Emergency Administration of n-3 Polyunsaturated Fatty

Acids to Correct Fatal Arrhythmias

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**Introduction**

N-3 polyunsaturated fats (PUFAs), derived from fatty fish, have been proven to have protective cardiovascular effects due to their antiarrhythmic qualities (Nettleton, J. A., 1995). Epidemiologic studies have shown that populations that consume a large amount of dietary fish oil have fewer deaths to due cardiovascular events such as atrial and ventricular arrhythmias (Kang & Leaf, 1996). This discovery lead to animal studies that proved acute injections of fish oil could both prevent and terminate induced arrhythmias (Kang & Leaf, 2002). This is accomplished by the n-3 PUFAs directly interacting with the sodium channel protein of cardiomyocytes (Xiao, Wright, Wang, Morgan, & Leaf, 1998). This interaction causes a decrease in resting membrane potential, an increase in the excitation threshold, and an increased duration of the refractory period of myocytes, making them resistant to the excessive nerve firing characterizing arrhythmias (Li, Wang, Li, 2011 & Xaio et al., 1998). Because the n-3 PUFAs can have this effect on the cardiomyocytes in an acute way, the inclusion of n-3 PUFAs in resuscitative efforts during a cardiac event maybe successful at decreasing mortality due to arrhythmias in an inpatient setting (Kar, S, 2013 & Heidt, Vician, Stracke, Stadlbauer, Grebe, Boening, Erdogan, 2009). Fatal arrhythmias are especially common in post-operative patients following coronary artery bypass graft (CABG) surgery, and are a common cause of death during recovery (Perreto, Durante, Limite, Cianflone, 2014). Thus far, studies on the inclusion of n-3 PUFAs as drug therapy in patients prior to and following CABG surgery have all been administered intravenously (Kar, S, 2013, Heidt et al., 2009 & Heidarsdottir, Arnar, Skuladottir, Torfason, Edvardsson, Gottskalksson, Palsson, Indridason, 2010). The patients in these studies also took fish oil in the hours prior to their surgery, and every day during their recovery, not at the exact moment of a cardiac event (Kar, S, 2013, Heidt et al.,2009 & Heidarsdottir et al., 2010). Administration of n-3 PUFAs at the time of a cardiac event in post-operative coronary artery bypass graft patients has not yet been studied. Although, at the time of an event, intravenous administration would no longer be an appropriate method of delivery. An intracardiac injection may be more prudent than intravenous administration during a cardiac event because the blood would not move efficiently enough to circulate the n-3 PUFAs back to the myocytes. The myocytes would be immediately bathed in the n-3 PUFAs upon administration and would be able to take effect in the first critical minutes of a cardiac event. If successful, the administering of the n-3 PUFAs would terminate the event prior to the third failed defibrillation. Termination of the arrhythmia prior to the third failed shock would prevent the need for a resternotomy and would save the patient from further trauma to the chest or death. It would be worth creating in depth human trials to discover whether or not the acute administration of n-3 PUFAs to post-operative CABG patients at the time of a cardiac event could terminate an arrhythmia and decrease mortality due to them. Intracardiac injection should be studied more opposed to intravenous because of the implications it may have in an outpatient setting.

**Mechanism Action of n-3 PUFAs**

The suppressing effect n-3 PUFAs have on arrhythmic episodes call into question the mechanism of them doing so. “The precise mechanism by which free PUFAs slow the contractions of the cardiomyocytes remains unknown”, but there are a few schools of thought that have explored possible theories for how this reaction occurs (Kang et al., 1994). It is agreed that n-3 PUFAs correct arrhythmias by raising the threshold for excitation by suppressing voltage-gated Na+ channels as well as by increasing the refractory period (Li et al., 2011). The differences between the excitability of cardiac muscle cells with and without n-3 PUFAs present can be observed in Fig.1.

**Figure 1: Reduced Excitability of Cardiac Myocytes due to Presence of n-3 PUFAs**

This figure shows the differences between a regular action potential and an action potential changed by the presence of n-3 PUFAs. The resting potential is lower and the excitation threshold is higher in cells affected by n-3 PUFAs. The time taken during the refractory period is also significantly longer.

Peak Action Potential

Resting Potential with n-3 PUFAs

Time

+30

-70

-90

*Membrane Potential (mV)*

Repolarization with n-3 PUFAs

Repolarization

Excitation threshold with n-3 PUFAs

Excitation threshold

Hyperpolarization

Resting Potential

At rest, cardiac muscle cells have a high number of sodium ions surrounding them and low numbers of sodium ions inside of them. The reverse is true for potassium ions which have a high concentration inside the cell and a low concentration outside the cell at rest. This resting state causes a concentration gradient maintained by channel protein, ATPase. When a cardiac muscle cell is being depolarized it is dependent on the movement of sodium and potassium ions in and out of the cell when it receives an electrical signal to contract. The signal must be strong enough to reach the excitation threshold, which for muscle cells is around -70 millivolts. Resting potential is around -90 millivolts. The resting potential and excitation threshold for cardiac muscle is slightly different than for skeletal muscle. Once this threshold is reached the myoctyes will completely depolarize. There are no half depolarizations. The reaction is all or nothing once the excitation threshold is reached. This depolarization is marked by sodium ions rushing into the cell. Once the cell reaches peak action potential the cell must repolarize, also known as the refractory period. The cell cannot be fired again until the refractory period has passed. The repolarization of a muscle cell is marked by potassium ions rushing out of the cell. This is the mechanism by which the myocytes in the heart are fired. When the heart is experiencing a fatal arrhythmia, such as ventricular tachycardia/fibrillation or atrial fibrillation, this process will happen over and over at a rapid speed. Rapid speed of contraction does not allow the heart to relax long enough to move the necessary volume of blood to supply the body with oxygen.

N-3 PUFAs change this mechanism. N-3 PUFAs “slightly hyperpolarize the resting membrane potential and make more positive the threshold for the gating of the fast Na+ channels so that a 40-50% stronger electrical stimulus is required to elicit an action potential” (Xiao et al., 1998). This makes it harder to initially start the contraction of a myocyte receiving the excessive signaling that occurs during fatal arrhythmias such as ventricular tachycardia, flutter, or fibrillation or atrial fibrillation. The potassium pathway is affected by n-3 PUFAs as well. The n-3 PUFAs inhibit or block potassium channels and, therefore, “prolong the relative refractory period 2-3-fold” (Xiao et al., 1998).

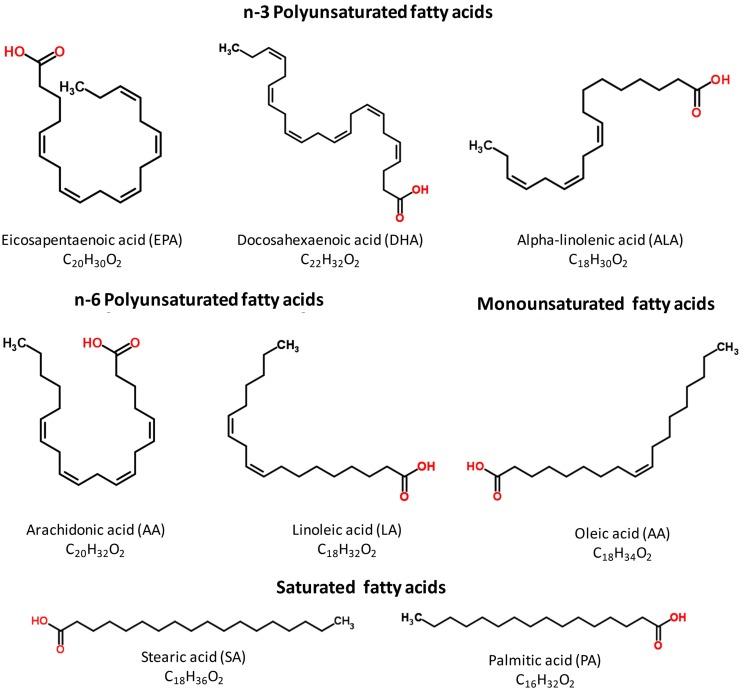
This effect has been proven to work in several laboratory settings. Tests have been administered using isolated myocytes as well as in living animals, both of which had the same results. In the year 2000, Kang and Leaf did two studies testing the antiarrhythmic action of n-3 PUFAs. These researchers studied the effect of n-3 PUFAs on cultured neonatal rat heart cells. The cells were bathed in a calcium rich fluid which caused the myocytes to contract “irregularly and asynchronously: this was the in vitro equivalent of fibrillation in vivo” (Kang et al., 2002). It was found that when 10 μmol of n-3 PUFAs were added to the bathing medium of the myocytes “the arrhythmia was terminated and the cell resumed a regular beating rate despite the continued presence of the toxic concentrations of Ca2+” (Kang et al., 2002).

This result appeared to be replicated in myocytes of living animals as well. In another study in 2000 by Kang and Leaf, exercising dogs were used. These dogs had been surgically prepared with a hydraulic cuff which occluded the left circumflex artery during exercise. This occlusion caused the dogs to enter ventricular flutter and fibrillation. After it was established that the dogs would enter a ventricular arrhythmia in these conditions, n-3 PUFAs were given to the dogs. 50-60 minutes prior to the beginning of the test, the dogs were given “an intravenous infusion of 2-5 g concentration of n-3 PUFAs from fish oils” (Kang et al., 2002). In 11-14 dogs, a fatal arrhythmia was prevented (Kang et al., 2002).

These studies, among others, show “the antiarrhythmic action of n-3 PUFAs by electrically [stabilizing] the heart cells” (Kang et al., 2002). Because fatal arrhythmias are marked by excessively high heart rates, this change of mechanism is an effective protector against arrhythmias. Current research has not pinpointed exactly how n-3 PUFAs inhibit Na+ and K+ channels. It is possible that “they modify the current through indirect effects on the lipid bilayer or directly interact with the channel protein,” but the “dominant view is that n-3 PUFAs directly interact with the protein of the ion channel” (Xiao et al., 1998).

Research has suggested that this antiarrhythmic effect only seems to be consistent in n-3 polyunsaturated acids derived from fish oils. The exact portion of the n-3 PUFAs that interact with the cell membranes is the free carboxyl group on the end of the chemical structure of the three types of n-3 PUFAs (Kang et al., 2002). In order for an antiarrhythmic reaction to occur, the fatty acid must be a “molecule with a long acyl or hydrocarbon tail, ≥2 unsaturated carbon-carbon double bonds, and a free carboxyl group at one end” (Kang et al., 2002). This type of chemical structure is able to directly interact with voltage-gated sodium channels in the cell membrane. Sodium channels are voltage-gated and are closed until a stimulus is given. The pore region of the channel can be “penetrated by fatty acyl chains that extend into the central cavity which may allow the entry of small hydrophobic pore-blocking drugs” (Kar, 2013). This is how n-3 PUFAs can block sodium channels despite the impulses being sent to the cell. The chemical structure of the n-3 PUFAs can be observed in Fig. 2. The three types of n-3 PUFAs are Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), and Alpha-linolenic acid (ALA) (Source 12). In experiments using rat cardiomyocytes, DHA was found to be “the most potent n-3 PUFA blocking sodium channels” (Moreno, Macías, Prieto, Cruz, González, & Valenzuela, 2012). For this reason, it may be reasonable to continue research on DHA because it seems to have the most powerful antiarrhythmic effect. Upon closer inspection, n-6 PUFAs have the same chemical structure as n-3 PUFAs; also having at least two carbon-carbon double bonds and a free carboxyl group on one end, as seen in Figure 2. However, for unknown reasons, research suggests n-6 PUFAs do not have consistent antiarrhythmic qualities as n-3 PUFAs do. In the studies done by Kang and Leaf in 2000, they found that n-6 PUFAs were antiarrhythmic but were anomalous “because in ≈60% of tests it either had no antiarrhythmic action or induced violent arrhythmias” (Kang et al., 2002). Due to the risks of actually causing more arrhythmias, n-3 PUFAs were chosen for further research because they are proven to be “more dependably only antiarrhythmic” (Kang et al., 2002).

**Figure 2:**  Structure of the main n− 3 (EPA, DHA, and ALA), n− 6 (AA and LA), monounsaturated (OA), and saturated (SA and PA) PUFAs present in the human diet. Taken from the free ChemSpider Database.



**History of Fish Oil**

Heart disease has a powerful hold over the United States, serving as the number one cause for mortality. Heart disease is now considered an epidemic, as the number of cases has climbed year after year. At present, one out of every three deaths in the U.S.A. can be attributed to heart disease (Benjamin, EJ et al., 2017). While organizations such as the American Heart Association provide endless campaigns for changes in lifestyle to prevent heart disease, the search continues for new and better ways to help minimize the effects of the disease that is already well underway in so many Americans. Even with changes in lifestyle, those with heart disease are still extremely likely to suffer potentially fatal cardiac events.

The current standard of care for those who experience cardiac events involves many medications, options for surgery, rehabilitation services, nutritional counseling, and resuscitative measures. Many cardiologists and nutritionists may recommend that patients with or at risk of heart disease take fish oil in the form of a supplement in addition to their change of food intake. N-3 polyunsaturated fatty acids (n-3 PUFAs), a component of fish oil, have been proven to “favorably affect atherosclerosis, coronary artery disease, [and] inflammatory disease” in several thousand papers in the current literature (Nettleton, J. A., 1995).

Evidence of n-3 PUFA’s role in heart disease was clearly displayed when examining the causes of mortality in Eskimos, a small ethnic group in Greenland. In an epidemiologic study, it was noticed that despite the overall high-fat diets of this group, mortality due to heart disease was incredibly low (Kang & Leaf, 1996). Subsequent research suggests that because the primary dietary fat being consumed were n-3 PUFAs, coming from seafood, the Eskimos were protected from heart disease. In fact, when this study was conducted in the 1980’s, heart disease accounted for only 3.5% of deaths among this ethnic group (Nansen & Archer, 1980). These numbers are even more significant when examining other countries’ rates of mortality due to heart disease. According to the British Heart Foundation’s “Trends in coronary heart disease, 1961-2011”, heart disease accounted for 49% of deaths in the United Kingdom during 1981. This is a shocking 45.5% difference in heart disease mortality in two countries very geographically close to one another (Scarborough, Wickramasinghe, Bhatnagar, Rayner, 2011). The United States showed a similar trend in the 1980’s. Disease of the heart was the leading cause of death in both sexes as well as every ethnic group (CDC/NCHS, 2010).

This remarkable epidemiologic report caused a flurry of additional studies on fish oil to determine what exactly about them causes such a protective effect on heart disease. Subsequent research shows that the primary way that n-3 PUFAs prevent heart disease are by causing a “strong antiarrhythmic action on the heart”, making it less likely for fatal arrhythmias such as ventricular tachycardia and fibrillation and atrial fibrillation to occur (Nettleton, J. A., 1995). In 2013, “[atrial] fibrillation (AF) [was] the most common cardiac arrhythmia, affecting more than 2.6 million people in the United States” (Schrepf, Limmert, Weber, Theisen, Sellmayer, 2004). At present, the survival rate of ventricular arrhythmias that occur outside of a clinical environment is less than 10% and there are “50-100 sudden cardiac deaths per 100,000 population per year in Europe and the USA” due to them (Harris & Lysitsas, 2016). The antiarrhythmic action of n-3 PUFAs alone shows promise for further research in the role of n-3 PUFAs in medicinal therapy to prevent or terminate fatal cardiac arrhythmias.

**Acute Effects of Fish Oil**

The protective cardiovascular effects of dietary n-3 PUFAs have been well researched, but the acute effects of PUFAs has failed to find a strong place in the body of research thus far. Usually, it takes time and consistent use for dietary supplements to be absorbed in order to gain the benefits from them. Previous clinical trials in humans have been conducted in the following manner (Kar, S, 2013, Heidt et al., 2009, Heidarsdottir et al., 2010). Patients were given a dosage of n-3 PUFAs directly before their surgery as well as during their recovery every day (Kar, S, 2013, Heidt et al., 2009, Heidarsdottir et al., 2010). Although this method showed success in multiple trials, n-3 PUFAs may work even more acutely than this (Kar, S, 2013, Heidt et al., 2009). It seems that n-3 PUFAs may not need consistent use to give protective benefits.

In 1995, Kang and Leaf conducted a study using rat myocytes to test the acute effects of n-3 PUFAs and to see “whether fish oil fatty acids could terminate isoproterenol-induced arrhythmias” (Kang & Leaf, 1995). It was found that after only 2-3 minutes of adding the n-3 PUFAs, the arrhythmias “subsided followed by a reduction in the beating rate” (Kang et al., 1995). Because the n-3 PUFAs did not need to be present prior to the induction of an arrhythmia for them to terminate arrhythmias, there is a possibility that n-3 PUFAs have a place in resuscitation during major cardiac events.

The most severe types of arrhythmias seriously impair the delivery of oxygen to the heart, brain, and rest of the body. If these arrhythmias are not terminated within minutes, the result can be fatal. If n-3 PUFAs can correct fatal arrhythmias within a few minutes of being administered, injection of these may serve as a life-saving medication in medical emergencies.

Fatal arrhythmias are extremely common in cardiac patients post-surgery. Complications with heart electrophysiology are common and can frequently be “a major cause of morbidity, increased length of hospital stay, and economic costs” (R., 2018). Atrial fibrillation (a-fib), for example, “most often [occurs] within the first few days after surgery, with a peak incidence on postoperative days 2 and 3. A-fib has been reported in up to 15 to 40% of patients in the early postoperative period after CABG, in 37 to 50% after valve surgery, in as many as 60% undergoing valve replacement plus CABG, and in 11 to 24% after cardiac transplantation” (R., 2018). These are only the numbers accounting for a-fib. Including incidences of other fatal arrhythmias would dramatically increase the percentage of post-operative patients who experience a cardiac event during their recovery.

It is possible that including emergency administration of n-3 PUFAs to post-op patients experiencing an arrhythmia in order to terminate the excessive electrical activity of the heart into the standard of care would decrease the occurrence of arrhythmias and mortality due to them. The hope would be that the inclusion of the n-3 PUFAs would expedite the process of correcting the arrhythmia and decrease mortality.

**Antiarrhythmic Effects of PUFAs in Humans**

It is clear that n-3 PUFAs have a protective effect against arrhythmias in rat and dog myocytes, but this discovery is only useful if n-3 PUFAs affect human myocytes in the same manner (Kang et al., 2002, Billman, Kang, & Leaf, 1999, & Kang & Leaf, 1994). Particular interest was given to rat studies because “there are many similar electrophysiological characteristics between rat and human cardiomyocytes” (Li, Wang, & Li, 2011). After the success of animal studies in the 1990’s, particularly in rats, researchers began testing n-3 PUFAs against human arrhythmias.

The prevention of both ventricular and atrial arrhythmias in humans have been tested with success. In a study conducted in 2004, ten patients with implanted cardioverter defibrillators at high risk for sudden cardiac death were tested (Schrepf et al., 2004). These defibrillators could be controlled to induce a cardiac arrhythmia. In “seven of the ten patients, sustained monomorphic ventricular tachycardia was inducible at baseline” prior to the infusion of n-3 PUFAs (Schrepf et al., 2004). After n-3 PUFAs were administered, “monomorphic sustained ventricular tachycardia was no longer inducible” in five of the seven patients (Schrepf et al., 2004).

Antiarrhythmic action was shown in studies regarding atrial arrhythmias as well. Atrial fibrillation (a-fib) is “the most common arrhythmia following cardiac surgery”, so n-3 PUFAs were tested in 160 patients undergoing coronary artery bypass graft (CABG) surgery to see if the cases of a-fib could be reduced (Kar, 2013). In 2005, Calo and his colleagues from Reviews in Cardiovascular Medicine, tracked 160 patients during their recovery from CABG surgery (Kar, 2013). These patients received 2 g/d of PUFAs intravenously “before surgery, which was continued until hospital discharge” (Kar 2013). The control group, which did not receive PUFAs, experienced 27 cases of a-fib (33.3%), while the “PUFA-treated patients had only 12 cases of [a-fib] (15.2%)” (Kar 2013). Considering the PUFAs seemed to reduce the risk of a-fib by more than 50%, PUFAs “may be considered as a preventative medication for a-fib prior to CABG” (Kar 2013). The same results were found in a study of 102 patients using intravenous administration of n-3 PUFAs 12 hours prior to surgery and all throughout their recovery in the ICU (Heidt, 2009). The results of this study almost directly mirrored the study by Calo and his colleagues finding that “post-operative [a-fib] occurred in 15 patients (30.6%) in the control group and in 9 (17.3%) in the PUFA group” (Heidt, 2009). Other studies with larger sample sizes (530 patients) saw similar results (Mariscalco, Sarzi, Banach, 2010).

Considering there are so few studies on the acute effects of n-3 PUFAs on arrhythmias in an inpatient setting, more human trials are warranted. Additional data with larger sample sizes would reveal if n-3 PUFAs do indeed have an acute antiarrhythmic effect or if they have no effect. If additional studies were done and turned out to show success, medical professionals can decide if the inclusion of n-3 PUFAs in the standard of care in coronary artery bypass surgery is called for. A human trial such as this would need to be conducted by including a large sample size of individuals run over a decent span of time. This trial would need to be explicit in its informed consent and need to include careful tracking and monitoring in order to not find skewed results.

Based on the available literature supporting that acute injection of n-3 PUFAs could terminate fatal arrhythmias, testing should be done on this specifically. In a study such as this, the effect of emergency administered n-3 PUFAs via intracardiac injection at the time of a fatal arrhythmia could be testing starting in an inpatient setting. The test subjects could include patients in inpatient recovery following coronary artery bypass graft surgery. If an arrhythmia should occur during inpatient recovery of the patient, fish oil or a placebo, such as olive oil, could be administered via intracardiac injection at the soonest possible time. Intracardiac injection is accomplished by inserting a needle through the chest cavity and straight into the heart muscle. The fish oil or placebo would then be administered through the syringe. Following this, the needle would be promptly removed, and all other standards of care would be continued in an attempt to terminate the arrhythmia.

To track the success of this treatment, several types of statistical research would need to be conducted. The primary research being collected will be mortality due to arrhythmias. A Pearson Chi-Squared test could be implemented on this data. Whether the patient simply survived or not is important, but additional data should be included as well. Tracking the length of time each arrhythmia lasts will reveal if n-3 PUFAs reduce the time it takes to correct an arrhythmia. This is significant because the body will incur less damage if a resternotomy could be avoided by resolving the arrhythmia quickly. A study such as this would be able to reveal if an intracardiac injection of n-3 PUFAs at the time of a cardiac event can terminate fatal arrhythmias.

**Future Implications**

If intracardiac injection of n-3 PUFAs at the time of an arrhythmia can be proven to terminate these arrhythmias in an inpatient setting, this practice could become part of the standard of care in emergency cardiovascular medicine. The injection of n-3 PUFAs would not have to stop at inpatient patients either. Because an intracardiac syringe is small, portable, and able to be administered anywhere, outpatient cardiac rehabilitation would be an ideal place for this treatment to be implemented. Cardiac rehabilitation centers have nurses on staff who are qualified to administer medications and injections. Should a cardiac patient enter cardiac arrest during their exercise session at rehab, the nurses could respond with this treatment while the code team is on their way to the emergency. The nurse who responds would be able to remove the patient’s shirt, sterilize the area for injection, and administer the n-3 PUFAs. This would prepare the patient for CPR and defibrillation which would be administered by the code team. This would then lead to decreased mortality due to cardiac events in outpatient cardiac rehab. This process, of course, would have to be tested through human trials as well.

The success of this injection working in an outpatient setting leads to even more possibilities. Fish oil could be prescribed in an auto injector to patients at high cardiovascular risk. First responders trained in first aid would not have the expertise to administer an intracardiac injection, but a vessel similar to an epinephrine auto-injector (epipen) could serve its purpose. The appropriate dose of fish oil to serve a large range of patients would be prescribed by a doctor following CABG surgery to patients who have no contraindications to n-3 PUFAs in the form of an auto injector. The training would be the same for this injection as an epipen, meaning an intramuscular injection to the lateral portion of the thigh. In the case of a cardiac event, first responders would learn how to administer the injection as soon as possible as another first responder prepares the skin and places the AED pads in place. There is a chance that the lack of blood movement in the body would not circulate the medication effectively. Although, there is also a chance that chest compressions would successfully move the fish oil back to the heart enough for it to take effect. The addition of fish oil during cardiac events outside of a hospital setting may increase the chance of survival.

Should the experiments using intracardiac injection of n-3 PUFAs at the time of a cardiac event fail, there is still much to be studied regarding this topic. Intravenous doses of n-3 PUFAs before surgery and during inpatient recovery still show a lot of promise. Research on this is limited, but there have been some studies showing success (Kar, 2013, Schrepf, 2004, & Heidt, 2009). The possibility of n-3 PUFAs as a preventative or emergency medication when undergoing CABG surgery is a question worth years of research and trial.

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