Oxylipin Profiles during the First Day of Mechanical Ventilation in an Intensive Care Unit Cohort: Research Letter

To the Editor:

Lipid mediators derived from arachidonic acid and other precursor polyunsaturated fatty acids, collectively known as oxylipins, are metabolized along different distinct pathways and play important roles in the modulation of inflammation.[1,2] Blood oxylipin profiles have been shown to correlate with the survival and development of acute respiratory distress syndrome in patients with sepsis or septic shock.[3–5] We aimed to explore serum oxylipin profiles using liquid chromatography coupled to tandem mass spectrometry quantification as previously described[6] during the first day of mechanical ventilation in the intensive care unit (ICU). Previously, we have noted elevated plasma concentrations of thromboxane B_2, prostaglandin E_2, 15-hydroxyeicosatetraenoate, and 11-hydroxyeicosatetraenoate in response to experimental hyperinflation lung injury[7] in a large animal model. Based on this, we hypothesized that these metabolites would increase in response to mechanical ventilation in patients. Decreases in a subset of oxylipins have been observed, however, in relation to critical illness.[8]

With ethical approval (Linköping, 2010/427-31 and 2018/16-32), all consecutive adult patients (n = 589) with indwelling arterial cannulas after admission to the ICU in Östersund Hospital, Sweden, between February 1, 2012, and January 31, 2013, were screened for inclusion in the study cohort unless transferred from another ICU.[9] Blood samples were collected in EDTA tubes during 2012 and 2013. Within 30 min, the samples were spun for 10 min at 2,000*g*. The plasma was then frozen in aliquots to –70°C, then unfrozen, and analyzed in 2021. In the cohort,[9] 147 cases with complete data and samples were identified. Of these, 22 men and 3 women with mixed diagnoses were intubated and included in the study with case characteristics in Supplemental Table 1 (https://links.lww.com/ALN/D48). Samples were collected at the time of intubation and on the following morning.

Of 67 oxylipins in the analysis panel, 57 were detected (fig. 1). Of these, 23 were above the limit of quantification in at least 80% of the samples, which was the predetermined limit for oxylipins to be included in formal analysis. The detected metabolites included all major metabolic pathways, cyclooxygenase, lipoxygenase, and cytochrome P450. Complete oxylipin analysis results are given in Supplemental Table 1 (https://links.lww.com/ALN/D48). None of the oxylipins was assumed to be normally distributed. After log transformation, 19 oxylipins were deemed to be normally distributed and were thus evaluated with paired Student's *t* test and Hedges' g. The remaining four oxylipins were compared using the Wilcoxon signed-rank test (table 1). Correction for multiple comparisons was performed with the false discovery rate set to 10% for $\alpha = 0.05$, yielding a significance level at $P < 0.001$.

For samples after up to 1 day of mechanical ventilation (after intubation), 12-hydroxyeicosatetraenoate showed significantly lower plasma concentrations, and no oxylipin increased (table 1).

The current study supports decreased concentrations of 12-hydroxyeicosatetraenoate in response to mechanical ventilation in contrast to previous reports of 12-hydroxyeicosatetraenoate being considered a proinflammatory mediator.[10] Thromboxane B_2 and prostaglandin E_2 were not among the oxylipins with sufficient detection frequencies for formal analysis. In contrast to the main hypothesis, 15-hydroxyeicosatetraenoate and 11-hydroxyeicosatetraenoate did not increase during the first day of mechanical ventilation.

In conclusion, this study demonstrates that several oxylipins may be detected in intensive care patients and that plasma concentration of 12-hydroxyeicosatetraenoate decreases during the first day of mechanical ventilation in the ICU.

Research Support

This work was supported by the Swedish Research Council VR (2014–6354; Stockholm, Sweden), Marie Sklodowska Curie Actions, Cofund, Project INCA 600398 (European Union), Åke Wiberg's Foundation (M17-0219; Stockholm, Sweden), research funding from Umeå University (Umeå, Sweden), and the ALF-LUA cooperative Region Västerbotten-Umeå University (Umeå, Sweden) intramural research funding system.

Competing Interests

Dr. Larsson has received speaker fees for lecturing in clinical symposia sponsored by Dräger Medical (Götesburg, Sweden),

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

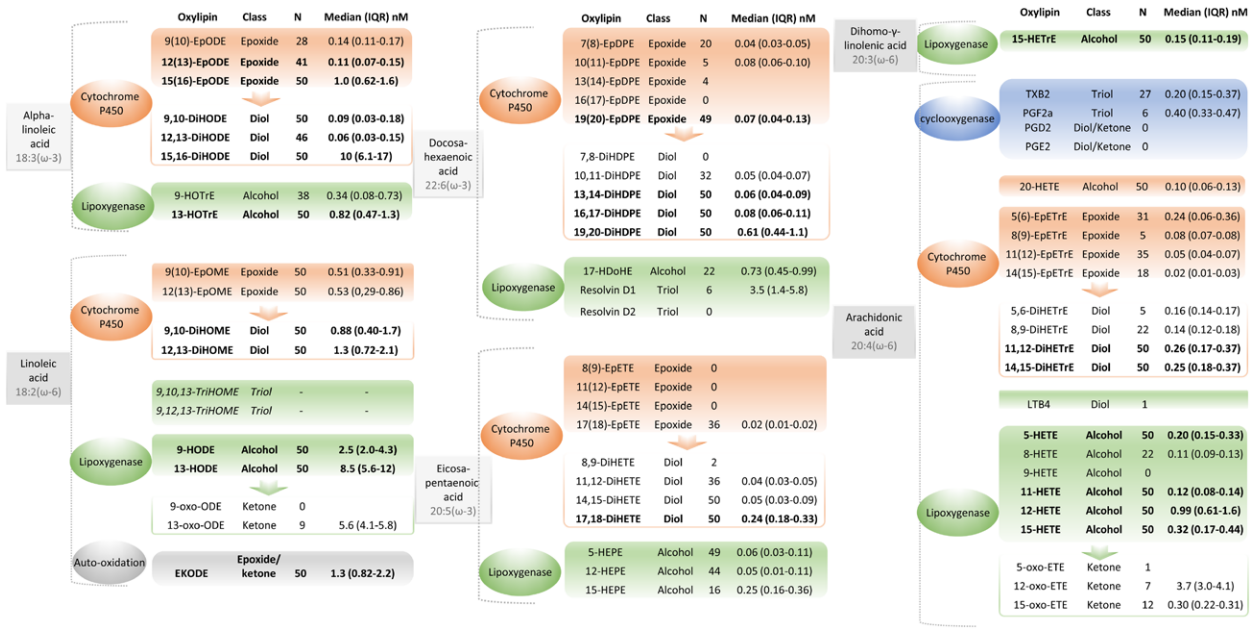

Fig. 1. Investigated oxylipins grouped according to precursor polyunsaturated fatty acid as well as metabolic pathway. Number of samples above the limit of detection is shown as N. Median (interquartile range) for both sample times together (nanomoles per liter) is shown for metabolites detected in 10% or more of samples. Bold font indicates metabolite included in formal analysis. Italic font indicates uncertain values due to multiple peaks.

Table 1. Oxylipins with More Than 80% of Observations above the Limit of Quantification

Oxylipin	Timepoint 1, median (25th–75th), nmol/L	Timepoint 2, median (25th–75th), nmol/L	Hedges' g [95% CI]	*P* Value
9,10-Dihydroxy-octadecenoic acid	0.97 (0.42–1.7)	0.88 (0.39–1.4)	−0.12 [−0.40 to 0.16]	0.394
12,13-Dihydroxy-octadecenoic acid	1.5 (0.86–2.5)	1.1 (0.61–1.7)	−0.32 [−0.65 to 0.02]	0.055
9,10-Dihydroxy-octadecadienoic acid	0.10 (0.04–0.16)	0.08 (0.02–0.18)	−0.19 [0.53 to 0.16]	0.268
12,13-Dihydroxy-octadecadienoic acid	0.06 (0.04–0.16)	0.03 (0.02–0.08)	—	0.019
15,16-Dihydroxy-octadecadienoic acid	11 (6.7–20)	9.6 (5.6–13.2)	−0.26 [−0.55 to 0.03]	0.062
11,12-Dihydroxy-eicosatrienoic acid	0.29 (0.2–0.38)	0.22 (0.16–0.35)	−0.20 [0.42 to 0.02]	0.065
14,15-Dihydroxy-eicosatrienoic acid	0.3 (0.19–0.37)	0.21 (0.17–0.31)	−0.27 [−0.55 to 0.01]	0.051
17,18-Dihydroxy-eicosatetraenoic acid	0.25 (0.2–0.4)	0.24 (0.18–0.32)	−0.20 [−0.44 to 0.04]	0.082
13,14-Dihydroxy-docosapentaenoic acid	0.08 (0.06–0.1)	0.06 (0.04–0.08)	−0.36 [−0.67 to −0.05]	0.019
16,17-Dihydroxy-docosapentaenoic acid	0.08 (0.06–0.12)	0.07 (0.06–0.09)	−0.26 [−0.55 to 0.02]	0.055
19,20-Dihydroxy-docosapentaenoic acid	0.68 (0.44–1.1)	0.53 (0.47–0.95)	−0.18 [−0.46 to 0.09]	0.173
9-Hydroxyoctadecadienoic acid	2.8 (2.2–4.7)	2.4 (1.7–3.5)	−0.30 [−0.67 to 0.08]	0.107
13-Hydroxyoctadecadienoic acid	8.8 (7.0–13)	8.2 (5.7–11)	−0.27 [0.61 to 0.07]	0.107
13-Hydroxyoctadecatrienoic acid	0.62 (0.19–1.1)	0.45 (0.16–0.66)	—	0.143
5-Hydroxyeicosatetraenoic acid	0.21 (0.18–0.35)	0.19 (0.12–0.31)	−0.34 [−0.73 to 0.05]	0.078
11-Hydroxyeicosatetraenoic acid	0.13 (0.1–0.15)	0.11 (0.07–0.14)	−0.50 [−0.95 to −0.06]	0.021
12-Hydroxyeicosatetraenoic acid	**1.3 (0.96–1.7)**	**0.61 (0.45–1.1)**	**−0.98 [−1.5 to −0.43]**	**< 0.001**
15-Hydroxyeicosatetraenoic acid	0.34 (0.2–0.49)	0.29 (0.15–0.42)	−0.24 [−0.51 to 0.02]	0.059
15-Hydroxyeicosatrienoic acid	0.15 (0.11–0.19)	0.13 (0.1–0.19)	−0.08 [−0.42 to 0.26]	0.632
12(13)-Epoxy-9-keto-octadecenoic acid	1.4 (0.98–2.2)	1.1 (0.77–2.1)	−0.26 [−0.49 to 0.02]	0.025
12(13)-Epoxy-octadecadienoic acid	0.1 (0.06–0.15)	0.08 (0.03–0.12)	—	0.067
15(16)-Epoxy-octadecadienoic acid	1.3 (0.7–1.6)	0.88 (0.57–1.5)	−0.32 [−0.72 to 0.08]	0.102
19(20)-Epoxy docosapentaenoic acid	0.08 (0.04–0.16)	0.06 (0.03–0.08)	—	0.109

12-Hydroxyeicosatetraenoic acid was the only lipid with statistically significant change after one day of ventilation, indicated in bold.

Samples were collected at intubation (Timepoint 1) and 06.00 the following morning (Timepoint 2) in 25 cases at both timepoints. Oxylipins without reported Hedges' g were analyzed with Wilcoxon signed-rank test. Oxylipins with reported Hedges' g had a normal distribution after log transformation and were analyzed with paired Student's *t* test.

and not related to this specific topic. We do not consider this relevant to the report. The authors declare no other conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Niklas Larsson, M.D., Malin L. Nording, Ph.D., Jonas Tydén, M.D., Ph.D., Joakim Johansson, M.D., Ph.D., Richard Lindberg, Ph.D., Michael Haney, M.D., Ph.D., M.Sc.
Umeå University, Umeå, Sweden (N.L.).
niklas.larsson@regionvasterbotten.se

DOI: 10.1097/ALN.0000000000004518

This Research Letter is featured in "This Month in Anesthesiology," page A1.

Supplemental Digital Content

Supplemental Digital Content, https://links.lww.com/ALN/D48

References

1. Shearer G, Walker R: An overview of the biologic effects of omega-6 oxylipins in humans. Prostaglandins Leukot Essent Fatty Acids 2018; 137:26–38
2. Morisseau C, Hammock BD: Impact of soluble epoxide hydrolase and epoxyeicosanoids on human health. Annu Rev Pharmacol Toxicol 2013; 53:37–58
3. Dalli J, Colas RA, Quintana C, Barragan-Bradford D, Hurwitz S, Levy BD, Choi AM, Serhan CN, Baron RM: Human sepsis eicosanoid and proresolving lipid mediator temporal profiles: correlations with survival and clinical outcomes. Crit Care Med 2017; 45:58–68
4. Hamaguchi M, Wu HN, Tanaka M, Tsuda N, Tantengco OAG, Matsushima T, Nakao T, Ishibe T, Sakata I, Yanagihara I: A case series of the dynamics of lipid mediators in patients with sepsis. Acute Med Surg 2019; 6:413–8
5. Jones TN, Janani L, Gordon AC, Al-Beidh F, Antcliffe DB: A novel role for cytochrome P450 epoxygenase metabolites in septic shock. Crit Care Explor 2022; 4:e0622
6. Späth J, Brodin T, Cerveny D, Lindberg R, Fick J, Nording M: Oxylipins at intermediate larval stages of damselfly Coenagrion hastulatum as biochemical biomarkers for anthropogenic pollution. Environ Sci Pollut Res Int 2021; 28:27629–38
7. Larsson N, Lehtipalo S, Gouveia-Figueira S, Claesson J, Pourazar J, Isaksson Mettävainio M, Haney M, Nording ML: Plasma and bronchoalveolar lavage fluid oxylipin levels in experimental porcine lung injury. Prostaglandins Other Lipid Mediat 2022; 160:106636
8. Biagini D, Franzini M, Oliveri P, Lomonaco T, Ghimenti S, Bonini A, Vivaldi F, Macera L, Balas L, Durand T, Oger C, Galano J-M, Maggi F, Celi A, Paolicchi A, Di Francesco F: MS-based targeted profiling of oxylipins in COVID-19: A new insight into inflammation regulation. Free Radical Biol Med 2022; 180:236–43
9. Tydén J, Herwald H, Sjöberg F, Johansson J: Increased plasma levels of heparin-binding protein on admission to intensive care are associated with respiratory and circulatory failure. PLoS One 2016; 11:e0152035
10. Kulkarni A, Nadler JL, Mirmira RG, Casimiro I: Regulation of tissue inflammation by 12-lipoxygenases. Biomolecules 2021; 11:717

(Accepted for publication January 23, 2023. Published online first on March 1, 2023.)

Sign-reversed *versus* Orthodox Granger Causality Analysis of the Electroencephalogram in General Anesthesia: Research Letter

To the Editor:

We wish to report on a serendipitous technical observation regarding the calculation of the Granger causality between electroencephalogram (EEG) channels in subjects given propofol, as reported by Pullon *et al.*[1] From subsequent application of this analysis to a separate patient dataset in 2022, it became apparent that there is no accepted convention for the sign of the autoregressive coefficients returned by the "armorf.m" MATLAB function; this means that the transfer function we used in the original analysis had been derived from sign-reversed coefficients. This letter compares the results from the originally published sign-reversed Granger analysis with the "corrected" orthodox Granger analysis methods for the Pullon dataset. The first stage of the Granger algorithm derives the auto- and cross-regression coefficients; thus, the sign reversal alters the subsequent transformation to the frequency domain, effectively acting like a complicated filter. Further mathematical investigations into this are underway, but, empirically, the sign-reversal filter produces very low amplitude auto- and cross-spectra in which narrowband oscillations are not represented and power is shifted to high frequencies. This is evident in figure 1, which shows the frequency spectrum