Received: 7 September 2021 | Revised: 6 October 2021 | Accepted: 18 October 2021

DOI: 10.1111/all.15161

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

LETTER

Platelet-activating factor acetylhydrolase: A biomarker in Hymenoptera venom allergy?

To the Editor

Anaphylaxis is a rapid, potentially fatal, immediate hypersensitivity reaction. Preformed and newly formed biochemical mediators, including histamine, tryptase, carboxypeptidase A, prostaglandin D2, leukotrienes, and platelet-activating factor (PAF), are released systematically during the degranulation of mast cells and basophils. PAF is a proinflammatory phospholipid, synthesized and secreted by mast cells, monocytes, and fixed tissue macrophages whose binding to its receptor on target cell—platelet, monocytes, macrophages, and neutrophils results in many of the manifestation of acute allergic reaction and anaphylaxis. Circulating levels of PAF are controlled by the activity of platelet-activating factor acetylhydrolase (PAF-AH), which is an enzyme that degrades PAF. Due to the quick elimination of PAF (halftime, 3–13 min), PAF-AH has been proposed as a surrogate biomarker for PAF activity correlated with the severity of anaphylaxis.[1–5] However, it was investigated in Hymenoptera venom allergy (HVA) only in one previous study, in a real-world population.[4]

The objectives of this study were to investigate the role of PAF-AH as a predictive biomarker for the severity of the reaction in a HVA selected population (HVA-alone population), without confounding factors, and to compare their PAF-AH values with healthy subjects and patients with allergic asthma or rhinitis. We also investigated the correlation of PAF-AH activity with other factors (demographic factors, concomitant diseases and medications, serum tryptase values, venom sIgE levels, and culprit insect), in a larger HVA real-world population.

HVA patients were consecutively enrolled at the Allergy Unit of the "Ospedali Riuniti" hospital of Ancona, in Italy, with a history of systemic reaction after hymenoptera sting, according to Mueller classification, or of large local reaction.[6] A blood sample was taken before the start of venom immunotherapy.

Participants signed an informed consent. No formal approval by the Ethics Committee was needed, as all the interventions were part of routine clinical practice.

PAF-AH activity was measured blindly by the Department of Clinical Sciences, Section of Biochemistry, Biology and Physics of the Marche Polytechnic University, using a colorimetric kit (methods available on the Online Supplementary File).

A sample size of 54 subjects has been calculated to detect the minimum clinically significant difference (MCSD) in PAF-AH activity of 10 nmol/mL/min, among healthy subjects and the different grades of severity of the HVA-alone group (power = 80%, $\alpha = 0.05$), and between severe reactions and the control groups of rhinitis and asthma (power = 94%, $\alpha = 0.05$). Additional HVA patients with concomitant diseases/medications (HVA real-world group) were enrolled to complete the total available 140 PAF-AH assessments. ANOVA test with Bonferroni adjustment was performed using STATA v.13 (StataCorp College Station, Texas, USA). From 2017 to 2019, PAF-AH activity was measured in 103 consecutive HVA patients, 12 healthy controls, 13 patients with allergic rhinitis, and 10 patients with allergic rhinitis and asthma, who were controlled with maintenance medium to high dose of inhaled corticosteroids plus long-acting beta agonists. No asthmatic patients were in treatments with oral steroids and/or biologics (Figure S1, Table 1). In the HVA-alone population, the mean PAF-AH activity (24.5–27.9 nmol/mL/min) was significantly lower, compared to healthy subjects (40.4 nmol/mL/min, $p < .001$), patients with allergic rhinitis (36.7 nmol/mL/min, $p < .001$), and asthma too (30.7 nmol/mL/min, unadjusted analysis only, $p = .046$; Table S2). However, no correlation with the severity of reaction was observed (Figure 1A). PAF-AH activity was lower in asthma, compared to healthy subjects ($p = .001$) and patients with rhinitis (unadjusted analysis only, $p = .014$) (Figure 1B). These results were confirmed when the analyses were extended to the HVA real-world population (Table S3). PAF-AH activity was not correlated with gender, age, hypertension, dyslipidemia, diabetes, or baseline serum tryptase levels. A markedly decreased PAF-AH activity was found in the only HVA patient with asthma (PAF-AH: 10.9 nmol/mL/min). A significant but modest PAF-AH increase was found in patients taking beta-blockers (+4 nmol/mL/min, $p = .015$), and in patients allergic to vespid venom, compared to bee venom (+3.6 nmol/mL/min, $p = .0133$), but no correlation was found between the PAF-AH values and the sIgE values of the whole extract of the culprit insect.

This is the first study assessing the role of PAF-AH as a biomarker in an HVA-alone selected population, compared to both healthy subjects and patients with respiratory allergic diseases.

Our results apparently disagree with those of Pravettoni et al. about the observed difference across different degrees of reaction severity. However, the difference in the enzyme values in the Mueller III (M-III) and Mueller IV (M-IV) and Mueller II (M-II) reactions, in Pravettoni et al, is lower (about 7.5 nmol/mL/min) than the

TABLE 1 Baseline features

	Overall HVA (*N* = 103)	HVA-alone group (*N* = 49)	Allergic asthma (*N* = 10)[a]	Allergic rhinitis (*N* = 13)	Healthy (*N* = 12)
Median age (IQR)	54 (39–61)	43 (33–58)	47 (29–56)	43 (28–48)	52 (47–60)
M/F	71/32 (69/31%)	34/15 (69/31%)	2/8 (20/80%)	6/7 (46/54%)	3/9 (25/75%)
Allergic comorbidities					
Allergic asthma	1%	0	100%	0	0
Allergic rhinitis	5%	0	100%	100%	0
Airborne sensitization	8%	0	100%	100%	0
Other comorbidities					
Cardiac disease	14%	0	0	0	0
Hypertension	24%	0	10%	0	0
Diabetes	4%	0	0	0	0
Dyslipidemia	9%	0	10%	0	0
Concomitant treatments[b]					
Beta-blockers	11%	0	0	0	0
Statins	10%	0	10%	0	0
Sartans	12%	0	10%	0	0
ACE inhibitors	4%	0	0	0	0
Antiarrhythmics	4%	0	0	0	0
Anticoagulants	13%	0	0	0	0
Hymenoptera allergy					
Bee	27%	31%	n.a.	n.a.	n.a.
Vespid	73%	69%			
Type of reaction					
LLR	10%	20%	n.a.	n.a.	n.a.
Mueller I	7%	12%			
Mueller II	10%	8%			
Mueller III	37%	24%			
Mueller IV	36%	35%			
Median serum tryptase levels, ng/nl (IQR)	4.6 (3.4–6.6)	4.9 (3.2–5.9)	n.a.	n.a.	n.a.

Abbreviations: IQR, Interquartile range; n.a., not applicable.

[a]One outlier patient was excluded by the analysis (PAF-AH: 68.4 nmol/mL/min)

[b]All the asthmatic patients were in treatment with medium–high doses of inhaled corticosteroids + long-acting beta agonists.

MCSD that we have estimated (10 nmol/mL/min); hypotension is a feature present in M-IV grade only, and it is not clear the reason why subjects who have experienced M-III reactions have the same values as those with M-IV reactions. It should be also noted that the two studied populations are different in terms of their place of origin and potential concomitant diseases/treatments, possibly reflecting genetic differences and different confounding effects of comorbidities and medications, as demonstrated by our results in asthmatics and beta-blocker users.

Our results do not support the role of PAF-AH as a biomarker of reaction severity, for HVA. However, since PAF-AH values in the HVA population were lower than those of the control groups, we can assume that PAF-AH was able to characterize HVA patients as a separate population from healthy subjects and patients with allergic asthma and/or rhinitis.

PAF-AH is not a reliable predictor biomarker of the severity of allergic reactions, to be used in clinical practice, possibly because it is not an adequate surrogate biomarker of PAF activity. It is also possible that the PAF alone is not sufficient to determine the reaction severity, as several mediators and factors, both biochemical and clinical, take part in the onset and severity of the anaphylactic reaction.

Moreover, standardization of the methods to measure PAF-AH activity is needed before its implementation in clinical practice.

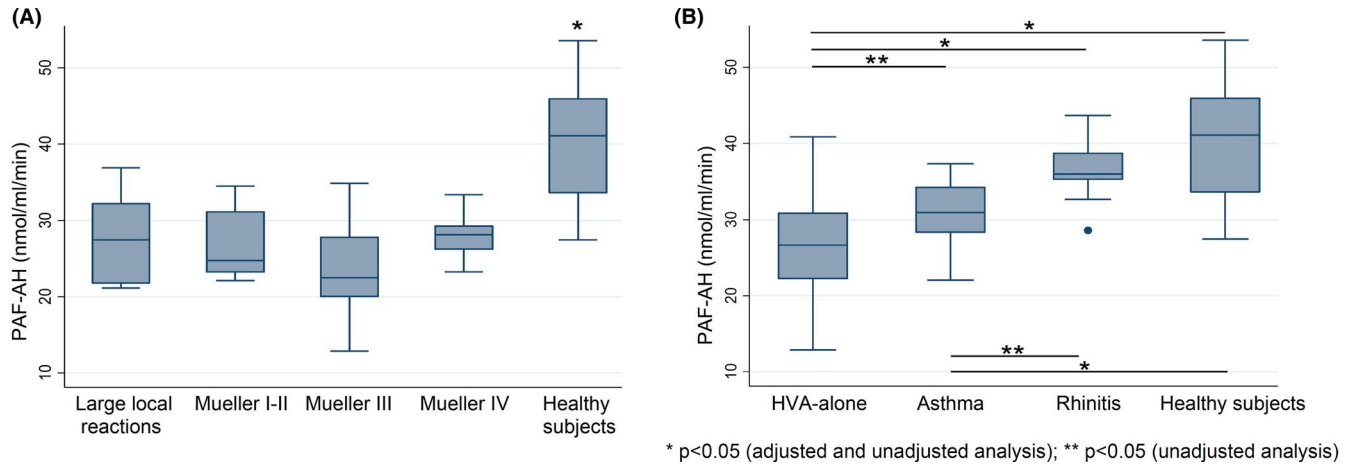

FIGURE 1 PAF-AH activity in patients with different reaction grades due to Hymenoptera venom allergy compared with healthy subjects (A), and in the overall patients with Hymenoptera venom allergy compared with the control groups (B). (HVA-alone population)

KEYWORDS

anaphylaxis, asthma, biomarkers, Hymenoptera venom allergy, platelet-activating factor acetylhydrolase

Correspondence

Maria Beatrice Bilò, Department of Clinical and Molecular Sciences – Marche Polytechnic University, Ancona, Italy.

Email: m.b.bilo@univpm.it

FUNDING INFORMATION

Open Access Funding provided by Universita Politecnica delle Marche within the CRUI-CARE Agreement.

ACKNOWLEDGMENTS

The authors would like to thank Valerio Pravettoni for his contribution to the discussion of the results of the paper.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

Maria Beatrice Bilò[1,2,3]
Alice Corsi[3]
Matteo Martini[4]
Maria Giovanna Danieli[1,3,5]
Sonila Alia[6]
Alice Di Paolo[6]
Gianluca Moroncini[1,5]
Arianna Vignini[6]

[1]*Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy*
[2]*Allergy Unit, Department of Internal Medicine, Ospedali Riuniti Ancona University Hospital, Ancona, Italy*
[3]*Postgraduate School of Allergy and Clinical Immunology, Marche Polytechnic University, Ancona, Italy*
[4]*Allergy Unit, "Santa Croce" Hospital, Fano, Italy*
[5]*Department of Internal Medicine, Clinica Medica, Ospedali Riuniti Ancona University Hospital, Ancona, Italy*
[6]*Department of Clinical Sciences, Section of Biochemistry, Biology and Physics, Marche Polytechnic University, Ancona, Italy*

ORCID

Maria Beatrice Bilò https://orcid.org/0000-0002-9324-6039
Matteo Martini https://orcid.org/0000-0001-9873-9695
Maria Giovanna Danieli https://orcid.org/0000-0002-9608-2252
Sonila Alia https://orcid.org/0000-0002-3038-854X
Alice Di Paolo https://orcid.org/0000-0003-0269-6331
Gianluca Moroncini https://orcid.org/0000-0002-0380-0105
Arianna Vignini https://orcid.org/0000-0002-2496-7932

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SUPPORTING INFORMATION

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