBR_{MDS}	3,4475 (2,621 - 5,905)	2,5541 (2,226 - 2,994)	0,0061
TBR_{GLOBAL}	2,6599 (2,154 - 4,378)	2,07 (1,798 - 2,490)	0,0469
TBR_{ABD}	2,8806 (2,318 - 4,958)	2,1978 (1,866 - 2,710)	0,0171
TBR_{ARC}	2,7169 (1,997 - 4,284)	2,0989 (1,740 - 2,538)	0,0398
TBR_{ASC}	2,7169 (2,113 - 4,524)	2,2302 (1,741 - 2,558)	0,0574
TBR_{DSC}	2,7402 (2,162 - 4,085)	2,0922 (1,796 - 2,385)	0,0215
CRP	42(37,5 - 146,5)	1 (0,3 - 1,82)	0,0002
ESR	55 (34,25 - 111,5)	5 (3 - 12)	0,0005

Alanine	300257,8895 (254650,42 - 346576,12)	480454,16 (399395,94 - 547632,03)	0,0034
Choline	10119,46 (8303,11 - 11927,35)	12093,28 (8925,9 - 14793,92)	0,021
Dimethyl sulfone	9504,69 (7603,63 - 13241,41)	18106,75 (13461,28 - 32069,63)	0,0342

Development of composite indices for assessing disease activity and remission

To enhance the accuracy of assessing disease activity in LV-GCA, composite indices were generated. Composite Index 1, which summed TBR_{MDS}, CRP-categorical, and ESR-categorical, showed a significant reduction between the active and inactive phases ($p = 0.0005$, Figure 84A) (Figure 3D). Composite Index 2, which added choline to TBR_{MDS}, CRP-categorical, and ESR-categorical, also displayed a significant reduction ($p = 0.001$, Figure 84B). Composite Index 3, comprising CRP-categorical, ESR-categorical, and choline-categorical without TBR_{MDS}, similarly showed a significant reduction between the active and inactive phases ($p = 0.001$, Figure 84C).

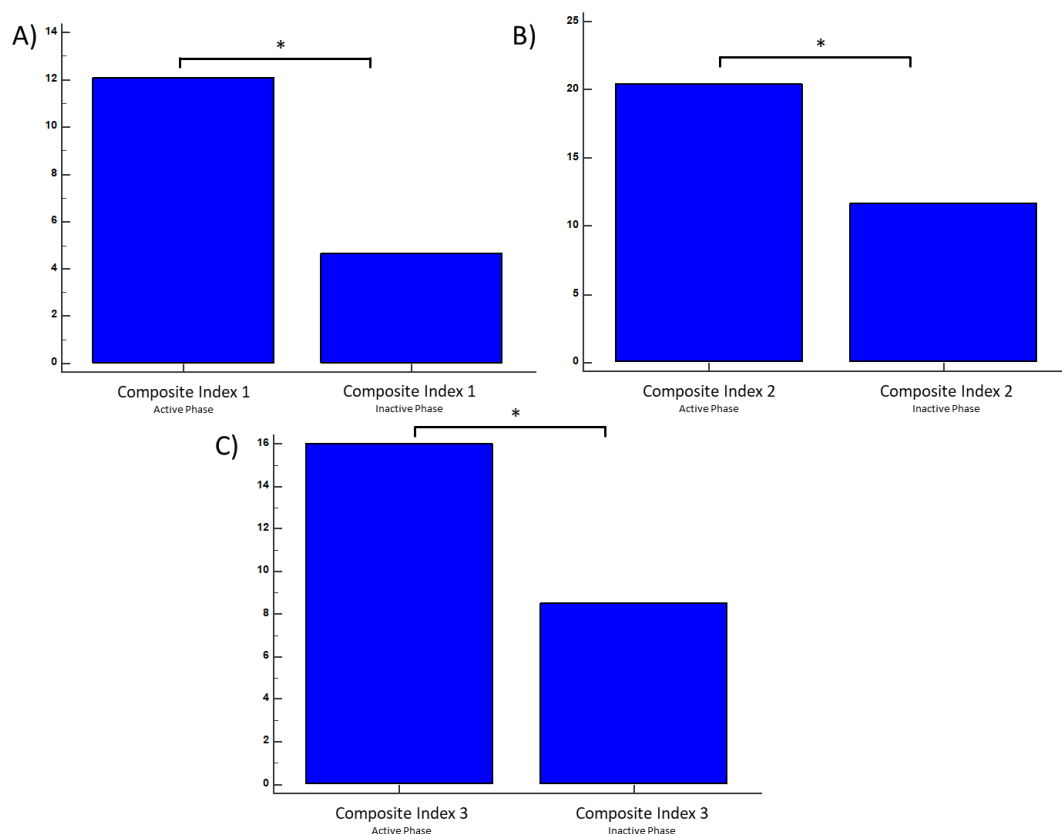


Figure 84 A) Composite Index 1; B) Composite Index 2; C) Composite Index 3 during activity and inactivity. * $p < 0.05$, Composite Index 1 = TBR_{MDS}, CRP-categorical, and ESR-categorical, Composite Index 2 = Choline, TBR_{MDS}, CRP-categorical, and ESR-categorical, Composite Index 3 = CRP-categorical, ESR-categorical, and choline-categorical

4.1.4 Discussion

In this study, we demonstrated that ^{18}F -FDG PET/CT imaging, particularly TBR_{MDS} , effectively differentiates between active disease and remission in patients with LV-GCA. The significant decrease in TBR_{MDS} from the active phase to remission reflects a reduction in vascular inflammation following treatment. TBR_{MDS} serves as a quantitative measure of metabolic activity in the most affected arterial segment, providing a focal assessment of disease activity [314]. Interestingly, despite the clear changes in TBR_{MDS} values, we did not observe a significant correlation between serum choline levels and TBR_{MDS} measurements. This lack of correlation suggests that while both TBR_{MDS} and choline levels are indicative of disease activity, they may reflect different aspects of the underlying pathophysiology. TBR_{MDS} captures the peak metabolic activity in a specific vascular region, indicating localized inflammation. In contrast, choline levels represent systemic metabolic changes and may be influenced by broader physiological processes such as liver function, lipid metabolism, and dietary intake [315], [316]. During active inflammation, choline utilization by proliferating immune cells may increase, leading to decreased serum levels. As inflammation subsides, choline demand decreases, and serum levels rise, which may not directly correlate with localized vascular inflammation detected by TBR_{MDS} . This metabolic divergence may contribute to the lack of correlation between TBR_{MDS} and choline levels.

Regarding alanine, we observed significantly higher serum levels during the inactive phase compared to the active phase of LV-GCA. Alanine plays a role in gluconeogenesis and acts as a key amino acid in nitrogen transport and metabolism [317]. The elevated alanine levels during remission may reflect a normalization of metabolic processes and reduced inflammatory catabolism. Although specific studies on alanine in LV-GCA are limited, alterations in amino acid profiles have been reported in other inflammatory conditions, indicating their potential role as biomarkers [318].

Dimethyl sulfone showed significantly increased serum levels during the inactive phase. Known for its anti-inflammatory and antioxidant properties, dimethyl sulfone may contribute to the resolution of inflammation [319]. The relationship between dimethyl sulfone levels and TBR_{MDS} is not well established, but the lack of correlation may again be due to the localized nature of TBR_{MDS} measurements versus the systemic representation of serum metabolites.

4.1.5 Conclusions

The absence of significant correlations between TBR_{MDS} and serum levels of choline, alanine, and dimethyl sulfone underscores the complexity of LV-GCA pathophysiology. TBR_{MDS} provides a localized assessment of vascular inflammation, while serum metabolites reflect systemic metabolic changes. This disparity highlights the importance of a multimodal approach in evaluating disease activity. Our findings suggest that integrating ^{18}F -FDG PET/CT imaging, specifically TBR_{MDS} measurements, with serum metabolomic profiling offers a comprehensive assessment of disease activity in LV-GCA. Future studies with larger cohorts are warranted to validate these observations and to further elucidate the interplay between vascular inflammation and systemic metabolism in LV-GCA.

4.2. Automated Aortic Segmentation in Low-Dose Chest CT Images with PET-Based Standard Uptake Value (SUV) Analysis for Vasculitis and Lymphoma Patients

4.2.1 Introduction

The combination of Positron Emission Tomography and Computed Tomography (PET-CT) with Fluorodeoxyglucose (FDG) can improve the diagnosis and treatment of many diseases like vasculitis and lymphoma [320]–[323]. PET-CT offers both metabolic data (PET) and precise anatomical features (CT), providing the clinicians with a comprehensive view of each particular case. PET-CT plays a fundamental role in the detection of vascular inflammation in vasculitis cases, thus facilitating the early diagnosis and the monitoring of treatment efficiency [324]. In lymphoma, it can accurately detect the stage of the disease, measure the metabolic activity of the tumor via Standard Uptake Value (SUV), and finally, track the outcome of the applied treatment [325]. SUV is a critical feature of PET-CT, which is able to mark active disease regions, since an increased metabolism is typically associated with cancerous or inflammatory tissue. Currently, the calculation of SUV involves a time-consuming procedure prone to produce variable results -depending on the user- during which Regions of Interest (ROI) are selected manually slice by slice. To overcome this, there have been developed various open-source tools like 3D Slicer [326] and ITK-SNAP which enable a semi-automated segmentation, minimizing the involvement of the user to the seed placement at the beginning of the process and to the correction of putative segmentation errors. Deep learning algorithms such as the Residual Networks (ResNets) [327] and UNet architectures[186], have managed to significantly improve the classification and segmentation fields, including the medical image segmentation techniques. These algorithms are able to handle and analyze complex imaging data and perform the segmentation process in an accurate and rapid manner, by delineating the aorta and other regions automatically, while overcoming the technical issues deriving from the anatomical variability and from low-dose poor image quality. The potential of deep learning techniques to increase the accuracy of vasculitis and lymphoma diagnosis highlights the importance of ongoing development in the field for the analysis of low-dose CT image.

Our aim is to examine the possibility of developing an end-to-end automatic system for the calculation of tracer uptake in the aorta of patients with vasculitis or lymphoma, using low-dose CT and FDG-18 in full-body PET/CT scans. This method could replace

the time-consuming manual, slice-by-slice ROI selection which is being used at the moment.

4.2.2 Methods

Population

This proof-of-concept study involved 36 patients diagnosed with vasculitis and lymphoma that have performed low dosed CT and PET.

Imaging Procedure

¹⁸F-FDG PET/CT Imaging

Patients underwent ¹⁸F-FDG PET/CT imaging after fasting for a minimum of 6 hours, ensuring blood glucose levels were under 180 mg/dl. Following intravenous administration of ¹⁸F-FDG (140 μ Ci/kg), CT images were acquired for attenuation correction of PET emission data and anatomical mapping of radiotracer uptake. Acquisition parameters included 30 mA, 110 kV, and a 1.25 mm slice thickness in the axial plane. PET images were reconstructed using the standard OSEM (ordered-subset expectation maximization) algorithm, set at 3 iterations and 8 subsets.

Manual SUV Calculation and Ground Truth Segmentation

For our study, we conducted manual ground truth segmentation of the aorta using 3D Slicer software ^{Figure 85} and SUV calculation using a specialized PET/CT imaging tool ^{Figure 86}. Regions of Interest (ROIs) were meticulously identified for precise SUV analysis in patients with vasculitis and lymphoma using a custom build software. Specifically, the ¹⁸F-FDG PET/CT images were assessed blinded to the patients' history. Regions of Interest (ROIs) were manually selected along the entire vessel of the thoracic and abdominal aorta in 5 mm consecutive slices in the axial plane, while for the superior vena cava, circular ROIs with a diameter of 3-4 mm were placed internally. ¹⁸F-FDG uptake was measured using the Standard Uptake Value (SUV). For quantifying ¹⁸F-FDG uptake, the average maximum SUV (SUV_{max}), representing the pixel value with the highest activity within the ROI was calculated. This approach ensured accurate and consistent measurements essential for evaluating the effectiveness of automated segmentation methods against a robust ground truth established through 3D Slicer. Automatic vs Manual segmentation comparisons were performed using paired Wilcoxon test. A p value < 0.05 was considered statistically significant.

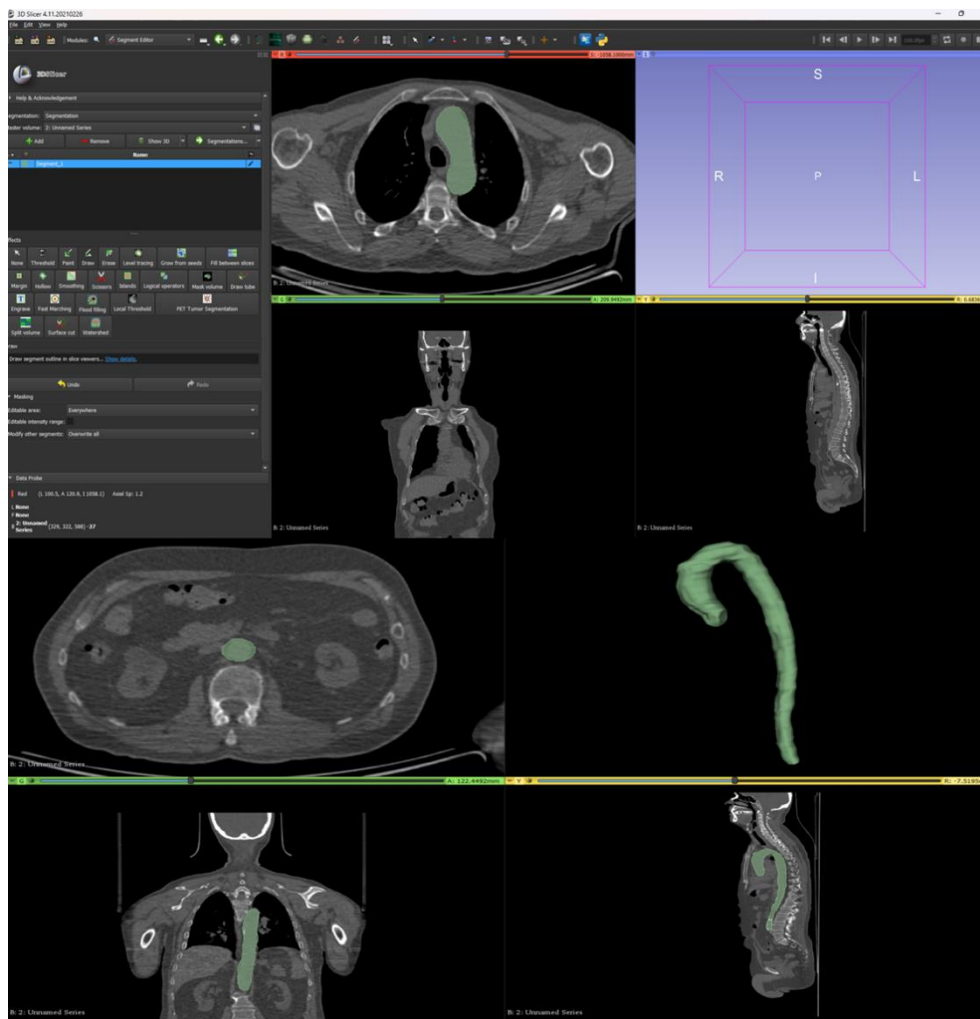


Figure 85 Manual Segmentation Aortic study using 3D slicer Software

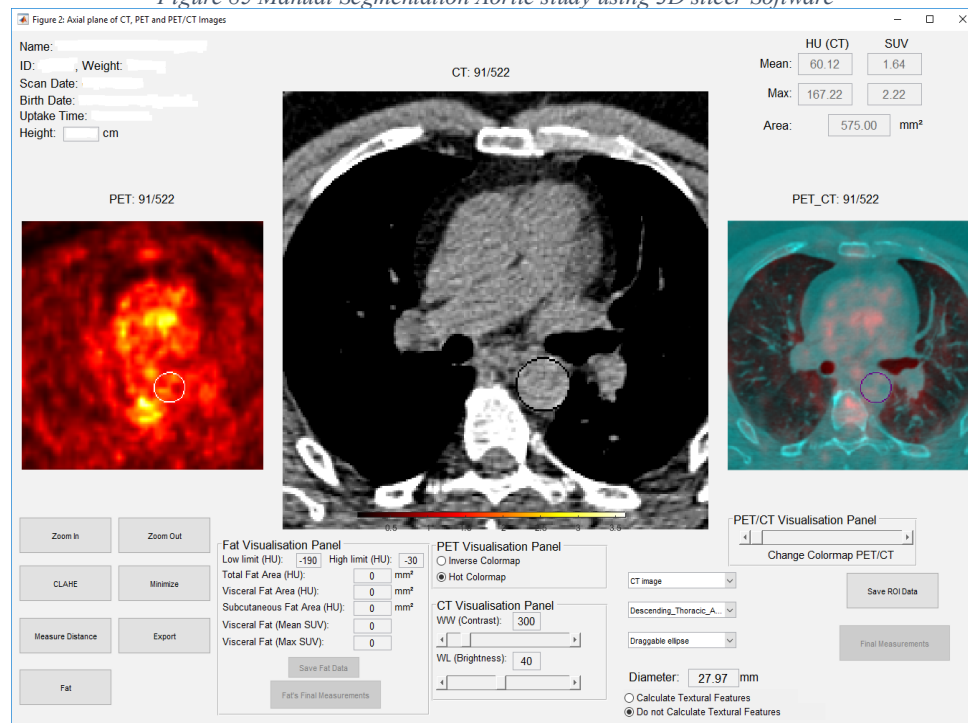


Figure 86 Manual Quantification of PET studies using Kafouris et al. software

Segmentation Algorithm Training

In order to simplify the training process, only images with positive ground truth mask were selected for the total training dataset. The study's segmentation models were developed using Python 3.10.12 with TensorFlow 2.0.0, standardizing the experimental setup. Input images were resized to 512x512 pixels for uniform processing. The segmentation task employed a UNET model architecture with a ResNet-18 backbone, chosen for its efficiency in handling complex image features. A train set of 20 patients (~8200 slices) and a validation set of 6 patients (~1800 slices) was developed for the task. The model was trained for a total of 150 epochs using batch size of 4 images, utilizing Stochastic Gradient Descent (SDG) optimizer to minimize the binary cross-entropy loss, aiming to improve both pixel-level accuracy and the overlap metric. Model performance was primarily evaluated on the Intersection over Union (IoU) metric, with the best-performing model during validation phases being saved for further analysis.

4.2.3 Results

Segmentation and SUV quantification Results

In the present study we used 26 patients and ~10000 image slices in order to train and validate our segmentation model, while 10 patients were used for the evaluation of the SUV assessment results. The validation set performed an average IOU of 0.772 following by an F1 score of 0.867. Precision was 0.879 and Recall performance was 0.861 at 0.5 threshold cut off. We found no statistical difference between the automatic and traditional manual segmentation as far as the calculation of the mean SUV_{max} for the total aortic segment is concerned (2.56 [95% CI: 2.11 to 3.02] vs 2.29 [95% CI: 2.15 to 2.58], p -diff = 0.16, Figure 87A). The automatic and the manual segmentation were in good agreement as shown in the Bland and Altman plot, with no measurements resides outside of the -1.96 standard error limit ^{Figure 87B}. Concerning the time needed for the application of the two different methods, we noticed that the automatic segmentation was significantly less time-consuming –as measured in minutes- when an inference on GPU was utilized (6.7 [95% CI: 4.986 to 7.370] vs [36 [95% CI: 32.621 to 38.567], $p < 0.001$, Figure 88).

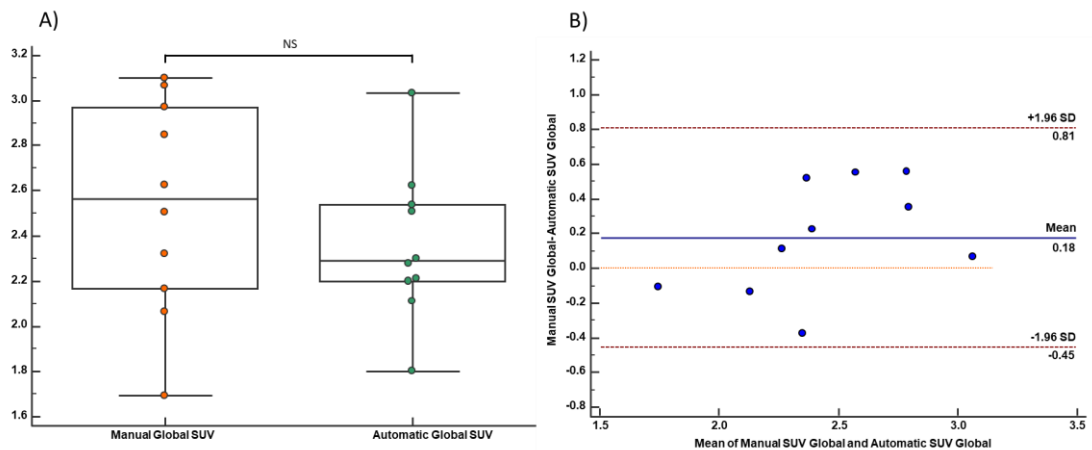


Figure 87 A) Average SUVmax values of automatic vs manual segmentation; B) Bland Altman plot for comparing automatic and manual differences in average SUVmax calculation.

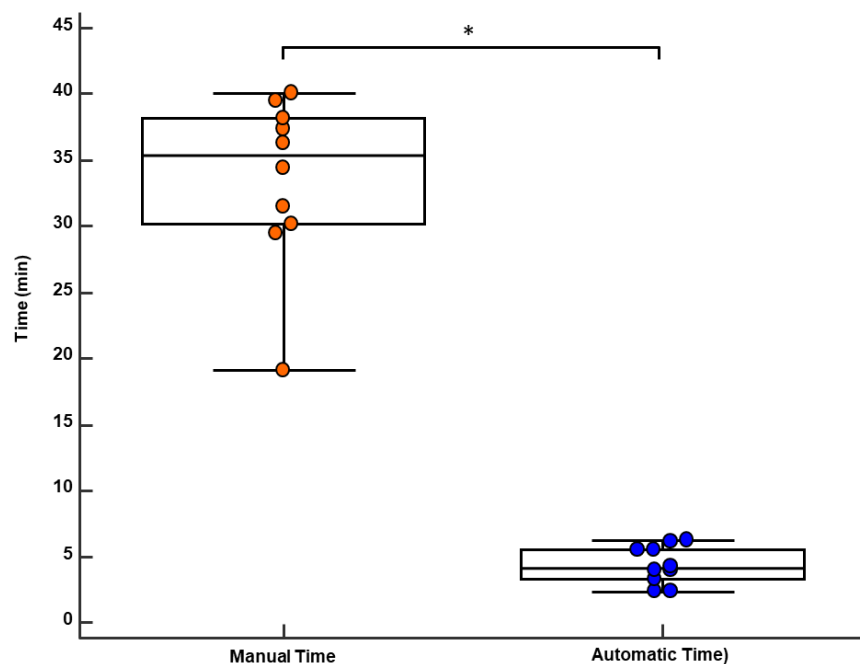


Figure 88 Time difference between automatic and manual segmentation * $p < 0.05$

Visualization Aid

We implemented a relatively simple graphical user interface in order to develop an end-to-end framework for SUV automatic calculation ^{Figure 89}. In the certain framework the operator first needs to select the respective group of CT and PET images, and then the platform automatically performs and visualizes the segmentation area and the SUV metrics in a two-step process. In more detail, first the user uploads the specific study under examination to the platform and the preprocess algorithm reads the images (in DICOM format) and collects all the necessary information regarding the technical image characteristics, and the data which will be needed for the following calculation of

the SUV ^{Figure 90}. Secondly, the operator is asked to determine the region of interest, which, here, is the total aortic segment and the SUV ^{Figure 91}. When the algorithm has completed the necessary calculations, the user is given access to all the SUV and total metrics for every slice ^{Figure 92}.

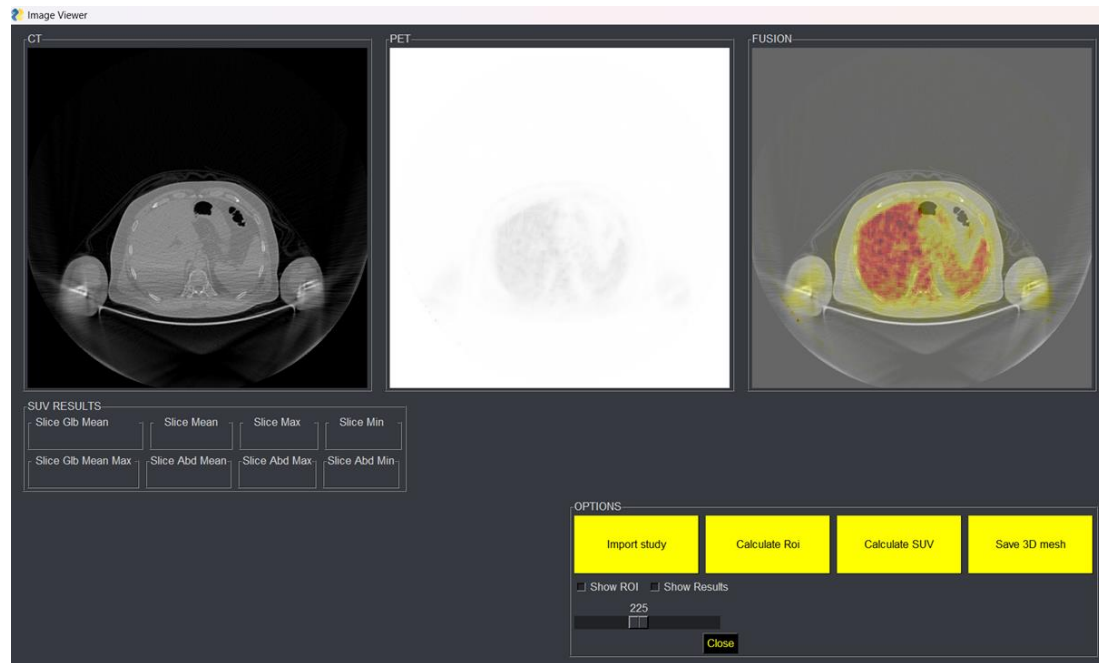


Figure 89 Initial screen of GUI loaded with CT-PET images in the left and middle window and Fusion in the right one

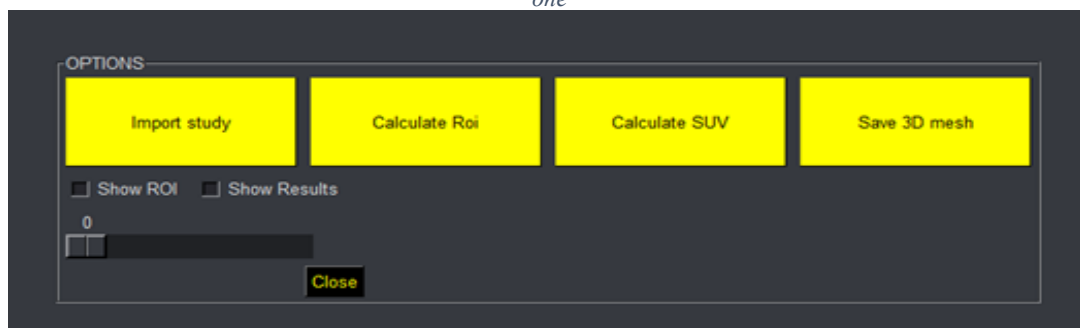


Figure 90 Close up of the users' action selection tools

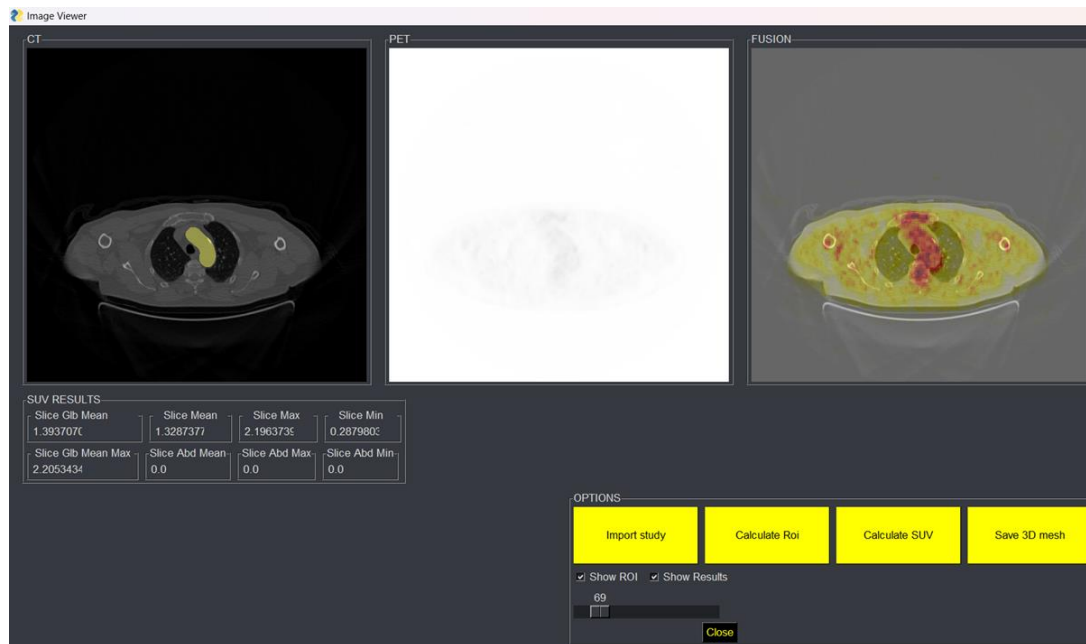


Figure 91 Results screen after segmentation and SUV calculation

4.2.4 Discussion

Our work in the present study highlights the significant developments in the field of medical imaging via the utilization of learning techniques. Specifically, we used a UNET model with a ResNet-18 backbone, for the development of an automatic method for the segmentation of the aorta and the calculation of the SUV, from low-dose CT and FDG-PET scans in vasculitis and lymphoma patients ^{Figure 93}. Both the accuracy of our method, as reflected in the absence of statistical difference between the manually and automatically calculated SUVmax values, and the significant decrease of the segmentation time, set a pivotal step towards improving diagnostic workflows. In agreement with our results, previous studies have also proven the feasibility of the development of accurate segmentation aortic results from low dosed CT images, by means of image analysis-derived algorithms and deep learning techniques [328]–[330]. Our segmentation model achieved comparable results with previous attempts in terms of IOU score [331], [332]. All the above validate the design of our algorithm (network architecture, selection of hyperparameters), reaffirming the possibility of deep learning models to efficiently operate despite the complex variability of aortic anatomy. Nevertheless, our algorithm produced some segmentation inaccuracies, which were manifested mostly as deviations at the vessel borders and at sites located substantially far from the predefined Regions of Interest (ROI) ^{Figure 92}. Such errors were observed in older reports too, where 3D segmentation methods were used in combination with bigger cohort of patients [333], [334]. The above highlight the inherent difficulties of developing a

model intended for a variety of related tasks in the context of the extensive heterogeneity and the complex structures that are produced by pathological conditions like vasculitis and lymphoma. In more detail, such conditions often result in the development of enlarged or irregularly shaped regions at the vessels, which make the segmentation process more difficult [328], despite the fact that the circular shape of aortic segments facilitates the human interpretation. In addition to that we present the feasibility of using such methods in order to produce acceptable 3D models for downstream research tasks, utilizing such an automatic system in combination with a simple GUI ^{Figure 94}. Concluding, this heterogeneity is a substantial obstacle for automatic segmentation algorithms, and underscores the difficult task of achieving sufficiently high accuracy in variable conditions and anatomical formations.

Our model could benefit from certain improvements in order to overcome the inaccuracies often produced at vessel edges and non-ROI related sites. In more detail, we could redesign our training approach to achieve higher accuracy and reliability by including a more varied set of anatomical formations and disease conditions. A more efficient recognition and mapping of the vessel borders could lead to less errors, more reliable SUV calculations and higher diagnostic value.

Even though our model produced promising results, we should acknowledge that further examination is needed. Specifically, the SUV values should be tested at multiple segments of the aorta, including the ascending, the descending, and the aortic arch regions. This detailed examination is essential for the overall validation of a model's performance and for the identification of any putative commonly occurring site-specific errors.

4.2.5 Conclusions

Concluding, the present study can serve as a first test of how automated segmentation and SUV calculation could be utilized in clinical practice. We believe that with such automated systems the clinicians will be able to get accurate analyses' results in a substantially reduced time frame and thus make timely and informed treatment decisions, significantly improving patient care. In the future we need to continue our research in order to confirm our system's credibility and to assess its value for the improvement of diagnostic accuracy and patient outcomes.

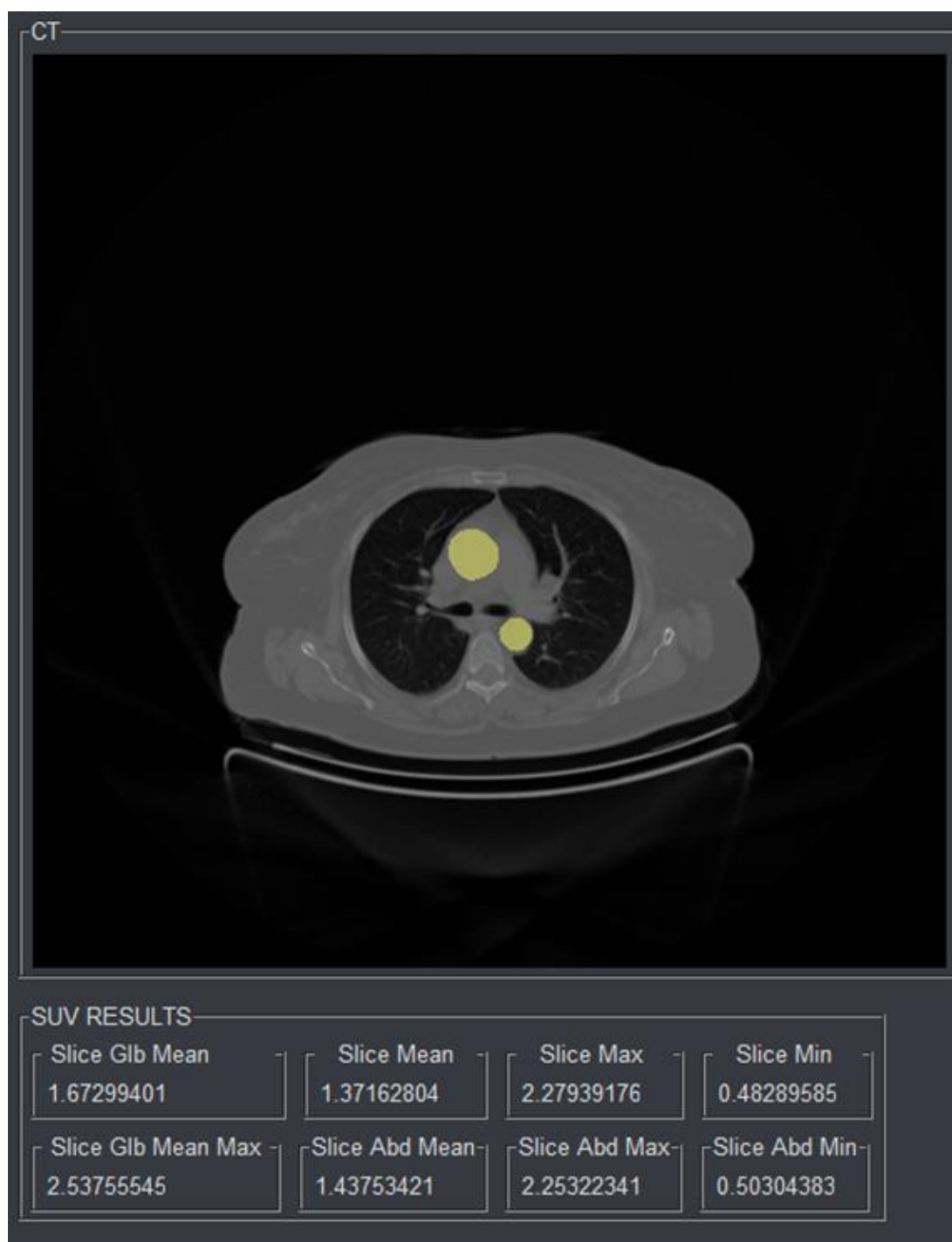


Figure 92 Close up scree of CT segmentation. SUV results are presenting multiple aspects of analysis

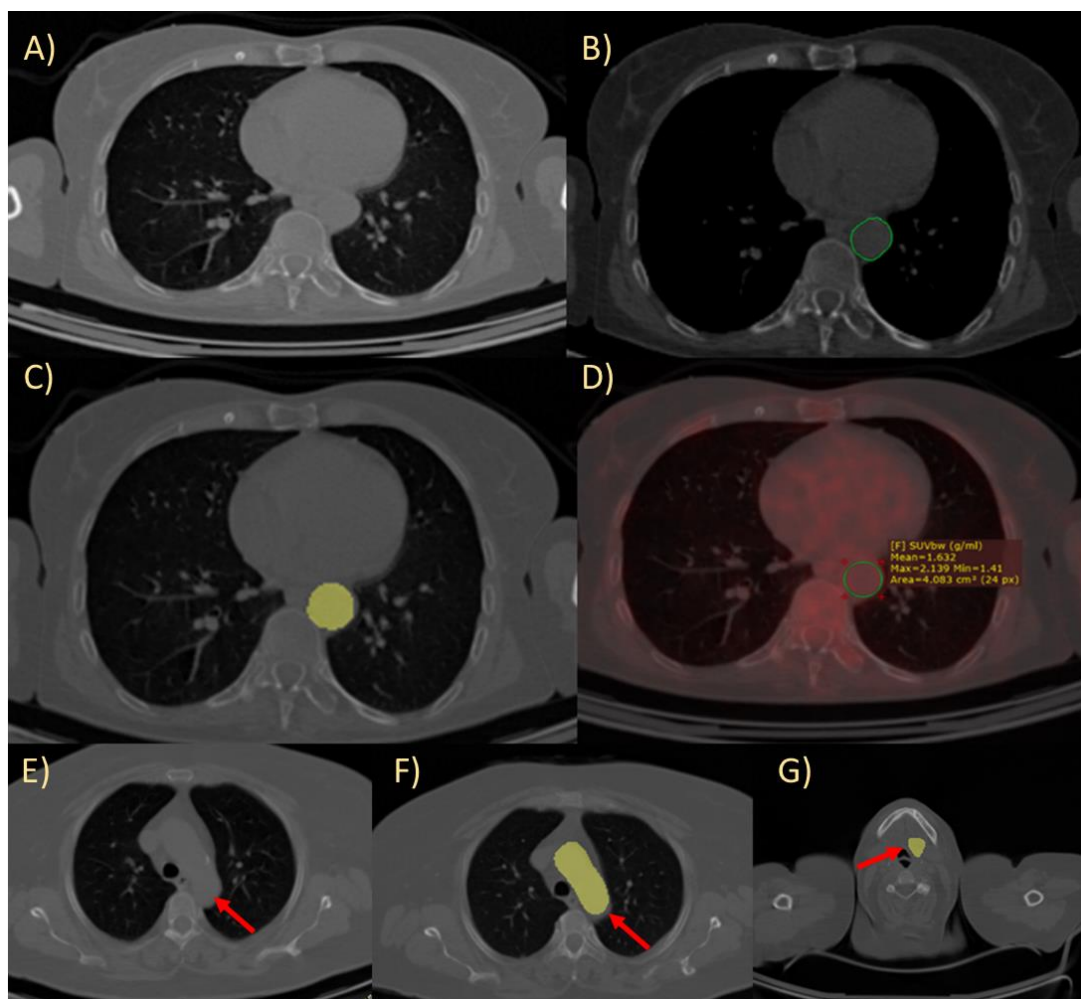


Figure 93 A) CT image and B) Corresponding ground truth segmentation) Automatic segmentation result; D) SUV ground truth calculation; E) Region of interest (red arrow); F) Automatic segmentation did not achieve correct boundary detection in the aortic arch segment (red arrow); G) Wrong segmentation result in head area.

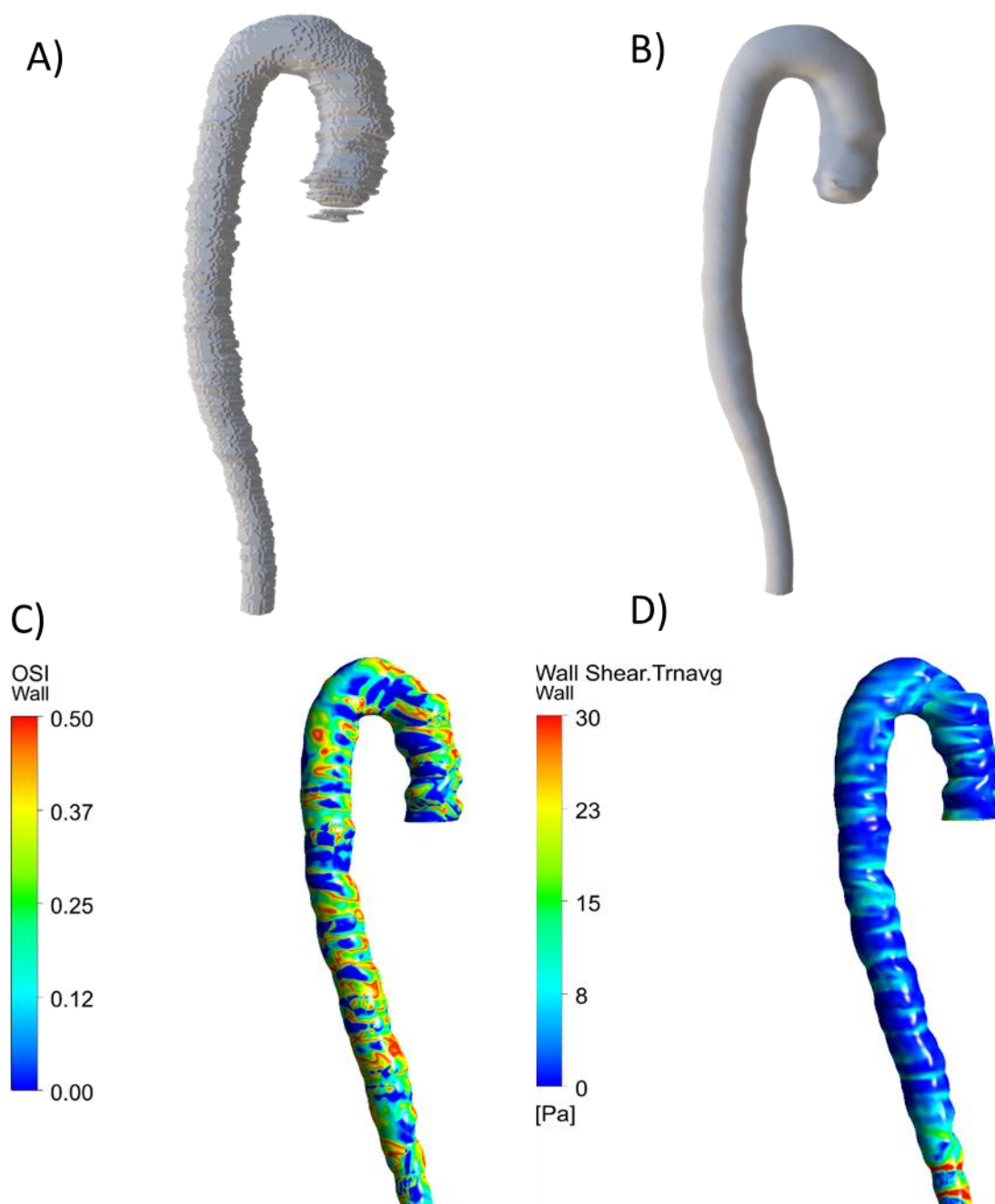


Figure 94 A) Raw semantic segmentation 3D model; B) Smoothed Semantic segmentation Aorta output; C) Oscillatory shear index visualization; D) Wall shear stress visualization

5. Publications and Congresses

1. **G. Kalykakis**, P. Siogkas, C.D. Anagnostopoulos, and T. Exarchos, (2024) Automated System for Low dosed CT images and SUV quantification in aorta, MDPI Biomed Informatics (Submitted)
2. **G. Kalykakis** et al (EVINCI consortium) (2024). Machine learning-based analysis of coronary CT angiography radiomic features improves the identification of functionally significant lesions. Journal Of Nuclear Cardiology (Submitted).
3. **G. Kalykakis**, P. Siogkas, C.D. Anagnostopoulos, and T. Exarchos, (2024). Building a GUI Tool for Automated Aortic Segmentation in Low-Dose Chest CT Images with PET-Based Standard Uptake Value, in the 6th “Genomics, Neuroscience, Therapeutics and Data Innovation Summit” (GENEDIS 2024).
4. **G. Kalykakis**, et al (EVINCI consortium) (2022). Radiomics-based analysis by machine learning techniques improves characterization of functionally significant coronary lesions. European Heart Journal. 43. 10.1093/eurheartj/ehac544.216.
5. **G. Kalykakis**, et al (EVINCI consortium) (2021). Relationship of Endothelial Shear Stress with Plaque Features with Coronary CT Angiography and Vasodilating Capability with PET. Radiology. 300. 204181. 10.1148/radiol.2021204381.
6. **G. Kalykakis**, et al (EVINCI consortium) (2021). Prediction of impaired myocardial blood flow (MBF) with the use of machine learning techniques on CCTA based parameters. European Heart Journal - Cardiovascular Imaging. 22. 10.1093/ehjci/jeaa356.433.
7. **G. Kalykakis**, et al (EVINCI consortium) (2021). CCTA-derived functional and morphological features and their comparative performance in predicting impaired coronary vasodilatation by PET-myocardial perfusion imaging. European Heart Journal - Cardiovascular Imaging. 22. 10.1093/ehjci/jeaa356.241.
8. P. Siogkas, **G. Kalykakis**, C.D. Anagnostopoulos, T. Exarchos, (2021). CORONARY ATHEROSCLEROSIS ASSESSMENT: A NEW ANATOMICAL, FUNCTIONAL, MORPHOLOGICAL AND BIO-MECHANICAL APPROACH. Journal of the Serbian Society for Computational Mechanics. 15. 23-31. 10.24874/jsscm.2021.15.02.03.
9. P. Siogkas, **G. Kalykakis**, C.D. Anagnostopoulos, T. Exarchos, (2021). Fluid Dynamics–Derived Parameters in Coronary Vessels. In Genetics, Geriatrics and Neurodegenerative Diseases Research (GENEDIS 2020), Adv Exp Med Biol 2021:1337: 291-297.doi: 10.1007/978-3-030-78771-4_32.

10. P. Siogkas, **G. Kalykakis**, C.D. Anagnostopoulos, T. Exarchos, "The effect of the degree and location of coronary stenosis on the hemodynamic status of a coronary vessel," 2020 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), Montreal, QC, Canada, 2020, pp. 2671-2674, doi: 10.1109/EMBC44109.2020.9175302.
11. P Kafouris, **G Kalykakis**, et al (EVINCI consortium) Coronary CT angiography derived features for predicting an abnormal pet myocardial perfusion imaging: a machine learning approach, European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.3455.
12. C.D. Anagnostopoulos, **G. Kalykakis**, et al (EVINCI consortium) Relationship between endothelial shear stress, plaque burden and stenosis severity and their comparative performance in predicting impaired coronary vasodilation by pet myocardial perfusion imaging, European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.0184.
13. C.D. Anagnostopoulos, **G. Kalykakis**, et al (EVINCI consortium) (2019). Assessment of endothelial shear stress and functional significance of coronary lesions by computed tomography coronary angiography (CCTA) and computational fluid dynamics: a comparison with PET. European Heart Journal. 40. 10.1093/eurheartj/ehz748.1019.

6. Conclusions

This research highlights the effectiveness of integrating advanced techniques in cardiovascular imaging, specifically focusing on **endothelial shear stress (ESS)** analysis, **radiomics**, and **machine learning techniques**, to enhance the prediction of myocardial perfusion abnormalities and the characterization of coronary plaques. The findings emphasize that **ESS**, derived from computational fluid dynamics models, plays a crucial role in understanding the mechanical forces acting on the vessel walls, contributing to plaque formation and progression. The combination of **ESS** with plaque morphological features provides better predictive insights into the presence of myocardial ischemia than traditional imaging metrics alone. In addition to that, **ESS** has been proven to have a moderate relationship with plaque volume characteristics. This finding also proves the difficulty to model atherosclerosis as a single factor problem.

Moreover, the study identified the potential of **radiomics**, to improve the prediction of **myocardial blood flow (MBF)** in combination **myocardial flow reserve (MFR)**. By analyzing the texture and shape of coronary plaques, radiomic signatures were able to differentiate between stable and vulnerable plaques, thus offering additional layers of diagnostic information that can guide clinical decision-making. In addition to that, specific textural plaque derived features have proven as predictors of ischemia in multiple machines learning derived features pipelines. That finding may be crucial in future research on the field of cardiology because we potentially can correlate imaging characteristics with omics data such as histopathological data, genes etc, in order to create a “complete” profile of the cardiovascular disease.

In the investigation of **Large Vessel Vasculitis (LVV)** and lymphoma, the application of **18F-FDG PET/CT** imaging, coupled with radiomics, provided significant insights into the metabolic and structural changes in these conditions. This approach enabled the differentiation of active and inactive disease phases, aiding in more accurate diagnosis and treatment monitoring for patients with aortic and systemic inflammatory conditions.

Additionally, the development and validation of **automated segmentation techniques** for imaging the aorta and coronary arteries proved to be valuable for enhancing diagnostic workflows. These automated tools, integrated with radiomic

analysis, reduced the time and effort required for manual segmentation, thereby improving efficiency and consistency in analyzing large datasets, particularly in clinical settings where quick and accurate assessments are critical. The difficulty of having integrated platforms in order to do a full-scale study, is prominent in the research field. The feasibility of that task, proves that we can start integrating module after module to simple GUI platforms in order to provide to the clinical as well as the research doctors with tools that are essential for their everyday work.

Future work should focus on further refining the **machine learning models** and improving the integration of **ESS** and **radiomic features** to broaden the clinical applicability of these approaches.

Specifically for ESS and radiomics analysis, we believe that an expanded elaborated study utilizing real histological data, such as genetics and tissue analytics, with computational methods like ESS calculation and radiomics analysis in the pathological segments will be an important step for understanding and connecting the computational word with the biology aspect of the disease.

Expanding the study to larger and more diverse patient populations will help validate the findings and pave the way for these advanced techniques to become routine tools in cardiovascular disease diagnosis and management. Furthermore, continued advancements in **automated image analysis** will be essential to fully leverage the potential of radiomics and machine learning in personalized patient care.

7. Abbreviations - Acronyms

LIST OF ABBREVIATIONS	
3D	3-Dimensional
3D-QCA	3-Dimensional quantitative coronary analysis
CAD	Coronary Artery Disease
CCA	Common Carotid Artery
CI	Confidence Interval
CT	Computed Tomography
CCTA	computed coronary tomography angiography
DEFACTO	Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography
DISCOVER-FLOW	Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve
ESS	Endothelial shear stress
EVINCI	Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease
FFR	Fractional Flow Reserve
GMM	Gaussian Mixture Model
ICA	Invasive Coronary Angiography
IFR	Instantaneous wave-free ratio
IVUS	intravascular ultrasound
LCX	left circumflex coronary artery
LDL	Low density lipoprotein
MRI	magnetic resonance imaging
OCT	optical coherence tomography
PDA	Posterior Descending Aorta
RCA	right coronary artery
ROI	Region of Interest

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