

Hepatitis C Viral Infection and Cardiovascular System

-Egyptian Experience in 10 Years-

Mohammad Haykal, MD

Lecturer of cardiology

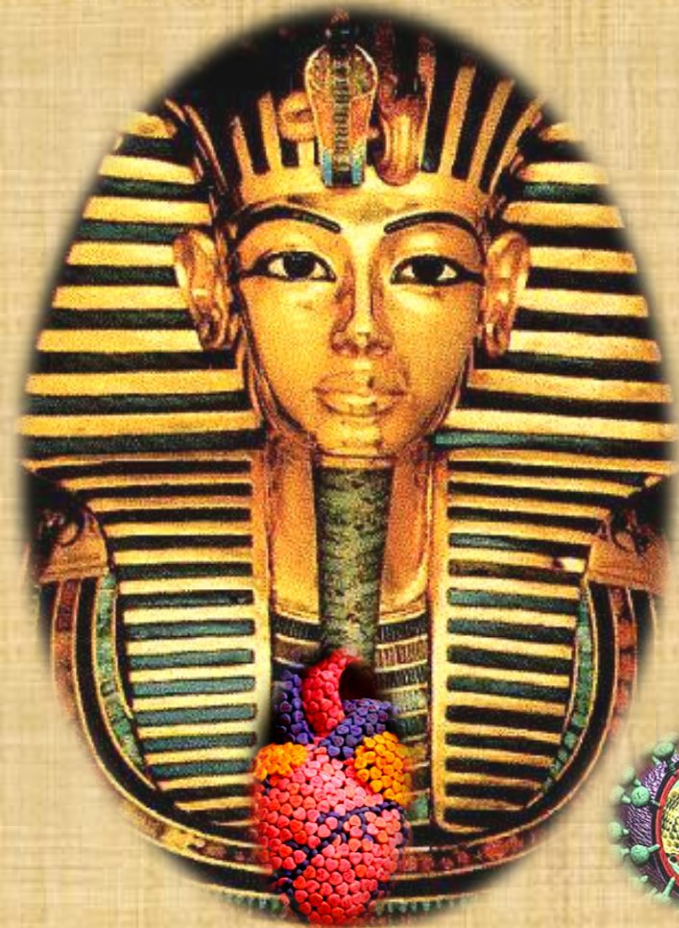
Cardiovascular and Ultrasonography unit

Research Institute of Ophthalmology

Egypt

ISCHF

(Kyoto, 2-4 Dec. 2016)



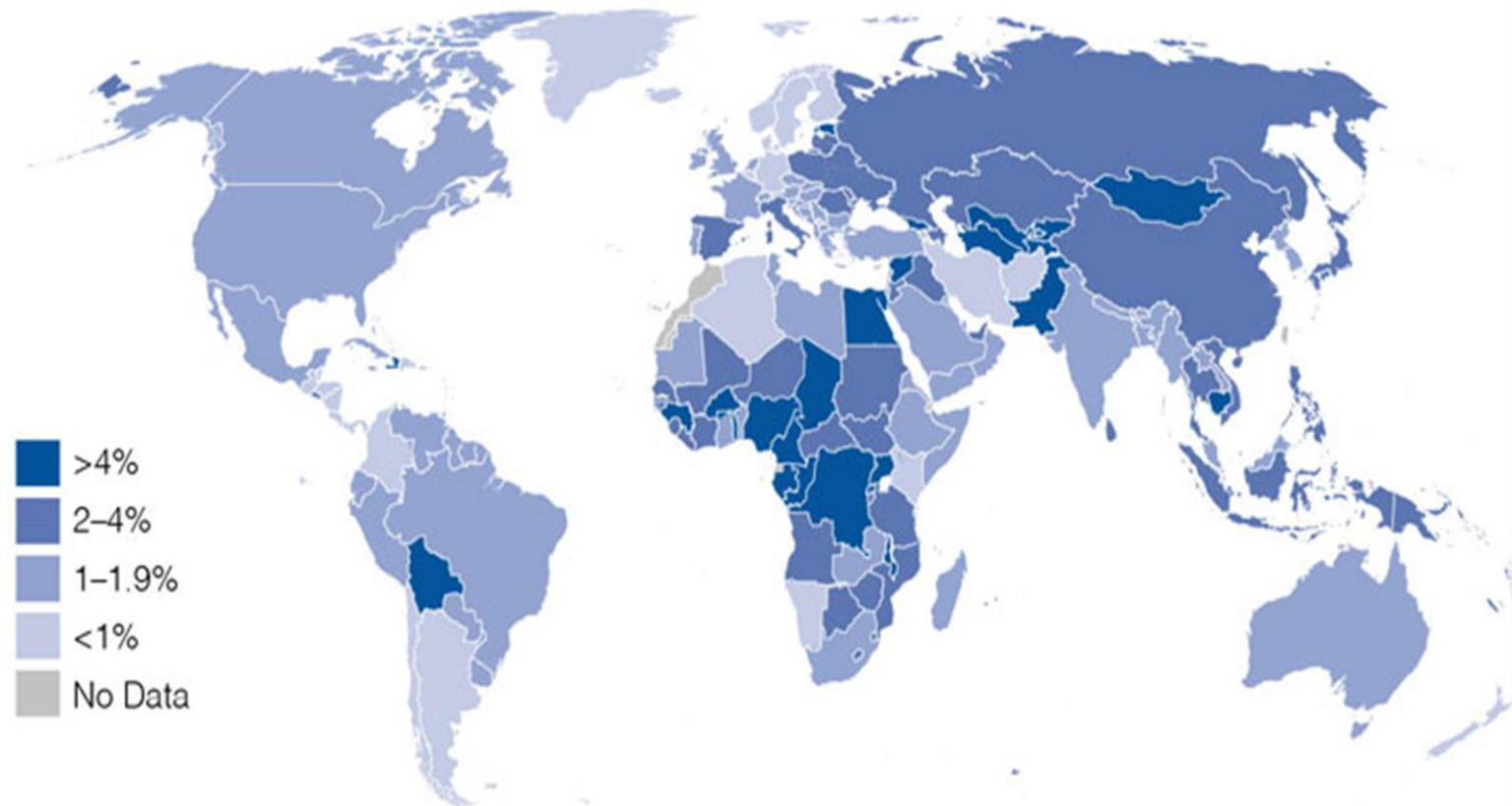
Introduction

About 130 – 150 million persons in the globe are infected with HCV.

Approximately 700 000 people die each year from hepatitis C-related liver diseases.

(WHO; 2016)

Global Hepatitis C Prevalence

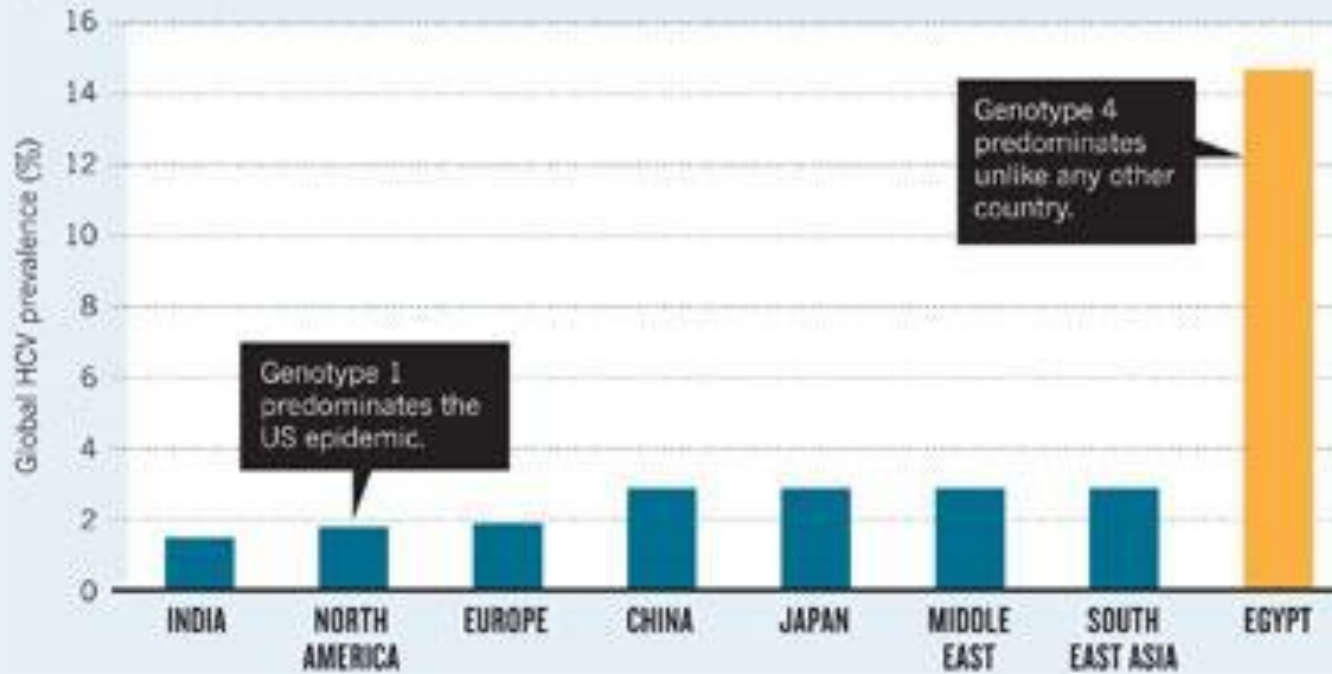


Source: Lavanchy, D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect. 2011; 17:107-115.

Global prevalence of HCV

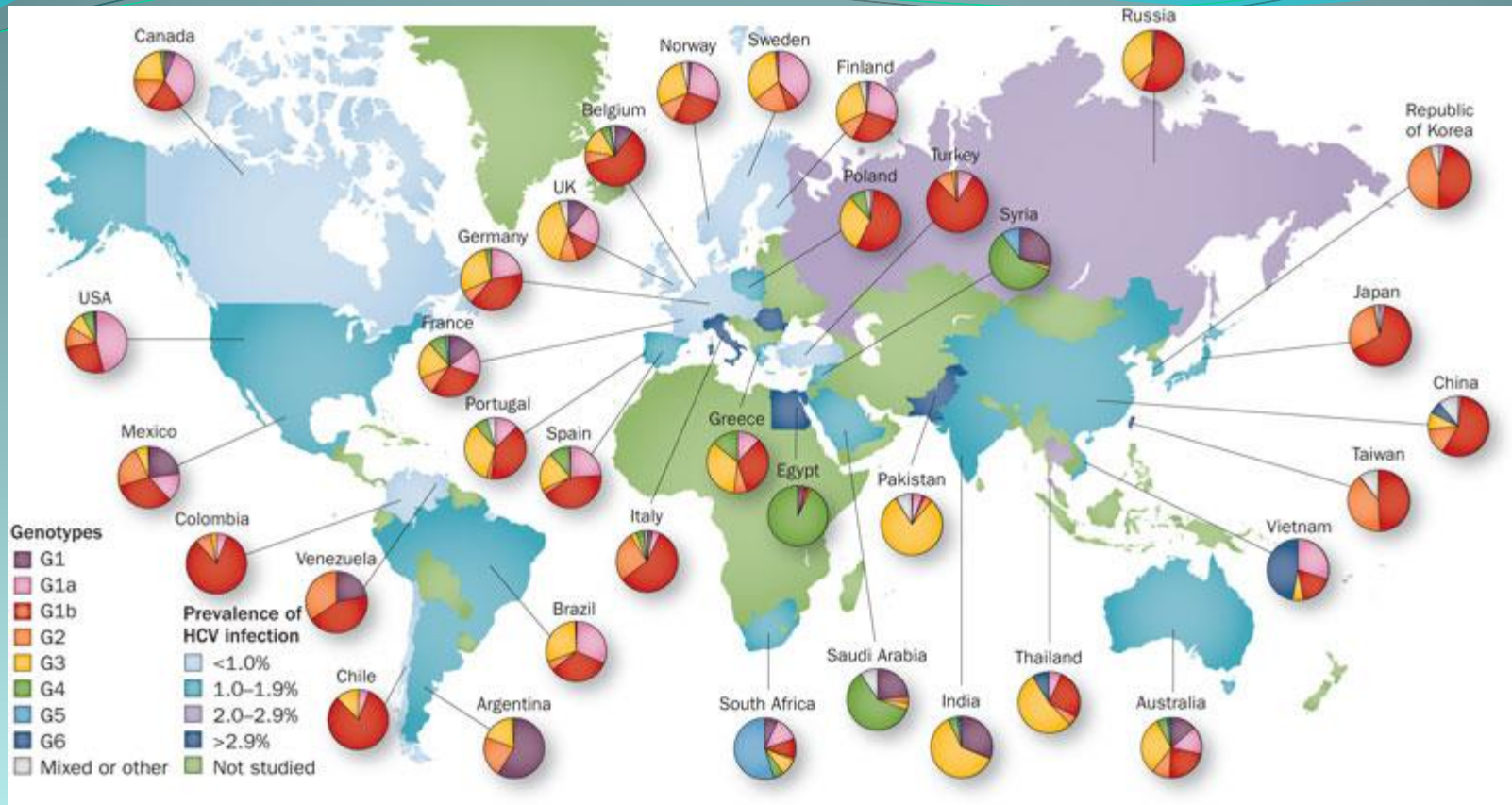
EGYPT'S BURDEN

Prevalence of infection with the hepatitis C virus is nearly five times higher in Egypt than many other countries.



Egypt has the highest prevalence of HCV in the world

(M. Yehia; 2011)



HCV genotypes distribution in the world (Behzad; 2011)

Hepatitis C infection

```
graph TD; A[Hepatitis C infection] --> B[Hepatic Manifestations]; A --> C[Extra-hepatic manifestations (syndrome)];
```

Hepatic
Manifestations

Extra-hepatic
manifestations
(syndrome)

Pathways of cardiovascular affection in HCV patients

HCV infection

Type II
DM

Atherosclerosis

Heart
disease

Cardiovascular events

HCV has been identified in patients with:-

Hypertrophic cardiomyopathy.

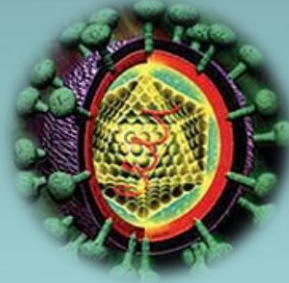
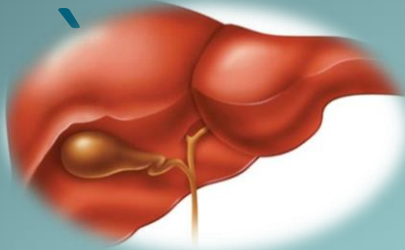
Dilated cardiomyopathy & LV aneurysm.

Restrictive cardiomyopathy.

ARVC/D.

Myocarditis

HCV infection



Acute Hepatitis

Chronic hepatitis 85%

Liver cirrhosis 20%

**Hepatic failure
6%**

**Hepatocellular
carcinoma 4%**

Acute myocarditis

Chronic myocarditis 85%

Myocardial fibrosis 20 %

**Dilated
cardiomyopathy
6%**

**Hypertrophic
cardiomyopathy
4%**

Matsumori; 2007

Pathogenesis of cardiac involvement in HCV patients:-

1- Direct cytopathic effect.

Badroff et al; 1999

2- Auto-immune-mediated.

Caforio et al; 2002

3- Both direct cytopathic effect and auto-immune mediated.

Matsumori; 2007

Professor Doctor/ Akira Matsumori; MD-PhD
Professor of cardiology – Kyoto university – Japan
President; International Society of cardiomyopathy and
Heart Failure (ISCHF)
Secretary; World Heart Federation. (WHF)
Treasurer; Asian-Pacific Society of Cardiology (APSC)



Scientific day of cardiovascular and ultrasonography unit - RIO - December; 4th ; 2007

“Cardiovascular effects of HCV”

In the center of the photo professor Prof. Dr. Akira Matsumori

To the right of him in order:-

Prof. Dr. Adel Ali Al-Dein (President of Research Institute of Ophthalmology)

Prof. Dr. Ahmad Ehab (Prof. of genetics and molecular biology – German University – Egypt)

Prof. Dr. Omar Haykal (Prof. of hepatology and president of military medical academy)

Prof. Dr. Ebrahim Negm (Prof. of hepatology – Al-Azhar University)

To the left of him in order:-

Dr. Safwat Al-Hawary (Prof. and head of cardiology department –Al-Azhar University)

Prof. Dr. Hany Negm (Prof. and head of cardiovascular and Ultrasonography Unit – RIO)

Prof. Dr.: - Mohamed Shalaby (Prof. of cardiology - Cardiovascular and Ultrasonography Unit – RIO)

Prof. Dr.: - Hossam Al-Dein Abd Al-Lateif (Prof. and head of hepatology department – Hepatology Institute – Al-Monofea University)

Phases of our research work:-

- 1- Assessment of Myocardial functions in Egyptian patients with HCV infection. (Haykal; et al 2008).
- 2-Assessment of left atrial functions in HCV patients with and without cardiovascular risk factors. (Haykal; et al 2010).
- 3- Assessment of cardiac involvement of hepatitis C virus; tissue Doppler imaging and NT pro BNP study. (Saleh; et al 2011).
- 4- Anti-inflammatory treatment with cetirizine improves refractory heart failure in patients with hepatitis C virus-induced myocarditis. (Haykal; et al 2013).
- 5- Non invasive assessment of atherosclerosis in Egyptian patients with HCV infection. (Moataz et al; 2014).
- 6- Cardiac function under anti-viral therapy “ COFACTOR” (CURU; 2016 till now).

Phase I:-

**Assessment of Myocardial functions in
Egyptian patients with HCV infection.
(Haykal; et al 2008).**

The aim was to >>>>

I - Assess myocardial functions in Egyptian patients with HCV infection compared to normal controls.

II - Precisely define the cardiovascular effects of the prevalent genotype of the virus in Egyptians.
(genotype 4).

Patients and methods

Confounding factors	Control group (n=50)		Patients with HCV infection (n=50)	
	Number	Percent	Number	Percent
Female patients	27	54%	22	44%
Male patients	23	46%	28	56%
Age (Years)	49.86(±9.8)		52.22(±9.13)	
Weight (Kgm)	75.28(±3.66)		75.54(±3.7)	

The two groups have been subjected to the following:-

- 1- Full medical history.
- 2- Complete clinical examination.
- 3- 12-leads resting ECG.
- 4- Echocardiographic study.
- 5- Statistical analysis of the results.

Echocardiography results

	Echocardiographic measurement	Control group (n=50)	HCV group (n=50)	P value	Significance
1.	IVSDd	0.84(±0.11)	0.905(±0.2)	<0.001	VHS
2.	LVPWDd	0.855(±0.13)	1.0(±0.2)	<0.01	HS
3.	LVEDd	4.94(±0.43)	4.78(±0.86)	>0.05	NS
4.	RVEDd	1.61(±0.47)	2.0(±0.4)	<0.01	HS
5.	LA	3.645(±0.45)	3.925(±0.6)	> 0.05	NS

Cardiac dimensions in HCV group compared to control group

Echocardiography results

	Echocardiographic feature	Control group (n=50)	Patients with HCV (n=50)	P value	Significance
1	FS	35.23(\pm 4.45)	33(\pm 8.47)	< 0.05	S
2	EF	65(\pm 6.02)	62.425(\pm 12.9)	<0.001	VHS
3	E/A ratio of mitral inflow.	1.38(\pm 0.31)	0.855(\pm 0.43)	<0.001	VHS
4	E/A ratio of tricuspid inflow.	1.45(\pm 0.32)	0.835(\pm 0.48)	<0.001	VHS

Systolic and diastolic functions in HCV group compared to control group

Echocardiography results

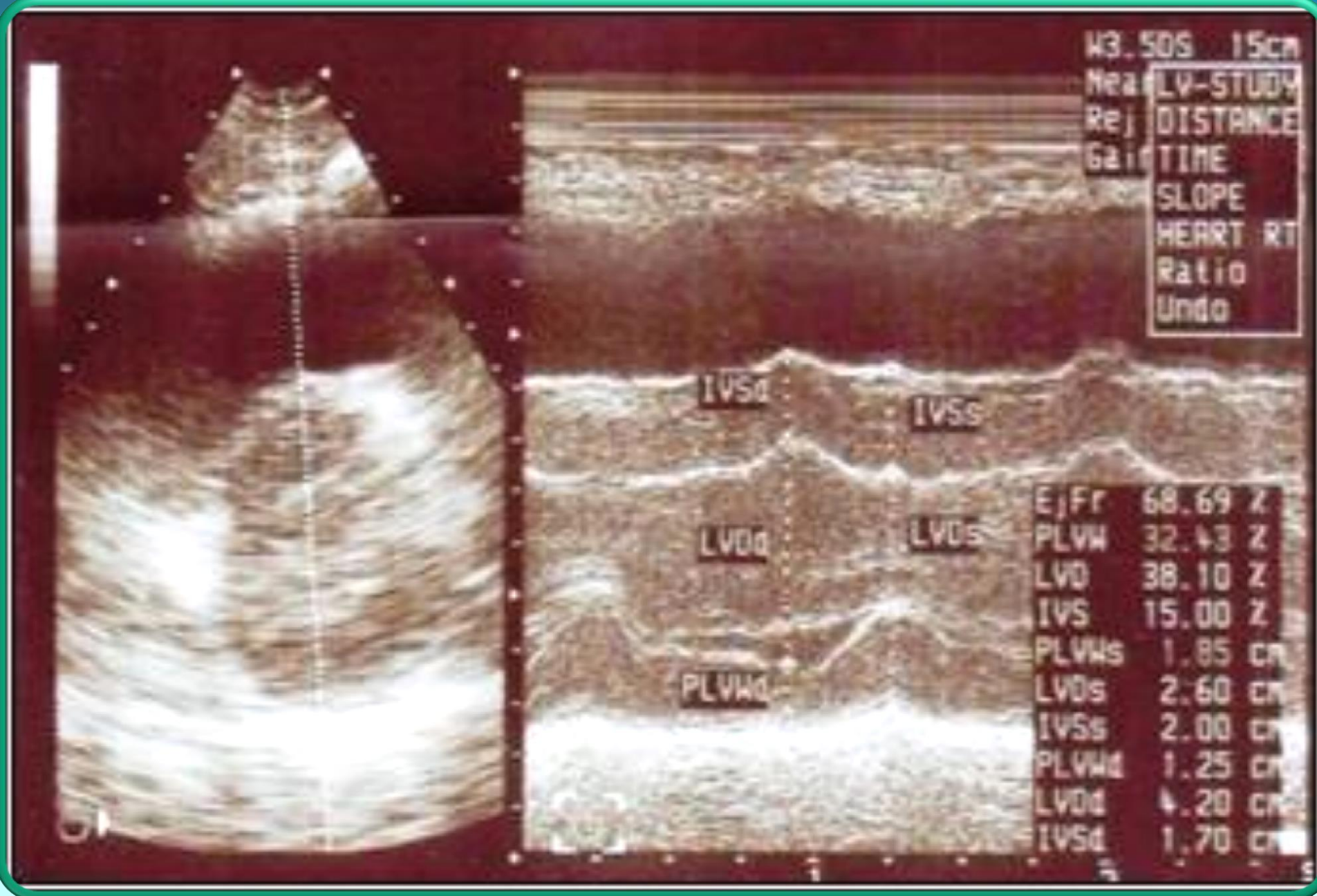
	Echocardiographic abnormality	Incidence
1	Impaired LV systolic function	32%
2	Impaired LV diastolic function	62%
3	Impaired RV diastolic function	60%

Incidence of impaired systolic and diastolic functions in HCV group

Echocardiography results

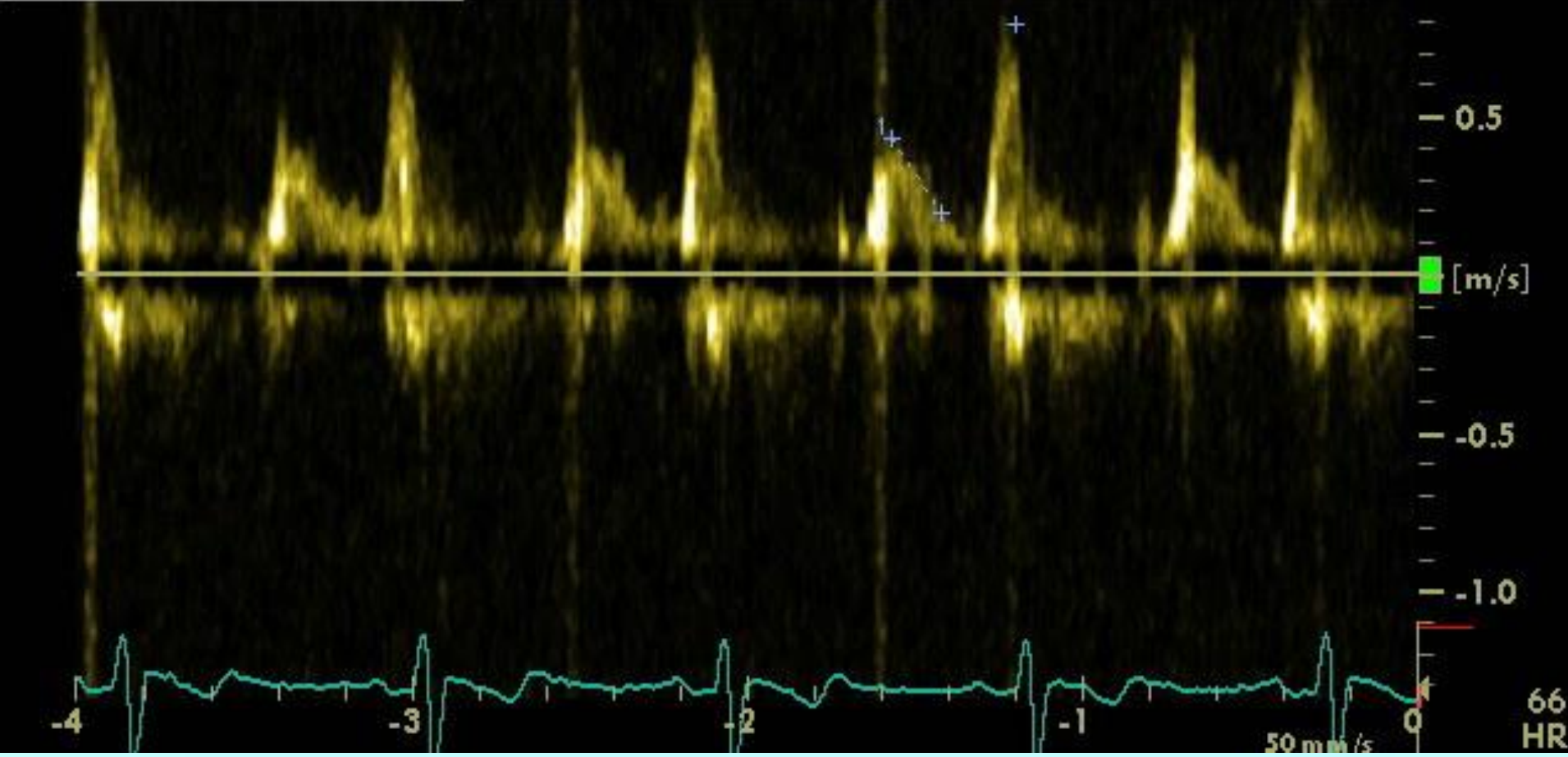
	Echocardiographic abnormality	Incidence
1	Sclerotic aortic valve	60%
2	Pericardial effusion (mild)	8%

Incidence of aortic sclerosis and pericardial effusion in HCV group



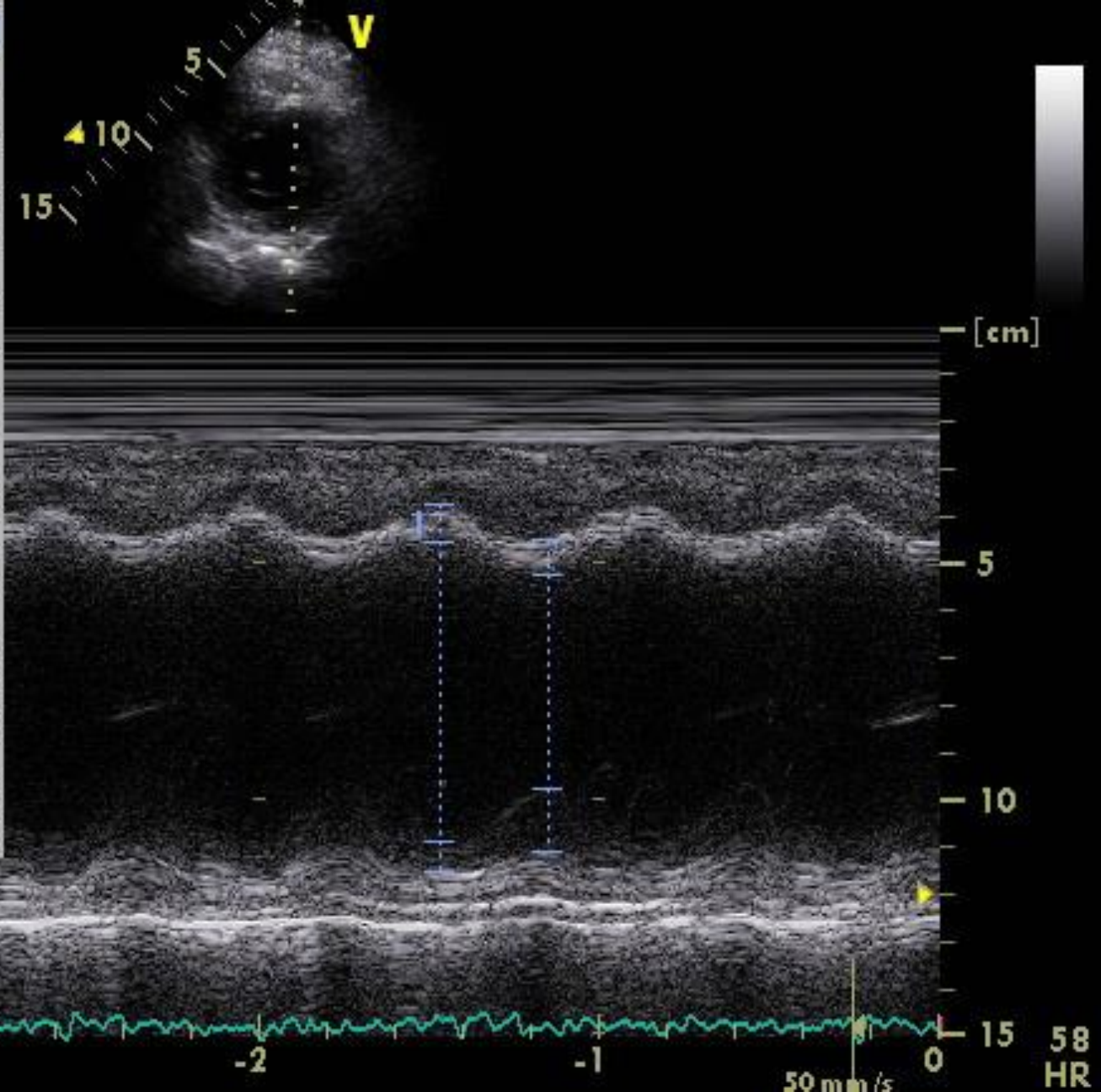
Asymmetrical septal hypertrophy
 (septum is 1.7 cm and posterior wall is 1.25 cm) in a patient with HCV.

1	MV E Vel	0.43 m/s
	MV DecT	271 ms
	MV Dec Slope	1.6 m/s ²
	MV A Vel	0.79 m/s
	MV E/A Ratio	0.54



Impaired diastolic function of LV ventricle

1	IVSd	0.8 cm
	LVIDd	6.3 cm
	LVPWd	0.6 cm
	IVSs	0.7 cm
	LVIDs	4.5 cm
	LVPWs	1.3 cm
	EDV(Teich)	203 ml
	ESV(Teich)	93 ml
	EF(Teich)	54 %
	%FS	29 %
	SV(Teich)	110 ml
	LVd Mass	209.75 g
	LVs Mass	188.70 g
	LVd Mass (ASE)	179.28 g
	LVs Mass (ASE)	162.44 g



left ventricular dilatation (6.3 cm) in a patient with HCV



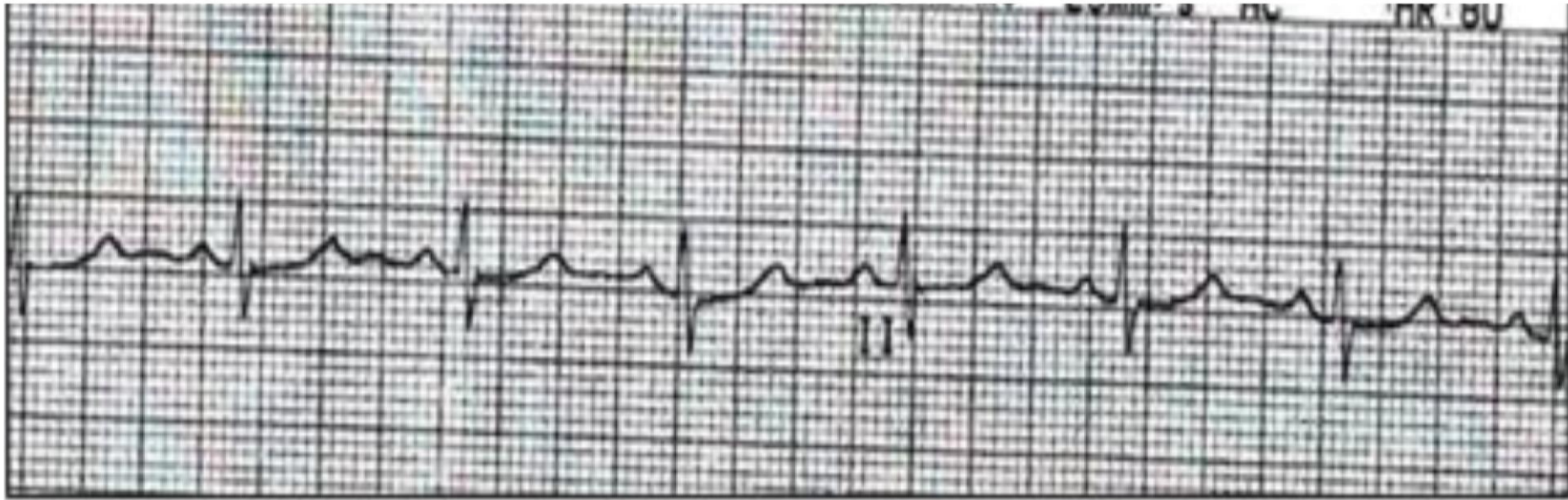
CXR P/A view showing increased cardiothoracic ratio in a patient with dilated cardiomyopathy associated with HCV infection

	Electrocardiogra- phic feature	Control group (n=50)	HCV group (n=50)	P value	Significance
1.	QTc interval	350(±27.5)	360(±34.92)	<0.05	S
2.	P-R interval	160(±19.22)	160(±33.03)	>0.05	NS

Comparison of P-R and QTc intervals between HCV group and control group.

	Electrocardiographic abnormality	Incidence
1.	Long QTc interval	38%
2.	First degree heart block	6%
3.	Right bundle branch block	6%
4.	Left bundle branch block	2%
5.	Left anterior fascicular block	10%
6.	Atrial fibrillation	4%
7.	Ventricular bigeminy	2%
8.	Sinus Tachycardia	6%
9.	Sinus bradycardia	2%
10.	Sinus rhythm with frequent premature ventricular complexes	6%
11.	Sinus rhythm with frequent premature supra-ventricular complexes	2%
12.	Pathological Q waves in LII,LIII& aVf	10%
13.	Pathological Q waves in V1,V2	4%
14.	Pathological Q waves in V1,V2,V3& V4	4%

Incidence of electrocardiographic abnormalities in HCV group.



Long QTc interval (400-440 ms) in a patient with HCV infection



Atrial fibrillation in a patient with HCV infection.

Conclusion

1- HCV is not only a hepatotropic virus, but also it is a cardiotropic virus.

2- HCV might be complicated by:-

- * Impaired systolic and diastolic functions.**
- * Pericarditis and pericardial effusion.**
- * Left ventricular hypertrophy or dilatation.**
- * Long QTc interval. (pro-arrhythmic).**
- * Several types of arrhythmias.**

Recommendations

- 1- Patients with hepatitis C should be screened for cardiovascular abnormalities.
- 2- Patients with unexplained cardiac abnormalities should be screened for hepatitis C and B infection.
- 3- HCV patients with prolonged QTc interval should be subjected to periodic follow up.
- 4- further investigations using cardiac biomarkers are required to diagnose cardiac injury :- CTnT- CTnI- NT-pro BNP – CRP ... etc.
- 5- HCV myocarditis may act as a potential reservoir for HCV and should be treated to avoid cardiac complications and HCV relapses.
- 6- Evaluation of therapeutic effects anti-HCV medications in treating HCV myocarditis is recommended

HCV Antibody Screening CURU 2009

*n= 300

*Total Prevalence of HCV 23%

*Prevalence in men 30% (country side barbers & anti Bilharzial injections).

*Prevalence in women 17% (less exposure)

*Total prevalence above 40 years of age 27%

*Total prevalence below 40 years of age 4.7%
(development of oral treatment for Bilharziasis,
disposable syringes & better sterilization ,sanitation,
public awareness)

Phase II:-

**Assessment of left atrial functions in
HCV patients with and without
cardiovascular risk factors.**

(Haykal et al; 2010)

Aim>>

To assess left atrial functions in HCV patients with and without cardiovascular risk factors

Patients and methods>>

20 HCV Abs +ve patients had been stratified in three groups:-

Group I:-

It included 8 HCV patients without any detectable cardiovascular risk factors.

Group II:-

included 6 HCV patients with cardiovascular risk factors i.e. DM, HTN, dyslipidemia, hyperuricemia...etc.

Group III:-

It included 6 normal healthy controls.

The three groups had been subjected to t :- Full medical history, Full clinical examination, Twelve leads resting ECG & Echocardiography study

The following LA parameters had been estimated:-

Left atrial excitation contraction interval :-

measured by pulsed Doppler study of mitral inflow in apical 4 chambers guided by ECG monitoring. Time interval was measured from onset of P wave in ECG monitor to the onset of A-wave of mitral inflow due to atrial kick. (Normal excitation contraction interval is up to 20 ms).

Left atrial ejection time :-

It is the duration of A-wave of mitral inflow measured by pulsed wave Doppler of mitral valve in apical 4 chamber view.

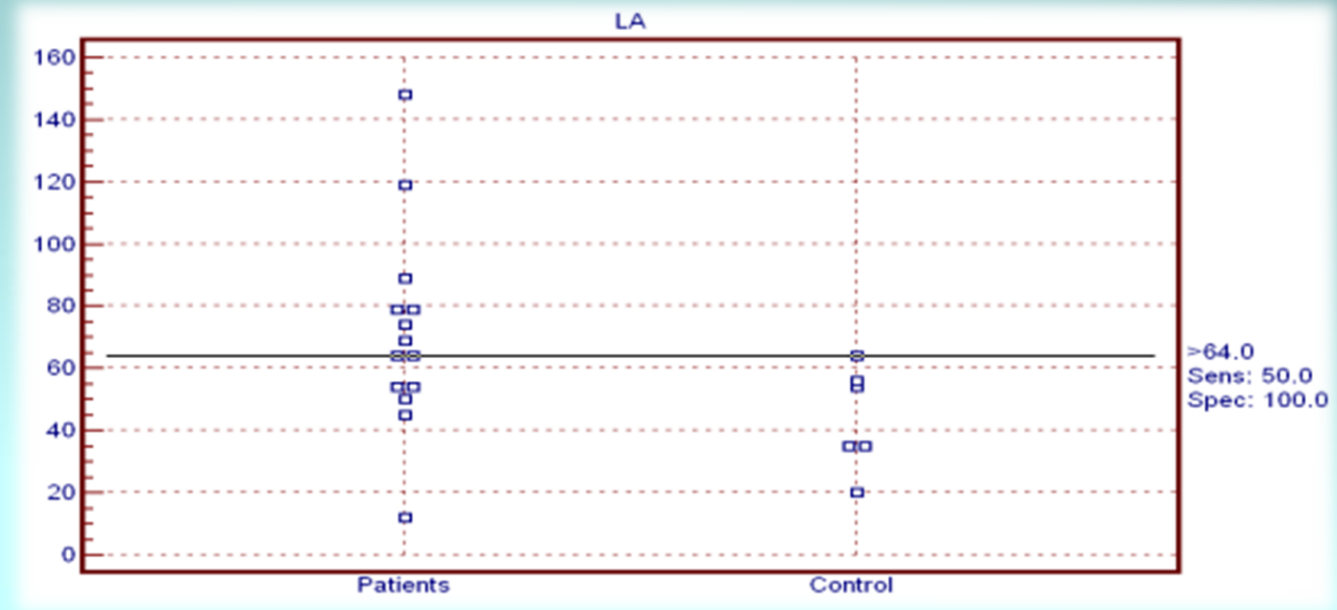
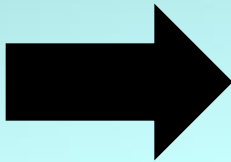
Left atrial systolic function was assessed by left atrial ejection force (LAEF):-

According to American Society of echocardiography; it is calculated by the following equation:-
$$\text{LAEF} = 0.5 \times 1.06 \times \text{mitral annular area} \times [\text{peak A velocity}]^2 / 1000 \text{ K dyne.}$$

Results:-

* There was a significant statistical difference in LA **excitation- contraction interval** in hepatitis C patients with or without cardiovascular risk factors when compared with normal controls ($p < 0.05$) with proved full specificity to hepatitis c patients and 50% sensitivity at 64 ms.

Excitation contraction interval in HCV patients compared to healthy Controls.



* There was no statistically significant difference in other parameters.

Conclusion :-

- 1- Left atrium might be affected earlier than left ventricle in hepatitis C myocarditis.
- 2- Prolongation of left atrial excitation contraction interval might constitute specific criteria for hepatitis C cardiac invasion that need more investigation on the biomarker and molecular levels.
- 3- The relation of this new finding might constitute an explanation for atrial arrhythmias frequently observed in hepatitis C patients through creating re-entry circuits.

Phase III:-

**Assessment of cardiac involvement of hepatitis C virus; tissue Doppler imaging and NT-pro BNP study.
(Saleh et al; 2011).**

Aim:-

To evaluate LV diastolic functions of HCV patients using tissue Doppler Imaging and NT- Pro BNP.

Patients and methods:-

30 HCV patients of 30 years, sex & BMI matched controls were evaluated by PCR, ECG, Echocardiography “conventional Doppler, pulsed wave tissue Doppler (PW-TD), strain rate imaging” & NTPBNP to assess LV diastolic functions.

Results

HCV group has shown:-

- * Significant increase in QTc interval ($p < 0.05$).
- * Significant statistical increase in A wave ($p < 0.05$).
- * Significant increase in deceleration time ($p < 0.05$).
- * Highly significant decrease in tissue Doppler Ea ($p < 0.001$).
- * Highly significant decrease in Aa ($p < 0.001$).
- * Highly significant increased E/Ea ratio (p value < 0.001),
 - * Significant decrease in Ea/Aa ratio.
- * Significant increase in SRa ($p < 0.05$).

Conclusion

- 1- Tissue Doppler was more sensitive to diagnose diastolic dysfunction than conventional Doppler.
2. NT-proBNP is a strong indicator of diastolic dysfunction in HCV patients and is directly related to echocardiographic parameters in addition to the level of viraemia hence we recommend its routine use as a follow up tool in HCV patients.

Phase IV

Anti-inflammatory treatment with cetirizine improves refractory heart failure in patients with hepatitis C virus-induced myocarditis.

(Haykal; et al 2013).

Heart failure is an inflammatory process

Mast cells also are found in the human heart and have been implicated in cardiovascular diseases. Mast cells increase in number in the failing heart, including dilated or ischemic cardiomyopathy and acute myocardial infarction.

(Matsumori; 2010)

Cetirizine:-

(a second generation anti-histaminic)

An agent that stabilizes mast cells and an H-1 receptor antagonist has been shown to improve heart failure caused by pressure overload and viral myocarditis in an animal model.

(Matsumori; 2010)

Patients and methods

Inclusion criteria :- HCV patients with systolic dysfunction and heart failure not associated with other causative or contributing factor of HF including valvular, CAD, DM, HTN.....etc. (**only 9 patients**)

Exclusion criteria:- any HCV patient associated with other possible cause of HF.

All patients were subjected to clinical evaluation, ECG, NT pro BNP and echocardiographic assessment including speckle tracking initially and during follow up visits.

Standard anti-failure therapy including B- blocker, ACEIs, Diuretics ± digoxin were prescribed to the 9 patients >>>>> Still NYHA III/IV after 1 month of ttt.

Cetirizine therapy was added to the standard anti-failure therapy in dose 10 mg once daily at bed time for three months

After three months of Cetirizine therapy

The 9 patients improved on both clinical, ECG , Echo and NT-Pro BNP basis.

Clinically >> all patients improved form NYHA III/IV to NYHA I

Results

1- ECG
QTc interval

Before Cetirizine (n =9)	After Cetirizine (n=9)	P value
465.56 ± 49.27	435.56 ± 41.57	0.005

Results

2- Conventional echocardiography

Parameter	Before Cetirizine (n =9)	After Cetirizine (n =9)	P Value
Left atrial diameters (mm)	48.78 ± 5.26	46.11 ± 4.34	0.001
LV end diastolic diameter (mm)	61.33 ± 15.58	59 ± 15.01	0.019
LV end systolic diameter (mm)	47.44 ± 16.95	42.89 ± 13.94	0.005
EF %	46.89 ± 16.59	54 ± 10.62	0.013

Results

3- speckle tracking

Average LV Strain %Global (GS)	Before Cetirizine (n =9)	After Cetirizine (n =9)	P value
	-11.9 ± 6.24	- 13.29 ± 6.07	0.009

Results

4- NT proBNP

NT Pro BNP	Before Cetirizine (n =9)	After Cetirizine (n =9)	P wave
pg/dL	1217.33 ± 1189.19	591.56 ± 644.88	0.021

Conclusion

1- Our study is the first to investigate the role of an antihistamine, cetirizine, in the treatment of HCV cardiomyopathy in human. Our results confirm those from an experimental study of viral myocarditis in mice, which showed the role of inflammatory cytokines and metalloproteinase in cardiac remodelling.

2- Cetirizine represents a new adjuvant drug that is effective for the treatment of refractory heart failure in HCV cardiomyopathy.



Phase V:-

**Non invasive assessment of
atherosclerosis in Egyptian patients
with HCV infection.**

(Moataz et al; 2014).

Aim >>>

To non- invasively assess the role of HCV infection as an accelerating and aggravating factor of atherosclerosis in hepatitis C Egyptian patients.

Patients and methods:

Brachial artery flow mediated dilatation (FMD), carotid intima media thickness (CIMT), prevalence of carotid plaques & their stenotic percentage & highly sensitive C reactive protein (hs-CRP) were used as surrogate markers to atherosclerosis in three groups: 20 HCV patients without cardiovascular (CV) risk factors, 20 HCV patients with CV risk factors & 20 healthy controls.

Results:-

- 1- Mean FMD values of HCV patients without & with CV risk factors groups were significantly lower when compared to control group ($p \leq 0.00001$ for both comparisons).
- 2- Both HCV seropositive groups had very highly statistically significant increased mean CIMT compared to control group (p value < 0.00001) for both comparisons.
- 3- Carotid artery plaques prevalence & their stenotic percentages specially in the right common carotid artery (CCA) was statistically higher in HCV without CV risk factor group when compared to control group ($p \leq 0.0025$ & ≤ 0.003 respectively) & also in HCV with CV risk factors group when compared to control ($p \leq 0.0005$ & ≤ 0.001 respectively).
- 4- HCV without cardiovascular risk factor group had decreased hs-CRP mean levels when compared to control group ($p \leq 0.0003$) & HCV with cardiovascular risk factor group ($p \leq 0.04$).

Conclusion: -

- 1- Hepatitis C virus infection might play important role in atherosclerosis progression & development.
- 2- Although HCV is chronic infection that stimulates inflammation, HCV seropositive patients had paradoxically decreased mean level of hs-CRP when compared to healthy controls.
- 3- hs-CRP isn't suitable marker for cardiovascular risk assessment in HCV patients. CIMT & FMD can be used for screening & follow up of atherosclerosis in HCV patients.

Phase VI:-

Cardiac function under anti-viral therapy “ COFACTOR” (CURU; 2016 till now).

Aim:-

To evaluate changes of cardiac involvement in patients with hepatitis C under therapy with the new HCV direct-acting antiviral agents.

Patients and methods:-

The study will be conducted at the Internal Medicine Department in Cairo University, Cardiology Department of Scientific Research Academy, both in Egypt, as well as Gastroenterology Department of Klinikum Coburg and Division of Hepatology at Würzburg University Hospital, both in Germany.

The study will last one year starting from March 2016 to March 2017. The aim is to enroll 140 patients.



Inclusion criteria

All HCV patients candidate for receiving the new HCV direct-acting antiviral agents.

Exclusion criteria

- * HBs Ag positive patients.
- * Patients with known manifested coronary heart disease or manifested heart failure.
- * Patients over 75 years old who are already prone to cardiac events without application of the new therapy.

All enrolled patients will be subjected to the following diagnostic measures: -

1-liver function tests : ALT , AST .

2-CBC , Troponin I, NTproBNP, hsCRP, IL6 and free light chain Immunoglobulin.

3-Quantitative HCV RNA by PCR .

4- HCV genotyping.

5- Abdominal US .

6- Fibro scan and eventually liver biopsy if indicated.

7- ECG .

8- Echocardiography including Tissue Doppler and Speckle Tracking .

9- Carotid duplex.

10-Cardiac MRI whenever applicable.

Take home message

- * Our mutual cooperation with Prof. Matsumori has put our research center in the front of the centers in the middle east in the field of HCV and heart.
- * Our experience started by preliminary screening epidemiological study that confirmed the size of the problem boosted by positive cardiovascular findings in Egyptian hepatitis C patients Which pushed us to study the pathological and functional roots for previous unexplained CV presentations and complications.
- * With all side effects of interferon and ribavirin we tested using (Cetirizine – 2nd generation antihistaminic) as an anti-inflammatory immune modulator oral therapy for the first time to treat HCV Cardiomyopathy patients based on professor Matsomuri early animal studies.
- * Now with introduction of oral anti hepatitis c virus we are open for cooperation to test the effects on the heart and its ability to treat or prevent extra-hepatic complications.