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Diastolic Dysfunction in Patients with Myeloproliferative Neoplasms

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ABSTRACT

Background: Cardiac diastolic dysfunction is largely unclear in patients with myeloproliferative neoblasms (MPNs).

Obgective: To evaluate the left ventricular diastolic function in MPNs patients by two-dimensional and Doppler echocardiographic studies.

Patients and Methods: The study included 44 MPNs patients, 20 of them have Chronic Myeloid Leukemia (CML), 7 with Essential Thrombocytosis (ET), 6 with Primary Myelofibrosis (PMF) and 11 have Polycythemia Vera.

Results: Echocardiographic studies showed that valvular lesions are common in MPNs patients with predominant tricuspid and mitral regurgitation. The Pulmonary Artery Systolic Pressure (PASP), Early Transmitral Deceleration Time (EDT) and IsoVolumic Relaxation Time of the left ventricle (IVRT) in MPNs patients are increased indicating Leftventricular diastolic dysfunction while, the ejection fraction (EF) representing systolic function is still within normal. Significant positive correlations between PASP and both EDT and IVRT confirming Left ventricular diastolic dysfunction with impaired diastolic filling.

Conclusion: The MPNs have deleterious effects on cardiac valves, pulmonary artery pressure and diastolic functions of the heart that can be early discovered by use of echocardiography in the initial clinical evaluation of subjects with MPNs.

Key Words: *MPNs – CML – PV – ET – PMF – PASP – Echo.*

INTRODUCTION

The myeloproliferative neoplasms (MPNs), previously termed the myeloproliferative disorders, are characterized by the clonal proliferation of one or more hematopoietic cell lineages, predominantly in the bone marrow, but sometimes in the liver and spleen **[1]**. The 2008 revision of the World Health Organization (WHO) classification of MPNs include: Chronic myelogenous leukemia (CML), chronic neutrophilic leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia, mastocytosis, and unclassifiable MPNs **[2-4]**.

CML is the only MPN that is characterized by the chromosomal translocation t(9;22), BCR-ABL fusion gene. The most commonly recognized mutation in the remainder of the MPNs is Janus kinase 2 (JAK2) V617F. It is present in greater than 90% of patients with PV and approximately half of those with PMF or ET **[5,6]**.

The cardiovascular system is involved in 4% to 21% of cases of MPNs. Acute ischemic coronary artery disease is the presenting symptom in these cases **[7]**. Other cardiovascular complications in patients with MPNs are valvular heart involvement, pericardial involvement, aortitis, and thrombosis of major vessels and pulmonary embolism **[8-11]**. The development of an effective and safe strategy for preventing these cardiovascular complications is the main challenge in the treatment and management of patients with MPNs **[12-14]**.

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole that occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function **[15]**. Doppler echocardiography is

widely used for the noninvasive assessment of diastolic filling of the left ventricle **[16]**. The assessment of left ventricular diastolic function should be an essential part of routine examination, particularly in patients presenting with dyspnea or heart failure. About half patients with new diagnoses of heart failure have normal or near normal global ejection fractions. These patients are diagnosed with "diastolic heart failure" or "heart failure with preserved EF" **[17]**. The assessment of LV diastolic function and filling pressures is of paramount clinical importance to distinguish this syndrome from other diseases such as pulmonary disease resulting in dyspnea, to assess prognosis, and to identify underlying cardiac disease and its best treatment **[18]**.

Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades. The use of Doppler Echocardiography in evaluating diastolic function in MPNs patient is still lacking, so the purpose of this study is to evaluate the diastolic function in patients with myeloproliferative neoplasms.

PATIENTS AND METHODS

The study was conducted on 44 patients with Myeloproliferative Neoplasms (MPNs) who were attending the Clinical Hematology Unit of Assiut University Hospitals and South Egypt Cancer Institute including 20 males and 24 females. The age of the studied patients was ranged from 21 to 72 years with median age 50 years and mean±SD was 47.12±15.46 years. Twenty patients had Chronic Myeloid Leukemia (CML), seven had Essential Thrombocytosis (ET), six had Primary Myelofibrosis (PMF) and eleven had Polycythemia Vera.

Each patient was subjected to thorough history and clinical examination. Complete Blood Counts, Kidney and Liver functions, Bone Marrow Biopsy, Philadelphia Chromosome and JAK2 mutations were done to confirm diagnosis. M-mode, 2-Dimensional and Doppler (Pulsed wave, Continuous wave and Color Doppler) Echocardiography was performed to all patients.

Statistical analysis:

Statistical analysis was performed using the SPSS 16.0 statistical software package. Continuous variables were expressed as Mean±SD while Categorial variables were expressed as numbers and percentages. Paired-samples and independent-samples student *t*-tests were used to compare variables. Bivariate-Pearson correlation was used to investigate potential relationships between variables.

Ethical considerations:

An informed consent was obtained from every patient included in the study and the study was approved by the Ethical Committee in our Faculty.

RESULTS

The study included 44 patients 20 males and 24 females. The disease duration was 2.97±1.85 with median duation 3 years. As regarding treatment, 16 patients (36.3%) were on Imatinib therapy, 9 patients (20.5%) were on Hydroxyurea while 19 patients (43.2%) were not on specific treatment. The mean treatment duration is ranging from 1 to 5 years (2.75±1.65). The recorded valvular lesions in all studied MPNs patients were present in 26 patients (59%) of patients while 18 (41%) showed normal valvular morphology and function. Mitral regurgitation was present in 13 (29.5%) of patients, tricuspid regurgitation in 20 patients (45.5%), mitral stenosis in only one patient (2.2%) and aortic regurgitation in two patients (4.5%). The patterns of valvular affections in individual diseases are represented in Table (1); some patients had multiple valvular lesions. Pulmonary hypertension was observed in 19 patients (43%). The mean values of estimated echocardigraphic parameters in the different disease patterns are illustrated in Table (2). There is no correlation between Pulmonary Artery Systolic Pressure, (PASP) and Ejection Fraction (EF) r=0.064 and p=0.696 but positive correlations are present between PASP and both Early Transmitral Deceleration Time (EDT) and IsoVolumic Relaxation Time of the left ventricle (IVRT) (Fig. 1-A, B). No correlations were found between duration of the disease and duration of treatment on one side and PASP, EF, EDT or IVRT on the other side (Table 3). Table (4) represents the correlation between hematological parameters and these estimated echo parameters in MPNs patients; positive correlation is only found between white blood cells (WBCs) and EDT (r= 0.334 and p=0.035).

Table (1): Estimated valvular lesions in all MPNs patients.

Valve lesions	CML n=20	ET n=7	PMF n=6	PV n=11
Normal	5 (25%)	3 (43%)	3 (50%)	7 (64%)
MR	9 (45%)	1 (14%)	0 (0%)	3 (27%)
TR	11 (55%)	4 (57%)	3 (50%)	2 (18%)
MS	1 (5%)	0 (0%)	0 (0%)	0 (0%)
AR	0 (0%)	1 (14%)	0 (0%)	1 (9%)

CML : Chronic Myeloid Leukaemia.
ET : Essential Thrombocytosis.
PMF : Primary Myelofibrosis.
PV : Polycythaemia Vera.
AR : Aortic Valve Regurge.
MR : Mitral Valve Regurge.
MS : Mitral Valve Stenosis.
TR : Tricuspid Valve Regurge.

Table (2): Echocardiographic Parameters in MPNs Patients.

Echocardiographic parameter		Disease category			
		CML n=20	ET n=7	PMF n=6	PV n=11
PASP/mmHg	Mean±SE	30.95±2.18	29.80±5.82	26.75±3.94	24.27±2.39
	Median	32.0	22.0	26.0	20.0
	Range	18.0-59.0	18.0-48.0	20.0-35.0	18.0-45.0
	p-value		0.274		
EF%	Mean±SE	63.60±2.27	70.40±2.91	65.50±3.75	61.91±3.79
	Median	65.0	74.0	65.5	64.0
	Range	41.0-79.0	60.0-75.0	59.0-72.0	30.0-75.0
	p-value		0.286		
EDT/ms	Mean±SE	260.55±24.09	224.60±24.85	236.25±9.23	229.55±17.03
	Median	250.0	230.0	243.0	236.0
	Range	169.0-684.0	150.0-277.0	209.0-250.0	120.0-335.0
	p-value		0.875		
IVRT/ms	Mean±SE	142.15±20.83	91.40±19.26	135.00±13.67	114.36±14.83
	Median	115.0	107.0	148.0	101.0
	Range	54.0-493.0	15.0-120.0	94.0-150.0	12.0-192.0
	p-value		0.551		

CML : Chronic Myeloid Leukaemia.
ET : Essential Thrombocytosis.
PMF : Primary Myelofibrosis.
PV : Polycythaemia Vera.
AR : Aortic Valve Regurge.
MR : Mitral Valve Regurge.
MS : Mitral Valve Stenosis.
TR : Tricuspid Valve Regurge.
EF : Ejection Fraction.
EDT : Early Transmitral Deceleration Time.
IVRT : IsoVolumic Relaxation Time of the left ventricle.
PASP : Pulmonary Artery Systolic Pressure.
ms : Milliseconds.
mmHg : Milimeter Murcury.

Table (3): Correlation between duration of the disease and duration of treatment with PASP, EF, EDT and IVRT.

Echocardiographic parameter	Duration of disease		Duration of treatment	
	r-value	*p*-value	*r*-value	*p*-value
PASP mmHg	0.114	0.484	0.038	0.856
EF%	–0.111	0.494	–0.029	0.891
EDT ms	–0.017	0.918	0.094	0.655
IVRT ms	–0.075	0.647	–0.041	0.845

PASP : Pulmonary Artery Systolic Pressure.
EF : Ejection Fraction of the left ventricle.
EDT : Early Deceleration Time of the left ventricle.
IVRT : IsoVolumic Relaxation Time of the left ventricle.
ms : Milliseconds.
mmHg : Milimeter Murcury.

Table (4): Correlation between hematological parameters and PASP, EF, EDT and IVRT.

Echocardiographic parameter		WBCs	RBCs	Hb	Hct	Plt
EF%	*r*-value	0.218	–0.085	0.007	–0.070	0.132
	p-value	0.176	0.601	0.964	0.668	0.416
EDT ms	*r*-value	0.334	0.044	0.071	0.122	–0.118
	p-value	0.035*	0.789	0.663	0.452	0.470
IVRT ms	*r*-value	0.002	0.013	–0.008	0.108	–0.236
	p-value	0.988	0.938	0.962	0.509	0.142
PASP mmHg	*r*-value	0.125	–0.113	–0.111	–0.059	0.150
	p-value	0.443	0.488	0.497	0.719	0.356

PASP : Pulmonary Artery Systolic Pressure.
EF : Ejection Fraction of the left ventricle.
EDT : Early Deceleration Time of the left ventricle.
IVRT : IsoVolumic Relaxation Time of the left ventricle.
ms : Milliseconds.
mmHg : Milimeter Murcury.

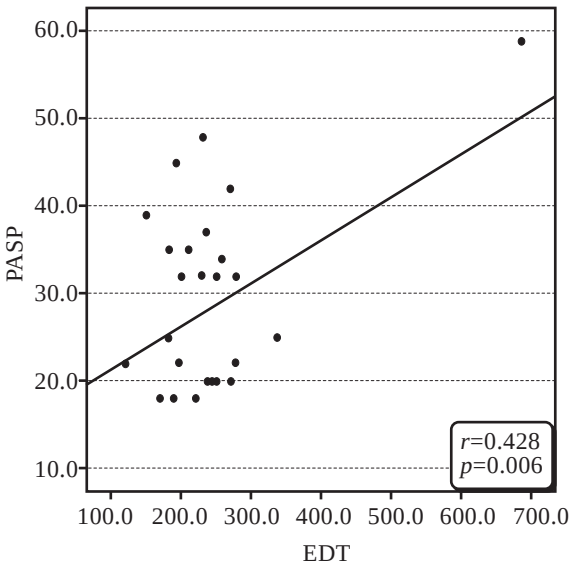

Fig. (1-A): Correlation between PASP and EDT.

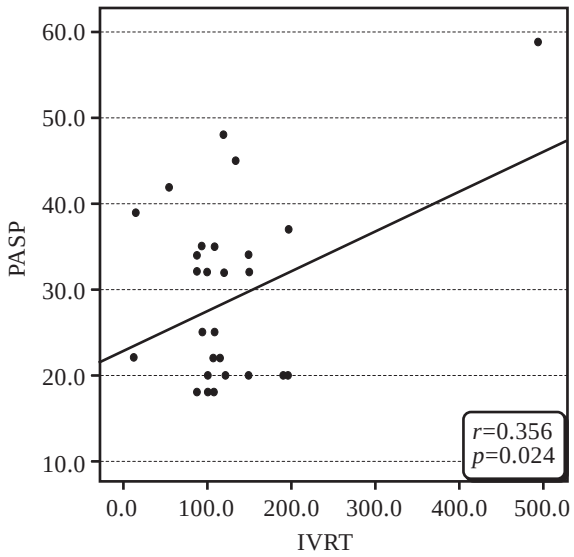

Fig. (2-B): Correlation between PASP and IVRT.

PASP : Pulmonary Artery Systolic Pressure.
EDT : Early Transmitral Deceleration Time.
IVRT : IsoVolumic Relaxation Time of the left ventricle.

DISCUSSION

Cardiac involvement in MPNs including coronary artery thrombosis, myocardial infarction, pulmonary hypertension, asymptomatic pericardial effusion, cardiac tamponade, intractable cardiac failure due to intra-ventricular thrombosis and stenosis of the Aortic and Mitral valves, even requiring surgical treatment, had been reported **[19]**.

The current study showed that cardiac valve lesions were encountered in 59% of MPNs patients. Tricuspid and mitral valves were the most commonly involved valves, a finding that is coinciding with previous reports **[8,20]**.

Pulmonary hypertension is well known in patients with MPNs but most of the literature consists of case reports or small studies as previously reported **[21-24,10]**. In the current study the pulmonary hypertension was present in 47.5% of the patients: 65% in CML, 40% in ET, 50% in PMF and 18.2% in PV. These results are higher than one previous report **[20]** but coinciding with others **[25-27]**. All patients in

the current study were asymptomatic with mild Pulmonary Hypertension, so none of them needed treatment. It is well known that symptoms of mild pulmonary hypertension are often subtle **[28]**. Since pulmonary hypertension is usually diagnosed after symptoms develop, it is possible that most cases of mild asymptomatic pulmonary hypertension remain clinically undiagnosed.

Trans-esophageal echocardiogram (TEE) is a good non-invasive method of diagnosing pulmonary hypertension **[29]** and has the advantage of excluding cardiac causes of pulmonary hypertension. The most important question is whether this high incidence of pulmonary hypertension in the current study is truly secondary to MPNs. These findings are coinciding with previous reports **[10,26,27]**. We believe that pulmonary hypertension in these cases is secondary to MPNs as the incidence of primary pulmonary hypertension in general population is very low and usually occurs in the third or fourth decade **[28]**. So the high incidence of Pulmonary Hypertension is not by chance.

Pathogenesis of pulmonary hypertension in MPNs is multi-factorial. It has been correlated to platelets in many studies **[20,21,24,30]**. Marvin and Spellberg **[22]** found obstruction of pulmonary capillaries by megakaryocytes leading to stasis and secondary micro-thrombosis in one patient with PMF and pulmonary hypertension; the right sided heart failure resolved with the correction of thrombocytosis in this patient. Furthermore, autopsy studies by **[31]** had demonstrated the presence of atypical megakaryocytes and thrombotic material in the lung capillaries of patients with pulmonary hypertension and MPNs. Other evidence implicating platelets in the pathogenesis of pulmonary hypertension is the presence of increased level of thrombopoietin in pulmonary arteries of patients with pulmonary hypertension **[30]**.

In the current study, left ventricular ejection fraction (LVEF), as an indicator of LV systolic function, was within normal expected values in different categories of MPNs patients. These results are similar to a previous report **[20]**. We did not find significant correlations between LVEF and duration of the disease, duration of treatment, WBCs, RBCs, Hb, Hct or Platelets that means the systolic function of the left ventricle represented by EF is not influenced by the disease process in our MPNs patients. Also, the used chemotherapeutic regemins was not containg direct cardiotoxic agents in treated patients.

In the current study, left ventricular diastolic function wass evaluated by measuring Early Transmitral Deceleration Time (EDT) and left ventricular Iso Volumic Relaxation Time (IVRT). LV diastolic dysfunction is diagnosed if EDT >220ms and IVRT >110ms. Diastolic dysfunction was found in 40% of all studied MPNs patients. These results are concordant with a previous report **[20]**.

The current study showed positive correlation between LV EDT and PASP and between LV IVRT and PASP. This can be explained by that prolonged LV EDT and LV IVRT indicate LV diastolic dysfunction. This, in turn, causes impaired diastolic filling of the LV with subsequent stagnation of blood in the LA causing pulmonary venous congestion. The end result is increased pulmonary vascular resistance and occurrence of pulmonary hypertension.

Conclusion:

Left ventricular diastolic dysfunction (LVDD) is a marker of evolving heart disease. Therefore, the high prevalence of LVDD in MPNs patients suggested by this study supports the use of echocardiography in the initial clinical evaluation of subjects with MPNs.

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