

## Alcoholic Cardiomyopathy: Old and New Insights

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### Abstract

Alcohol cardiomyopathy (ACM) is a chronic dilated heart disease with decreased left ventricular ejection fraction that may be detected in one-fourth of high-dose alcohol consumers. It causes progressive diastolic and systolic dysfunction, supra and ventricular arrhythmias leading to heart failure and increased mortality. The main etiological factor for ACM is ethanol consumption that affects the myocardium in a dose-dependent manner. The mechanisms of ACM are diverse, synchronic and synergistic. Alcohol alters the channel and receptor structure of the cell membrane, decreases intracellular calcium transients, increases oxidative and inflammatory damage, decreases structural protein synthesis and interferes with excitation-contraction coupling mechanisms. Subjects with excessive alcohol consumption may have a subclinical cardiomyopathy with atrial and LV diastolic dysfunction measured by echocardiography or cardiac MR. Subclinical LV dysfunction may progress and later appear clinical features of heart failure. Cardiac myocytes adapt to ethanol aggression by cell and nuclear hypertrophy and dilatation of heart chambers. Progressive myocyte structure disarray and apoptosis produce myocyte loss, hypertrophy of the remaining cells, subendocardial and interstitial fibrosis and low-degree myocyte regeneration. In addition, ethanol also interferes with cardiac repair and adaptation mechanisms. Thus, local cardiomyokines (FGF-21) and growth factors (myostatin, IGF-1, leptin) are modified by ethanol, limiting cardiac remodeling and myocyte regeneration, and leading to abnormal hypertrophy and eccentric ventricle dilatation. This imbalance between aggression and protection mechanisms induces progressive myocyte loss and heart dysfunction. Alcohol abstinence is the main goal in ACM, although control drinking (<60 g/day) may allow recovery of LV function. Monitoring of systemic mediated alcohol-damage, and correction of vitamin and ion deficiencies is needed. Heart failure in ACM should be treated similar to other dilated cardiomyopathies. Heart transplantation is limited to subjects without other organ damage who are able to abstain from alcohol. New preventive and therapeutic strategies are under development to decrease alcohol-mediated myocyte damage and increase heart protective and repair mechanisms.

**Keywords:** Alcohol; Ethanol; Dilated cardiomyopathy; Natural history; New treatments; Perspectives

### Introduction

Alcoholic beverages are consumed in different forms and doses by almost all human cultures and populations. Throughout history, many different effects of alcohol have been described in the human body, some related to injuries and others to protection. One one hand, there is a pleasant tonic and healthy cardiovascular effect when consumed at occasional low doses in a social context, decreasing, for instance, cardiovascular morbidity and mortality [1]. On the other hand, alcohol is a toxic able to induce a variety of noxious cardiac and vascular effects when consumed in binges or at a high-cumulated lifetime consumption, increasing cardiovascular morbidity and mortality [2,3].

The first recognition of alcohol-related cardiac damage was performed by Hippocrates in the old Greece, IV centuries B.C. Hippocrates already recognized a congestive heart failure in those subjects who consumed large amounts of alcohol beverages and, therefore, recommended to avoid alcohol consumption on this setting. However, no major scientific advances were made after that until the end of the XIX<sup>th</sup> century when alcohol-induced heart disease was described in German beer drinkers. At that time, the disease was not directly attributed to alcohol itself but rather to some additives or contaminants used in the processing of alcoholic beverages such as

arsenic [4] or cobalt contamination when used as beer antifoam [5]. Others attributed alcohol-induced heart damage to malnutrition and/or thiamine deficiency (Western beriberi) [6] or selenium [7] (Keshan disease in China) magnesium and phosphate deficiencies [8]. Finally, the identification of alcohol (ethanol) as the major factor for heart damage arose from the results of controlled clinical studies that observed the development of alcohol-induced heart damage in the absence of vitamin deficiencies, ionic derangement or malnutrition [9]. A clear dose-dependent effect was established between alcohol consumption and heart damage. In fact, the total lifetime dose of alcohol consumed by a subject was the most relevant parameter related to the development of LV dysfunction (low ejection fraction) and alcoholic cardiomyopathy (ACM). Chronic ACM is developed over a long period of time of usually more than 10 years and thus, usually starts between the third to fifth decades of [3,9]. Binge drinking is also an additional negative factor that may increase chronic alcohol-mediated heart damage and/or induce acute exacerbations of ventricular dysfunction, malignant arrhythmias and potential cardiac arrest [2,3].

### Natural History of ACM

Alcohol-mediated heart damage depends on the quantity and pattern of alcohol consumption as well as the presence of genetic and

susceptibility factors or other additional noxious factors such as tobacco and cocaine use [10,11].

### Acute high-dose binge drinking

Acute high-dose binge drinking (consumption of 5 or more drinks per occasion) [12] may induce a transitory depression of LV function and even may cause acute heart failure in subjects with previous heart disease.

### Chronic high ethanol intake

The usual pattern of ethanol consumption to inflict cardiac damage is continued moderate to high misuse of alcoholic beverages for more than 10 years. The Total Lifetime Dose of Ethanol (TLDE) consumed by one individual expressed as kg of ethanol consumed divided by kg of body weight (kg/kg) is inversely correlated with the LV Ejection Fraction (LVEF) [9]. A threshold of 5 kg/kg has been defined to induce diastolic ventricular dysfunction, a situation detectable in one third of chronic alcohol consumers [13]. This is the first manifestation of ACM, usually being subclinical and only detectable by cardiac echocardiography, Magnetic Resonance Imaging (MRI) or radionuclide angiography [3,14]. Subclinical systolic dysfunction was described in the Framingham Heart Study in males consuming >15 drinks per week or in females consuming >8 drinks per week [15]. We also found LV dysfunction with a decrease in the LVEF <50% and the LV shortening fraction as well as an increase in LV diameters and mass in 13% of male chronic alcohol consumers with a TLDE >20 kg/kg [3,16].

### Subclinical left-atrial dysfunction

Subclinical left-atrial dysfunction has also been detected in alcoholics with a TLDE >15 kg/kg using 2D speckle-tracking echocardiography, showing a significant reduction of left-atrial pump and reservoir function [17].

### The development of heart failure (HF)

The development of heart failure (HF) in ACM is similar to that of other causes of dilated cardiomyopathy with decreased left ventricular ejection fraction that lead to exercise dyspnea, orthopnea and peripheral edema or anasarca [9-11]. The relationship between ethanol consumption and HF follows a "U-shaped" curve, with the lowest prevalence of HF at a dose of 10-20 g/day and rising at higher doses. In a 5-year longitudinal study that included high-dose ethanol consumers, ACM with HF appeared in 26% of men consuming >100 g/day and 20% of women consuming >80 g/day [18]. In our experience, the development of ACM requires chronic consumption with a TLDE of more than 7 kg/kg in men and 5 kg/kg in women over a period of at least 10 years. This means a minimum daily dose of 100 g/day in men and 80 g/day in women [3,14]. In advanced cases, mortality is related to progression of HF and ventricular arrhythmias causing cardiac arrest and death. The annual mortality rate of advanced cases of ACM is 15% [10].

### Genetic susceptibility

Genetic susceptibility may also influence the damaging effect of ethanol on the heart. Some alcohol dehydrogenase (ADH) and acetaldehyde to acetate by aldehyde dehydrogenase (ALDH) polymorphisms increase the noxious effect of acetaldehyde on the

heart and impair heart function [19]. We also observed that the presence of the DD homozygous deletion genotype polymorphism of the angiotensin-converting-enzyme (ACE) gene increases the susceptibility to LV dysfunction in chronic alcohol consumers [20].

### Gender

Women are more sensitive than men to develop alcohol-induced heart damage. One study showed that the prevalence of subclinical LV dysfunction was similar in women and men, although women reported a significantly lower TLDE (14.2 vs. 23.1 kg/kg) [21]. In addition, compared to men, women show a significantly steeper dose-related inverse relationship between LVEF and TLDE [18]. This means that at a given dose of ethanol consumption, contractile LV function in women will be significantly lower than in men [2,3].

### Reversibility

ACM may partially reverse with abstinence from alcohol, which is the preferred goal [22]. However, in end-stage ACM with a LVEF <15% LV function reversibility is not usually observed [3]. We observed a significant improvement in LVEF in alcoholics who were able to reduce ethanol consumption to doses <50 g/day in a control drinking scenario [23]. In fact, any reduction of previous high-dose ethanol consumption improves LV function.

### Pathogenic Factors

Cardiac myocytes are excitable cells with complex mechanisms of signaling, energy production and contractility [24,25]. Ethanol induces persistent, progressive heart damage that involves almost all the structures of the cardiac cell, altering the two main physiological processes of the cardiac myocyte which are excitation-contraction coupling and cell energy availability [26,27]. Ethanol is a very active biological molecule that easily diffuses through all the biological membranes and targets intracellular organelles. It changes membrane composition, fluidity and permeability, the activity of membrane ion (VOCC) channels and pumps, and alters intracellular calcium-transients. The ryanodine L-type Ca<sup>2+</sup>-release VOC channel in the sarcoplasmic reticulum is also impaired by alcohol, decreasing sarcomeric [Calcium]<sup>2+</sup>-release that induces sarcomere excitation-contraction coupling [28]. Ethanol interferes and decreases the rates of protein heart synthesis and increases protein breakdown at different levels (protein synthesis rate, transcription, RNA content and translational processes) [29], causing a loss of miofibrillary contractile (myosin, actin, titin and troponin) as well as non-structural regulatory and heat-shock proteins. It also interferes with the mitochondrial energy supply, decreasing respiratory complex activities and changing the mitochondrial structure. Ethanol alters the total cardiac oxidant status, specifically superoxide dismutase (SOD) and alpha-tocopherol content [30] which induces ROS, malondialdehyde (MAD) and ethanol-acetaldehyde adducts generation, with additional potential inflammatory damage. Ethanol is also able to induce mitochondrial-dependent apoptosis through caspase activation and gene dysregulation [31] and also alters the cell 3D structure affecting desmosomes, connection channels and extracellular matrix structure [32].

In addition to these multiple damaging effects, ethanol also decreases the cardiac cell capacity to modulate this damage. This is mediated by interference with myokines (FGF-21) and local hormones and growth-factors such as myostatin [33], IGF-1 [34], ghrelin [35]

and leptin [36]. Thus, ethanol decreases the myocyte proliferation rate probably by myostatin up-regulation [33] and modifies the mechanisms of cardiac plasticity [37]. The final balance of alcohol-induced heart effects is a clear increase in the damaging factors and a decrease in protective heart mechanisms leading to progressive cardiac myocyte damage and loss by apoptosis and necrosis and the substitution of these cells by non-functional fibrosis [38,39].

At a structural level, the first steps of ACM are characterized by cell and nuclear hypertrophy, with an increase in myocyte size and saccome disarray [40]. This abnormal hypertrophy is associated with cardiac dysfunction and also increased morbidity and mortality. Progressive myocyte necrosis develops, being substituted by subendocardial and interstitial fibrosis with great hypertrophy of the remaining myocytes [3,24]. According to the Frank-Starling law, at a functional level, the LV develops eccentric enlargement and LV function progressively decreases, with low-output dilated cardiomyopathy (CMP). Patches of subendocardial fibrosis may be macroscopically seen in end-stage cases [21,38].

## Management of ACM

### Pharmacologic treatment

Pharmacologic treatment of acute heart failure in ACM is similar to that of other dilated CMP reducing preload with diuretics and after load with vasodilators acting on the renin-angiotensin-aldosterone system, with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor-II antagonists (ARA-II), and or  $\beta$  or  $\alpha_1$  adrenergic blockers [1-3]. Digoxin is indicated when high-rate atrial fibrillation coexists. Anticoagulant therapy to avoid thromboembolism should be balanced with the risk of bleeding, mainly in patients with liver cirrhosis. Anti-arrhythmic treatment should be considered as in other CMP during short-term periods. Dietary salt restriction, rest and oxygen administration may also be needed.

### Abstinence

As previously reported, the most important factor related to improvement of ACM is the degree of reduction or total abstinence from previous alcohol consumption [41]. The main efforts should address this goal with specific cognitive-behavioral support [42]. In subjects not able to abstain, we observed that a significant reduction of ethanol intake to 50-60 g/day in a control-drinking situation is enough to significantly improve LV function. In other words, any reduction of previous high-alcohol consumption is useful [23].

### Improving systemic alcohol-mediated damage

Similar to what happens in other alcohol-dependent organ damage [1], ACM should be considered as a part of the systemic damage inflicted by alcohol in a specific patient. Correction of protein and caloric malnutrition, a body mass index  $<18 \text{ kg/cm}^2$ , ionic derangements (deficiencies in  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{P}^{3+}/5^+$ , and  $\text{Mg}^{++}$  or  $\text{Fe}^{+}/+++$  and  $\text{Cu}^{+}/+++$  excess), vitamin (pyridoxine, thiamine, cobalamin) or cofactor (folic acid) deficiencies help to stabilize ACM [43]. Control of other systemic hepatic (encephalopathy, anasarca), renal (kidney failure) or neurological (withdrawal, seizures, Wernicke) diseases, as well as ongoing infections, sepsis and coexistent trauma is necessary to achieve ACM stability [44,45]. The use of antioxidant supplementation is currently under evaluation [46].

### Other toxic abuse

Because of the frequent coexistence of a multi-toxic consumption pattern in ACM [47,48] other cardiotoxic drug use, such as tobacco and/or cocaine, should be monitored and avoided. A specialized multi-disciplinary strategy with personalized cognitive-behavioral psychotherapy and use of pharmacological support should be established in these patients to control alcohol and drug-addiction [41].

### Heart transplantation

Heart transplantation in ACM is a restricted treatment considered only in subjects able to maintain alcohol abstinence up to 1 year, in the absence of other relevant systemic damage by alcohol (dementia, liver cirrhosis or cancer). In the usual care, this is a limited procedure applied to less of 15 % of end-stage ACM subjects [10,49].

### Personalized approach

Treatment of HF should be involve a personalized clinical approach considering all factors including medical, social and psychological aspects in a multi-disciplinary approach that is usually performed in specialized alcohol units [43].

### Future Perspectives

ACM is a relevant disease with a high social and public health impact [2-4]. In addition to the usual treatment of HF and support to maintain or achieve abstinence, new research in this field will allow specific treatments to be addressed to avoid disease progression [10]. Specific targets of research are aimed at reducing unhealthy myocyte hypertrophy [50], non-functional fibrosis [51] and myocyte apoptosis [39] as well as at improving local cardiac defensive mechanisms [2]. Table 1 summarizes the new treatment strategies and research approaches aimed at managing ACM.

<b>AVOID ALCOHOL-INDUCED HEART DAMAGE</b>
-Control drinking
- Avoid binge drinking
-Suppress tobacco and/or cocaine use
-Cognitive-behavioral therapy
<b>CONTROL OF SYSTEMIC NOXIOUS EFFECTS OF ETHANOL</b>
-Abstinence / Dependence
-Withdrawal, Wernicke, Seizures
-Uncompensated liver disease
-Kidney failure
-Concurrent systemic inflammation / sepsis/ infection
-Caloric/protein malnutrition
-Ionic and vitamin derangement
<b>AVOID UNHEALTHY MYOCYTE HYPERTROPHY</b>
-ACE inhibitors or ARA-II, $\beta$ or $\alpha_1$ adrenergic blockers
-Myostatin

- RhoA/ROCK inhibitors (Azaindole-1, SLx-2119, Fasudil)
-Sirtuins
-SIKE
-PPAR agonists
-Micro RNA
-Antioxidant supply
<b>AVOID NON-FUNCTIONAL FIBROSIS</b>
<b>Inhibition of myofibroblast activation</b>
-Relaxin
-TGF-beta antagonists
-Micro-RNA
<b>Antioxidant supply</b>
-Resveratrol
-Pioglitazone
<b>AVOID MYOCYTE LOSS</b>
<b>- Decrease apoptosis</b>
-Caspase, Myostatin and Sirtuins inhibitors
<b>-PI3K/Akt pathway: Catechins and polyphenols</b>
-ROCK1 modulation
-MicroRNA
-Catechins
-Ghrelin
<b>INCREASE LOCAL CARDIAC REPAIR MECHANISMS and HEART PLASTICITY</b>
- Relaxin
- IGF-1
- Myostatin
- Leptin inhibitors
- Ghrelin
-Cardiomyokines (FGF21)
<b>STEM CELL THERAPY</b>
-Bone marrow mononuclear cells
- Mesenchymal stem cells
-Cardiac-derived cells
<b>OPTIMIZE HEART TRANSPLANTATION STRATEGIES</b>

**Table 1:** New treatment strategies and research approaches to manage alcoholic cardiomyopathy.

Some growth factors (relaxin, IGF-1, myostatin, leptin, ghrelin), and cardiomyokines (FGF21) have recently been proposed as therapeutic

candidates to regulate cardiac plasticity at a local level and to decrease the intensity of heart damage, improving cardiac repair mechanisms [37].

To avoid unhealthy cardiac hypertrophy, the use of RhoA/ROCK inhibitors Azaindole-1 and SLx-2119 may be promising [52]. Fasudil is the only ROCK inhibitor approved for human use at present, although its specific effect has not been evaluated at a cardiac level [53]. Resveratrol and pioglitazone have relevant antioxidant cardiac properties and have also been suggested to inhibit cardiac hypertrophy [54,55].

Inhibition of the myofibroblast activation process through different mechanisms (relaxin, TGF-beta antagonists, and micro-RNA) may be useful to prevent cardiac fibrosis either in systemic or localized delivery [56,57].

Alcohol-mediated induction of apoptosis may be regulated in early stages by myostatin, sirtuins or caspase inhibitors [58]. Catechins and polyphenols have some antiapoptotic activity through the PI3K/Akt signaling pathway and should be considered as complementary treatments [59]. Cardiac stem cell therapy either stimulating cardiac progenitors or by local or systemic infusion of autologous or heterologous stem cells is a promising therapy [60,61].

Although these diverse potential treatment targets have been proposed for use in ACM, most have limitations and no clear results have yet been described. To include all the possible therapeutic strategies, a multidisciplinary approach for ACM combining the usual treatments and new specific targets will be required in the future.

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