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Alcoholic Cardiomyopathy: Multigenic Changes Underlie Cardiovascular Dysfunction

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Abstract

Alcoholism is the third leading cause of preventable death in the United States. Aside from promoting cardiomyopathies, chronic alcohol consumption is associated with an increased risk of dementia, the development of liver or pancreas failure, and cancers of the oral cavity and pharynx. Although a J-shaped curve for all cause mortality has been identified for average alcohol consumption, irregular heavy drinking also carries significantly greater risks for cardiovascular disease.

Alcohol induced cardiovascular disease has a complex multigenic etiology. There is significant variation in the initial presentation of alcoholic cardiomyopathy with diastolic dysfunction possibly being the first indication. Ethanol exposure generates toxic metabolites, primarily acetaldehyde and ROS, which activate several cell signaling systems to alter cell function across many levels. Sudden cardiac death is a known occurrence of alcoholism that may be linked to an arrhythmogenic effect of alcohol.

Microscopic and molecular examination of diseased hearts has demonstrated abnormal alterations to various cellular components, including the mitochondria and myofibrils.

These studies have shown not only the direct impact on myocardial contractility but also disrupted metabolism that determines the long-term survival of the myocardium.

Significant variations in the response to chronic alcohol consumption may be related to unique genotypes that modify the metabolic response to ethanol. Future studies to further characterize the role of different genotypes will help identify those genotypes are more susceptible to chronic alcohol consumption.

Keywords

Alcoholic cardiomyopathy; Heart failure; Alcoholism

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INTRODUCTION

Economic cost of ACM

As early as 1893, Graham Steell, a cardiologist noted the deleterious effects of alcohol on cardiac function [1]. Alcoholism remains a significant health problem and represents the third leading cause of preventable deaths in America [2]. More than 4% of the American population suffers from alcoholism and the annualized economic cost exceeds 223 billion dollars annually [3]. And it has been estimated that 20-30% of cardiology hospital admissions may be alcohol abusers [4,5]. Problematic with ACM is that it is a form of low output heart failure, and left ventricular disease progression leads to pathology in other regions of the body. FY2014 Congressional Budget Justification Alcohol induced cardiovascular disease has a complex multigenic etiology. As a small diffusible molecule ethanol readily crosses all membranes. Aside from promoting cardiovascular disease, chronic alcohol consumption has been associated with the development of liver or pancreas failure, cancers of the oral cavity and pharynx, as well as an increased risk of dementia [6-8]. A graph plotting all-cause mortality against alcohol consumption reveals a J-shaped curve. Light alcohol consumption inversely correlates with total mortality risk; whereas, there is a direct correlation between heavy alcohol consumption and total mortality risk [9]. Although a J-shaped curve has been identified for average alcohol consumption and cardiovascular heart disease there are some qualifiers [10]. Even in individuals that have low overall consumption, irregular heavy or binge drinking carries greater risks for cardiovascular disease [11,12].

Ethanol Metabolites in Alcoholic Cardiomyopathy

Ethanol is absorbed through the stomach and small intestine via passive diffusion [13]. In a two step process, ethanol is metabolized to acetate, via an acetaldehyde intermediate [14]. Although this process predominantly occurs in the liver, the alcohol metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), are also present in the heart and other tissues [13,15,16]. Acetaldehyde is ten times more toxic than ethanol, and has been shown to concentrate in cardiac tissue [13,16]. The consequence is a rise of intracellular free oxygen radicals (ROS) which is viewed as a major damage inducing pathway within the cell [17,18]. Experimental studies that used 4-methylpyrazole (an alcohol dehydrogenase inhibitor) or cyanamide (an aldehyde dehydrogenase inhibitor) found that ROS generation was blocked [19]. In addition to the two-step process of ethanol degradation to acetate, the enzyme fatty acid ethyl ester (FAEE) synthase performs an esterification reaction coupling ethanol to free fatty acids as a non-oxidative means of alcohol metabolism [20]. Circulating FAEEs increase following acute ethanol intoxication [21]. At autopsy, Lange and Sobel observed detectable levels of FAEE in the myocardium only in alcoholics [22]. Problematic with FAEEs is their distribution to mitochondria and inference with oxidative phosphorylation leading to generation of mitochondrial ROS [23].

Clinical Characteristics of Alcoholic Cardiomyopathy

Alcoholic cardiomyopathy (ACM) manifests as a class of dilated cardiomyopathy that is largely indistinguishable from the other subtypes. The delineation of ACM from idiopathic dilated cardiomyopathy in clinical diagnosis is difficult in that there is no one symptom that

uniquely distinguishes it and diagnosis is dependent upon a history of alcohol consumption [24]. More common in men aged 40-59, ACM comprises 3.8% of all cardiomyopathy and this rise to 16-19% as a cause of sudden cardiac death [25-27]. It is often under diagnosed due to alcoholic patients downplaying drinking patterns. In an effort to increase the frequency that clinicians recognize alcohol abuse, Skinner et al. (1986) created the Alcohol Clinical Index—a set of clinical signs and medical history items suggestive of alcohol abuse [28]. Their results achieved 90% accuracy in defining a history of alcohol abuse for patients positive in at least four of these parameters (Table 1). Because the clinical signs can be gathered during a physical exam, and the questions administered in the medical history seem unrelated to alcohol abuse, it is more likely that valid information will be obtained [24]. An alternative approach utilizes biochemical assays to differentiate individuals with ACM from other cardiomyopathies Wang et al. (1989).

Alcoholics were found to have increased levels of the plasma proteins bilirubin, alanine aminotransferase, and gamma-glutamyltranspeptidase as well as significantly elevated mean corpuscular volume [24]. Use of plasma profiles in combination with the alcohol clinical index may be more likely to reach an objective diagnosis of ACM.

clinical Pathophysiology

Early recognition of degradation of cardiovascular function in the alcoholic patient is essential for appropriate treatment. An asymptomatic patient may be defined as an individual who has a deterioration of some cardiac performance parameters but lacks overt clinical symptoms (ie. dyspnea). Postmortem studies, conducted by Steinberg and Hayden confirmed the presence of structural changes in the heart of patients who had never manifested symptoms of congestive heart failure [29]. These patients had a history of chronic alcohol consumption, but never sought clinical treatment for symptoms associated with cardiac abnormalities. Lazarevic et al. reported on cardiac function in asymptomatic alcoholics [30]. Inclusion criteria for this study included a history of heavy alcohol consumption for a minimum of five years, and the absence of symptoms indicative of cardiovascular disease. Using echocardiography, they demonstrated impaired LV diastolic function that included significantly altered isovolumic relaxation time, deceleration time of the early diastolic filling velocity, and late diastolic filling velocity [30]. Others have made similar findings of diastolic dysfunction (impaired deceleration time) as an early consequence of alcohol abuse [31-33]. In addition to diastolic impairment, an otherwise asymptomatic chronic alcoholic may also have systolic dysfunction upon testing. Levi et al. found that preclinical alcoholics have a prolonged pre-ejection period (PEP), and a decreased left ventricular ejection time (LVET)—both indicative of myocardial dysfunction [34]. A shortened ejection time is representative of a reduced stroke volume, and an increased PEP/LVET ratio is also demonstrative of poor myocardial performance [35].

Interestingly, Wu et al. using carotid pulse measurements, observed a gender dependent effect in preclinical ACM (asymptomatic ACM)—that is, female patients displayed no deviation in carotid pulse measurements values for either PEP or LVET while males did [36]. In contrast, Kupari et al. reported that alcoholic women presented with reduced ejection fraction [37]. These studies suggest that in patients presenting with no clinical signs

of heart disease, impaired diastolic function may serve as an early sign of ACM, while systolic dysfunction may represent move metn along the continuum towards failure. The presence of cardiac abnormalities in the asymptomatic alcoholic exemplifies the importance for clinicians to conduct an extensive examination when presented with an individual with a history of ethanol abuse.

The relationship between chronic heavy drinking and sudden cardiac death in men, with and without documented heart disease has been known for sometime [38]. In the latter case, the association between acute alcohol consumption and arrhythmias has been referred to as “holiday heart syndrome”. The most common presentation of acute and chronic alcohol consumption is that of atrial fibrillation (AF) [5,39,40]. Despite the prevalence of AF as an outcome of alcoholism, the underlying mechanisms have not been clearly defined. Collectively, alcoholism creates numerous problems and the changes in cardiac function and rhythmicity point towards dysfunction at the cellular level that are likely to be multigenic.

cellular Alterations in Alcoholic cardiomyopathy

Chronic alcohol consumption produces a myriad of structural and biochemical alterations in the heart, that are observed both intracellular and extracellular [41-44]. Those intracellular studies have centered predominantly on the contractile elements and mitochondrial dysfunction, but also calcium deregulation and the presence of cellular inclusions. The extracellular alteration is predominantly that of proliferative fibrosis.

Similar to human studies, chronic alcohol consumption by animals produced degradation of cardiovascular function allowing them to serve as models of human pathophysiology [45,46].

Early studies demonstrated that alcohol abuse produced cardiomyocytes containing swollen hyperplastic mitochondria, an increased presence of lipid vacuoles, and abundant lipofuscin pigment all suggesting that reactive oxygen species (ROS) may have served as the causal agent [41,42]. There is also structural disorganization as the contractile elements display reduced myofibrils and greater separation of the intercalated disks [42,47]. Compared to the human studies, the murine studies have been proven to be a viable experimental cohort for more highly controlled studies. The myocardial remodeling observed in ethanol treated rats mimics the effects seen in humans. These alterations include: lipofuscin pigments; increased vacuolization; lipid droplets; mitochondriosis accompanied by swelling and deranged cristae; nuclear indentation; and myofibril disorganization [42,48,49]. These structural alterations were observed in animal studies even when low amounts (5% vol:vol) were ingested [49], similar to findings in humans, chronic ethanol consumption resulted in evidence of apoptosis and significant decreases in the number of myocyte nuclei within the left ventricle [50,51]. This reduction in cell count implicates accelerated cardiomyocyte cell death as a contributive factor of congestive heart failure secondary to chronic alcohol consumption.

Myosin Alterations in Alcoholic cardiomyopathy

Several studies have demonstrated that chronic alcohol consumption decreased myocardial protein synthesis as well as myofibrillar protein synthesis and this correlated with a loss of

cardiac mass [52-55]. In part this may be accounted by an impairment of translation initiation, since ethanol induced decreases are reversed by withdrawal of ethanol feeding [54].

Chronic alcohol abuse also induces myofibril disorganization prompting investigations examining the impact of alcoholism on myocardial contractile function. Muscle contraction is dominated by myosin interactions with the cytoskeletal macromolecule actin. Cardiac ventricular myosin, a multisubunit ATP dependent motor protein exists in three isoforms: V1, V2, and V3 [56]. The heavy chains of the myosin isoforms V1 and V3 exist as the homodimers encoded by the alpha myosin heavy chain (MHC) and beta-MHC genes, respectively [57]. In the normal humans, the V3 isoform predominates representing 85-90% in the normal heart [58]. The isoform distribution is important and several studies have shown that isoform expression directly correlates with contractile function [59,60]. In patients, with heart failure, the relative proportion of alpha myosin that comprises total myosin is decreased [44,58,61]. And these small changes in the alpha MHC content are sufficient to cause a decrease in contractile function [59].

Both acute and chronic ingestion of ethanol are cardiodepressive [45, 62-65]. Different animal studies, an ethanol diet have observed a significant increase in the ventricular beta MHC isoform [44]. Changes in the alpha MHC are variable with both no change or a decrease being reported [44,52]. As expected, myocardial myosin ATPase activity was significantly reduced in the alcohol fed animals [44]. The alcohol-induced increase in beta-MHC was due mostly to increased transcriptional activity for the gene encoding beta MHC mRNA [52]. Paradoxically alpha MHC mRNA was also unregulated, but without a change in alpha MHC protein expression. This finding suggests a differential regulation of alpha MHC either as a function of the generalized decreases in protein synthesis or by increased degradation of myofibrillar proteins. Collectively, the shift towards incorporation of beta-MHC into the myocardial sarcomere is likely to contribute to decreases in myocardial contractility.

Mitochondrial Bioenergetics

Mitochondria function to generate ATP, a necessary constituent of muscle contraction [66]. The pioneering work of Krebs, Chance, and others had brought the field to a plateau with the focus on ATP generation. Since the early nineties, recognition of mitochondria's role in apoptosis and cell fate has brought about a strong resurgence of interest in mitochondrial biology [67,68]. More recently, the role of autophagy as a potential alternative to apoptosis has provided further insight into the management of mitochondria. Although secondary to the sarcoplasmic reticulum, mitochondria also serves as a calcium reservoir; another regulatory step of myosin activity and myocardial contractility. Given the heart's almost complete dependence upon aerobic metabolism maintaining mitochondrial function is critical to the well being of the heart. As a membrane delimited organelle, mitochondria possess their own genetic material that is used to encode 37 genes, 13 of which are proteins. Although a small number relative to the more than 1000 proteins localized to the mitochondria, they are critical in the formation and stability of the five complexes that perform oxidative phosphorylation [69].

Mitochondrial dysfunction has a significant role in the development and complications of alcoholic cardiomyopathy [64, 65,70]. Chronic alcohol exposure accelerates mitochondrial dysfunction and apoptosis across different organs including the heart, liver and pancreases [19,64,65,71]. Studies reporting degradation of mitochondrial function have shown significant decreases in mitochondrial protein content both across the whole mitochondrial fraction as well as specific proteins critical for mitochondrial function [52,53,72]. In part due to a decline in the production of mitochondrial proteins, but also a function of the degradation of mitochondrial DNA (mtDNA) [70,73,74]. As a membrane delimited organelle, mitochondria possess their own genetic material that is used to encode 37 genes, 13 of which are proteins. Although a small number relative to the more than 1000 proteins localized to the mitochondria, high fidelity mtDNA is critical in the formation and stability of the complexes important for oxidative phosphorylation [69, 75-78]. The consequence of the decrease in many mitochondrial proteins is poorly functioning mitochondria.

Ethanol induces oxidant stress as a significant cause of mitochondrial dysfunction. However, the role of radical oxygen species (ROS) in cellular metabolism is evolving. The cell's ability to generate different oxidant species in separate and distinct compartments indicates a significant and useful purpose [79,80]. Low concentrations of ROS appear to serve as signaling molecules, while higher levels propagate a destructive outcome [81-83]. The threshold for this biphasic effect appears to be dependent upon the oxidant buffering capacity of the cell, as decreases in glutathione (GSH) levels appear to lower the threshold for stress induced damage within the cell [84-87]. GSH depletion by ethanol feeding in the heart and other tissues as one cause of cellular degradation has been shown in a number of studies [65, 88-90]. In alveolar macrophages and bone, ethanol feeding increased NOX 1,2, & 4 expression increasing NADPH oxidase activity which elevated generation of cytosolic ROS [91,92]. In combination, the consequence is that cytosol-derived ROS may make significant contributions, a concept that is only now emerging from the viewpoint that all oxidant stress is derived from dysfunctional mitochondria.

The production of ROS due to ethanol consumption as much as it is a modifier of mitochondrial function is also directly involved in cell death. In concert with calcium overload, oxidative stress promotes the formation of the mitochondrial permeability transition pore (MPT), a complex composed of three mitochondrial proteins: adenine nucleotide translocase, cyclophilin-D, and the voltage dependent anion channel.

Formation of this pore is also dependent on a balance between pro-apoptotic (ie. Bad and Bax) and anti-apoptotic (ie. Bcl-Xl and Bcl 2) proteins [93-96]. This channel allows for the efflux of cytochrome c into the cytosol. Cytochrome c then interacts family of proteins termed caspases, triggering the signaling cascade leading to apoptosis [94]. Accelerated apoptosis significantly contributes to decreased cardiac mass observed in alcoholics and ethanol fed animals [27, 45, 46, 50, 97, 98]. Given time and progression of the myopathy a dilated cardiac phenotype will become evident.

Arrhythmogenic Effect of Alcohol

The relationship between chronic heavy drinking and sudden cardiac death in the presence or absence of documented heart disease has been known for sometime [38]. A common

presentation of excessive acute or chronic alcohol consumption is that of atrial fibrillation (AF) [5,39,40,99]. Despite the association of AF with alcoholism, the underlying mechanisms of ethanol induced alterations have not been clearly defined, and no clear management path is agreed upon. There are some links between AF, oxidant stress, and calcium dysregulation [100]. As discussed above, ethanol and its associated metabolites generate oxidant stress within the myocardium. However, antioxidant therapy studies targeting the cardiovascular system have yielded results that range from disappointing to a potentially detrimental effect of antioxidants [101-105]. This suggests a more complex interaction of alcohol consumption with oxidant stress leading to degradation of myocardial function.

Chronic alcohol ingestion induces numerous signaling pathways that alter myocardial function. Among them, ethanol-induced activation of the renin-angiotensin system is important for the pathology observed in ACM [100]. Ethanol feeding significantly increased plasma angiotensin II (Ang II) levels that were concomitant with systolic dysfunction, and these effects could be ameliorated by treatment with treatment with the AT1R blockers irbesartan or valsartan [96,106]. Meta-analysis found that the use of renin-angiotensin inhibitors (RAS) lowered the risk of AF compared to treatments using non-RAS inhibitors [107]. Complicating the issue are studies that have identified nucleotide polymorphisms of angiotensin converting enzyme (ACE) that directly altered plasma levels of Ang II [108,109]. These genotypes have been shown to have a significant effect on the incidence of alcohol-induced cardiomyopathy and may explain the variable effects of long-term alcohol consumption amongst patients [108,109]. Ang II is the bioactive molecule produced by the angiotensin converting enzyme (ACE) and linked to cardiac hypertrophy and other vascular disorders. Ang II activates a myriad of intracellular pathways among them cytochrome P450, calmodulin-dependent protein kinase II, NAD(P)H oxidase and inducible nitric oxide synthase (iNOS) [110,111]. Thus in addition to raising intracellular calcium, AT1 receptor activation stimulates the production of the free radical species superoxide anion and nitric oxide [111,112]. Ricci et al. observed two distinct phases of robust oxidant generation in cardiomyocytes exposed to Ang II [111].

The first phase was attributed to the induction of NAD(P) H oxidase and iNos activity. The second phase was due to mitochondrial generation of oxidants that induce mitochondrial DNA (mtDNA) damage that destabilizes the mitochondrial complexes as well as interfering with their formation [75-77,96,111,113]. At this time it is unknown if the combination of these changes have a greater effect on the myocardial conduction system compared to the cardiomyocytes, or that the much smaller number of cells in the conduction system makes them more vulnerable. Irrespective of the mechanisms of the pathology, AF is a significant concern in the management of alcoholics.

CONCLUSION

Alcoholism is the third leading cause of preventable death in the United States. Protocols for screening alcoholism will benefit detection and the long-term prognosis. Aside from promoting cardiomyopathies, chronic alcohol consumption is associated with the development of liver or pancreas failure, cancers of the oral cavity and pharynx, as well as

an increased risk of dementia. Although a J-shaped curve for all cause mortality has been reported for average alcohol consumption and cardiovascular heart disease, irregular heavy drinking also carries greater risks for cardiovascular disease.

Alcohol induced cardiovascular disease has a complex multigenic etiology. Ethanol exposure generates toxic metabolites, primarily acetaldehyde and ROS, which activate several cell signaling systems that alter cell function across many levels. Chronic heavy drinking and sudden cardiac death are known occurrences and likely a function the arrhythmogenic effect of alcohol. Microscopic and molecular examination of diseased hearts has demonstrated abnormal alterations to various cellular components, including the mitochondria and myofibrils. These studies have shown not only the direct impact on myocardial contractility but also disrupted metabolism that determines the long-term survival of the myocardium. Significant variation in the response to chronic alcohol consumption exists may be related to unique genotypes that modify the metabolic response to ethanol. Future studies to further characterize the role of different genotypes will help identify those genotypes are more susceptible to chronic alcohol consumption.

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Table 1

Alcohol Clinical Index

Clinical Signs	Medical History Items
Hand tremor	Inability to concentrate
Tandem gait	Troubled by mental confusion
Deep knee bend	Difficulty in remembering recent events
Spider naevi (>5)	Hallucinations
Collateral circulation	Hands shake in morning
Gynaecomastia	Troubled by frightening dreams
Abdominal tenderness	Wake up with a headache
Rhinophyma	Hands often tremble
Facial erythema	Injured in an assault or fight
Coated tongue	Wake up feeling thirsty
Edema of soft palate	Dry coated tongue
Nicotine Stains	Cough on most days
Palmar erythema	Bring up phlegm
Bruises or abrasions	
Scars (secondary to trauma)	
Cigarette burns	
Tattoos	

Adapted from Skinner et.al. 1986^[29]