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The Diagnosis of Alcoholic Cardiomyopathy

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Abstract

Moderate alcohol intake can decrease mortality risk; in contrast, the excessive alcohol consumption added extra burden to the cardiovascular system. The Alcoholic cardiomyopathy(ACM) is defined as cardiomyopathy caused by chronic excessive drinking or intermittent alcohol abuse characterized by dilated ventricular, cardiac hypertrophy with reduced ventricular wall thickness, disturbed myofibrillary architecture, dampened myocardial contractility. In spite of its clinical importance, the current clinical diagnostic criteria of ACM is not uniform; it lacks specific immunological indicators and diagnostic gold standards. In this review, we evaluate available evidence about the diagnosis of ACM from imaging, electrocardiogram, gene and laboratory. Additionally, we discuss the epidemiology, pathophysiology and histopathological changes, clinical manifestations and treatment of ACM.

Keywords: *Alcoholic, Imaging, diagnosis, Alcoholic cardiomyopathy, Cardiomyopathy.*

Introduction

The effect of alcohol on the human body should be divided into two aspects. The body's reaction to alcohol is dose-dependent. On the one hand, moderate alcohol intake can decrease mortality risk [1]; on the other hand, the excessive alcohol consumption added extra burden to the organizations[2]. The Alcoholic cardiomyopathy (ACM) is defined as cardiomyopathy caused by chronic excessive drinking or intermittent alcohol abuse characterized by dilated ventricular, cardiac hypertrophy with reduced ventricular wall thickness, disturbed myofibrillary architecture, dampened myocardial contractility[3].

ACM is one of the main reason of non-ischemic dilated cardiomyopathy. The existing researches[4, 5] suggest that in the etiology of ACM, the threshold of alcohol is about 80 g/day over several years (at least 5 years, usually 15 years).However, the condition can be asymptomatic. This effect is caused by ethanol and acetaldehyde (the first metabolite of ethanol, also may be exacerbated by interactions with other toxins[6]. Women are more sensitive than men to the toxic effects of alcohol on cardiac function[7].

Therefore, it is crucial for the early diagnosis of ACM. However, the current clinical diagnostic criteria of ACM is not uniform. ACM is different from other types of cardiomyopathy such as immune cardiomyopathy and viral myocarditis; it lacks specific immunological indicators and diagnostic gold standards[8]. The changes in cardiac structure and function, as well as histological changes of ACM patients, are similar to primary dilated cardiomyopathy (DCM) [4, 9].

This review is intended to describe the diagnosis of ACM, with particular attentionto myocardial changes in adults with chronic abuse alcohol.Additionally, we discuss the epidemiology, pathophysiology and histopathological changes, clinical manifestations and treatment of ACM.

Epidemiology

Recently, ACM related death and disability were the first time brought into the global burden of disease (GBD) mortality analyses[10]. Globally, 6.3% of patients with cardiomyopathy die from alcohol[11]. In general, the outcome of patients with ACM has dilated heart failure, but in 35% of cases, it is also the cause of sudden cardiac death(SCD)[12]. However, there are plenty of barriers in determining the ACM as the main cause of death. Based on the model in the study by Manthey, J. et al., the true death counts of ACM are likely underestimated [11].

Pathophysiology and Histopathological Changes

In terms of the pathogenesis of ACM, alcohol not only induces ACM directly byaffectingthe structure and function of the myocardiumbut also indirectly induces heart damage by acting on different components of the cardiovascular system[13]. It is currently believed that oxidative stress, impaired mitochondrial bioenergetics, accelerated protein catabolism, apoptotic cell death and derangements in fatty acid metabolism and transport are the main mechanisms that ACM may involve[13, 14]. Acute consumption of a large amount of alcohol leads to myocardial inflammation and raising in serum troponin concentration[15]. Chronic alcohol abuse can result in myocytes hypertrophy, apoptosis and necrosis, intracellular structures dysfunction,mitochondrial degeneration and fibrosis[14]. Studies have shown that chronic ethanol consumptionleads to many adverse cardiac intracellular effects, such as sarcoplasmic reticulum dysfunction[16] and changes in intracellular Ca^{2+} handling [17], decreased myofibrillar ATPase activity[18], decreased myofibrillar calcium sensitivity[19], contractile protein fragmentation and disarray[20] and fatty acid accumulation within intracellular organelles [21].The expression of Titin in the myocardium of patients with chronic ACM significantly reduced, which is closely related to the multifactorial pathogenesis of ACM[22]. Ion homeostasis and decreased counterpulsin activity are the basis for the formation of the latent phase of ACM[23].

Fibrosis, atrophy and hypertrophy of cardiac myocytes, glycogen and lipid accumulation, fatty degeneration alterations in the structure of the sarcoplasmic reticulum and the mitochondria are present at autopsy or biopsies from alcoholics and patients with ACM [24-26]. It has reported that myocytes lost their cross-striated appearance and had pyknotic nuclei in a histopathological examination of hearts of patients with the diagnosis of ACM [27]. However, these features are not specific to ACM and we cannot differentiate it from idiopathic or chronic inflammatory cardiomyopathy[28, 29].

Clinical Presentations

Depending on the signs and symptoms of congestive heart failure, the patient may be asymptomatic (preclinical phase) or symptomatic (clinical phase), which includes subclinical cardiomyopathy, clinical heart failure, and dilated low output cardiomyopathy [5]. Patients have exertional dyspnea, peripheraledema, fatigue, oliguria and nocturia. Tachyarrhythmia, jugular veins distention, third and/or fourth tone and a systolic murmur could be evidencedat physical examinations[5, 6].

Diagnosis

Electrocardiographic

Pathological ECG changes can occur both in healthy individuals and patients with alcohol intoxication. However, they are more frequent and prognoses are more significant in chronic alcoholics and ACM. Sinus-tachycardia and nonspecific ST-T changes are the most common electrocardiographic abnormalities in chronic alcoholics[30, 31]. In the study of Ryan JM and Howes LG, 20% of cases had sinus-tachycardia [31], 18% of patients had sinus tachycardia, and 9% of patients had nonspecific ST-T changes in the study of H.D. Attar et al.[30].

In another study, ventricular premature contractions (VPC) and sinus tachycardia were common findings in the electrocardiogram in patients with chronic alcoholism [32], these results are consistent with the previous study [31]. In chronic alcoholics most commonly observed ectopics are atrial premature contractions (APC) and VPC [30]. In their study 1% of patients have APCand 1% of patients have VPC.

Ventricular arrhythmias are possible complications of ACM, and individuals with high alcohol intake have an increased risk of ventricular tachycardia (VT) and SCD[33]. In 2003, the first study addressing the incidence of malignant arrhythmias in ACM was published [34]. In this study, 19% of ACM patients suffered a malignant arrhythmic event. Later, malignant ventricular arrhythmias were confirmed to be relatively common complicationsin ACM patients [35].

Known as the “holiday heart syndrome,” the supra ventricular arrhythmia (SVA) induced by drinking binges was first popularized in1978 [36].A prospective study confirmed that all types of SVA were associated with heavier alcohol intake[37]. Ethanol is a well-known cause of SVA [33, 38].

The most common arrhythmia in chronic alcoholics is atrial fibrillation (AF). It usually resolves spont aneously [30]. There are sufficient clinical and pathophysiological evidence to reveal the clear link between alcohol consumption and the risk of the onset of AF[39]. The previous study has shown the

relation between the consumption of alcohol and AF in men: heavy drinking was independently associated with a higher risk of AF[40]. However, it seemedthat this association doesn't exist in women[41].In 2008, a prospective study assessed the connection between regular alcohol consumption and incident AF among 34,715 initially healthy women. Their results suggested that heavier consumption was related to a small but significant increased AF risk [42].

Right bundle branch block (RBBB) can be observed in chronic alcoholic patients[43]. The long term drinking has adverse effects on cardiovascular functions, which leads to the ECG changes in the exercise[44]. Compared with nonalcoholic persons, chronic alcoholics had significantly increased ST segment, QT interval, and QTc interval during moderate exercise[44]. After adjusting for other risk factors, such as age, gender, ejection fraction and so on, heavy alcohol consumption was found to be a risk factor for a prolonged QTc interval [40]. A subtle prolongation of QRS duration, which may be a indictor of ischemia[44]. Due to diastolic dysfunction is the earliest mechanical abnormality during ischemia, abnormal prolongation of QTc interval and QT interval may be one of the signs of ischemia[45]. In total, the ECG changes are not specific changes.

Echocardiography

Researchers are now more concerned with the preclinical, early detection of asymptomatic heart changes than the clinical phase, which is more helpful for clinicians to make a diagnosis and prevent in advance. Before significant left ventricle (LV) systolic dysfunction, alcohol consumption may lead to disruption of myofibrillar structure, subclinical reduction of fibrosis and myocardial contractility[46, 47]. In a study of Asians, compared with those who had irregular intake, subjects who had light to moderate doses of habitual drinking weekly were associated with cardiac remodeling and impaired cardiac mechanics, despite globally preserved left ventricular ejection fraction (LVEF) [48]. In recent research, there was no significant difference in the conventional echocardiography parameters between asymptomatic alcoholic drinkers and the normal control group [49]. However, a community-based study of the elderly population showed that in both genders, increasing alcohol intake was related to the enlargement of left ventricular diastolic and systolic diameter (LVDd, LVDs) and left atrial diameter (LAD) [50]. What's more, they also found that increasing alcohol intake was related to greater LV mass (LVM) and higher E/E' ratio in men and lower LVEF in women. Later, H.D. Attar et al. found that in asymptomatic chronic alcoholic patients, the most common 2-dimensional echocardiography (2DE) changes were increased left ventricular postero-lateral diastolic wall thickness (LVPWTd) and followed by increased interventricular diastolic thickness (IVSTd) and decreased LVEF[30]. In previous studies, LV diastolic dysfunction (LVDD) was found in mild to moderate drinkers and was further confirmed by Doppler tissue imaging[25, 48]. Compared with mild group and control group, the moderate drinkers (consumed 90mg to 140mg ethanol 3–5 days per week for 9–20 years) had increased left ventricular end-diastolicand end-systolic volume (LVEDV, LVESV) by real-time 3-dimensional echocardiography (3DE). The LVEF is maintained at a normal level in this phase [51]. Among asymptomatic chronic alcoholics, global longitudinal and circumferential strain values of LV decreased with increasing alcohol consumption [48, 49].

In the clinical phase, ACM is characterized by depressed cardiac output, reduced myocardial contractility, and dilatation of all the chambers of the heart [2, 14, 52]. In the severe alcoholic (consumed >150mg ethanol 6–7 days per week for more than 10 years) group, the conventional echocardiography changes can be observed include increased LVDd, LVDs, LVPWTd, IVSTd and decreased LVEF and the ratio of the early (E) to late (A) ventricular filling velocities (E/A) [49]. This result is consistent with previous research [9]. Similar to conventional echocardiography, LV systolic function remained unchanged in the mild and moderate groups, significantly decreased LVEF and increased LVEDV and LVESV in severe alcoholics were further confirmed using 3DE[51]. 3DE can stereoscopically evaluate ventricular volume expansion relative to conventional echocardiography. LVM was a sensitive index for finding early changes in cardiac structure. LVM and left ventricular myocardial mass index (LVMI) showed a significant increase in alcohol drinkers, which were closely related to alcohol consumption[51]. Also, in that study, it introduced the parameter of systolic dyssynchrony index (SDI). Compared with asymptomatic alcoholics, SDI had a significant decline in the symptomatic group. In the clinical phase, the SDI was associated with the changes of LVEF [51].

The longitudinal strain was sensitive to occult left ventricular dysfunction and can detect early stages of ACM [50]. In the symptomatic group, the indictor of longitudinal, circumferential and radial strain values and rotation and twist values were decreased Figure 1 [49].It is worth noting that there is a hierarchical relationship between weekly alcohol consumption and decreased LV systolic function [48].

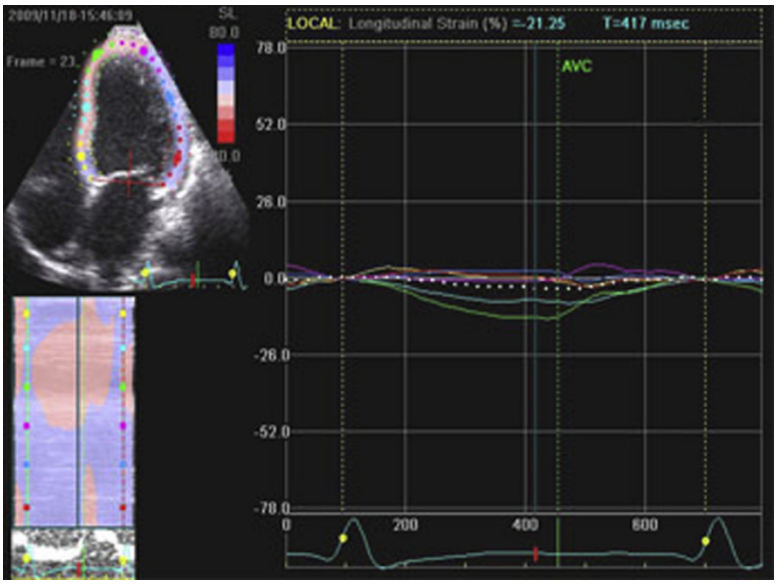

Fig 1. *Global peak longitudinal left ventricular strain rate from an apical four-chamber view of alcoholic patients with long duration of heavy drinking (severe).*

Compared with the right ventricle RV, people pay more attention to left ventricular function and deformation, whereas it is undeniable that the dilatation and dysfunction of RV are common findings in the patho genesis of ACM, and are closely related to the severity of LV diseases[53]. The significant dilation of the right ventricle end-diastolic diameter (RVEDD) and decreased tricuspid annular plane systolic excursion (TAPSE) can only be detected in the severe drinkers by 2DE. In asymptomatic moderate drinkers, the longitudinal early and late diastolic strain rate (SRe, SRa) of the RV free walland LV longitudinal strain were obviously lower than those of mild group and the control group, and in severe group, all the 2D STE parameters were obviously lower than those of other groups [54]. The reduced RV longitudinal strain can be interpreted as a decrease in myocardial contractility [55].

Chronic alcoholism is always accompanied with LVDD, and it also causes damages of the structure and the function of the left atrium (LA) [56, 57]. According to the latest guidelines, the volume of the LA is one of the most sensitive parameters of diastolic dysfunction when there is no change in systolic function, and even other parameters of LVDD remain unchanged [58]. Since the moderate stage, the LA volumes of alcoholics have increased, and a passive atrial emptying fraction (LAPEF) decreased. Active atrial emptying fraction (LAAEF), which measures the function of the booster pump, increased with the degree of alcoholism and then decreased during the severe phase [59]. SRs SRe gradually decreased as the degree of alcoholism increases, which means the movement of myocardial tissue has been slowed down [59]. The index of SRe and LAPEF showed the conduit function of LA was decreased. Also, due to the decreasing of atrial compliance, SRs, as a parameter for the evaluation of the reservoir function, declined [59].

DR, CT, MRI

The signs of ACM showing in Chest X-ray are included cardiomegaly, venous vessels enlargement, pulmonary edema [60]. John G. Demakis et al.observed the cardiac enlargements in 57 patients who were diagnosed ACM[61]. Cardiac CT is a noninvasive method to exclude coronary disease[6]. And cardiac MRI will help to rule out other cardiomyopathies[6].Research confirmed that among AF patients with habitual alcohol consumption, even mild-moderate drinks would lead to increased LA and injured mechanical function by MRI [62]. In radionuclide cardiac scanning, myocardial contractility and LVEF are generally reduced, echocardiographic measurements of LVEF were consistent with radionuclide measurements[63].

Gene

About 2–3% of microRNA expressions can be altered by ethanol in large-scale miRNA screens [64, 65]. It has been confirmed that, in heart tissue of mice with ACM, the non-coding RNA profile of heart tissue can be changed by chronic alcohol consumption. Compared with the control group, 19 microRNAs and 265 circular RNAs were differentially expressed among the alcohol-treated mice[66]. Several microRNAs in plasma from patients with ACM showed changes;among them, miR-138 may be considered as a new target for the early diagnosis and treatment of human ACM [67]. In the serum of humans with alcohol use disorders, microRNA-378 expressions were found significantly increased[68].

Cardiac protection of aldehyde dehydrogenase 2 (ALDH2) has been demonstrated in a variety of models, including ACM [69-72]. To improve ethanol-induced cardiac damage, ALDH2 decreased angiotensinogen (AGT) and Angiotensin II (Ang II) in the local cardiac RAS by inhibiting the p38MAPK/CREB pathway in ACM[73]. In acute ethanol exposure of rat cardiomyocytes, the expression of microRNA-378a-5p increased. MiR-378a-5p may stimulate cardiomyocyte apoptosis by participating in ALDH2 gene suppression. It may play a potential role in the pathogenesis of ACM[74].

Teragaki et al. obtained myocardial biopsies from ten habitual male drinkers with the diagnosis of DCM, the occurrence of mitochondrial deoxy-ribonucleic acid (mtDNA) point mutations were found in four of the ten subjects [75]. However, it is difficult to determine whether these changes are the cause or consequence of excessive alcohol consumption, in response tooxidative stress, point mutations in mtDNA may arise during the repair of mtDNA [75, 76]. As a prevalent genetic predisposition for ACM, titin truncating variants (TTNtv)is also connected with a worse LVEF in DCM patients who consumpthigher than the recommended level[77]. In another research, the presence of the angiotensin-converting enzyme gene increases the susceptibility to secondary cardiomyopathy after drinking and supports the genetic susceptibility to alcohol-induced myocardial damage[64]. A study has confirmed the role of the p53 gene in ethanol-induced cardiac remodeling in the rat.What's more,the expression of p53 is gender-dependent, males having higher p53 mRNA levels than females[78]. At present, the development of gene levels has been widely used in the diagnosis of various diseases, but there has not been a large-scale popularization of ACM in clinical practice. It is helpful to determine the corresponding genes at an early stage for the diagnosis of ACM.

Laboratory

Liver enzymes such as gamma-glutamyltransferase (GGT), glutamic oxalacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) are the markers for chronic alcohol consumption. A ratio of GOT/GPT higher than two might indicate the etiologies of liver disease is alcohol[79-81]. As the best marker of alcohol abuse, carbohydrate deficient transferrin (CDT) can both detects chronic alcohol consumption alone [82, 83] or in combination with the other markers [84]. Mean corpuscular volume (MCV) is also a marker of alcohol abuse, but the global predictive value of MCV is lower than CDT [84].hs-cTnT, a marker of chronic subclinical myocardial damage, in a community-based study of middle-aged adults without a history of cardiovascular diseases, moderate drinking was associated with lower level hs-cTnT[85]. The concentrations of NT-pro BNP are positively associated with moderate drinking [85].

Treatment

There are no specific treatments to heal the ACM. It is has been recognized that the clinical symptoms of ACM can be alleviated after six months of clinical diagnosis and alcohol withdrawal[52]. The survival rate and recovery of ventricular function were similar to those of abstinent patients when ACM patients had reduced alcohol intake[86]. It was reported that restoring LVEFto > 40% is a reasonable objective for all ACM patients[87]. The common treatment with betablockers and angiotensin-converting enzyme inhibitors//angio-tensin II receptor agonists can provide effective improvement of cardiac function [86]. Also, the diuretic should not be used during the congestive phase[87]. There are also some new measures to recovery functional, such as the use of cardiomyokines or myocardial growth and regulation factors[87].

Conclusions

The ECG and laboratory are notthe specific diagnoses, but they can assist in the diagnosis of myocardial injury. Cardiac CT and MRI help to rule out other cardiovascular diseases. The 2D STE can accurately evaluate the early myocardial movement in ACM. 3DE can evaluate the size and function of each chamber.

The gene detection is the trends in diagnosing ACM.

Above all, the history of drinking and the corresponding examinations can objectively and accurately reflect the changes of heart function, and help pre-clinical diagnosis and treatment, which are pivotal and have development prospects in decreasing the morbidity and mortality of ACM. Further researches in the field of ACM are required.

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Abbreviations:

alcoholic cardiomyopathy	ACM
dilated cardiomyopathy	DCM
global burden of disease	GBD
sudden cardiac death	SCD
ventricular premature contractions	VPC
atrial premature contractions	APC
ventricular tachycardia	VT
supraventricular arrhythmia	SVA
atrial fibrillation	AF
right bundle branch block	RBBB
left ventricle	LV
left ventricular ejection fraction	LVEF
left ventricular end-diastolic diameter	LVDd
left ventricular end-systolic diameter	LVDs
left atrium	LA
left atrial dimension	LAD
left ventricular mass	LVM
left ventricular myocardial mass index	LVMI
end-diastolic thickness of ventricular septum	IVSTd
end-diastolic thickness of left ventricular posterior w all	LVPWTd
ratio of peak early and late diastolic velocities	E/A
2-dimensional echocardiography	2DE
LV diastolic dysfunction	LVDD
left ventricular end-diastolic volume	LVEDV
left ventricular end-systolic volume	LVESV
3-dimensional echocardiography	3DE
systolic dyssynchrony index	SDI
right ventricle	RV
right ventricle end-diastolic diameter	RVEDD
tricuspid annular plane systolic excursion	TAPSE
left atrial passive emptying fraction	LAPEF
left atrial active emptying fraction	LAAEF
longitudinal early diastolic strain rate	SRe
longitudinal late diastolic strain rate	SRa
aldehyde dehydrogenase 2	ALDH2
angiotensinogen	AGT
Angiotensin II	Ang II
mitochondrial deoxy-ribonucleic acid	mtDNA
titin truncating variants	TTNtv
gamma-glutamyltransferase	GGT
glutamic oxalacetic transaminase	GOT
glutamic pyruvic transaminase	GPT
carbohydrate deficient transferrin	CDT
mean corpuscular volume	MCV

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