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Editorial

Association of a Low Serum Eicosapentaenoic Acid/Arachidonic Acid Ratio with the Risk of Acute Venous Thromboembolism

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In recent years, there have been sporadic reports suggesting the involvement of serum polyunsaturated fatty acid (PUFA) levels in the development and/or suppression of ischemic heart diseases[1-3]; however, no consensus has been reached from the results of published clinical studies investigating the suppressive effect of intervention, namely, therapy with PUFAs [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)], on the risk of atherosclerotic cardiovascular disease (ASCVD)[4, 5]. On the other hand, there are only a few reports until date on the relationship of the serum levels of PUFAs and plasma EPA/arachidonic acid (AA) ratio with the risk of development of venous thromboembolism (VTE).

Previous basic research has demonstrated a prophylactic effect of oral EPA administration against venous thrombosis[6], whereas a small-scale cross-sectional study has shown an increased incidence of pulmonary embolism in patients with low plasma EPA/AA ratios[7]. In a case-control study, known to yield a high level of evidence among observational researches, the authors found that depression of the serum EPA/AA ratio may contribute to the development of VTE in young individuals[8]. Although further investigation is needed because of the small size of the study population in the aforementioned study, the results of the study are expected to provide the basis for prevention and treatment of VTE, which poses a serious problem in the clinical practice setting.

The pathogenetic mechanism underlying the association between VTE and low serum EPA/AA ratios, which is the subject of the present study, involves imbalanced bioactivities of PUFAs (n-3 series, n-6 series) *in vivo*, based on the evidence accumulated through extensive basic and clinical studies[9]. Localized intravascular inflammation, vascular endothelial dysfunction, and blood coagulation abnormalities have been reported as being involved in the development of VTE, and depression of the serum EPA/AA ratio likely enhances vascular inflammatory reactions, giving rise to vascular endothelial dysfunction and platelet aggregation (**Fig. 1** and **2**).

A large-scale clinical study to verify whether the serum EPA/AA ratio, which is a marker of the risk of ASCVD development, as suggested by the Japan EPA Lipid Intervention Study (JELIS) in Japanese subjects[10], can serve as a predictor of the risk of VTE, or a multicenter randomized controlled clinical trial to verify the prophylactic effect of oral PUFA administration on the risk of VTE is warranted to clarify the association between the serum EPA/AA ratio and the risk of VTE.

Disclosure of Conflict of Interest

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References

1) Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S; JPHC Study Group: Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. Circulation, 2009; 113: 195-202
2) Nishizaki Y, Shimada K, Tani S, Ogawa T, Ando J, Takahashi M, Yamamoto M, Shinozaki T, Miyauchi K, Nagao K, Hirayama A, Yoshimura M, Komuro I, Nagai R, Daida H: Significance of imbalance in the ratio of serum n-3 to n-6 polyunsaturated fatty acids in patients with acute coronary syndrome. Am J Cardiol, 2014; 113: 441-445
3) Tani S, Nagao K, Hirayama A: Association of atherosclerosis-related markers and its relationship to n-3 polyun-

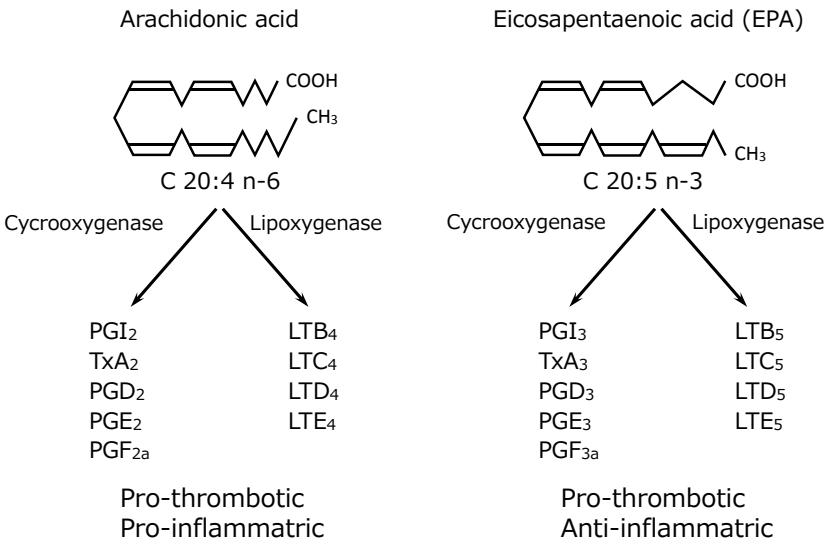

Fig. 1. Physiological Activities of Arachidonic Acid and Eicosapentaenoic Acid

It is well-known that proinflammatory lipid mediators, such as TXA2, PGE2, LTC4, and LTB4, are synthesized from arachidonic acid. On the other hand, eicosanoids biosynthesized from EPA, such as each of the 3-series prostaglandins and the 5-series leukotrienes, act to suppress the inflammation induced by the proinflammatory eicosanoids. Since the action of a metabolite of EPA antagonizes that of arachidonic acid, an inflammation-suppressing physiological environment is formed.
TX = thromboxane; PG = prostaglandin; LT = leukotriene; EPA = eicosapentaenoic acid

saturated fatty acids levels with a prevalence of coronary artery disease in an urban area in Japan. Heart Vessels, 2015; 30: 9-19
4) Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS: Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA, 2012; 308: 1024-1033
5) Casula M, Soranna D, Catapano AL, Corrao G: Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, placebo controlled trials [corrected]. Atheroscler Suppl, 2013; 14: 243-251
6) Kuma H, Nagashima R, Hatae H, Tsuda T, Hamasaki N: Beneficial effect of EPA (20:5 n-3 PUFA) on preventing venous thromboembolism: a rat tail thrombosis model experiment. Thromb Res, 2013; 131: 107-108
7) Oshima Y, Niki K, Hiramoto Y, Morimoto S, Takami H, Izumi M: Serum eicosapentaenoic acid/arachidonic acid ratio is low in patients with pulmonary thromboembolism. J Nutr Sci Vitaminol (Tokyo), 2013; 59: 474-477
8) Hiki M, Miyazaki T, Shimada K, Sugita Y, Shimizu M, Aikawa T, Ouchi S, Shiozawa T, Takasu K, Takahashi S, Takagi A, Miyauchi K, Daida H: Significance of Serum Polyunsaturated Fatty Acid Level Imbalance in Patients with Acute Venous Thromboembolism. J Atheroscler Thromb, 2017; 24: 1016-1022
9) Ohnishi H, Saito Y: Eicosapentaenoic acid (EPA) reduces cardiovascular events: relationship with the EPA/arachidonic acid ratio. J Atheroscler Thromb, 2013; 20: 861-877
10) Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T,Shimada K, Shirato K; Japan EPA lipid intervention study (JELIS) Investigators: Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet, 2007; 369: 1090-1098

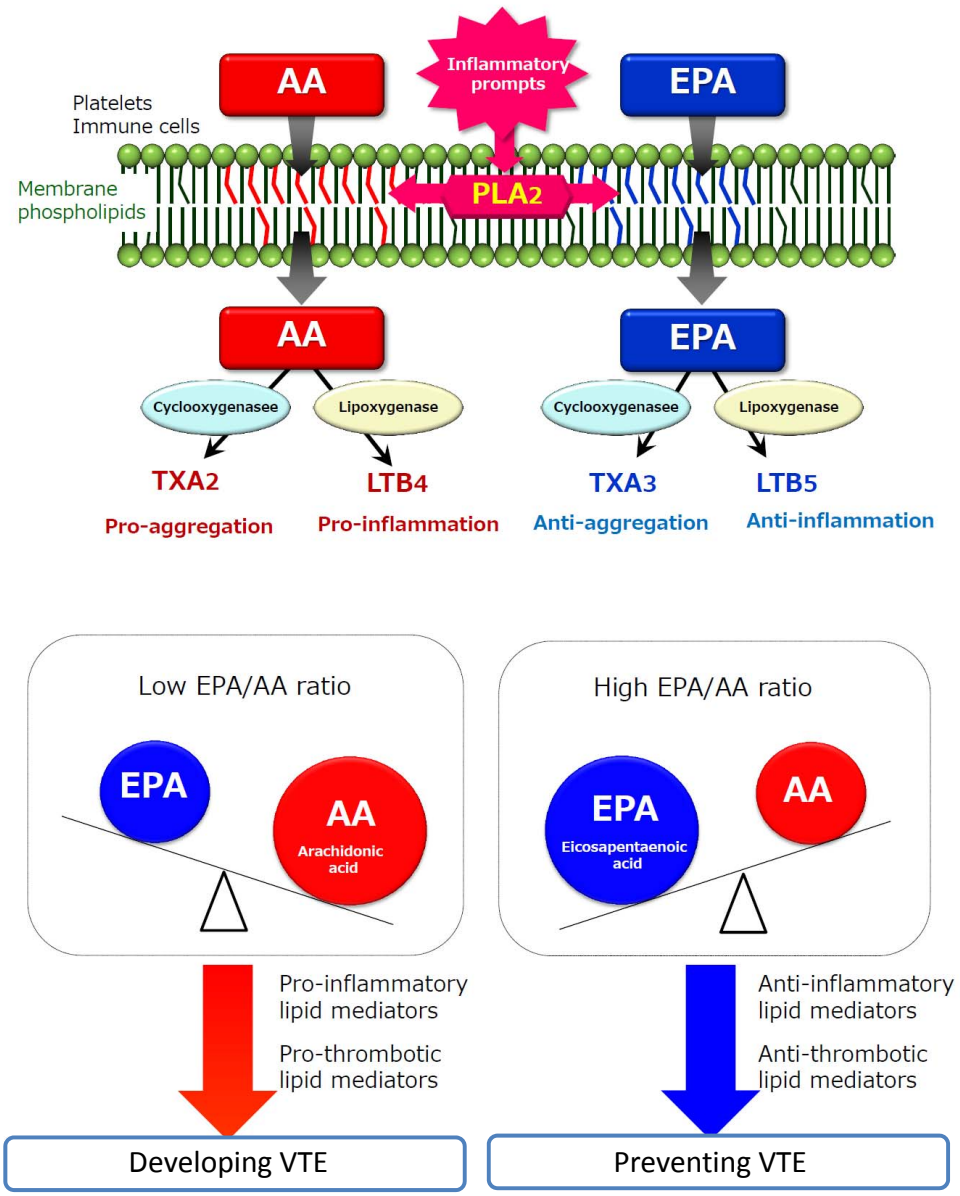

Fig. 2. Anti-thrombotic and Anti-inflammatory Effects of EPA versus AA, and the Effect of an Unbalanced EPA/AA Ratio on the Risk of Development of VTE

AA = arachidonic acid; EPA = eicosapentaenoic acid; PLA = phospholipase; X = thromboxane; PG = prostaglandin; LT = leukotriene; VTE = venous Thromboembolism