Review

Alcoholic Cardiomyopathy: Clinical and Molecular Findings

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It has been known for some decades that chronic alcoholism can lead to dilated cardiomyopathy. Although excessive drinking is known to result in alcoholic cardiomyopathy and light-to-moderate drinking may confer some cardiovascular benefits, recent studies suggest that it is not only the quantity, but also drinking patterns and genetic factors, that may influence the relation between alcohol consumption and cardiovascular disease. Alcoholic patients consuming > 90g of alcohol a day for > 5 years are at risk for the development of asymptomatic alcoholic cardiomyopathy. Those who continue to drink may become symptomatic and develop signs and symptoms of heart failure. We summarize the experimental and clinical evidence regarding the role of alcohol in pathophysiology of alcoholic cardiomyopathy.

Key words: Alcoholic Cardiomyopathy, Heart Failure, Congestive Heart Failure

Introduction

Regular heavy ethanol consumption has been associated with a type of non-ischemic dilated cardiomyopathy termed alcoholic cardiomyopathy (ACM). In general, alcoholic patients consuming > 90g of alcohol a day (approximately seven to eight standard drinks per day) for over 5 years are at risk for the development of asymptomatic ACM, which is clinically expressed as an impairment of left ventricular function (non-symptomatic stage). Those who continue to drink may become symptomatic and develop signs and symptoms of HF (symptomatic stage).[1] ACM is a specific heart muscle disease of a known cause and is classified as a dilated cardiomyopathy.[2,3] ACM is usually discussed in the category of agents that is toxic to the myocardium.

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The prevalence of ACM is variable and, fortunately, not all heavy drinkers have developed ACM. Excessive ethanol intake is reported in 3% to 40% of patients with idiopathic dilated cardiomyopathy (IDC).[4] Among ACM cases, men show the largest percentage, whereas women represent approximately 14%.[5]

However, a greater risk of ACM, as well as skeletal myopathy, exists in women than in men for any given lifetime amount of alcohol.[6]

This distinct form of congestive heart failure (CHF) is responsible for 21-36% of all cases of non-ischemic dilated cardiomyopathy in Western Society. Without complete abstinence, the 4-year mortality for ACM approaches 50%.[7]

Similar to other dilated cardiomyopathies (idiopathic, viral or immune), ACM is characterized by a dilated left ventricle (LV), normal or reduced LV wall thickness, and increased LV mass. Unlike other cardiomyopathies, such as immunologic cardiomyopathies, there are no

specific immuno-histochemical, immunologic, or other criteria for the diagnosis of ACM. Therefore, its diagnosis is usually by exclusion.

In terms of the amount and duration required to produce symptomatic ACM and heart failure, the data are very limited. Even though there is lack of a specific dose-response relationship, as well as variability among studies in terms of the amount of alcohol consumed and duration of alcohol abuse, some general conclusions can be made regarding alcohol consumption and ACM. In general, asymptomatic alcoholic patients with changes in cardiac structure and function had a history of consuming > 90 g/d of alcohol (some studies report > 200 g/d) for > 5 years.[8-13] However, the average duration of drinking reported in the majority of studies was 15 years. [8-13] As a point of reference, there is 12 g of alcohol in a standard drink; Emerging evidence suggests that moderate alcohol consumption is not associated with significant cardiotoxicity. Moderate alcohol consumption has been associated with lower risk of CHF in prior studies of healthy individuals.[14,15] Recent studies suggest it is not only the quantity, but also drinking patterns and genetic factors, that may influence the relation between alcohol consumption and cardiovascular disease.[16] Basic research exploring the effect of ethanol on cardiomyocyte contractility is therefore obviously needed to propose new concepts and mechanisms.

Pathophysiologic mechanisms

Alcoholic cardiomyopathy is manifested as ventricular dysfunction although its pathogenesis remains obscure. The pathophysiology of ACM may involve cell death (possibly due to apoptosis) and changes in many aspects of myocyte function. Animal models have demonstrated that long-term alcohol consumption produces a number of histologic and cellular changes. These changes fall into the following categories: myocyte loss, intracellular organelle dysfunction, contractile proteins, and calcium homeostasis. These changes can alter several aspects of myocyte function and therefore may lead to myocyte dysfunction. This may represent the primary injury caused by alcohol, which eventually culminates in reduced myocardial function and ACM.

Myocyte loss

In many organ systems, including the heart, myocyte loss or cell death may be an important component of organ dysfunction and pathology.[17] Cell death can result from either necrosis or apoptosis (programmed cell death).[17] Others[18] have shown that ethanol-induced apoptosis is probably a critical mechanism underlying ethanol-induced disorders. There are several early reports in humans with ACM and animal models of cardiomyopathy that support a role for myocyte loss as a mechanism underlying alcohol-induced cardiac dysfunction. Capasso et al[19] found a significant loss of myocytes in the LV from rats fed ethanol in their drinking water for 8 months. Recently, Chen et al.[20] using primary neonatal myocyte cell cultures, examined the effects of acute alcohol on the process of apoptosis which increased the protein levels of the pro-apoptotic protein Bax and increased caspase-3 enzyme activity (the latter is a member of a family of intracellular proteases activated in apoptosis). In this same experiment, the application of insulin-like growth factor (IGF)-1 attenuated the apoptotic effects of ethanol on serum withdrawal.[20] IGF-1 has multiple effects on the cell, including cell proliferation and

differentiation, whereas activation of signaling components downstream to the IGF receptor is linked to the development of hypertrophy. In contrast to the findings of Chen et al.[20], Jänkälä et al.[21] found no evidence of apoptosis following an acute infusion of alcohol but did find increased messenger RNA p21 levels. P21 is an inhibitor of cyclin-dependent kinases, and may be one of the many proteins involved in the hypertrophic response.[21] However, it remains unknown whether the process of apoptosis is important in the pathogenesis of ACM.

Intracellular organelle dysfunction

Changes in cardiac metabolism in myocardial failure and after alcohol ingestion are discussed. However, a single key factor involved in the development of cardiac insufficiency is not established, although it is well known that ethanol interferes with lipid metabolism and fatty acid composition of sarcolemma, as well as the properties of the membrane function of the sarcoplasmic reticulum.[22] There are many early reports [23-25] documenting the adverse effects of long-term alcohol consumption on mitochondrial and sarcoplasmic reticulum function. In fact, alcohol and its metabolite acetaldehyde confer a toxic effect on mitochondria as well as on the sarcoplasmatic reticulum, which is dependent on both the mean daily consumption and the duration of alcohol intake.[26] Changes in mitochondrial function can affect cell function in many ways and therefore maybe a key contributor to intrinsic cell dysfunction. Alcohol inhibits mitochondrial respiration and the activity of enzymes in the tricarboxylic acid cycle and interferes with both mitochondrial calcium uptake and binding. Ethanol profoundly affects myocardial lipid metabolism. Beckemeier et al.[27] have found an increased level of fatty ethyl esters in the alcoholic heart, which can attach to the mitochondria and disrupt their function.

Contractile proteins and calcium homeostasis

In isolated cardiomyocyte, acute ethanol treatment induces a dose-dependent reduction of maximum shortening. This negative inotropic effect is significant at very low concentrations (0.05%), and the dose-response relationship is not linear, which suggests that ethanol may act upon cardiac myocyte contraction in several ways.[28] As a potential mechanism of alcohol-induced cardiac damage, Preedy et al, demonstrated that 6 weeks of alcohol consumption was associated with a decrease in cardiac myofibrillary proteins and that there were no changes in actin, vientiane, tropomyosin, and myosin light chains I and II.[29]

At least in the latter stages of ACM, abnormalities in Ca^{2+} homeostasis have been implicated as a cellular mechanism. Calcium homeostasis is essential for normal cellular function, and similar to other cell types, the myocyte tightly regulates intracellular shifts in Ca^{2+}. Normal Ca^{2+} regulation is rather complex and depends on a number of factors, such as the abundance and functioning of sarcolemmal L-type Ca^{2+} channels, sarcolemmal transport pumps (Na/Ca exchanger), and the sarcoplasmic reticulum (storage and release Ca^{2+}). Therefore, changes in any one of these modulating factors can alter Ca^{2+} homeostasis. Guppy and Littleton[30] reported that a short period of heavy alcohol exposure is associated with an increase in calcium channels and found a decrease in diastolic pressure and attenuated increase in systolic pressure in response to increasing concentration of extra-cellular calcium and the calcium channel agonist,

Bay K 8644. Based on this abnormal contractile response to calcium, these investigators speculated that alcohol induces an upregulation of L-type calcium channels, which then increases the threshold of the heart for calcium overload. It is important to note that their model is one of short alcohol exposure and these changes are found in the absence of detectable hypertrophy (no change in heart weight-to-body weight ratios).

Others[31-33] have also found the negative inotropic effect of acute alcohol still existing in the presence of increasing concentrations of extracellular calcium or calcium channel agonists, such as Bay K 8644. This suggests that the negative inotropic affect of acute alcohol is due to alterations in myofilament sensitivity or myofilament alterations. Figueredo et al.[34] have also shown that changes in myocardial contractility due to chronic ethanol exposure do not result from altered calcium management but rather from changes at the myofilament level.

Acetaldehyde diminishes myocardial protein synthesis and inhibits Ca++-activated myofibrillary ATPase. It is well established that ethanol impairs excitation-contraction coupling, leading to impaired cardiac contractility.[35] Excitation-contraction coupling could be disturbed at the levels of the sarcolemma, sarcoplasmic reticulum, mitochondria, and between calcium and the regulatory proteins. L-type calcium channels, involved in excitation-contraction coupling, are disturbed in animal models of persistent ethanol consumption.[36] Deficiencies in Ca++ delivery systems of excitation-contraction coupling on the myosin ATPase activity could be responsible for the diminution in cardiac contractility.

Aistrup[37] report expands our understanding of the changes in cellular excitation-contraction coupling in cardiac myocytes during the transition period where acute ethanol exposure becomes chronic. These results show that soon after the onset of chronic ethanol consumption, the well-documented negative inotropic effect of acute ethanol exposure is temporarily counteracted by adaptive mechanisms, leading to the expression of a temporary positive inotropic effect. This observation shows how the acute effects of ethanol on excitation-contraction coupling at the cellular level translate into chronic conditions and thus the onset of ethanol-induced cardiac disease may be of fundamental significance. They may help understand the ambiguous effect of ethanol on the heart in the clinical setting. In future, identifying the precise mechanisms responsible for this compensatory adaptation and its subsequent loss may allow us to design new approaches for the prevention and treatment of ACM.

Neurohormonal systems

As a consequence of myocyte dysfunction, other cell types or systems might be activated, such as sympathetic nervous system (norepinephrine), rennin angiotensin system (RAS) and natriuretic peptide system (NP). Sustained and high levels of norepinephrine exert adverse effects on the myocardium, some of which include myocyte hypertrophy, toxicity, and apoptosis.[38] All of these cellular events are linked to LV remodelling.[39] Adams and Hirst[40-42] demonstrated in male Sprague-Dawley rats that severe alcohol (10% weight / volume) intoxication over a 2- to 4-day period (via gastric intubation) was associated with marked increases in urinary norepinephrine and epinephrine levels, which are correlated with increases in heart weight to body weight ratios. In these studies, heart weight to body weight ratios were used

as an indirect measure of hypertrophy; therefore, these investigators[40-42] postulated a direct role for catecholamine in the induction of alcohol-induced hypertrophy.

Activation of the RAS may contribute to the development of alcoholic cardiomyopathy. Cheng. et al.[43] have evaluated the effect of angiotensin II (Ang II) type 1 receptor (AT1) blockade on the development of alcoholic cardiomyopathy. Alcohol ingestion caused sustained RAS activation with progressive increases in plasma levels of Ang II, renin activity, LV angiotensin-converting enzyme activity, and LV myocyte Ang II (AT1) receptor expression. The RAS activation was followed by a progressive fall in LV contractility; reductions in the peak velocity of myocyte shortening and re-lengthening and decreased peak systolic Ca2+ transient ([Ca2+] iT) and L-type Ca2+ current (ICa-L). More Recently, Jing et al.[44] also suggested that RAS is activated during the development of ACM. Moreover, extra-cellular signal regulated kinase 1 and 2 (ERK1/2) plays a key role in the regulation of protein expression of peroxisome proliferator-activated receptors (PPAR-alpha and PPAR-gamma) by RAS in ACM.

Oxidative stress

The major ethanol metabolite acetaldehyde is suspected to play a culprit role in the onset of this myopathic state. Animal models have demonstrated that both acute[45] and chronic[46] ethanol exposure increases myocardial lipid peroxidation and protein oxidation and reduces mitochondrial glutathione (GSH) content, suggesting that reactive oxygen species play an important role in the onset of ardiac toxicity. These oxidative damages to lipids and proteins along with the decrease in endogenous antioxidant capacity due to the reduced GSH concentrations indicate alcohol-induced oxidative stress. The acute ethanol administration produced a significant decrease in the mitochondrial GSH concentrations and a slight decrease in cytosolic GSH. The decrease in GSH concentration in the mitochondria would thus be highly responsible for reactive oxygen species (ROS) generation and the structural and functional damage in this organelle. Reinke et al.[46] have observed that ROS played an important role in the onset of cardiac toxicity in chronically ethanol-intoxicated animals.[46] Accumulation of ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals along with a compromised antioxidant capacity contribute to excess damage to cellular carbohydrates, proteins, lipids, and nucleic acids.[47,48] Among the endogenous antioxidant systems, reduced glutathione (GSH) plays multiple roles in the detoxification of toxic chemicals.[49] However, the mechanism of ROS and reactive nitrogen species (RNS) generation by alcohol and its metabolites and their differential contributions to the overall oxidative injury have not been probed, which would be an important undertaking in the future.

Genetic findings

There are inter-individual variations in the sensitivity of the myocardium to alcohol-induced myocardial damage, suggesting that ACM may be a multifactorial disease in which environmental and/or genetic traits influence the occurrence, pathogenesis, and progression of disease. For example, chronic ethanol exposure in vivo induces rat cardiac left ventricular p53 gene expression. Expression of p53 is also gender-dependent, males having higher p53 mRNA levels than females. This

preliminary finding suggests a role for the p53 gene in ethanol-induced cardiac remodelling. The results might also have some relevance for the known gender-dependent differences in propensity to cardiovascular disease.[50]

In summary, the pathophysiology and progression of ACM is complex and involves changes in many aspects of myocyte function.[51] The point at which the changes in mitochondrial, sarcoplasmic reticulum, contractile protein, and calcium homeostasis culminate in intrinsic cell dysfunction is incompletely understood.

Clinical characteristics

Alcoholics can present with either a preclinical (asymptomatic) or symptomatic ACM. The latter is primarily distinguished from the former by signs and symptoms of HF.[52,53] The development of symptoms may be insidious, although some patients have acute and florid left-sided congestive heart failure.[54] The symptoms of CHF in these patients do not differ from any other cause of CHF. In fact dyspnea, orthopnea and paroxysmal nocturnal dyspnea are frequently observed. Palpitations and syncope may be present. A paroxysm of atrial fibrillation is a relatively frequent initial presenting finding. Supra-ventricular arrhythmias are also frequently observed in patients with overt ACM.[54] Clinical characteristics as well as age of onset are similar in patients with IDC and ACM.[8,55] An equal percentage of dilated cardiomyopathy and ACM patients presented with either New York Heart Association (NYHA) class I-II or class III-IV functional status, and all echocardiographic and hemodynamic parameters were similar between the groups.[55] The deterioration of systolic function is significantly related with the level of alcohol consumption and duration of abuse.[56] Symptomatic ACM patients are also likely to be in NYHA class III-IV, have systolic dysfunction (decreased EF), and signs and symptoms of HF, such as elevated jugular venous pressure, S_3-S_4 heart sounds, pulmonary rales, and peripheral edema.[52] The prognosis *quo ad vitam* for alcoholics seems to be worse when compared with patients with dilated cardiomyopathy.

Diagnosis

The recognition of ACM in patients with dilated cardiomyopathy is essential as they may regress, at least partially in a relatively short period, with abstention. The diagnosis still rests on the coincidence of alcoholism and a dilated hypo-contractile heart in the absence of any other cause of dilated cardiomyopathy. Chronic ethanol consumption significantly deteriorated left ventricular diastolic function irrespective of its effect on blood pressure and left ventricular mass.[56] Systolic left ventricular dysfunction is relatively common in even asymptomatic alcoholics, but whether diastolic function is also altered is much less well-studied. In work of Kupari M et al.[57] LV mass index and posterior wall thicknesses were higher in alcoholics than in controls, but there was no statistically significant difference either in end-diastolic size or in systolic ventricular function. However, more abnormalities were found in the Doppler indices of diastolic function. The alcoholics had a prolonged relaxation time, a decreased peak early diastolic velocity, a slower acceleration of the early flow, and a higher atrial-to-early peak velocity ratio. This pattern of changes suggests a primary abnormality in the relaxation of the left ventricle. In multivariate analyses, the abnormalities in the Doppler indices were

independent of the duration of alcoholism, the quantity of the most recent ethanol exposure and the increased mass of the LV. Impaired early filling of the LV due to delayed relaxation is common in asymptomatic alcoholics and may in fact be the earliest functional sign of preclinical ACM.[57] Lazareviç et al.[11] concluded that LV dilation is a very early finding that precedes changes in LV mass and diastolic dysfunction.[11] Interestingly, EF was essentially the same between the alcoholic and control groups. Their findings are similar to those of Kupari et al.[10] who found that diastolic dysfunction rather than systolic function appears to be an early finding in asymptomatic alcoholic patients with a similar duration of drinking (median, 11 years). In summary, it appears that in asymptomatic male alcoholics, the most prominent early finding was LV dilation and an increase in LV mass. Diastolic dysfunction appears to be an early finding; however, patients may have both diastolic and/or systolic dysfunction. Some patients may also have a mild degree of wall thickening. More than likely, both the drinking histories and other unidentified individual variables may account for differences in these studies.

Therapy

Some reports[58,59] indicated prognosis was better in ACM patients compared to patients with other types of cardiomyopathies but the prognosis is poor after development of HF. In alcoholics who develop cardiac dysfunction, abstinence is thought to be essential to halt further deterioration of cardiac contractility.[60] Abstinence after development of milder HF can stop progression or even reverse symptoms in some cases, otherwise severe HF ensues leading to a poor prognosis. Except abstinence, treatment of alcoholic cardiomyopathy is based on the regimen of therapy for HF to reduce the size of the dilated heart and to mitigate the symptoms of HF.[26] In fact there are no studies that have examined specific pharmacotherapeutics in patients with ACM. Patients with ACM presenting in HF with systolic dysfunction (EF $\leq$40%) should be treated according to the Agency for Health Care Policy and Research and Heart Failure Consensus recommendations.[61,62] These guidelines recommend the use of pharmacologic agents that inhibit the LV remodelling process, as well as treat the patient's symptoms. The findings of Fauchier et al.[8] and Gavazzi et al.[55] indicate that Agency for Health Care Policy and Research-guided therapy is associated with an improvement in LV function. The different classes of agents include diuretics, cardiac glycosides, ß-adrenergic blockers and angiotensin-converting enzyme (ACE) inhibitors.

Learning point

Long-term alcohol consumption is an important cause of a dilated cardiomyopathy.

- Men and women who consume alcohol (> 90 g/d or more than eight drinks per day) for >5 years are at risk for the development of ACM.
- There is an asymptomatic stage of ACM, characterized by LV dilatation, increased LV mass, and diastolic dysfunction.
- The symptomatic ACM stage is characterized by pronounced LV dilatation, systolic dysfunction, and signs and symptoms of HF.
- The pathophysiology of ACM is complex and involves many aspects of myocyte function.
- Treatment includes alcohol abstinence and recommended heart failure pharmacotherapies.

Conclusion

The pathophysiology of ACM is complex and involves many aspects of myocyte function. The reasons for changes in mitochondria, sarcoplasmic reticulum, contractile protein, and calcium homeostasis result in cell dysfunction are incompletely understood. There are inter-individual variations in the sensitivity of the myocardium to alcohol-induced myocardial damage, suggesting that ACM may be a multifactorial disease in which environmental and/or genetic traits influence the occurrence, pathogenesis, and progression of disease.

Treatment of both groups of ACM patients should include alcohol abstinence, and symptomatic patients should be treated with recommended heart failure pharmacotherapies.

Conflicts of Interest no declare.

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