In the United States, in both sexes and all races, long-term heavy alcohol consumption (of any beverage type) is the leading cause of a nonischemic, dilated cardiomyopathy, herein referred to as alcoholic cardiomyopathy (ACM). ACM is a specific heart muscle disease of a known cause that occurs in two stages: an asymptomatic stage and a symptomatic stage. In general, alcoholic patients consuming > 90 g of alcohol a day (approximately seven to eight standard drinks per day) for > 5 years are at risk for the development of asymptomatic ACM. Those who continue to drink may become symptomatic and develop signs and symptoms of heart failure. ACM is characterized by an increase in myocardial mass, dilation of the ventricles, and wall thinning. Changes in ventricular function may depend on the stage, in that asymptomatic ACM is associated with diastolic dysfunction, whereas systolic dysfunction is a common finding in symptomatic ACM patients. The pathophysiology of ACM is complex and may involve cell death (possibly due to apoptosis) and changes in many aspects of myocyte function. ACM remains an important cause of a dilated cardiomyopathy, and in latter stages can lead to heart failure. Alcohol abstinence, as well as the use of specific heart failure pharmacotherapies, is critical in improving ventricular function and outcomes in these patients.

Key words: alcohol; cardiomyopathy; contractile dysfunction; heart failure

Abbreviations: ACE = angiotensin-converting enzyme; ACM = alcoholic cardiomyopathy; AHMD = alcoholic heart muscle disease; EDD = end-diastolic dimension; EF = ejection fraction; ESD = end-systolic dimension; IDCM = idiopathic dilated cardiomyopathy; IGF = insulin-like growth factor; LV = left ventricle; mDNA = mitochondrial DNA; MHC = myosin heavy chain; NP = natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAS = renin-angiotensin system; SERCA2 = sarcoplasmic reticulum Ca$^{2+}$ adenosine triphosphatase pump

In the United States, in both sexes and all races, long-term heavy alcohol consumption (of any beverage type) is the leading cause of a nonischemic, dilated cardiomyopathy, herein referred to as alcoholic cardiomyopathy (ACM). ACM is a specific heart muscle disease of a known cause that occurs in two stages: an asymptomatic stage and a symptomatic stage. In general, alcoholic patients consuming > 90 g of alcohol a day (approximately seven to eight standard drinks per day) for > 5 years are at risk for the development of asymptomatic ACM. Those who continue to drink may become symptomatic and develop signs and symptoms of heart failure. ACM is characterized by an increase in myocardial mass, dilation of the ventricles, and wall thinning. Changes in ventricular function may depend on the stage, in that asymptomatic ACM is associated with diastolic dysfunction, whereas systolic dysfunction is a common finding in symptomatic ACM patients. The pathophysiology of ACM is complex and may involve cell death (possibly due to apoptosis) and changes in many aspects of myocyte function. ACM remains an important cause of a dilated cardiomyopathy, and in latter stages can lead to heart failure. Alcohol abstinence, as well as the use of specific heart failure pharmacotherapies, is critical in improving ventricular function and outcomes in these patients.

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abnormalities can be called a dilated cardiomyopathy, is not well established and is highly individualized. Also, unlike other cardiomyopathies, such as immunologic cardiomyopathies, there are no specific immunohistochemical, immunologic, or other criteria for the diagnosis of ACM. Therefore, the diagnosis of AHMD is often considered presumptive and is usually one of exclusion. The key factor in ruling in AHMD is a long-term history of heavy alcohol abuse.

INCIDENCE, PREVALENCE, AND MORBIDITY RELATED TO AHMD

The occurrence of ACM correlates with a high daily level and duration of alcohol consumption; however, the prevalence of ACM is variable and, fortunately, not all heavy drinkers have ACM develop. ACM represents about 3.8% of all cardiomyopathy cases. This statistic may seem rather insignificant; however, long-term heavy alcohol consumption is the second-leading cause of a dilated cardiomyopathy. Furthermore, if one considers the incidence of dilated cardiomyopathy in the general population, the incidence of a dilated cardiomyopathy in alcoholics is much greater. The incidence of ACM has remained constant over the last several decades, despite a gradual downward trend in per capita alcohol consumption in the United States.

The prevalence of ACM is variable and ranges from 23 to 40%. Among ACM cases, men represent the largest percentage, whereas women represent approximately 14%. In all races, death rates due to ACM are greater in men compared to women, and are greater in African-American men and women compared to white men and women with ACM.

WHAT DURATION AND LEVEL OF ALCOHOL CONSUMPTION IS ASSOCIATED WITH ACM?

Alcoholics can present with either a preclinical (asymptomatic) or symptomatic ACM (the latter is primarily distinguished from the former by signs and symptoms of heart failure). Therefore, a question clinicians often ask is: What duration and level of alcohol consumption produces an asymptomatic ACM, as well as symptomatic ACM? Even after decades of study, the exact amount and duration of alcohol consumption that is required to produce asymptomatic and symptomatic ACM has not been clearly established. There appears to be no simple linear alcohol concentration-to-injury relationship that clinicians can use when assessing their patients for alcohol-induced changes in myocardial structure or function. In general, others have reported that the duration and amount of alcohol consumed by asymptomatic alcoholics does not correlate with changes in myocardial structure and function. The only exception to these studies is the findings of Urbano-Márquez and colleagues, who found the total lifetime dose of alcohol was correlated to an increase in LV mass and a decrease in ejection fraction (EF).

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. However, the average duration of drinking reported in the majority of studies was 15 years. As a point of reference, there is 12 g of alcohol in a standard drink (see Appendix); therefore, these alcoholics self-reported consuming from 8 to 21 standard drinks per day.

In terms of the amount and duration required to produce symptomatic ACM and heart failure, the data are very limited. However Mathews et al found that alcoholics with congestive heart failure had a longer duration of drinking (10 years) compared to the asymptomatic alcoholics (duration of at least 6 years), while the daily amount of alcohol consumed was essentially the same between the groups. Similarly, Urbano-Márquez et al found in alcoholic patients with heart failure that the average duration of drinking (24.8 years) was longer compared to patients in the asymptomatic group (16.2 years). In the latter study, there was a modest difference in daily alcohol consumption (asymptomatic group, 243 g/d; heart failure group, 286 g/d). Therefore, the key variable linked to the development of heart failure appears to be the duration of heavy daily alcohol consumption. However, it is possible that other morbidities or variables, such as hypertension or arrhythmias, may predispose alcoholic patients to the development of heart failure.

MYOCARDIAL STRUCTURAL AND FUNCTIONAL CHANGES ASSOCIATED WITH ACM

Similar to other dilated cardiomyopathies, ACM is characterized by an increased LV mass, dilation of the ventricles, wall thinning, and ventricular dysfunction, and these changes are present in the absence of coronary artery disease and nutritional deficiencies. As will be discussed in more detail, the
degree of LV dilation and change in LV mass, wall circumference, and LV function may depend on the stage and severity of ACM.

As noted earlier, AHMD occurs in stages, beginning with a preclinical or asymptomatic stage, and then progressing to a symptomatic stage and eventually heart failure. In the late 1970s, the concept emerged of a preclinical (asymptomatic) form of ACM that may precede the more severe form of symptomatic ACM. Since that period of time, numerous studies have conducted to determine the changes in LV structure (remodeling) that are involved in the progression of ACM. In general, early signs of ACM appear to be LV dilation, exemplified by increased end-diastolic dimension (EDD) and increased systolic dimension, increased LV mass, and modestly increased posterior and septal wall thickness. Other reports suggest that hypertrophy, exemplified by an increase in posterior and/or septal wall thickness and LV mass other than LV dilation, are early findings in asymptomatic alcoholics.

Recently Lazarević et al. used two-dimensional and M-mode echocardiography and pulsed Doppler echocardiographic techniques, evaluated cardiac structure and function in healthy subjects and those with a history of alcohol consumption. They found that hypertrophy, exemplified by either an increase in posterior and/or septal wall thickness and LV mass other than LV dilation, are early findings in asymptomatic alcoholics.

In summary, it appears that in asymptomatic male alcoholic patients, 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 modest degree of wall thickening; the former change coupled with LV dilation would serve to offset wall tension and therefore would lead to a compensated and asymptomatic form of ACM. More than likely, both the drinking histories and other unidentified individual variables may account for differences in the studies. Interestingly, age is not variable, since in all of the studies reviewed, the mean age of asymptomatic male subjects ranged from 38.5 to 44 years.

**Clinical Characteristics of ACM**

Clinical characteristics as well as age of onset are similar in patients with idiopathic dilated cardiomyopathy (IDCM) and ACM. As shown in Table 1, an equal percentage of patients with IDCM and ACM have a history of alcohol abuse. The alcoholic subjects varied in their drinking duration, which allowed these investigators to separate the alcoholics into three groups according to their duration of heavy drinking (group S, drinking history of 5 to 9 years; group I, drinking history of 10 to 15 years; and group L, drinking history of > 15 years). All alcoholic subjects were asymptomatic for cardiovascular disease. These investigators found increases in LV dimensions (increased EDD and end-systolic dimension (ESD)) and isovolumic relaxation time in group S. In group I, no further increases were found in EDD and ESD; however, both LV myocardial mass index, posterior wall thickness, and diastolic interventricular septum thickness were significantly increased, and there were corresponding increases in isovolumic relaxation time and deceleration time.

In group L, all the aforementioned parameters were similar to those in group I; however, a significant decrease was found in the ratio of the amplitude of the waves created by early diastolic filling and atrial contraction. Based on their findings, these investigators concluded that LV dilation is a very early finding that precedes changes in LV mass and diastolic dysfunction. Interestingly, EF was essentially the same between the alcoholic and control groups. Their findings are similar to those of Kupari et al., who found that diastolic dysfunction rather than systolic function (as evaluated by fractional shortening percentage, and was not different between the control and alcohol groups) appears to be an early finding in asymptomatic alcoholic patients with a similar duration of drinking (median, 11 years). Likewise, Fernández-Solá et al. found diastolic impairment occurs in alcoholics with cardiomyopathy. This is in contrast to the findings of Urbanó-Márquez et al., in which EFs (percentage) were significantly lower in asymptomatic alcoholic patients (mean duration of drinking, 16.2 years) compared to control subjects (these investigators did not evaluate diastolic function).

### Table 1—Characteristics of Patients With IDCM and Alcohol Abuse

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IDCM</th>
<th>Alcohol Abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>44 ± 12</td>
<td>45 ± 10</td>
</tr>
<tr>
<td>NYHA class I–II</td>
<td>175 (68)%</td>
<td>51 (65)%</td>
</tr>
<tr>
<td>NYHA class III–IV</td>
<td>83 (32)%</td>
<td>29 (33)%</td>
</tr>
<tr>
<td>Heart failure at presentation</td>
<td>142 (55)</td>
<td>44 (56)</td>
</tr>
<tr>
<td>Left atrial dimension, mm/m²</td>
<td>22 ± 5</td>
<td>24 ± 4</td>
</tr>
<tr>
<td>LV EDD, mm/m²</td>
<td>38 ± 5</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>LV ESD, mm/m²</td>
<td>32 ± 6</td>
<td>32 ± 6</td>
</tr>
<tr>
<td>LV FS, %</td>
<td>13 ± 7</td>
<td>14 ± 7</td>
</tr>
<tr>
<td>Echo-derived EF, %</td>
<td>28 ± 9</td>
<td>28 ± 9</td>
</tr>
<tr>
<td>LV mass, g/m²</td>
<td>199 ± 50</td>
<td>211 ± 61</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>20 ± 11</td>
<td>22 ± 11</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>17 ± 11</td>
<td>18 ± 11</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>3.17 ± 1.04</td>
<td>3.01 ± 0.95</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%). Used with permission from Gavazzi et al. CI = cardiac index; EDP = end diastolic pressure; FS = fractional shortening.
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. Fauchier et al reported identical results. These latter investigators also examined smoking and not surprisingly found that larger percentage of ACM patients were current, intermediate, and heavy smokers compared to the IDCM group. Also, Fauchier et al found differences in the proportion of women and men with IDCM and ACM, in that 48 men and 2 women had ACM, whereas 69 men and 23 women had IDCM.

How do clinicians distinguish asymptomatic from symptomatic ACM? Others have found that symptomatic ACM is characterized by a greater degree of LV dilation and increased cardiac mass. For example, Mathews et al found LV EDD values and LV mass values were 40% and 60% greater, respectively, in symptomatic alcoholics compared to asymptomatic alcoholics, and LV ESD values were twice as large in the symptomatic patients. Symptomatic ACM patients are also likely to be in NYHA class III-IV, have systolic dysfunction (decreased EF), and have signs and symptoms of heart failure, such as elevated jugular venous pressure, S3-S4 heart sounds, pulmonary rales, and peripheral edema.

**Outcomes and Treatment of Patients With ACM**

Some reports indicated prognosis (survival) was better in ACM patients compared to patients with other types of cardiomyopathies. However, these studies did not examine the effect of alcohol abstinence; in one study, a percentage of the patients classified as having ACM also had coronary artery disease or hypertension. Recently, Gavazzi et al and Fauchier et al conducted prospective studies, with mean follow-ups of 59 ± 35 months and 47 ± 40 months, respectively, and both investigators separated alcoholic patients who were abstinent and those who were not. Both groups of investigators found a similar prognosis (transplant-free survival) for patients with IDCM and ACM with abstinence. However, in both investigations, survival was significantly lower for ACM patients without abstinence compared to IDCM and abstinent ACM patients (Fig 1). These data clearly underscore the need for abstinence in the ACM patients. This finding is particularly interesting in light of the finding that ventricular function (as indicated by LV ejection fraction) improved in ACM patients without abstinence. As noted below in these two studies, all patients were receiving standard heart failure ther-

![Image of survival curves](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21977/)
apy, and this may have accounted for the improvement in ventricular function. However, treatment in the presence of continued drinking did not confer a mortality benefit.5,7

Other determinants of outcomes in ACM patients may be hemodynamic factors, such as hospital admission pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure (PCWP). La Vecchia et al23 evaluated male alcoholic subjects (n = 19) with systolic dysfunction (EF < 40%). Fifteen of these patients abstained, while 4 patients reduced their alcohol intake to < 40 g/d (approximately three drinks). All of these ACM patients received digitalis and diuretics. At 23 months of follow-up, approximately one half of the patients had significant improvement in LV EF (baseline EF, 28.5 ± 9%; follow-up EF, 53.3 ± 10%), whereas the other one half of the patients did not exhibit an improvement in ventricular function (no change in EF). The difference between the improved and nonimproved groups were baseline (enrollment) PAP and PCWP values, in that baseline PAP and PCWP values were significantly higher in the nonimproved group (40.3 ± 12.4 mm Hg and 26.5 ± 7.7 mm Hg, respectively) compared to the improved group (27.8 ± 13.3 mm Hg and 18.4 ± 8.9 mm Hg, respectively). These large PAP and PCWP values may be indicative of very diseased hearts and heart failure, such that medical therapy is not very effective; however, these patients were only receiving diuretics and digoxin. In addition, there is another caveat to these findings: it was not indicated by the authors if the patients who cut back their alcohol intake (n = 4) were equally distributed between groups or were included in the nonimproved group. In this author's opinion, cutting back on alcohol intake should not be an option, since these patients are alcoholics, and complete cessation of alcohol intake rather than a reduction is the recommended therapy.

To the author’s knowledge, there are no studies that have examined specific pharmacotherapeutics in patients with ACM. Therefore, patients with ACM presenting in heart failure with systolic dysfunction (EF ≤ 40%) should be treated according to the Agency for Health Care Policy and Research and Heart Failure Consensus recommendations. These guidelines recommend the use of pharmacologic agents that inhibit the LV remodeling process, as well as treat the patient’s symptoms. The different classes of agents include diuretics, cardiac glycosides, angiotensin-converting enzyme (ACE) inhibitors, and β-adrenergic blockers. The findings of Fauchier et al5 and Gavazzi et al7 indicate that Agency for Health Care Policy and Research-guided therapy is associated with an improvement in LV function. In the former investigation, all patients with ACM received dietetic and alcohol abstinence counseling. An equal percentage of both IDCM and ACM patients received ACE inhibitors (IDCM, 76%; ACM, 78%), diuretics (IDCM, 71%; ACM, 68%), and digoxin (IDCM, 64%; ACM, 56%). Mean ± SD duration of follow-up was 47 ± 40 months. Ventricular EF improved in alcoholic patients who remained abstinent and also in those who did not remain abstinent; however, as noted above, overall survival was not improved in those who continued to drink.2 Gavazzi et al7 also found increased mortality in alcoholics who continued to drink. In that study, a greater percentage of IDCM patients received ACE inhibitors (91%) and β-blockers (34%), compared to the ACM patients (ACE, 81%; β-blocker, 9%, respectively), and both groups of patients received an equal percentage of oral anticoagulants. These investigators found that LV function (as indicated by EF) was only significantly improved in the ACM group that abstained from alcohol; only modest nonsignificant improvements were found in LV EF in the patients who continued to abuse alcohol.

In terms of the findings with LV function, these results differ from those of Fauchier et al5 who found significant improvements in LV function regardless of drinking status. The major difference between these two studies is that in the study by Fauchier et al,5 a larger percentage of ACM patients received β-blocker therapy. Collectively, it appears that standard pharmacologic therapies improve ventricular function in ACM patients who abstain as well as those who do not; however, there appears to be no mortality benefit in those who do not abstain.

WHAT ABOUT WOMEN WITH ACM?

There are very few studies that have examined the incidence, clinical characteristics, or outcomes of women with ACM, and no study has considered the effects of estrogen. However, similar to men, long-term heavy alcohol consumption in women is associated with the development of a dilated cardiomyopathy. Similar to men, ACM occurs in women of a relatively young age (45 to 50 years).8 The clinical features resemble those found in men, and include a dilated LV, modest degree of hypertrophy, and reduced systolic dysfunction. Fernández-Solá and colleagues8 examined the clinical characteristics of alcoholic women with ACM (n = 10) and with signs of heart failure. For comparison, alcoholic male subjects (n = 26) were also studied. Cardiopulmonary ratios were similar between alcoholic men and women (0.58 ± 0.11 women, 0.58 ± 0.04 men).8 Women with ACM experienced similar heart failure
signs compared to men; however, some signs occurred more often in men. Interestingly, 50% of the women were in NYHA functional class II, whereas the majority of men in this sample had NYHA class III or IV heart failure. One might conclude, that since the women had a lower NYHA functional class, alcoholic women had a greater functional status.

Women appear to get a preclinical, asymptomatic form of this disease with less total lifetime exposure to alcohol, suggesting that female gender may be a risk factor for the development of ACM. In terms of the amount and duration of alcohol consumption correlated with the development of AHMD, Urbano-Márquez and colleagues suggested that a 55-kg woman who drinks approximately 270 mL (9 oz) of 86-proof (43%) spirits or approximately 1 L of wine a day for 20 years is at risk for the development of AHMD. In some individuals, genetic background or environmental exposure to other toxins may also play a role in the pathogenesis of AHMD. The American Heart Association recommends that women drink no more than one standard drink per day (ie, 12 fluid oz of regular beer, 5 fluid oz of wine, 1.5 fluid oz of 80-proof distilled spirits; each of these contains approximately 12 g of alcohol). This is because in women, the effect of alcohol on conditions other than cardiovascular disease needs to be considered. Specifically, alcohol intake between 30 g/d and 60 g/d is associated with an increase in the relative risk of breast cancer, whereas alcohol intake of ≤10 g/d was associated with a lower relative risk. Women should be advised to discuss the potential risk-to-benefit ratio of low-to-moderate drinking with their health-care provider. Each woman, depending on her personal history (eg, familial history of breast cancer or ischemic heart disease), will have different risk factors and should be advised accordingly.

Pathophysiologic Mechanisms Underlying ACM

Even though there is a substantial amount of work documenting the adverse effects of alcohol on the myocardium, the exact pathogenesis of ACM is incompletely understood. Animal models of ACM have contributed a great deal to our understanding of ACM. These 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. However, it is also possible that other cell types or systems are activated, such as the sympathetic nervous system (norepinephrine), renin-angiotensin system (RAS), cytokines, and natriuretic peptide (NP) system. In the section that follows, these categories of alcohol-induced changes are reviewed with an emphasis on more recent data.

Myocyte Loss

In many organ systems, including the heart, myocyte loss or cell death may be an important component of organ dysfunction and pathology. Cell death can result from either necrosis or apoptosis (programmed cell death). Others have shown that ethanol-induced apoptosis is probably a critical mechanism underlying ethanol-induced disorders such as fetal alcohol syndrome. 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. In 1965, in a histopathologic examination of hearts of patients with the diagnosis of ACM, Hibbs and colleagues reported that myocytes lost their cross-striated appearance and had pyknotic nuclei. The latter, a reduction in the size of the nucleus, can be a characteristic of apoptosis. Capasso et al found a significant loss of myocytes in the LV from rats fed ethanol in their drinking water for 8 months.

Recently, Chen et al, using primary neonatal myocyte cell cultures, examined the effects of acute alcohol (500 mg/dL and 1,000 mg/dL) exposure (24 h) on the process of apoptosis. Apoptosis was induced by rinsing cells twice in phosphate-buffered saline solution and then replacing the medium with a serum-free suspension. Both concentrations of alcohol potentiated the apoptotic effect of serum withdrawal (as measured by DNA acid fragmentation). In addition, both alcohol concentrations 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). Interestingly, in this same experiment, the application of insulin-like growth factor (IGF)-1 attenuated the apoptotic effects of ethanol on serum withdrawal. It is important to note that these concentrations of alcohol are very high (in human beings who cannot tolerate alcohol, 500 mg/dL can be associated with respiratory depression and death); however, these investigators also found lower concentrations of alcohol, 200 mg/dL, potentiated the effects of serum withdrawal. It is interesting that IGF-1 attenuated the
effects of alcohol. IGF-1 has multiple effects on the cell, some which include cell proliferation and differentiation, whereas activation of signaling components downstream to the IGF receptor are linked to the development of hypertrophy. In contrast to the findings of Chen et al., Jänkälä et al. found no evidence of apoptosis following an acute infusion of alcohol (500 mg/dL for 150 min) but did find increased messenger RNA p21 levels. p21 is an inhibitor of cyclin-dependent kinases, and p21 may be one of the many proteins involved in the hypertrophic response.

In summary it remains unknown whether the process of apoptosis is important in the pathogenesis of ACM. However, further studies are clearly needed, even though speculative apoptosis may indeed be an early inciting event that precedes other events, such as myocyte hypertrophy and activation of neurohormonal systems.

**Intracellular Organelle Dysfunction**

There are many early reports documenting the adverse effects of long-term alcohol consumption on mitochondrial and sarcoplasmic reticulum function. In fact, changes in mitochondria structure/function have been one of the most ubiquitous findings among studies. There are many reports of mitochondrial enlargement that is accompanied by disorganization and degeneration of the cristae. These changes in structure have been supported by the findings of others in animal models of ACM, who have found changes in mitochondrial function, exemplified by decreases in indexes of mitochondria respiration and/or calcium uptake by the mitochondria. Others have found an increased level of fatty ethyl esters in the alcoholic heart, which can attach to the mitochondria and disrupt mitochondria function. Changes in mitochondria function can affect cell function in many ways and therefore maybe a key contributor to intrinsic cell dysfunction. Intrinsic cell dysfunction may also arise from impaired sarcoplasmic reticulum function. There are reports of decreases in sarcoplasmic reticulum calcium biding and uptake. These findings corroborate those of others who have found electron micrographic evidence of sarcoplasmic reticulum swelling and disorganization.

**Contractile Proteins**

Changes in the structure and/or function of the contractile proteins can affect many aspects of cross-bridge cycling as well as force production. As a potential mechanism of alcohol-induced cardiac damage, Freed and colleagues have extensively examined changes in cardiac contractile protein synthesis. Initial work from this laboratory demonstrated that 6 weeks of alcohol consumption was associated with a decrease in cardiac myofibrillar proteins. More recent work from this laboratory found that there were no changes in actin, vimentin, tropomyosin, and myosin light chains I and II.

Shifts in the relative expression of the contractile proteins, β-myosin heavy chain (MHC) to α-MHC have been reported in animal models of pressure overload, thyroid deficiency, and heart failure. The author and colleagues have also demonstrated that a short period of alcohol consumption is associated with a myosin isoform change. Following 2 months of alcohol consumption, Meehan et al. found a shift in the ratio of β-MHC to α-MHC isoforms in rat myocardium (ie, there was an increase in the relative proportion of β-MHC protein and an increase in β-MHC messenger RNA levels). This was accompanied by a decrease in myofibrillar and myosin adenosine triphosphatase activities. It has been postulated that this shift in the myosin isoforms allows the heart to reduce the rate of contraction, as well as reduce the level of adenosine triphosphate consumption, allowing the heart to reside in a more energy efficient state.

**Calcium Homeostasis**

At least in the latter stages of ACM, contractile function is depressed, and similar to other cardiovascular diseases, abnormalities in Ca²⁺ 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 Ca²⁺. Calcium is critical in the initiation of cross-bridge cycling and in regulating myocardial force. Myocardial contractility can be regulated by altering the Ca²⁺ transient or myofibrillar sensitivity to Ca²⁺. Normal Ca²⁺ regulation is rather complex and depends a number of factors, such as the abundance and functioning of sarcolemmal L-type Ca²⁺ channels, sarcolemmal transport pumps (Na/Ca exchanger), and the sarcoplasmic reticulum (storage and release Ca²⁺). Therefore, changes in any one of these modulating factors can alter Ca²⁺ homeostasis. With regard to calcium transients, others have examined cytosolic Ca²⁺ transients in hearts isolated from rats fed alcohol (36% v/v in drinking water) for 7 months and found no differences in systolic or diastolic intracellular Ca²⁺ rise and fall between alcohol and control hearts. There were also no differences between groups in the protein levels of sarcoplasmic reticulum Ca²⁺ adenosine triphosphatase pump (SERCA2) and phospholamban (a protein attached to SERCA2 that modulates the function of...
cardiomyopathy and contractile dysfunction, but consumption in rats is associated with a dilated right, as evidenced by a significantly larger effective concentration causing a 50% fall in $\text{Ca}^{2+}$. However, the maximal $\text{Ca}^{2+}$-induced force development was similar between the groups (ie, force at the greatest concentration of $\text{Ca}^{2+}$). Therefore, a relatively short period of alcohol consumption altered the sensitivity of the myofilaments to physiologic levels of calcium.

Others have also speculated that alcohol may increase the threshold of the heart for calcium overload and mitochondrial dysfunction. Wu et al. found that 6 months of alcoholic administration in hamsters was associated with a significant decrease in developed force, lower adenosine triphosphate levels, and higher phosphate levels. Co-treatment with the calcium antagonist verapamil prevented the development of the contractile and metabolic dysfunction. These findings support the idea of abnormal or increased calcium influx into the cell. Guppy and Littleton reported that a short period of heavy alcohol exposure (via exposure to alcohol vapor) is associated with an increase in calcium channels (exemplified by a twofold increase in dihydropyridine binding sites). In a subsequent report using a isolated Langendorff preparation, these investigators found a decrease in diastolic pressure and attenuated increase in systolic pressure in response to increasing concentration of extracellular 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 (ie, no change in heart weight-to-body weight ratios). This is an intriguing hypothesis; however, one would predict that, as time progressed and drinking continued, heart failure and early death would ensue similar to the Syrian hamster model of cardiomyopathy, in which calcium overload is considered a key pathologic factor. However, work of the author and others has shown that 12 months of alcohol consumption in rats is associated with a dilated cardiomyopathy and contractile dysfunction, but there are no signs of heart failure and, at least in the author’s experience, early death has never occurred.

There are reports that acute alcohol administration (concentrations ranging from 100 to 200 mg/dL) depresses myocardial contractility without altering the calcium transient. However, higher concentrations of alcohol (>$300$ mg/dL) were associated with a decrease in the amplitude of the calcium transient as well as myocyte twitch amplitude. It is not likely that the decrease in contractile force was due to changes in inorganic phosphate levels or pH, since others have found similar concentrations of alcohol had no effect on these parameters. Others have also found the negative inotropic effect of acute alcohol is still present in the presence of increasing concentrations of extracellular calcium or calcium channel agonists, such as Bay K 8644, suggesting the negative inotropic affect of acute alcohol is due to alterations in myofilament sensitivity or myofilament alterations. These reports suggest that perhaps similar to short-term alcohol administration (2 months), acute alcohol administration alters myofilament sensitivity.

Neurohormonal Systems

As noted earlier, as a consequence of myocyte dysfunction, other cell types or systems might be activated, such as sympathetic nervous system (norepinephrine), RAS, and NP system. Reviewed below is the potential role of these systems in ACM pathophysiology.

Sustained and high levels of norepinephrine exert adverse effects on the myocardium, some of which include myocyte hypertrophy, toxicity, and apoptosis. All of these cellular events are linked to LV remodeling. Adams and Hirst demonstrated in male Sprague-Dawley rats that severe alcohol (10% w/v) intoxication over a 2- to 4-day period (via gastric intubation) was associated with marked increases in urinary norepinephrine and epinephrine levels, and that these increased levels correlated to 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 postulated a direct role for catecholamines in the induction of alcohol-induced hypertrophy. In a series of investigations using a $\alpha_1$-adrenergic (prazosin) and $\beta_1$-adrenergic (metoprolol) antagonists, these investigators found that the effects of norepinephrine and epinephrine in the induction of alcohol-induced hypertrophy were more than likely mediated via the myocyte $\beta_1$-adrenergic receptor subtype rather than the $\alpha_1$ subtype. Several cytotoxic effects of norepinephrine...
are mediated via the B1-receptor subtype and include myocyte toxicity and apoptosis.63

Interestingly, administration of prazosin (an α1-adrenergic antagonist) did not block the alcohol-induced cardiomyopathy.62 Work from the author’s laboratory has also demonstrated that a relatively short period of alcohol consumption (60 days of a liquid ethanol diet) was not associated with changes in α1-adrenergic–stimulated phosphoinositide turnover.63 However, this duration of alcohol consumption was associated with depressed contractile function (as exemplified by a decrease in developed twitch tension in alcoholic atria compared to control atria). Collectively, these findings are interestingly, in light of the fact that others14 have shown that activation of myocardial α1-adrenergic receptors stimulates myocyte hypertrophy, via the subsequent activation of the phosphoinositide second messenger system and activation of protein kinase C. Perhaps with a longer duration of alcohol drinking, one would find involvement of the α1-adrenergic receptors subtype and associated signal transduction system.

Recently, in a rodent model of ACM, the author examined whether changes in cardiac structure corresponded to activation in the RAS and the NP system.64 Using echocardiography, it was shown that 8 months and 12 months of alcohol consumption in male Sprague-Dawley rats was associated with a dilated cardiomyopathy, exemplified by increases in EDD, ESD, LV mass, and heart weight to body weight ratio. It is important to note, though, that these structural changes were not significantly different from the control group until the 12-month time point (Table 2).64 In addition, the pressure-volume relationship in the alcohol-treated animals was shifted down and to the right, which is characteristic of a dilated heart. In this study, as a measure of RAS activation, the author measured plasma and LV tissue levels of ACE activity. LV tissue activity was significantly greater in the 12-month alcohol group (782 ± 20 fmol/mg wet weight) compared to the 8-month alcohol group (580 ± 38 fmol/mg wet weight) and control group (588 ± 37 fmol/mg wet weight) [plasma ACE levels were similar among groups].64 Since we found beginning evidence of a dilated cardiomyopathy at 8 months, these data suggest that the increase in LV tissue ACE activity is a late finding in ACM, and perhaps a consequence rather than a cause of ACM. We also examined atrial and brain NP plasma and tissue levels and messenger RNA levels and found no differences among the groups. This was a rather surprising finding and differs from other models65,66 of cardiac disease, which found increased NP tissue levels and messenger RNA levels. However, work by others67 has provided evidence that suggests that the NPs, specifically atrial NP, may not be a ubiquitous marker of LV hypertrophy and cardiomyopathy. The signals involved in stimulating NP production, as well as the pattern of NP synthesis and secretion, may be specific to the experimental animal model or etiology of the disease.

In summary, the pathophysiology and progression of ACM is complex and involves changes in many aspects of myocyte function. The point at which the changes in mitochondrial, sarcoplasmic reticulum, contractile protein, and calcium homeostasis culminate in intrinsic cell dysfunction is incompletely understood. Data are limited with respect to neurohormonal systems, although increases in norepinephrine may be an important factor, and it is unknown if cytokine systems are activated, such as tumor necrosis factor and endothelin. Although hypothetical, a proposed schema for the pathogenesis of ACM is presented in Figure 2.

CONCLUSION

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>EDD, mm</th>
<th>ESD, mm</th>
<th>IVSD, mm</th>
<th>PWD, mm</th>
<th>LV mass, g</th>
<th>RWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>6.25 ± 0.14</td>
<td>3.68 ± 0.18</td>
<td>1.23 ± 0.03</td>
<td>1.51 ± 0.07</td>
<td>0.52 ± 0.04</td>
<td>0.49 ± 0.03</td>
</tr>
<tr>
<td>8 mo</td>
<td>6.90 ± 0.20</td>
<td>4.06 ± 0.23</td>
<td>1.26 ± 0.03</td>
<td>1.78 ± 0.10</td>
<td>0.69 ± 0.06</td>
<td>0.51 ± 0.02</td>
</tr>
<tr>
<td>CON</td>
<td>7.65 ± 0.37</td>
<td>4.40 ± 0.23</td>
<td>1.42 ± 0.04</td>
<td>1.68 ± 0.07</td>
<td>0.83 ± 0.06</td>
<td>0.44 ± 0.04</td>
</tr>
<tr>
<td>ETOH</td>
<td>6.70 ± 0.34</td>
<td>4.10 ± 0.22</td>
<td>1.30 ± 0.09</td>
<td>1.69 ± 0.06</td>
<td>0.65 ± 0.06</td>
<td>0.51 ± 0.03</td>
</tr>
<tr>
<td>12 mo</td>
<td>7.81 ± 0.20</td>
<td>4.89 ± 0.26</td>
<td>1.34 ± 0.07</td>
<td>1.99 ± 0.17</td>
<td>0.93 ± 0.10</td>
<td>0.51 ± 0.04</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD. Used with permission from Kim et al.64 CON = control; ETOH = alcohol; IVSD = interventricular septum in diastole; PWD = posterior wall thickness in diastole; RWT = relative wall thickness.

p = 0.017.
lp = 0.032.
ALCOHOL

Alcohol consumption ↓ > 90gms > 5 years

- Apoptosis (either directly via alcohol or indirectly via ↑ NE levels)
- ↓ synthesis and/or accelerated degradation of contractile proteins
- ↓ myofilament Ca²⁺ sensitivity
- Intrinsic myocyte dysfunction due to mitochondrial and sarcoplasmic dysfunction (due to Ca²⁺ overload, fatty ethyl esters or NE)

Cell drop out and weakly contracting myocytes

Decreased cardiac output

- LV dilation to increase EDV (preload) to compensate for ↓ cardiac output, however this is may be accompanied by wall thinning due to cell drop out
- Hypertrophy of normal myocytes to compensate for weakly contracting neighboring myocytes

Continued drinking ↓ > 15 years

- Progressive LV dilation and wall thinning
- Activation of other neurohormonal systems
- Signs and symptoms of heart failure

Figure 2. Proposed hypothetical schema for the pathogenesis of ACM. gms = grams; NE = norepinephrine.

ACM is lower in women compared to men, and occurs most often in alcoholics in their late 40s. Although the amount and duration of alcohol that results in ACM is not clearly established, 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. Women may be more vulnerable to the development of ACM, since others have reported that ACM develops in women with a less total lifetime exposure to alcohol compared to men. There is an asymptomatic stage of ACM that, characterized by LV dilation, increased LV mass, and diastolic dysfunction. The symptomatic ACM stage is characterized by pronounced LV dilation, increased LV mass, wall thinning, systolic dysfunction, and signs and symptoms of heart failure. Treatment of both groups of ACM patients should include alcohol abstinence, and symptomatic patients should be treated with recommended heart failure pharmacotherapies.

The pathophysiology of ACM is complex and involves many aspects of myocyte function. The point at which changes in mitochondrial, sarcoplasmic reticulum, contractile protein, and calcium homeostasis culminate in intrinsic cell dysfunction may depend on the level, duration, and consistency of the person’s drinking. Furthermore, in women, it is unknown as to how the incidence and pathophysiology of ACM is influenced by estrogen.

In closing, there are interindividual 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, Tera-gaki et al. evaluated 10 ACM patients for point mutations in mitochondrial DNA (mtDNA), since others have found that point mutations in mtDNA are associated with the occurrence of some cardiomyopathies. These investigators found that 4 of the 10
ACM patients had multiple-point mDNA mutations. Further research is needed to identify these vulnerable patients.

APPENDIX

Assessing a Patient’s Drinking Status: Important Facts to Know

In westernized countries, approximately two thirds of men and nearly one half the women drink alcohol on an occasional basis, which means that the average person in our society drinks alcohol. However, only approximately 10 to 18% of this drinking population have an alcohol abuse problem develop or become alcoholics. Alcoholism and alcohol abuse are associated with profound individual, familial, societal, and health consequences. Alcoholism is defined as a “primary disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by impaired control over drinking, and preoccupation with the drug alcohol.” Alcoholics in the absence of the drug alcohol show evidence of drug withdrawal and drug dependence. Alcohol abuse is characterized by repetitive problems, such as failure to attend work/school, frequent family/friend arguments, physical fighting, and driving while intoxicated. In particular, young men (approximately 25%) may experience transient alcohol abuse problems (missing a day at work, fighting with friends or relatives). Clinicians have specific criteria for the diagnosis of alcohol abuse and alcoholism (substance dependence).

The challenge in our society is to identify those who are at risk for developing adverse health consequences, as well as alcoholism. To this end, others have suggested a third category of at-risk drinking, defined as a level of drinking at the present time that is not associated with adverse medical or social consequences, but which over time might lead to adverse health and societal consequences. Therefore, how much is too much? To begin with, in the United States, a standard drink contains approximately 12 g of alcohol. In terms of different beverage types and fluid amounts, this translates into 12 fluid oz or 340 mL of beer (5% v/v), 5 fluid oz or 142.2 mL of wine (12.5% v/v), and 1.5 fluid oz or 42.6 mL of 80-proof (40% v/v) spirits/liquor. There are numerous medical consequences of excessive alcohol consumption, and there are many unidentified individual factors that may influence the effects of alcohol. Therefore, at the present time, there are insufficient data to make a precise recommendation. However, the National Institute on Alcoholism and Alcohol Abuse has recommended that men drink no more than 14 drinks per week or no more than 4 drinks on any given occasion, and women should drink no more than 3 drinks on any given occasion and no more than 7 drinks per week. The latter recommendation should be considered the “upper limit” and differs from what is considered “moderate drinking,” a level of drinking that is safe and sensible. In the United States, moderate drinking is defined as no more than one standard drink per day for women and two standard drinks per day for men, as well as anything less than this amount.

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