

10-1-2011

# Alcoholic cardiomyopathy: a review.

Anil George

*Einstein Institute for Heart and Vascular Health, Albert Einstein Medical Center*

Vincent M Figueredo

*Jefferson Medical College, FigueredoV@einstein.edu*

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### Recommended Citation

George, Anil and Figueredo, Vincent M, "Alcoholic cardiomyopathy: a review." (2011). *Division of Cardiology Faculty Papers*. Paper 11.<https://jdc.jefferson.edu/cardiologyfp/11>

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**As submitted to:**  
*Journal of Cardiac Failure*

**And later published as:**

**Alcoholic Cardiomyopathy: A review.**

**Volume 17, Issue 10, October 2011, Pages 844-849**

**DOI: 10.1016/j.cardfail.2011.05.008**

Anil George, MD<sup>1</sup>, Vincent M. Figueredo, MD<sup>1,2</sup>

<sup>1</sup> Einstein Institute for Heart and Vascular Health, Albert Einstein Medical Center  
and <sup>2</sup>Jefferson Medical College, Philadelphia

Key words: cardiomyopathy, alcohol, heart failure, systolic dysfunction, diastolic dysfunction

Address correspondence to:

Vincent M. Figueredo, MD

Einstein Institute for Heart and Vascular Health

5501 Old York Road, Levy 3232

Philadelphia, PA 19141

Tel: 215-456-8819

Fax: 215-456-3533

## Abstract

Alcohol abuse can cause cardiomyopathy indistinguishable from other types of dilated non-ischemic cardiomyopathy. Most heavy drinkers remain asymptomatic in the earlier stages of disease progression and many never develop the ever too familiar clinical manifestations that typify heart failure. We will review the current thinking on the pathophysiology, clinical characteristics and treatments available for alcoholic cardiomyopathy. The relationship of alcohol to heart disease is complicated by the fact that in moderation alcohol has been shown to afford a certain degree of protection against cardiovascular disease.

## Introduction

Alcoholic cardiomyopathy (ICD-10, 142.6) as a unique disease entity has been familiar to physicians for close to two centuries. William Mackenzie is credited for having coined the term *alcoholic heart disease* in his treatise titled "*Study of the pulse*" in 1902<sup>1</sup>. There exist in most societies and all religions, taboos and proscriptions pertaining to the use and abuse of alcohol. Nevertheless, references to ill effects from excess alcohol usage abound in most societies. Examples

include the 'Tubingen Wine Heart' described in 1877 and the 'Munich Beer Heart' as reported by German pathologist Otto Bollinger in 1884 <sup>2,3</sup>.

Using the Alcohol-Related Disease Impact (ARDI) tool, the CDC reports that there were approximately 79,000 deaths annually attributable to excessive alcohol use (2001–2005) <sup>4</sup>. Furthermore, the rates of excessive drinking and binge drinking in young people including college students is concerning <sup>5</sup>. Excessive alcohol use is the 3rd leading lifestyle-related cause of death for people in the United States each year, behind tobacco and improper diet/ lack of physical activity which are ranked one and two respectively <sup>6</sup>.

Yet a meta-analysis of 34 prospective studies comprising of over 1 million subjects and 10,000 deaths reveals a J shaped relationship between alcohol and total mortality as shown in Figure 1 <sup>7</sup>. While alcohol consumed in moderation may offer protection against cardiovascular events, alcohol abuse can damage the heart. Alcohol abuse initially causes asymptomatic left ventricular dysfunction but when continued, can cause the ever too familiar signs and symptoms of congestive heart failure. Here in, we review current concepts and controversies regarding the etiology, pathology and management of patients with alcoholic cardiomyopathy.

Definition and Dose-time Effects

Long-term heavy alcohol consumption leading to non-ischemic dilated cardiomyopathy is referred to as 'alcoholic cardiomyopathy'. Ever since it became evident that moderate alcohol consumption has cardio-protective effects in normal individuals and those with known heart disease, a matter of great debate has been the amount and duration of alcohol abuse required to produce detrimental clinical effects. Moderate alcohol consumption (1-2drinks/day) decreases cardiovascular and all cause mortality as well as other "hard outcomes" including coronary heart disease (CHD), ischemic strokes and amputations due to peripheral vascular disease <sup>8</sup>. A study of 490,000 men and women found that although all cause mortality increased with heavier drinking, moderate drinking reduced cardiovascular mortality especially in middle-aged subjects <sup>9</sup>. A study of over 10,000 European hypertensive women found evidence of reduced risk of CHD and stroke with moderate alcohol consumption <sup>10</sup>. A recent large meta-analysis of 8 studies consisting of over 16,000 patients with cardiovascular disease confirmed that light to moderate alcohol consumption (5 to 25 g/day) was significantly associated with a decreased incidence of cardiovascular and all-cause mortality <sup>11</sup>. Pleiotropic effects of moderate alcohol consumption have been proposed to produce this protection against cardiovascular events including increased HDL cholesterol, reduced plasma

viscosity, decreased fibrinogen concentration, increased fibrinolysis, decreased platelet aggregation and coagulation, and enhanced endothelial function <sup>12</sup>.

The potential beneficial effects from alcohol tend to decline as the number of drinks consumed per day increases. Although there is a lack of consensus, it appears that most alcoholic patients with detectable changes in cardiac structure and function report consuming >90 g/day of alcohol for at least 5 years <sup>13-16</sup>. It is important to note that potential damage to the heart with longstanding alcohol abuse is not beverage specific, nor quantity specific, but will vary based on the population studied and the individual; genetic and environmental factors and types of beverage consumed by a culture or person playing potential roles.

The CDC estimates that 61.2% of U.S. adults are current drinkers, 14% were former drinkers and 5% were classified as heavier drinkers. <sup>17</sup> There are 12 -14 g or 0.5-0.6 fl oz of alcohol in a standard drink. A 12 oz bottle of beer, a 4 oz glass of wine, and a 1 ½ oz shot of 80-proof spirits all contain the same amount of alcohol (one half ounce) as shown in Table 1.

Each of these is considered a "drink equivalent" <sup>18</sup>. Mild to moderate alcohol consumption has not been shown to be associated with alcoholic cardiomyopathy. In fact, data from the Framingham study showed a much lower hazard ratio (<0.41) for congestive heart failure in men who imbibed 8-14

alcoholic drinks per week indicating a protective effect <sup>19</sup>. Moderate alcohol consumption was found to lower the risk of heart failure in the Cardiovascular Health Study by 34% in patients > 65 years and in the Physician's Health Study by 58% <sup>20, 21</sup>.

## Epidemiology

Reported incidences of alcoholic cardiomyopathy have ranged from 21 percent to 32 percent of dilated cardiomyopathies in surveys conducted at referral centers, but might be higher among patient populations where there is a higher frequency of alcoholism <sup>22</sup>. Some researchers suggest that at least half of all cases of dilated cardiomyopathy are caused by alcohol <sup>23</sup>. There also is evidence to suspect that the majority of alcoholics are affected by preclinical heart muscle disease. Autopsy studies have revealed enlarged hearts and other signs of cardiomyopathy in alcoholics who did not show overt symptoms of heart disease <sup>24</sup>.

Men more commonly develop alcoholic cardiomyopathy, both because more men than women drink and do so in greater amounts. But, women consistently attain higher maximum blood alcohol concentrations than men for comparable levels of alcohol consumption. This is likely due to the greater proportion of body water in men and larger proportion of body fat in women <sup>25</sup>. The latter



results in a slower distribution of alcohol from the blood. Further more women have lesser amounts of alcohol metabolizing enzymes such as alcohol and aldehyde dehydrogenases <sup>26</sup>. Thus, women may develop alcoholic cardiomyopathy earlier and at a lower lifetime dose of alcohol (approximately 40%) compared to men <sup>27</sup>.

### Etiology and Pathophysiology

It will be difficult to establish a definite causal relationship between heavy alcohol consumption and heart failure, given the beneficial effects seen with moderate to lower levels of consumption and given the fact that some heavy alcohol users never develop overt heart failure. Nevertheless there are data incriminating alcohol in heavy drinkers with asymptomatic and symptomatic left ventricular dysfunction (systolic and diastolic). Environmental factors (cobalt, arsenic) and genetic predisposition (HLA-B8, alcohol dehydrogenase alleles) have been proposed as triggers or abettors in the etio-pathogenesis of alcoholic heart disease. For example, 'Quebec beer-drinkers' cardiomyopathy appeared as an epidemic among heavy beer drinkers in Canada in mid-1960s <sup>28</sup>. It resembled typical a dilated cardiomyopathy except for purplish skin coloration and high early mortality rate (42%). This alcoholic cardiomyopathy was associated with development of large pericardial effusions and low-output heart failure. 'Quebec

beer-drinkers' cardiomyopathy disappeared when brewers discontinued the practice of adding cobalt to beer to stabilize the foam. Cobalt is thought to compete with calcium and magnesium leading to inhibition of enzymes involved in the metabolism of pyruvate and fatty acids.<sup>29</sup>

Genetic factors can determine how well alcohol is metabolized and can play a role in determining the interactions between alcohol and its metabolites and the heart.<sup>30</sup> For example, polymorphism of the alcohol dehydrogenase type 3 (ADH3) gene alters the rate of alcohol metabolism. It has been shown that moderate drinkers who are homozygous for the slow-oxidizing ADH3 allele have higher HDL levels and a decreased risk of myocardial infarction.<sup>31</sup> In contrast, polymorphism of the angiotensin converting enzyme (ACE) gene has been implicated in alcoholic cardiomyopathy. The ACE DD genotype has been noted to increase the likelihood of development of left ventricular dysfunction in alcoholics<sup>32</sup>. In contrast to previous beliefs, there is a positive correlation between development of alcoholic cardiomyopathy and alcoholic cirrhosis<sup>33</sup>.

Alcohol causes structural and functional changes in the myocardium. Animal studies have shown increased myocyte loss (due to apoptosis) in hearts exposed to high concentrations of alcohol<sup>34,35</sup>. Ethanol and its metabolites are thought to be toxic to the myocyte sarcoplasm and mitochondria<sup>36,37</sup>. Alcohol has been

shown to have an unfavorable impact on cardiac myofibril shortening and the composition of myoproteins<sup>38,39</sup>. Calcium sensitivity at the myofilament level, and not altered calcium management, has been shown to produce changes in myocardial contractility<sup>40</sup>.

Heavy drinkers have lower ejection fractions, greater end diastolic volumes, lower mean fractional shortening and a greater mean left ventricular mass when compared with healthy controls in a dose-dependent fashion<sup>27</sup>. Such pre-clinical abnormalities affecting the left ventricle appear to be independent of nutritional status or other habits such as tobacco smoking<sup>41</sup>.

Echocardiographic abnormalities such as increased left atrial dimension, increased left ventricular wall thickness and decrease in fractional shortening abnormalities precede onset of clinical symptoms or physical findings in heavy drinkers<sup>42</sup>. Several investigators have reported that diastolic impairment occurs commonly and consistently and may precede systolic dysfunction<sup>43</sup>. Animal and some human studies suggest plausible pathophysiologic mechanisms for the alterations in systolic and diastolic function seen in alcoholic cardiomyopathy.

Studies on mice and human tissue have shown that alcohol is a direct myocardial toxin and causes ultrastructural damage. This has myriad effects such as edema of the sarcoplasmic reticulum, fragmentation of contractile elements, expansion

of intercalated disc, and fatty deposits<sup>44</sup>. Rat cardiomyocytes exposed to alcohol have a dose dependant depression in contractility due, at least in part, to a depletion of sarcoplasmic calcium <sup>45</sup>. Potential pleiotropic mechanisms underlying the development of alcoholic cardiomyopathy are shown in Figure #2<sup>46</sup>.

### Clinical features and diagnosis of alcoholic cardiomyopathy

There exist no unique identifying features that set apart alcoholic cardiomyopathy from other causes of heart failure. This diagnosis is further complicated by the frequent presence of other risk factors for cardiomyopathy. History is key, as is a definite lack of other inciting factors such as certain prescribed or non-prescribed drugs (e.g. doxorubicin, cocaine) or ischemic heart disease, helps strengthen the diagnosis, which remains one of exclusion. When clinically manifest, alcoholic cardiomyopathy demonstrates four chamber dilatation, low cardiac output and normal or decreased left ventricular wall thickness. Clinical stigmata of heart failure such as a third heart sound, elevated jugular venous pulse and cardiomegaly with or without rales may be seen especially in decompensated states. The co-existence of liver disease due to cirrhosis may give rise to diagnostic confusion when the picture may be less straightforward. The association of supraventricular arrhythmias with heavy alcohol intake (holiday heart syndrome) as well as an association with sudden cardiac death are further complications of alcohol abuse in alcoholic cardiomyopathy patients <sup>2, 47, 48</sup>. Based on the observations of Fauchier and colleagues, the cause of death in patients with alcoholic cardiomyopathy are similar to those with idiopathic cardiomyopathy; progressive chronic heart

failure and sudden cardiac death<sup>13</sup>. Of note, alcoholics with simultaneous cardiomyopathy and cirrhosis carry a worse prognosis.<sup>49</sup>

## Treatment

There exist no formal guidelines for the treatment of patients with alcoholic heart failure. Multiple studies have shown a tendency towards improvement in left ventricular ejection fractions in patients who abstained or drastically decreased their intake of alcohol. A small study of 11 patients reported significant improvements in ejection fractions of patients who abstained from alcohol when coupled with medical therapy<sup>50</sup>. Another study of 55 heavy drinking men showed improvement in ejection fractions in those who abstained as well as those who controlled drinking (< 60 g of ethanol/day) as shown in Figure 3.<sup>51</sup> Interestingly, in a subset analysis of the Studies of Left Ventricular Dysfunction (SOLVD) light to moderate drinkers with ischemic cardiomyopathy had significantly lower mortality rates when compared to abstainers<sup>52</sup>.

Medical therapy available for alcoholic cardiomyopathy is no different from that for other etiologies of heart failure except it should include abstinence from alcohol as a cornerstone<sup>53, 54</sup>. Survival is poor in those who continue to drink heavily with 4-year mortality levels close to 50%. One should follow the heart

failure guidelines such as those adopted by the European Society of Cardiology or the American College of Cardiology/American Heart Association referenced to earlier, that incorporate the use of certain beta-blockers and angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Diuretics and digitalis can be used in the management of symptomatic alcoholic cardiomyopathy patients. Some of these patients may have co-existing nutritional (vitamins, minerals such as selenium or zinc) deficiencies, which may need correction as well since they can independently worsen outcomes or hamper attempts at treatment. While little data is published regarding the benefit of heart transplantation in patients with end-stage alcoholic cardiomyopathy, relapse would be a major concern. One study did report alcohol relapse rates following liver transplant of 5.6 cases per 100 patient per year for any alcohol use and 2.5 cases per 100 patients per year for heavy alcohol use <sup>55</sup>.

## Conclusions

Alcohol in moderation appears to protect against cardiovascular disease. However excess use of alcohol results in a type of dilated cardiomyopathy, which is indistinguishable from that due to other etiologies of non-ischemic cardiomyopathy. Diagnosis remains one of exclusion with strong emphasis on a history of heavy alcohol usage. Men are more commonly affected. Asymptomatic

impairment of systolic and diastolic functional parameters on echocardiogram is increasingly thought to precede the overt manifestation of alcoholic cardiomyopathy and is in fact found in the majority of heavy drinkers. Mainstay of therapy is abstinence although benefits have been noted even when subjects have substantially decreased their intake of alcohol. Medications dictated by heart failure guidelines such as beta-blockers, ACEIs and ARBS should be used in these patients.

Disclosures: There are no conflicts of interest for Anil George, MD or Vincent M Figueredo, MD.

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## Figure legends

FIGURE 1. Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed-effects and random-effects models. Reprinted with permission from ref#7

FIGURE 2. Proposed hypothetical schema for the pathogenesis of ACM. gms = grams;  
NE = norepinephrine. Reprinted with permission from ref#46

FIGURE 3. Changes in left ventricular ejection fraction in patients with alcoholic cardiomyopathy, according to daily ethanol intake during the first year of the study. Group values (squares) are expressed as means; error bars represent 95% confidence intervals. Reprinted with permission from ref#50

Table 1. Modified with permission from Department of Agriculture. Provisional Table on the Nutrient Content of Beverages. Human Nutrition Information Service. Washington, DC, Department of Agriculture. (1982)