

Liver cirrhosis prevents atrial fibrillation: A reality or just an illusion?

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ABSTRACT

Objectives: In cirrhotic patients, despite presence of significant metabolic abnormalities and enlarged left atria, we have seldom observed atrial fibrillation (AF) rhythm. The aim of this study was to evaluate the prevalence of AF among cirrhotic patients and comparing it with that reported in the general population. **Materials and Methods:** Medical documents of 1302 adult cirrhotic patients, booked in the waiting list of liver transplantation, were evaluated retrospectively. Electrocardiograms were reviewed for the presence of AF rhythm, and echocardiographies were reviewed to obtain left atrial (LA) size. **Result:** Only two patients (0.15%) were detected to have AF rhythm, which was significantly lower than that reported in our general population, even after age and sex adjustment. Six hundred and sixty-eight patients (51%) had enlarged left atria (LA diameter more than 39mm); both AF patients belonged to this group. **Conclusion:** The result of this study suggests the protective effect of liver cirrhosis on development of atrial fibrillation. Further studies are needed to verify the possible mechanisms.

Key words: Atrial fibrillation, liver cirrhosis, liver transplantation

INTRODUCTION

An electrocardiogram (ECG) showing atrial fibrillation (AF) was first published in 1906^[1] but the pathophysiology has remained to some extent undiscovered. In recent years, the pathophysiologic concept of AF has widely extended from the effect of conventional risk factors such as age, diabetes mellitus and hypertension to recently interesting factors such as inflammation and atrial remodeling. The severity of inflammation is proportional with the amount of inhomogeneity in atrial conduction, which can potentiate the initiation of AF. Several studies have

shown that increased serum levels of inflammatory markers such C-reactive protein (CRP) and Interleukin-6 (IL-6) is associated with high occurrence of AF rhythm.^[2] On the other hand, consumption of anti-inflammatory medications such as statins, angiotensin converting enzyme (ACE) inhibitors and aldosterone receptor blockers (ARBs) seems to be effective to reduce the recurrence of AF.^[3,4]

The size of left atrium (LA) is also an objective index to predict the initiation of AF. Patients with increased LA dimensions are predisposed to the development of either paroxysmal or chronic AF.^[5] LA enlargement starts a chain of events, which causes activation of renin-angiotensin-aldosterone system that leads to progressive atrial fibrosis and remodeling, which is known to play a major role in initiation of AF.^[6]

According to our previous studies, LA size and volume increase in patients with liver cirrhosis.^[7,8] However unexpectedly, during evaluation of cirrhotic patients in our

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Liver Transplant Clinic, we noticed that the frequency of AF is substantially low. This clinical observation brought up this idea to our minds that liver cirrhosis may have a protective role against development of AF. In this study, we aimed to investigate the prevalence of atrial fibrillation among cirrhotic patients in the waiting list of liver transplant and to compare it with that of general population.

MATERIALS AND METHODS

Patients

A retrospective analysis of patients with proved liver cirrhosis, who were booked in waiting list for liver transplantation, was conducted in Namazee Hospital Transplant Centre, Shiraz, Iran. Patients with concomitant congenital heart disease, rheumatic heart disease and also those younger than 20 years old were excluded; 1302 cirrhotic patients met the criteria to enter this study.

Electrocardiogram

A standard 12-lead resting ECG is taken for every cirrhotic patient in our centre as a part of routine cardiovascular evaluation before liver transplantation. We evaluated 1302 ECGs available in patients' files for the presence of AF rhythm; defined as absence of P wave and presence of fibrillatory F waves that vary in amplitude, shape and frequency in association with an irregular ventricular rhythm.

Echocardiogram

A complete transthoracic echocardiography (TTE) is done for every cirrhotic patient as a part of routine cardiovascular evaluation before liver transplantation, and 1261 echocardiographies were available to review. Using parasternal long-axis view, LA anteroposterior diameter was measured routinely by M-mode electrocardiography as the distance from the leading edge of the posterior aortic root to the leading edge of the posterior left atrial cavity at end of systole. This method is proved to be an accurate determinant of LA size and is also compatible with recommendations of "American Society of Echocardiography."^[9] We considered LA to be enlarged if the diameter was greater than 39 mm.^[10]

Other comorbidities

We considered the patient as hypertensive if recorded systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg, or when the patient

used antihypertensive drugs. Diabetes was defined as the consumption of anti-diabetic medication or a fasting blood sugar ≥ 126 mg/dL. We also checked the list of patients' medications to find any drugs with a protective effect on AF, such as spironolactone and β -blockers.

Statistical analysis

The prevalence of AF was determined in total study population, for men and women, and also for different age groups separately. Mean LA size was calculated in total population also using Leven's test, association of LA size with different age groups was assessed.

RESULTS

Age and sex spectrum of our study population is shown in Figure 1. The age group 50–59^{y/o} with 390 participants was the most populated category. Only two of 1302 available ECGs showed AF rhythm [Table 1]. Both patients were men and one of them was a diabetic patient, and none of them was on medications such as spironolactone or β -blockers. One of the AF cases was a 71^{y/o} man and the other one a 45^{y/o} man. So the prevalence of AF is 0.13% among cirrhotic patients under 50^{y/o} and 0.19% in the patients 50 years old or more. Only 2 of 1302 available ECGs showed AF rhythm. Both patients were men and one of them was a diabetic patient and none of them was on medications such as Spironolactone or β -blockers. One of the AF cases was a 71^{y/o} man and the other one a 45^{y/o} man [Table 2]. So the prevalence of AF is 0.13% among cirrhotic patients under 50^{y/o} and 0.19% in the patients 50 years old or more. Mean LA size of total population was 40 mm (Std. Deviation=5.54); 668 patients (51%) had enlarged LA (mean=44.6 mm). The maximum size was 60 mm belonging to a patient with normal sinus rhythm [Table 3]. 611 patients had ascites (47%), 162 patients were diabetic (12.4%) and only 35 cases were diagnosed as hypertensive (2.7%). Thirty percent of patients were using spironolactone and/or β -blocker.

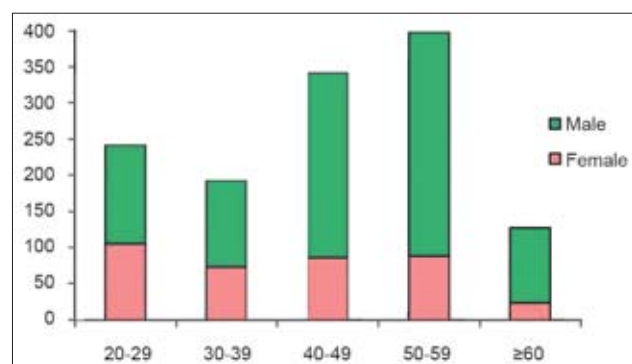


Figure 1: Shows age and sex distribution of the study population

Table 1: Age and sex distribution of the study population and prevalence of atrial fibrillation

Age group (year)	Male	Female	Total	Age ratio (%)	AF (%)
20-29	137	105	242	18.5	0
30-39	120	73	193	14.8	0
40-49	256	86	342	26.3	1 (0.29)
50-59	310	88	398	30.6	0
≥60	104	23	127	9.8	1 (0.78)
Total	927	374	1302	100	2 (0.15)

Table 2: Characteristics of cirrhotic patients with atrial fibrillation rhythm

Age (y/o)	Sex	LA size (mm)	Child score	HTN	Diabetes	Medication
71	Male	48	B	-	+	-
45	Male	55	C	-	-	-

Table 3: Mean left atrial size according to each age group

Age group (year)	Mean LA size (mm)	Age group	LA size (mm)	Std. deviation
20-29	38.6	≤49	39.5	5.465
30-39	39			
40-49	40.5			
50-59	40.6	≥50	40.7	5.655
>60	40.9			
Total	40			

DISCUSSION

A rough comparison of AF prevalence in different races shows that the prevalence of AF in the United States and European people is similar, but it seems to be lower among Asian people.^[11]

In a cohort study in United States among nearly 3 million adults aged 20 years or more, the overall prevalence of AF was defined to be 0.95%, which changed from 0.1% in people younger than 55 years to 3.8% in 60 years and older people. It reached to 9% among those 80 years and older.^[12] In a cross-sectional study among 65 years or older people in United Kingdom, prevalence of AF was found to be 4.7%.^[13] A cross-sectional study among 40–69 years Korean people showed overall AF prevalence of 0.4%; in age group 60–69 years it reaches 1%.^[14]

In Iran, the prevalence of AF is 2.8% among those 50 years old and more. It increases from 0.6% in patients aged 50–59 to 1.4% in age group 60–69 and 6.4% in age group 70–79.^[15] In our study, among 1302 cirrhotic patients, only two patients were found to have AF rhythm (0.15%), which is significantly lower than that reported in the general population.

LA size more than 40 mm increases the risk of development of AF. For example, AF occurs in more than 54% of patients with mitral valve stenosis and enlarged left atria.^[16] Among our cirrhotic patients, 668 patients had LA size equal to or more than 40 mm (mean=44.16 mm). Both AF cases belonged to this group. The prevalence of AF among cirrhotics with enlarged LA is surprisingly low (0.30%).

Diabetes is another risk factor for development of AF and is counted as an independent determinant of AF. Prevalence of AF in diabetics is shown to be higher than non-diabetics, even after adjustment for other risk factors (3.6% vs 2.5%);^[17] 12.4% of our cirrhotic patients were diabetic which is more than that observed in our general population in Iran (6.1%).^[18] One of our two AF cases was diabetic, so prevalence of AF in cirrhotic diabetics is significantly less than diabetic patients without cirrhosis (0.6%).

The prevalence of AF among patients with chronic renal failure non on dialysis is reported to be significantly higher than the general population.^[19] Increase in systemic inflammation was described as guilty by the authors. Now the question is that why in cirrhotic patients the scenario is different?

Low prevalence of AF despite extensive metabolic derangement and LA enlargement in cirrhotic patients may be the result of accumulation of a toxin or a humoral substance with possible anti-arrhythmic and/or anti-inflammatory property, which is normally metabolized by a normal functioning liver.^[20] Interestingly, during early post-transplantation period in ICU, we have noticed that many patients would develop AF rhythm (unpublished observation). The susceptibility to AF in early post-transplantation period may be the result of detoxifying and metabolizing function of transplanted liver.

Lower prevalence of systemic hypertension and taking medications such as spironolactone and β -blockers may be associated with low prevalence of AF in cirrhotics. The inhibitory effect (via anti-inflammatory mechanism or another unknown mechanism) of these drugs on development of AF following myocardial infarction (MI) and cardioversion is confirmed in several studies.^[21,22] It should be mentioned that only 30% of our cases were on spironolactone or β -blockers. Statins, ACE inhibitors and ARBs were not used by any of our patients.

Desensitization of cardiac myocytes to catecholamine in cirrhotic patients is reported,^[23] which may be due to down-regulation of β -adrenergic receptors in myocardium.^[24] This process could be a protective mechanism against occurrence of tachyarrhythmias, including AF in cirrhotic patients.

In conclusion, the result of this study suggests that the prevalence of AF among cirrhotic patients is significantly less than the general population. Further studies seem beneficial to verify the possible protective mechanisms against development of AF in cirrhotic patients. Hopefully, the results of such studies may lead to new concepts regarding pathophysiology, prevention and treatment of AF.

Study limitation

In clinical practice, diagnosis of AF is usually based on physical examination, ECG and 24-h Holter monitoring. In our study, diagnosis of AF was based on only physical examination and ECG. Fortunately, our transplant center is a large referral center and detailed electrocardiographic information of these referred patients over a long period is available. Our hypothesis regarding AF in cirrhotic patients is based on these long-period ECG data.

We do believe that there are many factors that may trigger AF (medications, sex, age, alcohol consumption, obesity, hyperthyroidism, pulmonary disease, etc. Matching of patients with all these factors in a large number of patients, if not impossible, is very difficult.

Finally, we believe that our idea is just a fillip to think and work more in this issue. That is why we have used the term “Reality or Just an Illusion.” Further multicenter randomized studies may change this illusion into reality.

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