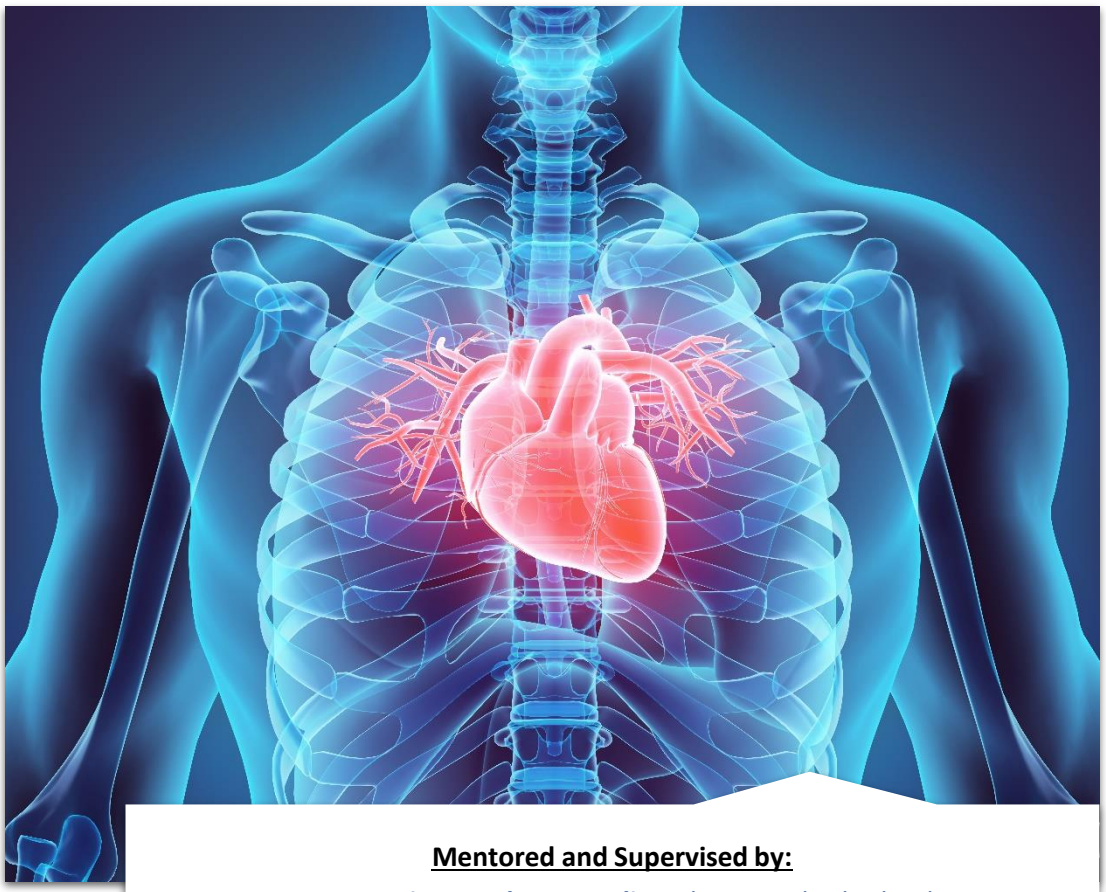
ALCOHOLIC CARDIOMYOPATHY



Mentored and Supervised by:

Dr. Panagiotopoulos Vangelis, Athens Medical School

Research and Writing by CLC's students:

Andreas Papandreou / Christoforos Foteinelis / Konstantinos Boukouvalas / Katerina Pavlakaki/ Evangelia Chaldeaki

Powered by:

TABLE OF CONTENTS

Abstract……3

Dilated Cardiomyopathy:……4-5

- Definition
- Risk factors
- Symptoms
- Diagnosis
- Complications

Alcohol metabolism:……..6-8

- Metabolism
- Effect on heart muscle
- Association with alcoholic cardiomyopathy

Discussion whether alcohol can be protective against cardiovascular diseases……9-10

Conclusion……11

Bibliography……12

Abstract

The heart muscle is the most valuable muscle of the human body. When it malfunctions people are at high risk of developing heart failure and finally dying. One of the main causes of heart failure is dilated cardiomyopathy (DCM), a disease in which the chambers of the heart, especially the left ventricle, stretches and becomes thinner. There are a lot of risk factors that can lead to DCM depending on one's genetic predisposition and lifestyle choices. Chronic alcohol abuse may be one of the most important causes leading to DCM, which is then called alcoholic cardiomyopathy(ACM). However there is a lot of discussion whether a frequent low alcohol consumption can be beneficial for the cardiovascular system.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is an “umbrella term” which includes a wide variety of genetic and non-genetic etiologies, leading to left ventricular systolic dysfunction and dilation, not explained by abnormal loading conditions or coronary artery disease. Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) systolic dysfunction and LV enlargement, in the absence of abnormal loading conditions such as hypertension, valvular disease, or coronary artery disease (CAD) which could be an explanation for myocardial abnormality. DCM includes heterogenous risk factors that are categorized as genetic or non-genetic. However, DCM remains a mixed disease in which environmental and functional factors interact with genetics. Factors such as gender, age, ethnicity or family history of DCM are irreversible risk factors. However, there are factors that are reversible like physical inactivity, alcohol consumption or drug use in excessive amounts as well as poor nutrition that can be controlled by the everyday habits of each individual. In addition, other factors include serious heart diseases like hemochromatosis, neuromuscular disorders such as muscular dystrophy and long-term high blood pressure.

Although, there are some major symptoms of DCM like fatigue, swelling, chest pain, cough, shortness of breath during an activity or even abnormal heartbeat, in the early stages of the disease there are no symptoms recorded as many cases have mentioned. DCM patients often show intermediate phenotypes not fulfilling the standard diagnostic criteria due to variable phenotypic expression and age-dependent penetrance. Due to this it is often hard to diagnose DCM. Some ways to diagnose DCM are: Echocardiogram (which is the main test for diagnosing DCM), blood tests, chest X-ray, Electrocardiogram, Holter monitor, heart CT or MRI scan and cardiac catheterization.

Main complications of DCM include strokes caused by blood clots, irregular heart rhythms, heart valve problems, sudden cardiac arrest that can lead to death, heart failure that can be life-threatening unless is treated correctly and fluid retention. Genetics have a promising potential

to unlock and demystify many of the “blind spots” of the current management of DCM. The rapid expansion and advancements in genetics have come with its own challenges. The interpretation of genetic test results and accurate categorization of variants is a laborious and complicated process and should ideally be performed by multidisciplinary teams of molecular cardiologists, molecular pathologists, clinical geneticists, and genetic counselors. With the development of genetics, the concept of directing the treatment according to the genotype seems promising. The understanding of gene-specific pathogenetic mechanisms and the unraveling of the functional effects of each variant should dictate different therapeutic strategies.

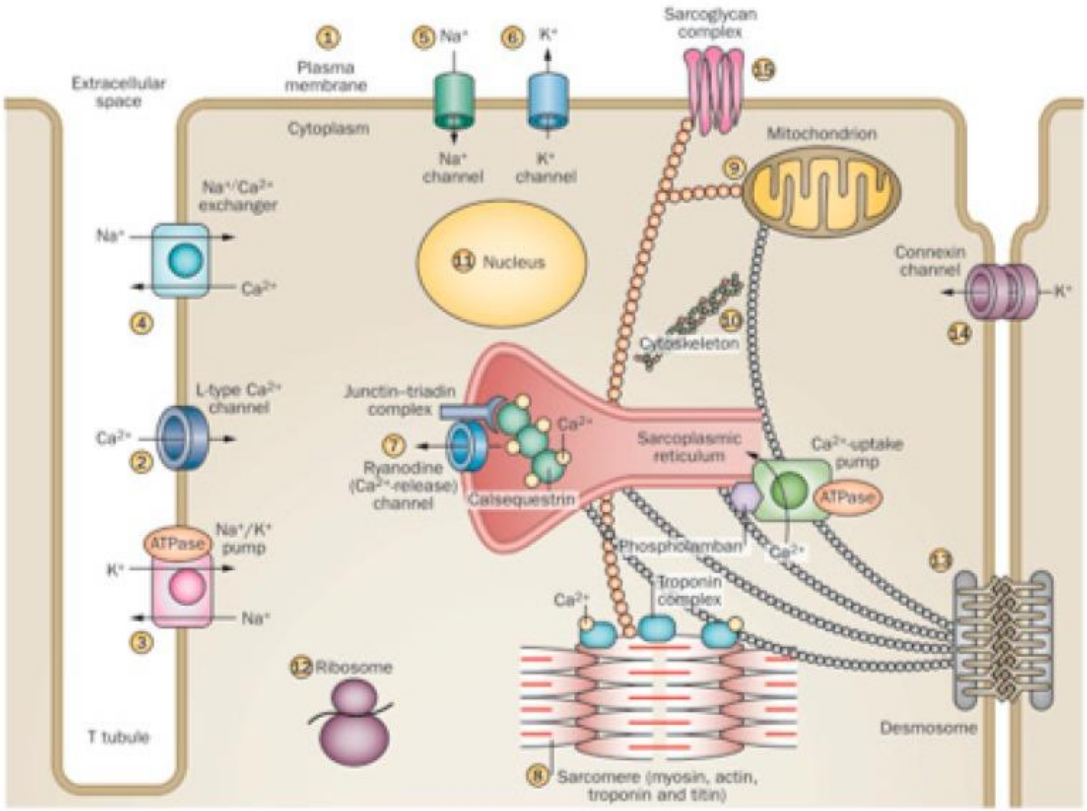
The effect of alcohol on the heart muscle and how it can lead to alcoholic cardiomyopathy

Once alcohol is consumed and swallowed, one part of it is absorbed directly by the mucosal lining of the mouth and the other one by the stomach. Then it enters the bloodstream and it is carried to all the organs of the human body, including the heart. In the majority of people, blood circulates through the body in 90 seconds, thereby allowing alcohol to affect the organs in a short amount of time. The main effects of drinking are felt within 15 to 45 minutes.

Alcohol is a toxin that is either neutralized or eliminated from the body via sweat, breath and urine. The liver is the primary organ responsible for the detoxification of alcohol, whose chemical name is ethanol. Most of the ethanol is broken down by an enzyme called alcohol dehydrogenase (ADH), which transforms ethanol into a toxic compound named acetaldehyde. Acetaldehyde is then quickly broken down to a less toxic compound called acetate, by the enzyme aldehyde dehydrogenase. Finally, acetate is broken down to carbon dioxide and water. There has been a debate whether ethanol or its active metabolite acetaldehyde, is responsible for cardiac damage. The answer is that both molecules are directly cardiotoxic, decreasing protein synthesis and increasing oxidative stress in the heart muscle.

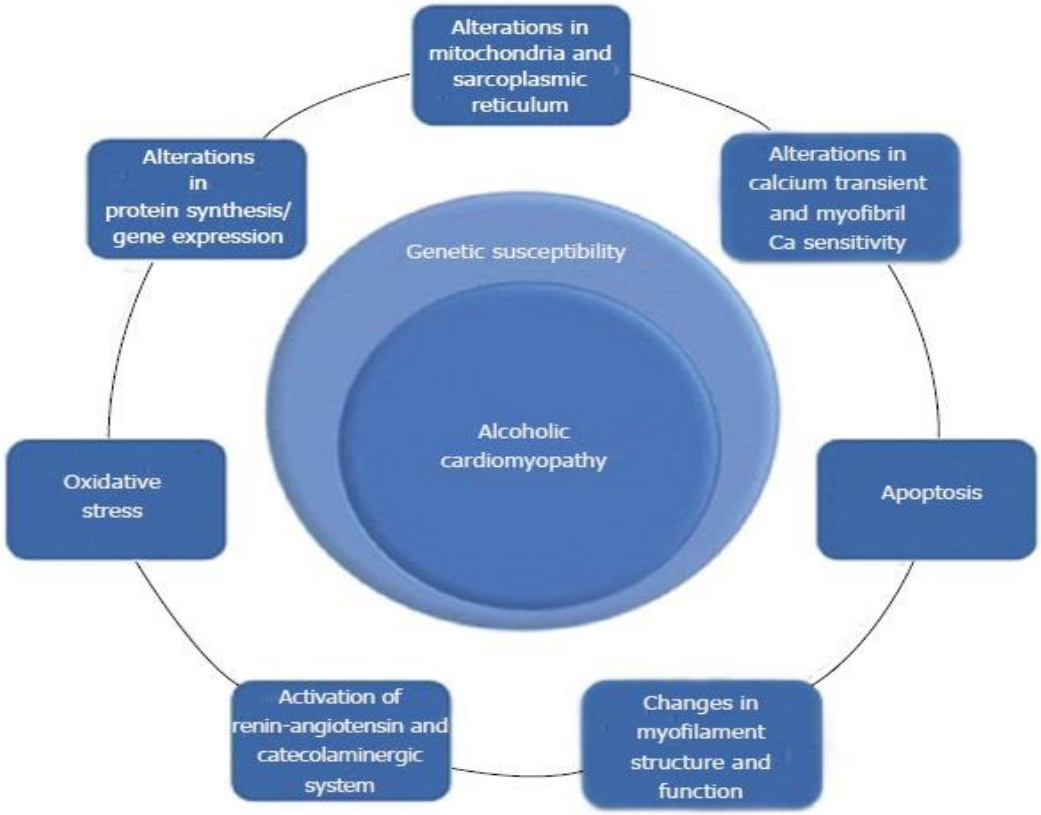
As far as ethanol-induced cardiac damage is concerned, it is proven that ethanol affect the cardiac myocytes at multiple sites, due to the fact that ethanol molecule has a small size and is highly reactive with many cell targets. These targets are membranes, receptors, mitochondria, ribosomes, sarcolemma, DNA and cytoskeleton. In particular, ethanol enhances permeation in model membranes by interfering with plasma membrane composition and permeability, disturbing signaling mechanisms, and activating apoptosis, as well as disturbing L-Type Ca^{2+} channel activity, Na^{+}/K^{+} ATPase channel activity, Na^{+}/Ca^{2+} exchanger

activity, and Na^+ and K^+ channel currents. Specifically, ethanol disturbs the ryanodine Ca^{2+} release, the sarcomere Ca^{2+}sensitivity, the excitation–contraction coupling and myofibrillary structure, and protein expression, decreasing heart contraction. Ethanol-induced disruption of ribosomal protein synthesis also contributes to non-contractile protein depletion. Several aspects of mitochondrial function, including respiratory complex activities and mitochondrial-dependent oxidative damage and apoptosis, are also induced by ethanol. Myocyte cytoskeletal structure, connexin channel communication, and desmosomal contacts are affected by ethanol, causing structural cell instability. Ethanol may induce changes in nuclear regulation of transcription with a dose-dependent translocation of NFkB into the nucleus. The resulting effect in those multiple sites may be additive and synergistic, increasing the final damage.



Different effects of ethanol on cardiomyocyte organelles. (Adapted form Nature 451; 929–936, 2008). Cardiac myocytes are excitable cells with complex signaling and contractile structures and are highly sensitive to the toxic effect of alcohol on: (1) plasma membrane composition and permeability, signaling, and activation of apoptosis; (2) L-Type Ca^{2+} channel activity; (3) Na^+/K^+ ATPase channel activity; (4) Na^+/Ca^{2+} exchanger activity; (5) Na^+ channel currents; (6) K^+ channel currents; (7) ryanodine Ca^{2+} release; (8) sarcomere Ca^{2+} sensitivity, excitation–contraction coupling, myofibrillary structure, and protein expression; (9) several aspects of mitochondrial function, including respiratory complex activities; (10) cytoskeletal structure; (11) nuclear regulation of transcription; (12) ribosomal protein synthesis; (13) desmosomal contacts; (14) connexin channel communication; (15) sarcoglycan complex interactions.

The final step of this destructive process is the myocyte apoptosis. It is induced by ethanol through mitochondrial membrane permeabilization and the release of pro-apoptotic factors, such as cytochrome c, from the mithochondrial inter-membrane space to the cytosol. However, there is also a theory in which the cardiac myocytes remove the defective organelles and cell debris with a mechanism called autophagy. The result is the same with both processes. After myocyte apoptosis or necrosis, the heart tries to repair and regenerate this tissue damage, but the heart regenerative capacity is low as a result of the ethanol aggressive damage and develops ineffective repair mechanisms such as progressive fibrosis. Subendocardial and interstitial fibrosis progressively appear in the course of ACM, usually in advanced stages. More than 30% of the myocyte ventricular fraction can be replaced by fibrotic tissue, thus decreasing the heart elasticity and contractile capacity.



Alcoholic Cardiomyopathy. Pathophysiology.

Discussion whether alcohol can be protective against cardiovascular diseases

Cardiovascular diseases constitute the worldwide leading cause of death. There have been conducted multiple studies to investigate the biphasic impact that the consumption of ethanol has on the cardiovascular system depending on actors like the drinking pattern, the amount and the type of alcohol. To start with, when it comes to arrhythmias, high consumption of alcohol can lead to developing atrial fibrillation which is characterized by rapid and irregular beating of the atrial chambers of the heart but also to malignant ventricular arrhythmias and even sudden death. Even when a small proportion 12 grams of alcohol are consumed daily, there is a 16% increase in the risk of having arrhythmias regardless the type of alcohol beverage. Regarding alcoholic cardiomyopathy there are no safe amounts of ethanol that can prevent it but in contrast favor its emergence. In addition, high alcohol consumption can increase blood pressure and if done frequently it can result in high prevalence of hypertension. Thus, regardless the drinking levels of ethanol it doesn't constitute a protective factor for blood pressure. Lastly, excess drinking positively correlated with peripheral atherosclerotic plaque volume which results in atherosclerotic vascular disease and can also lead to high risk of mortality form coronary heart disease. Although, alcohol consumption seems to provoke several cardiovascular diseases, more studies need to be conducted regarding the low to moderate alcohol intake's cardiovascular implications. The heterogeneous response to low to moderate alcohol exposure can be partially justified by race, ethnic origin, genetic background and type of alcoholic beverage. Specifically, regarding the genetics, the coexistence of titin truncating variants has been proven that leads to a more severe alcoholic cardiomyopathy phenotype. Finally, red wine has been proven to have positive effects on cardiovascular diseases as it possesses antioxidant and anti-inflammatory properties, improving endothelial function and insulin resistance.

Alcohol has a hormetic physiological activity that increases or decreases cardiovascular risk depending on the amount ingested, the frequency with which it is consumed, the pattern with which it is consumed, and the outcomes under research, as well as the type of alcoholic beverage consumed. However, the great majority of research clarifying the role of alcohol in cardiovascular and world disease burden rely on associative epidemiological studies, which have significant drawbacks. As a result, the cardiovascular advantages of low–moderate alcohol intake are being called into doubt, and they may have been exaggerated. Aside from recent data linking low and moderate alcohol intake to a lower risk of cardiovascular disease, various concerns about the precise quantity of safe consumption, the kind of alcoholic beverage, and age, sex, and genetic/ethnic disparities in alcohol consumption remain unsolved. Excessive alcohol consumption has been linked to a variety of heart disorders including heart failure. However, a J-shaped relationship has been discovered between alcohol use and the risk of cardiovascular disease and death. Nonetheless, there are some aspects of alcohol intake that are linked to cardiovascular disease. By taking into consideration all of the varied features of alcohol use, an alcohol-drinking pattern can enhance the evaluation of cardiovascular disease risk. The Mediterranean diet has been shown to reduce the risk of cardiovascular death, myocardial infarction, and stroke. Moderate alcohol consumption is an integral part of this eating plan. Red wine consumption, moderate intake, and wine drank with meals and in moderation are all characteristics of the Mediterranean alcohol-drinking habit.

Conclusion

As a result of all the information mentioned above, we believe that chronic alcohol consumption can have destructive effects on heart muscle even in moderate doses. Ethanol abstinence allows for recovery in the majority of cases, whereas subjects who continue drinking at moderate to high doses (more than 60 g ethanol/day in men—equivalent to four standard drinks—and 40 g of ethanol/day in women—equivalent to 2.5 standard drinks), experience progressive functional and structural cardiac impairment, with repeated episodes of cardiac left or congestive failure, arrhythmias, and progression to death, with a mortality rate of 10%/year. Therefore, complete abstinence from ethanol is the most useful measure to control the natural course of ACM.

Bibliography

- Orphanou, N., Papatheodorou, E., & Anastasakis, A. (2021). Dilated cardiomyopathy in the era of precision medicine: latest concepts and developments. *Heart failure reviews*, 1–19. Advance online publication. https://doi.org/10.1007/s10741-021-10139-0
- Schultheiss, H. P., Fairweather, D., Caforio, A., Escher, F., Hershberger, R. E., Lipshultz, S. E., Liu, P. P., Matsumori, A., Mazzanti, A., McMurray, J., & Priori, S. G. (2019). Dilated cardiomyopathy. *Nature reviews. Disease primers*, *5*(1), 32. https://doi.org/10.1038/s41572-019-0084-1
- Anghel, L., Sascău, R., Zota, I. M., & Stătescu, C. (2021). Well-Known and Novel Serum Biomarkers for Risk Stratification of Patients with Non-ischemic Dilated Cardiomyopathy. *International journal of molecular sciences*, *22*(11), 5688. https://doi.org/10.3390/ijms22115688

- Fernández-Solà J. (2020). The Effects of Ethanol on the Heart: Alcoholic Cardiomyopathy. *Nutrients*, *12*(2), 572. https://doi.org/10.3390/nu12020572

- Guzzo-Merello, G., Cobo-Marcos, M., Gallego-Delgado, M., & Garcia-Pavia, P. (2014). Alcoholic cardiomyopathy. *World journal of cardiology*, *6*(8), 771–781. https://doi.org/10.4330/wjc.v6.i8.771
- Steiner, J. L., & Lang, C. H. (2017). Alcoholic Cardiomyopathy: Disrupted Protein Balance and Impaired Cardiomyocyte Contractility. *Alcoholism, clinical and experimental research*, *41*(8), 1392–1401. https://doi.org/10.1111/acer.13405
- Steiner, J. L., & Lang, C. H. (2017). Etiology of alcoholic cardiomyopathy: Mitochondria, oxidative stress and apoptosis. *The international journal of biochemistry & cell biology*, *89*, 125–135. https://doi.org/10.1016/j.biocel.2017.06.009

- Maisch B. (2016). Alcoholic cardiomyopathy : The result of dosage and individual predisposition. Alkoholische Kardiomyopathie : Eine Folge der Dosis und der individuellen Prädisposition. *Herz*, *41*(6), 484–493. https://doi.org/10.1007/s00059-016-4469-6

- Stătescu, C., Clement, A., Șerban, I. L., & Sascău, R. (2021). Consensus and Controversy in the Debate over the Biphasic Impact of Alcohol Consumption on the Cardiovascular System. *Nutrients*, *13*(4), 1076. https://doi.org/10.3390/nu13041076

- Chiva-Blanch, G., & Badimon, L. (2019). Benefits and Risks of Moderate Alcohol Consumption on Cardiovascular Disease: Current Findings and Controversies. *Nutrients*, *12*(1), 108. https://doi.org/10.3390/nu12010108

- Vasdev, S., Gill, V., & Singal, P. K. (2006). Beneficial effect of low ethanol intake on the cardiovascular system: possible biochemical mechanisms. *Vascular health and risk management*, *2*(3), 263–276. https://doi.org/10.2147/vhrm.2006.2.3.263

- Hernandez-Hernandez, A., Gea, A., Ruiz-Canela, M., Toledo, E., Beunza, J. J., Bes-Rastrollo, M., & Martinez-Gonzalez, M. A. (2015). Mediterranean Alcohol-Drinking Pattern and the Incidence of Cardiovascular Disease and Cardiovascular Mortality: The SUN Project. *Nutrients*, *7*(11), 9116–9126. https://doi.org/10.3390/nu7115456