Omega-3 PUFA vs. NSAIDs for Preventing Cardiac Inflammation

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INTRODUCTION

Inflammatory cell accumulation occurs in the cardiac muscle during cardiac injury and repair (1). From an evolutionary perspective, inflammation is required for immunosurveillance and host defense. However, such cardinal signs of acute inflammation, such as redness, pain, swelling etc., due to injury or infection. Might be typically absent in chronic low-grade inflammation (LGI). Current literature suggests that chronic low-grade inflammation (LGI) is a primary causative factor behind chronic diseases like cardiovascular diseases (CVD), non-alcoholic fatty liver disease (NAFLD) and obesity (2).

COMMON MECHANISMS FOR NSAIDs

NSAIDs are anti-inflammatory drugs which as a class block the generation of prostaglandins (PGs), leukotrienes (LT) or epoxides (3), which are upregulated during inflammation Therefore, NSAIDs are commonly used for prevention of multiple chronic inflammatory conditions including CVD. The major enzyme participating in PG biosynthesis is cyclooxygenase (COX), which is subdivided as constitutive COX-1 and inducible COX-2 forms. These isoforms of COX show differential activity in inflamed tissues. COX-2 is expressed 10- to 80-fold, whereas COX-1 expressed 2- to 4-fold (4). Both COX isoforms are responsible for converting arachidonic acid (ARA) to intermediate PGs, the PGG2, and the PGH2. ARA is the precursor of eicosanoids which is cleaved by phospholipase A2 (PLA2) from membrane phospholipids. Then thromboxane synthase and various isomerases are activated which generates thromboxane A2 (TxA2) and PGs (PGE2, PGF2α, PGD2, PGI2) (5). These four PGs have the common function of vasodilation as well as increasing permeability of membranes (thus promoting “redness” due to increased blood flow). PGE2 and PGF2α are mainly produced by monocytes and macrophages, mast cells produce PGD2 and endothelial cells produce PGI2 (6). Long-term treatment with NSAIDs lower beneficial PGs as well (7). PGE2 and PGF2α control water and electrolyte absorption and maintain secretion in gastric mucosa. Thus, NSAIDs can decrease the secretion of mucous-bicarbonate barrier between the gastric lumen and epithelial cells. Subsequently, in contact with low pH of the stomach, epithelial cells are killed and the integrity of the mucosa is lost, causing ulceration (7).

ASPIRIN

Aspirin is a widely used anti-inflammatory drug. Aspirin inhibits the COX activity by acetylating the hydroxyl group on COX, which specific acts on serine residues. This leads to the irreversible inhibition of COX, as well as causes the ARA binding restriction (8).

Aspirin is easily and quickly absorbed in the GI tract and hydrolyzes to salicylic acid (SA) in the stomach and intestine. However, SA and aspirin can strongly bind to albumin. This avoids the hydrolysis of aspirin too fast (9), as albumin concentration often decreases dramatically under acute inflammation due to the formation of complex albumin-hyaluronic acid or due
to decreased albumin synthesis (9, 10). Thus, SA and aspirin hydrolyze faster under acute inflammation. In this case, regulating the range of SA (or aspirin dose) concentration is critical in order to avoid further adverse effects. The half-life of aspirin is relatively short, for 15–20 min in adults. Aspirin inhibits the PGs production mainly due to the blockage of COX-2. However, aspirin also inhibits the cytoprotective PGs in gastric mucosa, which impairs the integrity of epithelial cells and also destabilizes the lysosomal membrane (11).

**INDOMETHACIN**

Indomethacin is a NSAID, and is effective against fever and pain. Like aspirin, indomethacin is a non-selective NSAIDs, which block both COX-1 and COX-2 (12). Thus, PGE$_1$ and PGE$_2$ in gastric mucosa can be reduced, resulting in gastric and intestinal ulceration (11). Similarly, with the inhibitory effect of TxA$_2$, the platelet aggregation ability decreases dramatically to induce bleeding (13). Studies also show that indomethacin can potentially increase the blood pressure in patients (14). It is easily absorbed by the GI tract and bind with the protein in plasma and injured tissues, specifically albumin as aspirin.

**IBUPROFEN**

Ibuprofen is an effective analgesic and antipyretic and especially recommended for children because of its better safety profile. Ibuprofen needs longer time than other NSAIDs as an antipyretic and it has a more intense effect on pain relief than aspirin (15). The advantage of this drug is the lighter side effects on the GI tract. High dose for long-term use is mainly for the chronic inflammatory diseases, including arthritis (15).

**RECENT PROBLEMS WITH USING NSAIDs IN CARDIAC DISEASES**

NSAIDs like aspirin has been used for decades to protect against low grade inflammation in cardiovascular disorders. It was initially thought to be safe and effective against systemic inflammation affecting the cardiovascular system (16, 17). However, evidence of benefit as not been consistent (18) and is plagued by major side effects like GI bleeding, which can make this therapeutic approach questionable in vulnerable populations (19). In essence, a core impact of NSAIDs is to inhibit COX activity. However, COX activity, especially COX-2, is responsible for also maintaining aorta function. COX2 disruption can harden aorta leading to aortic fibrosis (20) and atheroclerosis (21). In addition, inhibition of COX2 reduces the benefits of statin on cardioprotection (22). This might be the reason why all NSAIDs like ibuprofen and naproxen in addition to aspirin in recent years have demonstrated cardiovascular effects including heart attacks (23, 24). More importantly, according to a recent study, long-term users of aspirin have >30% increased chance of a cardiovascular event upon withdrawal of the drug (25) Therefore, preventative therapies that avoid long term NSAID use is warranted in chronic inflammatory diseases including CVDs.

**OMEGA-3 PUFA**

Omega-3 PUFA are polyunsaturated fatty acids with the first double bond on the third carbon from the terminal methyl end. Fish and flaxseed oils are rich in omega-3 PUFA with protective functions for the heart (26), liver (27), and brain (28). The major fatty acids contained in the fish oil supplement are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the long chain members of the omega-3 family. In contrast, flaxseed oil is mainly composed of alpha-linolenic acid (ALA), the parent omega-3 PUFA.

**MECHANISM OF ANTI-INFLAMMATORY RESPONSE**

Similar to NSAIDs, omega-3 PUFA, especially EPA and DHA inhibit the production of pro-inflammatory eicosanoids. However, instead of blocking COX activity, they use the same COX to increase the production of anti-inflammatory eicosanoids by providing a different substrate. Twenty-carbon omega-3 PUFA and ARA compete with each other for the use of the COX enzyme. This increases the production of the anti-inflammatory mediators like LTB$_4$ and PGE$_3$ from EPA and at the same time limits the inflammatory LTB$_4$ and PGE$_2$ production from ARA (29). In this case, the mucosa protective PGs (PGE$_2$) are still available, albeit reduced. As a result, the side effects caused by anti-inflammatory drugs are drastically reduced. Given the basic differences in the mechanism of NSAIDs and omega-3 PUFAs in blocking COX vs. providing an alternate substrate to COX enzyme, the timeline for actions are vastly different. NSAIDs are more acute in action due to direct enzymatic blockade, whereas omega-3 PUFAs act slower due to its gradual replacement of membrane phospholipid ARA, which might take weeks if not months to have a biologically plausible effect. Clearly, NSAIDs are preferred for acute inflammatory challenges resulting from physical injury or trauma whereas omega-3 PUFAs are at best a long term, mild anti-inflammatory solution. Thus, consuming omega-3 supplement can be considered as a preventative therapy, alternate to NSAIDs on resolving long-term chronic inflammatory stage, with some major differences as listed in Table 1 (65).

In addition to modulating PGs, EPA and DHA produce lipid mediators responsible for anti-inflammation and resolution: resolvins and protectins (66). Due to the different substrates of resolvins’ production, they are divided into E-series from EPA and D-series from DHA (66). Although they are from different sources, they show very similar effects on preventing inflammation. Both of them increase with the presence of aspirin or with higher EPA/DHA consumption, which are stimulated by the aspirin acetylated COX-2. As mentioned before, COX-2 is the rate-limiting enzyme promoting the synthesis of pro and anti-inflammatory eicosanoids, depending on the different substrates. COX-2 dependent resolvins attenuate inflammation and block...
inhibition of pro-inflammatory signaling, nitric oxide (NO) production increases (45). This leads to improved endothelial function (70).

Considering of the close relation between inflammation and oxidative stress, omega-3 PUFA can also lower oxidative stress through increased cellular antioxidant capacity. However, this result can only be reached with over 3.4 g/day EPA/DHA consumption (71). Having a high dose of omega-3 PUFA on the other hand can cause excess fatty accumulation, which potentially can also increase oxidative stress, given that omega-3 PUFAs have multiple double bonds amenable to oxidation.

### POTENTIAL RISKS OF OMEGA-3 PUFA SUPPLEMENTATION

Inflammation exists to fight off infection or injury. Thus, while LGI may be perceived as detrimental, acute inflammation especially in the context of infection is a protective response that needs to be sustained at least for some time. In a chronic inflammatory state, such as rheumatoid arthritis (RA), EPA/DHA reduce RA inflammation and benefits the patient. However, the similar effects during infection or tumor surveillance can result in a negative health outcome (72–74). In 2005, IOM summarized that intake of 0.9–9.4 g/day of EPA and 0.6–6 g/day of DHA was linked to an impairment of immune responses. It is now known that DHA and EPA can both improve and impair host resistance to a number of pathogens (75, 76). These adverse outcomes of omega-3 intake were observed with bacterial, fungal and viral pathogen models (77). Given the potent anti-inflammatory effects of DHA and EPA, it is thus conceivable omega-3 PUFA can be both helpful or detrimental specific to the disease context. Moreover, like most nutrients or anti-inflammatory drugs, there is a potential for negative health effects under excess intakes.

### NSAIDs AND OMEGA-3 PUFA IN COMBINATION?

An intriguing idea would be to use both low dose NSAID and long chain omega-3s like DHA/EPA in combination for prevention of cardiac and other LGI states. In theory, as both these classes of drugs act on the same COX/LOX pathway, the requirements/dosing of each might be lower due to their synergistic effects. The problem with such an approach is that long term safety of omega-3 supplementation in the pill form still remains unestablished in patients with various LGI states including CVD. With recent reports of long term ill effects of NSAIDs at the current dosing levels in cardiac patients, there is evidence that it might be risky to carry on such a trial for potential negative effects on coagulation (78).

In conclusion, the effectiveness of NSAIDs for acute inflammation has not translated to a safe strategy for long term prevention of CVD. Controversy also surrounds the long term impact of omega-3 PUFA as a preventative measure against chronic low grade inflammation (77). However, in patients unable to take NSAIDs in the long term due to GI or bleeding problems, due to the similarity in their mechanism of action,
low dose omega-3 PUFA could be a substitute to prevent LGI associated with cardiovascular diseases.

AUTHOR CONTRIBUTIONS
JY wrote the paper. SG edited and revised the paper. Both authors read and approved the final manuscript.

REFERENCES

1. Epelman S, Liu PP, Mann DL. Role of innate and adaptive immune mechanisms in cardiac injury and repair. *Nat Rev Immunol*. (2015) 15:117–29. doi: 10.1038/nri3800

2. Calder PC, Ahlawatia N, Brouns F, Bueter T, Clement K, Cunningham, K, et al. Dietary factors and low-grade inflammation in relation to overweight and obesity. *Br J Nutr*. (2011) 106:S1–78. doi: 10.1017/S0007114511005460

3. Vane J, Botting R. Anti-inflammatory drugs and their mechanism of action. *Inflamm Res*. (1998) 47:78–87. doi: 10.1007/s000110050284

4. DeWitt DL, Meade EA, Smith WL. PGH synthase isoenzyme selectivity: the potential for safer nonsteroidal antiinflammatory drugs. *Am J Med*. (1993) 95:S40–44. doi: 10.1016/0002-9343(93)90396-7

5. Smith WL. The eicosanoids and their biochemical mechanisms of action. *Biochem J*. (1989) 259:315–324. doi: 10.1042/bj259315

6. Calder PC. Long-chain polyunsaturated fatty acids and inflammation. *Scand J Food Nutr*. (2006) 50:54–61. doi: 10.1080/17482970601066389

7. Ivey KJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage: actions of therapeutic agents. *Am J Med*. (1988) 84:41–8. doi: 10.1016/0002-9343(88)90253-7

8. Vane J, Botting R. The mechanism of action of aspirin. *Thromb Res*. (2003) 110:255–8. doi: 10.1016/S0049-3848(03)00379-7

9. Aarons L, Clifton P, Fleming G, Rowland M. Aspirin binding and the effect of albumin on spontaneous and enzyme-catalysed hydrolysis. *J Pharm Pharmacol*. (1980) 32:537–43. doi: 10.1111/j.2042-7158.1980.tb12991.x

10. Don BR, Kaysen G. Poor nutritional status and inflammation: serum albumin: a Bayesian meta-analysis of individual patient data. *BMJ* (2017) 357:j1909. doi: 10.1136/bmj.j1909

11. Masterton G, Plevris J, Hayes P. omega-3 fatty acids–a promising novel therapeutic agent? *Cureus*. (2017) 9:e98165. doi: 10.17719/cureus.98165

12. Varga Z, Rafay ali Sabzwari S, Vargova V. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus*. (2017) 9:e1144. doi: 10.7759/cureus.1144

13. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* (2017) 357:j1909.

14. Vane J, Botting R. The mechanism of action of aspirin. *Thromb Res*. (2003) 110:255–8. doi: 10.1016/S0049-3848(03)00379-7

15. Aarons L, Clifton P, Fleming G, Rowland M. Aspirin binding and the effect of albumin on spontaneous and enzyme-catalysed hydrolysis. *J Pharm Pharmacol*. (1980) 32:537–43. doi: 10.1111/j.2042-7158.1980.tb12991.x

16. Rainsford K. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology*. (2009) 17:275–342. doi: 10.1007/s10332-009-0016-x

17. Boardman P, Hart FD. Side-effects of indomethacin. *J Clin Pharmacol*. (1982) 22:197–201. doi: 10.1007/BF00545214

18. Rainsford K. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology*. (2009) 17:275–342. doi: 10.1007/s10332-009-0016-x

19. Guirguis-Blake JM, Evans CV, Senger CA, O’Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the u.s. preventive services task force. *Ann Intern Med*. (2016) 164:804–13. doi: 10.7326/M15-2113

20. De Caterina R, Ruigómez A, Rodríguez LA. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. *Arch Intern Med*. (2010) 170:1430–5. doi: 10.1001/archinternmed.2010.305

21. Kirkby NS, Lundberg MH, Wright WR, Warner TD, Paul-Clark MJ, Mitchell JA. COX-2 protects against atherosclerosis independently of local vascular prostacyclin: identification of COX-2 associated pathways implicate Rgl1 and lymphocyte networks. *PLoS ONE*. (2014) 9:e98165. doi: 10.1371/journal.pone.0098165

22. Varga Z, Rafay Ali Sabzwari S, Vargova V. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus*. (2017) 9:e1144. doi: 10.7759/cureus.1144

23. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ* (2017) 357:j1909.

24. Vane J, Botting R. The mechanism of action of aspirin. *Thromb Res*. (2003) 110:255–8. doi: 10.1016/S0049-3848(03)00379-7

25. Shau WY, Chen HC, Chen ST, Chou HW, Chang CH, Kuo CW, et al. Risk of new acute myocardial infarction hospitalization associated with use of oral and parenteral non-steroidal anti-inflammatory drugs (NSAIDs): a case-crossover study of Taiwan’s National Health Insurance claims database and review of current evidence. *BMC Cardiovasc Disord*. (2012) 124. doi: 10.1186/2216-2261-12-4

26. Endo J, Arita M. Cardioprotective mechanism of omega-3 polyunsaturated fatty acids. *J Cardiol*. (2016) 62:22–7. doi: 10.1002/hjcc.20502

27. Masterton G, Plevris J, Hayes P. Omega-3 fatty acids—a promising novel therapy for non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. (2010) 31:679–92. doi: 10.1111/j.1365-2633.2009.04230.x

28. Innis SM. Dietary omega 3 fatty acids and the developing brain. *Brain Res*. (2008) 1237:35–43. doi: 10.1016/j.brainres.2008.08.078

29. Lee S, Kim HJ, Chang KC, Baek JC, Park JK, Shin JK, et al. DHA and EPA down-regulate COX-2 expression through suppression of NF-κ B activity in LPS-treated human umbilical vein endothelial cells. *Korean J Physiol Pharmacol*. (2009) 13:301–7. doi: 10.4196/kjpp.2009.13.4.301

30. Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. *J Am Coll Nutr*. (2002) 21:495–505. doi: 10.1080/07315724.2002.10719248

31. Vane J, Botting R. Mechanism of action of anti-inflammatory drugs. *Scandinavian J Rheumatol*. (1996) 25:9–21. doi: 10.3109/030094796097226

32. Ilfingworth DR, Harris WS, Connor WE. Inhibition of low density lipoprotein apo B activity by omega-3 fatty acids. *J Nutr*. (1998) 128:495–502. doi: 10.1093/jn/128.5.495

33. Vane J, Botting R. Mechanism of action of anti-inflammatory drugs. *Scandinavian J Rheumatol*. (1996) 25:9–21. doi: 10.3109/030094796097226

34. Bhosale UA, Quraishi N, Yegnanarayan R, Devasthale D. A cohort study to evaluate the relationship of cardiovascular risk factors and low dose aspirin in cardiovascular disease prevention. *Scand J Clin Lab Invest*. (2009) 69:132–7. doi: 10.1080/00365510903344661

35. Ye and Ghosh Omega-3 PUFA and Drugs in Inflammation

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fungal infection in mice. *Biochim Biophys Acta* (2003) 1622:151–60. doi: 10.1016/S0304-4165(03)00136-3

73. Byleveld PM, Pang GT, Clancy RL, Roberts DC. Fish oil feeding delays influenza virus clearance and impairs production of interferon-gamma and virus-specific immunoglobulin A in the lungs of mice. *J Nutr.* (1999) 129:328–35. doi: 10.1093/jn/129.2.328

74. Fritsche KL, Shahbazian LM, Feng C, Berg JN. Dietary fish oil reduces survival and impairs bacterial clearance in C3H/Hen mice challenged with *Listeria monocytogenes*. *Clin Sci* (Lond). (1997) 92:95–101. doi: 10.1042/cs0920095

75. Anderson M, Fritsche KL. (n−3) Fatty acids and infectious disease resistance. *J Nutr.* (2002) 132:3566–76. doi: 10.1093/jn/132.12.3566

76. Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr.* (2002) 56 Suppl. 3:S14–9. doi: 10.1038/sj.ejcn.1601478

77. Fenton JI, Hord NG, Ghosh S, Gurzell EA. Immunomodulation by dietary long chain omega-3 fatty acids and the potential for adverse health outcomes. *Prostaglandins Leukot Essent Fatty Acids* (2013) 89:379–90. doi: 10.1016/j.plefa.2013.09.011

78. Block RC, Kakinami L, Jonovich M, Antonetti I, Lawrence P, Meednu N, et al. The combination of EPA+DHA and low-dose aspirin ingestion reduces platelet function acutely whereas each alone may not in healthy humans. *Prostaglandins Leukot Essent Fatty Acids* (2012) 87:143–51. doi: 10.1016/j.plefa.2012.08.007

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