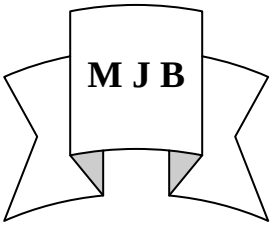
Relationship between Anemia and Diastolic Dysfunction of the Heart

Mohammed Abd Abdul Hussein
College of Medicine, Kufa University, Najaf, Iraq.



Abstract

Background: Diastolic dysfunction is an echocardiographic pattern identified via transthoracic echocardiography. It is classified as primary or isolated when the systolic function is normal and secondary when there is systolic dysfunction.

Aim of the study: This study is conducted to evaluate the relationship between anemia and diastolic dysfunction of the heart.

Patients and methods: 200 participants were enrolled in this study and classified into two groups; anemic and non-anemic (n=100 for each) according to the definition of WHO.

Measurements were taken for blood pressure, heart rate, and BMI. Standard biochemical indices, ECG and transthoracic Doppler echocardiography examination were also performed.

Results: Of the anemic group, 8 participants had diastolic dysfunction and 92 patients did not. None of the control group had diastolic dysfunction. The difference was statistically significant. Among the anemic group, 12 participants had left ventricular hypertrophy while no subject from the control group had left ventricular hypertrophy. The correlation was statistically highly significant. Among these participants who had diastolic dysfunction, 6 participants had left ventricular hypertrophy and 2 participants had not. The correlation between left ventricular hypertrophy due to anemia and diastolic dysfunction was statistically highly significant. The severity of anemia was not correlating with the development and severity of diastolic dysfunction. Sex had no significant influence on the development of diastolic dysfunction in anemic participants.

Conclusion: Anemia was identified to correlate well with the development of left ventricular hypertrophy and with the resultant diastolic dysfunction. The severity of diastolic dysfunction was unrelated to the severity of anemia and sex of the patients.

فقر الدم واختلال وظيفة القلب الانبساطية

الخلاصة

خلفية الدراسة: الاعتلال الانبساطي هو ظاهرة يتم تشخيصها من خلال فحص الايكو. يصنف الاعتلال الانبساطي كأولي أو منعزل عندما تكون وظيفة القلب الانقباضية طبيعية ويكون ثانوي عندما يترافق مع اعتلال في الوظيفة الانقباضية للقلب.

الهدف من الدراسة هذه الدراسة اجريت لتقييم العلاقة بين فقر الدم والاعتلال الانبساطي للقلب.

المرضى وطرائق العمل تم اشراك مئتي شخص في هذه الدراسة وتم توزيعهم الى مجموعتين. المجموعة الاولى مصابة بفقر الدم والمجموعة الثانية غير مصابة بفقر الدم وفي كلتا المجموعتين تم استبعاد العوامل الاخرى المسببة لاعتلال عضلة القلب الانبساطي.

كلتا المجموعتين تم مقاربتهما من حيث معدل العمر والعدد والجنس حيث ان كل مجموعة تحتوي على مئة شخص نصفهم اناث ونصفهم ذكور. لقد تم استعمال مستوى الهيموغلوبين حسب تعريف منظمة الصحة العالمية. خلال الدراسة تم قياس ضغط الدم ونبض القلب والطول والوزن لكل شخص كما تم اخذ عينات من الدم لفحص نسبة اليوريا والكرياتنين والسكر ومعدل الهيموغلوبين كما اجري لهم تخطيط للقلب وفحص بجهاز الايكو.

النتائج: من مجموعة المرضى المصابين بفقر الدم ثمانية منهم تم تشخيصهم بانهم مصابون باعتلال وظيفة القلب الانبساطية فيما لم يتم اكتشاف ذلك في بقية المرضى ولا في المجموعة الغير مصابة بفقر الدم. وفي هذه الحالةتم اكتشاف وجود قيمة حسابية معتبرة. من ضمن المجموعة المصابة بفقر الدم، ١٢ مشترك كان لديهم تثخن في عضلة البطين الايسر. احصائيا كانت العلاقة بين فقر الدم وتثخن جدران البطين الايسر معتبرة. المرضى المصابون بفقرالدم تم تقسيمهم بعد ذلك الى مجموعتين حسب مسوى الهيموغلوبين وتم اكتشاف ان خمسة مرضى من اصل ستين مريض لديهم اعتلال وضيفي ونسبة دم بين عشرة واقل من الحد الطبيعي فيما تم اكتشاف وجود ثلاث مرضى من اصل اربعين لديهم اعتلال وظيفي ونسبة دم دون العشرة. حسابيا فأن القيمة المستحصلة من ذلك كانت غير معتبرة. المرضى المصابون بفقر الدم و اعتلال وظيفي تم مقارنتهم بالمراحل الوظيفية لاعتلال العضلة القلبية التي لديهم وتم اكتشاف ان القيمة الحسابية غير معتبرة ايضا. بعد ذلك تمت دراسة تاثير الجنس على الاعتلال الوظيفي الانبساطي مرة باستخدام مرضى فقر الدم ومرة اخرى باستخدام الاشخاص الغير مصابين بفقر الدم. في كلتا الحالتين لم تكن القيمة الحسابية معتبرة.

الاستنتاج: ان فقر الدم مرتبط بشكل معتبر مع تثخن جدران البطين الايسر وبالنتيجة مع اعتلال وظيفة القلب الانبساطية. لايوجد ارتباط بين شدة الاعتلال الانبساطي ومستوى فقر الدم او جنس المريض.

List of abbreviations

AR;	Atrial reversal pulmonary venous flow velocity
ASE	American society of echocardiography
AV;	Aortic vale
A wave;	Atrial systolic transmitral flow velocity
BMI;	Body mass index
BNP;	Brain natriuretric peptide
BPM;	Beats per minute
DT;	Deceleration time of the early diastolic flow velocity wave
ECG;	Electrocardiography
EF;	Ejection fraction
E wave;	Peak early diastolic transmitral flow velocity
Hb;	Hemoglobin
HF;	Heart failure
IHD;	Ischemic heart disease
IVS	Interventricular septum
LA;	Left atrial
LV;	Left ventricle
LVEDD	Left ventricular end-diastolic dimension
LVEF	Left ventricular ejection fraction
MV;	Mitral valve
No.;	Number
PWT	Posterior wall thickness
WHO;	World Health Organization

Introduction

A substantial portion of patients with heart failure have nearly preserved left ventricular EF (generally above 40 or 50%)[1-4] and are classified as having diastolic heart failure or heart failure with preserved ejection fraction.[5] The terms ‘‘diastolic HF’’ and ‘‘systolic HF’’ are often used instead of ‘‘HF with preserved EF’’ or ‘‘HF with reduced EF’’, respectively but this is

controversial. Recently ‘‘HF with preserved EF’’ has become the more accepted term used by the American Heart Association and the American College of Cardiology rather than ‘‘diastolic HF’’.[6] LV volume, geometry, and function differ substantially in these two conditions.[7] Even brain natriuretic peptide (BNP) levels and survival differ. Despite these major differences, the clinical signs and symptoms of heart failure are present to a similar degree in patients with systolic and diastolic heart failure. Thus, the clinical history and physical examination do not always provide information that allows a differentiation of systolic from diastolic heart failure.[8]

From physiological point of view, four phases of diastole have been described. Briefly, isovolumic relaxation phase begins with aortic valve closure and lasts until mitral valve opening. During this period of ventricular relaxation, the ventricle is a "closed" chamber and both aortic and mitral valves are closed, hence LV volume is unchanged as ventricular pressure is decreasing. The rapid filling phase begins as the MV opens. The rate of filling is related to the pressure gradient between the LA and LV. This pressure gradient is mostly determined by the LA pressure at MV opening, and the rate of active decline of the LV pressure. The ventricle continues to actively relax, and the LV volume continues to increase, despite a decreasing LV pressure. The third phase of diastole is diastasis, which consists of passive LV filling in which LA and LV pressures are nearly equal. The fourth phase is atrial systole (atrial contraction) in which about 15% of LV filling occurs in normal patients, and probably more in myocardial disorders. Atrial systole ends with MV closure.[9]

If diastolic function is truly normal then relaxation, filling, and distensibility must remain normal both at rest and during stress of a variable heart rate, stroke volume, end-diastolic volume, and blood pressure. Diastolic dysfunction is a functional abnormality of myocardial relaxation, filling, or dispensability in the diastolic phase and is classified into secondary when associated with systolic dysfunction and primary when the systolic function is normal. Diastolic dysfunction thus occurs regardless of whether the EF is normal or abnormal, or patients are symptomatic or asymptomatic.[10]

Because diastole comprises approximately two-thirds of the cardiac cycle, left ventricular diastolic pressure is transmitted to the left atrium and hence the pulmonary veins for a relatively longer period than is systolic pressure. Transmission of elevated diastolic pressures to the pulmonary venous bed can be a substantial driving force for development of pulmonary hypertension. Because diastole comprises two-thirds of the cardiac cycle, diseases that elevate diastolic pressure are often more likely to be associated with secondary pulmonary hypertension than are diseases with isolated elevation of systolic pressure.[11] Because the process of left ventricular relaxation is more energy dependent than contraction, abnormalities of left ventricular diastolic function occur earlier than systolic dysfunction in virtually all cardiac diseases.[12] During the lag period between diastolic dysfunction pattern identified non-invasively via transthoracic echocardiography and the development of secondary pulmonary hypertension and thus symptoms, patients may be completely

asymptomatic and referred to as having diastolic dysfunction of the heart. When symptoms and signs of heart failure developed, these patients are referred to as having diastolic heart failure or more recently heart failure with preserved EF.[13]

Diastolic dysfunction often has a cause different from that of systolic dysfunction. The distinction is important, however, because most of the randomised controlled trials that generated the evidence for treatment of heart failure included only patients with reduced left ventricular ejection fraction. Clinical conditions responsible for primary diastolic heart failure are listed in Table 1.[14]

Table 1 Causes of primary diastolic heart failure

Hypertension	Coronary artery disease
Cardiomyopathy	Diabetes mellitus
Hypertrophic	Obesity
Restrictive	Constrictive pericarditis
Infiltrative	Aging

Among the various underlying diseases causing diastolic heart failure, hypertensive heart disease is the most common and ischemic heart disease is the second most common in clinical practice.[15]

Anemia was defined in this study using the World Health Organization criteria as follows: hemoglobin less than 12 g/dl in women and less than 13 g/dl in men.[16] Epidemiological studies have documented that patients with anemia had a higher plasma brain natriuretic peptide concentrations than those with normal hemoglobin and this association was statistically independent of renal impairment, hypertension and the presence of microvascular disease, suggesting a direct link between plasma BNP and anemia.[17]

The aim of this study is to evaluate the relationship between anemia and diastolic dysfunction of the heart in the absence of other known risk factors predisposing to diastolic dysfunction.

Patients and Methods

In a cross section observational analytic variant study, consecutive patients (n=100) with anemia (50 males and 50 females) were recruited from inpatient ward, out patient internal medicine clinic, and emergency department in Alsadr medical city and compared with controlled participants (n=100) free of anemia (50 males and 50 females) during the period from October 2009 to February 2011.

Exclusion Criteria [18, 19]

1. Age more than 65 years.
2. Presence of uncontrolled hypertension (Systolic blood pressure > 160 mm Hg and/or diastolic blood pressure > 90 mm Hg).
3. Resting heart rate > 120 bpm or arrhythmias.
4. Valvular heart disease (e.g. more than mild regurgitant or stenotic mitral, aortic, tricuspid, or pulmonic valve disease).
5. Prosthetic heart valves.
6. Infiltrative cardiac disease such as haemochromatosis.
7. Hypertrophic cardiomyopathy.

8. Renal failure (GFR < 15 ml/min).
9. BMI > 30 kg/m^2.
10. Known history of ischemic heart disease.
11. Patients who are known to be pregnant.
12. History of diabetes mellitus.
13. History of Malignancy.

Determination of Variables

Measurements were taken for blood pressure and heart rate and height and weight for determination of BMI. For categorical analysis, obesity was defined by a BMI >30 kg/m^2. Standard biochemical indices in the form of blood urea, serum creatinine, blood glucose and hemoglobin concentration were obtained in all subjects. Creatinin clearance is obtained using the Cockcroft and Gault equation which stated that

$$\text{Crcl (C and G)} = \frac{\text{(140-Age in yr) X lean body weight (Kg) X 1.22 males or 1.04 females}}{\text{Serum creatinine } \mu\text{mol/l}}$$

The presence of anaemia followed the gender-specific definition of Hb <13 g/dl in men and <12 g/dl in women established by the WHO with mild to moderate anemia defined as Hb 10 to <13 g/dl and severe anemia defined as Hb < 11 g/dl.[20] ECG and transthoracic Doppler echocardiography examination were performed at the time of standard indices collected.

Transthoracic Echocardiography

Transthoracic Doppler echocardiography examination was performed using a commercially available ultrasound system (3.5 MHz transducer; General Electric; LOGIC 3) in the supine and left lateral decubitus position. Standard parasternal and apical views were used to assess for systolic and diastolic dysfunction. Recordings and measurements were obtained according to the published recommendations of the American Society of Echocardiography.[21] M-mode echocardiography was used to measure cardiac dimensions and wall thickness. LV mass was measured on echocardiogram at rest according to the following formula:

$$\text{LV mass} = 0.8 \times [1.04\,(\text{LVID} + \text{PWT} + \text{IVS})^3 - (\text{LVID})^3] + 0.6\ \text{g}$$

Which was then corrected to body surface area (ASE guidelines for measurements) where IVS is diastolic interventricular septal thickness, LVID is diastolic LV internal dimension and PWT is diastolic posterior LV wall thickness. We considered female participant who had left ventricular mass index > 96 g/m^2 to have LVH and male participant > 116 g/m^2 to have LVH.[22]

LV EF was calculated using the two-dimensional directed M-mode method at two occasions and the modified Simpson's rule when possible. Systolic dysfunction was defined by evidence of regional wall motion abnormalities and/or an EF of <50%. Traditional parameters of diastolic function were measured at the mitral leaflet tips over three consecutive cardiac cycles and included peak mitral E and A (early and

late diastolic peak filling velocities) waves, E/A ratio, and mitral E wave DT. The normal values for E wave, A wave, E/A ratio, and the E wave deceleration time are shown in Table 2. [24]

Table 2 Normal mitral inflow waves values	
E wave (E_m)	< 100 cm/s
A wave (A_m)	< 80 cm/s
E/A ratio	0.7 – 1.5
E wave deceleration time	150 – 250 ms

Diastolic function assessed by this method was classified according to published guidelines into normal, abnormal relaxation pattern (mild or grade I), the intermediate or pseudonormal pattern (moderate or grade II) and the restrictive (severe or grade III) patterns.[25] Additionally grade I is further classified into grade I and grade Ia. Like wise, grade III is further classified into grade III (reversible with Valsalva maneuver) and grade IV (irreversible with Valsalva maneuver). [26] These grades are shown in Table 3.

Table 3 Grading of diastolic dysfunction	
Grade 1	Impaired relaxation pattern
Grade 1a	Impaired relaxation pattern with increased filling pressure
Grade 2	Pseudonormalized pattern
Grade 3	Reversible restrictive pattern
Grade 4	Irreversible restrictive pattern

The isovolumetric relaxation time (IVRT) defined as the time from aortic valve closure to mitral valve opening and normally averaged 76 ± 13 ms in adults was also obtained. Typically, diseases that result in elevation of left atrial pressure will shorten the IVRT. Indeed diastolic dysfunction often leads to prolongation of IVRT.[11]

The pulmonary veins flow was not routinely performed because of the presumed difficulty in imaging this flow.[11] Normal pulmonary vein inflow consists of a diastolic and systolic phases as well as an atrial reversal (AR) called the pulmonary vein A wave. The normal values in pulmonary vein flow pattern are listed in Table 4.

Table 4 Normal values of the pulmonary veins flow waves	
S wave	35 - 85 cm/sec
D wave	30 - 65 cm/sec
A wave	12 - 35 cm/sec
PV duration	< 30 ms

The differentiation between normal diastolic transmitral flow pattern and pseudonormal pattern was performed with the use of either Valsalva maneuver or pulmonary vein inflow pattern. In patients with normal filling pressure, the Valsalva maneuver decreases both the E and A velocities and lengthens deceleration time (DT) while in patient with pseudonormalised pattern; Valsalva maneuver will disclose the genuine abnormal pattern (Figure 1). In addition, in patients with a restrictive filling pattern the reversibility of advanced diastolic dysfunction was assessed with the Valsalva maneuver.

The diastolic Doppler velocity pattern sometimes was triphasic not diphasic (i.e., three waves instead of two waves). This additional wave is termed an L wave (Figure 2) and it represents abnormal relaxation with marked delayed active relaxation and elevated filling pressures. Typically, the L wave may be seen a patient who has LVH with excellent systolic function.[14]

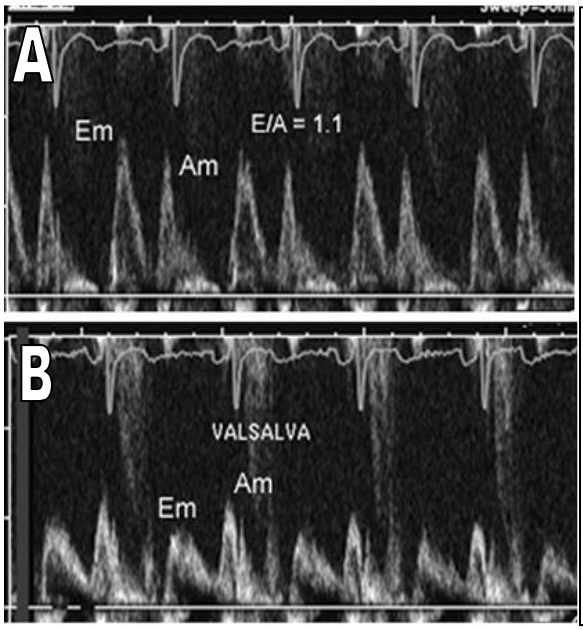
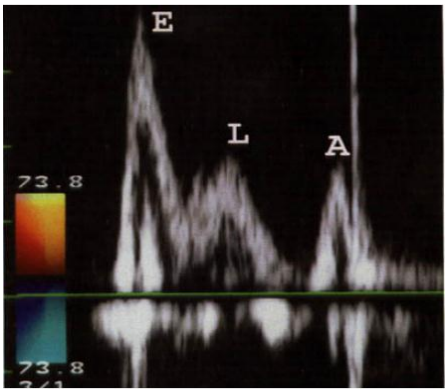


Figure 1 Valsalva maneuver effect on mitral valve inflow pattern. Note the E/A ratio of about 1:1 in Figure A. During the Valsalva maneuver in Figure B, there is a reversal of the E/A ratio and the appearance of a slow relaxation pattern which indicates grade II diastolic dysfunction.

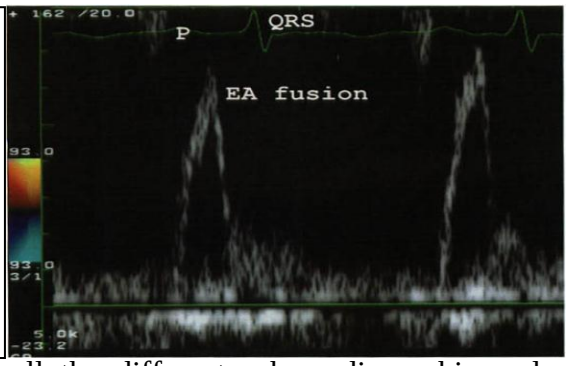
The E and A waves are occasionally merged and fused together producing a single wave (Figure 3) and the mitral valve inflow patterns were not helpful. This pattern is frequently seen in tachycardia and because of the pulmonary vein inflow pattern is not always helpful in this way, presence of tachycardia with a rate more

Figure 2 Demonstration of the so called L wave.



than 120 BPM had been excluded. In patient with atrial fibrillation, the mitral inflow A wave was not present (like that of pulmonary vein flow A wave). Presence of AF was also excluded in this study.

Figure 3 Fusion of both E and A waves.



clearly defines diastolic dysfunction and predicts elevated filling pressure[14], evaluation of diastolic function required integration of the anatomic and all the different echocardiographic and Doppler parameters. Guideline diagnosis of diastolic dysfunction are listed in Table 5.[24]

Table 5 Guideline diagnosis of diastolic dysfunction

Category	Transmitral filling pattern	Duration of PV A-wave reversal	PV A-wave peak vel. (cm/s)	E/A ratio	E wave deceleration time (ms)
Normal	Normal	Normal (<30 ms)	< 35	0.7–1.5	150–250
Mild dysfunction	Slow	Normal (<30 ms)	< 35	<0.7	>250
Moderate dysfunction	Pseudo-normal	Prolonged (>30 ms)	> 35	0.7–1.5	150–250
Severe dysfunction	Restrictive	Prolonged (>30 ms)	> 35	>1.5	<150

Newer modality of tissue Doppler echocardiography provides much improved diagnostic accuracy compared with conventional methods for differentiating the pseudonormal pattern. This modality is still not available yet at the time of the research study. Additional assessment of diastolic function can also be made by cardiac catheterization, radionuclide angiography, and magnetic resonance imaging or computed topographic scanning.[26]

Left atrial size

LA diameter was determined using two-dimensionally guided M-mode echocardiography. An M-mode echocardiogram through the base of the heart offers one approach to measuring LA size. By convention, the measurement was performed at end-systole when LA volume was greatest.[3] Normal value in this view is 2-4 cm.[11] Planimetry of left atrial area from the four chamber view was also used.[3] Normal value for LA area in this view is less than 20 cm^2. Normal LA

size is seen in grade 1; however, patients with grade 1a, pseudonormal or restrictive filling certainly have a dilated LA.[27]

Statistical Analysis

The social package statistical service (SPSS) version 11.5 was used for categorical variables and p value <0.05 was considered to indicate statistical significance. Calculations were done also via SPSS.

Results

The baseline clinical characteristics of the participants are shown in Table 6.

Table 6 Baseline Clinical Characteristics and Echocardiographic Values

Clinical Characteristic	All Participants	Anemia*	No Anemia**
Mean age, yr	43 ± 10	42 ± 11	44 ± 10
Male sex	100	50	50
Female sex	100	50	50
Mean hemoglobin level, g/dL	12.2 ± 1.7	10.9 ± 1.0	13.7 ± 1.1
Mean LVEF (%)	60 ± 10	60 ± 9	60 ± 10
Mean LVEDD (cm)	4.6 ± 0.9	4.5 ± 0.9	4.7 ± 0.8
LV mass index (g/m^2)	94 ± 21	96 ± 24	93 ± 23
E wave (cm)	75.5 ± 13	74 ± 13	76 ± 13
A wave (cm)	54 ± 12	55 ± 12	53 ± 12
E/A ratio	1.04 ± 0.3	1.03 ± 0.3	1.05 ± 0.3
LA dimension (cm)	3.17 ± 0.3	3.21 ± 0.3	3.13 ± 0.3
LA area (cm^2)	15.7 ± 0.5	16.3 ± 0.4	15.2 ± 0.3

LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic dimension.
*Hemoglobin level of <12 g/dL in women, <13 g/dL in men
**Hemoglobin level of ≥12 g/dL in women, ≥13 g/dL in men

Of the 200 participants enrolled in this analysis, 100 (50%) were anemic with a mean age of 42 ± 11 years and 100 (50%) were non anemic (50%) with a mean age of 44 ± 10 years according to the gender-specific definition of the WHO.[16] The latter was the control group. Of the former, 8 (8%) participants were discovered to have diastolic dysfunction evident via echocardiography (Figure 4) and 92 (92%) participants had no diastolic dysfunction. None of the non-anemic participants was discovered to have diastolic dysfunction.

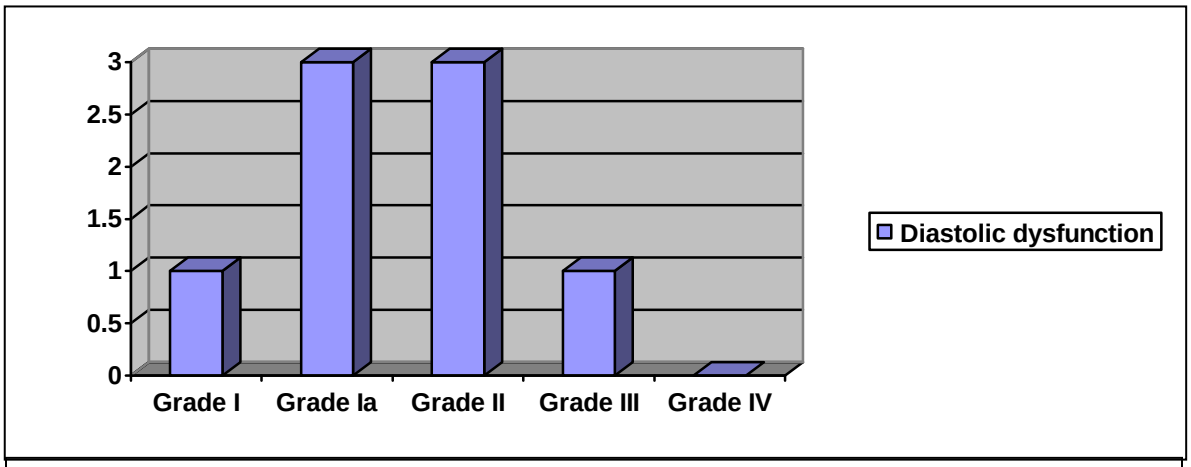


Figure 4 Diastolic dysfunction grades among participants.

The relation between hemoglobin level and diastolic dysfunction had been studied then as shown in Table 7.

Table 7 Association between level of hemoglobin and diastolic function

Level of hemoglobin	Diastolic function		Total
	Normal	Abnormal	
Normal	100	0	100
Anemic	92	8	100
Total	192	8	200
P value = 0.004 (significant)			

Among the anemic participants, 12 (12%) had discovered to have left ventricular hypertrophy while no one from the non-anemic participants had been discovered to have LVH. Anemic and non-anemic individual are then cross-tabulated to prove that anemia can correlate with left ventricular hypertrophy as shown in Table 8

Table 8 Association between level of hemoglobin and left ventricular hypertrophy

Level of hemoglobin	LVH		Total
	Present	Absent	
Normal	0	100	100
Anemic	12	88	100
Total	12	188	200
P value = 0.00004 (highly significant)			

Of the anemic participants who had LVH, 6 (50%) participants had diastolic dysfunction evident via the variable parameters of echocardiography. Among

the remaining anemic participants without LVH, only two had been discovered to have diastolic dysfunction. This relation is shown in Table 9.

Table 9 Association between left ventricular hypertrophy and diastolic dysfunction

Diastolic dysfunction	LVH		Total
	Absent	Present	
Present	2	6	8
Absent	86	6	92
Total	88	12	100
P value = 0.00004 (highly significant)			

Anemic participants are then classified into two groups according to the level of hemoglobin; group one with hemoglobin level that is less than normal but more than 10 g/dl and group two with hemoglobin level that is less than 10 g/dl. The former group included 60 participants (60%) and diastolic dysfunction was obtained in only 5 patients. The latter group included 40 participants (40%) and diastolic dysfunction was only obtained in 3 participants. Diastolic dysfunction irrespective to the grade is thus obtained in 8 patients (8%). This cross sectional study is performed to prove that severe anemia was the cause behind diastolic dysfunction as shown in Table 10.

Table 10 Association between diastolic dysfunction and severity of anaemia

Diastolic function	Severity of anaemia		Total
	> 10 g/dl	< 10 g/dl	
Abnormal	5	3	8
Normal	55	37	92
	60	40	100
P value = 0.880 (non-significant)			

Diastolic dysfunction had been found using the variable parameters of echocardiography as shown in Table 11. After that, the two groups of anemic participants (as classified above whom totaling 100 patients) who had diastolic dysfunction (8%) are then grouped according the degree of diastolic dysfunction they had to assess whether the severity of anemia correlates with diastolic dysfunction grade as shown in Table 12.

Table 11 Echocardiographic findings in participants with diastolic dysfunction			
Diastolic dysfunction grades	E/A ratio	E wave deceleration time (ms)	Number of participants
Grade I	0.6	300	1
Grade Ia	0.5	310	3
Grade II	1.2	215	3
Grade III	1.6	120	1

Table 12 Association between the severity of anaemia and diastolic dysfunction grades			
Diastolic dysfunction	Anemic patients		Total
	> 10 g/dl	< 10 g/dl	
Grade 1	1	0	1
Grade 1a	3	0	3
Grade 2	1	2	3
Grade 3	0	1	1
Grade 4	0	0	0
	5	3	8
P value = 0.161 (non-significant)			

Anemic participants who were classified according to the sex into 50 anemic male and 50 anemic female were studied in relation to diastolic dysfunction to analyze and verify the effect of sex of anemic participants upon diastolic function as shown in Table 13.

Table 13 Association between diastolic function and anemic sex			
Diastolic function	Anemia according to the sex		Total
	Anemic male	Anemic female	
Normal	45	47	92
Abnormal	5	3	8
Total	50	50	100
The P value = 0. 461 (non-significant)			

Discussion

The presence of anemia is associated with adverse outcomes in many clinical conditions like myocardial ischemia and its relation to heart failure has also been appreciated.[28] Recent studies have demonstrated that anemia is highly prevalent in patients who have heart failure and is strongly associated with systolic dysfunction.[29] However, ≤ 50% of patients who have heart failure have preserved systolic function[30] and the association of anemia with

diastolic dysfunction in this population was analysed in this study.

In patients with heart failure, anemia has been linked to more severe cardiac dysfunction, increased brain natriuretic peptide and a worse prognosis even after adjustment for conventional risk factors such as coronary heart disease, hypertension, and renal dysfunction. Anemia has a range of effects on cardiac structure, including myocyte hypertrophy and interstitial fibrosis leading to left ventricular hypertrophy. Over time functional changes occur, with impaired left ventricular relaxation and compliance leading to diastolic dysfunction.[31]

In this study, anemia had a statistically significant (P = 0.004) detrimental effect on diastolic function of the heart when other known risk factors for diastolic dysfunction were excluded. This is because the process of left ventricular relaxation is energy dependent. This was consistent with Sarnak, M.J. et al. [32] who demonstrated the impact of anemia on diastolic function and showed a correlation between anemia and left ventricular filling disturbances. Likewise, Steinborn W. et al.[17] had also related anemia with left ventricular diastolic dysfunction.

There was a statistically high association (0.00004) between anemia and left ventricular hypertrophy. This was consistent with Amin et al. [33] who had examined the relation between anemia and left ventricular hypertrophy. In his study and after adjusting for confounders, there was a small but significant association between hematocrit and left ventricular mass.

A highly statistical correlation (0.00004) between left ventricular hypertrophy due to anemia and diastolic dysfunction of the heart had been found in this study. This was consistent with studies predominantly done in cohorts that had established kidney disease that found anemia to be linked to LVH.[34] LVH is therefore the leading hypothesis believed to explain the association of anemia with diastolic heart failure. On the other hand, Slama M. et al.[35] had suggested that overt LVH is not required for diastolic dysfunction to occur and Nair et al.[36] had even suggested that in the absence of LVH, anemia remained strongly associated with diastolic dysfunction, implying that this could be a unique complication of anemia and explaining the development of diastolic dysfunction in some anemic participant (2%) who had no LVH.

We might enroll some participants in the lag period between the development of LVH and the appearance of functional disturbance of diastolic heart function. This might explain the development of LVH in 6% of anemic participants who showed no diastolic dysfunction.

The hemodynamic effects of severe anemia had also been studied and shown that there was no statically significant association with diastolic dysfunction when firstly taken as a whole (P = 0.880) and when secondly graded (P value = 0.161). This was inconsistent with Varat MA et al.[37] who had studied the hormonal and metabolic effects of anemia on cardiac functions and suggested a direct myocardial toxicity and indirect cardiac strain through salt and water retention. He had related these specific effects to the more severe degree of anemia (Hb <10 g/dl).

The effect of sex of anemic participants was a statistically non-significant (P = 0. 461) upon diastolic dysfunction. This was inconsistent with Amin et al. [33] who had suggested that

there was a modest association between anemia and LVH in men as a cause of diastolic dysfunction, but the relation was not statistically significant in women.

Conclusion

Anemia is significantly related to the development of left ventricular diastolic dysfunction when other known causes are excluded. Despite any level of hemoglobin reduction below normal can result in any grade of diastolic dysfunction ranging from mild to severe form. With this study, diastolic dysfunction appears not to be influenced by sex.

Recommendations

1. The measurement of hemoglobin, which is inexpensive test, may be a useful tool to identify patients with diastolic cardiac dysfunction.
2. Measurement of BNP in patients with anemia.
3. Measurement of diastolic function for anemic patients by tissue Doppler echocardiography when become available.
4. For the future studies, the cause of anemia is to be focused on to correlate with diastolic dysfunction.
5. Further work is needed to determine whether treatment of anemia improves outcomes.

References

1. Douglas L. mann. Heart failure and cor pulmonale. Eugene Braunwald. Harrison's textbook of internal medicine. 17th edition. 2008; 1443-1455.
2. Barry M. Massie. Heart failure: pathophysiology and diagnosis. Goldman. Cecil textbook of internal medicine, 23rd edition. 2007; 345-372.
3. John A. A. Hunter. Heart failure. Churchill livingstone. Davidson's principles and practice of medicine. 20th edition. 2006; 542-551.
4. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure. Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002;105: 1387–93.
5. Zile MR. heart failure with preserved ejection fraction: is this diastolic heart failure? J Am Coll Cardiol 2003: 1519-1522.
6. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to update the 2001 guidelines for the evaluation and management of heart failure). J Am Coll Cardiol. 2005;46:e1–82.
7. Cuocolo A, Sax FL, Brush JE, et al. 1990. Left ventricular hypertrophy and impaired diastolic filling in essential hypertension: diastolic mechanisms for systolic dysfunction during exercise. Circulation 81:978– 86.20.
8. Kitzman DW, Higginbotham BM, Cobb FR et al. 1991. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J. Am. Coll. Cardiol. 17:1065–72.
9. Carolyn Y. Ho. Echocardiographic assessment of diastolic function. Scott D. Solomon. Essential Echocardiography: a practical handbook. 2007; 119-131.
10. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with

emphasis on regional systolic function. Circulation. 2006;113:296–304.
11. Harvey Feigenbaum. Evaluation of Systolic and Diastolic Function of the Left Ventricle. Lippincott Williams & Wilkins. Feigenbaum's Echocardiography, 6th Edition. 2005; 139- 180.
12. Christopher P. Appleton, Diastolic Heart Function, Myo Clinic Cardiology. 3rd edition. 2007;1087-1100.
13. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 2002;39:1780 –1786.
14. Jae K. oh. Assessment of diastolic function and diastolic heart failure. Lippincott Williams and Wilkins. The echo manual. 3rd edition. 2006; 121-142.
15. Schannwell CM, Schneppenhiim M, Perings S, Plehn G, Strauer BE 2002 left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. Cardiology 98:33-39.
16. Sarnak KJ, Tighiouart H. Manjunath G. MacLeod B. Griffith J. Salem D. Levey AS, for the ARIC study. Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (ARIC) study. J Am Coll Cardiol 2002; 40:27-33.
17. Steinborn, W., Doehner, W. and Anker, S.D. (2003) Anaemia in chronic heart failure: frequency and prognostic impact. Clin. Nephrol.60 (sppl.1), S103-S107.
18. Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. Am J Med 2003;114:112–119.
19. Owan, TE, Hodge, DO, Herges, RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355:251.
20. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000; 35:1737–1744.
21. Schiller, N. B., Shah, P. M., Crawford, M. et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J. Am. Soc. Echocardiogr. 2, 358–367.
22. Byrd BF III, Wahr D, Wang YS, Bouchard A, Schiller NB. Left ventricular mass and volume/mass ratio determined by two-dimensional echocardiography in normal adults. J Am Coll Cardiol 1985; 6:1021–1025.
23. Garcia, M. J., Palac, R. T., Malenka, D. J., Terrell, P. and Plehn, J. F. (1999) Color M-mode Doppler flow propagation velocity is a relatively preload-independent index of left ventricular filling. J. Am. Soc. Echocardiography 12, 129–137.
24. Helen Rimington and John chambers. Left ventricle. Helen Rimington and John Chambers. Echocardiography: a practical guide to reporting. 2ed edition; 5-20.
25. Rakowski, H., Appleton, C., Chan, K. L. et al. (1996) Recommendations for

the measurement and reporting of diastolic function by echocardiography. J. Am. Soc. Echocardiography 9, 736–760.
26. Takatsuji H, Mikami T, Urasawa K, Teranishi J, Onozuka H, Takagi C, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J Am Coll Cardiol. 1996;27:365–71.
27. Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. J Am Coll Cardiol. 2003;42:1206–7.
28. Szachniewicz J, Petruk-Kowalczyk J, Majda J, Kaczmarek A, Reczuch K, Kalra PR, Piepoli MF, Anker SD, Banasiak W, Ponikowski P. Anaemia is an independent predictor of poor outcome in patients with chronic heart failure. Int J Cardiol 2003;90:303–308.
29. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928 –1936.
30. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol 2002;39:138 –141.
31. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A, LV systolic and diastolic functional abnormalities in asymptomatic patients with NIDDM. J Am Soc Echocardiogr, 2001, 14, 885-91.
32. Sarnak MJ. Anemia as a risk factor for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;38:955–962.
33. Amin MG, Tighiouart H, Weiner DE, Stark PC, Griffith JL, MacLeod B, Salem DN, Sarnak MJ. Hematocrit and left ventricular mass: the Framingham Heart study. J Am Coll Cardiol 2004;43:1276 –1282.
34. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol 2003;14:462– 468.
35. Slama M, Susic D, Varagic J, Frohlich ED. Diastolic dysfunction in hypertension. Curr Opin Cardiol 2002;17:368-73.
36. Nair D, Shlipak MG, Angeja B, Liu HH, Schiller NB, Whooley MA. Association of anemia with diastolic dysfunction among patients with coronary artery disease in the Heart and Soul Study. Am J Cardiol 2005; 95:332-6.
37. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 1972;83:415– 426.