UNIVERSITY OF LATVIA

DIPLOMA THESIS

RIGA 2023

UNIVERSITY OF LATVIA
FACULTY OF MEDICINE
MEDICAL DOCTOR DEGREE PROGRAM
DEPARTMENT OF CARDIOLOGY

12-LEAD ECG IN LEFT VENTRICULAR HYPERTROPHY PATIENTS BEFORE AND AFTER ALCOHOL SEPTAL ABLATION

DIPLOMA THESIS

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RIGA 2023

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ABSTRACT

Background – Alcohol septal ablation (ASA) is a procedure performed in some patients with left ventricular hypertrophy (LVH) in order to improve their symptoms. A 12-lead ECG, which is a common diagnostic tool used in relation to cardiovascular diseases, allows for the evaluation of the effect of ASA on cardiac function.

Aim – To analyze the ECGs of LVH patients who underwent ASA, and to determine if the post-procedural ECG changes were significant.

Methods and Results – The ECGs of 48 patients who underwent ASA, in the cardiology department of Paul Stradinš Clinical University Hospital between 2015 – 2022, were analyzed. The pre- and post-ASA ECGs were compared with each other and differences in various parameters were statistically analyzed using the IBM SPSS software. Both the PR interval and QRS complex duration were significantly increased after ASA ($p = 0.011$ and $p < 0.001$ respectively), resulting in there being seven new cases of an AV block (1st degree) and 23 new cases of a RBBB (four incomplete and 19 complete). There was also a statistically significant decrease in the mean R wave amplitude in lead V6 ($p = 0.001$) and the mean S wave amplitude in lead V1 ($p = 0.003$) after ASA to an extent that they did not fulfill the Sokolow – Lyon criteria. The QRS complex α angle and QT interval also increased after ASA, but the mean values in both parameters were still within the normal range.

Conclusions – ASA produced noticeable changes in the ECGs of LVH patients, which were the following: a significant decrease in the R wave amplitude (lead V6) and S wave amplitude (lead V1), and a significant increase in the PR interval and QRS complex duration. The most common conduction disturbance seen after ASA was RBBB. Males were more likely to display a larger decrease in R and S wave amplitudes after ASA. Females and individuals over the age of 60 were more likely to develop an AV block (1st degree).

Keywords – left ventricular hypertrophy, hypertrophic cardiomyopathy, alcohol septal ablation, electrocardiogram.

KOPSAVILKUMS

Nosaukums – 12 Novadījumu EKG kreisā kambara hipertrofijas pacientiem pirms un pēc alkohola septālas ablācijas

Priekšvēsture – Alkohola septala ablācija (ASA) ir procedūra, ko dažiem pacientiem ar kreisa kambara hipertrofiju (KKH) veic, lai uzlabotu simptomus. 12 novadījumu EKG, kas ir izplatīts sirds un asinsvadu slimību diagnostikas instruments, ļauj novērtēt ASA uz sirds darbību.

Mērķis – Analizēt EKG kreisā kambara hipertrofijas pacientiem, kuriem tika veikt ASA, un noteikt, vai pēcprocedūras EKG izmaiņas bija nozīmīgas.

Metodes un Rezultāti – Tika analizētas EKG 48 pacientiem, kuriem Paula Stradiņa Klīniskās universitātes slimnīcas kardioloģijas nodaļā no 2015. līdz 2022. gadam veikta ASA. EKG pirms un pēc ASA tika salīdzinātas savā starpā, un dažādu parametru atšķirības tika statistiski analizētas, izmantojot IBM SPSS programmatūru. Gan PR intervāls, gan QRS kompleksa ilgums tika ievērojami palielināts pēc ASA (attiecīgi $p = 0.011$ un $p < 0.001$), kā rezultātā tika konstatēti septiņi jauni AV blokādes gadījumu (1. pakāpe) un 23 jauni RBBB gadījumu (četri nepilnīgi un 19 pabeigts). Pēc ASA bija arī statistiski nozīmīga vidējās R viļņa amplitūdas samazināšanās novadījuma V6 ($p= 0.001$) un vidējās S viļņa amplitūdas samazināšanās novadījuma V1 ($p= 0.001$) tādā mērā, ka tie neatbilda Sokolova – Lionas kritērijiem. QRS kompleksa α leņķis un QT intervāls palielinājās pēc ASA, bet vidējās vērtības abos parametros joprojām bija normas robežās.

Secinājums – ASA radīja ievērojamas izmaiņas KKH pacientu EKG, kas bija šādas: ievērojams R viļņa amplitūdas (novadījumos V6) un S viļņa amplitūdas (novadījumu V1) samazinājums un ievērojams PR intervāla un QRS kompleksa ilguma palielinājums. Visbiežāk novērotie vadīšanas traucējumu pēc ASA bija RBBB. Vīriešiem pēc ASA, visticamāk, bija lielāks R un S viļņu amplitūdas samazinājums. Sievietēm un personām, kas vecākas par 60 gadiem, bija lielāka iespēja attīstīties AV blokādi (1. pakāpe).

Atslēgas vārdi – kreisā kambara hipertrofija, hipertrofiskā kardiomiopātija, alkohola septala ablācija, elektrokardiogramma.

INTRODUCTION

Left ventricular hypertrophy (LVH) is a condition that affects the heart, characterized by an increase in the mass of the left ventricle (Bornstein et al., 2022). This increase in mass is caused by increased wall thickness, expansion of the left ventricular cavity, or both. The term hypertrophy refers to the increase in size of cardiomyocytes, which is the underlying mechanism leading to the increased left ventricular mass. LVH can result from a variety of causes, including hypertension, aortic stenosis, and hypertrophic cardiomyopathy (HCM) (Bornstein et al., 2022). HCM is a genetic disorder that often leads to left ventricular outflow tract obstruction (LVOTO), which manifests with symptoms such as dyspnea, chest pain, and syncope (Maron et al, 2003). Various diagnostic tools are used to evaluate patients with LVH; one of them being electrocardiography (ECG) (Aronow, 2017). Previous studies have shown that ECG can be a useful tool in the diagnosis of LVH (Maron, 2002).

A 12-lead ECG is a non-invasive diagnostic tool used to evaluate the electrical activity of the heart. It is commonly used in the diagnosis and monitoring of patients with cardiovascular diseases (Sattar and Chhabra, 2023). In LVH patients, a 12-lead ECG can provide information about the extent and severity of the hypertrophy (Mirvis and Goldberger, 2022). In addition to this, it can help identify associated arrhythmias or other abnormalities (Sattar and Chhabra, 2023). Although ECG is the most affordable and readily available diagnostic tool for the diagnosis of LVH, it is still less sensitive than other diagnostic modalities used to diagnose LVH, such as echocardiography (ECHO) and cardiac magnetic resonance imaging (MRI) (Sattar and Chhabra, 2023). However, ECG is still a valuable tool and is utilized in majority, if not all, studies (Bornstein et al., 2022).

Alcohol septal ablation (ASA) is a minimally invasive procedure used to treat LVH in select patients. The procedure involves injecting alcohol into the basal interventricular septum (IVS) of the heart, via a branch of the coronary artery, to reduce the thickness of the hypertrophied myocardium. This injected alcohol creates an iatrogenic infarction, thereby resolving the obstruction of the left ventricular outflow tract (LVOT). ASA has been shown to improve symptoms and outcomes in the majority of the patients with LVH (Pelliccia et al., 2019). The use of 12-lead ECG in HCM patients before and after ASA has been suggested as a potential tool to evaluate the effect of the procedure on LVH and electrical remodeling of the heart (Gersh et al., 2011). However, the impact of the procedure on 12-lead ECG findings is not deeply understood, as there are only a handful of publications covering this.

The aim of this diploma work is to investigate whether or not there will be any significant ECG changes in LVH patients who have undergone alcohol septal ablation. The goals of this diploma work are to review the ECG findings in left ventricular hypertrophy patients, and to assess if the possible post-procedural ECG changes are correlated to the age or gender of the participants. By examining the changes in different ECG parameters, I hope to gain insights into the effects of ASA on conduction patterns and the electrical activity in the heart. The hypothesis for this diploma work is that the tall R wave seen in lead V6, and the deep S wave seen in lead V1 will decrease in amplitude after ASA. Another hypothesis is that after ASA there will be ECG changes of a conduction disturbance in numerous patients who do not already have these prior to the procedure. This hypothesis is based on the fact that alcohol septal ablation targets the basal IVS. Overall, this diploma work may provide important insights into the use of 12-lead ECG in the monitoring of ASA.

LITERATURE REVIEW

I.1. Left ventricular hypertrophy

I.1.1. Overview of left ventricular hypertrophy

Left ventricular hypertrophy is defined as a condition in which there is an increase in the mass of the left ventricle (LV) due to an increase in wall thickness, the enlargement of the left ventricular cavity, or both (Bornstein et al., 2022). Generally, the thickening of the left ventricular wall occurs as a result of pressure overload, and on the other hand, the dilation of the LV occurs as a result of volume overload (Bornstein et al., 2022). In order to differentiate the patterns of hypertrophy, LVH can be subclassified according to the relative wall thickness (RWT). RWT is the ratio between the thickness of the left ventricular wall and the left ventricular chamber diameter. When the RWT is increased, the hypertrophy can be classified as "concentric", and when the RWT is decreased, the hypertrophy can be classified as "eccentric". Traditionally, this 2-tiered classification system has been used, however, a more detailed 4-tiered classification system was introduced in the Dallas Heart Study, which will be discussed later (Khouri et al., 2010).

The term hypertrophy is used to describe this condition because the increase in the mass of the LV is in fact due to hypertrophy of the cardiomyocytes instead of hyperplasia. This can be concretely said because cardiomyocytes become terminally differentiated already shortly after birth (Lorell and Carabello, 2000). Left ventricular hypertrophy is considered a marker for patients with hypertension and plays a role in the development of other cardiovascular diseases and events, such as strokes, myocardial infarction (MI), heart failure, and peripheral artery disease (Aronow, 2017).

I.1.2. History of left ventricular hypertrophy

The earliest English literature, available today, mentioning left ventricular hypertrophy can be traced back to the 1800s. Dr. Gibson's book titled "Diseases of the Heart and Aorta" was published in 1898, and it went over the historical timeline of the establishing of LVH, while simultaneously describing the key findings of previous authors. This book contained the findings of several international authors, in English, since the original writings were not always published in English. Although this book was about numerous diseases of the heart and aorta,

there was a specific section devoted to cardiac hypertrophy. General facts about cardiac hypertrophy, and LVH in particular, were established, followed by a detailed breakdown of the specifics (Gibson, 1898).

Massa was the first author to notice and write about hearts of large size, however, Albertini was the first author to observe and write about the increased thickness of ventricles. These observations were already made a few centuries prior to the publishing of Dr. Gibson's book. The relationship between an increase in heart size and an underlying pathology was first established by Mayow, who described it as a result of mitral valve abnormality. Subsequently, Vieussens described a case of left ventricular enlargement from aortic disease in the 1700s. Morgagni studied cases of cardiac hypertrophy, without dilation, and from his time almost every researcher of cardiac disease has investigated cardiac hypertrophy. The classification system for LVH was established by Bouillaud in the early 1800s. The microscopic examination to demonstrate the increase of muscular tissue in hypertrophy was conducted by Bertin, who also distinguished between the types of LVH. Despite all this research, cardiac hypertrophy was not a feasible diagnosis, until the appearance of Laennee's work, which was the first work to correctly describe the changes in heart sounds in cases of cardiac hypertrophy (Gibson, 1898).

Dr. Gibson's book established several key facts about left ventricular hypertrophy, which were known at that time. Left ventricular hypertrophy was understood to be a process of adaptation under physiological circumstances, and on the other hand, a process of compensation under pathological circumstances. It was established that when there is stress for any period of time, it will lead to the process of cardiac hypertrophy. Furthermore, it was stated that any obstacle to systemic circulation produces LVH. The writings of Senac introduced the idea that excessive physical exertion can cause LVH. This was later validated by several writers, such as Allbutt, Myers, Fothergill, Seitz, Francel, and Laache. However, generally, it was considered that LVH is related to extended periods of life. This was connected with the fact that in elderly people there is loss of arterial elasticity and contractility, which in turn leads to a progressive increase in myocardial size (Gibson, 1898).

By the end of the 1800s, LVH was already associated with several underlying causes, such as chronic renal cirrhosis, and aortic valve abnormalities. It was very clear at the point of the publishing of this book, that in the case of pressure overload (e.g. aortic stenosis) there is thickening of the LV, and in the case of volume overload (e.g. aortic regurgitation) there is dilation of the LV, possibly accompanied by thickening. The exact mechanism for the

hypertrophy of cardiomyocytes was not yet established by Gibson or any previous studies. However, it was stated that hypertrophy of cardiomyocytes can only take place when the blood supply of healthy blood to the heart is sufficient. The thickness of ventricular walls was established to be directly proportional to the amount of work they must perform. This fact was indeed established by studies conducted by Gillespie and Gibson, in which, the thickness of both ventricles was shown to be similar during fetal life, since that is when blood pressure on both sides of the heart is essentially equal (Gibson, 1898).

In addition to the previously mentioned facts, specific diagnostic findings related to LVH were also established, such as accentuated heart sounds, presence of murmurs in specific underlying pathologies, presence of cardiac thrills, downward and lateral displacement of the apex beat, and typical cardiogram changes. Unfortunately, ECG changes of LVH were not described in this book, since majority of the foundational studies were already published before the introduction of the first electrocardiogram (Gibson, 1898).

I.1.3. Epidemiology of left ventricular hypertrophy

The Framingham Heart Study demonstrated that LVH can be seen in approximately 15% of the general population (Levy, 1988). The prevalence of LVH is higher in the following groups: the elderly, the obese, black people, and people with hypertension (Bornstein et al., 2022). A factor that does not influence the prevalence of LVH is gender. Previous studies have demonstrated that the difference between males and females is not significant. A review, based on the echocardiographic data of 37 700 individuals, demonstrated that LVH was present in approximately 40% of males and in approximately 42% of females (Cuspidi et al., 2012). As mentioned in the previous section, LVH has been historically considered as a condition of the elderly. The Framingham study indicated that the prevalence of LVH increases clearly with age. The prevalence of LVH in participants aged 49 to 54 was less than 2%, whereas in participants aged 75 to 82 it was 10% (Kannel et al., 1987). The presence of obesity has been shown to increase the risk of developing LVH two-fold (Cuspidi et al., 2012).

There have been several studies that demonstrated that LVH is more prevalent in black people than people of other ethnicities. A prospective study, comparing the incidence of complications of hypertension between black people and white people, demonstrated that echocardiographic LVH was more prevalent in black people. The study contained 84 hypertensive black participants and 326 hypertensive white participants, all older than the age of 62 years, and it

was seen that LVH was present in 71% of the black participants and 56% of the white participants (Aronow et al., 1991). The Dallas Heart Study demonstrated that the prevalence of LVH was two to three times higher in black people than in white people. This ethnic variation persisted despite body composition, blood pressure, gender, age, and socioeconomic status (Drazner et al., 2005).

Hypertension has been established to be a key predecessor of LVH in the general population (Kannel et al., 1987). Systolic blood pressure has a larger role in the development of LVH, since hypertrophy of the left ventricle is a direct response to the stress of elevated blood pressure. Out of all the participants in the Framingham Heart Study with a systolic blood pressure above 180 mmHg, half developed LVH within 12 years (Kannel et al., 1987). The incidence of LVH was demonstrated to increase approximately 10-fold in individuals with hypertension when compared to normotensive individuals (Levy, 1988). A review, based on the echocardiographic data of 37 700 individuals, demonstrated a 19-48% prevalence of LVH in individuals with untreated hypertension and a 58-77% prevalence of LVH in high-risk hypertensive individuals (Cuspidi et al., 2012). The Systolic Blood Pressure Intervention Trial (SPRINT) included 8 164 participants with hypertension, and 7.4% of the participants already had LVH at the time of selection (Soliman et al., 2017). An Italian study investigating sudden cardiac death in hypertensive patients was published in 2019, and showed that at entry point, 13.9% of the 3 242 participants had LVH (Verdecchia et al., 2019). Based on the findings of the previously mentioned studies, it can be said that approximately 20% of individuals with untreated hypertension have LVH.

Left ventricular hypertrophy has been demonstrated to increase the risk of developing other diseases. Individuals with LVH are five times more likely to develop congestive heart failure and also other forms of cardiovascular disease, such as a MI, stroke, and peripheral artery disease. When LVH develops in an individual with hypertension, the risk for congestive heart failure increases 15-fold (Levy, 1988). The Atherosclerosis Risk in Communities Study stated that individuals with LVH are at risk of developing multiple cardiovascular diseases simultaneously. This finding was also elaborated by establishing that in middle-aged individuals, the first cardiovascular disease that developed in men was coronary heart disease, while in women it was congestive heart failure. After a 15-year follow up in the Atherosclerosis Risk in Communities Study, approximately 29% of the patients with LVH had developed a cardiovascular disease (Desai et al., 2012).

The relation between LVH and mortality is extremely significant. This was displayed in the Framingham Heart Study, where LVH preceded 30% of overall deaths and 45% of cardiovascular deaths (Kannel et al., 1987). The five year mortality rate for individuals with LVH was established to be approximately 28% on average, and 43% in the elderly (Levy, 1988). Furthermore, a 30-year follow-up, done on the Framingham Heart Study participants, showed that risk ratios for all-cause mortality increased to three to seven-fold in participants with established LVH (Kannel et al., 1987).

I.1.4. Etiology of left ventricular hypertrophy

There are numerous conditions that can lead to the occurrence of LVH (Bornstein et al., 2022). Despite there being numerous etiologies, the clinical presentation and morphologic features are similar (Sayin and Oto, 2022). As mentioned previously, it has been historically known that LVH can be a process of adaptation under physiological circumstances. In addition to this, it was historically established that when there is stress for any period of time, it will lead to cardiac hypertrophy (Gibson, 1898). The clinical condition athlete's heart leads to physiological LVH, which is generally considered a benign condition. Intensive training that athletes undergo in their lifetime, leads to an increased muscle mass and wall thickness of the LV. Despite these changes, both the systolic and diastolic function remain normal (Bornstein et al., 2022).

When speaking about the pathological conditions leading to LVH, hypertension and aortic valve stenosis are the frontrunners (Bornstein et al., 2022). These conditions have been linked to LVH already for a few centuries. As previously stated, the relation between LVH and aortic disease was already established in the 1700s by Vieussens (Gibson, 1898). In both of these conditions, there is an elevated afterload, which the heart has to contract against (Bornstein et al., 2022). In other words, there is pressure overload, which then leads to concentric hypertrophy (Khouri et al., 2010). Other causes of LVH that exhibit the same effect include renal artery stenosis, aortic coarctation, and hypertrophic cardiomyopathy without or with outflow tract obstruction (HOCM). On the other hand, eccentric hypertrophy is caused by conditions that lead to diastolic overload. These most commonly include aortic regurgitation and mitral regurgitation. Other less common causes that cause eccentric hypertrophy are dilated cardiomyopathy and ventricular septal defect. Other rarer causes of LVH include infiltrative cardiac processes, such as Amyloidosis, Danon disease, and Fabry disease (Bornstein et al., 2022).

In addition to the solidified etiologies, there are also numerous risk factors that are worth mentioning. Some of these were stated in the previous section, such as increasing age and obesity (Bornstein et al., 2022). In addition to these, there are several risk factors such as obstructive sleep apnea, chronic kidney disease, diabetes mellitus, tobacco use, and sodium intake (Sayin and Oto, 2022). Studies have also shown a correlation between alcohol intake and left ventricular mass (Phillips, 1993). Some of the above mentioned risk factors have been shown to clearly amplify the risk of developing LVH (Kannel et al., 1987) (Cuspidi et al., 2012).

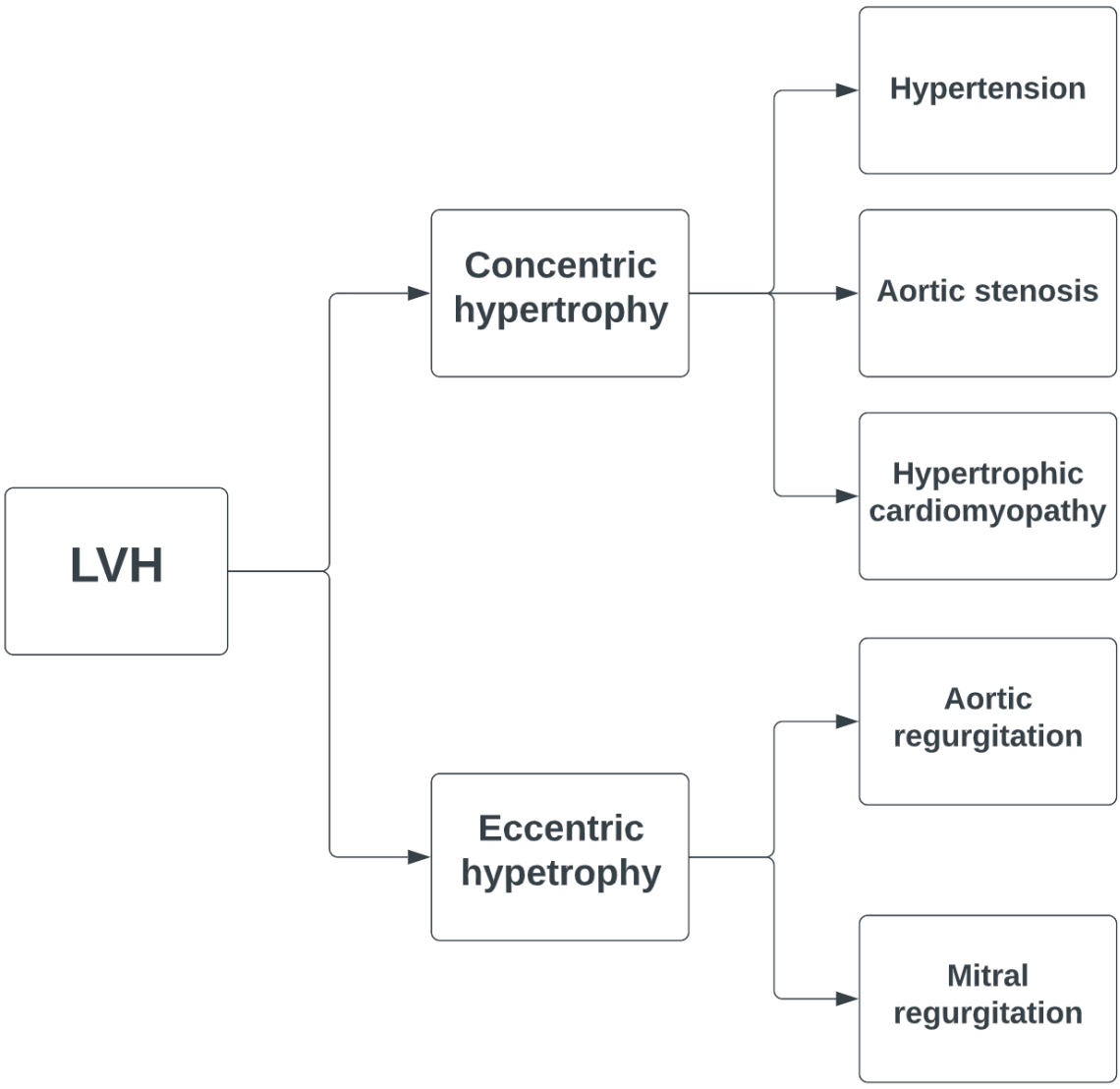


Figure 2.1. Main etiologies of LVH

I.1.5. Pathophysiology of left ventricular hypertrophy

When the heart is faced with hemodynamic stress, there are three main mechanisms, which allow the heart to compensate. The first one is the use of the Frank-Starling mechanism to increase crossbridge formation, but this is limited in its extent. The second mechanism is to recruit neurohormonal mechanisms to increase contractility, however, this is harmful as a chronic adaptation. The last, and the key, compensatory mechanism is the augmentation of muscle mass to endure the increased load. As mentioned earlier, this increase in muscle mass is due to cardiomyocyte hypertrophy, and not hyperplasia, since cardiomyocytes become terminally differentiated shortly after birth (Lorell and Carabello, 2000).

Left ventricular hypertrophy has been established to be an important compensatory process that results from wall stress or any notable hemodynamic pressure or volumetric burden. This sustained increase in ventricular wall stress together with cytokine and neuro-activation leads to development of myocardial hypertrophy (Bornstein et al., 2022). The increased muscle fiber mass or wall thickness initially acts as a compensatory mechanism, which allows for the maintenance of contractile forces and counteracts the increased stress on the LV wall. However, the advantages of this increased wall thickness to compensate for the increased amount of wall stress are counterbalanced by a major increase in the stiffness of the hypertrophied left ventricular wall associated with a significant increase in the diastolic pressure of the LV, which is eventually transmitted back into the left atrium and from there to the pulmonary vessels. Although LVH is initially a compensatory process, eventually the increase in the muscle mass of the left ventricular myocardium is considered an abnormal process, which is induced by an elevated workload on the myocardium over a long period of time (Bornstein et al., 2022).

The most common reason for the development of LVH is an increased afterload. As mentioned previously, the main culprits for an increased afterload are hypertension and aortic stenosis. The other main reason for the development of LVH is an increased left ventricular filling, which induces diastolic overload. The causes of this are mainly aortic or mitral regurgitation, but in some cases may be caused by dilated cardiomyopathy. An increased afterload causes concentric hypertrophy, while an increased ventricular filling causes eccentric hypertrophy (Bornstein et al., 2022). Concentric hypertrophy is characterized by the parallel addition of sarcomeres, which causes an increase in cardiomyocyte width, eventually leading to an increased wall thickness. On the other hand, eccentric hypertrophy is characterized by cardiomyocyte

lengthening by sarcomere replication series and an increase in ventricular volume (Lorell and Carabello, 2000).

The central part of hypertrophy is the increase in the amount of cardiomyocyte sarcomeres. This is initially triggered by the increased mechanical stress, which is transduced into a biochemical event that alters gene transcription in the cardiomyocyte nucleus. Tyrosine-phosphorylated kinases and serine-threonine kinases play a key role in the signaling of cardiomyocyte hypertrophy, and they are found in the extracellular matrix. Studies have shown that acute biomechanical signal transduction includes the recruitment of G-protein-coupled neurohormones, such as angiotensin II and endothelin 1. The activation of these particular neurohormones amplifies the growth signaling process. In addition to this, angiotensin II has also been shown to have a key role in the induction of cardiomyocyte hypertrophy, since it is able to directly bring about the molecular events of early cardiac hypertrophy (Lorell and Carabello, 2000).

In order for cardiomyocyte hypertrophy to actually take place, coordinated increases in surrounding connective tissue architecture, and neurovascular network are required. Collagen synthesis occurs as an adaptive process when there is mechanical stress (Lorell and Carabello, 2000). Studies have shown that angiotensin II plays a role in this by exhibiting a profibrotic effect (Jia et al., 2018). When there is eccentric hypertrophy, the myocyte lengthening is accompanied by changes in collagen cross linking and the collagen weave itself. The collagen weave undergoes dissolution, which leads to an increased elasticity and an increased chamber size. This dissolution is triggered by the activation of matrix metalloproteinases. This activation of matrix metalloproteinases can be seen in concentric hypertrophy; however, their role is less well understood in this type of hypertrophy (Lorell and Carabello, 2000). The actual degree of hypertrophy is, to an extent, determined by the following factors: presence of coronary artery disease or valvular disease, and inflammatory cytokines calcium/calmodulin-dependent protein kinase II signal transducer and activator of transcription-3 (Maillet et al., 2013).

Genetics have also been shown to play a role in the development of LVH. Both concentric and eccentric hypertrophic are normally accompanied by gene reprogramming changes. One of the main focuses the changes are immature fetal cardiac genes, which are re-expressed. The fetal cardiac genes include genes that alter energy metabolism, genes that alter motor unit composition and regulation, and genes that encode components of the hormonal pathway. In addition to the fetal cardiac genes, genes that modify intracellular ion homeostasis are also

affected, causing a downregulation sarcoplasmic reticulum calcium ATPase, and an upregulation of the sodium-calcium exchanger. Lastly, sympathetic, and parasympathetic receptors are affected by altered gene expression, causing them to be downregulated (Lorell and Carabello, 2000).

Studies have also shown that mutated genes that encode sarcomere-associated proteins have a direct cause-effect relationship with LVH. These gene mutations are seen in the case of HCM, which is one of the causes of LVH. The most common genes involved are MYH7 and MYBPC3, which encode beta-myosin heavy chain and myosin binding protein C, respectively. In addition to this, infiltrative cardiac processes that cause LVH, such as Amyloidosis, Fabry disease, and Danon disease, all have a genetic component to them. Evidence has also shown that some patients with mild hypertension develop LVH while others do not. The above mentioned findings confirm that there definitely is a genetic predisposition to LVH (Marian and Braunwald, 2017).

At a cellular level, in addition to the actual cardiomyocyte hypertrophy, there is up-regulation of protein synthesis, and intensified organization of the sarcomere (Samak et al., 2016). Already within hours after the onset of pressure overload, the synthesis of myosin heavy chains increases by approximately 35%. On the other hand, in the case of volume overload, there is a decrease in the degradation rate of myosin heavy chains (Lorell and Carabello, 2000). The prolonged stress wall stress gives rise to a hypertrophic response downstream of mechanosensitive molecular structures. The Z-disc of the sarcomere, and its proteins, are the ones that drive the stress-induced signal transduction. Calsarcins are Z-disc-specific proteins that are mechanosensitive and play a key role in cardiomyocyte hypertrophy. They connect the cardiac sarcomeres to signaling molecules, which have a direct impact on gene expression. These particular signaling molecules bind to the Z-disc myofilament anchor proteins (alpha-actinin and telethonin) and then attach them to calcineurin. Calcineurin, which is a calcium-dependent phosphatase, then directly causes cardiomyocyte hypertrophy by transcriptional pathways downstream (Samak et al., 2016). Calcineurin is considered the “master switch” in cardiomyocyte hypertrophy (Lorell and Carabello, 2000).

I.1.6. Classification of left ventricular hypertrophy

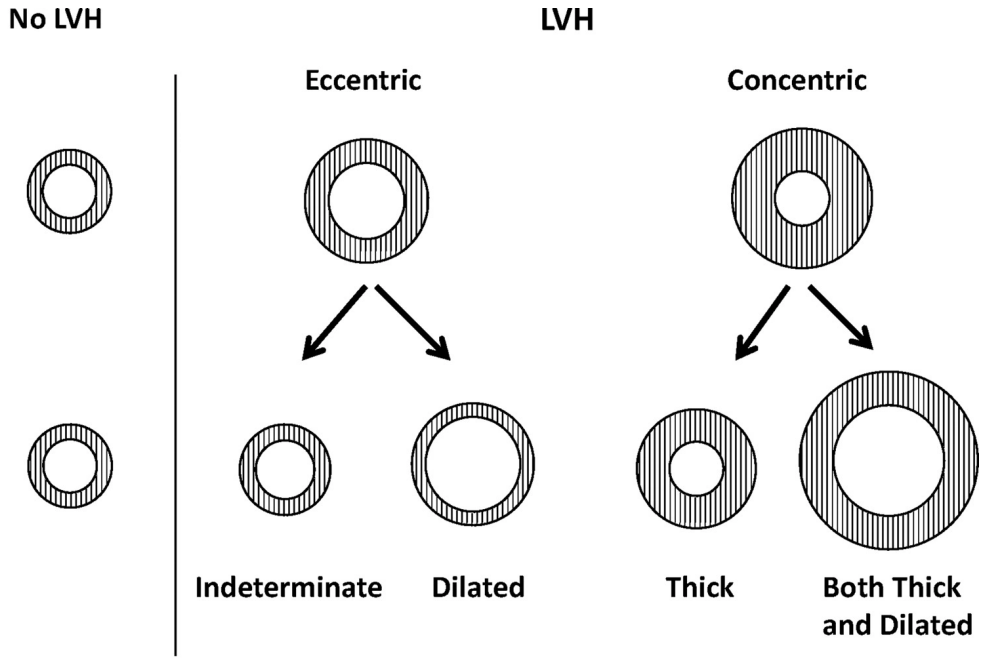
Left ventricular hypertrophy can be classified according to the RWT (posterior wall thickness x2 / LV internal diameter at end-diastole), and the LVM index (left ventricular mass normalized

for body surface area or height). Based on the above mentioned factors, LVH is generally categorized into two types, which are concentric and eccentric. Concentric hypertrophy is when there is an increased RWT (above 0.42) and an increased LVM index. On the other hand, eccentric hypertrophy is when a decreased RWT (below or equal to 0.42) and an increased LVM index. The underlying causes of both types of hypertrophies can be seen in the previous sections (Bornstein et al., 2022).

Conventionally, the above mentioned 2-tiered classification system has been used. However, a more detailed 4-tiered classification system was introduced in the Dallas Heart Study. The additional factors used in this classification, in addition to the previously mentioned one, are LV concentricity and LV end-diastolic volume (LVEDV). The reason for developing this new classification was the presence of two potential limitations with the conventional classification. The first limitation was that the conventional classification system does not isolate the independent changes in wall thickening and ventricular dilation. The second limitation was that RWT relies on M-mode and 2D ECHO to measure the LV diastolic dimension, and these modalities are not so effective in measuring the LVEDV. For this reason, cardiac MRI was used in the development of this new classification (Khouri et al., 2010).

The new 4-tiered classification includes the following forms: increased concentricity without increased LVEDV (thick hypertrophy), increased LVEDV without increased concentricity (dilated hypertrophy), increased concentricity with increased LVEDV (thick and dilated hypertrophy), and neither increased concentricity nor LVEDV (indeterminate hypertrophy). Thick hypertrophy, and thick and dilated hypertrophy are subgroups of concentric hypertrophy. On the other hand, dilated hypertrophy, and indeterminate hypertrophy are subgroups of eccentric hypertrophy. The schematics of these forms can be seen in the figure below (Khouri et al., 2010).

The potential benefit of this refined classification was shown by finding major differences in biomarkers reflecting pathological cardiac stress. More than half of the participants who had an increased LV mass, did not have increased LV concentricity of LV dilation. In addition to this, these participants did not have elevated biomarkers of cardiac stress either. This raised the question whether or not it is considered pathological LVH if only the left ventricular mass (LVM) is increased. Despite these findings, it was stated that long-term data is necessary to determine whether they actually carry some prognostic information. Therefore, currently, we mainly see the conventional 2-tier classification system being used (Khouri et al., 2010).



Increased LV mass/height$^{2.7}$	—	+	+	+	+
Increased concentricity$^{0.67}$	NA	—	—	+	+
Increased LV EDV/BSA	NA	—	+	—	+

Figure 2.2. The 2-tiered and 4-tiered LVH classification system (Khouri et al., 2010)

I.1.7. Diagnosis of left ventricular hypertrophy

The diagnosis of LVH is mainly based on ECHO and ECG findings. However, a thorough history and physical examination may bring forth some signs and symptoms of specific underlying causes. Early literature mentioned heart sounds being accentuated in the presence of ventricular hypertrophy. In addition to this, the presence of a systolic murmur in the case of aortic stenosis, which is a common cause of LVH, was also established (Gibson, 1898).

ECG is the cheapest and most available diagnostic method for LVH. Although the specificity of ECG is high, the sensitivity is considered to be low. The reason for ECG being insensitive is the fact that it relies on the measurement of the heart's electrical activity to estimate the mass of the LV. This can be problematic, since the measurement can be affected elements that are between the ECG electrodes and the myocardium, such as adipose tissue, fluid, and air. LVH

tends to be underdiagnosed by ECG in cases of obesity, chronic obstructive pulmonary disease (COPD), pleural effusions, and pericardial effusions. Although the clinical usefulness of ECG is rather limited, but since it is cheap and readily available, it does play a diagnostic role. Over the years, there have been several criteria for LVH, which have been proposed. The most commonly used established criteria are the Sokolow-Lyon criteria, the Cornell voltage criteria, and the Romhilt-Estes point score system (Bornstein et al., 2022). These will be discussed later in the ECG section of the literature review.

The diagnostic method of choice in establishing the diagnosis of LVH is echocardiography. When compared to ECG, the sensitivity is remarkably higher. In addition to higher sensitivity, ECHO can be used to diagnose other cardiac abnormalities as well, such as valvular diseases, and left ventricular dysfunction. ECHO is essentially an ultrasound of the heart, which allows for the measurement of the posterior wall and IVS thickness, and the LVEDV. These measurements are then used to determine the LVM index (Bornstein et al., 2022). According to the American Society of Echocardiography and European Association of Cardiovascular Imaging, LVH can be defined as an LVM index is greater than 115 g/m^2 in men and greater than 95 g/m^2 in women (Lang et al., 2015).

Currently, the gold standard for diagnosing LVH is considered to be cardiac magnetic resonance imaging. The precision of cardiac MRI is proven to be superior to that of ECHO, and it is accurately able to estimate the mass of the LV and also diagnose other cardiac abnormalities. However, due to high cost and limited availability, the use of cardiac MRI is significantly limited in clinical practice. Cardiac MRI is mainly seen to be used in clinical research (Bornstein et al., 2022).

I.1.8. Treatment options of left ventricular hypertrophy

The treatment of LVH depends on the underlying cause. A general treatment involves lifestyle changes, such as dietary changes and physical exercise. In addition to this, there are several etiological treatment options, such as medications, surgery, and implantable cardiac devices to prevent sudden cardiac death. The treatment should be aggressive to decrease the risk of possible cardiovascular events. As mentioned, several times before, hypertension and aortic stenosis are the main culprits. Therefore, control of blood pressure is crucial for preventing possible cardiovascular events (Bornstein et al., 2022). Antihypertensive therapy may lead to the regression of LVH, which is eventually accompanied by a decreased risk of cardiovascular

events. The most effective drugs associated with the regression of LVH are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) (Williams et al., 2018). The concept of the regression of hypertrophy was already described in the 1800s by Gibson. It was established that hypertrophy does disappear when the cause is removed. This was demonstrated by using patients with renal changes, in whom LVH regressed with a return to optimal renal conditions (Gibson, 1898). Aortic stenosis, on the other hand, generally requires surgical treatment. Generally, patients with aortic stenosis are asymptomatic for approximately 10 to 20 years. During this asymptomatic period, the increase in outflow obstruction and pressure load on the LV may lead to LVH. The treatment of choice in symptomatic patients is aortic valve replacement (AVR). This procedure is done even in asymptomatic patients, if ECHO shows that the aortic stenosis is rapidly progressing and if there is LV dysfunction (Bornstein et al., 2022).

Hypertrophic cardiomyopathy patients are initially treated with medications, and then with invasive procedures if there is no improvement with medications. The preferred medications in this case are beta-blockers and calcium channel blockers (CCB), which reduce the heart rate and decrease the contractility of the myocardium. The invasive procedures include surgical myomectomy and alcohol septal ablation (Bornstein et al., 2022). ASA will be discussed in detail at the end of the literature review, since this is the procedure that patients of this research underwent.

I.2. Electrocardiogram (ECG)

I.2.1. Overview of ECG

An electrocardiogram (ECG) is the visual representation of the electrical activity of the heart. It was invented in 1902, and some years after the invention, it became a part of the evaluation of patients with cardiac problems (Krikler, 1987). The conventional ECG setup consists of 12 leads, which can be categorized into two groups: limb leads and precordial leads. The limb leads are further divided into standard bipolar limb leads, which are leads I, III, and III, and augmented unipolar leads, which are leads aVL, aVF, and aVR. The precordial leads are leads V1 to V6. The limb leads observe the heart in a vertical plane, whereas the precordial leads observe the heart in a horizontal plane. The key concept of an ECG is that there is an electromagnetic current with both magnitude and direction. When a depolarization current travels towards an electrode, it is registered as a positive deflection. On the contrary, when a

depolarization current travels away from the electrode, it is registered as a negative deflection. The opposite happens when the current in question is a repolarization current. When the current is perpendicular to the electrode, it is registered as a biphasic deflection (Sattar and Chhabra, 2023).

Electrocardiogram machines register electrical activity changes by drawing a trace on a moving electrocardiograph paper. The electrocardiograph paper generally moves at a speed of 25 mm/sec, but some move at a speed of 50 mm/sec. Time is represented on the x-axis, while voltage is represented on the y-axis. The moving electrocardiograph paper consists of large and small squares. When speaking about the 25 mm/sec speed, one small square is 0.04 seconds and one large square is 0.2 seconds. When speaking about voltage, 1 mV is two large squares. The squares of the y-axis can also be depicted as millimeters, with a large box being 5mm and a small box 1 mm (Sattar and Chhabra, 2023). A visual representation of ECG graph paper can be seen in the figure below.

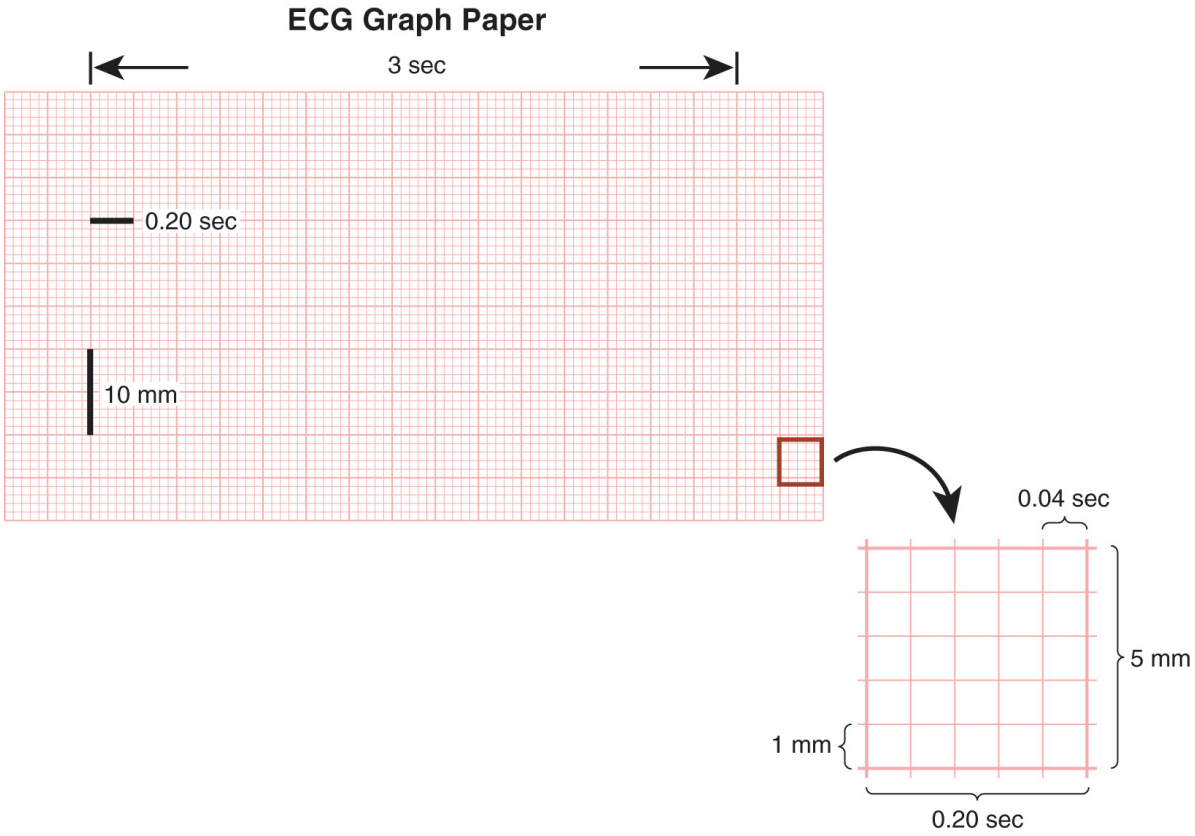


Figure 2.3. 25 mm/sec ECG graph paper (Goldberger et al., 2017)

I.2.2. Basic principles of ECG analysis

The essence of analyzing an ECG is to determine whether or not the ECG waves are pathological. The analysis of an ECG is done systematically, and it goes in the following order: rate, rhythm, cardiac axis, P wave, PR interval, QRS complex, ST segment, T wave, QT interval, and U wave. There are several methods to calculate the rate, however the most common ones are the following: 300 divided by the number of big squares between an RR interval, or 1500 divided by the number of small squares between an RR interval. For a correct interpretation of the rhythm, leads I, II, aVF, and VI are inspected. The goal of the rhythm analysis is to figure out whether the rhythm is a sinus rhythm or not. Sinus rhythm is the normal rhythm in which electrical activity starts from the sinoatrial (SA) node and propagates downwards to the atria and the ventricles. A sinus rhythm demonstrates positive P waves in leads I, II, and aVF, and regular P waves before QRS complexes. The cardiac axis refers to the direction of depolarization in the frontal plane. A normal cardiac axis is between -30 and +90 degrees. The P wave depicts atrial depolarization. The normal duration of a P wave is 0.12 seconds, and the normal amplitude is 2.5mm. The PR interval depicts the time period from the beginning of atrial depolarization to the start of ventricular depolarization. The normal duration of the PR interval is 0.12 to 0.2 seconds (Sattar and Chhabra, 2023).

The part of the ECG that is most related to the topic of this research is the QRS complex. The QRS complex depicts ventricular depolarization. The normal duration of the QRS complex is 0.06 to 0.11 seconds. It consists of three waves: the Q wave, the R wave, and the S wave. The Q wave depicts the depolarization of the interventricular septum, and it is generally seen as a small negative deflection in the lateral leads (I, aVL, V5, and V6). Pathological Q waves, on the other hand, can indicate a previous MI. The R wave is the tallest wave of the whole complex, and it depicts the electrical impulse passing down the ventricles during depolarization. The amplitude of the R wave increases when moving from right to left in the precordial leads, since the left leads are located in front of the LV, which is thicker than the right. The S wave depicts the final depolarization of the Purkinje fibers. It can be seen as a negative deflection after the R wave. It is the largest in lead V1 and progressively becomes smaller when moving towards lead V6 (Sattar and Chhabra, 2023). Changes in the QRS complex related to LVH will be discussed in the next section.

The ST-segment is of high value when analyzing an ECG. It represents the end of ventricular depolarization and the beginning of ventricular depolarization. Essentially it is an isoelectric

line that is on the same level as the PR-interval. ST segment elevations or depressions, that are 1 mm or more in amplitude, are abnormal. These elevations or depressions are measured at the J point, which is the point between the QRS complex and the ST-segment. ST-segment elevations are highly specific for acute myocardial infarctions if they are present in at least two contiguous leads. ST-segment depressions, which are greater than 1 mm, are generally indicative of myocardial ischemia. However, ST-segment elevations and depressions may have other causes too (Sattar and Chhabra, 2023). Relevant to this research, ST-segment depressions may be seen in LVH (Goldberger et al., 2017).

T waves are seen after the ST-segment, and they depict ventricular repolarization. They are normally seen as positive waves, but in the case of underlying pathologies they may be seen as inverted, tall, flat, or biphasic. T wave abnormalities may be seen in the case of LVH, these will be discussed in detail in the next section. The QT interval depicts both the depolarization and the repolarization of the ventricles. Generally, the normal duration of the QT interval is considered to be less than 440 ms. A prolonged QT interval drastically increases the risk for serious ventricular arrhythmias. Lastly, the U wave is a small wave that may be seen after the T wave. It depicts delayed repolarization of the Purkinje fibers or the papillary muscles and is generally related to hypokalemia (Sattar and Chhabra, 2023). All the above mentioned ECG components can be seen in the figure below.

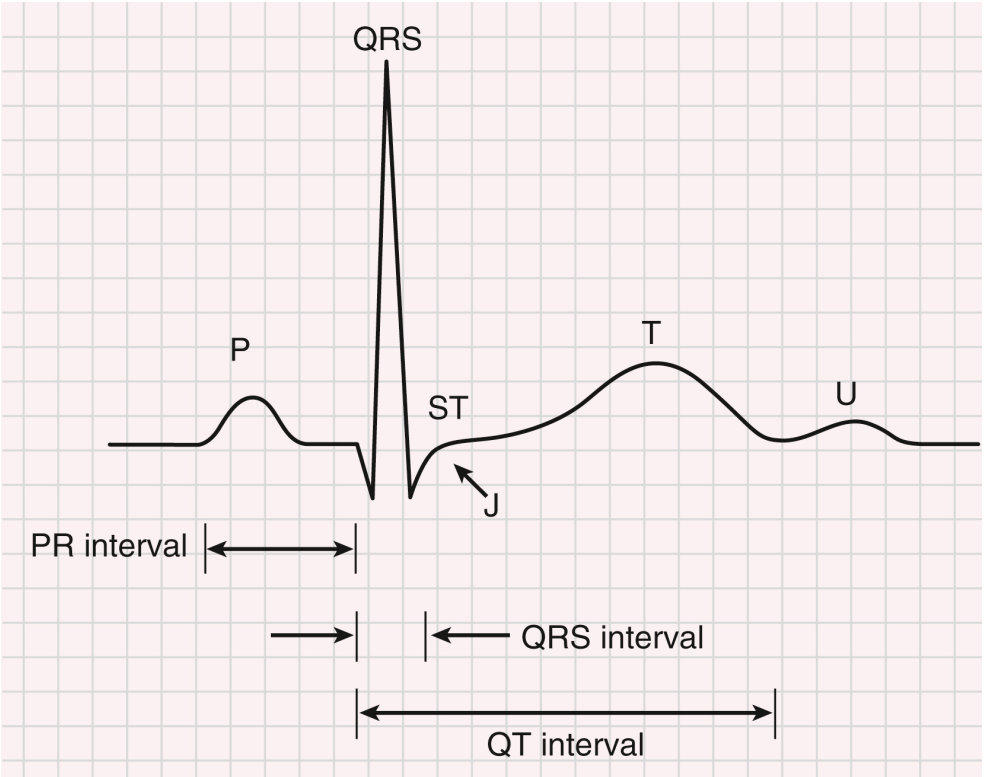


Figure 2.4. ECG components (Mirvis and Goldberger, 2022)

I.2.3. ECG findings of left ventricular hypertrophy

There are five major ECG findings that LVH can produce. These include an increased QRS complex voltage, increased QRS complex duration, left axis deviation, ST segment changes, and left atrial abnormality. However, in most cases, only some of these findings are present. The main ECG finding is the increased voltage of the QRS complex, as two of the three existing ECG criteria are solely based on this finding. The increased QRS complex voltage develops due to increase in the LVM, which increases the magnitude of the voltage generated by the myocardial fibers. This manifests as an increased amplitude of R waves in the left chest leads (V5 and V6) and an increased amplitude of S waves in the right chest leads (V1 and V2) (Goldberger et al., 2017).

The duration of the QRS complex may also be increased in the case of LVH. This increase is generally very minor and is associated with a left bundle branch block (LBBB). Left axis deviation, which means that the axis is -30 degrees or more negative, may also be seen in the case of LVH. However, generally the electrical axis is horizontal, meaning that there is no axis deviation. The ST-segment changes in LVH are due to ventricular overload. Previously referred to as LV "strain", ventricular overload manifests as an ST-segment depression and T wave inversion. These changes can be best seen in the leads with tall R waves (V5 and V6) (Goldberger et al., 2017). The Strong Heart Study indicated that in cases without evidence of coronary disease, increasing LVM was in correlation with an increasing magnitude of ST depressions (Okin et al., 2002). Lastly, left atrial abnormality may be seen in cases of LVH, since most of the etiologies of LVH eventually cause left atrial overload as well. Left atrial abnormality manifests as broad P waves in the extremity leads or biphasic P waves in lead V1 (Goldberger et al., 2017).

There are three commonly used ECG criteria for diagnosing LVH: Sokolow – Lyon criteria, Cornell voltage criteria, and the Romhilt – Estes point score system. The Sokolow – Lyon criteria is based on either the sum of the S wave in lead V1 and R wave in V5 or V6, which should be at least 3.5mV (35mm), or only on the voltage/amplitude of the R wave in lead aVL, which should be at least 1.1mV (11mm). The Cornell voltage criteria is based on the sum of S wave in lead V3 and R wave in lead aVL, which should be > 2.8mV (28mm) in males and > 2.0mV (20mm) in females. These boundaries are directly based upon echocardiographic correlative studies aimed to detect an enlarged LVM index. Lastly, the Romhilt-Estes point score system is based on all the five major ECG findings that LVH can produce. Each finding

has a specific amount points, which are then added together. In order to indicate “definite” LVH, a score of 5/15 is needed. The points assigned to each finding can be seen in the table below (Mirvis and Goldberger, 2022).

Table 2.1. Diagnostic criteria for LVH (Mirvis and Goldberger, 2022).

Measurement	Criteria
Sokolow-Lyon voltages	$SV_1 + RV_5 > 3.5$ mV
	RaVL >1.1 mV
Romhilt-Estes point score system *	Any limb lead R wave or S wave >2.0 mV (3 points)
	or SV_1 or $SV_2 \geq 3.0$ mV (3 points)
	or RV_5 to $RV_6 \geq 3.0$ mV (3 points)
	ST-T wave abnormality, no digitalis therapy (3 points)
	ST-T wave abnormality, digitalis therapy (1 point)
	Left atrial abnormality (3 points)
	Left axis deviation ≥−30 degrees (2 points)
	QRS duration ≥90 msec (1 point)
	Intrinsicoid deflection in V_5 or $V_6 \geq 50$ msec (1 point)
Cornell voltage criteria	SV_3 + RaVL >2.8 mV (for men)
	SV_3 + RaVL >2.0 mV (for women)

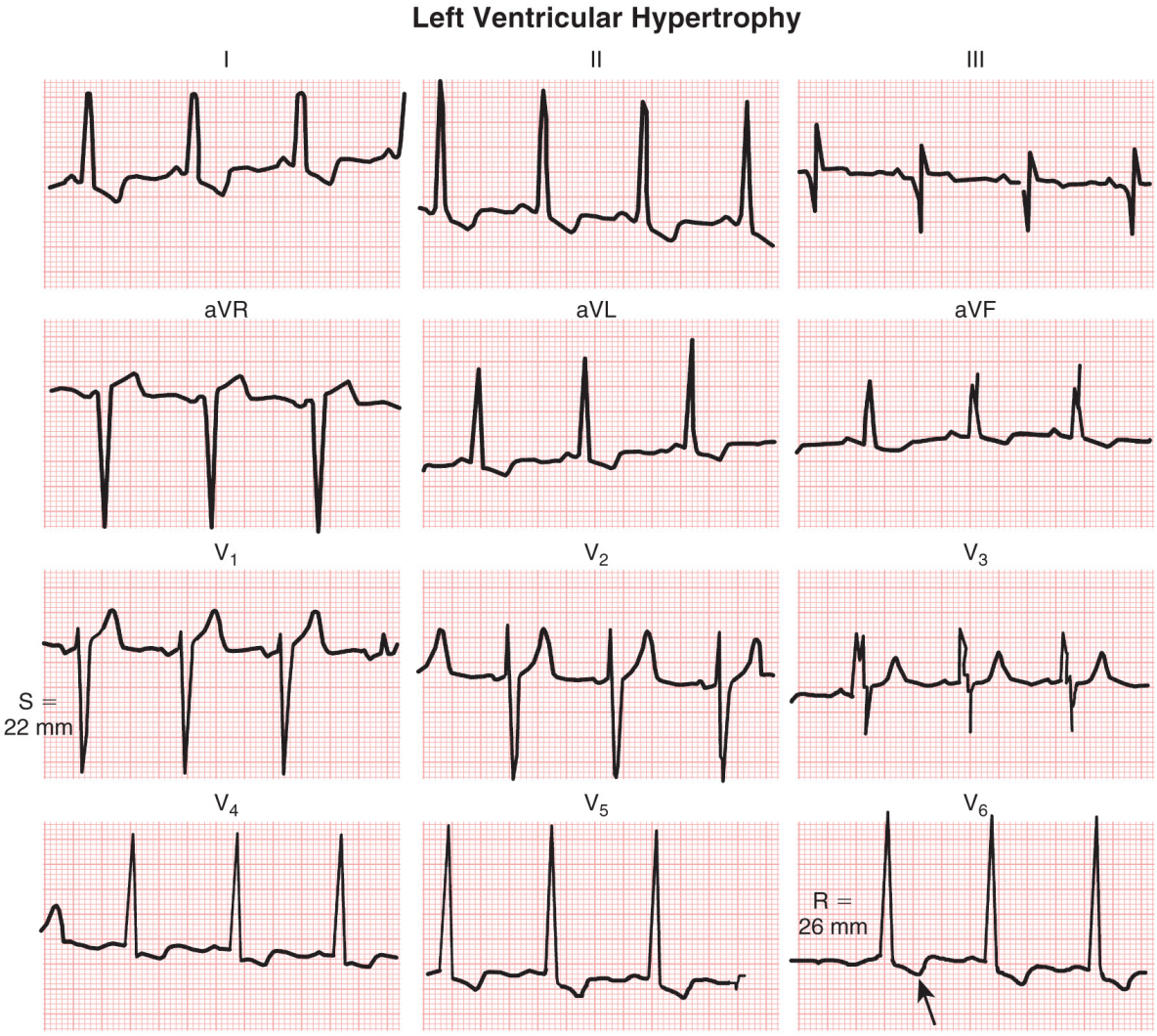


Figure 2.5. ECG changes in LVH with the black arrow depicting ventricular overload (Goldberger et al., 2017)

I.3. Alcohol septal ablation

As mentioned earlier, ASA is performed on patients with hypertrophic cardiomyopathy. HCM is an inherited disease in which there is unexplained LVH. In patients with HCM, the thickness of the LV wall is > 15 mm and there are a few different patterns of hypertrophy, such as asymmetric, septal, and concentric (Pelliccia et al., 2019). The hypertrophy is generally asymmetric, involving the basal interventricular septum. Due to the hypertrophy of the basal IVS, there is a hyperdynamic ejection, which leads to the systolic anterior motion (SAM) of the anterior mitral valve leaflet. This anterior mitral valve leaflet then adjoins the hypertrophied IVS, resulting in an outflow obstruction. This is present in approximately 1/3 of HCM patients, already at rest. Out of the remaining patients, half have provokable outflow obstruction. A byproduct of this obstruction is the increase in systolic pressure gradient between the aorta and

the LV. This LVOT obstruction can manifest as dyspnea, chest pain, syncope, and even heart failure. When discussing the treatment options of HCM, the initial step is pharmacotherapy. However, patients, which remain symptomatic despite medical therapy, are treated with septal reduction therapy, which is performed either by surgical septal myectomy or ASA (Marian and Braunwald, 2017). ASA is recommended in HCM patients with symptoms correlating to New York Heart Association (NYHA) Class III-IV, or Canadian Cardiovascular Society grade III-IV angina pectoris. The latest guidelines state that the septal thickness cut-off to perform a safe procedure and to decrease the risk of ventricular septal defect is 17 mm. On the other hand, patients with severe hypertrophy, meaning that the basal septum thickness is 25 mm or more, may not benefit from ASA (Pelliccia et al., 2019).

ASA is a percutaneous, minimally invasive procedure performed to resolve obstruction of the LVOT in patients with hypertrophic cardiomyopathy. This procedure was first introduced in 1994 by Sigwart, and since then several studies have proved its safety and efficacy (Pelliccia et al., 2019). The idea of ASA initially came from electrophysiologic studies conducted by Brugada, which described treating ventricular arrhythmias using intracoronary alcohol injection. These studies led Berghöfer, a German cardiologist, to first describe the technique of this procedure in 1989. Some years after this, Sigwart published a body of work covering three cases of percutaneous ASA in HCM patients that were resistant to medical therapy. There was improvement of symptoms in these patients already from the day after the procedure. To this date, ASA is considered an effective minimally invasive method in symptomatic HCM patients with an LVOT gradient of 50 mmHg or more (Pelliccia et al., 2019).

The essence of ASA is creating an iatrogenic infarction of the basal part of the IVS in order the decrease the obstruction of the LVOT. ASA consists of the infusion of 95-96% absolute alcohol into the septal perforator coronary artery branch, which supplies the LV side of the basal interventricular septum. The first septal perforator coronary artery branch is often chosen, since in most cases it supplies the basal IVS. It commonly arises from the left anterior descending (LAD) artery and its track is close to the His bundle and right bundle branch. The mechanism of this procedure is to induce an occlusion of the artery, leading to a controlled infarction of the basal IVS that gradually turns from hypertrophic myocardium to a thin scar. This transformation then leads to the reduction of the obstruction of the LVOT (Pelliccia et al., 2019).

The procedure consists of several steps, which are the following. Diagnostic catheterization may initially be done to evaluate the LVOT gradient. An arterial sheath and temporary

pacemaker are then positioned. Coronary angiography is then performed in order to select the septal branch where the alcohol will be infused. The septal perforator coronary artery branch can be accessed either via the radial approach or the femoral approach. Once the left main coronary artery is engaged with a guide catheter, a short over-the-wire balloon is passed over an extra support wire and placed into the septal perforator branch. This balloon allows for selective septal perforator branch angiography while inflating the balloon. Excluding the filling of any other coronary arteries through septal collaterals and excluding contrast misplacement in other regions must be done before injecting the alcohol. Once this exclusion is done by injecting 1-2 ml of contrast, the alcohol injection can be done. 1-3 ml of ethanol is injected into the septal perforator branch over a one- to five-minute time period. For every 10 mm of septal thickness, the amount of alcohol used is approximately 1 ml (Pelliccia et al., 2019).

Although this procedure has been proven to be effective, there are some complications that may occur. The most common complications related to this procedure are conduction disturbances, especially atrioventricular (AV) blocks. The AV blocks may either be temporary, in approximately 30% of the cases, or permanent, in approximately 10% of cases. In addition to this, right bundle branch blocks (RBBBs) occur in approximately 50% of cases. This is because the septal perforator branches are anatomically close to the conduction system. Conduction disturbances may be eradicated with pre-procedural pacemakers. Other possible complications include infarctions of other areas, such as the anterior wall, papillary muscles, or the right ventricle. This may occur due to the collateral septal flow to the LAD artery of the right coronary artery (Pelliccia et al., 2019).

Over time, ASA has been proven to be effective and safe, despite the relevant complication rate. Studies comparing ASA and surgical myectomy have demonstrated similar rates of complications (Pelliccia et al., 2019). Although the clinical results are similar, the results of ASA depend heavily on the septal perforator branch. Some patients, especially young patients with significant hypertrophy, do not necessarily experience complete relief of symptoms. On the other hand, elderly patients with mild hypertrophy may be more suitable for ASA (Nishimura et al., 2017).

I.4. Previous studies

I.4.1. Studies focusing on ECG findings after ASA

The earliest study dedicated solely on investigating the ECG changes after ASA was conducted by Karmierczak et al. in 1998 titled "Electrocardiographic changes after alcohol septal ablation in hypertrophic obstructive cardiomyopathy". This study included nine symptomatic patients with subaortic hypertrophic obstructive cardiomyopathy (HOCM) in whom ASA was performed. The procedure was performed in a similar manner in all patients; the first septal branch of the LAD artery was ablated, and the amount of alcohol used was 3-4 ml per patient. Resting 12-lead ECGs (50 mm/s speed) were recorded before ASA, one hour after the procedure, three, seven, and nine days after the procedure, and three and six months after the procedure. The key findings in the post-procedural ECGs were the following: new ST segment elevation, new Q waves, AV block, and the presence of a bundle branch block. The new ST segment elevation, present in the anterior leads, was seen in the five out of the nine patients already in the first ECG after the procedure. This elevation only persisted in one out of the nine patients on discharge, and then returned back to normal by the last ECG taken. The new Q waves were also seen in the first ECG after the procedure in four out of the nine patients. The AV block developed in two out of the nine patients but did not persist until the very last ECG taken. The bundle branch block was observed in all nine patients right after the procedure. The results of the study showed that a new bundle branch block was the most common finding in patients who underwent alcohol septal ablation (Karmierczak et al., 1998).

The second study solely on investigating the ECG changes after ASA was conducted by Runquist et al. in 2002 titled "Electrocardiographic findings after alcohol septal ablation therapy for obstructive hypertrophic cardiomyopathy". This study was more inclusive than the first study studying the ECG changes after ASA conducted by Karmierczak et al. 1998, as the number of patients included was 165. Resting 12-lead ECGs were recorded before ASA and then post-ASA within 2 to 236 days. This study used the Romhilt-Estes point system criteria to diagnose LVH. Out of all the patients, 82 had ECG findings indicating LVH. Other significant pre-procedural findings were left atrial enlargement, which was seen in 67 patients, and Q waves, which were seen in 49 patients. After the alcohol septal ablation, a RBBB was the most common finding, as it was seen in 96 patients, whereas pre-procedural only six patients had it. 14 patients lost the Q waves, while 9 patients without Q waves initially developed them after the alcohol septal ablation. Almost all of the patients developed ST-elevations during the

procedure, however these changes were not seen in the ECGs recorded several days after the procedure. Unlike any of the previously mentioned studies, this study focused on the amplitude of S and R waves post-procedurally, pointing out whether or not post-procedural ECGs showed smaller amplitudes. Post-procedurally, the criteria for LVH were seen only in 37 patients out of the 82 that had them initially. Although reports show that the sensitivity of an ECG in indicating LVH is not high, the findings in this study were confirmed by echocardiography. Echocardiography showed reduction in both septal thickness and reduction in the thickness of other walls (Runquist et al., 2002).

I.4.2. Studies briefly covering ECG findings after ASA

In addition to the above mentioned studies, there were several studies which were not solely dedicated to investigating the ECG changes after ASA, however, they did touch on the main ECG changes. Knight et al. conducted a study in 1997 titled "Nonsurgical septal reduction of hypertrophic obstructive cardiomyopathy. Outcome in the first series of patients.", which mentioned the ECG changes seen in the participants directly after the procedure. The study included 18 patients, out of which five patients had permanent pacemakers implanted during the procedure. Out of the remaining 13 patients, 11 developed a new RBBB, making this the most common ECG change. A new ST segment elevation, in the anterior leads, was seen in five patients, and a new Q wave was seen in two patients. The major finding of this study was that the most common ECG change in patients who underwent ASA was the new bundle branch block (Knight et al., 1997).

Shortly after the study by Knight et al., there was a study conducted by Seggewiss et al. in 1998 titled "Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and 3-month follow-up in 25 patients". The major finding of this study was also that the most common ECG change in patients who ASA was the bundle branch block, as 13 out of the 25 patients developed it (Seggewiss et al. 1998).

Gietzen et al. conducted a study in 1999 titled "Acute and long-term results after transcoronary ablation of septum hypertrophy in hypertrophic obstructive cardiomyopathy". The ECG changes were identical to the ones in the study conducted by Karmierczak et al. in 1998. The ECG changes were the following: new ST segment elevations, new Q waves, AV blocks, and new bundle branch blocks. Contrary to the other studies, the most common finding in this study was the development of the AV block, which was seen in 32 out of 50 patients. Although this

was a major finding directly after ASA, only five patients still had this ECG sign at the seven month follow up. The second most common ECG finding in this study was the development of a bundle branch block, as 29 out of 50 patients developed it. 26 out of these 29 patients developed a RBBB, whereas only three developed a left bundle branch block (Gietzen et al., 1999).

I.4.3. Strength of previous studies

The main strength of the previously mentioned studies is their correlating findings. Although some of the studies did not go over the ECG changes in depth, in the majority of the studies the most common ECG change was the development of a new bundle branch block, mainly RBBB. The number of participants may have varied, but the procedure was done in a similar manner in all cases and led a similar ECG outcome. In addition to the bundle branch block, the other ECG findings were the same and were noted in the majority of the studies. The prevalence of the minor findings may have varied between the studies, but the fact the findings were still the same lays a strong foundation of what ECG changes to expect in patients undergoing ASA.

I.4.4. Limitation of previous studies

The major limitation of the previously mentioned studies is the small sample size. Only one of the above mentioned studies included over 100 patients. The rest of the studies had approximately 10-50 participants, which may be considered as a rather small sample size. It can be argued that the small sample size, in majority of the above mentioned studies, makes it questionable whether or not the ECG findings would be as common on a larger scale. Although in most of the previous studies the development of a new bundle branch block was the most common ECG finding after the alcohol septal ablation, this may not necessarily be the case if the studies included a significantly larger number of participants.

I.4.5. The insufficiency of the post-ASA ECG analysis

Although there are a handful of studies highlighting the ECG changes in patients who have undergone ASA, there remains one feature that is not generally highlighted. As stated earlier, the main ECG criteria for LVH is based on the amplitude of the R and S waves in the precordial leads. The commonly used Sokolow – Lyon criteria clearly states that the sum of the S wave in lead V1 and R wave in lead V5 or V6 should be at least 3.5 mV (35mm). Majority of the studies

did not mention if and how this key finding was changed after ASA. The amplitude of the R and S wave directly correlates to the thickness of the LV, hence the large amplitude. ASA decreases the thickness of the basal IVS; therefore it is possible that there is no change in the R and S wave amplitude. However, it would be interesting to see if there would possibly be any changes to the R and S wave amplitudes. Majority of the studies were not focused solely on the ECG changes; therefore it can be understood why changes in pre-established ECG changes are not analyzed, however, out of the studies that were solely conducted to analyze the ECG changes, only one covered these changes.

METHODS AND MATERIALS

II.1. Inclusion and exclusion criteria

The inclusion criteria were the following: patient must be an adult (at least 18 years of age), LVH must be seen on echocardiography, patient must have given the consent for their data to be used, patient must be eligible for ASA, and patient must have pre- and post-procedural ECGs in the hospital archive. The exclusion criteria were the following: patient below the age of 18, absence of LVH on echocardiography, patient unable to express their will regarding their data processing, and no pre- and/or post-procedural ECG in the hospital archive.

II.2. Study design

This study is a retrospective study in which data of patients who underwent alcohol septal ablation in the cardiology department of Paul Stradinš Clinical University Hospital between the years 2015 – 2022 was analyzed. The sample of study was 48 patients, including 20 males and 28 females. Transthoracic echocardiography was performed in all patients before and after ASA, thus confirming the presence of LVH prior to ASA. The transthoracic echocardiography was performed using ultrasound apparatus belonging to the Paul Stradinš Clinical University Hospital. A standard 12-lead electrocardiogram was also obtained from all patients before and after ASA. The ECG obtained on the day prior to ASA and on the day after ASA were analyzed. The points of focus in the ECG were the following: the PR interval, the QRS complex duration, the QRS complex α angle, the amplitude of the R wave in lead V6, the amplitude of the S wave in lead V1, the ST segment, the T wave, and the QT interval. The Sokolow – Lyon criteria was applied to check the extent of LVH before and after ASA.

II.3. Data collection

The data collection was carried out from February 2023 until April 2023. The data of the patients was collected from the hospital archive of the cardiology department of Paul Stradinš Clinical University Hospital. The data that was collected was the patients' gender, age, echocardiogram findings, and electrocardiogram findings. The data was collected from the patient files and each patient was assigned with a distinctive code by the researcher, which maintained their anonymity. The codes were kept throughout every stage of data processing.

II.4. Data analysis

The statistical analysis of the data was performed using the IBM SPSS software (version 29.0). The data was analyzed using descriptive statistics and paired samples t-test. Descriptive statistics were used to determine the details of the data, such as the minimum and maximum values, the mean, and the standard deviation. The paired samples t-tests allowed for a comparison between the pre- and post-ASA values. The statistical significance value was set to be $p < 0.05$. Some of the graphs and charts were plotted using the IBM SPSS software, however, the graphs presenting the pre- and post-ASA values of various ECG parameters were generated using Microsoft Excel. The mean values of the ECG parameters were used to generate the graphs presented in this study, since this allowed for the analysis of the overall trend of the data and for the accurate comparison between the pre- and post-ASA values. In addition to this, using the mean values simplifies the data presentation and makes it easier for the reader to interpret the results.

II.5. Ethical evaluation

All the participant's data was saved in the archive of the hospital with their informed consent. Upon admission, the participants gave their consent (via the hospital database system) for their data to be used for research purposes in the future. For this reason, a separate informed consent form was not prepared specifically for this study. Although a separate informed consent form was not prepared, this study was conducted in accordance with the requirements of Article 10(8') of the Patient's Rights Act. The approval of the ethical committee of the Faculty of Medicine of University of Latvia was obtained in January 2023 (approval number 19-25/37).

RESULTS

III.1. Study sample

The study involved 48 patients, out of which 20 were males and 28 were females. In other words, 41.7% of the study participants were male, and 58.3% of the study participants were female. A visual representation of this statistic can be seen in the figure below. Although the amount of male and female participants was not exactly equal, it was close enough to eradicate any limitation in the findings pertaining to gender.

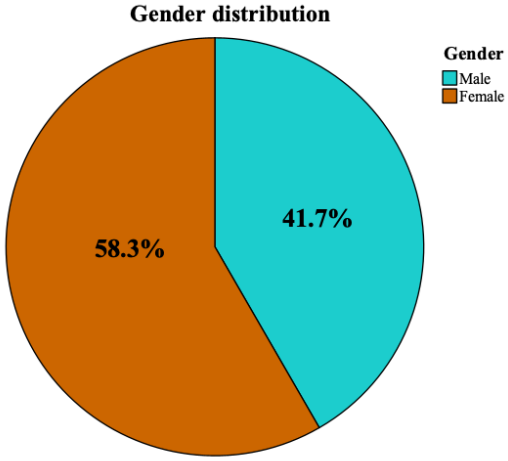


Figure 4.1. Gender distribution of the study participants

The mean age of the participants was 61.2 years ± 11.9 years. The youngest participant was 28 years old, and the oldest patient was 87 years old. A visual representation of the age of the participants can be seen in the figure below.

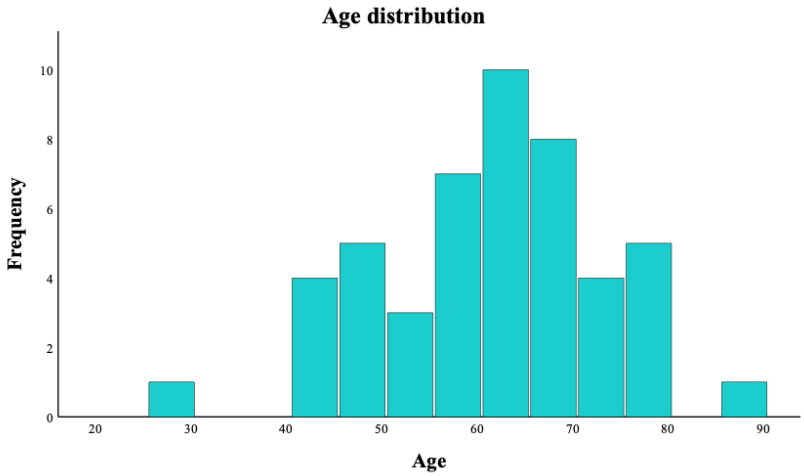


Figure 4.2. Age distribution of the study participants

III.2. ECG parameters before and after ASA

III.2.1. PR interval

Before ASA, the longest PR interval was 244ms and the shortest PR interval was 116ms. The mean was 173ms ± 27.8ms, and the median was 175ms. After ASA, the longest PR interval was 258ms and the shortest PR interval was 116ms. The mean was 179.7ms ± 29.2ms, and the median was 181ms. The highest change was recorded to be a positive increase of 55ms (129ms before ASA to 184ms after ASA).

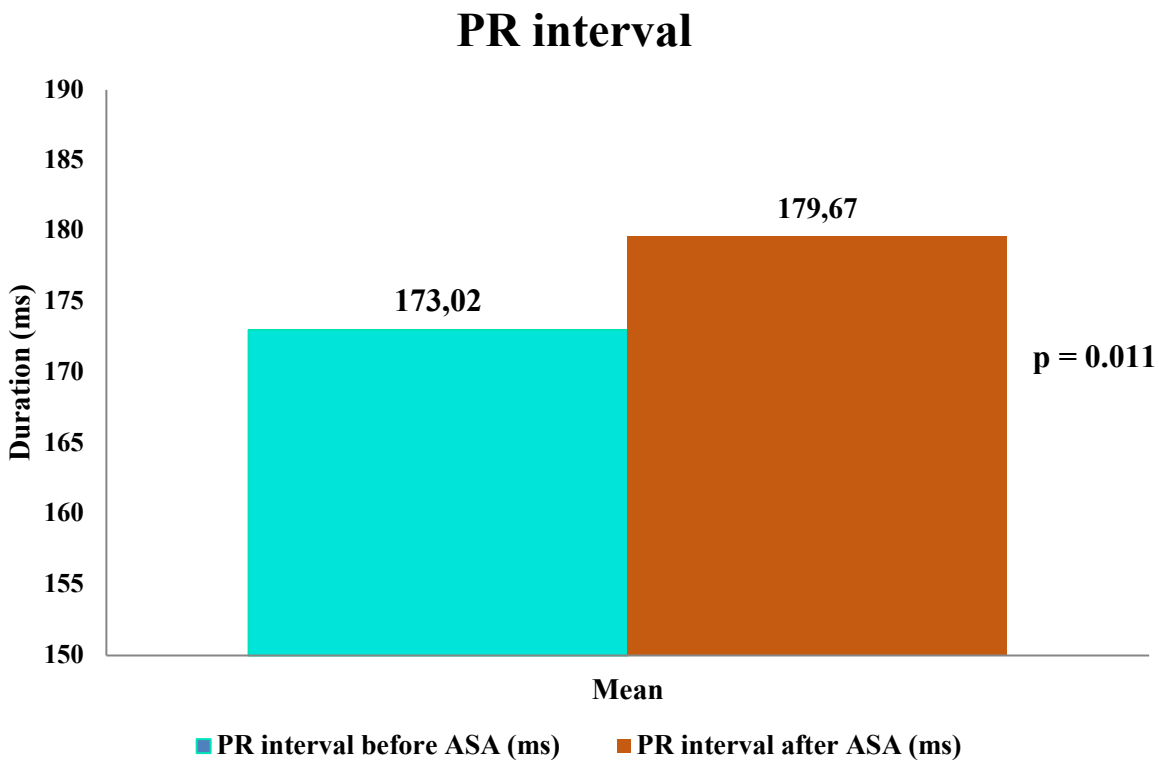


Figure 4.3. PR interval mean before and after ASA

III.2.2. QRS complex duration

Before ASA, the longest QRS complex duration was 149ms and the shortest QRS complex duration was 86ms. The mean was 105.8ms ± 12.6ms, and the median was 105ms. After ASA, the longest QRS complex duration was 199ms and the shortest QRS complex duration was 92ms. The mean was 134.4ms ± 24.6ms, and the median was 137.5ms. The highest change was recorded to be a positive increase of 63ms (136ms before ASA to 199ms after ASA).

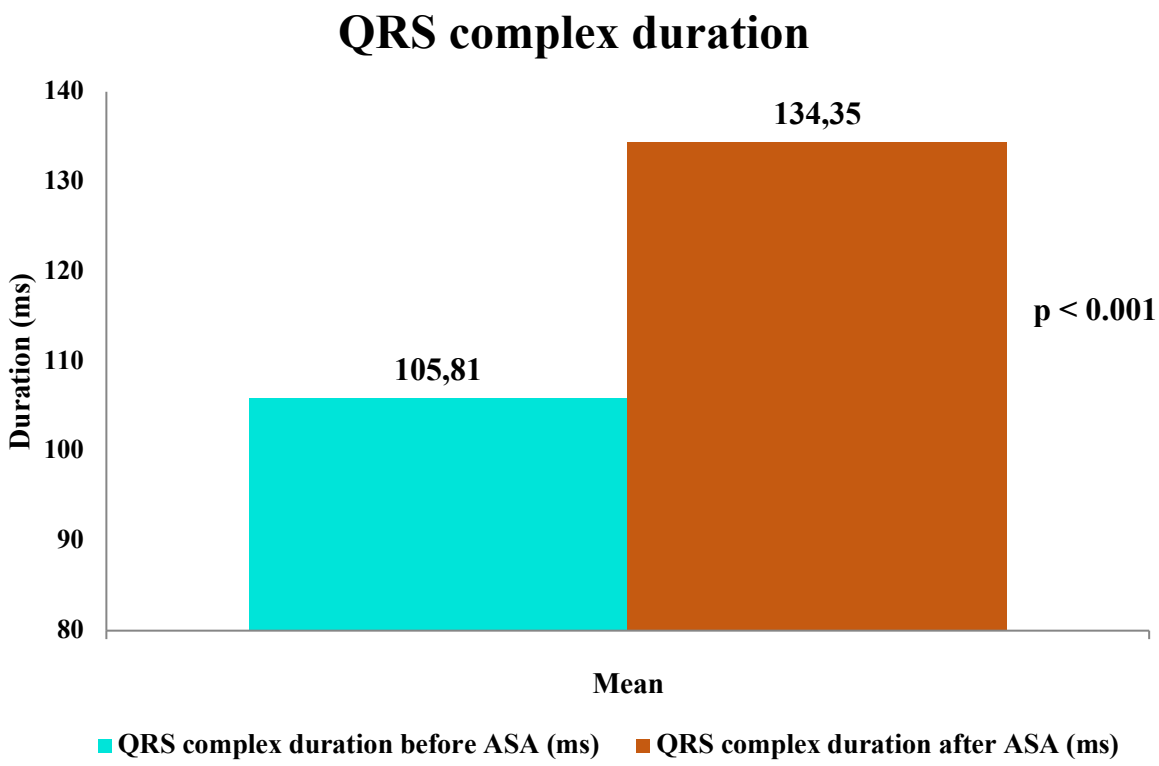


Figure 4.4. QRS complex duration mean before and after ASA

III.2.3. QRS complex α angle

Before ASA, the highest value recorded was 90° and the lowest value recorded was -85°. The mean was 17.2° ± 37.4°, and the median was 20°. After ASA, the highest value recorded was 179° and the lowest value recorded was -90°. The mean was 29.9° ± 49.3°, and the median was 25°. The highest change was recorded to be a positive increase of 244° (-85° before ASA to 159 after ASA).

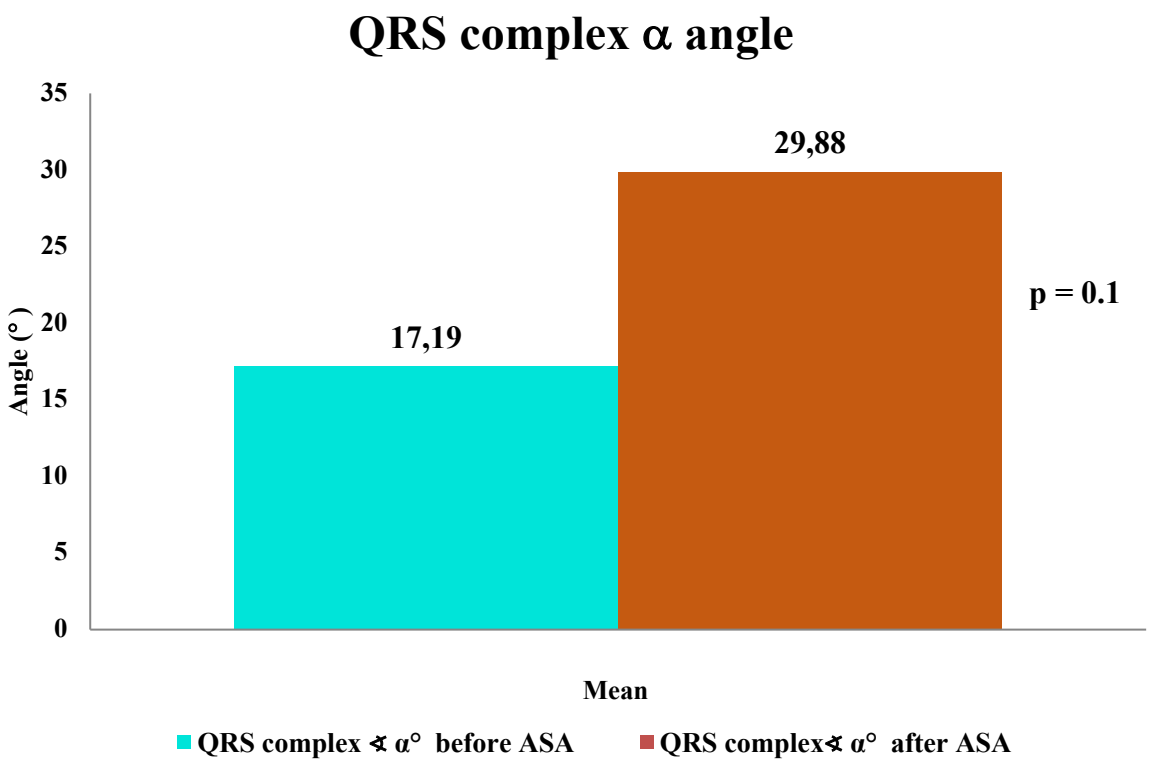


Figure 4.5. QRS complex α angle mean before and after ASA

III.2.4. R and S wave amplitudes

Before ASA, the highest R wave amplitude (lead V6) was 37mm and the lowest was 8mm. The mean was 20.5mm ± 9.2mm, and the median was 18.5mm. After ASA, the highest R wave amplitude (lead V6) was 31mm and the lowest was 3mm. The mean was 13.7mm ± 8.1mm, and the median was 12.5mm. The highest change was recorded to be a negative decrease of 18mm (37mm before ASA to 19mm after ASA).

Before ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 6mm. The mean was 18.1mm ± 7.8mm, and the median was 17.5mm. After ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 1mm. The mean was 10.4mm ± 7.9mm, and the median was 8.5mm. The highest change was recorded to be a negative decrease of 21mm (29mm before ASA to 8mm after ASA).

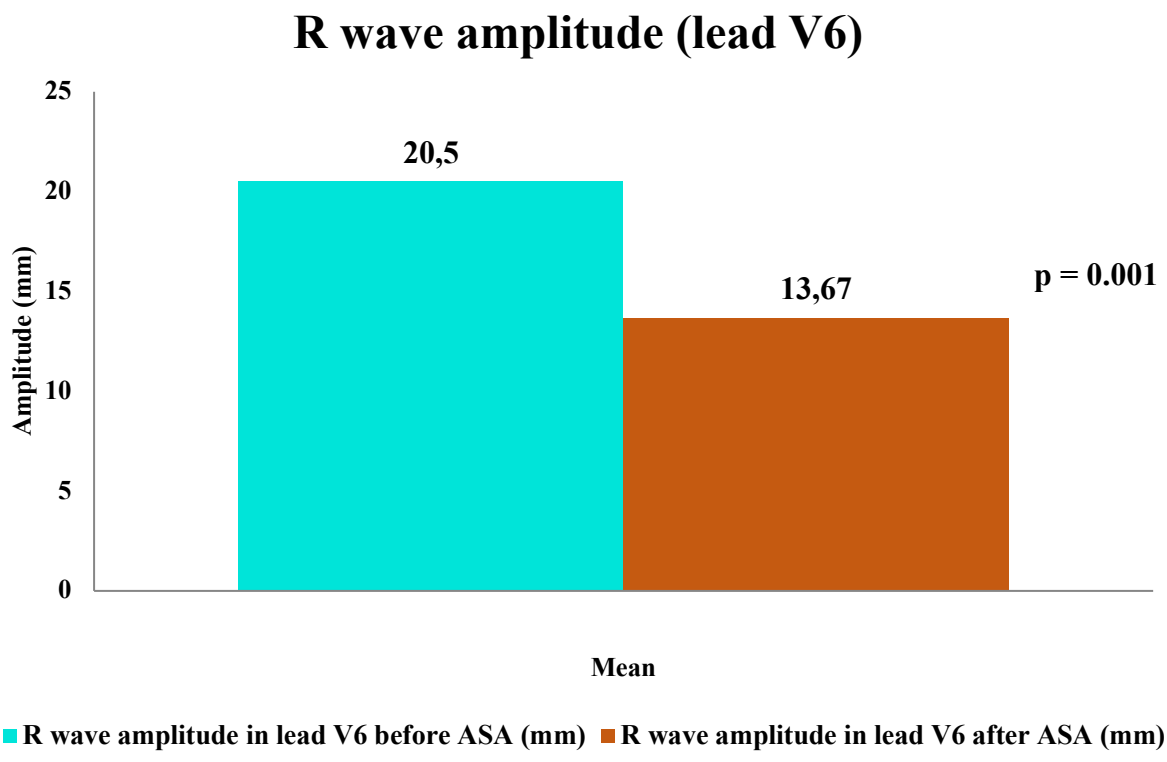


Figure 4.6. R wave amplitude (lead V6) mean before and after ASA

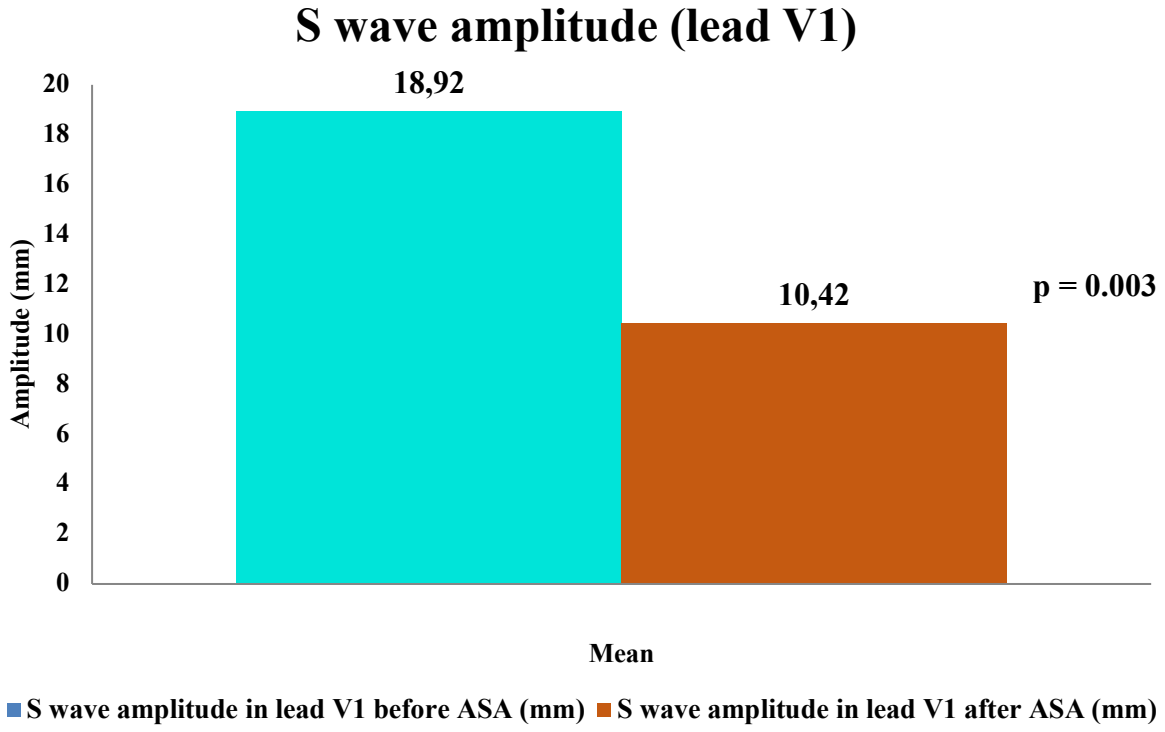


Figure 4.7. S wave amplitude (lead V1) mean before and after ASA

III.2.5. ST segment and T wave

Out of all the patients, 32 patients had ST segment depressions in V5 or V6 before ASA. Out of the 32 patients that had ST segment depressions, 24 had T wave inversions before ASA. In the post-ASA ECGs these changes still persisted.

III.2.6. QT interval

Before ASA, the longest QT interval was 444ms and the shortest QT interval was 402ms. The mean was 424.8ms ± 14.6ms, and the median was 428ms. After ASA the longest QT interval was 509ms and the shortest QT interval was 378ms. The mean was 425.9ms ± 37.2ms, and the median was 425ms. The highest change was recorded to be a positive increase of 85ms (424ms before ASA to 509ms after ASA). The corrected QT interval (QTc) was calculated using the Bazett formula and the values were the following. The longest QTc before was ASA 459ms and the shortest was 409ms. The longest QTc after ASA was 522ms and the shortest was 396ms. The mean before ASA was 446ms and mean after ASA was 450ms.

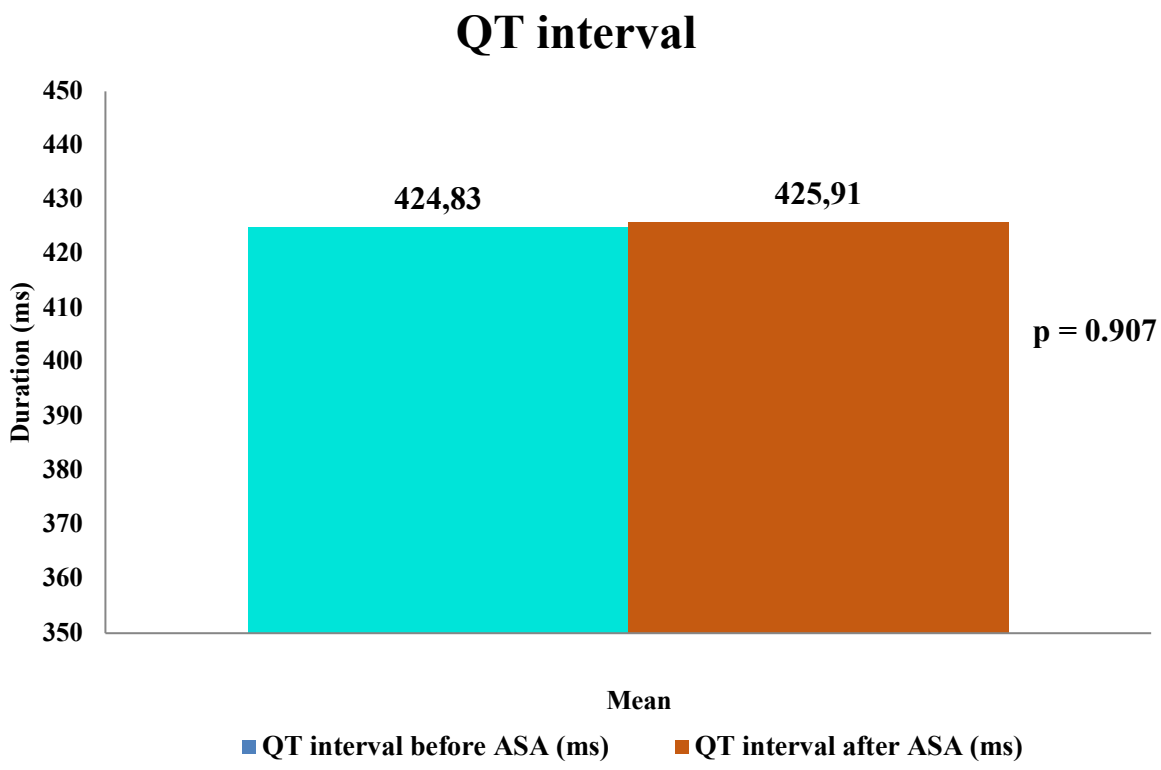


Figure 4.8. QT interval mean before and after ASA

III.3. Statistical analysis of ECG parameters

Table 4.1. Descriptive statistics of ECG parameters.

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
PR interval before ASA (ms)	48	116	244	173.02	27.805
PR interval after ASA (ms)	48	116	258	179.67	29.190
QRS complex duration before ASA (ms)	48	86	149	105.81	12.566
QRS complex duration after ASA (ms)	48	92	199	134.35	24.648
QRS complex ∢ α° before ASA	48	-85	90	17.19	37.365
QRS complex ∢ α° after ASA	48	-90	179	29.88	49.310
R wave amplitude (lead V6) before ASA (mm)	48	8.00	37.00	20.5000	9.22940
R wave amplitude (lead V6) after ASA (mm)	48	3.00	31.00	13.6667	8.12777
S wave amplitude (lead V1) before ASA (mm)	48	6.00	32.00	18.0833	7.80976
S wave amplitude (lead V1) after ASA (mm)	48	1.00	32.00	10.4167	7.90234
QT interval before ASA (ms)	48	402.00	444.00	424.8333	14.60905
QT interval after ASA (ms)	48	378.00	509.00	425.9167	37.20083

Table 4.3. Paired samples t-test of the ECG parameters.

		Paired Differences					t	Significance	
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper		One-Sided p	Two-Sided p
Pair 1	PR interval before ASA (ms) - PR interval after ASA (ms)	-6.646	17.472	2.522	-11.719	-1.573	-2.635	.006	.011
Pair 2	QRS complex duration before ASA (ms) - QRS complex duration after ASA (ms)	-28.542	22.968	3.315	-35.211	-21.872	-8.609	<.001	<.001
Pair 3	QRS complex ∢ α° before ASA - QRS complex ∢ α° after ASA	-12.687	52.352	7.556	-27.889	2.514	-1.679	.050	.100
Pair 4	R wave amplitude (lead V6) before ASA (mm) - R wave amplitude (lead V6) after ASA (mm)	6.83333	5.54048	1.59940	3.31308	10.35359	4.272	<.001	.001
Pair 5	S wave amplitude (lead V1) before ASA (mm) - S wave amplitude (lead V1) after ASA (mm)	7.66667	6.98483	2.01635	3.22872	12.10462	3.802	.001	.003
Pair 6	QT interval before ASA (ms) - QT interval after ASA (ms)	-1.08333	31.42801	9.07248	-21.05174	18.88507	-.119	.454	.907

A paired samples t-test showed that the participants' PR interval increased from before ASA (M = 173.02ms $\pm$ 27.81ms) to after ASA (M = 179.67ms $\pm$ 29.19ms) (t = - 2.635, p = 0.011). The null hypothesis i.e., that there is no difference between the PR interval before and after ASA is thereby rejected at 5% level of significance. Hence, the alternative hypothesis, that there will be a significant difference between the pre- and post-ASA PR interval, is accepted.

A paired samples t-test showed that the participants' QRS complex duration increased from before ASA (M = 105.82ms $\pm$ 12.57ms) to after ASA (M = 134.35ms $\pm$ 24.65ms) (t = -8.609, $p < 0.001$). The null hypothesis i.e., that there is no difference between the QRS complex duration before and after ASA is thereby rejected at 5% level of significance. Hence, the alternative hypothesis, that there will be a significant difference between the pre- and post-ASA QRS complex duration, is accepted.

A paired samples t-test showed that the participants' QRS complex α angle increased from before ASA (M = 17.19° $\pm$ 37.37°) to after ASA (M = 29.88° $\pm$ 49.31°) (t = - 1.679, p = 0.1). The null hypothesis i.e, that there is no difference between the QT interval before and after ASA is thereby failed to be rejected at 5% of level of significance.

A paired samples t-test showed that the participants' R wave amplitude (lead V6) decreased from before ASA (M = 20.5mm $\pm$ 9.22mm) to after ASA (M = 13.67mm $\pm$ 8.13mm) (t = 4.272, p = 0.001). The null hypothesis i.e, that there is no difference between the R wave amplitude (lead V6) before and after ASA is thereby rejected at 5% level of significance. Hence, the alternative hypothesis, that there will be a significant difference between the pre- and post-ASA R wave amplitude in lead V6, is accepted.

A paired samples t-test showed that the participants' S wave amplitude (lead V1) decreased from before ASA (M = 18.92mm $\pm$ 8.32mm) to after ASA (M = 10.42mm $\pm$ 7.90mm) (t = 3.802, p = 0.003). The null hypothesis i.e., that there is no difference between the S wave amplitude (lead V1) before and after ASA is thereby rejected at 5% level of significance. Hence, the alternative hypothesis, that there will be a significant difference between the pre- and post-ASA S wave amplitude in lead V1, is accepted.

A paired samples t-test showed that the participants' QT interval increased from before ASA (M = 424.83ms $\pm$ 14.61ms) to after ASA (M = 425.92ms $\pm$ 37.20ms) (t = -0.119, p = 0.907). The null hypothesis i.e, that there is no difference between the QT interval before and after ASA is thereby failed to be rejected at 5% of level of significance.

III.4. Conduction disturbances

III.4.1. Overall findings

In the post-ASA ECGs it was seen that there were seven new cases of an AV block (1st degree) and 23 new cases of a RBBB (four incomplete and 19 complete). Before ASA, it was seen that 18 patients (37.5% of the study sample) had either one or more conduction disturbances. After ASA, it was seen that 38 patients (79.2% of the study sample) had either one or more conduction disturbances. This means that 20 patients developed a conduction disturbance after undergoing ASA. A visual depiction of these results can be seen in the graphs below.

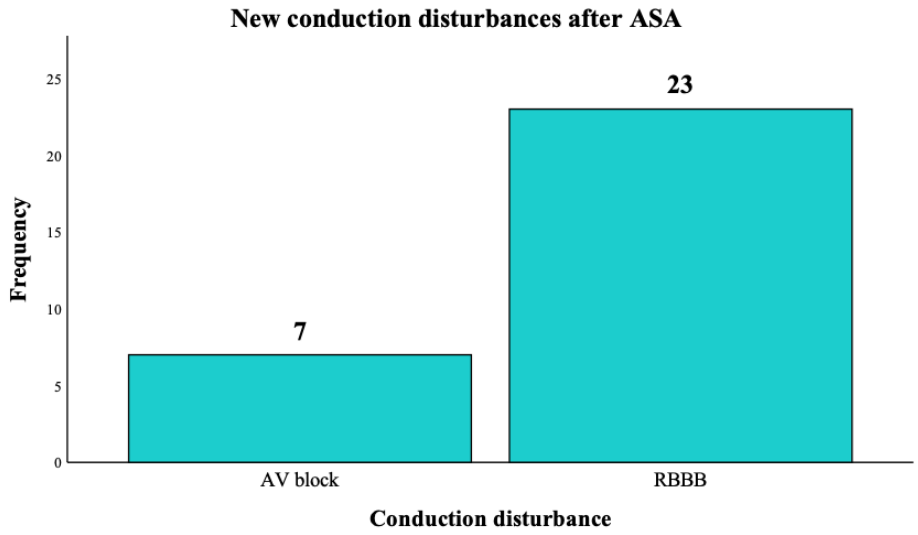


Figure 4.9. New conduction disturbances after ASA

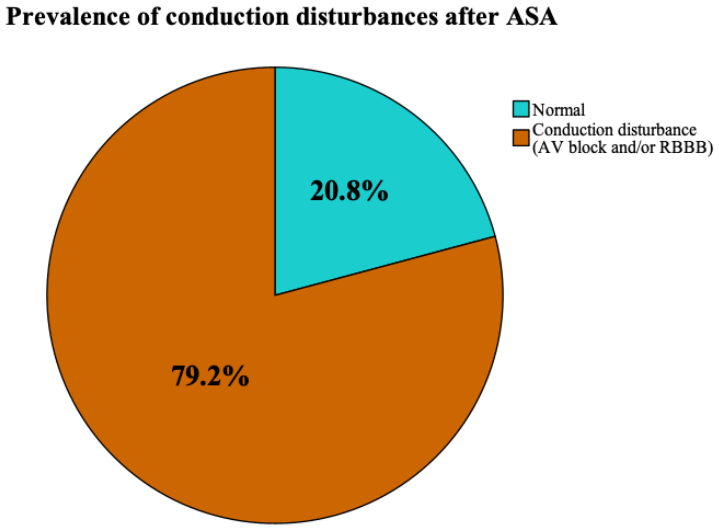


Figure 4.10. Prevalence of conduction disturbances after ASA

III.4.2. Findings related to age

In patients that were 60 years of age or below, two out of 20 patients already had an AV block (1st degree) prior to ASA. Out of the remaining 18 patients, three developed an AV block (1st degree) after ASA. The mean of the PR interval was 174ms before ASA and 179.5ms after ASA ($t = -1.293$, $p = 0.212$) In patients above the age of 60, five out of 28 patients already had an AV block (1st degree) prior to ASA. Out of the remaining 23 patients, four patients developed an AV block (1st degree) after ASA. The mean of the PR interval was 172.3ms before ASA and 179.8ms after ASA ($t = -2.374$, $p = 0.025$)

In patients that were 60 years of age or below, six out of 20 patients already had a RBBB (QRS complex of 110ms or more) prior to ASA. Out of the remaining 14 patients, eight developed an RBBB after ASA. The mean of the QRS complex duration was 108.2ms before ASA and 131.2ms after ASA ($t = -4.045$, $p = 0.001$) In patients above the age of 60, nine out of 28 patients had a RBBB prior to ASA. Out of the remaining 21 patients, 15 developed an RBBB after ASA. The mean of the QRS complex duration was 104.1ms before ASA and 136.1ms after ASA ($t = 8.352$, $p = 0.000$)

III.4.3. Findings related to gender

Out of the 20 males in study, four had an AV block (1st degree) prior to ASA. Out of the remaining 16 males, two developed an AV block (1st degree) after ASA. The mean of the PR interval was 179.4ms before ASA and 186.1ms after ASA ($t = -1.536$, $p = 0.141$). Out of the 28 females, four had an AV block (1st degree) prior to ASA. Out of the remaining 24 females, five developed an AV block (1st degree) after ASA. The mean of the PR interval was 168.3ms before ASA and 175.1 after ASA ($t = -2.134$, $p = 0.042$).

Out of the 20 males in the study, eight had a RBBB (QRS complex duration of 110ms or more) prior to ASA. Out of the remaining 12 males, eight developed a RBBB after ASA. The mean of the QRS complex duration was 109.5ms before ASA and 135.7 after ASA ($t = -5.145$, $p < 0.000$). Out of the 28 females in the study, eight had a RBBB prior to ASA. Out of the remaining 20 females, 16 developed a RBBB after ASA. The mean of the QRS complex duration was 103.2ms before ASA and 133.4ms after ASA ($t = -6.80$, $p = < 0.000$).

III.5. R and S wave amplitudes

III.5.1. Findings related to age

In patients that were 60 years of age or below, before ASA, the highest R wave amplitude (lead V6) was 37mm and the lowest was 8mm. After ASA, the highest R wave amplitude (lead V6) was 31mm and the lowest was 3mm. The mean was 20.9mm before ASA and 14.4mm after ASA ($t = 3.127$, $p = 0.017$). In patients that were above the age of 60, before ASA, the highest R wave amplitude (lead V6) was 27mm and the lowest was 15mm. After ASA, the highest R wave amplitude (lead V6) was 17mm and the lowest was 8mm. The mean was 19.8mm before ASA and 12.3mm after ASA ($t = 2.9694$, $p = 0.074$).

In patients that were 60 years of age or below, before ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 6mm. After ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 1mm. The mean was 17.5mm before ASA and 11.5mm after ASA ($t = 2.457$, $p = 0.044$). In patients that were above the age of 60, before ASA, the highest S wave amplitude (lead V1) was 29mm and the lowest was 12mm. After ASA, the highest S wave amplitude (lead V1) was 9mm and the lowest was 8mm. The mean was 21.8mm before ASA and 8.25mm after ASA ($t = 3.576$, $p = 0.03$).

III.5.2. Findings related to gender

In the male participants, before ASA, the highest R wave amplitude (lead V6) was 31mm and the lowest was 8mm. After ASA, the highest R wave amplitude (lead V6) was 31mm and the lowest was 3mm. The mean was 20.3mm before ASA and 15.4mm after ASA ($t = 3.074$, $p = 0.018$). In female participants, before ASA, the highest R wave amplitude (lead V6) was 37mm and the lowest was 10mm. After ASA, the highest R wave amplitude (lead V6) was 19mm and the lowest was 5mm. The mean was 21mm before ASA and 10.3mm after ASA ($t = 3.638$, $p = 0.036$).

In the male participants, before ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 6mm. After ASA, the highest S wave amplitude (lead V1) was 32mm and the lowest was 1mm. The mean was 19.8mm before ASA and 11.6mm after ASA ($t = 2.733$, $p = 0.029$). In female participants, before ASA, the highest S wave amplitude (lead V1) was 23mm and the lowest was 10mm. After ASA, the highest S wave amplitude (lead V1) was 10mm and

the lowest was 6mm. The mean was 17.3mm before ASA and 8mm after ASA ($t = 2.559$, $p = 0.083$).

DISCUSSION

IV.1. Research goals and expected outcomes

As mentioned in the introduction, the aim of this diploma work was to investigate whether or not there will be any significant ECG changes in LVH patients who undergo alcohol septal ablation. In addition to this, the goals of this diploma work were to generally review the ECG changes in LVH patients, and to assess if the post-ASA ECG changes are correlated with the age or gender of the participants. The expected outcomes were that there would be noticeable changes in at least some ECG parameters since this was seen in the previous studies. As ASA induces an iatrogenic infarction of the interventricular septum (Pelliccia et al., 2019), the hypotheses of this diploma work revolved around changes in R and S wave amplitudes, and new conduction disturbances. By calculating the mean values of the various ECG parameters, I was able to highlight the key features of the data and derive relevant conclusions from the analysis.

IV.2. Findings and comparison with previous studies

The main hypothesis for this study was that the R wave amplitude in lead V6 and S wave amplitude lead V1 will decrease after ASA. This hypothesis was clearly proved to be true, as was seen in the results. The mean R wave amplitude in lead V6 decreased from 20.5mm to 13.67mm, and the mean S wave amplitude in lead V1 decreased from 18.92mm to 10.42mm. The decrease in both the R and S wave amplitude mean was significant, with the p value of 0.001 and 0.003 respectively. The sum of the mean R and S wave amplitudes before ASA fulfilled the Sokolow – Lyon criteria as their sum was at least 35mm. Whereas, after ASA, this was not the case, as the sum of the R and S wave amplitude means was only 24.09ms. Although this was not the case for every patient, it was still seen in most of the patients. The only prior study on this topic that covered the R and S wave amplitudes was the study conducted by Runquist et al. in 2002 titled “Electrocardiographic findings after alcohol septal ablation therapy for obstructive hypertrophic cardiomyopathy”, which also had similar findings. This study demonstrated that post-procedurally, that the criteria for LVH was fulfilled only in 37 patients out of the 82 that initially had them. It is worth mentioning that the study by Runquist et al. used the Romhilt-Estes point score system instead of the Sokolow-Lyon criteria, which was used in this study. The Romhilt-Estes point score system’s criteria regarding the R and S wave amplitudes are that one of the following must be fulfilled: any limb lead R or S wave

amplitude is larger than 20mm, S wave amplitude in lead V1 or V2 is at least 30mm, or R wave amplitude in lead V5 or V6 is at least 30mm. On the other hand, the Sokolow Lyon criteria states that either the sum of the S wave in lead V1 and R wave in V5 or V6 should be at least 35mm (Mirvis and Goldberger, 2022). Although different criteria were used in both studies, it can still be said that the results are similar.

Another hypothesis for this study was that after ASA there will ECG changes of a conduction disturbance in numerous patients who do not already have these prior to the procedure. This hypothesis was also proved to be true as there were seven new cases of an AV block (1st degree) and 23 new cases of a RBBB (four incomplete and 19 complete). It was seen that there was a significant difference between the pre- and post-procedural PR interval, and the pre- and post-procedural QRS complex duration. The PR interval mean before ASA was 173.02ms and 179.67 after ASA, indicating that this increase was significant ($p = 0.011$). Although the mean post-procedural PR interval was only 179.67, which does not qualify as an AV block, there were still new cases of AV blocks (1st degree) seen. A significant increase was also noted in the QRS complex duration mean, which went from 105.81ms before ASA to 134.35ms after ASA ($p < 0.001$). In this case, the post-procedural QRS complex duration mean qualified as a complete bundle branch block (Mirvis and Goldberger, 2022). In this study, all new bundle branch blocks were RBBB. This can be explained by the fact that the right bundle of the conduction system is supplied by septal perforators, which are the branches utilized in ASA (Runquist et al., 2002). The findings related to conduction disturbances i.e., the PR interval and QRS complex duration, were like those seen in previous studies. Most of the previous studies on this topic showed that a new bundle branch block (in most cases RBBB) was the most common finding, and this was also seen in this study. The study conducted by Gietzen et al. in 1999 was the only previous study that showed that an AV block was the most common finding. In my study a RBBB was the most common finding, as there were 23 new cases (four incomplete and 19 complete) of it, but the appearance of new AV blocks (1st degree) was also a noticeable finding.

Other ECG parameters, apart from the previously mentioned ones, that were statistically analyzed were the QRS complex alpha angle, and the QT interval. The mean QRS complex alpha angle changed from 17.19 degrees to 29.88 degrees, and the mean QT interval increased slightly from 424.8ms to 425.9ms. The changes in these parameters were not statistically significant. When looking at the mean QRS complex alpha angle, there was neither any axis deviation before nor after the procedure. Although a minority of the patients displayed a left

axis deviation prior to ASA, for most of the patients this was not the case. As mentioned earlier, the QT interval shows the depolarization and repolarization of the ventricles, and generally a QT interval of less than 440ms is considered to be normal (Sattar and Chhabra, 2023). As was seen in the results, the QT interval mean belonged to the normal range before and after ASA. The mean QTc was also calculated using the Bazett formula, and the mean before ASA was 446ms and mean after ASA was 450ms. According to the American Heart Association, and several other cardiological organizations, the normal QTc is 460ms or below for women and 450ms or below for men (Mirvis and Goldberger, 2022). Thus the QTc mean also belonged to the normal range before and after ASA. As established earlier, a prolonged QT interval increases the risk of ventricular arrhythmias (Sattar and Chhabra, 2023). Therefore, based on the results, it can be said that ASA does not increase the risk for ventricular arrhythmias. In addition to these ECG parameters, the ST segment and T wave were also inspected. It was seen that there were no changes in ST segment and T waves after ASA. The ST segment depressions and T wave inversions remained after ASA, and the patients who did not have ST segment depressions or T wave inversions did not develop them after ASA. The persistence of ST segment depressions and T wave inversions can be explained by the fact that the post-ASA ECGs analyzed were obtained only one day after ASA. There was no longer follow-up ECG to assess these parameters again.

One of the goals of this diploma work was to assess if the ECG changes are correlated to the age or gender of the patients. In terms of the PR interval, the change was more significant in patients above the age of 60 ($p = 0.025$ compared with $p = 0.212$). A similar PR interval finding was also seen between genders, with the change in females being more significant ($p = 0.042$ compared with $p = 0.141$). Therefore it can be implied that people over the age of 60 and females are more prone to developing an AV block (1st degree) after ASA. When it came to R wave amplitude, the decrease was larger in patients who were 60 years of age or below ($p = 0.017$ compared with $p = 0.074$). A similar trend was noted between genders, where the decrease was larger in males ($p = 0.018$ compared with $p = 0.036$). The S wave amplitude showed no significant difference between age groups, but there was a significant difference between genders. The S wave amplitude decrease was larger in males ($p = 0.029$ compared with $p = 0.083$). The S wave amplitude decrease was statistically significant in males, but not in females. Based on these findings, it can be implied that males are more prone show a larger decrease in R and S wave amplitudes after ASA. As this was the first study to investigate the correlation between ECG parameter changes after ASA, and age and gender, further studies are

needed to confirm these findings. The further studies should aim to have a similar distribution of male and female, participants but consist of a larger sample size.

IV.3. Limitations of the study

One major limitation of this study, which was also seen in some of the previous studies, was the small sample size. This study only included 48 patients, which was more than most previous studies, but is still a rather small sample size. The reason for this was that there were not any more patients who underwent ASA at Paul Stradinš Clinical University Hospital between 2015 – 2022. Another limitation was the lack of long-term follow-up, which did not allow for analysis of the long-term effects of ASA. In this study, only one post-procedural ECG was analyzed, and this was the ECG from the day after the procedure. Most patients had a few ECGs in their file, including ones from a few days after the procedure. However, since some patients only had the ECG from the day after the procedure, only this one was analyzed in all patients. Some of the prior studies included follow-up ECGs after many months to investigate if the post-procedural changes were still present. Unfortunately, this analysis was not possible in this study. No patient had an ECG from several weeks or months after ASA in their files, thus eliminating the chance of investigating the long-term effects of ASA. Therefore, further studies are needed to investigate the long-term ECG changes after ASA.

IV.4. Strengths of the study

This study had two major strengths, which were the following: the results being similar to those of previous studies, and the demographic of the sample. As mentioned previously, the results were similar to those of previous studies, hence strengthening the prior results. As only one prior study investigated R and S wave amplitudes, it is safe to say that further studies are needed to confirm these results. However, on the other hand, the conduction disturbance results are more solidified as all prior studies covered these, and all except one demonstrated that a bundle branch block was the most common conduction disturbance after ASA. The other strength of this study is the demographic of the sample, meaning that in the 48 patients, there is an almost equal distribution of age and gender. This study included 20 males and 48 males, which is not exactly equal, but it was close enough to eradicate any limitation in the findings pertaining the gender. The same can be said about age, since there were 20 patients that were 60 years of age or below, and 28 patients who were above the age of 60.

CONCLUSIONS

This study suggests that the changes in ECG parameters may provide important insights about the effects of ASA on cardiac function. The results of this study demonstrated significant decreases in the R wave amplitude (lead V6) and the S wave amplitude (lead V1), after ASA, to an extent that the post-ASA mean amplitudes did not fulfill the Sokolow – Lyon criteria. Male participants were more likely to show a larger decrease in the R and S wave amplitudes after ASA.

The most noticeable ECG change was the appearance of new conduction disturbances. The most common conduction disturbance seen after ASA was a RBBB. Nevertheless, another noticeable conduction disturbance was an AV block (1st degree). Individuals over the age of 60 and females were more likely to develop an AV block (1st degree).

This study displayed noticeable changes in the ECG parameters, which mainly correlated with previous studies. Therefore, the results of this study may have important implications for the use of 12-lead ECG in monitoring LVH patients undergoing ASA.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my heartfelt appreciation to God for guiding me throughout this journey of completing my diploma work, and for providing me with the strength and patience to overcome the challenges that I faced along the way.

Secondly, I would like to express my sincerest gratitude to my thesis supervisor, Dr. Kaspars Kupics, for his continuous guidance and support throughout my research. His expertise and encouragement have been vital in shaping my diploma work and helping me to achieve my goals.

I would also like to thank Paul Stradinš Clinical University Hospital cardiology resident, Dr. Santa Strazdiņa, for her invaluable feedback and guidance. Her efforts and perspectives have greatly enriched my diploma work and helped me to stay motivated and focused.

I am also grateful to my colleagues and family for their unwavering support and inspiration throughout the whole diploma work process. Their encouragement, advice, and feedback has been the foundation upon which my diploma work has been built.

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APPENDIX

Appendix 1. List of abbreviations

ASA = alcohol septal ablation

AV = atrioventricular

ECG = electrocardiogram / electrocardiography

ECHO = echocardiogram / echocardiography

HCM = hypertrophic cardiomyopathy

HOCM = hypertrophic obstructive cardiomyopathy

IVS = interventricular septum

LAD = left anterior descending artery

LV = left ventricle / ventricular

LVEDV = left ventricular end-diastolic volume

LVH = left ventricular hypertrophy

LVM = left ventricular mass

LVOT = left ventricular outflow tract

MI = myocardial infarction

MRI = magnetic resonance imaging

RBBB = right bundle branch block

DOCUMENTATION PAGE

This Diploma Thesis „12-Lead ECG in left ventricular hypertrophy patients before and after alcohol septal ablation" was developed at the Faculty of Medicine of the University of Latvia.

With my signature, I attest, that this research has been carried out without aid or assistance. Used information was obtained only from indicated sources and the electronically submitted copy of this diploma work complies with printout.

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The diploma thesis was submitted to the Faculty of Medicine on: 10.5.2023

(date)

International students' coordinator, _____

(signature)

The diploma thesis is presented at the meeting of the State Examination Commission of Higher Professional Study Program „Medicine"_____2023. Protocol No. _____

Secretary of Commission: _____ _____

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