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THE GENDER GAP IN THE DIAGNOSIS AND TREATMENT OF HEART DISEASE

Bachelor's Thesis
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ABSTRACT

Elina Lassila: The Gender Gap in The Diagnosis and Treatment of Heart Disease
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Heart diseases have historically been considered male diseases, even though they are also the leading cause of death for women. The prevalence of cardiac diseases in women is lower than in men, but the mortality rates of women have seen to rise above men. The difference cannot only be explained by the longer life expectancy of women.

This thesis is a literature review that aims to find out how the gender gap between male and female patients affects their diagnosis and treatment of heart disease. This paper also discusses how the biological differences between sexes influence male and female heart functions, and how the differences could be considered more thoroughly by medical professionals to offer better health care for everyone regardless of their sex.

The anatomy and electro-physiology of the heart differ between sexes. Women's heart is typically smaller than male heart and has different dimensions between the heart chambers. The difference affects the heart's activity including heart rate and stroke volume. Therefore, the traditional diagnostical methods provide different results for male and female hearts.

The most common risk factors for cardiac disease include physical inactivity, smoking, obesity, high alcohol use, diabetes, high blood pressure, and an unhealthy diet. These risk factors concern both men and women, but their importance can be sex specific. For instance, diabetes and smoking are considered bigger heart disease risks for women than men. Hormonal changes during pregnancy and menopause are unique risk factors related to female heart diseases.

Heart diseases are prevented and treated with healthier lifestyle choices. Knowing the risk factors affecting an individual is an important step toward a better lifestyle and cardiac health. Medication and surgical operations are often needed for heart disease therapy. To accomplish the best results, the treatment options need to be personalised to match the patient's needs. In addition to many other things, the sex of the patient needs to be considered while making a therapy plan for the individual.

Historically speaking, most of the research work considering heart diseases has been done using male patients. The importance of sex was realised only a couple of decades ago. Even today, heart diseases are diagnosed a lot earlier in males than in females. This might be caused by the lack of specific and universal guidelines considering the sex of the patient.

The anatomical and electrophysical differences between sexes need to be taken into consideration while diagnosing and treating patients. Although the knowledge of the effect of sex on cardiac disease diagnosis and treatment is constantly rising, more research is needed to fully understand, how to surpass the existing gender gap.

Keywords: cardiac disease, coronary artery disease, heart disease, the gender gap

The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

TIIVISTELMÄ

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Sydänsairauksia on pitkään pidetty miesten sairauksina, vaikka ne ovat myös yksi naisten yleisimmistä kuolinsyistä. Sydänsairauksien esiintyvyys on naisia suurempi miespotilailla, mutta naisten kuolleisuus on useissa tapauksissa suurempi. Tätä eroa on yritetty selittää naisten korkeammalla eliniänodotteella, mutta se ei yksinään riitä selittämään sukupuolten välisiä eroavaisuuksia.

Tämä kandidaatintyö on kirjallisuuskatsaus, jonka tarkoituksena on selvittää, kuinka sukupuolten välinen epätasa-arvo vaikuttaa sydänsairauksien diagnostiikkaan ja hoitoon. Lisäksi työ käsittelee miesten ja naisten sydänten välisiä biologisia eroja, ja kuinka ne voitaisiin huomioida paremmin terveydenhuollossa, jotta jokaiselle potilaalle taattaisiin sukupuolesta riippumatta yhtä laadukas hoito.

Sydämen anatomia ja elektrofysiologia eroaa sukupuolten välillä. Naisen sydän on tyypillisesti miehen sydäntä pienempi ja omaa erilaiset mittasuhteet. Naisilla on myös miehiä matalampi verenpaine ja heidän sydämensä iskutilavuus on pienempi. Tämän takia perinteiset diagnostiikkakeinot eivät anna yhteneviä tuloksia miesten ja naisten sydänongelmien ratkaisuun.

Sydänsairauksien yleisimpiin riskitekijöihin kuuluvat liikunnan puute, tupakointi, ylipaino, alkoholin liikakäyttö, diabetes, korkea verenpaine sekä epäterveelliset ruokailutottumukset. Nämä riskitekijät koskevat sekä miehiä että naisia, mutta niiden painoarvo on sukupuoleen sidonnainen. Esimerkiksi diabetes ja tupakointi ovat naisille merkittävämpiä riskitekijöitä kuin miehille. Raskaus ja vaihdevuodet puolestaan ovat esimerkkejä riskitekijöistä, jotka vaikuttavat naispotilaisiin.

Sydänsairauksia voidaan ehkäistä ja hoitaa elintapamuutosten avulla. Paremman sydänterveyden saavuttamiseksi ja elintapojen korjaamiseksi on tärkeää tunnistaa potilaaseen vaikuttavat riskitekijät. Elintapamuutosten lisäksi lääkitys ja kirurgiset operaatiot ovat usein tarpeen sydänsairauksien hoidossa. Jotta saavutetaan parhaat tulokset, hoidon tulee vastata yksilön tarpeita. Yksilöllisen hoitosuunnitelman onnistuminen vaatii sukupuolen huomioimista.

Suurin osa tähän mennessä saavutetusta tutkimustiedosta on kerätty käyttäen pääasiallisesti miespotilaita. Sukupuolen vaikutus sydänsairauksiin huomatiin vasta hiljattain. Vielä tänäkin päivänä miesten sydänsairaudet diagnosoidaan huomattavasti naisia varhaisemmassa vaiheessa. Tämä voi johtua sukupuolet huomioivan diagnostiikka- ja hoitokriteeristön puutteesta.

Sydämen anatomiset ja toiminnalliset erot tulee huomioida potilaiden diagnostiikassa ja hoidossa. Tietoisuus sukupuolen merkityksestä sydänsairauksia koskien lisääntyy koko ajan. Jotta sairauksiin liittyvä sukupuolten välinen epätasa-arvo saadaan korjattua, tarvitaan lisää sukupuolierot huomioivaa tutkimustietoa sekä diagnostiikka- ja hoitokriteeristöjä terveydenhuollon ammattilaisten työn tukemiseksi.

Avainsanat: sydänsairaudet, sepelvaltimotauti, sukupuolten välinen epätasa-arvo

PREFACE

Before choosing my thesis topic, I had heard multiple examples of women being underrepresented in medical research. I had never studied the theme myself, but I was interested in finding out what kinds of aspects have an impact on one's cardiac health, and how sex-specific differences can be considered when treating patients. While doing the research for my thesis, I got to learn many new things and satisfy my curiosity about the gender gap in health care.

I would like to thank my supervisor, Jussi Koivumäki, for his guidance and quick answers to my questions during the writing process. I am also grateful to have friends and family members that supported and encouraged me when I felt like giving up.

Tampere, 25 February 2023

Elina Lassila

CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

AHA	American Health Association
AP	Action potential
AV	Atrioventricular
CT	Computed tomography
CTA	Computed tomography angiography
CHD	Coronary heart disease
ECG	Electrocardiogram
GABG	Coronary artery bypass graft
ICS	Intercostal space
LV	Left ventricular
NHLBI	The National Heart, Lung, and Blood Institute
OPCAB	Off-pump coronary artery bypass
SA	Sinoatrial
SVR	Systemic vascular resistance

I	Current
R	Resistance
V	Voltage

.

1. INTRODUCTION

Heart diseases are a range of diseases that influence the heart. The diseases and their symptoms vary a lot based on which part of the heart the disease is damaging. Heart diseases can cause changes to the heartbeats, damage the vessels, and the heart muscle physically, build up plaque that blocks the veins and disturbs the blood flow, or damage the heart valves. Many hear diseases can be prevented, and even treated, with a healthy lifestyle including a proper diet. [1]

Both gender and sex are important factors when looking at how women are getting treated in the health care system. The gender typically influences the lifestyle of the individual, which is a big part of the explanation considering multiple health conditions. Gender also has an impact on the employment of the person, and it, therefore, affects drug costs and the individual's access to care. Biological influences on the other hand are acting on factors such as sex, race, age, hormonal status, and co-existing conditions. Even though it is important to remember the environmental and lifestyle factors affecting the health of an individual, this paper concentrates on the biological factors, in this case, sex and its effects on cardiac disease. [2]

The terms gender and sex are often used in the spoken language to describe the same thing. It is however important to understand the difference between these two terms. The word sex is used to describe the biological differences between generally males and females that can be determined by their chromosomes, hormones, and anatomy. On the other hand, gender is used to describe the individual's way to see themselves. It is understood as a spectrum between man and woman, leaving people to be able to define themselves freely without using the pre-defined categories of male and female. [3]

Cardiovascular diseases have been the leading cause of mortality for the past decades all over the world. Even though the matter concerns both men and women, in general, cardiac diseases are considered men's diseases. However, cardiovascular diseases are one of the leading causes of death in females as well. Although the electrophysical functions of the heart differ between the two sexes, the research work about cardiac diseases is done mainly using Caucasian male test subjects. Therefore, female patients suffering from cardiac diseases will get misdiagnosed or not diagnosed at all and receive insufficient treatment for their condition.

Even though the prevalence of cardiac diseases seems to be lower in women, the mortality rates of women have seen to raise above men. Explaining the high female mortality with their longevity can seem convenient, but it does not explain the situation properly: cardiac disease mortality has been decreasing for both young and old men. At the same time, the death rates in older women are decreasing but increasing in younger females. Ischemic heart disease and heart failure are great examples of heart conditions that are more diagnosed in men than women. Yet more women die from these diseases. [4]

Even though the mortality rate of women considering cardiac diseases is every year higher than the mortality rate of men, when the numbers are set in proportion to the age of the patients, the mortality of men rises above women. Also, the rate of sudden cardiac death seems to be twice as big in men than in women [5]. Regardless, the significance of sex differences in cardiac disease cannot be underestimated any longer.

The differences between a male and a female heart and their functions have been discovered relatively late and the problem has only been taken into consideration within the past three decades. The lack of research on women's health issues was addressed for the first time in 1985 in the Women's Health magazine. This caused a trend of focusing more the female biology in both the diagnosis and treatment of different health concerns. In 1994 the NIH guidelines stated that women need to be considered in all research about human subjects, and in 2011 American Heart Association (AHA) published guidelines on how to effectively prevent cardiac diseases in women. [6] In addition to these, the increased amount of personalized treatment methods has expedited the acknowledgment of sex differences in disease diagnosis and treatment and has therefore made the world realise the importance of the role that sex plays in disease research.

2. BACKGROUND

2.1 The Structure of the Heart

The heart is an organ located in the chest cavity that supplies blood, and the oxygen it is carrying, into all parts of the body. A partition called a septum divides the heart into left and right half that are again divided into two chambers. The upper two chambers are called atria and the lower two ventricles. The chambers are protected by three heart walls that are from the outermost to the innermost layer epicardium, myocardium, and endocardium. The whole organ is surrounded by a double-walled fluid-sac called pericardium. The main function of the heart is to produce electrical impulses that cause the heart muscle to contract and blood to keep circulating. [7]

The natural pacemaker called sinus node controls the heart rhythm by sending an electrical signal to start the heartbeat. The signal moving over the atria causes the heart to contract. This leads to the blood flow to the lungs or the rest of the body depending on the contracting chamber. Normally, when the signalling process is working as it should, the heart beats at a rate of 60 to 100 beats per minute. [8]

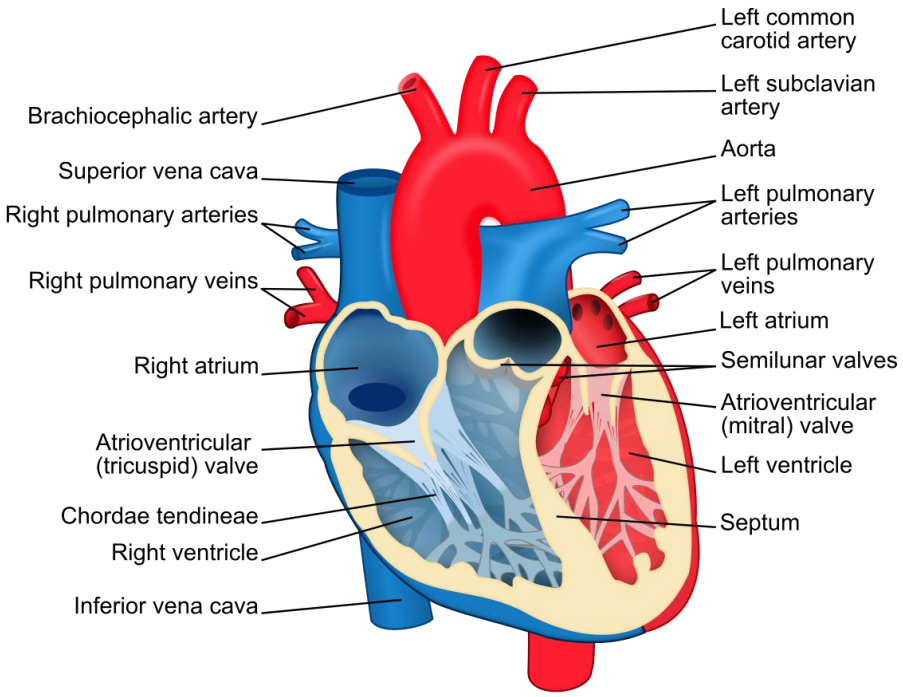

Figure 1. *The structure of the heart [9]*

The location of the heart chambers, valves, and the surrounding arteries and veins can be seen in figure 1. Atrioventricular (AV) valves called tricuspid valves between the right atrium and right ventricle and mitral valve between the left atrium and left ventricle let the blood flow into the heart. Semilunar valves are the ones allowing the blood flow out of the heart to the aorta and pulmonary arteries. During the contracting phase of the heart (systole) the ventricles pump the blood forward, out from the heart. Semilunar valves open allowing the blood to flow. Simultaneously tricuspid and mitral valves close preventing the blood to flow backward from the ventricle to the atrium.

During systole, the blood builds up to the atriums. When the ventricles are emptied, the semilunar valves close and AV valves let the blood to flow from the atriums to the ventricles. The phase, where the ventricles are filling with blood, is called diastole. Diastole can be divided into two phases. The early diastole is caused by the pressure difference between the atrium and the ventricle and the energy-requiring active expansion of the ventricles. Later in the atrial phase the atrium contracts and therefore furthers the forward blood flow. [10]

The cardiac cycle refers to all the mechanical and electrical functions that occur in a heart during one heartbeat. For a heart rate of 75 beats/min, the cardiac cycle lasts for 0.8 seconds. [10]

The cardiac cycle can be divided into phases in multiple different ways. When it comes to the division based on the ventricles and their valves, the phases can be separated into 4 parts:

1. *Inflow phase* refers to the state where the AV valves are open, and the ventricles are filled with blood.
2. During *isovolumetric contraction* all the valves are closed, and the blood is not flowing.
3. During the *outflow phase* the pulmonary and aortic valves are opened and the blood flows out of the ventricles.
4. *Isovolumetric relaxation* is the last phase, where all the valves are closed again, and the ventricles are in a relaxed state.

Blood pressure refers to the force the heart uses while pumping blood inside a body. While measuring the blood pressure, two values are taken. The first number represents the top pressure during the systolic part of the cardiac cycle. This so-called systolic pressure ranges between 90 mmHg and 120 mmHg in a healthy adult. The bottom number,

diastolic pressure ranges between 60 mmHg and 90 mmHg. Systemic vascular resistance (SVR) describes how much vascular resistance the heart needs to overcome while pumping the blood. SVR is commonly analysed by health care professionals since it gives important information about the blood viscosity and length and diameter of the blood vessel. [10]

2.2 The Electrical Functions of the Heart

The electrical functions of the heart are the responsibility of multiple different cardiac tissue types. The pacemaker activity refers to the time-dependent and spontaneous depolarisation of the cell membrane. This function is carried out by three kinds of tissues, the SA node, the AV node, and the Purkinje fibres. The cardiac cells ten do be quiescent unless an action potential is caused by the pacemaker activity. The action potential (AP) propagating throughout the heart causes a continuum of events which include atrial muscles expelling the blood from the atria, and ventricular muscles expelling the blood from the ventricles. All the mentioned tissues contribute to the electrical properties of the cardiac system, and lead to a heartbeat in a healthy, normally functioning heart.

APs in the heart are different than the ones that can be found elsewhere in the body. They originate in the right atrium, more specifically in the sinoatrial (SA) node. The cells in the SA node depolarize instinctively causing action potentials at the rate of 60 to 100 times per minute when the person is resting. This so-called intrinsic pacemaker activity is modulated by both parasympathetic and sympathetic neural input.

The cardiac APs conduct from cell to cell through electrical synapses, gap junctions. The signal is carried further to the surrounding cells similarly than in nerves through an axon, which can be seen in figure 2. The signal leaves from the SA node and conducts from cell to cell till it reaches the right atrial muscle. From there it spreads to the left atrium and arrives at the atrioventricular (AV) node. Finally, the signal reaches the His-Purkinje fibre system, which is a network of cells that transmits the impulse to the muscles of the right and left ventricles. [11]

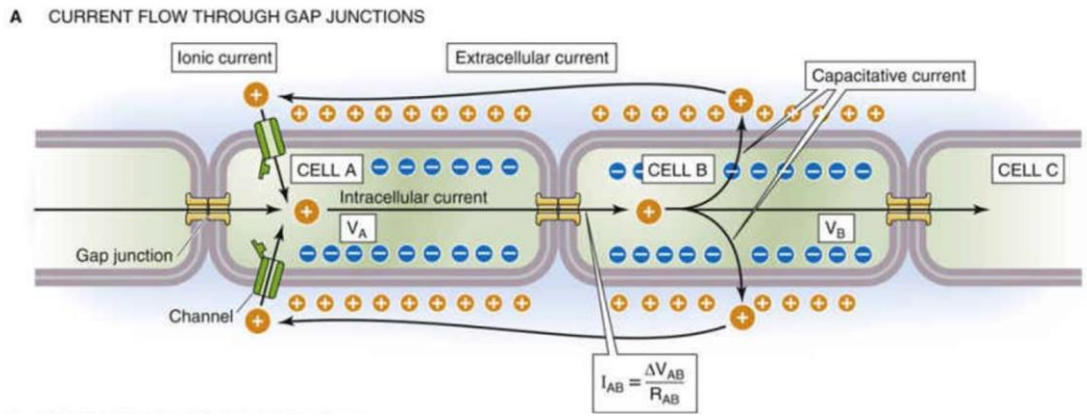

Figure 2. *The current flow through gap junctions in the heart [11]*

The resistance of the connecting gap junction and the voltage between the cells define the electrical influence of one cardiac cell. The flow between cell A and the adjacent cell B can be calculated from the formula

$$I_{AB} = \frac{V_A - V_B}{R_{AB}} = \frac{\Delta V_{AB}}{R_{AB}},$$

where the ΔV_{AB} is the voltage difference between the cells A and B, and R_{AB} is the resistance between then. [11]

Cardiac APs can be divided into 5 different phases, whose shape and duration vary depending on the location of the AP. The variations are caused by differences in the myocytes found in the cardiac system. Cardiac APs consist of four membrane currents, that are voltage-gated and time-dependant:

1. The fast-depolarising phase in the cardiac muscles and Purkinje fibres is caused by the Na^+ current (I_{Na}).
2. The fast-depolarising phase in the SA and AV nodes is caused by the Ca^{2+} current (I_{Ca}).
3. The K^+ current (I_K) causes the repolarising phase in all cardiomyocytes.
4. The pacemaker activity in SA and AV nodes and Purkinje fibres is caused by the pacemaker current (I_f).

In addition to these currents, multiple other currents and two electrogenic transporter molecules can be found in the channels of the heart cells interfering with cardiac functions.

The 5 phases of the APs are defined by the membrane potential (V_m) changes during the cardiac AP:

1. The upstroke of the AP is called phase 0. Upstroke caused by only the I_{Ca} current is slow, but when both I_{Ca} and I_{Na} are responsible for it, it's fast.
2. The rapid repolarisation of the AP is called phase 1. This phase doesn't always exist and is caused by almost complete inactivation of I_{Na} and I_{Ca} currents.
3. The plateau phase of the AP is named phase 2. The continuous entry of Ca^{2+} or Na^{+} ions through the ion channels is the main reason behind this phase.
4. The repolarisation component of the AP, phase 3, is caused by the current I_K.
5. During the phase 4, the V_m is called the diastolic potential since this phase forms the electrical diastolic phase of the AP. In the nodal cells of SA and AV, changes in the I_K, I_{Ca}, and I_f currents create pacemaker activity. In Purkinje fibres, the activity is caused by I_f only. During this phase, the cardiac muscles do not have any time-dependent currents.

Na^{+} is the largest current in cardiac APs in atrial and ventricular myocytes and Purkinje cells, since the membrane can include up to 200 Na^{+} channels per square micrometre. The ventricular APs can be considered starting from the phase 4 (figure 3), where the membrane is in the resting potential of $-90\ mV$, K^{+} channels are open, and Na^{+} and Ca^{2+} channels closed. The fast Na^{+} channel activation happens during the phase 0, when the local depolarisation in response to the action potential in the neighbouring cells triggers the fast Na^{+}channels to open rapidly within 0.1 to 0.2 ms. The current depolarises the transmembrane potential opening Ca^{2+} channels at $-40\ mV$ and continues raising the potential till it reaches a little over 0 mV and the Na^{+} channels close. [11]

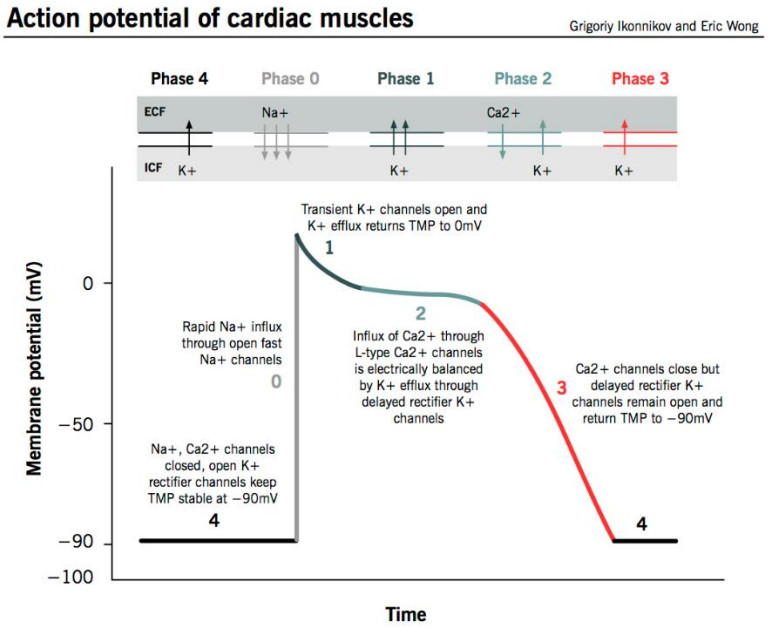

Figure 3. *The phases of a ventricular AP [12]*

Phase 1 starts from a slightly positive membrane potential. Since the K^+ channels are still open, the positive ions are flowing out of the cell lowering the transmembrane potential to $0\,mV$. However, the open Ca^{2+} are still running inward down the concentration gradient. During phase 2, both Ca^{2+} and K^+ are flowing down their concentration gradient but to opposite directions. This keeps the membrane potential balanced a little below the $0\,mV$. Phase 3 starts, when the Ca^{2+} channels gradually close and K^+ exiting the cell outweighs the inward flow of calcium. Therefore, the membrane potential is descending back to the $-90\,mV$ and the cell is back to the resting potential at phase 4. [11]

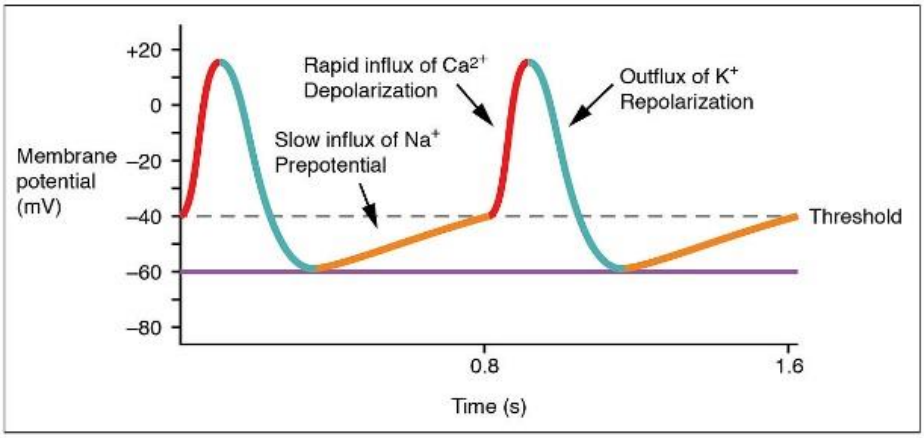

Figure 4. *Pacemaker AP [13]*

3. CARDIAC DISEASES

The most common heart diseases include congenital heart disease, coronary artery disease, dilated cardiomyopathy, pulmonary stenosis, and heart arrhythmia. Most of the traditional risk factors for cardiac diseases including lack of exercise, smoking, obesity, high use of alcohol, diabetes, high blood pressure, and an unhealthy diet are the same for males and females, but there are some unique factors, that can be considered sex specific. For example, smoking and diabetes tend to be a bigger risk for females. Therefore, diagnostics and therapy should be done taking sex into account. Yet the research done on cardiac diseases is not representing women, and too often the published results aren't reported considering the sex of the patient, which makes it difficult to carry out personalised medicine properly. [14]

3.1 Diagnostics

It is normal, that the heart rhythm changes when the person is for example sleeping or exercising because the functions require a different amount of oxygen supply. Heart arrhythmia, however, is a condition, where the heart beats irregularly because the electrical signals of the heart do not coordinate as they should. The condition of the heart beating too fast is called tachycardia, and the opposite of it, when the heart beats too slow or just irregularly, is called bradycardia. Mild arrhythmias are usually harmless for the patient and might just leave them feeling that their heart is racing. More severe arrhythmias might cause even lethal injuries. [15]

Ischemic heart disease is one of the most common causes of mortality in the developed world. Ischemia refers to insufficient blood circulation which leads the organ to lack oxygen supply. Ischemic heart disease that is also called coronary heart disease (CHD) refers to heart problems where the coronary arteries have narrowed typically because of atherosclerosis, a build-up of plaque. When the heart is not receiving enough oxygen, the patients typically feel discomfort in their chest, shoulder, back, or jaw. This symptom is called angina pectoris, and it is typical in CHD patients, but can also be related to other heart conditions. If the blood flow to the heart stops completely, the cells in the heart die, causing a myocardial infarction (MI) which is also known as a heart attack. [16]

Heart failure refers to a condition, where the heart muscle is unable to pump as much blood as it should. A typical symptom of heart failure is shortness of breath that is caused by the blood backing up from the heart and building up to the lungs. Other symptoms of

the condition include fatigue, leg swelling, rapid or irregular heartbeat, fluid build-up especially in the stomach area, and nausea or lack of appetite. Usually, heart failure is caused by an underlying heart condition such as CHD which weakens the heart gradually and eventually leads to heart failure. Also, obesity, diabetes, faulty heart valves, damage in the heart muscle, high blood pressure, and other diseases can be heart failure risk factors. [17]

Many diagnostic methods are used to diagnose cardiac diseases. Electrocardiogram (ECG) is a quick method to monitor the rhythm and the electrical signals of the heart, and it is very commonly used to make diagnostics. It allows the interpretation of the electric functions of different areas of the heart. ECG is measured through electrodes that are specifically positioned on the body using typically a 12-lead system (Figure 5).

The 12-lead way of ECG monitoring requires the placement of 10 electrodes. 4 of them are placed on the limbs and 6 on the chest of the patient. The limb electrodes are called RA (right arm), LL (left leg), LA (left arm), and RL (right leg). The electrodes on the chest, more specifically on the precordium, are called V1, V2, V3, V4, V5, and V6. V1 is placed in the 4th intercostal space (ICS) on the right margin of the sternum, V2 is placed in the 4th ICS but on the left margin, V4 in the 5th ISC, V3 between the V2 and V4 electrodes, V5 in the 5th ICS on the anterior axillary line, and V6 in the 5th ISC as well but on mid-axillary line as can be seen in figure 2. The electrodes V4-V6 are on the same level as each other. The system monitors the 12 leads called V1-V6, I, II, III, aVR, aVF, and aVL. [18]

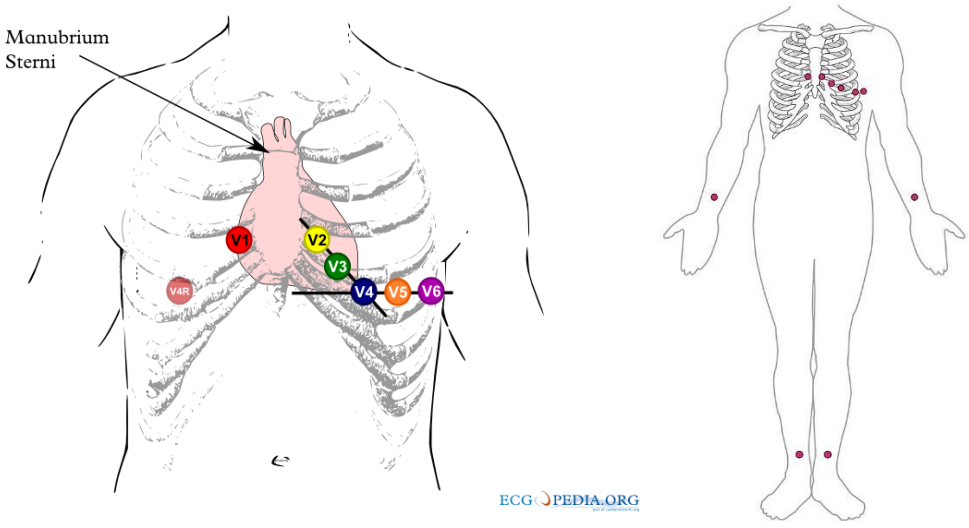

Figure 5. *The placement of ECG electrodes [19] [20]*

ECG can tell the physicians many things considering the heart. Normal ECG contains the P wave, QRS complex, T wave, and usually also the U wave. The spaces between the waves are called intervals and include the PR interval, QT interval, and ST interval. The flat areas in the ECG figure are called PR and ST segments.

The P wave represents the contraction of the left and right atriums, the T wave talks about the relaxation of the ventricles, and the U wave is seen with patients that have low blood potassium levels. The QRS complex is the most conspicuous part of the ECG figure and represents the contraction of the ventricles. The Q wave is a small negative wave in comparison to the big positive R wave. S wave is typically a little bigger than the Q wave and negative. PR interval represents the time between the atrium and ventricle contraction, whereas the QT interval represents the time period including the ventricle contraction and relaxation. [18]

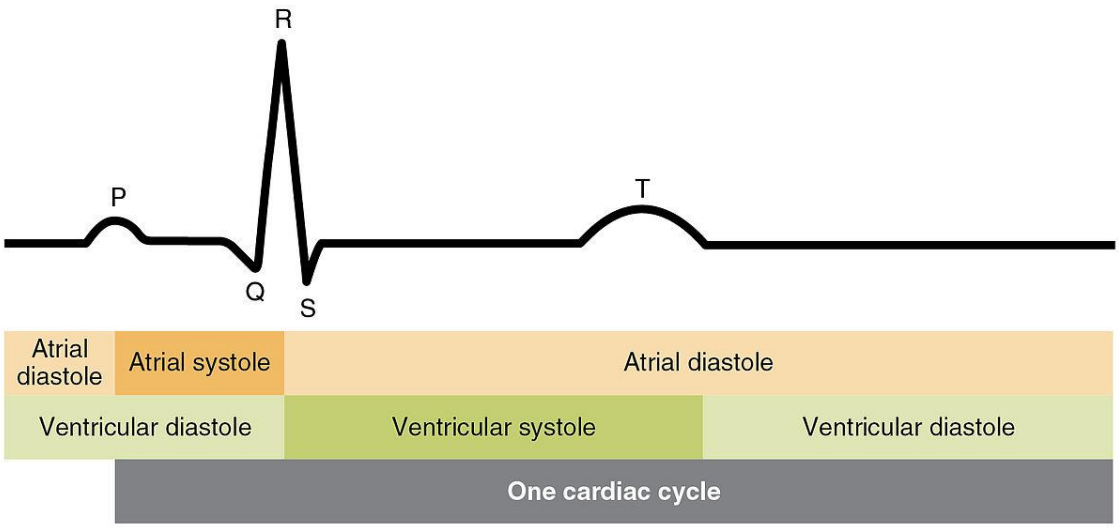

Figure 6. *Normal ECG waves [21]*

Exercise ECG test is used to evaluate the heart's ability to respond to stress and exercise. It can be used as a diagnostic tool for coronary artery disease or a way to determine how much the patient can exercise after recovering from a cardiac event like myocardial infarction. During the test, the patient is usually exercising either on a stationary bike or a treadmill. The difficulty level of the exercise is increased until a target heart rate is achieved, or the patient cannot continue due to tiredness, chest pain, shortness of breath, or other symptoms. The ECG is measured at different levels on the way to the final heart rate. [22]

Coronary angiography is a very commonly used way to search for blockages in the vessels. The procedure is typically performed if the patient is suffering from unstable angina, chest pain, inexplicable heart failure, or aortic stenosis (narrowing of the aortic valve that causes problems in the valve opening). During coronary angiography, dye is injected into the patient's bloodstream through a thin plastic tube. The flow of the dye through the heart is inspected from an X-ray screen. The results are evaluated to see if the blood flow in the cardiac system seems normal, but it doesn't give specific information on the type of abnormalities seen on the screen. [23]

Computed tomography (CT) is another diagnostical tool for heart disease and can be used for viewing the heart. During the CT scan, the organ is pictured with an X-ray from multiple different angles. The computer composes the final image of the separate shots. CT scans give important information about the heart anatomy, condition of the vessels, and blood circulation in the cardiac system, which can be used when diagnosing the patient.

Calcium-score screening scans, coronary computed tomography angiography (CTA), and the CT scan of the whole body are forms of computed tomography that can be used for cardiac disease diagnostics. Calcium-score screening detects calcium in the arteries and can be used to locate atherosclerosis even before the patient notices any symptoms. CTA gives information on a plaque or fatty build-up in the arteries by forming a 3D image of the moving heart. The test is done in approximately 10 minutes and provides detailed information on the heart with less radiation exposure than the traditional CT scan. The total body scan can also be used since it gives additional information from the lungs and pelvis, but it is not as accurate as CTA, since it cannot give a specific location for the diseased part of the cardiac system. [24]

3.2 Therapy

The therapy options for heart disease depend a lot on the diagnosis and condition the patient is suffering from. Lifestyle plays a big role in overall health but also cardiac illness treatment. Usually, heart diseases can be treated or even prevented by healthy lifestyle choices considering for example food and exercise. Heart health can be improved by maintaining a healthy diet, controlling one's blood pressure, treating possible diabetes, exercising, controlling one's weight, sleeping enough, managing stress, and avoiding smoking [15]. Health is a combination of many things, and the same lifestyle choices will not work for every individual, therefore the instructions are just indicative.

In many cases, a lifestyle change is not enough to treat heart disease. Therefore, medication may be needed to control the condition, its symptoms, and possible complications. Medication is always chosen considering the individual's other health conditions and the specific diagnosis. Some heart conditions cannot be treated without surgery or other procedures in addition to medication. Even if the heart disease is treated with medication or surgical procedures, maintaining a healthy lifestyle is a crucial part of heart disease therapy and cardiac rehabilitation. The success of the therapy needs to be monitored with check-up appointments for a cardiac professional. Different support groups may also further the recovery of the patient by helping with stress management and giving peer support. [1]

Coronary artery bypass graft (GABG) is a medical procedure used to treat the narrowing of the arteries in CHD. It is typically done by extracting a vessel from elsewhere in the body and using it as a graft to bypass the clogged part of the artery. [25] Coronary angioplasty or percutaneous coronary intervention on the other hand is a procedure to open the blocked arteries by inserting a balloon catheter inside the blood vessel. The procedure typically also includes placing a stent, a wire mesh tube that prevents the artery from narrowing again. [26]

4. DIFFERENCES BETWEEN GENDERS

4.1 Sex Difference in Cardiac Electrophysiology

The human heart differs between the sexes. The difference can be seen even after considering the size difference between average men and women. A normal male heart is 15-30% bigger than a female heart and beats 3-5 times less per minute. Scaling the heart size to lean body mass does not eliminate the differences but can be used to make them smaller. Both men and women have approximately the same cardiac output, even though women's hearts have smaller dimensions in their left ventricular (LV). Due to the smaller LV chambers, the stroke volume of women is smaller than men, but the same cardiac output is reached since women have a higher resting heart rate. [27]

In addition to the heart rate, the woman's heart has a higher stiffness speaking of systolic and diastolic left ventricular elastance. The stiffness also increases more with age in women than in men. Another component increasing with age is the LV ejection factor, which also increases more in women. However, the amount and size of cardiomyocyte cells decrease more when it comes to women's hearts. At birth, both men and women have about the same number of cardiomyocytes. [28]

Cardiac electrophysiology includes all the electrical activity happening in the cardiomyocytes, the contractile cells of the cardiac muscle, that are the backbone for the muscular contraction of the heart. Both research work and daily patient care suggest that there are clear sex differences in cardiac electrophysiology and arrhythmia. The reasons behind these differences are still to be studied, but they seem to be related to the different gene expressions and ion channel functions caused by estrogen, testosterone, and other hormones. The sex differences can be seen in the ionic currents, ventricular AP, and ECG traces that are seen in figure 6. Men are generally at a higher risk of early repolarisation, Brugada syndromes, and idiopathic ventricular fibrillation when women are the target of for example long QT-associated arrhythmias. [5]

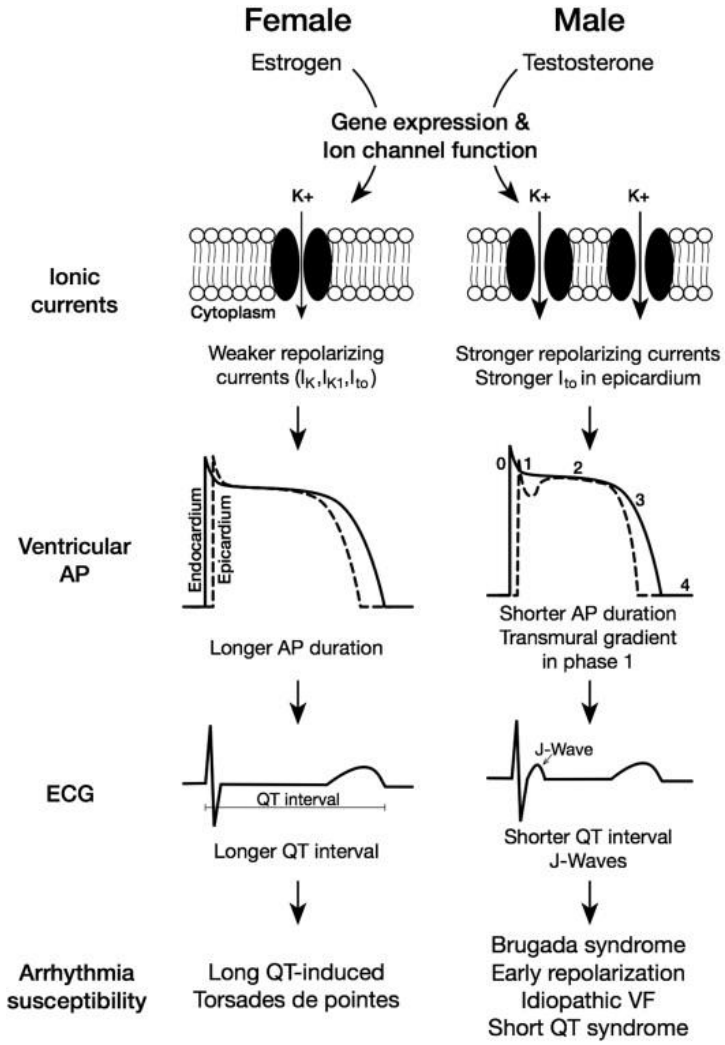

Figure 7. *Hormonal effects on the sex difference in cardiac functions [5]*

The difference in ventricular repolarisation is one of the most studied sex differences in cardiac disease research. The characteristics in a male heart include early repolarisation, J-point elevation, and bigger ST slopes. In women, longer QT, and corrected QT intervals independent of autonomic modulation are typical. The sex differences before puberty are poorly known, but in adults, these differences seem to be comparable to hormone-mediated differences.

Due to a pathway difference between sexes, women also bear a higher risk of AV node re-entrant tachycardia and focal atrial tachycardia whereas men have a higher risk of suffering accessory pathway tachycardias and asymptomatic pre-excitation that signifies an early activation of the ventricles caused by the impulses in accessory pathway bypassing the AV node. The reason behind these so-called supraventricular arrhythmias is still unknown.

Considering the specialized electrical system, women have been shown to have a greater SA node automaticity compared to men. This leads to a shorter sinus cycle length with a higher heart rate, and shorter corrected recovery time for the SA node. During pregnancy, women's heart rate, and pacemaker current density also increase. Women's AV node also differs from men, and it is considered to be functioning more effectively because of the shorter PR and AH intervals, refractory period for the AV node, the Wenckebach cycle length. Female QRS duration and HV intervals are also shorter than the ones in males. [5]

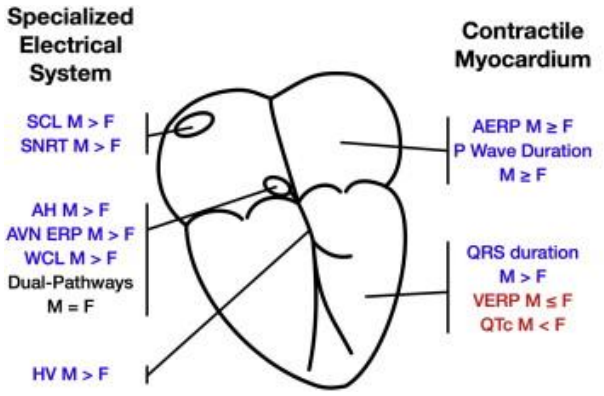

Figure 8. *Sex differences in cardiac electrophysiology. [5]*

The difference in ECG results between men and women was known already in the 1960's, when the normal standards were shown to lack logic while some of them were portraying only men and others both biological sexes. This caused discriminative value in the interpretation of the ECG results. Already during a young age, the heart functions seen from the ECG vary between boys and girls leading to a longer QRS complex duration with boys' hearts. During adulthood, the difference can also be seen in the QT interval and ST amplitudes. It is important for physicians to know the main differences between sexes for them to make suitable diagnoses for the patient. [29]

The biggest difference between the sexes can be seen in the QRS complex. QRS complex represents the depolarization of the ventricles and normally lasts from 70 to 110 seconds in adult hearts. The QRS complex doesn't only depend on the sex but also on the age of the patient. The mean left ventricular mass is bigger in males than in females which leads to larger electrical signals in males. Therefore, the QRS voltages are also higher when it comes to male patients. The female hearts take a longer time between the contraction and relaxation which can be seen in a longer QT interval in the ECG graphs.

The difference between the S-L index can be seen especially in young adults, but it lessens with age. Nonetheless, the index is much higher in young males than young females leading to a difference from a maximum of 5.5 mV in males and 4.2 mV in females based on a Nigerian study. Usually, cardiac disease patients are older than 50 years, and the ECG results are quite accurate even without the S-L index correction. To avoid false diagnostics of cardiomyopathy in young patients, the S-L index should be age and sex corrected. [29]

Besides differences, the ECG results between sexes also have similarities. The P wave is the first positive spike in normal ECG. It represents atrial depolarisation and lasts normally less than 0.12 seconds. The highest P wave amplitudes can be seen in the II and aVF leads, and the normal upper limit of 0.25 mV is generally the same between men and women. The adult P wave duration is usually considered to be 120-140 ms at maximum for both sexes. [28]

4.2 Sex Difference in Diagnosis and Treatment

Until the last 20 years, any heart disease was considered to be a male disease. It was not understood that the risk factors and symptoms of heart conditions vary between the sexes. Women were experiencing abnormal heart disease symptoms and they were sent home with the wrong diagnosis. The female symptoms might have been diagnosed as emotional distress or the result of the vivid imagination of the female sex. In addition to the underestimation of their symptoms, females were not equally represented in clinical trials. [30]

Gender bias in heart disease has a long history. In 1768, a British medical professional, William Heberden described angina pectoris as a symptom he had seen in hundreds of males but only a couple of women [31]. In 1960, AHA was having a conference and telling women how to help their husbands cope with heart diseases. [32]

The first gender-specific recommendations for heart disease treatment were published in 1999 by AHA [33]. The publication educated the readers on the sex-specific risk factors and how to spot female heart disease early enough. These days the importance of women taking part in clinical trials is also taken into consideration better, since the biological differences between the male and female hearts are known more thoroughly, and it is widely acknowledged that the sex of the patient matters. [34] [35]

The advocation for better consideration of females in health care has not only considered heart diseases. The gender-based differences have been seen in all parts of the

healthcare system. “The bikini approach” to women’s health is a way of describing how women’s health was for a long time considered to differ from males only from the body parts that a bikini typically covers [36]. Women’s health was mainly concentrated on reproductive health causing a gender bias in health care. Especially menopausal years of women’s health were very poorly studied since the research tended to concentrate on pregnancy and ages when women are still able to bear children. [37]

Since the importance of studying especially women’s heart diseases was recognized, the National Heart, Lung, and Blood Institute (NHLBI) of the United States started to pay more attention to the enrolment of women in clinical trials. Many clinical trials were arranged only for women which increased the total amount of women in clinical trials even though the percentage of them in 2-sex studies wasn’t raising that much. Anyhow, the need for women in clinical trials was clear, since the sex-specific differences were acknowledged but the physicians did now know how to respond to the difference. The participation of women was also increased by the public demand for giving women more autonomy considering their own health and treatment. [37]

The data collected from cardiac disease studies carried out between the years 1965 and 1998 were analysed and the enrolment percentage of women was divided based on different heart diseases. This showed that the type of the diseases paid a big role in the number of women participating in the trials. Table 1 describes how the sex distribution of clinical trials was fulfilled considering different types of cardiac disease. When it comes to coronary artery disease and hypertension, the enrolment of women was proportionally compared to the prevalence of the disease. Unfortunately, the situation with heart failure was not as successful. [37]

Table 1. *The enrolment of men and women in NHLBI-funded clinical trials between 1965 and 1998, adapted from [37]*

Disorder	No. of Trials	Total Enrolment no.	Men no.	Women no. (%)	Prevalence (%)
Coronary artery disease	52	140,609	86,562	54,047 (38)	40
Hypertension	21	26,792	14,485	12,307 (46)	44
Congestive heart failure	6	17,349	12,922	4,427 (26)	43
Arrhythmia	11	18,822	13,411	5,411 (29)	NA
Congenital disorder	3	1,125	651	474 (42)	NA
Other cardiac diseases	2	1,113	525	588 (53)	NA
Total	95	205,810	128,556	77,254 (38)	49

*NA denotes not available. The prevalence is the estimated prevalence of the disorder among women in the general population.

The studies about the sex-specific treatment have shown that women less than 55 years are less likely to be assigned to an ECG testing while experiencing chest pain than males of the same age, even though ECG testing is recommended by AHA to be done for all patients seeking treatment while suffering from chest pain. [38] The false reading seems to occur especially in the ST intervals monitored during the exercise ECG [39]. In addition to that, the exercise ECG for women is nowhere near the accuracy of the male equivalent and is even less precise when the women reach the menopausal age [40].

The summary of “Joint British recommendations on prevention of coronary heart disease in clinical practice” introduces a risk prediction chart for the primary prevention of CHD for patients that do not yet have a major heart condition. The chart is seen in figure 9 and it compares the risk between male and female patients with and without diabetes. [41]

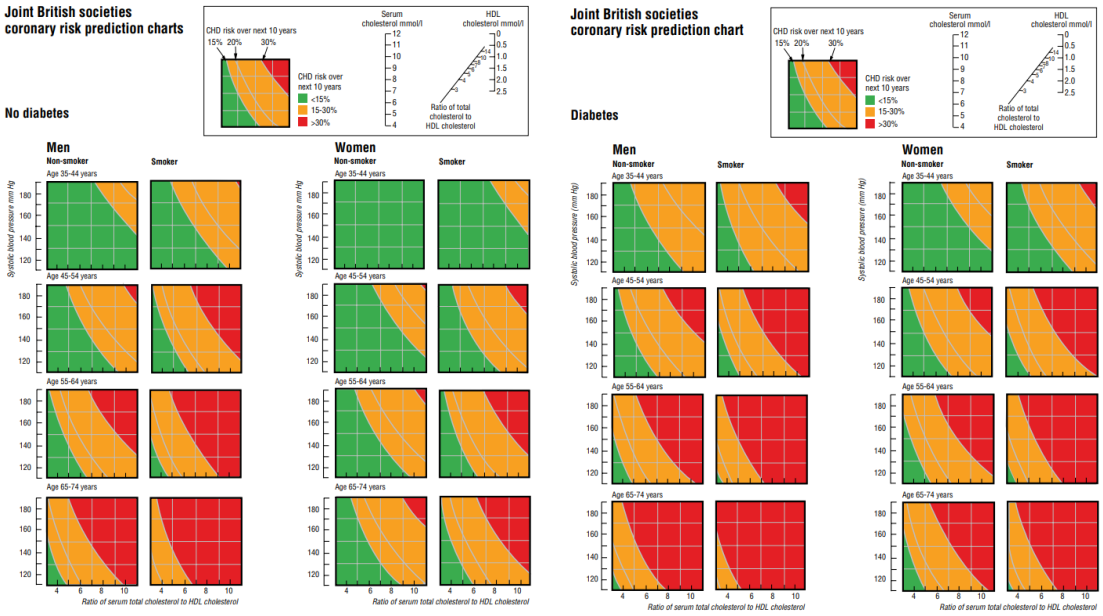

Figure 9. *Chart for coronary risk prediction [41]*

The chart can be used for very approximate forecast of the individual's risk of getting a CHD, since it does not talk about how long the individual has been smoking. The chart is concentrating on only two common risk factors and failing to recognize other aspects such as family history, overweight, pre-diabetic patients, and women's menopause and hormonal changes during it. Therefore, it does not give the most truthful picture of individual's risk for CHD and is not the greatest tool for preventing cardiac diseases.

A factor that has been proven useful for preventing cardiac diseases is to make individuals aware of the risks of getting one. The awareness of cardiac health risks and how to affect them is associated especially with preventing women from getting cardiac diseases. [42] In 2010 Lori Mosca and her colleagues collected data on modern-day cardiovascular disease awareness with a 12-year follow-up. The survey was completed by contacting 2300 women online and via telephone in 2009 and comparing the received information with the one from the year 1997. During the 12-year-period the number of women being aware of heart disease being their number one cause of death had risen approximately 20 percentage points. [42] [43]

Even though the awareness seemed to be rising, the study showed, that many women still underestimated their personal risk of getting a cardiac disease. The participants estimating themselves to be at moderate or high risk of getting a cardiac disease were more aware of how many women are affected by cardiac diseases than the ones estimating themselves in the low-risk group of falling ill. However, it was more common for

the participants to mention cardiac diseases as the most common cause of death for men than for women. [42]

The Framingham risk score estimates the risk of getting CHD within a 10-year time spam [44]. It is used as a guideline for preventing CHD and choosing the right medication for treating it. Yet, the experts are not unanimous if the score is usable for treatment decisions, since individuals getting a low 10-year risk score might still have a risk factor that will raise them into the high-risk group during a longer time interval if the risk factor is not treated. [45] Nevertheless, the risk factor can be a valid tool for forecasting the short-time risk for cardiac disease in both men and women and works as a guideline for clinical practice.

When it comes to treating cardiac diseases, medical the prevalence of different medical procedures varies between the sexes. GABG is far more common in male patients than female patients, and most of the research done about it also concentrates on men [46] [47]. Figure 10 shows the percentage of females participating in GABG studies between the years 1991 and 1999 [46]. Multiple studies show that women are more likely to die from the procedure [48] [49]. This can be seen especially in women younger than 50 years [49]. The higher mortality rate can be caused by the smaller vessel size of women leading to the surgery being more difficult. Women also tend to have more underlying health conditions than men, and their diseases are typically noticed in a more severe state [50] [51].

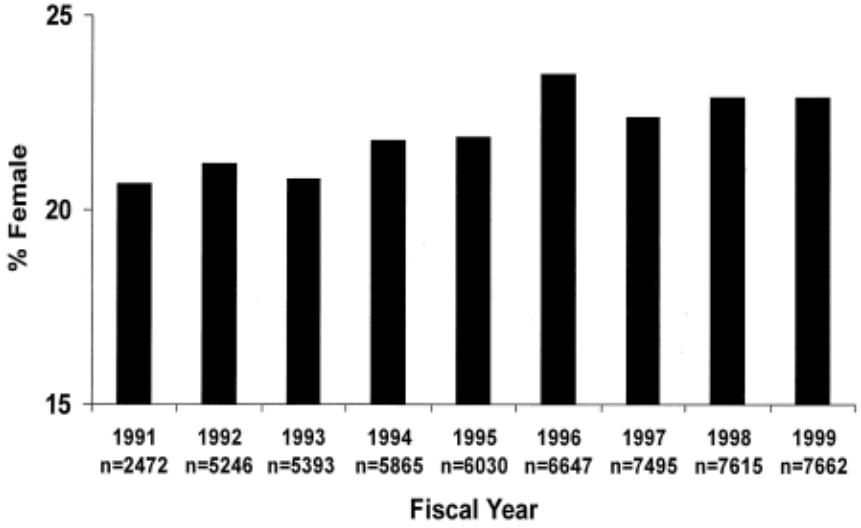

Figure 10. *The percentage of female patients in GABD procedures in Ontario between 1991 and 1999. [47]*

More research is needed to determine the cause of the higher mortality rate in women treated with GABD. Nonetheless, several new outcomes have been suggested to overcome the issue. Off-pump coronary artery bypass (OPCAB) is a less invasive version of GABD, since the procedure does not include putting the patient into cardiopulmonary bypass. In OPCAB the heart keeps beating during the surgery, while in GABD the heart is stopped. OPCAB is also said to cause less damage to the heart muscle leading to shorter hospital stay, less blood transfusions needed, and reduced risk for the patient suffering a stroke after the procedure. [52] [53]

Even though, women seem to be dying to GABD more than men, the long-term results are equally good in both sexes. In a Canadian study 54,425 GABD patients of which 12,079 were women were observed for 8 years. The 30-day prognosis after the procedure was significantly worse for women. When the data was risk-adjusted to take into consideration the older age and bigger amount of other, underlying health conditions in the female patients, the numbers between the sexes started to even out, and after one year no statistically relevant difference was seen. [47]

Heart diseases are typically treated with drugs like statins lowering cholesterol, anticoagulants preventing blood from clotting, aspirin making the blood thinner, and beta-blockers controlling the heart rate [54]. Historically, female patients have received less aggressive medication for their heart conditions [55] [56]. For example, aspirin is not as commonly used in female patients as it is in males, even though it is proven to affect positively both genders suffering a similar heart condition. [56] [57]

The study “Sex Differences in the Use of Statins in Community Practice (Circulation, 2019)” compared the medication of 5,693 patients that could have received statins for their heart condition. Women were less like to be offered the medication, but they also accepted them more rarely, than the males it was offered to. The effectiveness of the drug was found to be about the same for both men and women. According to the study, the female patients did not however believe that the high cholesterol was affecting drastically their heart health and therefore tended to refuse the medication or quickly stop using it. [55] The same misconception that the patients have might have also affected the professionals less likely to prescribe statins to women.

Regardless of the existing gender gap in the diagnosis and treatment of heart disease, evidence suggests that the progress of heart disease can be hindered in both men and women. Following clinical guidelines and recommendations can help the healthcare professionals and individuals to follow and estimate their cardiac health in order to prevent

the outbreak of serious health conditions. Not doing anything to maintain the individual's cardiac health is the greatest risk of getting a heart condition.

5. DISCUSSION

This aim of this thesis was to find out if gender gap in the diagnosis and treatment of heart disease exists between man and women. As a conclusion a clear difference was seen, but the reason behind it is not easily defined. The research about heart diseases has generally been done for male subjects, which helps to explain, why the illnesses considering women are not diagnosed as quickly and effectively as the ones considering male patients.

The medication between men and women was also seen to be different. Male patients received stronger medication after their heart disease than women. Medication affects the sexes differently due to their different bodily functions, but this does not fully explain why males receive more medication than females. Even though aspirin and statins affect both genders as well, women are less likely to be treated with them. Also, coronary by-pass surgeries and cardiac rehabilitation after treatment are done a lot more to male patients.

Due to differences in diagnosis and treatment efficiency the prognosis for women tends to be worse than for men. Women have a higher change of dying soon after experiencing heart illnesses. This can be partly explained by the higher female life expectancy: older patients tend to have additional diseases affecting their health and causing the heart condition to be more severe. However, the difference was also seen in younger women and therefore could not have been completely explained by women living longer.

The most common symptom of heart disease is chest pain for both men and women, but women do not necessarily experience this symptom as strongly as men do. Women also suffer atypical heart disease symptoms such as discomfort in the upper back, nausea, and fatigue more often than males. These symptoms aren't easily recognized as heart-related symptoms. The explanation for the symptoms might be caused by the different locations of the artery blockages leading to heart conditions. Usually, men have the blockage in the main arteries, but it is not unusual for women to have them also in the smaller ones further away from the heart.

The risk factors like smoking and diabetes were seen to affect females more than males. Also, emotional symptoms like stress and depression were noticed to affect the health of a female heart more than a male heart. Suffering from mental disease is a risk factor

because it tends to make it more difficult to maintain healthy lifestyle and follow the treatment assigned for the heart condition. Also, menopause and the lower estrogenic levels during it in addition to pregnancy complications are risk factors affecting mainly women.

Monitoring is one of the most important diagnostical methods used to diagnose heart diseases. At the moment, the used methods do not work as well for female diseases as they do for male diseases. The laboratory tests do not consider the differences between men and women well enough which is increasing the gap between the sexes.

Arranging single-sex clinical trials for only women is an efficient way of addressing some issues considering specifically women. Even though the method increases the number of women participating in heart disease research, it cannot be the solution for the lack of women in general studies considering both sexes.

When it comes to equality between the sexes and their heart disease treatment, the field is evolving in the right direction. The gender gap between the sexes has been acknowledged relatively late and more and more research on the subject is done all the time. To solve the issue, more specific and universal guidelines also considering the sex of the patient need to be created. It is also important to let the individuals know about the different risk factors and symptoms between men and women so that they can pay more attention to their personal health and seek medical help when needed.

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