Reversible Cardiomyopathies: A clinical case of Alcoholic Cardiomyopathy

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No conflicts of interest to declare
49yo male, chronic heavy alcohol consumption, without known disease to his medical history. Alcohol consumption (≥10 beers/day = ≥ 80gr/d) for several years

appear at ER with paroxysmal nocturnal dyspnoea and severe peripheral edema, reporting progressively worsening exertional dyspnoea since the last two weeks.

at auscultation: S1, S2, S3 gallop with arrhythmia and crackles at his lung fields.

BP =115/70mmHg and SatO₂ 92–94%

blood count and chemistry: Ht 40.5%, Hb 12.9mg/dl, urea: 110mg/dl, creatinine: 1.9 mg/dl, total proteins: 6.07 g/dl, SGOT: 243 U/L, SGPT: 356 U/L, ALP: 171 U/L, CRP: 43.95mg/l, troponin I 0.17ng/ml
His chest x-ray and ECG at presentation
His initial echo
His coronary angiography revealed normal coronaries
He commenced **conventional heart failure therapy** with i.v furosemide, rate control agent (carvedilol), LMWH, ACEI, spironolactone and O2

Some days later showed good clinical and hemodynamic response with improvement (deletion) of swelling, normalization of breathing and lower heart rate at “normal” levels
repeated echo after a month
In younger individuals, where HF is less prevalent, cardiomyopathies caused by a heterogeneous group of diseases, represent the leading cause of HF and HTx.

Among cardiomyopathies, DCM is the 1st cause of HTx among young.

Excessive alcohol consumption is the major cause of non-ischemic DCM in Western countries.
At present ACM is considered a specific disease both by ESC and by AHA.

Diagnosis of ACM is usually one of exclusion in a patient with DCM, no identified cause and long history of heavy alcohol abuse.

Alcohol required is >80g/d during at least 5y or more.
Table 2. The effects of high-dose alcohol on short and long-term cardiovascular damage.

<table>
<thead>
<tr>
<th>Short-Term Effects on the Heart</th>
<th>Long-Term Effects on the Heart</th>
<th>Long-Term Effects on the Vascular System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunction of cardiac contractility</td>
<td>Dysfunctional ventricular dysfunction</td>
<td>Diastolic dysfunction</td>
</tr>
<tr>
<td>Acute arrhythmias</td>
<td>Atrial dysfunction</td>
<td>Systolic dysfunction</td>
</tr>
<tr>
<td>supraventricular ventricular (holiday heart syndrome)</td>
<td>Chronic arrhythmias</td>
<td></td>
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<tr>
<td>Arterial hypertension</td>
<td>Alcoholic cardiomyopathy</td>
<td>Subclinical cardiomyopathy</td>
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<tr>
<td>Transitory ischemic cerebral attack</td>
<td>Alcoholic cardiomyopathy</td>
<td>Clinical congestive heart failure</td>
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<td></td>
<td>Low-output dilated cardiomyopathy</td>
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<tr>
<td>Sudden death</td>
<td>Coronary heart disease</td>
<td>Angina</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td></td>
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<td></td>
<td>Increased cardiovascular mortality</td>
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</tbody>
</table>

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Epidemiology of ACM

Prevalence of ACM among IDCM

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>ACM (%)</th>
<th>IDCM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haissaguerre et al., 1989</td>
<td>236</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Prazak et al., 1996</td>
<td>75</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>Fauchier et al., 2000</td>
<td>134</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>McKenna et al., 1998</td>
<td>100</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Gavazzi et al., 2000</td>
<td>338</td>
<td>23%</td>
<td>77%</td>
</tr>
</tbody>
</table>

WJC 2014 Aug 26;6(8): 771
Evidence linking excessive alcohol consumption and ACM

- **Epidemiological studies** higher prevalence of excessive alcohol consumption has been reported among individuals diagnosed with ACM than in the general population.

- **Experimental studies** analyzing the amount of alcohol required to depress cardiac contractility.

- **Echocardiographic and hemodynamic studies**

- **Histological studies**

- **Basic studies on molecular mechanisms of myocardial damage**
pathophysiology

- Alterations in mitochondria and sarcoplasmic reticulum
- Alterations in protein synthesis/gene expression
- Alterations in calcium transient and myofibril Ca sensitivity
- Genetic susceptibility
- Oxidative stress
- Apoptosis
- Activation of renin-angiotensin and catecolaminergic system
- Changes in myofilament structure and function
Alcohol → Acetaldehyde

Disruption of myocyte oxidative status/nitrative stress

Disruption of mitochondrial function

↑ ROS Free-radical

- Overexpression of antioxydative enzymes
- Disruption of ion channels/reduction of coronary blood flow
- Inhibition of redox-sensitive transcriptional factors
- Decreased protein synthesis/turnover
- DNA damage/ Decreased myocyte proliferation rate
- Increased cardiac steatosis, myocyte hypertrophy and fibrosis
- Increased cardiac apoptosis

↑ cardiac tissue damage

Int. J. Mol. Sci. 2016, 17, 1651
Genetic susceptibility

- There are inter-individual variations in the sensitivity of the myocardium to the alcohol induced heart damage
  - Left ventricular p53 gene expression (gender dependent)
  - Presence of polymorphism of ACE–DD genotype (study 2002 compared 27 alcoholics and 30 ACM, DD was more frequent among ACM 56% vs 8%) – (furthermore 89% of alcoholics with DD genotype developed ACM)
  - The cardio-depressive power of alcohol vary according to the activity of enzymes that metabolize alcohol genetic polymorphisms of aldehyde dehydrogenase
Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study

Alexandra Gonçalves¹,², Brian Claggett¹, Pardeep S. Jhund¹,³, Wayne Rosamond⁴, Anita Deswal⁵, David Aguilar⁶, Amil M. Shah¹, Susan Cheng¹, and Scott D. Solomon¹*

Aim

Alcohol is a known cardiac toxin and heavy consumption can lead to heart failure (HF). However, the relationship between moderate alcohol consumption and risk for HF, in either men or women, remains unclear.

Methods and results

We examined 14,629 participants of the Atherosclerosis Risk in Communities (ARIC) study (54 ± 6 years, 55% women) without prevalent HF at baseline (1987–89) who were followed for 24 ± 1 years. Self-reported alcohol consumption was assessed as the number of drinks/week (1 drink = 14 g of alcohol) at baseline, and updated cumulative average alcohol intake was calculated over 8.9 ± 0.3 years. Using multivariable Cox proportional hazards models, we examined the relation of alcohol intake with incident HF and assessed whether associations were modified by sex. Overall, most participants were abstainers (42%) or former drinkers (19%), with 25% reporting up to 7 drinks per week, 8% reporting ≥7 to 14 drinks per week, and 3% reporting ≥14–21 and ≥21 drinks per week, respectively. Incident HF occurred in 1,271 men and 1,237 women. Men consuming up to 7 drinks/week had reduced risk of HF relative to abstainers (hazard ratio, HR 0.80, 95% CI 0.68–0.94, P = 0.006); this effect was less robust in women (HR 0.84, 95% CI 0.71–1.00, P = 0.05). In the higher drinking categories, the risk of HF was not significantly different from abstainers, either in men or in women.

Conclusion

In the community, alcohol consumption of up to 7 drinks/week at early-middle age is associated with lower risk for future HF, with a similar but less definite association in women than in men. These findings suggest that despite the dangers of heavy drinking, modest alcohol consumption in early-middle age may be associated with a lower risk for HF.
Meta-analysis of 34 prospective studies in men and women, >1 million subjects

J shaped relationship between alcohol intake and mortality
Sex differences

Women more sensitive to harmful effects probably:
- Increased risk of breast cancer
- Differences in the way alcohol is metabolized
- Threshold dose is less

Di Castelnuovo et al, Arch Inter Med 2006
A total of 282pts (94 patients with ACM) from 1993–2011 median follow up 59 months
Predictors of death/HT in ACM

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
<th>AUC</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of beta-blocker therapy</td>
<td>4.4</td>
<td>1.35-14.49</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS width &gt;120 ms</td>
<td>7.2</td>
<td>2.02-26.00</td>
<td>0.002</td>
<td>0.82</td>
<td>0.73-0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9.7</td>
<td>2.56-36.79</td>
<td>0.001</td>
<td></td>
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</tbody>
</table>

Variables entered into multiple regression analysis included age (p = 0.186; per 5-year increase); left ventricular ejection fraction (LVEF; p = 0.256; per 5-U decrease); left end-diastolic diameter (p = 0.059; per 5-mm increase); alcohol abstinence (p = 0.789); atrial fibrillation (p = 0.004); QRS >120 ms (p = 0.003); beta-blocker therapy (p = 0.001); ACEI/ARB therapy (p = 0.075); digoxin (p = 0.005); and loop diuretic agent therapy (p = 0.064).

AUC = area under the curve; CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Previous mean alcohol consumption, duration of abuse, type of alcoholic beverage consumed were not associated with outcome.
Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy

![Graph showing comparison between ACM and IDCM survival rates over time.](image)

PATIENTS AT RISK AT EACH TIME INTERVAL

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>ACM</th>
<th>IDCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>94</td>
<td>188</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>109</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

ACM: Alcohol Cirrhosis Manifestations
IDCM: Idiopathic Dilated Cardiomyopathy

p = 0.002
Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy

Figure 1  Survival curves of cardiac deaths in patients with alcoholic dilated cardiomyopathy (with (—) and without (---) abstinence) and idiopathic dilated cardiomyopathy (---). Idiopathic dilated cardiomyopathy vs alcoholic dilated cardiomyopathy with abstinence, P=ns; idiopathic dilated cardiomyopathy vs alcoholic dilated cardiomyopathy without abstinence, P=0.002; alcoholic dilated cardiomyopathy with abstinence vs alcoholic dilated cardiomyopathy without abstinence, P=0.003.
ACM patients who decreased alcohol intake to moderate levels had outcomes similar to those who abandoned alcohol.
Treatment

- **Drug therapy as recommended for DCM in current HF guidelines (beta blocker therapy necessary)**

- **ICD implantation if LVEF < 35%**
  
  (Malignant ventricular arrhythmias are more frequent in ACM than in IDCMI. LBBB identifies ACM patients with increased risk of SCD.

  No malignant ventricular arrhythmias were found during follow-up in ACM patients when LVEF was \( \geq 40\% \).

  *Int J Cardiol.* 2015 Nov 15;199 “Malignant ventricular arrhythmias in alcoholic cardiomyopathy”.

- **Alcohol withdrawal**
Follow up 14 months later

Sinus rhythm
Normalization of LVEF
normal LVEDD/LVESD
GLS = -16,6%
Long term alcohol consumption is an important cause of dilated cardiomyopathy. Age, genetic polymorphisms, gender, behavioral and environmental factors, can modify personal susceptibility to ethanol-induced cardiac damage. Women are more sensitive to damage effects of alcohol compared to men. The currently accepted definition of ACM requires chronic exposure to >80gr/d of alcohol for > 5 years. The pathophysiology is complex and involves many aspects of myocyte function. ACM in pts with abstinence has a better prognosis than IDCM. Treatment of ACM should include alcohol abstinence and symptomatic patients should be treated with recommended HF pharmacotherapies.
Thank you for your attention
Commander HN, Coborozos Christoforos MD