Assessment of diastolic function in Egyptian patients with hepatitis C viral infection using Tissue Doppler Imaging combined with N-Terminal pro Brain Natriuretic peptide

Thesis

Submitted for partial fulfillment of master degree in cardiology

BY

Ahmed Mostafa Saleh Mostafa M.B.B.CH

Supervisors

Professor Dr.HANY FOUAD HANNA, M.D.

Assistant Professor of Cardiology, AinShams university

DR.AHMED MOHAMMED ONSY, M.D.

Lecturer of Cardiology, AinShams university

Professor Dr.HANY ABDELRAHMAN NEGM, M.D.

Professor of Cardiology, Research Institute of Ophthalmology, Academy of Scientific Research and Technology

Faculty of Medicine

Ain Shams University

2010

تقييم الوظائف الانبساطية للمرضى المصرين المصابين بالتهاب الكبد الفيروسى سي باستخدام الدوبلرالنسيجي والدليل الحيوى المدر للصوديوم ذو النهاية الامينية

توطئة للحصول على درجة الماجستير في أمراض القلب و الاوعية الدموية

طبيب/ احمد مصطفى صالح مصطفى

تحت اشراف

استاذ دكتور / هانى فؤاد

استاذ مساعد امراض القلب , طب عين شمس

دكتور/ أحمد أنسي

مدرس أمراض القلب , طب عين شمس

استاذ دكتور/ هانى نجم

أستاذ باحث أمراض القلب و رئيس وحدة القلب, معهد بحوث امراض العيون ,

وزارة التعليم العالى و البحث العلمى

قسم أمراض القلب و الاوعية الدموية

كلية الطب,جامعة عين شمس

2010

Acknowledgement

I owe a great deal of gratitude for professor Hany Fouad, “Assistant Professor of Cardiology,Faculty of Medicine,AinShams University”, for putting the cornerstone of this subject. His advices and support have been of inestimable great value. His meticulous review of related literature and discussion and his valuable additions were indispensible for finalizing this work.

The generosity and great support of Dr.Ahmed Onsy, “Lecturer of Cardiology,Facult of Medicine,AinShams University”, had been of great value to support bringing up this work to light. His vast knowledge and experience were the source of many useful channels in our work. Moreover, I thank him for the personal advices which helped me a lot through my career.

Words can’t express my deep and faithful appreciation for Professor Hany Negm, “Professor and Head of Cardiology Unit, Research Institute of Ophthalmology”. He has always been a father and a role model to be followed. His guidance and help had major impact on my personal life before my scientific one. Always stood by me at moments of hesitation and weakness and gave me solutions for issues I stood against. With his mixture of loving kind strictness, a better person I believe I became now. For Him I refer any uniqueness in this work and any future one I will go through.

I am deeply grateful for professor Akira Matsumori,“Professor of Cardiology, Kyoto University Graduate School of Medicine, President of International Society of Cardiomyopathy and Heart Failure and World Heart Federation Vice President”, for bringing up the idea of this work. His support was of great value as he provided all the biomarkers materials .He offered so much of his vast experience and valuable advices through co-operation in this work.

I am also so grateful for Professor Gamal Esmaat,”Professor of Tropical Diseases and GIT, Faculty of Medicine,Cairo University and President of International Association of Liver Diseases”, for referring HCV patients to our institute and for his generous scientific advices. My friends Dr.Mohammed Gamal Esmaat, “Senior Resident of GIT diseases, National Liver Institute” and Dr. Hany Amin “Senior Resident of Hepato-surgery, National Liver Institute” had also great impact in the matter of referring HCV patients and for them I am so thankful.

I must thank Professor Azza Khaleel, “Professor and Head of Clinical Pathology Unit, Research Institute of Ophthalmology”, and all the Clinical Pathology team at our institute for their great assistance, If it wasn’t for them, none of this results would have been come to light. I am grateful for Dr.Inas Hamdy , “Lecturer of Clinical Pathology, Faculty of Medicine, Cairo University”, for her amazing distinguished work analyzing biomarkers data. It was a harsh mission but she made it through under kind supervision of

Professor Nadida Gohar "Professor of Clinical Pathology, Faculty of Medicine, Cairo University and Head of Clinical Chemistry Unit".

I appreciate the co-operation of my fellow colleagues and Professors at Cardiology Unit, Research Institute of Ophthalmology. I appreciate the most the great assistance and guidance of Professor Mohammed Shalaby, "Assistant Professor of Cardiology, Research Institute of Ophthalmology" and Dr.Mohammed Haykal, "Assistant Lecturer of Cardiology, Research Institute of Ophthalmology".

Ahmed Mostafa Saleh 2010

List of Tables:

List of Figures:

List of Abbreviations:

Introduction	
HF	Heart Failure
DHF	Diastolic Heart Failure
HFNEF	Heart failure with Normal Ejection Fraction
HFPEF	Heart failure with Preserved Ejection Fraction
HCV	Hepatitis C Virus
EF	Ejection Fraction
LV	Left Ventricle
NTPBNP	N Terminal Pro Brain Natriuretic Peptide
Chapter I : HCV	
RNA	Ribonucleic acid
ALT	Alanine Aminotransferase
EIA	Enzyme Immunoassay
PCR	Polymerase Chain Reaction
PEG-IFN	Pegylated Interferon
ARVC	Arrythmogenic Right Ventricular Cardiomyopathy
MHC	Major Histocompatibility Complex
TNF	Tumor Necrosis Factor
NO	Nitric Oxide
Chapter II : Heart Failure with Normal Ejection Fraction	
SR	Sarcoplasmic Reticulum
SERCA	Ca2+ adenosine triphosphatase of the SR
PLB	Phospholamban
MMP	Matrix Metalloproteinases
AGEs	Advanced Glycation End products
EDPVR	End-Diastolic Pressure-Volume Relationship
PNF	Pseudonormal filling
Vp	Flow propagation velocity
TVI	Tissue velocity imaging
SVI	Strain velocity imaging
SRI	Strain Rate Imaging
TDI	Tissue Doppler Imaging
PCWPm	mean Pulmonary Capillary Wedge Pressure

CHARM study	Candesartan in Heart failure – Assessment of Reduction in Mortality and morbidity study in Preserved EF
Chapter III : N Terminal pro Brain Natriuretic Peptide	
ANP	Atrial Natriuretic Peptide
CNP	C-type Natriuretic Peptide
DNP	Dendroaspis Natriuretic Peptide
NYHA	New York Heart Association
ACS	Acute Coronary Syndrome
PE	Pulmonary Edema

Introduction: Hepatitis C disease burden is substantially increasing in Egyptian community, it is estimated that prevalence of HCV in Egyptian community reach 22% of total population. Recently there is a global alert of HCV cardiovascular complications.

Objective: To evaluate LV diastolic functions of HCV patients using Tissue Doppler Imaging and NTPBNP.

Methods: 30 HCV patients and 30 age, 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. Mean age was 32.8 years ± 5.1 in HCV group, 29.8 yrs.± 6.6 in control group. Cardiovascular anomalies and predisposing factors were excluded.

Results: HCV group has shown significant increase in QTc interval, significant statistical increase in A wave, 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 and significant increase in SRa ($p < 0.05$).

NTPBNP levels showed highly significant increase with mean value 222 pg/ml ±283 in HCV group and 32.7 pg/ml ± 21.2 in control group (p value < 0.001).
The best Cut-off value of NTPBNP to detect diastolic dysfunction in HCV group was 213 pg/ml .

No statistical differences in SRe/SRa and E/SRe ratios were observed, however they had significant correlation with NTPBNP level and tissue Doppler parameters. The best cut-off value of E/SRe ratio to detect diastolic dysfunction in HCV group was 0.91, with 75% sensitivity and 100% specificity.

Conclusion and Recommendation: This data show the first direct evidence that HCV infection causes diastolic dysfunction without any other predisposing factors, probably due to chronic inflammatory reaction with mild fibrosis in the heart.
Previous studies didn't follow strict inclusion and exclusion criteria that confirm the independent role of HCV to cause diastolic dysfunction.
Tissue Doppler was more sensitive to diagnose diastolic dysfunction than conventional Doppler.
NTPBNP is a strong indicator of diastolic dysfunction in HCV patients and is directly related to the level of viraemia hence we recommend its routine use as a follow up tool in HCV patients.
Further studies should evaluate E/SRe value to diagnose diastolic dysfunction.

Introduction

The predominance of systemic and pulmonary congestion in the clinical presentation of HF first directed investigators and clinicians to consider HF as a disorder of volume regulation, the so-called cardio-renal paradigm of HF. As contrast ventriculography, radionuclide ventriculography, and echocardiography became available, the syndrome of HF began to be equated with a reduced EF and treatment strategies focused on HF as a syndrome of contractile dysfunction. This has been referred to as the hemodynamic paradigm of HF. During this era, certain rare conditions were recognized to produce the HF syndrome despite preserved EF. However, the possibility that large numbers of patients with HF may have normal EF (HFNEF) was never entertained [(1)] .

Considerable debate exists as to whether these patients should be labeled as having diastolic heart failure (DHF), heart failure with preserved systolic LV function (HF-PSF), or heart failure with normal Ejection fraction (HFNEF). In the absence of a discriminatory role for LV diastolic dysfunction, the latter term is preferred in the recently revised American College of Cardiology–American Heart Association guidelines for the diagnosis and management of heart failure [(2)].

Hepatitis C virus (HCV) is the cause of many different forms of heart diseases worldwide. Up till now, few cardiologists are aware of (HCV) as an etiology of heart disease and its treatment. HCV infection is seen globally, and is often undetected and therefore untreated. The burden of HCV-derived heart diseases is global, with higher prevalence in Asia, Africa, and low-and middle-income countries [(3)].Egypt has the highest prevalence of HCV in the world, apparently due to previous mass parenteral anti-schistosomal therapy [(4)].HCV derived heart diseases are chronic, persistent, and devastating diseases[(3)] .

The myocardium may be the target of several types of viral infections. Recently, the importance of hepatitis C virus (HCV) infection has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis and left ventricular diastolic dysfunction[5,6].

Echocardiography is an excellent noninvasive tool for the assessment of ventricular size and both systolic and diastolic function, and it is routinely used in patients with heart failure. The evaluation of diastolic function is not easily obtained by other techniques, and this feature is where echocardiography has its advantages [7].

In practice, a normal EF on 2-D echocardiography in patients with clinical evidence of heart failure immediately suggests the potential diagnosis of LV diastolic dysfunction. Doppler, color flow imaging, and myocardial tissue imaging can confirm or exclude the diagnosis of LV diastolic dysfunction by assessing valvular abnormality and intrinsic diastolic function and estimating diastolic filling pressure [8,9] .

Early identification of diastolic dysfunction in asymptomatic (stage B) patients by echocardiography may provide an opportunity to manage the underlying etiology appropriately to prevent its progression to overt DHF (stage C of development of heart failure). [7]

Several findings suggest that the peak velocity of early diastolic displacement of the annulus is a relatively preload independent index of global LV that can be useful in unmasking pseudo normalization of the mitral inflow [10].

Because of its high reproducibility, feasibility, and relatively preload-independence, tissue Doppler recording of the early diastolic mitral annular velocity (Ea) in conjunction with the mitral inflow

velocity (E) has become the first line of diastolic evaluation. Myocardial relaxation is impaired in almost all patients with diastolic dysfunction, which is best assessed by the Ea velocity of the mitral annulus using TDI. While early diastolic trans-mitral velocity (E) increases progressively as LV filling pressure increases, the mitral annular Ea velocity remains decreased at all stages of diastolic dysfunction [7].

Other recent tool is demonstrated to assess LV diastolic function which is strain and strain rate imaging, Strain, in daily language means, “stretching”. In scientific usage, the definition is extended to mean “deformation " [12] .

Extending the utility of BNP as a diagnostic marker to screen for asymptomatic or preclinical ventricular dysfunction (Stage B heart failure) according to the ACC/AHA guidelines in the general population has not proved cost-effective as the prevalence of heart failure is low[11].

However, if the test is used in patients stratified for risk using clinical criteria, BNP has proved useful to “rule out” ventricular dysfunction, thus eliminating the need for other more expensive diagnostic tests in this group [13].

Of all investigated neurohormones and natriuretic peptides, B type natriuretic peptide and N-terminal pro BNP are the best markers for ruling out left ventricular dysfunction and to detect the degree of severity[14,15,16].