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Comparison of mean platelet volume values among different causes of pulmonary hypertension*

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Abstract

Background: *Pulmonary hypertension is caused by a heterogenous group of disorders with diverse pathophysiological mechanisms, with ultimate structural changes in the pulmonary vascular bed. Platelet activation plays an important role in the development of pulmonary arterial hypertension, while it is unknown whether it contributes to pathogenesis in other conditions. We aimed to investigate platelet activation in different causes of pulmonary hypertension by means of mean platelet volume measurement.*

Methods: *A total of 67 patients with different causes of pulmonary hypertension, and 31 controls, were retrospectively reviewed. Patients with pulmonary hypertension were further grouped according to underlying disease, including pulmonary arterial hypertension, pulmonary hypertension due to left ventricular failure, and pulmonary hypertension due to chronic obstructive pulmonary disorder. All patients and controls' past medical data, admission echocardiograms and complete blood counts were reviewed.*

Results: *Patients with pulmonary hypertension had higher mean platelet volume levels compared to healthy controls (8.77 ± 1.18* vs *7.89 ± 0.53; $p < 0.001$), and statistical significance was still present when pulmonary arterial hypertension patients were not included in the pulmonary hypertension group (8.59 ± 1.23* vs *7.89 ± 0.53; $p < 0.001$). Among patients with pulmonary hypertension, the pulmonary arterial hypertension group and the pulmonary hypertension due to left ventricular failure group had higher mean platelet volumes compared to healthy controls. Mean platelet volume did not correlate with pulmonary artery pressure.*

Conclusions: *Our results indicate that mean platelet volume is not only elevated in pulmonary arterial hypertension, but also due to other causes of pulmonary hypertension.* (Cardiol J 2012; 19, 2: 180–187)

Key words: pulmonary hypertension, mean platelet volume, echocardiography

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Introduction

Pulmonary hypertension (PH) is defined as elevation of resting pulmonary artery pressure (PAP) above 25 mm Hg, as measured by right heart catheterization [1]. As PH is a hemodynamic definition, rather than being a primary disease state, virtually all disorders that affect pulmonary vasculature may cause PH. Pulmonary arterial hypertension (PAH), which forms group 1 of the Venice classification, constitutes a group of disorders that are characterized by hypertrophic and thrombotic obstructive changes in the pulmonary arterial tree [2, 3]. Platelet abnormalities and abnormal platelet activation are important mediators of disease progression, as they both contribute to thrombotic obstruction of pulmonary arteries and induce vessel remodeling [4]. Other causes of PH, such as left ventricular failure (LVF) or chronic lung diseases, have different pathogenetic mechanisms that lead to PH, while in advanced stages they may cause similar changes in pulmonary vasculature including vessel remodeling [5]. The role of platelets in the development of PH in these patients is less well defined.

Mean platelet volume (MPV) is a well-studied marker of abnormal platelet activity [6]. Increased mean platelet volumes correspond to enhanced platelet reactivity, as well as more secretion of platelet-derived mediators such as 5-hydroxy--triptamine that induce smooth muscle cell proliferation [7, 8]. MPV values are increased in a number of disease states, including myocardial infarction, unstable angina, and stroke [9]. Recently, MPV levels have been shown to be increased in patients with PAH [10].

In this study, we aimed to retrospectively observe and compare MPV levels and total thrombocyte counts in patients with different etiologies for PH and in normal controls.

Methods

Databases from a PH clinic, a cardiac transplantation clinic and a pulmonary diseases clinic were reviewed for patients with PH of any cause. PH is defined as an echocardiographically measured peak tricuspid regurgitant velocity of more than 3.4 m/s and calculated systolic PAP of more than 50 mm Hg. Patients who were more than 18 years old, had PH as defined above, and at least one complete blood count obtained at admission were included in the analysis. Those with known disorders of the coagulation system, liver dysfunction or renal failure were excluded from analysis. A total of 67 patients were included. PH patients with idiopathic PAH, PAH secondary to congenital heart disease or systemic disorders formed the PAH group, which consisted of 26 patients. The PH due to congestive heart failure (LVFPH) group consisted of eligible patients with a left ventricular ejection fraction of less than 40%, and who had PH as defined above. This group comprised 26 patients. Fifteen patients with a forced expiratory volume in first second to forced vital capacity ratio (FEV_1%) of less than 75%, and who had PH as defined above with no other apparent cause that may caused PH, formed the PH secondary to chronic obstructive pulmonary disease (COPDPH) group. A random 31 patients who were referred to echocardiography for other reasons who had calculated peak PAP below 36 mm Hg and peak tricuspid velocity of less than 2.8 m/s served as healthy controls, in whom PH was not considered.

For all patients, MPV and total thrombocyte count values were obtained from first complete blood count (in EDTA) that was performed by a Coulter counter (Gen-S, Coulter Corporation, Miami, FL, USA) on admission to our institution. Data was recorded regarding age, gender, past medical records and medications at the time of initial measurements. Peak PAP and maximal tricuspid regurgitation flow velocities were obtained from the first echocardiographic examination that was measured using a Vivid 3 (GE Healthcare, Piscataway, NJ, USA) system equipped with a 2.5 MHz phased array transducer, which is standard equipment in an institutional echocardiography laboratory.

Appropriate permissions were obtained from institutional science and ethics commissions for this study.

Statistical analysis

Statistical analyses were performed using SPSS v.13 software (formerly SPSS Inc., Chicago, IL, USA). Results were expressed as the mean ± ± SD. We used Kolmogorov-Smirnov and Levene tests to determine the distribution characteristics of variables and variance homogeneity. Independent samples Student's *t* test or Mann-Whitney U test was used, as appropriate, to determine differences for continuous variables between two groups. One--way ANOVA was used to test statistically significant differences when more than two independent groups were present and variances were equal, while Kruskal-Wallis test was used when equal variances were not present. *Post-hoc* analysis was performed with Scheffe and Mann-Whitney U tests according to tested variables. Pearson's R was used for

Table 1. Demographic and laboratory data of pulmonary hypertension and control groups.

Parameter	Pulmonary hypertension group (n = 67)	Control group (n = 31)	P
Demographic variables			
Age [years]	44.54 ± 15.94	42.58 ± 11.78	0.54
Gender (%male)	65%	45%	0.055
Past medical history			
Systemic hypertension	46%	41%	0.67
Diabetes mellitus	18%	15%	0.75
Hyperlipidemia	25%	26%	0.89
Smoking history	32%	30%	0.86
Coronary heart disease	19%	19%	0.93
Congenital heart disease	32%	4%	< 0.01
Systemic inflammatory disease	2%	0%	1
Previous medications			
Antiaggregants	49%	24%	< 0.05*
Anticoagulants	28%	4%	< 0.05**
ACE inhibitors/ARBs	43%	36%	0.58
Beta-blockers	43%	16%	< 0.05
Calcium channel blockers	24%	8%	0.21
Diuretics	46%	4%	< 0.001
Digitalis compounds	28%	0%	< 0.01
Inhaled corticosteroids	13%	0%	0.09
Inhaled beta agonists	11%	0%	0.17
Theophylline	13%	0%	0.09
Laboratory and echocardiographic data			
Systolic PAP [mm Hg]	70.16 ± 24.09	22.77 ± 4.29	< 0.001
Mean platelet volume [fL]	8.77 ± 1.18	7.89 ± 0.53	< 0.001
TTC [× 10^3/mm^3]	234.10 ± 71.10	261.61 ± 59.01	0.064
PDW [%]	16.58 ± 0.81	16.27 ± 1.18	0.17
Hemoglobin [g/dL]	14.57 ± 0.57	13.8 ± 1.66	0.14
RBC count [× 10^6/mm^3]	5.15 ± 0.94	4.44 ± 0.56	< 0.001
MCV [fL]	85.61 ± 7.73	89.06 ± 5.57	< 0.05
RDW [%]	16.4 ± 3.65	14.02 ± 2.06	< 0.001

Data is given as ± standard deviation; *statistical significance persists after pulmonary arterial hypertension patients are excluded; **is not statistically significant when pulmonary arterial hypertension patients are excluded; ACE — angiotensin converting enzyme; ARB — angiotensin receptor blocker; PAP — pulmonary artery pressure; TTC — total thrombocyte count; PDW — platelet distribution width; RBC — red blood cell count; MCV — mean cytosolic volume; RDW — red cell distribution width

correlation analysis of linear variables when appropriate. Multiple regression analysis (with dummy variables) was used when more than one variable was found to influence MPV values. A p value of less than 0.05 was accepted as statistically significant, while correlation was said to be present when r value was more than 0.25.

Results

Demographic variables, past medical history, medications and laboratory findings for PH patients, PH subgroups and healthy controls are set out in Tables 1 and 2. Age and gender did not differ between PH patients and healthy controls, while subgroup analyses revealed statistically significant differences between subgroups (Table 2). Systolic PAP was significantly higher in the PH group (70.16 ± 24.09 mm Hg) compared to the controls (22.77 ± 4.29; $p < 0.001$); while PAH (90.31 ± ± 26.44 mm Hg) patients had significantly increased PAP compared to other PH subgroups ($p < 0.001$). Patients with PH used drugs that affect the coagulation system significantly more than the control group (49% *vs* 29% for antiaggregants and 28% *vs* 4% for anticoagulants; $p < 0.05$ for both); while significance did not persist for anticoagulant usage after excluding idiopathic PAH. There was no statis-

Table 2. Demographic and laboratory findings in pulmonary hypertension subgroups and healthy controls.

Parameter	Pulmonary hypertension group (n = 67)			Control group (n = 31)
	PAH (n = 26)	LVFPH (n = 26)	OPDPH (n = 15)	
Gender (%male)	31%	88%**	87%*	45%
Age [years]	36.42 ± 12.75	41.27 ± 10.83	64.27 ± 11.81**	42.58 ± 11.78
Systolic PAP [mm Hg]	90.31 ± 26.44**	58.19 ± 7.00**	56.00 ± 12.84**	22.77 ± 4.29
Mean platelet volume [fL]	9.06 ± 1.05**	8.83 ± 1.27**	8.19 ± 1.08	7.89 ± 0.53
TTC [× 10^3/mm^3]	225.77 ± 72.46	234.12 ± 68.09	248.53 ± 76.32	261.61 ± 59.01
PDW [%]	16.60 ± 0.85	16.56 ± 0.51	16.56 ± 1.16	16.28 ± 1.18
Hb [g/dL]	15.33 ± 3.14	13.89 ± 2.28	14.50 ± 2.19	13.80 ± 1.66
RBC [× 10^6/mm^3]	5.59 ± 0.96**	4.80 ± 0.68*	5.02 ± 1.06	4.44 ± 0.57
MCV [fL]	83.96 ± 9.14*	85.19 ± 4.55**	89.19 ± 8.74	89.06 ± 5.57
RDW [%]	17.37 ± 4.47**	16.00 ± 3.04**	15.39 ± 2.75*	14.01 ± 2.06

Data is given as ± SD; *difference is significant at $p < 0.05$ level compared to control group; **difference is significant at $p < 0.01$ level compared to control group; PAH — pulmonary arterial hypertension; LVFPH — pulmonary hypertension due to left ventricular failure; COPDPH — pulmonary hypertension due to chronic obstructive pulmonary disease; PAP — pulmonary artery pressure; TTC — total thrombocyte count; PDW — platelet distribution width; RBC — red blood cell count; MCV — mean cytosolic volume; RDW — red cell distribution width

tically significant difference between the LVFPH (58.19 ± 7.00 mm Hg) and the COPDPH (56.00 ± ± 12.84 mm Hg) groups, while both groups had elevated PAP compared to controls ($p < 0.001$).

Individual groupings for past medical history and drug usage had identified history of coronary artery disease, history of congenital heart malformations, usage of anticoagulant drugs, endothelin receptor antagonists or digoxin as factors that may affect MPV in patients and controls. Multiple regression analysis had shown the presence of PH as an individual marker for increased MPV ($p = 0.009$) and statistical significance persisted even after exclusion of idiopathic PAH patients ($p = 0.017$). Other independent variables that had an effect on MPV were history of coronary artery disease, and medications including endothelin receptor antagonists and digoxin.

Mean platelet volume was higher in the PH group compared to normal controls (8.77 ± 1.18 *vs* 7.89 ± 0.53; $p < 0.001$) (Table 1, Fig. 1A). This finding was still statistically significant when PAH patients were excluded from the PH group (8.59 ± ± 1.23 *vs* 7.89 ± 0.53; $p < 0.001$) (Fig. 1B). Total thrombocyte count was higher in normal controls than PH patients, while this finding had no statistical significance (261.61 × 103 ± 59.01 × 103 *vs* 234.10 × 103 ± 71.10 × 103; $p > 0.05$). When individual groups were considered, significant differences existed between groups ($p < 0.001$). *Post hoc* analysis of individual groups showed that patients in the PAH (9.05 ± 1.05 fL) and LVFPH (8.82 ± 1.27 fL) subgroups had higher MPV values than healthy controls (7.89 ± 0.52 fL, $p < 0.001$ and $p < 0.05$; respectively). Additionally, MPV values were significantly elevated in the PAH group compared to the COPDPH group (9.05 ± 1.05 fL *vs* 8.05 ± 0.97 fL, $p < 0.05$). While mean MPV was elevated in the COPDPH group compared to the control group, this finding had no statistical significance (8.05 ± 0.97 fL *vs* 7.89 ± 0.52 fL, $p > 0.05$). There were no statistically significant differences between groups when total thrombocyte count was considered ($p > 0.05$) (Table 2, Fig. 2).

In patients with known PAH, MPV did not correlate with systolic PAP ($r = 0.13$; $p > 0.05$), or age ($r = –0.12$; $p > 0.05$); while a weak negative correlation was present between MPV and thrombocyte count ($r = –0.26$; $p < 0.05$) (Fig. 3).

Discussion

This study showed that patients with PH, when considered as a group, have higher mean platelet volume compared to normal controls, and that those patients with PH but not PAH had higher mean platelet volume compared to normal controls. Subgroup analysis showed patients with PH caused by PAH or LVF had higher MPV values compared to normal controls. While MPV was higher in the PH group, no correlation was present between MPV and peak PAP.

The role of platelets in the development and progression of PAH is well established. Platelets are an integral part of the coagulation system that contributes to thrombotic pulmonary arteriopathy [3, 4]. Platelets appear to be activated during pulmonary transit, and they may contribute to thrombin and clot generation [11]. Moreover, mediators

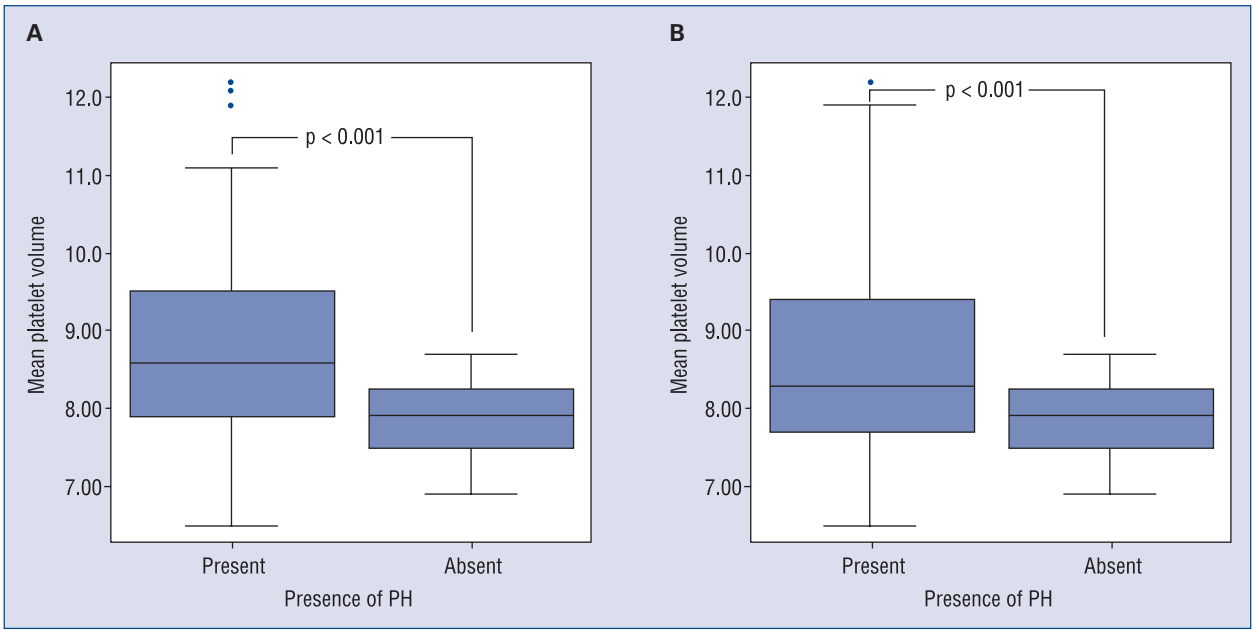

Figure 1. Mean platelet volume values in the pulmonary hypertension (PH) group and healthy controls (**A**). Difference was statistically significant at $p < 0.001$ level. Mean platelet volume values in the PH group after exclusion of pulmonary arterial hypertension patients compared with healthy controls (**B**). Difference was statistically significant at $p < 0.001$ level.

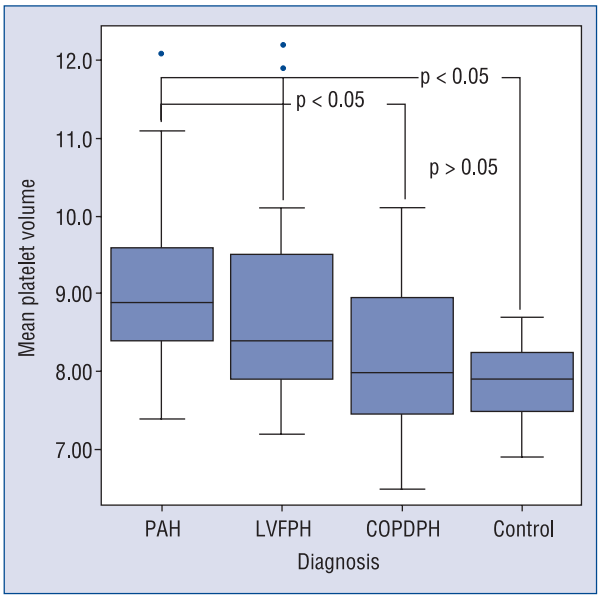

Figure 2. Mean platelet volume values in the pulmonary hypertension subgroups and healthy controls. Statistically significant differences existed between the pulmonary arterial hypertension (PAH) group and the pulmonary hypertension due to left ventricular failure (LVFPH) group compared to healthy controls. Mean platelet volume values were also significantly increased in the PAH group compared to the pulmonary hypertension due to chronic obstructive pulmonary disease group (COPDPH).

liberated from thrombocytes, such as seratonin and platelet derived growth factor, stimulate smooth muscle cell proliferation and medial hypertrophy [12, 13]. High plasma seratonin levels were found in patients with primary PH, which was responsive to epoprostenol [12]. Interestingly, platelets of patients with PAH appear to contain smaller amounts of seratonin compared to healthy controls. In their article, the authors suggested that this finding may imply that degranulation during pulmonary transit could be responsible for the unexpectedly low platelet seratonin content [14]. Findings from an experiment using a hypoxic model of PH, in which a decrease in mean platelet volume was observed after pulmonary passage that is compatible with platelet degranulation, further supports this hypothesis [15].

Increased mean platelet volume reflects heightened platelet activity. Large platelets are more reactive and produce more prothrombotic compounds [6]. They also contain more dense granules and 5' hydroxytriptamine [7, 8]. Relationship of MPV with a variety of cardiovascular conditions, including myocardial infarction and stroke, are well established [9]. Recently, Can et al. [10] have shown increased MPV values in patients with PAH, along with an enhanced aggregation in response to adenosine diphosphate. Similarly, we found increased MPV values in patients with PAH, and this increase

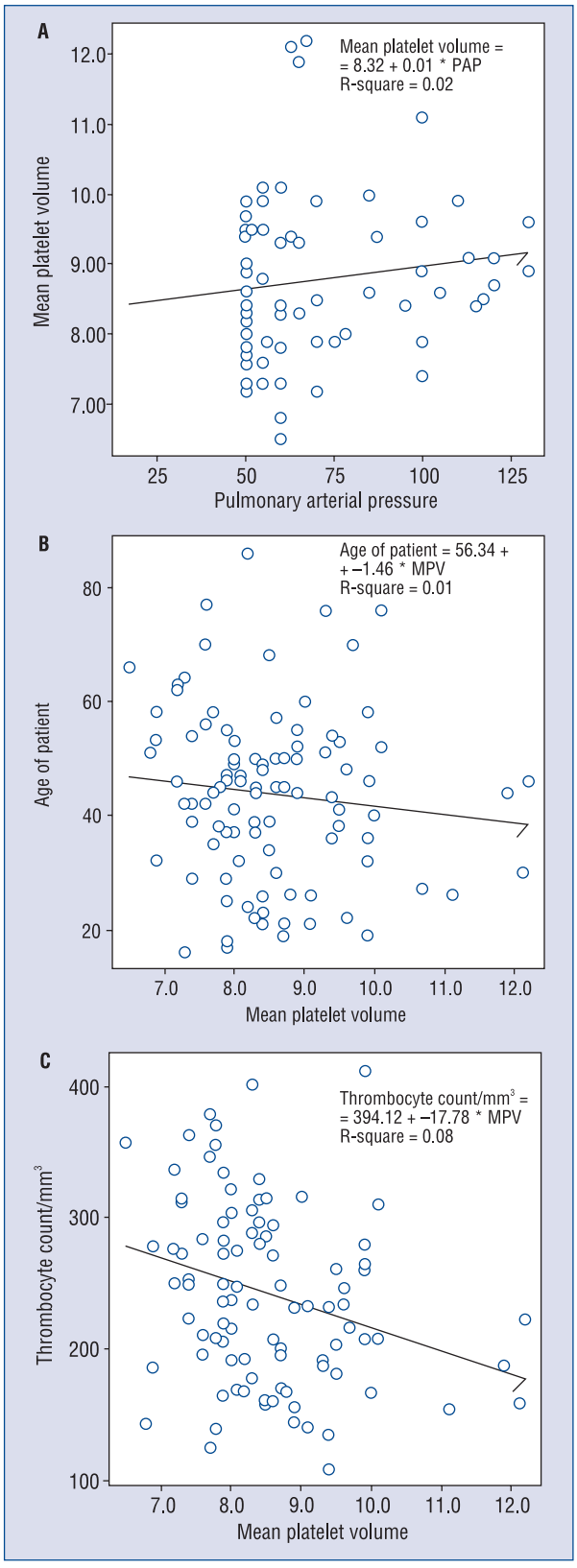

Figure 3. Linear regression analysis results between mean platelet volume (MPV) and pulmonary artery pressure (PAP) (**A**), age (**B**), and total thrombocyte count (**C**). The only statistically significant correlation was between total thrombocyte count and mean platelet volume ($p < 0.05$).

was only weakly related to total thrombocyte count, thereby suggesting a primary abnormality rather than a response to total thrombocyte number.

The pathophysiology of PH observed in patients with LVF or COPD is different from PAH, and is thought to be the result of underlying disease state rather than primary reactive changes in the pulmonary arterial tree. However, there are certain pathophysiological similarities, such as arterial vasoconstrictive response and trophic changes in arterioles in patients with PH caused by LVF and COPD [2, 16]. As these responses are partly elucidated by platelets or mediators released by platelets in patients with PAH, it is reasonable to consider that platelet activation may play a role in other forms of PH. Indeed, we found that MPV values of patients in the PH group were increased compared to healthy controls, even when the PAH group was excluded. This finding implies generalized platelet activation in all causes of PH is present, and this may contribute to progression of PH, even if it is not the cause of PH itself.

Platelet activation in patients with PH due to LVF or COPD may be caused by PH itself or by the underlying disease state [17–19]. In both of these conditions, however, platelet activation may lead to a further increase in pulmonary vascular resistance. It has been shown that patients with LVF exhibit increased platelet activation [18], and increased MPV values in patients with LVF predicted left ventricular thrombosis [20]. Previous studies also indicated that patients with COPD have increased MPV values, especially in those with known PH [19, 21]. In our study, subgroup analysis revealed increased MPV levels in patients with PH caused by LVF. While MPV levels in the COPD group were higher compared to normal controls, this finding did not reach statistical significance. This contradiction of our results with previous studies may be due to the relatively small number of COPD patients included in this analysis.

While our results indicate that patients with PH exhibit increased MPV values compared to controls, MPV values do not correlate with systolic PAP in patients with PH. It is possible that activation of platelets can be a generalized primary response in all types of PH and can be independent of disease severity. Also, different etiologies for PH may also cause different MPV values, as underlying disease also has an effect on the degree of platelet activation and MPV. Another possible explanation for that finding is that the echocardiographic measurement of PAP may not be sufficiently precise to determine a correlation between MPV values and PAP [22].

According to current guidelines, oral anticoagulation is considered as a treatment option to halt the progress of PH in PAH patients [22]. Some studies have found coumadine has an impact on disease outcome, while others have not [4]. In addition, a small study found aspirin and clopidogrel effectively inhibits platelet aggregation, while aspirin was also effective in decreasing thromboxane synthesis without affecting prostacycline production [23]. Except for the PAH group, anticoagulation is currently not recommended in PH patients if another indication does not exist [22].

Limitations of the study

As this study was retrospective in nature, obtained MPV values are subject to measurement errors; it has previously been shown that MPV tends to increase when withdrawn blood has spent more than two hours in EDTA. However, institutional procedures dictate blood should be collected in EDTA and should be analyzed within two hours of collection. While we consider procedural errors to have been minimal, no absolute guarantees can be provided.

Similarly, peak tricuspid regurgitant velocity and PAP measurements were obtained from previously performed echocardiographic investigations. As institutional laboratories use the same echocardiography devices (GE Vivid 3) and probes, and all measurements were made by expert echocardiographers, these effects should be minimal. Because measurements were performed by different echocardiographers, peak PAP measurements were subject to interobserver variability. We consider that peak PAP, a marker of disease severity, can be affected by this fact rather than a diagnosis of PH. It is more frequent to mistakenly measure a peak velocity as being below the actual figure, so those measured above predefined limits were probably correct.

A final limitation arises from the fact that echocardiographic measurement of PAP is not considered as a gold standard measurement for diagnosis of PH. Still, echocardiographically measured peak PAP of more than 50 mm Hg, combined with a maximal tricuspid regurgitant velocity of more than 3.4 m/s, are considered as diagnostic under European guidelines [22]. Also, cardiac catheterization does not alter treatment options in patients with LVF or COPD, so it would not be ethical to measure pulmonary pressure invasively in these patients.

Conclusions

We have shown that mean platelet volume is higher in patients with PH, even when patients with PAH are excluded. This finding implies platelet activation occurs in all patients with PH, with possible pathophysiologic similarities regarding platelet-mediated progression of PH between PAH and other causes of PH.

Further studies are needed to address the role of platelets in patients with PH, especially those with PH caused by etiologies different from PAH, and the possible role of treatments specifically targeting platelet activation.

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Conflict of interest: none declared

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