Review Article

DIGITALIS PURPUREA IMPROVE OBESITY INDUCING ALTERNATION OF CARDIAC INFARCTION : A META ANALYSIS

Abstract

Patients with heart failure (HF) and atrial fibrillation (AF) who have systolic dysfunction or no systolic dysfunction are ideal candidates for first therapeutic choices that involve regulating either heart rate or rhythm. Patients with heart failure (HF) without systolic dysfunction are not ideal candidates for these first therapeutic choices. If one want to attain rate control, the consumption of a beta-blocker is virtually essential. It is conceivable to have a resting ventricular rate that is even lower than 100, which is the standard for what is considered a normal resting ventricular rate. However, this is not always the case. It is not standard practise to give nondihydropyridine calcium channel blockers in the presence of systolic dysfunction, heart failure, and atrial fibrillation all at the same time (AF). Recent arguments have centred on the possibility of a lowered efficacy of beta-blockers and the safety dangers connected with the use of digoxin in the treatment of heart failure patients who develop AF. The extremely high prevalence of overweight and obesity in today's culture represents a significant threat to the health of the population. Another health issue that has been shown to have a direct correlation to obesity and the medical conditions that are typically connected with it is heart disease (hypertension, diabetes, insulin resistance, and sleep apnoea syndrome). When a person carries excess fat around their middle, they put themselves at a greater risk of developing coronary artery disease and atherosclerosis. Obesity is linked to a number of changes in the structure and function of the heart, some of which can lead to heart failure. As a consequence of the aberrant structure of the heart, a person has a greater risk of developing atrial fibrillation as well as sudden cardiac death. However, there is a phenomenon that is known as the "obesity paradox,"

which asserts that a person who already has cardiovascular disease may potentially benefit from being overweight and having a higher body mass index. Because of advancements in cardiac imaging, it is now possible to detect structural and functional alterations in the hearts of obese persons earlier than was previously possible. In the following paragraphs, we will make an attempt to provide a high-level overview of the data that links obesity and cardiovascular disease, as well as the factors that contribute to this relationship.

Keywords: Herbal treatment, Obesity, Cardiac vascular disease, Fox Glove

Introduction

Since the first reports of the obesity epidemic appeared in the media forty years ago, rapid globalisation has taken place. It is presently assumed that one-third or more of the population of the world is either overweight or obese[1]. From 4% in 1975 to 18% in 2016, the prevalence of overweight and obesity among children and adolescents has more than tripled throughout this time period. There has been a remarkable increase in the frequency of this occurrence. The percentage of overweight or obese Americans in the United States increased from 2015 to 2020 across all age groups in the country, from 39.8% among adults to 20.6% among teenagers to 18.4% among children to 13.9% among children ages 2-5. This increase occurred across all age groups in the country[2,3]. In 2019, it was estimated that 38.2 million children younger than five years old would suffer from obesity or overweight. The accumulation of visceral white adipose tissue (WAT) is associated with an increased risk of dyslipidemia, systemic insulin resistance, hypertension, the metabolic syndrome, obstructive sleep apnea, and type 2 diabetes (T2D), in addition to atherosclerosis and cardiovascular disease[4]. It is projected that cardiovascular diseases were the cause of 17.9 million deaths worldwide in 2016, which accounts for 31% of all deaths. The heart and its associated blood vessels were responsible for the deaths of 95% of these people. One third of these premature deaths are attributable to individuals who are under the age of 70, and the majority of them take place in countries with low and intermediate incomes[5-8]. Patients with a body mass index (BMI) of 35 or less have a 30% greater probability of passing away from cardiovascular disease than those with a BMI of 35 or more, and the risk increases by another 2 to 3 times for every additional 5 kilogrammes that the patient carries. Obese people are

known to have visceral adipose tissue inflammation that persists over long periods of time (VAT)[9]. In adipose tissue, inflammation and oxidative stress lead to a reduction in the production of adiponectin and an increase in the release of pro-inflammatory adipokines and cytokines, in addition to the hunger hormones resistin and leptin[10]. The cumulative effect of all of these factors is malfunction of the diastolic chamber of the heart, decreased vascular relaxation, and increased arterial stiffness. Obesity triggers the activation of an endocrine axis known as the renin-angiotensin-aldosterone system (RAAS), which plays an essential role in the process of preventing cardiovascular bleeding. Under pathological situations, RAAS is responsible for driving structural remodelling and inflammation, two processes that are detrimental to the cardiovascular system[11]. Patients who are obese often have chronic inflammation of the visceral adipose tissue in their bodies (VAT). When there is inflammation and oxidative stress in the adipose tissue, the hunger hormones resistin and leptin, as well as pro-inflammatory adipokines and cytokines, are secreted in greater amounts, whereas the synthesis of adiponectin is suppressed. Other hormones that are secreted include adiponectin[12-16]. All of these factors contribute to dysfunction in the diastolic phase of the heart, which manifests as diminished vascular relaxation and increased arterial stiffness. In addition, obesity triggers the activation of an endocrine axis known as the renin-angiotensin-aldosterone system, which helps to stop blood loss in the cardiovascular system (RAAS)[17]. The peroxisome proliferator-activated receptor controls the expression of a large number of genes, a small subset of which are those involved in lipid beta-oxidation (PPAR). In the meantime, PPAR regulates the expression of genes that are involved in glucose metabolism, the growth of adipocytes, and the storage of lipids. Because of this process, PPARs have been identified as potentially useful pharmaceutical targets for the treatment of cardiovascular disease[18-20].

There has been a significant amount of research conducted both in vivo and in vitro to investigate the processes that are involved in the connection between obesity and cardiac injury and dysfunction. Research on obesity brought on by a high-fat diet (HFD) is conducted using a number of different animal models, the mouse being the one used the most frequently[21]. We refer to the biochemical changes that occur in a tissue or organ as biomarkers. These biochemical changes play an important part in the diagnosis and evaluation of sickness, and they also serve as surrogate endpoints in therapeutic research[22]. Research in recent years has shown that the gut

microbiota plays a significant role in human health, with effects on glucose and lipid balance, appetite, vitamin production, and critical metabolites. Since then, the gut microbiota's significance to human health has been widely acknowledged. Furthermore, both rat models of hypertension and human hypertension have linked dysbiosis in the gut microbiota to hypertension[23]. Obesity is known to cause damage to the heart, which can lead to alterations in DNA methylation. Numerous studies have found a connection between histone methylations and cardiac hypertrophy and failure. In the contexts of both pressure overload and ischemia/reperfusion, histone deacetylases, also known as HDACs, have been shown to be related with cardiac remodelling[24-27]. It has also been suggested that these enzymes play a role in the progression of fibrosis (in models of both hypertrophy and ischemic heart disease).

This issue has turned into a huge concern for the health of people all over the world as a direct result of the rising rates of obesity that can be found everywhere, including the industrialised world and the developing regions of the remainder of the planet[28]. According to the World Health Organization, just 13% of adults around the world are considered obese, while 39% are classified as overweight. Extensive evidence demonstrates that a person's likelihood of having cardiovascular disease is increased if they are overweight (stable coronary disease, acute myocardial infarction, heart failure, cardiac arrhythmias, and sudden cardiac death). People who have obesity, hypertension, diabetes mellitus, dyslipidemias, and the sleep apnea syndrome all at the same time are thought to have an increased risk of getting cardiovascular disease[29-31]. This risk is thought to be larger than the risk among people who only have one of these conditions. This is because of the fact that having a higher body mass index is related with an increased risk of developing cardiovascular disease[32]. The body mass index, also known as BMI, is a useful tool for estimating the likelihood of developing cardiovascular disease; however, it provides no information whatsoever regarding the distribution of fat in the body. In order to define the concept of "central" or "abdominal" obesity in a manner that is more accurate, new clinical tests have been developed. The waist-to-hip ratio and the abdominal circumference are two of the clinical metrics that have been developed more recently[33]. There is a correlation between having central obesity and an elevated risk of cardiovascular disease. Central obesity is measured by having a waist circumference that is greater than 102 centimetres in males and greater than 88

centimetres in women. If an individual has a waist-to-hip ratio that is 0.90 or higher in men or 0.85 or higher in women, then they are deemed to have central obesity[34-35].

Material & Method

Due to the fact that many patients do not feel comfortable discussing their use of herbal medications with their doctors, it is essential that the safety and efficacy of commonly used herbal medicines for obesity and cadiac illnesses be verified. The objective of this article is to investigate the data that supports the use of the most prevalent herbal medicines for the treatment of glaucoma, as well as to evaluate the downsides associated with the utilisation of such treatments. We searched PubMed, Google Scholar, and the Cochrane Library for papers that were pertinent to our research.

Obesity & Heart failure

Obesity and coronary atherosclerosis have been associated for a considerable amount of time. According to studies that were carried out on younger people, the onset of atherosclerosis occurs several years before coronary artery disease becomes clinically apparent[36]. Patients who have higher BMI values, as compared to patients who are of normal weight, have a higher prevalence of atherosclerotic vascular lesions, as well as a higher severity of these lesions. When looking at the long-term impacts of weight development, researchers have determined that being overweight for more than twenty years is a major risk factor for coronary artery disease[37-40]. Increases in systolic and diastolic blood pressure of 3 and 2.3 millimetres of mercury, respectively, are directly related to this phenomenon. Each additional 10 kilogrammes of body weight is associated with a 12% increase in the risk of coronary artery disease, and this is directly related to the fact that obesity raises the risk of coronary artery disease[41]. Both the systolic and diastolic measurements of blood pressure contribute to an increased likelihood of adverse outcomes (Figure 1). When it comes to young people and non-ST-elevation myocardial infarction (NSTEMI), obesity may be regarded as the single most important risk factor, even more so than smoking. Because being overweight increases the likelihood of having a heart attack that does not involve an ST-elevation[42-45]. In people who are otherwise healthy, having a greater body mass index is linked to an earlier start of symptoms associated with NSTEMI.

There is a correlation between myocardial infarction and ST-segment elevation in the same way (STEMI). According to the findings of our study, obesity is a separate risk factor for first-time STEMI in younger patients[46]. In addition to these vascular problems, obesity is associated to a wide variety of other health problems as well. The risk of having an ischemic stroke increases by 4% and the risk of having a hemorrhagic stroke increases by 6% for every unit that your body mass index rises[47-50].

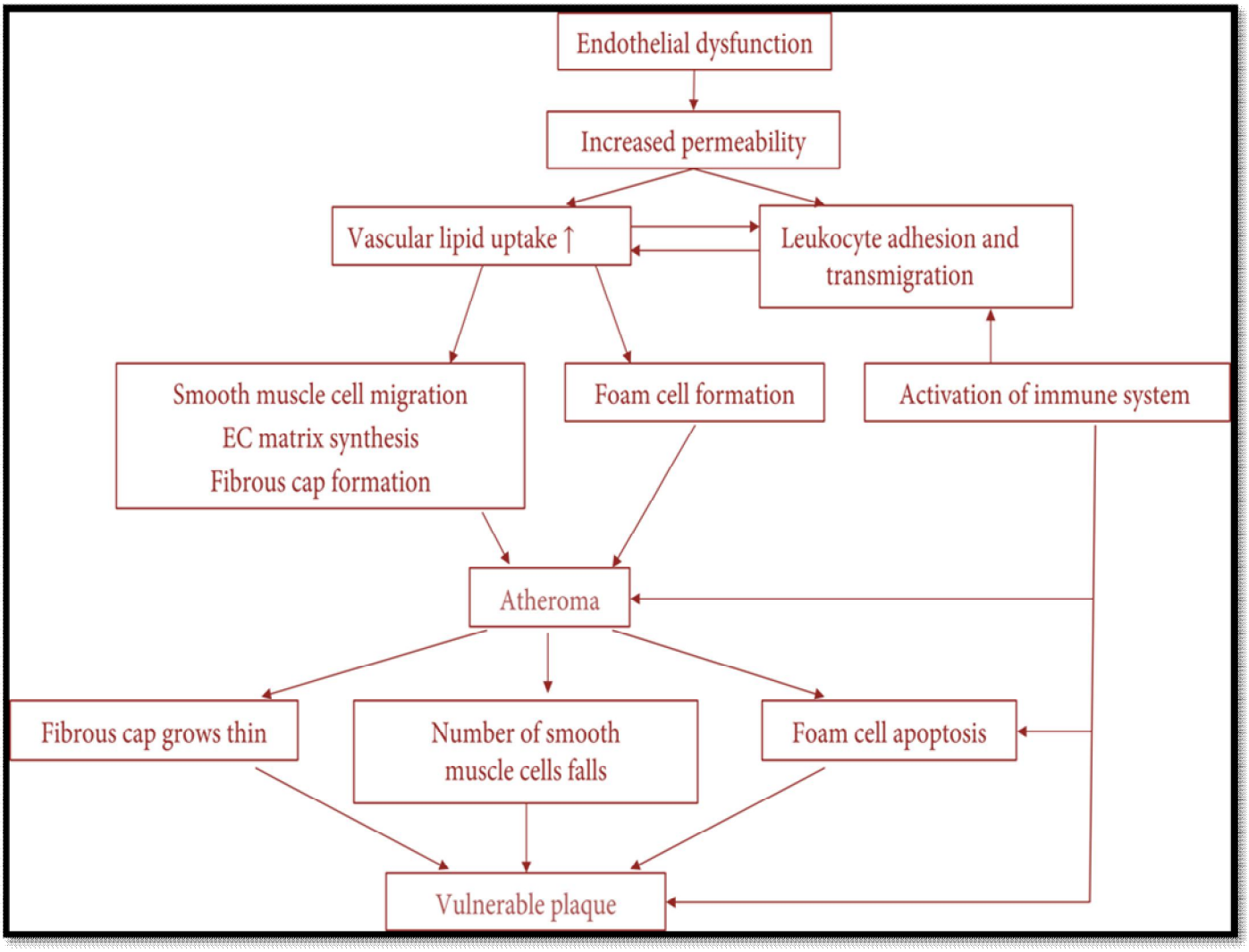

Fig: 1 Obesity and the Pathophysiology of coronary artery disease.

Around 3% of the population in countries with high levels of wealth are affected by heart failure, making it the top cause of death on a global scale. It has been discovered that a considerable rise

in the chance of developing heart failure is associated with having an unhealthy quantity of body fat[51]. According to the findings of the Framingham Heart Study, the likelihood of developing heart failure increases by 5% in men and 7% in women for every 1 kg/m2 increase in body mass index. According to the findings of recent studies, between 32 and 49 percent of people who have heart failure are either overweight or obese[52]. People who have a body mass index (BMI) that is above the normal range are at an increased risk of developing heart failure by a factor of ten years. There is a correlation between twenty years of morbid obesity and a 70% increase in the prevalence of heart failure[53-55]. There is a correlation between thirty years of morbid obesity and a 90% increase in the prevalence of heart failure. According to the findings of the Framingham Heart Study, which highlighted the pathogenic role that obesity plays in the development of heart failure, the fact that 11% of men and 14% of women acquire heart failure after being overweight or obese is suggestive of the significance of obesity. Furthermore, the fact that 11% of men and 14% of women acquire heart failure after being overweight or obese is suggestive of the significance of obesity[56]. The decrease in cardiac function that is characteristic of obesity cardiomyopathy is caused by the morphological and functional abnormalities of the heart that are seen in obese people. Obese people are more likely to have these heart abnormalities. People who are overweight have an increased likelihood of developing cardiomyopathy[57-60]. There is a connection between being overweight and getting heart failure, and this connection can be both direct and indirect. Obesity is characterised by a number of different symptoms, some of which include changes in vital signs such as blood pressure and heart rate. When a person's body mass index goes up, they often experience an increase in both their cardiac output and their blood pressure[61]. An increase in systolic blood pressure that corresponded with a rise of 5 kg/m2 in body mass index was associated with a rise of 5 mmHg in systolic blood pressure. The activation of the renin-angiotensin-aldosterone pathway and the increased activity of the sympathetic nervous system are both to blame, at least in part, for this phenomenon. The increased expression of aldosterone and mineralocorticoid receptors that is formed as a result of obesity is what makes interstitial cardiac fibrosis, platelet aggregation, and endothelial dysfunction all the more likely to occur[62-64]. Obesity also increases the risk of type 2 diabetes. According to the findings of the EMPHASIS-HF research, the use of the medicine eplerenone to treat heart failure in individuals with a lower ejection fraction was found to be more beneficial in patients who had abdominal obesity. This finding can be explained by the

mechanisms discussed previously[65]. When there is a greater amount of blood in the body, the blood's ability to flow in the opposite direction through the veins is facilitated. Because of this, there is an increase in the preload of the ventricles and tension on the walls of the ventricles, both of which lead to ventricular dilatation. A little malfunction of the left ventricle of the heart has been linked to the buildup of fat in the middle of the body. Patients who have hypertension are at a greater risk of having structural and electrical myocardial remodelling as a result of the increased afterload that is placed on the left ventricle of the heart as a result of having hypertension[66]. Left ventricular hypertrophy and dysfunction, including diastolic and finally systolic dysfunction of the ventricle, are the long-term repercussions of this illness. The malfunction of the ventricle can occur at any stage of the cardiac cycle[67]. Another factor that obesity brings to the table in the development of heart failure is an increase in the production of cytokines that are pro-inflammatory (TNF-, IL-1, IL-6, IL-8, etc.). Myocardial stiffness can increase as the process of fibrosis in the heart muscle begins. As a result of this, there is a possibility that diastolic heart failure, and then finally systolic heart failure, will develop in the heart[68]. A condition known as heart muscle fibrosis can be triggered by circulating inflammatory mediators and acute-phase proteins. Because of the influence they have on metabolism, the structure of tissue, and the extracellular matrix, hormones like leptin and adiponectin play a significant part in the remodelling process of the myocardium. It is usual for obese people to have an accumulation of triglycerides in their cardiac muscle. This accumulation encourages the production of toxic metabolites (such as ceramide and diacylglycerol), which in turn increases the number of cells that perish[69,70]. If you wish to maintain your mobility throughout time, it is absolutely necessary for your skeletal muscles to remain at a healthy weight. Poor dietary habits contribute to obesity, which in turn increases the likelihood of muscle atrophy and catabolism. Poor dietary habits are a vicious cycle. This stage is critical for the development of cardiovascular disease in obese people since it determines the course of the disease. Obesity has been related to a wide variety of adverse health effects, including heart failure, which is just one of them. Insulin resistance, which also reduces myocardial contractility, can lead to a number of negative cardiac consequences, including myocardial fibrosis, heart hypertrophy, and the death of myocytes[71-73]. When there is a disruption in lipid metabolism, the risk of developing ischemic cardiomyopathy increases. Given this information, it is reasonable to draw the conclusion that carrying around excess weight plays a substantial part in the development of coronary artery

disease. The buildup of lipids in the heart muscle, which can lead to an increase in fibrosis and ultimately heart failure, is one of the potential causes of this condition Figure 2.

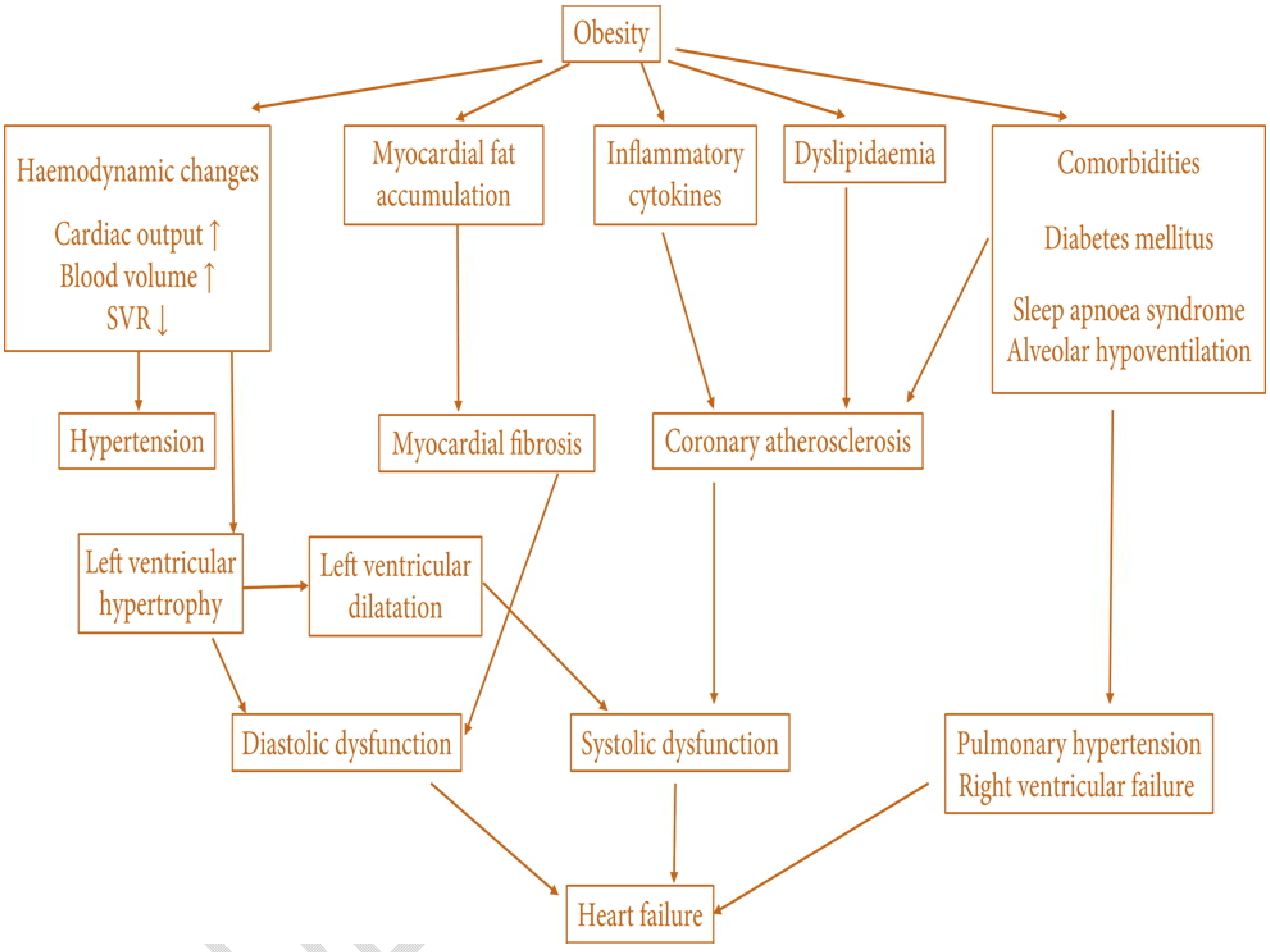

Fig: 2 Mechanisms underlying obesity-related cardiac failure.

Obesity impact on the cardiac proteome

In reaction to shifts in the conditions of its surrounding environment, the heart has the capacity to go through remodelling of both a healthy and a pathological variety. Following the presentation of the concept by Cohn and his colleagues, the concept of cardiac remodelling, also abbreviated

CR, has gained widespread acceptance[74]. CR is characterised by changes in genomic expression in addition to changes at the molecular, cellular, and interstitial levels. These changes lead to clinical manifestations that include abnormalities in heart size, shape, and function after cardiac injury. Damage to the heart, brought on by excessive and prolonged stress, is what causes the systemic clinical symptoms of heart failure (HF). Obesity is now known to be a risk factor for the development of heart failure, and one possible explanation for this is that fundamental changes in the structure and function of the heart occur (HF). Numerous studies have discovered a connection between being obese and having CR; however, the exact mechanisms that underlie this association are not yet fully understood. However, researchers have hypothesised that there may be distinct processes at the cellular, tissue, and chamber levels[75].

There are many different kinds of changes that can take place in the biology of cardiomyocytes, and one of these is cell hypertrophy. Characteristic features of hypertrophy in cells include the proliferation of myofibrils and mitochondria, as well as enlargement of both nuclei and mitochondria. It is the first line of defence in maintaining the health of the heart and making use of the additional energy substrates, particularly fatty acids, that are made available to the cardiomyocyte in obese persons. In the later stages of this stressful event, myocytolysis, or the destruction of components involved in contractile activity, takes place[76]. The Z band, the parallel arrangement of the sarcomeres, and the mitochondria all have defects, which may be seen when the ultrastructure is analysed. abnormalities in excitation-contraction coupling as a result of modifications in the expression of essential Ca2+ regulatory proteins; disruption of the beta-adrenergic system; and deregulation of and myosin heavy chain gene expression, which is analogous to the process of foetal gene reprogramming. This metabolic profile of the heart can lead to oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction, all of which can, in turn, lead to aberrant energy generation, disruptions in myocardial efficiency, and impairments in cardiac function[77]. Additionally, "cardiac lipotoxicity," which occurs when the heart is subjected to an excessive amount of fatty acids, can lead to the accumulation of ectopic fat as well as the development of cardiotoxic lipid intermediates such as diacylglycerol and ceramide within the cardiac cell, which in turn lowers the performance of the heart. This occurs when the heart is exposed to an excessive amount of fatty acids. When an abnormally high concentration of fatty acids is present in the heart, disease might develop. These irregularities in

energy metabolism are a strong predictor of the malfunction of the heart that is linked with obesity. In addition to the well-described processes that have already been provided, it is important to keep in mind that there are other factors that play a role in the pathophysiology of cardiac lipotoxicity[78]. Recent research has uncovered a number of elements that, when combined, contribute to the lipid overload-induced ventricular dysfunction that is associated with obesity. Epoxyeicosatrienoic acids, membrane phospholipids (such as phosphatidylethanolamine and cardiolipin), and non-coding RNA, in particular microRNA-320 and microRNA-451, are included in this category[79]. A pair of previously unknown microRNAs paved the way for this discovery. Atrial fibrillation and other arrhythmias can be caused by a number of conditions that affect cardiac repolarization. One factor that helps create these issues is obesity[80].

Last but not least, anomalies in chamber geometry have been linked to left atrial enlargement, incompetent aortic and mitral valves, and the development of functional regurgitation. In the left and right ventricles, these anomalies include an increased thickness/radius (referred to as concentric hypertrophy), as well as a decreased thickness/radius (referred to as eccentric hypertrophy).

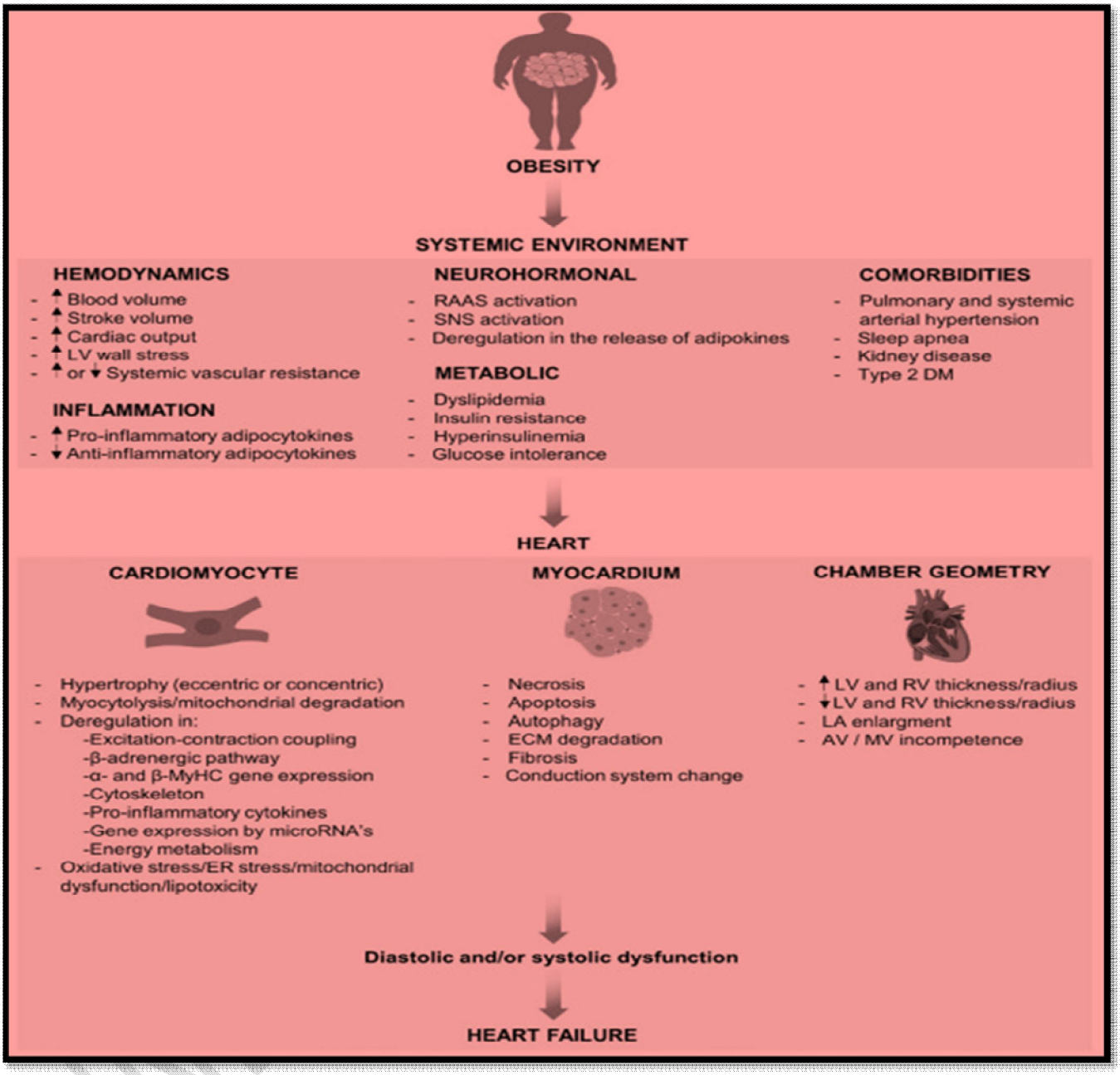

Fig: 3 Comorbidities or not, alterations in hemodynamics, neurohormones, metabolism, and inflammation set off a cascade of molecular to structural changes in the heart that ultimately lead to heart failure. The LV indicates the left ventricle. The renin, angiotensin, and aldosterone system (RAAS). The SNS refers to the sympathetic branch of the autonomic nervous system. The disease of diabetes mellitus. Simply put, the term "myosin heavy chain" (MyHC) implies "myosin." The endoplasmic reticulum (ER) is the organelle in question. Matrix that separates cells. That's the right ventricle for those of you keeping

score at home (RV). The left atrial node is referred to as "LA" in the medical field. Aortic valve, also abbreviated as "AV," is a vital heart valve. Involving a replacement of the mitral valve (MV).

Many of the previously mentioned factors have been shown to have a multiplicative effect, with one event often leading to another (for example, disturbance of energy metabolism can affect excitation-contraction coupling, which in turn leads to necrosis; or lipotoxicity producing apoptosis). However, a dynamic series of systemic alterations, including hemodynamic, neurohormonal, metabolic, and inflammatory abnormalities, may also play a role in the development of potentially fatal cardiac events in obese patients[81]. Increases in blood volume, stroke volume, cardiac output, and left ventricular wall stress are all signs of a hyperdynamic circulatory response to the increased metabolic needs of more adipose tissue and fat-free mass. Maladaptive remodelling and cardiac dysfunction can also result from an increase or reduction in systemic vascular resistance[82]. Obesity can alter cardiac structure and function because of neurohormonal disturbances like the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and the dysregulation in the release of a number of hormones (adipokines) like leptin, adiponectin, resistin, omentin, apelin, and visfatin. Obesity is a contributing factor to these alterations. Cross-talk between obesity and HF may be more pronounced because obesity is associated with disorders like dyslipidemia, insulin resistance, hyperinsulinemia, and glucose intolerance. An increased amount of inflammatory cytokines (including interleukin IL-6, IL-18, IL-1, and tumour necrosis factor- [TNF-α] are released from adipose tissue in obese people. and adipokines associated with inflammation (such leptin and resistin) than those seen in slim people[83]. Blood levels of anti-inflammatory molecules have declined, however, because adipose tissue has reduced its production of these substances. Adiponectin, transforming growth factor beta, interleukin-10, and interleukin-4 are some of them.

Inhibiting sodium-potassium ATPase is how cardiac glycosides like digitalis work to improve myocardial contractility. This most likely leads to increased calcium levels in the cytoplasm of heart muscle cells. Over two centuries have passed since the cardiac glycosides, which were initially isolated from the purple foxglove flower, were first introduced into clinical practise (Digitalis purpurea)[84]. Instead of cardiac glycosides, beta-blockers and ACE inhibitors are the medications of choice for treating congestive heart failure, atrial fibrillation, and other heart

conditions. This is due to the fact that these drugs have been found to improve overall survival rates over the long term while simultaneously having superior safety profiles[85]. Angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, in that order, have supplanted cardiac glycosides as the therapeutic method considered to be the gold standard. People who have left ventricular systolic dysfunction and atrial fibrillation are good candidates for treatment with cardiac glycosides[86]. People who have congestive heart failure in sinus rhythm and who continue to experience symptoms despite receiving maximal alternative therapy are also good candidates for treatment with cardiac glycosides. Since digitalis was initially made accessible to purchase in the market, the passage of time has surpassed one hundred years. Digitoxin's rapid adoption can be attributed to the fact that it is the most widely used cardiac glycoside and that it is derived from Digitalis lanatus, the plant from which it is distinguished by its superior predictability in pharmacokinetics. In addition, Digitoxin's rapid adoption can be attributed to the fact that it is the most widely used cardiac glycoside and that it is derived from Digitalis lanat Cardiac glycosides are medications that can cure mild to severe cases of congestive heart failure[87]. They are also employed to modulate the ventricular response rate in patients who suffer from atrial fibrillation. Under the brand names Lanoxin and generic variants, digoxin tablets are available in strengths ranging from 0.0625 mg to 0.5 mg. These strengths are available in tablet form. The normal suggested daily dosages range from 0.125 mg to 0.25 mg, however this might vary greatly depending on each person's response and tolerance. Normal recommended daily dosages range from 0.125 mg to 0.25 mg[88]. Now, in addition to the oral solution, digoxin can also be obtained in the form of a solution for intravenous use. There have been many different adverse responses that have been connected to cardiac glycosides. Since these reactions tend to be dose-dependent, it is vital to carefully monitor the levels of medication being taken. Lightheadedness, sleepiness, headache, anxiety, stomachache, altered taste, and double vision are some of the common side effects of this medication[89]. A few examples of adverse reactions that might be fairly significant include seizures, coma, heart block, atrial and ventricular arrhythmias, and sudden cardiac death.

It has been demonstrated that the cardiac glycosides that are present in plants such as foxglove (particularly *D. purpurea* and *Digitalis lanata*) have significant inotropic and electrical effects on the heart tissue. There are several plant species, including Digitalis (also known as foxglove), *Cascabela thevetia* (also known as yellow oleander), and *Convallaria majalis*, from which hundreds of cardiac glycosides have been extracted and characterised (lily of the valley).

Digitoxin and digoxin, two cardiac glycosides with significant medical use, can be extracted from the plant species *Digitalis purpurea* and *Digitalis lanata,* respectively[90].

The foxglove (Figure 4) is a plant that was brought over from Europe and has since become native to the temperate regions of North America. Because of its obvious blossoms and distinctively bitter taste, foxglove is not commonly consumed by accident. This plant does not develop flowers in its first year despite the fact that it is sometimes misidentified as borage1 or comfrey in its juvenile stage due to the rosette of basal leaves that it possesses[91]. Before the two cases that we are going to detail here, there have been other instances of symptomatic cardiac glycoside poisoning from plant intake in British Columbia that required antidote treatment. These cases can be found in the past.

Fig: 4 Mature springtime blooming of mature foxglove plants (*Digitalis purpurea*).

Myocardial tissue is where digoxin exerts its primary biochemical mode of action. In myocardial tissue, digoxin boosts intracellular sodium content by inhibiting sodium-potassium adenosine triphosphatase (Na+-K+ ATPase). This increases the amount of sodium within the cell. When there is an increase in the amount of calcium produced inside the cell, a mechanism known as the Na+-Ca2+ exchange becomes active[92]. The beneficial benefits of digoxin are not limited to the direct implications it has on the function of myocytes; rather, they may also be observed in the ways it modifies other physiological variables such as blood pressure, levels of neurohormones, and electrophysiological activity.

Cardiac glycosides have been vital to the treatment of congestive heart failure ever since William Withering published his book on the usefulness of the leaves of the common foxglove plant in the late 18th century (Digitalis purpurea)[93]. Despite widespread use in medicine over the past two centuries, this group of drugs has been the source of ongoing dispute over its effectiveness and safety. Although the alpha-subunit of sarcolemmal Na+K+-ATPase (also called the sodium pump) present on most eukaryotic cell membranes has been known to be the molecular target of the cardiac glycosides for decades, whether the sympatholytic or positive inotropic effects of these agents is the mechanism that is most relevant to relief of heart failure symptoms in humans with systolic ventricular dysfunction is still up for debate[94]. This article discusses the symptoms and possible treatments for digitalis poisoning. Clinical and molecular pharmacology of these time-tested medicines are also discussed. Furthermore, we discuss the results of recent clinical investigations performed to determine whether or not these drugs are useful in treating heart failure, with a focus on the data acquired by the Digoxin Investigation Group. We conclude that the findings on equilibrium are consistent with the continued use of digitalis preparations in the treatment of symptoms of heart failure in patients receiving current modern combination therapy[95]. As new cutting-edge pharmacotherapies become available, digitalis formulations will be used less frequently. The use of digitalis in patients with coronary artery disease and myocardial infarction is currently being reevaluated due to the development of more potent diuretics and the established efficacy of vasodilators in left ventricular unloading.

Digoxin and other cardiac glycosides have reportedly been used to treat heart failure (HF) for over 200 years, and to slow the heart rate of people with atrial fibrillation (AF) for over 100

years. The use of digoxin in the treatment of HF with systolic dysfunction has gradually declined since the results of the Digitalis Investigation Group (DIG) trial showed that digoxin decreased HF hospitalisation but had no meaningful overall effect on death[96]. Reason being that the DIG experiment demonstrated that digoxin decreased HF hospitalisation. Many questions remain about its mechanism of action and its optimal application in the treatment of present AF. Digoxin may increase the risk of dying from cardiovascular reasons and all causes combined, but studies on this topic have yielded conflicting results in people with atrial fibrillation. In individuals with atrial fibrillation (AF), digoxin can be helpful in reducing HR, but it is not without its hazards, such as the potential for catastrophic ventricular tachyarrhythmias and severe bradyarrhythmias and a small therapeutic index.

An enzyme called Na+/K+ ATPase is located in cell membranes, and both digoxin and cardiac glycosides work by blocking its activity. The result is a blockage of sodium exit from the cell. Digitalis is thought to have a beneficial inotropic effect because it raises intracellular Ca2+ concentrations by abolishing the transmembrane sodium gradient. There is a subsequent rise in intracellular Ca2+ content as a result of this. Digoxin has extracardiac effects as a neurohormonal modulator[97]. In order to achieve this effect, it raises parasympathetic nervous system tone and lowers sympathetic nervous system and renin-angiotensin-aldosterone system activity. Digoxin has an indirect effect on the sympathetic nervous system in addition to its direct sympatholytic effects at low doses. For this purpose, it enhances the responsiveness of baroreceptors in the carotid sinus. Overall, the rest of the conduction system is relatively immune to digoxin's electrophysiological effects. Conduction at the atrioventricular node is prolonged while the sinoatrial node's firing is slowed.

Digoxin has been demonstrated to be beneficial in the control of HR in persons who have been diagnosed with atrial fibrillation. This is accomplished without the potentially dangerous side effect of reducing blood pressure, which is another benefit of using digoxin. However, during physical activity or when sympathetic tone is elevated, digoxin may not be sufficient to appropriately moderate heart rate. Digoxin is currently considered a first-line drug for the control of HR in AF in patients with HF, hypotension, or possibly in those who are mostly sedentary, according to guidelines issued in the United States[98]. An older classification for digoxin called

for it to be treated as a class 1 indication (obviating the need for rate control during activity). This is why digoxin is frequently prescribed to elderly people with a poorer prognosis due to their increased risk profile. Findings from the Stockholm Cohort of Atrial Fibrillation (SCAF) study indicate that digoxin is more commonly prescribed to elderly patients with diminished physical capacity. Digoxin use was found to have no influence on long-term mortality in individuals with atrial fibrillation after these and other patient factors were considered.

Recent post-hoc and observational studies have demonstrated that patients who were administered digoxin had a greater mortality rate than those who did not receive the medication. Over the course of one year, patients who were treated with digoxin for atrial fibrillation (AF), congestive heart failure (HF) with reduced or preserved ejection fraction (EF), or both were compared to a comparable group of patients who did not receive digoxin treatment. Both patient groups had been diagnosed with atrial fibrillation[99]. When compared to the 16 587 controls at discharge, the overall death rate was higher in the 4426 patients who had AF but no history of HF and were treated with digoxin (hazard ratio 1.42, 95% confidence interval [1.28-1.56]). Patients diagnosed with HF did not exhibit this diversity in their symptoms. Despite the large number of people who participated in the study, it is difficult to generalise the findings to other clinical settings because the research was carried out in an intensive care unit (ICU).

The patients who were given digoxin for their AF were found to have an elevated risk of death from any cause in a substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. This held true irrespective of the presence or absence of preexisting heart failure in the patient population. Digoxin was included as a time-dependent covariate in the Cox proportional hazard model that we used here[100]. If a patient's drug status changed during the course of the trial, they would be classified as "on-digoxin" or "off-digoxin," and their relative risk of death would climb or fall, respectively. On the other hand, Gheorghiade et alAFFIRM .'s study found no difference in overall mortality between the two groups. Only at the time of random assignment of treatment did it become known whether or not the individuals were digoxin-positive. Digoxin, as part of a rate control strategy, may help people with atrial fibrillation and significant left ventricular dysfunction, as suggested by a post hoc analysis of the AFFIRM study[101]. A post hoc investigation of the AFFIRM study discovered, if that weren't

already perplexing enough, that. One possible explanation for the increased mortality rate observed in the post hoc analysis of Whitbeck et alAFFIRM .'s study is the use of digoxin as a time-dependent treatment variable. Whether or not the effect of time-dependent treatment on survival can be deemed valid depends on whether or not changes in therapy were arbitrary and unrelated to declines in health. Another major flaw in Whitbeck and coworkers' study is that age wasn't used as a covariate in creating the propensity score. Digoxin is primarily prescribed to the elderly, therefore it stands to reason that the increased mortality rate associated with getting older would also apply to this group. Given that digoxin is typically prescribed to the elderly. It's also possible that drug interactions contribute to the symptoms these people are experiencing. Evidence from the Permanent Atrial fibrillation Outcome Study Using Dronedarone in Addition to Standard Therapy (PALLAS) suggests that taking digoxin at the same time as a beta-blocker can significantly reduce the risk of death from cardiovascular causes[102].

In a study involving 1269 consecutive patients with both AF (permanent or nonpermanent) and HF, we discovered that therapy with either beta-blocker alone or with beta-blocker + digoxin was linked with a similar decrease in the risk of death. We discovered that therapy with either beta-blocker alone or with beta-blocker plus digoxin was linked with the finding after controlling for baseline variables (preserved or reduced LVEF). Digoxin alone resulted in outcomes similar to those of patients who did not receive any rate control therapy. A more recent meta-analysis that combined data from observational studies and randomised controlled trials indicated that digoxin was related with a reduction in the overall number of hospitalizations needed and did not reduce the risk of death in the randomised trials. Digoxin, when administered in therapeutic serum concentrations, significantly reduces the pro-arrhythmic effects of the medicine (SDC). Atrioventricular block and escape rhythms are electrocardiographic signs of poisoning. Depending on whether or not hypokalemia is present, these symptoms may occur at SDC levels that are therapeutic or even higher. Digoxin impact and/or toxicity are not yet understood, and it is unclear how amounts relate to either. However, post hoc analysis by Rathore and coworkers indicates that the patients' serum medication concentrations affected digoxin's efficacy. Experts agree that 0.5–0.8 ng/ml is the sweet spot for digoxin therapy, but a different AFFIRM study indicated that doses of 2 ng/ml or above may be hazardous to the patient. Digoxin doses within the therapeutic range have been demonstrated to have no additional neurohormonal benefit, and

may even have a sympathetic impact, as compared to lower doses. However, the overall neurohormonal profile in severe HF is improved by low doses of digoxin, therefore this is not the case. These results suggest a role for digoxin in the development of a variety of diseases. Although the AFFIRM trial's strict rate control criteria a resting heart rate of 80 beats per minute and a training heart rate of 110 beats per minute are usually reached in ordinary clinical practise, they may not be with an SDC of 1.0 ng/ml and higher doses of digoxin.

Conclusion

Prevalence of obesity is associated with elevated cardiovascular disease danger. It's a result of being overweight and the associated health problems (hypertension, diabetes, insulin resistance, and sleep apnoea syndrome). The term "obesity paradox" is used to describe the phenomenon in which people who are overweight or obese have a lower risk of death from cardiovascular disease than people who are of a normal body weight. The latter's inner workings are shrouded in mystery, to say the least. As a result of their elevated risk of cardiovascular disease, asymptomatic obese individuals must undergo regular cardiology screening and control in order to detect and treat preclinical abnormalities at an early stage. Reason being: being overweight raises one's risk of cardiovascular disease. Digoxin is commonly prescribed to elderly patients with atrial fibrillation, heart failure, and impaired LV function. Therefore, observational studies have discovered a link between its use and increased death rates. Although it is possible that digoxin has an independent link to higher mortality, the nature of this link is still unclear when patient characteristics are taken into account. The quality of the conclusions that can be taken from these data is low, but they suggest that digoxin might not be the best first-line treatment for people who engage in vigorous physical exercise. If beta-blockers are unsuccessful or cannot be administered owing to intolerance or contraindications, this medication may be used to regulate heart rate in persons with atrial fibrillation who are inactive or who have left ventricular systolic dysfunction. Patients with atrial fibrillation who are not physically active or who have left ventricular systolic dysfunction should only use this medication to manage their heart rate.

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