Pak Heart J

RHEUMATIC MITRAL STENOSIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES: DO THEY AFFECT MEAN PLATELET VOLUME, RIGHT AND LEFT VENTRICLES ?

Inas Eweda [1], Gehan Elassal [2]

[1]Cardiology Department, Ain Shams University Hospitals, Abbassia, Cairo-Egypt.

[2]Chest Department, Ain Shams University, Cairo-Egypt

Inas Eweda

Cardiology Department, Ain Shams University Hospitals, Abbassia, Cairo-Egypt.

E-Mail: ime_1940@yahoo.com

Date Received: September 17,2016

Date Revised: September 20,2016

Date Accepted: September 21,2016

Contribution
IE did literature review, research design and finalized the manuscript. GE helped in data collection, analysis in the final draft. All authors contributed significantly to the submitted manuscript.

All authors declare no conflict of interest.

This article may be cited as: Eweda I, Elassal G. Rheumatic mitral stenosis and chronic obstructive pulmonary diseases: do they affect mean platelet volume, right and left ventricles ?. Pak Heart J 2016;49(04): 164 -71.

ABSTRACT

Objective: The aim of this study was to find out the effects of two different groups of causes of pulmonary hypertention (PH) on mean platelet volume(MPV), left and right ventricles by echocardiography.

Methodology: This case control study was conducted in Cardiology Department of Ain Shams University Hospital Cairo , Egypt from 1st January 2015 to 30th June 2015.The study included consecutive patients from outpatient clinics suffering from pulmonary hypertension, chronic obstructive pulmonary disease (COPD) and rheumatic mitral stenosis (RMS). The healthy persons were matched in age and gender. Non COPD, non-rheumatic constituted the control group. Echocardiographic study, respiratory function tests and mean platelet volume (MPV) of study population were done. $P<0.05$ was taken as significant.

Results: This study included ninety persons. About thirty patients had COPD and thirty patients had rheumatic mitral stenosis. Additionally thirty healthy individuals were also enrolled. MPV was 11.29 $\pm$ 2.39 fl in patients suffering from COPD, 11.06 $\pm$ 1.56 fl in patients with RMS and 9.61 $\pm$ 1.02 fl in control persons ($p=0.007$). As regards to the left side of the heart there were significant statistical difference only in end systolic dimension, aortic root and left atrial dimensions between the three groups. RMS effected the right side of the heart significantly . When subgroup analysis was done, patients with rheumatic mitral stenosis showed significant differences between all the studied parameters while patients with COPD did not show this significance.

Conclusions: MPV is higher in patients with different causes of PH than the normal subjects but the effect on both sides of the heart are different according to the cause of PH.

Keywords: Pulmonary hypertension, rheumatic mitral stenosis, COPD

INTRODUCTION

Increase of resting pulmonary artery pressure more than 25mmHg is defined as pulmonary hypertension (PH).[1] All conditions that alter pulmonary vasculature can lead to pulmonary hypertension which is a hemodynamic definition. A clinical classification was approved in order to individualize different causes of PH having same hemodynamic criteria, pathological finding and management.[2] There are five groups of disorders that lead to PH, group two include those who suffer from left heart disease and group three are those who suffer from chronic lung disease and/or hypoxia.[3-5] This classification was updated in 2013, classifying PH due to valvular disease as class (2.3) and chronic obstructive pulmonary disease as class (3.1).[6]

Chronic obstructive pulmonary disease (COPD) is the second commonest cause of PH after left sided heart disease.[7] The significance of the right heart involvement in healthy and diseased individuals has been illustrated in recent work. Obesity, exercise and usual cardiovascular risk factors effect right ventricle in otherwise healthy individuals.[8,9]

PH is the elevation of pulmonary artery pressure which can be a consequence of thrombosis, remodeling and vasoconstriction which all lead to increase pulmonary vascular resistance. Platelet activation occurs in patients of PH as proved by previous studies.[10] Mean platelet volume is a marker of platelet activation and is recognized as a risk predictor of cardiovascular diseases.[11]

The aim of this study was to observe and compare the effects of two different classes of pulmonary hypertension, COPD and RMS on MPV, right ventricle and left ventricle.

METHODOLOGY

This case control study was conducted in Cardiology Department of Ain Shams University Hospital Cairo , Egypt from 1st January 2015 to 30th June 2015. Patients with COPD , rheumatic mitral stenosis from outpatients clinic were included in the study. Additionally we enrolled healthy individuals with no history of COPD or rheumatic heart disease . They were matched in age and gender ad were labeled as controls. Before inclusion, informed written consent was obtained from each patient after full explanation of the study protocol, and the protocol was reviewed and approved by our institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013.

Pulmonary function tests (PFT) were done in the pulmonary function unit by using the Flow-Volume curves (FVC); the subject performed FVC maneuver by inspiring fully and then exhaling as rapidly as possible, to complete the loop, the subject inspired as rapidly as possible from the maximal expiratory level back to maximal inspiration. The criteria for diagnosis of COPD was according to the GOLD 2013 FEV1/FVC less than 70% of the normal.

Blood samples were drawn after a fasting period of 12 h. We measured MPV in a blood sample collected in EDTA. The measurements were performed immediately after blood sampling in order to prevent in vitro platelet activation. A Beckman Coulter Gen-S Hematology Analyzer was used for whole blood counts.

This was performed to all subjects according to the same protocol with use of GE Medical system Vivid 7 ultrasound machine equipped with 2-4M Hz sector transducer probe. Routine echocardiography with the standard projections was done initially and followed by Doppler flow tracing registration at the level of mitral and tricuspid valves. All echo-Doppler measurements were analyzed by the average of five cardiac cycles, to minimize difference during the breath cycles.

Parameters obtained through parasternal approaches in the M-mode projection were analyzed: left ventricular end diastolic diameter (EDD), left ventricular end systolic diameter (ESD), interventricular septum (IVS), left ventricular posterior wall thickness (PW), aortic root dimension (Ao) and left atrial diameter (LA). The assessment of the left ventricular systolic function consisted of left ventricular ejection fraction (EF%) obtained according to Simpson´s formula.

Right ventricular global systolic function was assessed as tricuspid annular plane systolic excursion (TAPSE), by two-dimensional difference of end-diastolic and end-systolic lines (in mm) traced between the center of the ultrasound fan origin and the junction of right ventricular lateral tricuspid annulus, in apical four-chamber view.

The right ventricle was assessed in the apical four-chamber view by measuring basal, mid-cavity and longitudinal dimensions. The right ventricular lateral wall thickness was also measured in this view.

We used the same GE Vivid Seven machine using a commercially available imaging system equipped with a 2-4 MHZ transducer and secondary harmonic imaging to optimize endocardial border visualization. The spectral pulsed Doppler signal filters were adjusted until a Nyquist limit of 15-20 cm/s and the minimal optimal gain was used. From the apical four chamber view, the longitudinal tricuspid annular velocities were recorded from lateral right ventricular site using PW-DTI. The values from the above site were used to assess global systolic and diastolic function. Three major velocities were taken into account: the positive peak systolic velocity when the tricuspid ring moved towards the cardiac apex due to longitudinal contraction of the RV (S) and two negative diastolic

velocities when the tricuspid annulus moved towards the base away from the apex, one during the early phase of diastole (E) and the other in the late phase of diastole (A). A mean of five consecutive cycles was used to calculate all echo-Doppler parameters.

Data are presented as mean ± SD. The Chi-squared test was used to compare differences between proportions. The Analysis of variance (ANOVA) test was used for analysis of continuous data. Post- Hoc test was performed for comparison between each two of the three variables. A probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS version 12.0 statistical package (SPSS Inc., Chicago, IL, USA). Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

RESULTS

Total of 90 patients were included in the study. There was no significant difference of age and gender between the three studied groups . The mean age was 49.97 ± 8.45 years for the control group, 48.57 ± 6.82 for COPD group and 48.2 ± 5.53 years for MVD group. Male patients were 15 (50%) in control group, 22 (73.3%) in COPD group and 17 (56.7%) in MVD group.

The results of the respiratory function test are shown in table 1 where there were significant statistical differences between the three groups and individual groups. In the COPD group, the age was above 40 years old and FEV1/FVC ratio < 0.7 as the diagnostic criteria for the group. The mitral valve group showed decreased FVC level with normal FEV1/FVC ratio (i.e restrictive pattern) ($p<0.05$).

This study showed that MPV was 11.29 ± 2.39 fl in patients suffering from COPD, 11.06 ± 1.56 fl in patients with RMS and 9.61 ± 1.02 fl in control persons ($p=0.007$). There was no significant statistical difference between COPD and RMS patients. Similarly there was no significant statistical difference between the three groups as regards the platelets ($p>0.05$) as shown in table 2 .

Table 1: Respiratory Function Tests of the Pulmonary Hypertension Subgroups and Healthy Control Subjects (n=90)

Parameter	COPD Mean ±SD	MS Mean ±SD	Control Mean ±SD	ANOVA p-value	P1	P2	P3
MMEF	23.61 ± 10.98	91.24 ± 39.05	116.47 ± 36.98	0.000	0.000	0.043	0.000
FEV1	43.63 ± 15.15	83.98 ± 19.83	96.66 ± 12.96	0.000	0.000	0.022	0.000
FVC	57.42 ± 17.45	70.72 ± 24.66	87.09 ± 13.15	0.000	0.000	0.013	0.056
FEV1/FVC	59.03 ± 7.27	93.23 ± 6.78	95.10 ± 6.63	0.000	0.000	0.384	0.000

COPD=chronic obstructive pulmonary disease, MS=mitral stenosis,MMEF=maximal mid expiratory flow, FEV1=forced expiratory volume 1, FVC=forced vital capacity, MPV=mean platelet volume

P1: Comparison between Control group and COPD group. P2: Comparison between Control group and MS group. P3: Comparison between COPD group and MS group. P >0.05: NS, P <0.05: S, P <0.01: HS

Table 2: Laboratory Findings in Pulmonary Hypertension Subgroups and Healthy Control Subjects (n=90)

Parameter	COPD Mean ±SD	MVD Mean ±SD	Control Mean ±SD	ANOVA p-value	P1	P2	P3
MPV (fl)	11.29 ± 2.39	11.06 ± 1.56	9.61 ± 1.02	0.007	0.006	0.001	0.726
PLT (L)	259.70 ± 102.74	256.30 ± 109.27	258.15 ± 78.24	0.994	0.957	0.951	0.920

COPD=chronic obstructive pulmonary disease, MS=mitral stenosis, MPV=mean platelet volume, PLT=platelet

P1: Comparison between Control group and COPD group.
P2: Comparison between Control group and MS group.

P3: Comparison between COPD group and MS group.

P >0.05: NS, P <0.05: S, P <0.01: HS

Table 3: Echocardiographic Parameters of the Left Side of the Heart of study population(n=90)

Parameter	COPD Mean ± SD	MS Mean ± SD	Control Mean ± SD	ANOVA p-value	P1	P2	P3
IVS (mm)	9.95 ± 1.43	9.50 ± 1.57	9.00 ± 1.03	0.097	0.021	0.241	0.350
EDD (mm)	44.35 ± 5.03	48.15 ± 6.01	46.30 ± 6.87	0.145	0.312	0.370	0.036
ESD (mm)	27.20 ± 5.36	32.25 ± 5.51	30.45 ± 4.27	0.009	0.040	0.256	0.006
PW (mm)	10.20 ± 1.28	9.90 ± 1.17	9.50 ± 1.00	0.167	0.062	0.251	0.443
EF (%)	66.35 ± 6.52	62.05 ± 6.57	65.95 ± 5.89	0.068	0.840	0.055	0.045
AO (mm)	28.35 ± 3.18	31.35 ± 3.66	30.10 ± 2.95	0.019	0.079	0.242	0.009
LA (mm)	38.60 ± 4.51	52.30 ± 7.62	36.10 ± 2.55	0.000	0.037	0.000	0.000

COPD=chronic obstructive pulmonary disease, MS=mitral stenosis, IVS=interventricular septum thickness, EDD=end diastolic dimension, ESD=end systolic dimension, PW=left ventricular posterior wall thickness, EF=ejection fraction, AO=aortic root, LA=left atrium

P1: Comparison between Control group and COPD group.
P2: Comparison between Control group and MS group.
P3: Comparison between COPD group and MS group.
P >0.05: NS, P <0.05: S, P <0.01: HS

Table 4: Echocardiographic Parameters of the Right Side of the Heart of study population(n=90)

Parameter	COPD Mean ± SD	MS Mean ± SD	Control Mean ± SD	ANOVA p-value	P1	P2	P3
TAPSE (mm)	2.10 ± 0.55	2.14 ± 0.40	5.87 ± 7.84	0.015	0.038	0.040	0.793
TR (mmHg)	39.00 ±9.46	43.75 ± 17.01	10.60 ± 3.47	0.000	0.000	0.000	0.282
RVSP (mmHg)	49.00 ± 9.46	53.75 ± 17.01	20.60 ± 3.47	0.000	0.000	0.000	0.282
PAT (msec)	81.20 ± 9.96	80.45 ± 10.04	132.00 ± 16.34	0.000	0.000	0.000	0.814
TV S (cm/sec)	14.25 ± 4.77	11.55 ± 2.67	14.95 ± 5.28	0.042	0.662	0.014	0.033
TV E (cm/sec)	11.00 ± 3.80	11.10 ± 3.40	15.50 ± 3.93	0.000	0.001	0.001	0.931
TV A (cm/sec)	11.75 ± 4.88	17.70 ± 4.09	11.90 ± 2.71	0.000	0.905	0.000	0.000
RV Base (mm)	33.00 ±6.70	35.60 ± 7.69	25.40 ± 6.18	0.000	0.001	0.000	0.262
RV Mid (mm)	26.20 ± 7.82	27.20 ± 6.01	19.15 ± 5.05	0.000	0.002	0.000	0.653
RV Long (mm)	54.00 ± 8.72	59.20 ± 8.92	31.85 ± 8.29	0.000	0.000	0.000	0.070

COPD= chronic obstructive pulmonary disease, MS=mitral stenosis, TAPSE = tricuspid annular plane systolic excursion, TR=tricuspid regurge, RVSP=right ventricular systolic pressure, PAT=pulmonary acceleration time, TV=tricuspid valve, S,E,A= Doppler velocities, RV=right ventricle.

P1: Comparison between Control group and COPD group.
P2: Comparison between Control group and MS group. P3: Comparison between COPD group and MS group.
P >0.05: NS, P <0.05: S, P <0.01: HS

Echocardiographic data of left ventricular assessment are shown in table3. Left ventricular end systolic, aortic root and left atrial dimensions were the only parameters that showed significant statistical difference between the patients suffering from pulmonary hypertension and healthy subjects. End systolic and artic root dimensions were less in COPD patients. Left atrium was increased in size in patients suffering from rheumatic mitral stenosis. When subgroup analysis was done, we found significant statistical difference between RMS and COPD in EDD, ESD, EF, Ao and LA dimensions.

Table 4 shows echocardiographic parameters of the right side of the heart. There were significant statistical differences between all the studied parameters. When subgroup analysis was done, patients with rheumatic mitral stenosis showed the significant differences between all the studied parameters while patients with COPD did not show this significance in T-velocity wave and T-velocityA wave.

DISCUSSION

The quantitative assessment of the right ventricle is very difficult due to the trapezoidal anatomy of it. Recently various methods as magnetic resonance and radionuclide ventriculography have been used to achieve this goal but none of them was established as the gold standard. [16] In reality, clinicians strongly depend on two-dimensional, M-mode, Doppler echocardiography and tissue Doppler imaging as they are approachable. These methods detect subclinical functional effects. [17] One of the most important screening tests for PH in high risk individuals is measuring right ventricular pressure by measuring the tricuspid regurge signal. [18] Estimation of right ventricular pressure and systolic pulmonary artery pressure can be achieved by measuring pulmonary acceleration time. [19] In our study, the diagnosis of PH was confirmed by the highly significant statistical difference between patients with COPD, RMS and control subjects found in TR, RVSP and PAT. Pulsed wave tissue Doppler of the tricuspid annulus is a simple tool to estimate pulmonary artery pressure and pulmonary vascular resistance. In patients with lower systolic velocity at the tricuspid annulus, a higher pressure and vascular resistance in patients with PH can be predicted. [20] Similar results were found in this study, as patients with RMS had the lowest TV S wave velocity with significant statistical difference between both control and COPD with RMS.

Right ventricular failure may be a consequence of RMS as pulmonary arterial hypertension is preceded by pulmonary venous hypertension. This can be attributed to the synergistic effects of back pressure pulmonary arteriolar constriction and obliterative changes in pulmonary vascular bed.[21] Also. in RMS ventricular interdependence and right ventricular ischemia may contribute to right ventricular dysfunction. [22] Left ventricular dysfunction can be detected by echocardiography in patients with group two of PH by many signs. Left atrial enlargement, left ventricular hypertrophy and indicators of increase of left ventricular filling pressure are among these criteria. [23] In concordance, the study of the left side of the heart measurements showed significant statistical difference between the three groups in ESD, Ao and LA dimensions.

Left ventricular systolic function evaluation in RMS remains a controversy matter. Some studies found it impaired and attributed this to myocardial fibrosis and chronic left ventricular underfilling. [24,25] Other studies found circumferential fiber shortening rate was decreased leading to myocardial dysfunction in these patients. [26] Also, another study demonstrated that subclinical systolic dysfunction exists in MS. [27] Other studies did not support these findings.[28] In COPD, pulmonary hyperinflation influences pulmonary hemodynamics, heart size and function. The intrathoracic volume and heart filling pressures are decreased by hyperinflation which compress the ventricles mechanically.[29] In patients with COPD, restriction in expiratory blood flow and in the pulmonary circulation lead to impairment of resting and exercise stroke volume. [30] In this study, COPD was diagnosed by respiratory function tests as FEV1/FVC ratio $<$ 0.7. The mitral valve group showed decreased FVC level with normal FEV1/FVC ratio (i.e restrictive pattern). All the parameters of assessing right ventricular dimensions, systolic and diastolic functions by Doppler echocardiography and tissue Doppler imaging showed affection in patients suffering from pulmonary hypertension especially RMS.

Dyspnea and right ventricular failure which complicate pulmonary hypertension occur due to multiple factors which narrow the lumen and increase pulmonary vascular resistance. These factors include in situ thrombosis , inflammation and excess vasoconstriction [31-33]

A mechanism concerning pulmonary microangiopathy was proposed in PH, where platelets shear upon flow through fibrin clots and plexiform lesions. [34] MPV is a main method of assessment of platelet production and stimulation. Younger platelets are more prothrombotic, larger and contain more granules. [35] Thrombus formation depends on platelet activation and aggregation at the site of vascular injury and atherothrombotic events. [36] Higher thromboxane A2 level and increased expression of glycoprotein Ib and IIb/IIIa receptors in large platelets may explain their higher thrombotic potential than small platelets. [37-39] The most popular marker for platelet activation is mean platelet volume (MPV) as it is most accurate measure of platelet size. [40] Risk stratification of many cardiological diseases such as coronary artery disease can be achieved by MPV. [41] MPV may be high in pulmonary arterial hypertension , decompensated heart failure, and hypertrophic cardiomyopathy which contributes to higher

thromboembolic events in these conditions [10,42-44] Increase secretion of platelet-derived mediators as 5-hydroxy-triptamine that causes smooth muscle cell proliferation and enhanced platelet reactivity correspond to increased MPV which is considered as a well established marker of abnormal platelet activity.[45]

LIMITATIONS

Our findings are based on a single-center study with a relatively small sample size. Multi-center studies employing the same protocol in a larger number of patients are needed. Another limitation was that we used maximal tricuspid regugitant velocity and pulmonary acceleration time for the diagnosis of pulmonary hypertension and not cardiac catheterization.

CONCLUSION

The effects of RMS as one of the causes of PH on the right side of the heart is more evident on all the studied parameters of the right side of the heart, not only while comparing RMS to control but even when comparing RMS to COPD as in TV S and TV A. The effects of both causes of PH on MPV is the same.

REFERENCES

1. Hatano S, Strasser T. Primary pulmonary hypertension. Report on a WHO meeting. Geneva: World Health Organization; 1975. 7-45.
2. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5-12.
3. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:43-54.
4. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J 2004;25:2243-78.
5. The task force for diagnosis and treatment of pulmonary hypertension of European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-63.
6. Simonneau G, Gatzoulis MA, Adatia I, , Denton C, , et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:34-41.
7. Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance United States, 1980-2002. MMWR Surveill Summ 2005;54(5):1-28.
8. Aaron CP, , Barr RG, Johnson WC, Bagiella E, Chahal H, et al. Physical activity and right ventricular structure and function. The MESA right ventricle study. Am J Respir Crit Care Med 2011;183:396-404.
9. Chahal H, McClelland RL, Tandri H, Jain A, Turkbey EB, Hundley WG, et al. Obesity and right ventricular structure and function: the MESA-right ventricle study. Chest 2012;141:388-95.
10. Varol E, Uysal BA, Ozaydin M. Platelet indices in patients with pulmonary arterial hypertension. Clin Appl Thromb Hemost 2011;17(6):171-4.
11. Zheng YG, Yang T, Xiong CM, He JG, Liu ZH, Gu Q, et al. Platelet distribution width and mean platelet volume in idiopathic pulmonary arterial hypertension. Heart Lung Circ 2015;24(6):566-72.
12. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187(4):347-65.
13. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, , et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease, an evidence-based guideline. Nat Rev Cardiol 2012;9(5):297-309.
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16(3):233-70.
15. Lindqvist P, Henein M, Kazzam E. Right ventricular outflow tract fractional shortening: an applicable measure of right ventricular systolic function. Eur J Echocardiogr 2003;4:29-35.
16. Rumberger JA, Behrenbeck T, Bell MR, Breen JF, Johnston DL, Holmes DR Jr, et al. Determination of ventricular ejection fraction: a comparison of available imaging methods. The Cardiovascular Imaging Working Group. Mayo Clin Proc 1997;72:860-70.
17. nci S, Erol MK, Bak ı rc ı EM, Hamur H, Değirmenci H, Duman H, et al. Effect of percutaneous mitral balloon valvuloplasty on right ventricular functions in mitral stenosis: short-and mid-term results. Anatol J Cardiol

2015;15(4):289-96.

18. Lau EM, Manes A, Celermajer DS, Galiè N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. Eur Heart J 2011;32:2489-98.
19. Yared K, Noseworthy P, Weyman AE, McCabe E, Picard MH, Baggish AL. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. J Am Soc Echocardiogr 2011;24:687-92.
20. Gurudevan SV, Malouf PJ, Kahn AM, Auger WR, Waltman TJ, Madani M, et al. Noninvasive assessment of pulmonary vascular resistance using Doppler tissue imaging of tricuspid annulus. J Am Soc Echocardiogr 2007;20(10):1167-71.
21. Tayyareci Y, Nisanci Y, Umman B, Oncul A, Yurdakul S, Altun I, et al. Early detection of right ventricular systolic dysfunction by using myocardial acceleration during isovolumic contraction in patients with mitral stenosis. Eur J Echocardiogr 2008;9(4):516-21.
22. Borer JS, Hochreiter C, Rosen S. Right ventricular function in severe non-ischaemic mitral insufficiency. Eur Heart J 1999;12:22-5.
23. Guazzi M, Galie N. Pulmonary hypertension in left heart disease. Eur Respir Rev 2012;21(126):338-46.
24. Sunamori M, Suzuki A, Harrison CE. Relationship between left ventricular morphology and postoperative cardiac function following valve replacement for mitral stenosis. J Thorac Cardiovasc Surg 1983;85:727-32.
25. Kaku K, Hirota Y, Shimizu G, Kita Y, Saito T, Kawamura K. Depressed myocardial contractility in mitral stenosis-an analysis by force-length and stress-shortening relationships. Jpn Circ J 1988;52:35-43.
26. Holzer JA, Karliner JS, O'Rourke RA, Peterson KL. Quantitative angiographic analysis of the left ventricle in patients with isolated rheumatic mitral stenosis. Br Heart J 1970;35:497-502.
27. Guven S, Sen T, Tufekcioglu O, Gucuk E, Uygur B, Kahraman E. Evaluation of left ventricular systolic function with pulsed wave tissue Doppler in rheumatic mitral stenosis. Cardiol J 2014;21(1):33-8.
28. Liu CP, Ting CT, Yang TM, Chen JW, Chang MS, Maughan WL, et al. Reduced left ventricular compliance in human mitral stenosis. Role of reversible internal constraint. Circulation 1992;85:1447-56.
29. Visca D, Aiello M, Chetta A. Cardiovascular function in pulmonary emphysema. Biomed Res Int 2013;2013:1846-78.
30. Boerrigter B, Trip P, Bogaard HJ, Groepenhoff H, Oosterveer F, Westerhof N, et al. Right atrial pressure affects the interaction between lung mechanics and right ventricular function in spontaneously breathing COPD patients. PLoS One 2012;7(1):302-08.
31. Pietra GG, Edwards WD, Kay JM, Rich S, Kernis J, Schloo B, et al. Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the NHLBI Primary Pulmonary Hypertension Registry. Circulation 1989;80(5):1198-206.
32. Price LC, Wort SJ, Perros F, Dorfmüller P, Huertas A, Montani D, et al. Inflammation in pulmonary arterial hypertension. Chest 2012;141(1):210-21.
33. McMurtry IF, Abe K, Ota H, Fagan KA, . Rho kinase-mediated vasoconstriction in pulmonary hypertension. Adv Exp Med Biol 2010;661:299-308.
34. Herve P, Humbert M, Sitbon O, Parent F, Nunes H, Legal C, et al. Pathobiology of pulmonary hypertension. The role of platelets and thrombosis. Clin Chest Med 2001;22(3):451-8.
35. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. Eur Heart J 2001;22(17):1561-71.
36. Marczewski MM, Postula M, Kosior D. Novel antiplatelet agents in the prevention of cardiovascular complications-focus on ticagrelor. Vasc Health Risk Manag 2010;6:419-29.
37. Ueno M, Kodali M, Tello-Montoliu A, Angiolillo DJ. Role of platelets and antiplatelet therapy in cardiovascular disease. J Atheroscler Thromb 2011;18(6):431-42.
38. Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. Arachidonic acid metabolism by platelets of differing size. Br J Haematol 1983;53(3):503-11.
39. Giles H, Smith RE, Martin JF. Platelet glycoprotein IIb-IIIa and size are increased in acute myocardial infarction. Eur J Clin Invest 1994;24(1):69-72.
40. Slavka G, Perkmann T, Haslacher H, Greisenegger S, Marsik C, Wagner OF, et al. Mean platelet volume may represent a predictive parameter for overall vascular mortality and ischemic heart disease. Arterioscler Thromb Vasc Biol 2011;31(5):1215-8.
41. Sansanayudh N, Anothaisintawee T, Muntham D, McEvoy M, Sansanayudh N, Anothaisintawee T, et al. Mean platelet volume and coronary artery disease: a systematic review and meta-analysis. Int J Cardiol 2014;175(3):433-40.
42. Kandis H, Ozhan H, Ordu S, Erden I, Caglar O, Basar C.

The prognostic value of mean platelet volume in decompensated heart failure. Emerg Med J 2011;28(7):575-8.

43. Icli A, Aksoy F, Dogan A, Arslan A, Akcay S, Yucel H. Increased mean platelet volume in hypertrophic cardiomyopathy. Angiology 2014;65(5):420-4.

44. Chung I, Choudhury A, Lip GY. Platelet activation in acute, decompensated congestive heart failure. Thromb Res 2007;120(5):709-13.

45. Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelet volume: Its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res 1983;32:443-60.