Echocardiographic evaluation of Cardiac Involvement in Myeloproliferative Disorders

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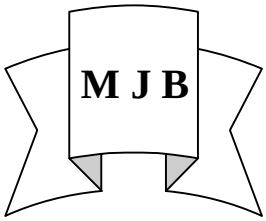


Abstrac

BACKGROUND

Thromboembolic events are common cause of death in patients with myeloproliferative disorders (MPD) especially those with cardiac involvement . In previous studies, cardiac involvement, including coronary arterial thrombosis, myocardial infarction, pulmonary hypertension (PHT), asymptomatic pericardial effusion, cardiac tamponade, intractable cardiac failure due to intraventricular thrombosis, and stenosis of aortic, mitral valves, even requiring surgical treatment had been reported in MPD

METHODS

This cohort study was carried out in three Iraqi teaching hospitals for Medicine including Al-Kadhimyya Teachginmg Hospital , Al-Yarmook Teaching Hospital (including National haematology Centre) and Merjan Teaching hospital in Babylon. The study groups were 26 patients (mean age female and male) with MPD and 30 age-matched healthy controls. MPD group included sixteen cases chronic phase chronic myelogenous leukemia (CML), two idiopathic myelofibrosis (MF) , seven polcythemia vera and one essential thrombocythemia . History regarding thrombotic and bleeding complications, examination and lab investigations are evaluated for these patients and transthoracic echocardiographic study was done for them and for the control subjects. The results are compared by statistical methods.

RESULTS

Mitral regurgitations were present in 9 patients (34.6%) and two controls (6.7%) ($P < 0.05$). Aortic regurgitation were present in 3 patients (11.5%) and no control (0.00%) ($p < 0.05\%$) . Rates of regurgitations of other valves were not different in-between MPD subgroups and control ($P>0.05$). The rates of annular calcifications and valvular thickening were not different between MPD and control groups. Pulmonary hypertension (PHT) was not detected in patients or control. Measurements of ejection fraction, fractional shortening of left ventricle, E/A ratio and aortic root dimension are significantly different between MPD and control ($P<0.05$). Left atrial dimension of patients with MPD was larger than controls ($P>0.05$). Left atrial dimension was the

largest in PV (P<0.005). End-diastolic diameter of left ventricle , opening of aortic valve and left atrial dimension were larger in patients with thromboembolic events than patients without thromboembolic events (P<0.05). Measurements of ejection fraction and fractional shortening of left ventricle were lower in MPD groups than control (P<0.05 and <0.005) respectively. The rates of all other echocardiographic parameters were not significantly different related to existence of thromboembolic events (P>0.05).

CONCLUSIONS

This study showed that valvular lesions were more prevalent in MPD. Erythrocytosis was more important than thrombocytosis in relation to cardiac parameters which related to thromboembolic events. Further evaluation of the cardiac changes in MPD subgroups with extended studies including trans-oesophageal echocardiography, right-heart catheterization and longer follow-up periods would be appropriate.

تقييم تأثير إصابات القلب لدى المصابين بأمراض نخاع العظم النقية باستخدام فحص ايكو القلب

الخـــلاصة:

حوادث الجلطات والخثرة الدموية من اهم اسبـــــاب الوفاة لـــدى المصابين بامراض نخـاع العظم النقية خاصة ممن لديهم اصابات في القلب .
في دراسات سابقة تشمل اصابات القلب بانسداد الشرايين التـــاجية ، احتـــشاء العضلة القلبية ، ارتفـــاع ضغـــط الشريـــان الرئـــوي ، انصباب شغاف القلب ، عجز القلب ، إضافة الى تضيق الصمام الابـــهر والإكليلي كلها ممكنة الحدوث لدى المصابين بأمراض نخـــاع العظم النقية .
في هذه الدراسة تبين إن إصابات صمامات القلب أكثـــــــر انتشارا لدى المصابين بأمراض نخاع العـــظم النقيـــــة وان مرضـــــــى زيادة خضاب الدم أكثـــــر تعرضا للإصابة مـــن مرضى زيـــادة الصفيحات الدموية و بالتالي أكثر تعرضا للجلطات و الخـــثرة الدموية السادة للشرايين الرئيسية في الجسم .

Introduction

Polycythemia vera, idiopathic myelofibrosis, essential thrombocytosis, and chronic myelogenous leukemia are traditionally classified under the rubric of the chronic myeloproliferative disorders (MPDs).[1] They are defined as neoplastic diseases that involve a proliferation of the myeloid stem cell or its derivatives . these disorders share several features including an origin in a multipotent hematopoietic progenitor cell , clonal dominance of the malignant progenitor cells over their normal counterparts , overproduction of one or more of the formed elements of the blood in the absence of a definable stimulus , megakaryocyte hyperplasia and dysplasia , transformation to acute leukemia but at widely varying rates , marrow hypercellularity , Exuberant extramedullary hematopoiesis , thrombotic and hemorrhagic diatheses , Abnormalities involving chromosomes 1, 8, 9, 13, and 20 , Mutation in Janus kinase (JAK2 protein and growth factor–independent colony formation in vitro .[2-7]

Thromboembolic complications are seen in 0–6% of the patients in CML, 0–17% in MF, 17–44% in ET, and 20–63% in PV [8-12] .These complications account for one-third of the deaths and mostly occur in coronary and peripheral arteries, pulmonary, portal, hepatic, cerebral, and deep veins [13]. Prophylaxis of thromboembolic events remains a key issue in the management of MPDs. [14]

The cardiovascular system is involved in 4% to 21% of cases of MPDs [15] Of the

spectrum of cardiac complications, coronary artery disease is the most common presentation and may be the first manifestation as reported in cases of PV [16] and ET [17] .Other cardiac abnormalities include systemic and pulmonary hypertension , various cardiac valve abnormalities including mitral valve regurgitation, aortic valve thickening, mitral annulus calcification, mitral valve thickening, and aortic valve regurgitation , cerebrovascular disease ..etc. [18-22]

The purpose of this study was to evaluate the cardiac involvement by transthoracic echocardiography in MPD and their relationship with thromboembolic events and thrombocytosis.

Methods

Twenty-six consecutive patients (16 female and 10 male), at a mean age of years (49.5±16.5 years, range 21–71) with MPD were enrolled to this study in-between March 2006 and February 2007. Sixteen patients had chronic phase CML, one ET, two MF and seven PV. The control group was consisted of 30 age-matched (43.6±16.4 years, range 18–81) healthy persons (15 female and 15 male), without history of cardiovascular diseases.

DISEASE EVALUATION

Previously or newly diagnosed patients were enrolled to this study. Previous diagnoses were reviewed and confirmed. The diagnosis of the diseases as PV, ET, CML and MF was established according to standard hematological criteria [23-25]. Previous or present, any arterial and/or venous thromboembolic, and hemorrhagic events were recorded.

ECHOCARDIOGRAPHIC EVALUATION

Three cardiologists in three different hospitals are blinded to the patient and control groups performed echocardiographic evaluations. *Kretze* Packard VOLUSON 5300 echocardiography system with multi-Hz (2-4 mHz) transducer and *PHILIPS* packed echocardiography system were used. Studies were recorded on videotape for storage and review.

Assessment of Left ventricular function Left ventricular volumes were calculated by an ellipsoid monoplane area–length method from apical four-chamber view. Left ventricular performance was evaluated by measuring fractional shortening (end-diastolic diameter-end-systolic diameter/end-diastolic diameter) and ejection fraction (end-diastolic volume-endsystolic volume/end-diastolic volume). [26]

Valve morphology The morphologic features of cardiac valves were characterized according to valve thickening and motion. Thickening of mitral leaflets of more than 5 mm noticed on multiple echocardiographic views with zoom process was defined as abnormal. Distal and mid portions of mitral anterior leaflets were measured three times on parasternal long axis, apical four-chamber and apical long axis views. Average of all values was accepted as mitral valve thickness. The presence of AVT was accepted according to visual evaluations of two experienced cardiologists.

The mitral and aortic annular calcifications were defined as the presence of a dense localized, highly reflective area at the base of the mitral and aortic valves on the two-dimensional echocardiography, respectively.

Valvular regurgitation Valvular regurgitation was diagnosed using color-coded Doppler imaging proximal to the valve plane during its closure and extended into the chamber from the valve. These were sought from the parasternal long-axis, apical four to five, and two-chamber, apical long axis, and subcostal views.

Mitral regurgitation (MR) or tricuspid regurgitation (TR) were considered to be present if blue, green, or mosaic signals were seen originating from the mitral or tricuspid valves and spreading into the atriums during systole. Aortic regurgitation (AR) was considered to be present if red, yellow, or mosaic signals were seen

originating from the aortic valve and spreading into the left ventricle during diastole.

Pulmonary artery systolic pressure (PAP) is considered present whenever TR was recorded, by the modified Bernoulli equation (P=4V2). PAP = 4_(TR jet velocity)2 + 25% for proximate right atrial pressure [27] . PHT was defined as systolic pulmonary pressure over 35 mmHg. However, no case of pulmonary hypertension is present.

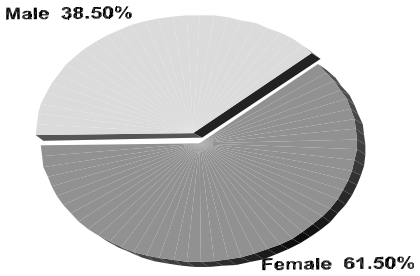
Assessment of left ventricular relaxation
The transmitral inflow pattern, the conventional method for the assessing left ventricular relaxation, was obtained from pulsed wave Doppler recording with the sample volume placed at the tips of mitral valve leaflets. Measurements consisted of the early (E) to late (A) peak velocity ratio of transmitral flow (E/A), the deceleration time of early transmitral filling (EDT, ms), and the isovolumic relaxation time (IVRT, ms). A reduced E velocity, a lengthened IVRT (>110 ms), a prolonged early diastolic deceleration time (>220 ms), and an E/A ratio < 1 were considered to indicate impaired left ventricular relaxation. [26]

General characteristics and laboratory findings of 26 patients with MPDs are shown in **Table 1**.

Age, sex and duration of the disease

References

The mean ages and duration of the diseases were not different in-between the MPD subgroups (P>0.05). Female: male ratio is seen in **Figure 1**. There are no sex differences in –between the



MPD subgroups. (p>0.05)

Figure 1– Sex ratio

Splenomegaly

The rates of splenomegaly is more frequent in PV than other MPD-subgroups (P<0.005). (See **table 1**)

Hypertension

Hypertension was mostly present in PV (P<0.05) . Hypertension was not significantly more frequent in patients with thromboembolic events compared to those without (P>0.05) (**Table 2**).

Thromboembolic events

Thromboembolic events were seen in 23.1% of the patients (**table 3 , figure 2**). The most frequently

noted thromboembolic events were those of coronary arteries (7.7%) and deep venous (7.7%) . These events were more often in PV (42.1%) than CML and MF (P < 0.05). (**table 1**)

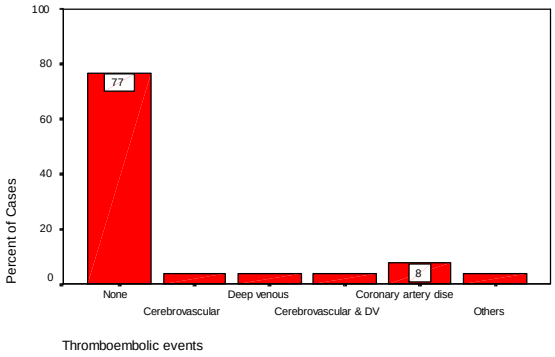


Fig 2 – Rate of thromboembolic events

Drugs used

Hydroxyurea was the most commonly (65.4%) used myelosupressive drug in MPD. (see **table 1**)

Hematological parameters

In hematological parameters, mean hemoglobin level was highest in PV (P < 0.005), and lowest in CML compared to other MPD subgroups (P < 0.05). Mean white blood cell count was not different in-between the MPD subgroups (P < 0.05). Mean platelet count was significantly higher in ET compared to other MPD subgroups (P < 0.005). (See **table 1**)

Death

Death occurs in 2 patients on 8-month follow up (7.7%) . (**Table 1**)

ECHOCARDIOGRAPHIC RESULTS

Echocardiographic findings of the patients with MPD and control group are shown in **Table 4**. (facing page)

Cardiac valvular lesions

Regurgitant lesions

We observed mild and more than mild valve regurgitations in 12 patients (46.1%) and two controls (6.7 %) (P<0.05) (Table **5**). Rates of regurgitations of other valves were not different in-between MPD subgroups and (P>0.05). (**Figure 3 , table 6**)

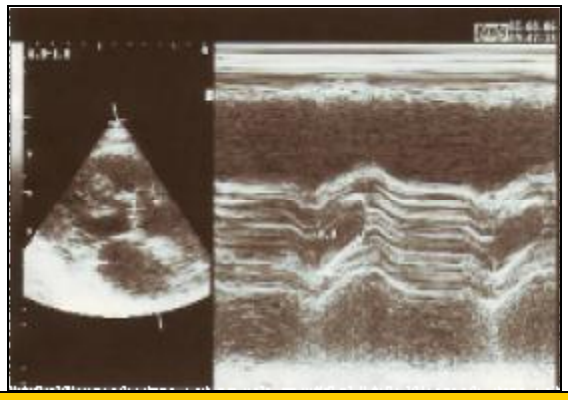


Figure 3- M-mode echocardiography shows the typical fluttering sign of aortic regurgitation obtained from a patient with PV with strong history of thrombosis

Annular calcifications

Calcification of mitral annulus was determined in three (5.4%) patients and no control (P>0.05). The rates of calcification of mitral annulus were not different in-between MPD subgroups and each MPD subgroup versus controls (P>0.05). (**Table 7 , Figure 4**)

Calcification of aortic valve is seen in one patient and no control . (p>0.05) (**Fig 4**)

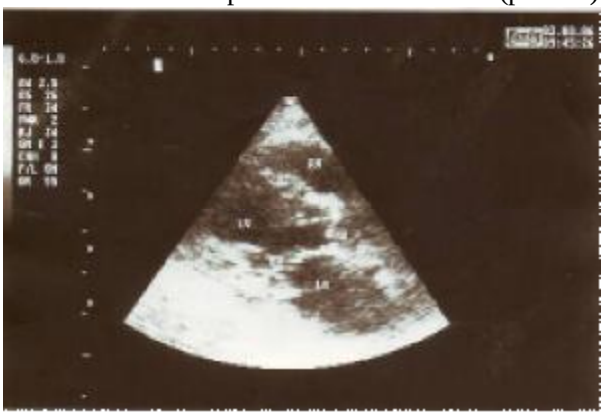


Fig 4– Two-dimensional four chamber view echocardiography reveals aortic thickening and calcification from the same patient in figure 3

Aortic valve Thickening (AVT)

The rate of AVT was not different in MPD compared to controls (P>0.05). The rates of AVT were not different in-between MPD subgroups and each MPD subgroup versus controls (P>0.05). (**Table 8**)

Other cardiac pathologies

PHT occurred in no patient with MPD or controls had PHT. The prevalences of diastolic dysfunction was not significantly different in-between MPD group versus controls, each MPD subgroup, and MPD subgroups versus controls (P>0.05). (See table 4).

Measurements of cardiac parameters

Aortic root dimension is significantly more larger in the MPDs group than control (P<0.005). PV has the largest aortic root in- between MPDs subgroups (P<0.05).
Measurements of end-diastolic diameter were not different between MPD and control groups but PV had the highest value in-between the MPD subgroups (P<0.05).
Measurements of ejection fraction and fractional shortening of left ventricle were higher in MPD groups than control (P<0.05 and <0.005) respectively.
Left atrial dimension of patients with MPD was larger than controls (P>0.05). Left atrial dimension was the largest in PV (P<0.005). E/A ratio was lower in MPD than control (P<0.05). (**Figure 7**)

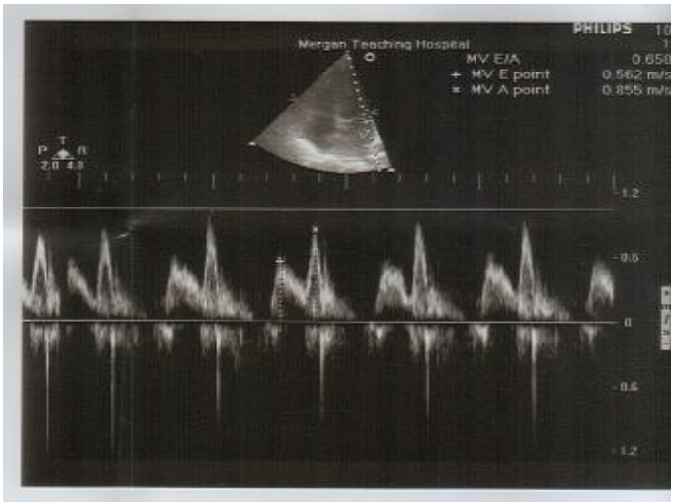


Fig 7- Echocardiograph taken from a patient with CML show that the E velocity is 0.562 and A velocity is 0.855 and E/A ratio = 0.657 (i.e < 1)

Other cardiac parameters including opening of aortic valve, end-diastolic and end-systolic diameters , thickness of interventricular septum and posterior wall were not different between MPD and control groups as well as the MPD subgroups P>0.05).

Mean hemoglobin levels in 8 patients with thrombocytosis was higher than 12 without thrombocytosis in MPD (p<0.05).

THROMBOCYTOSIS AND ECHOCARDIOGRAPHIC FINDINGS

The relationship between thrombocytosis and echocardiographic findings and thromboembolic events and echocardiographic findings were shown in **Table 9**..
(facing page)

Aortic root dimension was not different larger in patients without thrombocytosis from those without but it was greater than control (p<0.05) . The rates of all other echocardiographic parameters were not significantly

differing related to existence of thrombocytosis (P>0.05).

Thromboembolic Events and EchocardioGraphic Findings

Mean hemoglobin levels of 6 patients with thromboembolic events (13.3±0.3 g/dl) was significantly higher than 20 patients without thromboembolic events (10.7±2.9 g/dl) (P<0.05). End-diastolic diameter of left ventricle, opening of aortic valve and left atrial dimension were larger in patients with thromboembolic events than patients without thromboembolic events (P<0.05). The rates of all other echocardiographic parameters were not significantly different related to existence of thromboembolic events (P>0.05).

STATISTICAL ANALYSIS

All values were given as mean±standard deviation (S.D.). For comparison of scale parametric variables two-tailed, unpaired Student's t-test, and for comparison of nonparametric variables Wilcoxon W- and Mann–Whitney U-tests were used. One-way ANOVA test was performed for comparison between MPD subgroups. Pearson m2, Fisher's exact and continuity correction (Yates) tests were used for comparison of nominal variables. The data were analyzed by the computer software programme Statistical package for Social Sciences (SPSS 11.0, Chicago) for Windows was used for all tests. A P value <0.05 or less was considered as statistically significant.

TABLES **MPD**

Table 1-General characteristics and laboratory Findings in

Characteristics	ET [n(%)]	CML [n(%)]	MF [n(%)]	PV [n(%)]	MPDs [n(%)]
Number of cases	1	16	2	7	26
Sex (F/M)	1 / 0	10 / 6	2 / 0	3 / 4	16 / 10
Mean Age (years)	40	44.6 ± 15.4	62 ± 4.2	58.4 ± 17.7	49.5 ± 16.5
Duration of Disease (month)	36	26.1 ± 24.9	40.5 ± 44.5	31.6 ± 26.6	26.9 ± 24
Splenomegaly	1 (100)	9 (56.25)	1 (50)	**7 (100)***	18 (69.2)
Hypertension	1 (100)	**1 (6.25)**	1 (50)	3(42.9)*	6 (23.1)
Oedema	0 (0)	3 (18.75)	0 (0)	1 (14.2)	4 (15.4)
Hemorrhagic events					
Gastrointestinal	0 (0)	1 (6.25)	0 (0)	1 (14.3)	2 (7.7)
Intracerebral	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (3.8)
Cutaneous	0 (0)	3 (18.75)	0 (0)	1 (14.3)	4 (15.4)
Thrombotic events					
Cerebrovascular	0 (0)	1 (6.25)	0 (0)	1 (14.3)	2 (7.7)
Deep venous	0 (0)	0 (0)	0 (0)	**2 (28.6)***	2 (7.7)
Coronary artery	0 (0)	1 (6.25)	0 (0)	1 (14.3)	2 (7.7)
Portal vein	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Peripheral artery	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cavernous sinus	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missed abortion	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	1 (6.25)	0 (0)	0 (0)	1 (3.8)
Death	0 (0)	1 (6.25)	1 (50)	0 (0)	2 (7.7)
Hematological parameters					
Hemoglobin level (g/dl)	12	**11.5 ± 1.9***	10 ± 1.4	**14.6 ± 1.4****	12.2 ± 2.3
White blood cell count (x10E3 /µl)	14.2	73.8 ± 103.6	12.4 ± 0.49	12.6 ± 6.8	50.3 ± 85.9
Platelet count (x10E3 /µl)	**3000****	297.8 ± 177.7	195 ± 190.9	302.6 ± 128	395.1 ± 554.5
Thrombocytosis(>400x10E3 /µl)	1 (100)	6 (37.5)	0 (0)	1 (14.3)	8 (30.8)
Drugs					
Hydroxyurea	1 (100)	10 (62.5)	1 (50)	5 (71.4)	17 (65.4)
Gleevec		10 (62.5)			10 (38.5)
Warfarin				2 (28.6)	2 (7.7)
Interferon	1 (100)	8 (50)	1 (50)		10 (38.5)
Aspirin		2 (12.5)		3 (42.8)	5 (19.2)
None			1 (50)		

Table 2-Correlation between hypertension and thromboembolic events

		Thromboembolic events		
Hypertensior		**Present**	**Absent**	**Total**
Present	No.	2	4	6
	%	33.3%	20.0%	23.1%
Absent	No.	4	16	20
	%	66.7%	80.0%	76.9%
Total	No.	6	20	26
	%	100.0%	100.0%	100.0%

a.Correlation Not Significant (p value>0.05)

Tab le3- Rate of thromboembolic events in the MPD subgroup

Echocardiographic findings	ET [n(%)]	CML [n(%)]	MF [n(%)]	PV [n(%)]	MPDs [n(%)]	Control [n(%)]
Number of cases	1	16	2	7	26	30
Calcification of mitral annulus	0 (0)	2 (12.5)	0 (0)	1 (14.3)	3 (11.5)	0 (0)
AVT	0 (0)	2 (12.5)	0 (0)	1 (14.3)	3 (11.5)	0 (0)
Valve regurgitation						
MR	0 (0)	5 (31.25)	1 (50)	3 (42.9)	**9 (34.6) ****	2 (6.7)
AR	0 (0)	1 (6.25)	0 (0)	2 (28.6)	3 (11.5)	0 (0)
TR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PHT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diastolic dysfunction of left ventricle	0 (0)	1 (6.25)	0 (0)	2 (28.6)	0 (0)	5 (16.6)
Aortic root (mm)	32	29.9 ± 37	28.5 ± 2.1	**33.8 ± 5.6 ***	**31 ± 4.4 ****	34.2 ± 3.2
Opening of aortic valve (cm)	1.5	1.8 ± 0.3	1.8 ± 0.1	1.7 ± 0.4	1.7 ± 0.3	1.8 ± 0.1
Left atrial dimension (mm)	32	30.1 ± 4.5	**37.5 ± 2.1 ***	30.4 ± 3.7	30.8 ± 4.5	30.9 ± 2.6
End-systolic diameter of left ventricle (mm)	49	37.7 ± 8.4	30 ± 5.7	31.4 ± 5.6	35.8 ± 8.3	34.3 ± 6
End-diastolic diameter of left ventricle (mm)	32	45.6 ± 7.7	48.5 ± 10.6	**50.6 ± 5.5 ***	46.6 ± 7.8	50 ± 4.8
Ejection fraction of left ventricle	60	63.9 ± 10.3	67.5 ± 3.5	71.1 ± 6.9	**66 ± 9.3 ***	71 ± 6.3
Fractionation shortening of left ventricle	30	29.6 ± 4.7	30	35.6 ± 6.9	**31.3 ± 5.6 ****	34.7 ± 3.9
Thickness of interventricular septum (mm)	9	9.9 ± 0.9	9.5 ± 2.1	10.4 ± 2.7	10 ± 1.6	10.3 ± 0.9
Thickness of posterior wall (mm)	9	9.3 ± 0.9	10 ± 1.4	10 ± 2.3	9.5 ± 1.4	10.1 ± 0.6
E velocity (m/s)	0.7	9.7 ± 24	1.1 ± 0.7	4.2 ± 4.2	7.2 ± 19	7.8 ± 4.2
A velocity (m/s)	0.5	6.9 ± 17.6	1 ± 0.1	4.5 ± 4.8	5.6 ± 14	7.6 ± 3.7
E/A ratio	1.3	1.2 ± 0.4	0.8 ± 0.2	1 ± 0.3	**1.1 ± 0.4 ***	1.4 ± 0.5

Table 4 –Echocardiographic Findings in MPD and control group

			Type of disease				
Thromboembolic even			ET	CML	Polycythaemia vera	Myelofibrosis	Total
	None	No	1	13	4	2	20
		%	100.0%	81.3%	57.1%	100.0%	76.9%
	Cerebrovascular	No		1			1
		%		6.3%			3.8%
	Deep venous	No			1		1
		%			14.3%		3.8%
	Cerebrovascular &	No			1		1
		%			14.3%		3.8%
	Coronary artery di	No		1	1		2
		%		6.3%	14.3%		7.7%
	Others	No		1			1
		%		6.3%			3.8%
Total		No	1	16	7	2	26
		%	100.0%	100.0%	100.0%	100.0%	100.0%

a. Correlation is not significant

Table 5- Regurgitant lesions in MPDs and control group

	Mitral regurgitations		Aortic regurgiattions	
	No	Percent	No	Percent
MPDs Group	9*	34.6%	3*	11.5%
Control	2	6.7%		
Total	11	19.6%	3	5.4%

Correlation is significant

Table 6- Rate of regurgitant lesions in between the MPDs subgroups

		Regurgitating Valve	
Cases category		**Mitral regurgitations**	**Aortic regurgiattions**
CML	No	5	1
	%	31.3%	6.3%
Polycythaemia vera	No	3	2
	%	50.0%	33.3%
Myelofibrosis	No	1	
	%	33.3%	
Control	No	2	
	%	6.7%	
Total	No	11	3
	%	19.6%	5.4%

Table 7– Annular calcification in MPDs and control group

	Thrombosis		Thrombocytosis		
Echocardiographic findings	**Present**	**Absent**	**Present**	**Absent**	**Control [n(%)]**
Number of cases	6	20	8	18	30
Calcification of mitral annulus	2 (33.3)	1 (5)	1 (12.5)	2 (11.1)	0 (0)
AVT	2 (33.3)	1 (5)	1 (12.5)	2 (11.1)	0 (0)
Valve regurgitation					
MR	2 (33.3)	7 (35)	3 (37.5)	6 (33.3)	2 (6.7)
AR	1 (16.7)	2 (10)	1 (12.5)	2 (11.1)	0 (0)
TR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PHT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diastolic dysfunction of left ventricle	1 (16.7)	2 (10)	0 (0)	3 (16.7)	5 (16.6)
Aortic root (mm)	32.3 ± 5.3	30.6 ± 4.2	**28.8 ± 3.5 ***	**31.9±4.5**	34.2 ± 3.2
Opening of aortic valve (cm)	**1.4 ± 0.4 ****	1.8±0.2	1.7 ± 0.3	1.8 ± 0.3	1.8 ± 0.1
Left atrial dimension (mm)	**27.7 ± 5.9 ***	31.8 ± 3.6	31.6 ± 2.3	30.4 ± 5.2	30.9 ± 2.6
End-systolic diameter of left ventricle (mm)	37.5 ± 5.7	35.4 ± 9	39.4 ± 8.6	34.3 ± 7.9	34.3 ± 6
End-diastolic diameter of left ventricle (mm)	**52.8 ± 5.3 ***	**44.8±7.5**	47 ± 9.5	46.4 ± 7.2	50 ± 4.8
Ejection fraction of left ventricle	61.3 ± 13.8	67.4 ± 7.4	61.6 ± 7.6	67.9 ± 9.5	71 ± 6.3
Fractionation shortening of left ventricle	30 ± 11.1	31.7 ± 2.9	29.8 ± 4.1	32 ± 6.2	34.7 ± 3.9
Thickness of interventricular septum (mm)	10.2 ± 2.5	9.9 ± 1.2	10.1 ± 0.8	9.9 ± 1.8	10.3 ± 0.9
Thickness of posterior wall (mm)	9.7 ± 1.7	9.5 ± 1.4	9.8 ± 0.5	9.4 ± 1.7	10.1 ± 0.6
E velocity (m/s)	2.5 ± 4	8.6 ± 21.5	1.2 ± 0.5	9.9 ± 22.5	7.8 ± 4.2
A velocity (m/s)	3.1 ± 5.3	8.3 ± 15.7	1 ± 0.4	7.6 ± 16.5	7.6 ± 3.7
E/A ratio	0.9 ± 0.4	1.2 ± 0.4	1.3 ± 0.1	1.1 ± 0.4	1.4 ± 0.5

Discussion

In previous studies, cardiac involvement, including coronary arterial thrombosis, myocardial infarction, pulmonary hypertension (PHT), asymptomatic pericardial effusion, cardiac tamponade, intractable cardiac failure due to intraventricular thrombosis, and stenosis of aortic, mitral valves, even requiring surgical treatment had been reported in MPD [8,19,28].

Valvular Lesions

To the best of our knowledge, there is only two large studies in which cardiac lesions were evaluated by echocardiograpy in MPD by Reisner et al [20] and Kadikoylu et al [21].

Reisner et al [20] (**Table 10**) noted valvular lesions compatible with non-bacterial thrombotic endocarditis in 63% of patients with MPD. In their study, any of vegetation-like lesions, valvular thickenings, regurgitations, and annular calcifications were accepted as valvular lesions. Whereas valvular lesions in non-bacterial thrombotic endocarditis are remarkably typical and notably different from the morphology found in other causes of valvular involvement, such as chronic rheumatic valvular diseases [20]. In echocardiographic evaluation, a mass localized on a valve can be defined as vegetation-like lesion [29]. Aortic and mitral annular calcifications may simulate a valvular mass in elderly people. So the discrimination of these calcifications from vegetations or vegetation-like lesions may not be reliable by only TTE. Transoesophageal echocardiography (TEE) is shown to be superior for this purpose [30]. Reisner et al. [31] had reported vegetation-like lesions in five (one in mitral valve, four in aortic valves) patients (16%), however, all patients with vegetation-like lesions on aortic valve leaflets were older than 64 years. We report vegetation-like lesion on mitral and aortic valves in three cases with MPD patients (5.4%). A distinctive pattern observed in patients with nonbacterial thrombotic endocarditis is diffuse thickening of the aortic or mitral valve leaflets. AVT and calcification of mitral or aortic valve were not significantly different in-between MPD patients and controls in our study. There are several limitations in evaluation of valvular thicknesses by transthoracic echocardiography:

1. the measurements are observer dependent and average of several measurements of mitral valve leaflets in certain views by using zoom process may increase the reliability of the results.
2. focal and generalized thickenings of one or more aortic leaflets without associated valvular stenosis are not infrequent. Focal thickening is commonly seen with normal aging process [31].
3. We not mentioned the interobserver and intraobserver variabilities that are used by Kadikoylu et al [32] that may increase the diagnostic yield.

In previous studies, it was reported that valvular regurgitations might be found in healthy people [35]. Singh et al. [32] had detected mild or more than mild graded MR in 19%, TR in 16%, and AR in 11% of healthy adults. The rates of valve regurgitations in our controls were compatible with Reisner's study. The prevalence of valvular regurgitations was 33% in their MPD patients and this rate was significantly higher than their controls. In our study, the rates of valvular regurgitations were common in-between MPD group (46.1%) , as mitral (34.6%) and aortic (11.5%) , and controls (6.7%). Among our MPD subgroups, MR in CML was more common compared to controls ($P<0.05$). This finding should be further evaluated as only one patient of CML with valvular lesion was reported in the literature [33].

In the second study by Kadikoylu et al valvular regurgitatioins was not different in-between MPD group and the control ($p>0.05$) although mitral regurgitations in CML is more prominent. [21]

Table 10- Valvular regurgitation in this study and comparison with other studies

The Study	Rate of regurgitant lesions in MPD cases	Rate of regurgitant lesions in Control	**Clinical significance**
Reisner et al	33%	6.6%	**Significant**
Kadikoylu et al	39%	27%	**Not significant**
This study	**46.1%**	**6.7%**	**Significant**

Pulmonary Hypertension

In our study (**Table 11**) , PHT was not present in MPD group or control in comparison with the studis of Reisner's , Kadikoylu et al which show PHT in five and six patients with prevalence 17% and 13% respectively . These patients had strong history of thromboembolic events (P<0.05) as compared to controls (P < 0.05). In Reisner's study, the prevalence of PHT (17%) in MPD was comparable with Kadikoylu et al (13%). All Reisner's patients with PHT had TR While 5 out of 6 patients of Kadikoylu et al had TR. Reisner et al. concluded that PHT was another relatively common and clinically important finding in MPD. In Kadikoylu et al study, PHT was the most prominent cardiac pathology in MPD (especially in CML, MF and thromboembolic events subgroups) compared to controls ; the reason for absence of PHT in our study is that no TR is detected by echocardiography in these patient

s.

Table 11 .- Rates of pulmonary hypertension in various studies

The Study	**PTH**
Kadikoylu et al	**17%**
Reisner et al	**13%**
This study	**0%**

However, transoesophageal echocardiography (TEE) and right heart catheterization are needed to clarify the presence of PHT in these patients as done by the following investigators:

1. Dingli et al. [38] reported a retrospective series of 26 cases with PHT (median PAP: 71 mmHg) and MPD. The cause of death was available for 18 of their 21 deceased patients. Eight patients (38%) died from congestive heart failure, four patients (19%) died from pneumonia, two patients died from sudden cardiac death, two patients died from hemorrhagic strokes, one patient died from septicemia, and another patient died from uncontrollable seizures. The median survival time after the diagnosis of PH was 18 months (range, < 1–108 months). However, no autopsy examinations were conducted in their study. There are some other case reports on the association of MPD with PHT.
2. Garcia-Manero et al. [35] reported six patients with PHT accompanying MF secondary to MPD. In two of their six patients post-mortem evaluation had revealed pulmonary parenchymal infiltration by hematopoietic cells as the cause of PHT.
3. Nand and Orfei [19] reported two patients with PHT and PV. In the postmortem examination of one, the lungs showed numerous microthrombi in the septal and prelobular arterioles.
4. Marvin and Spellberg [36] reported a patient with MF and PHT secondary to thrombocytosis.
5. Hill et al. [37] reported a case of ET with PHT as a consequence of alveolar capillary plugging by malignant megakaryocytes.

In MPD, with the exception of CML, PHT may be observed as related to many factors such as thrombocytosis, pulmonary platelet activation,

thrombin generation, pulmonary microthrombosis, alveolar capillary plugging by malignant megakaryocytes, haematopoietic infiltration of lung parenchyma, myeloid metaplasia, left ventricular failure, and thromboembolism [29,37-40] .

Other Echocardiographic

Parameters

In the study by Kadikoylu et al left atrial dimension and thickness of interventricular septum in MPD were higher than controls. These differences might be related to the presence of systemic and PHT in MPD cases. [21] In their study , left atrial dimension, interventricular septum, and posterior wall thicknesses in patients with MF were significantly higher than both other MPD subgroups and controls. These findings are unexplained , however, in one study [41] heart failure was reported in 14 (13%) of 106 MF patients. In another study [42] heart failure was at least partially ascribable to posttransfusion hemochromatosis in three (5%) of 60 MF cases. Although they did not detect hemochromatosis clinically in our cases, none were examined with biopsy for this purpose. However , in our study left atrial dimension was higher than control and high in PV than other MPD subgroups ($p<0.05$) but thickness of interventricular septum is not different in-between MPD group and control ($p>0.05$) . Other cardiac measurements were not different.

Measurements of ejection fraction and fractional shortening of left ventricle were lower in MPD groups than control ($P<0.05$ and <0.005) respectively. The rates of all other echocardiographic parameters were not significantly different related to existence of thromboembolic events ($P>0.05$).

In the study by Kadikoylu et al, patients with thrombocytosis, PHT, cardiac valvular lesions, and regurgitations were not more frequent compared to controls. In the comparison of patient subgroups with and without thromboembolic events, there were no differences for cardiac lesions except the measurements of left atrial dimension and end-diastolic diameter of left ventricle. These differences might be related to higher rate of hypertension in MPD cases with thromboembolic events. However, in our study the correlation between hypertension and thromboembolic events was not significant ($p>0.05$) .

ThrOmboembolic Events And Echocardiographic Findings

Kadikoylu et al [21] rates of thromboembolic events in MPD were 44%; our study rates of thromboembolic events were 23.1% of MPD cases. This is attributed to the fact that Kadikoylu et al take his bulk of MPD cases from ET and PV where the rates of thromboembolic complications are relatively frequent (0-17% and 20-63% respectively) and our bulk of MPD cases is from CML where the rates of thromboembolic events is relatively infrequent (0-6%) . Most thromboembolic events seen in our study are coronary artery (7.7%) and deep venous (7.7%) which is not compatible with the study of Kadikoylu et al which show that the coronary arteries are involved in 22% of cases though Aspar et al [43] reported that the associated risk of coronary artery disease is low which contraray to the common belief. Thromboembolic events in MPD may result from several factors. The contribution of elevated platelet counts to thromboembolism is controversial [38, 44, 45]. A number of functional and biochemical abnormalities of platelets have been reported in MPD [38, 39,43] .

Compatible with the study of Kadikoylu et al [21] we did not find a relationship in-between thrombocytosis and thromboembolic events in this study .

Also, our study results were compatible with the study by Kadikoylu et al [21] in that patients with thromboembolic events had higher hemoglobin levels than those without thromboembolic events. Increased red cell counts and hyperviscosity are considered more important than the increased platelet counts in the formation of thrombus [17].

Valvular endothelial damage and hypertension are also other probable factors in the pathogenesis of thromboembolic events in MPD [39,43, 46]

Death occurs in 2 cases throught the duration of the study .One case was CML who died from bleeding complications (intracranial haemorrhage proved by brain CT scan) secondary to leukaemic transformation (blastic crises) and the other case is newly diagnosed MF who died after she developed jaundice and ascites with features suggestive of Budd-chiari syndrome . [8]

However, Thrombohaemorrhagic complications were less frequent after phlebotomy in PV and after therapy with hydroxyurea and imatinib mesylate in CML . The institution of cytoreduction therapy soon after the diagnosis was made may explain the reduced incidence of complications later in the disease. [8,43]

The results of our study showed that cardiac valvular lesions were more common in MPD although are not correlated with thromboembolic events in MPD, and are not correlated with thrombocytosis. Some echocardiographic parameters are changed with related to the thromboembolic events.

We recommend the following:

1. Further evaluation of the cardiac changes in MPD subgroups with extended studies including TEE and right-heart catheterization would be appropriate.
2. Longer follow up periods
3. Echocardiographic evaluation could be a part of evaluation of any case with MPD especially those with strong history of thrombosis and longer duration of the disease
4. The institution of aspirin and/or cytoreductive therapy soon after the diagnosis is crucial especially in older age , long duaration of the disease or with high risk factors for thrombosis . PV patients should receive aspirin once diagnosis is established if they do not have contraindications_

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