REVIEW

Beneficial effects of omega-3 fatty acids in cardiovascular disease

There is a large body of evidence supporting beneficial effects of omega-3 fatty acids for both primary and secondary prevention of cardiac disease in people. However, evidence is increasing for the use of omega-3 fatty acids in dogs with cardiac disease as well. Omega-3 fatty acids' anti-inflammatory and anti-arrhythmic effects may be beneficial in managing the loss of lean body mass and arrhythmias that are common in heart failure. However, omega-3 fatty acids also may have positive effects on myocardial energy metabolism, endothelial function, heart rate and blood pressure, and immune function. Additional research is needed to determine optimal indications, doses and formulations for dogs and cats with cardiac disease.

Lisa M. Freeman

Journal of Small Animal Practice (2010) **51**, 462–470

DOI: 10.1111/j.1748-5827.2010.00968.x

Accepted: 22 April 2010; Published online: 29 July 2010

Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA, USA

INTRODUCTION

Fat has gained a reputation as a "bad" component of food with numerous adverse health effects. One only has to think of the terms, "*saturated fat*", "*cholesterol*", "*trans-fatty acids*" and "*obesity*" to realise the unhealthy reputation fat has gained in society. However, small amounts of dietary fat are essential for life and have a role not only as a potent source of calories but also as carrier of fat soluble vitamins and a source of essential fatty acids. Fats also have important effects on immune function, inflammation, and even hemodynamics. Fats affect all body systems in some ways, but few systems are affected as much as the cardiovascular system. This results in important effects of fats on cardiovascular health – both positive and negative. One specific type of fatty acid that has received great attention for its effects in the cardiovascular system is the omega-3 fatty acids (also called n-3 or ω-3 fatty acids). The benefits of omega-3 fatty acids in people have been described for many years and fish/fish oil consumption has, therefore, been recommended as an important part of the human diet. Because the diseases for which omega-3 fatty acids have been best studied in people (i.e. coronary heart disease, essential hypertension) are uncommon in dogs and cats, recommendations for use of omega-3 fatty acids in dogs and cats are a more recent phenomenon. However, the evidence for benefits of omega-3 fatty acids in animals with cardiac disease is mounting.

OMEGA-3 FATTY ACIDS: BIOCHEMICAL BASIS FOR BENEFICIAL EFFECTS

The largest proportion of dietary fat is made up of triglycerides. Triglycerides are composed of a short glycerol backbone attached to three fatty acids. It is these fatty acids that contribute to the variability in the form and effects of fats. Fatty acids are a hydrocarbon chain with an even number of carbon atoms (Fig 1). Fatty acids are designated based on the number of carbons (from 4 to 26), the number of double bonds (0 to 6) and the location of double bonds (at the third, sixth, seventh or ninth carbons; Fig 1). Most fatty acids have a chemical designation (e.g. C18:1 n-9 – meaning a fatty acid with 18 carbons, one double bond, with the first double bond at the ninth carbon), as well as a common name (the common name for C18:1 n-9 is oleic acid). The structure affects not only the naming of the fatty acid but also, more importantly, its functional and health effects.

Fatty acids have a carboxyl group (COOH) at one end of the carbon chain and a methyl group (CH_3) at the other end. This biochemical fact is important because omega-3 fatty acids have their first double bond at the third carbon from the methyl end (hence, omega-3 fatty acids), while omega-6 fatty acids have their first double bond at the sixth carbon from the methyl end. There are several omega-3 fatty acids, but the most common ones are α-linolenic acid (ALA; C18:3 n-3), eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA; C22:6 n-3).

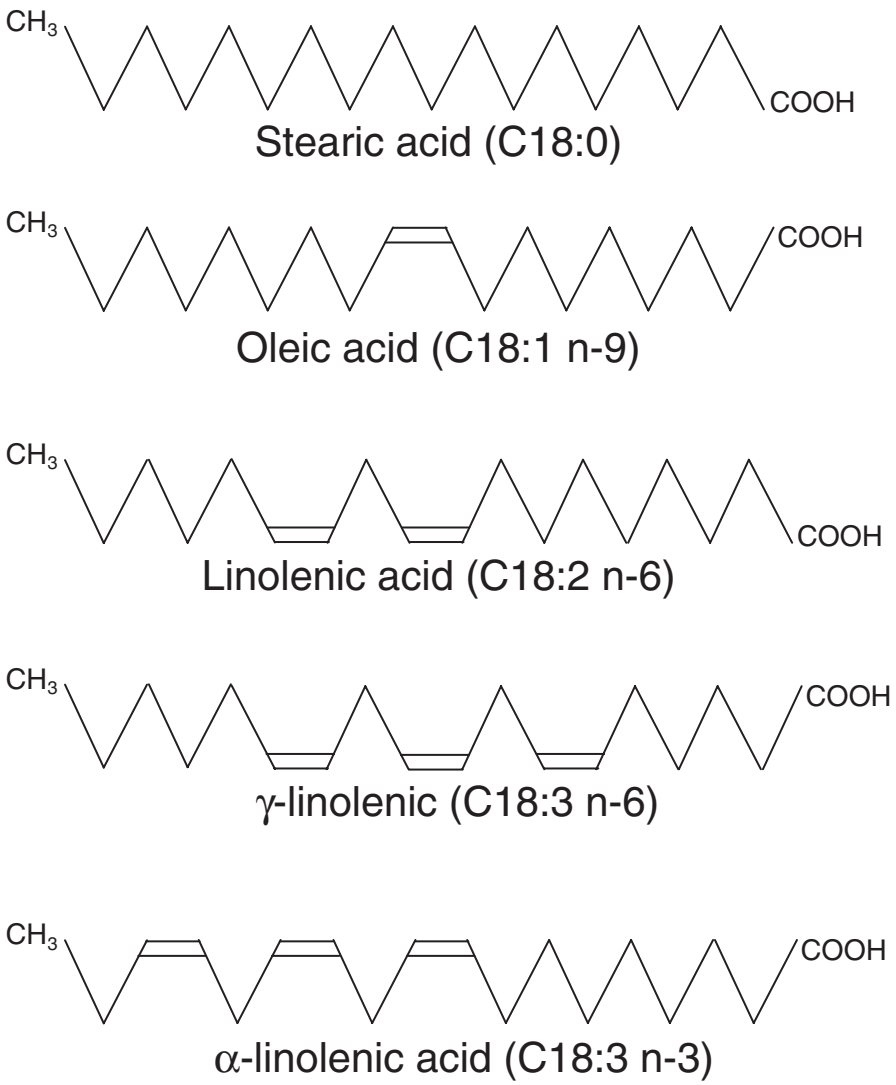

FIG 1. Structure of common 18-carbon fatty acids

While these structural differences between omega-3 and omega-6 fatty acids may seem minor, they impart very significant effects on fatty acid structure, cell membrane composition and fluidity, cell signalling pathways and inflammation. Fatty acids, whether omega-3 or omega-6, are incorporated into cell membranes. Within cell membranes, they have significant effects on membrane integrity and fluidity, as well as cell signalling (Torrejon and others 2007, Calder 2008). In addition, when released from cell membranes by phospholipases, they form eicosanoids through action by the enzymes, cyclooxygenase and lipoxygenase (Fig 2). Both the omega-3 fatty acid, EPA, and the omega-6 fatty acid, arachidonic acid (20:4 n-6), serve as primary precursors for eicosanoids. However, eicosanoids derived from arachidonic acid are of the 2- and 4-series (e.g. prostaglandin E_2, leukotriene B_4), whereas eicosanoids derived from EPA are of the 3- and 5-series (e.g. prostaglandin E_3, leukotriene B_5). Eicosanoids of 3- and 5-series are generally less potent inflammatory mediators compared with the 2- and 4-series and, as a result, cause vasodilation, anti-thrombotic effects and reduced chemotaxis (Ad Hoc Committee on Dog and Cat Nutrition 2006, Kang and Weylandt 2008) (Fig 2). Heart failure is now known to be an inflammatory disease associated with elevated production of eicosanoids and other inflammatory mediators (von Haehling and others 2009). Therefore, one of the key beneficial effects of omega-3 fatty acids is that the eicosanoids derived from them are less inflammatory.

In addition to the production of less inflammatory eicosanoids, omega-3 fatty acids also reduce the production of the inflammatory mediators that are known to be elevated in heart failure: the inflammatory cytokines, tumour necrosis factor-α (TNF), interleukin-1β (IL-1), and interleukin-6 (IL-6); transcription factor κB (NF-κB); and reactive oxygen species (Endres and others 1989, Caughey and others 1996, Kang and Weylandt 2008, LeBlanc and others 2008, von Haehling and others 2009). Omega-3 fatty acids also produce anti-inflammatory mediators called resolvins and protectins which may play an important role in the anti-inflammatory actions of the compounds (Kang and Weylandt 2008). Therefore, many of the beneficial effects of omega-3 fatty acids appear to be modulated via their anti-inflammatory effects but, as discussed below, there may also be other important effects that are provided by the omega-3 fatty acids on the heart.

DIETARY OMEGA-3 FATTY ACIDS

Both omega-6 and omega-3 fatty acids are considered to be essential fatty acids because they are required in the diet and cannot be synthesised by mammals (Ad Hoc Committee on Dog and Cat Nutrition 2006). Furthermore, ingestion of one does not obviate the need for the other because omega-6 and omega-3 fatty acids cannot be interconverted (i.e. γ-linolenic acid cannot be converted to ALA). The typical diets for cats, dogs and people are composed primarily of omega-6 fatty acids, as opposed to omega-3 fatty acids. However, dietary modification or supplementation of omega-3 fatty acids can significantly increase blood and tissue concentrations of omega-3 fatty acid as omega-3 and omega-6 fatty acids compete with one another for enzymes required for their metabolism. Therefore, the more omega-3 fatty acids in the diet, the more omega-3 fatty acids will be utilised and incorporated into cells.

In dogs and people, the 18-carbon omega-6 fatty acids can be converted to

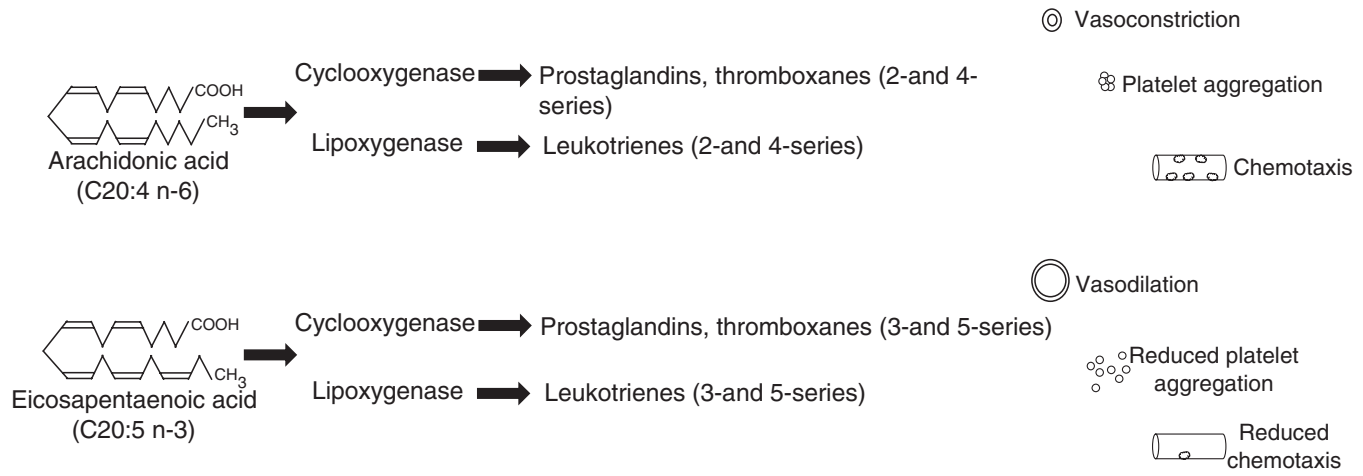

FIG 2. Pathway for biosynthesis of eicosanoids from omega-3 and omega-6 fatty acids

longer chain (20- or 22-carbon) fatty acids by a series of desaturation and elongation steps. Similarly, dogs and people can convert the 18-carbon omega-3 fatty acid ALA to DHA but the conversion rate is low (<5%) (Brenna 2002, Bauer 2007). Cats, because of low hepatic Δ6-desaturase enzyme, cannot elongate either the omega-3 or omega-6 fatty acids to any significant degree (which is why linoleic *and* arachidonic acids are considered essential fatty acid in cats compared with most species which only require dietary linoleic acid). Therefore, dietary intake of EPA and DHA is required in both dogs and cats for adequate levels of these very long-chain omega-3 fatty acids.

EFFECTS OF OMEGA-3 FATTY ACIDS IN CARDIAC DISEASE

Cardiac disease is one of the most common disorders in both dogs and cats, affecting 11% of all dogs and up to 20% of some feline populations (Buchanan 1999, Cote and others 2004, Paige and others 2009). While medical therapy for cardiac disease has improved, with newer and more effective drugs, it is still only palliative with the goals of controlling clinical signs, slowing the progression of disease and improving quality of life. Maintaining good quality of life is particularly important in dogs and cats, for whom owners often prefer *quality* of life to *quantity* of life (Oyama and others 2008).

Nutrition is critical for the optimal treatment of animals with cardiac disease and should be an integral part of their medical management. Nutritional goals for animals with cardiac disease include maintaining optimal body condition, avoiding nutritional deficiencies and excesses, and gaining potential benefits from pharmacologic doses of certain nutrients. Omega-3 fatty acids appear to have a role in each of these important goals.

Optimal body condition: the syndrome of cardiac cachexia

Cardiac cachexia is a loss of lean body mass that occurs in heart failure (Fig 3; (Freeman and Roubenoff 1994, Freeman and others 1998, von Haehling and others 2009). Cachexia has important detrimental effects in the cardiac patient and is an independent risk factor for mortality in people with heart failure (Anker and others 1997b, Anker and others 2003).

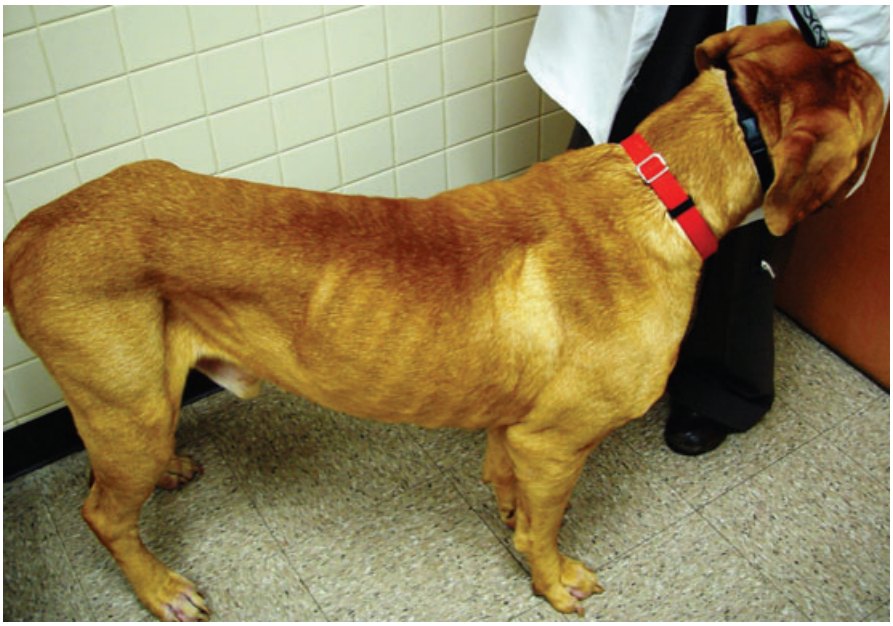

FIG 3. A dog with severe heart failure and cardiac cachexia. Careful attention to monitoring bodyweight and muscle condition allows the clinician to detect cachexia at an earlier and more subtle stage, when interventions such as omega-3 fatty acids are more likely to be beneficial

About half of all people with heart failure have cachexia, a similar finding to one study of dogs with heart failure (Freeman and others 1998, von Haehling and others 2009).

In health, weight loss is associated primarily with reductions in fat and lean tissue is relatively spared. Cachexia, however, is unusual in that it primarily depletes the metabolically active lean body mass. Cachexia is not unique to heart failure, as it also occurs in cancer, chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease and other diseases. While there appear to be some subtle differences between cachexia in these varied diseases, loss of lean body mass is a hallmark of all forms of cachexia.

Recent studies have underscored the deleterious effects of cachexia and emphasised the role of bodyweight and body composition in heart failure. While obesity is a risk factor for development of heart disease in people, obesity may actually be associated with a protective effect once heart failure is present – this is known as the obesity paradox. A recent meta-analysis of more than 28,000 people was published on this phenomenon and concluded that, once heart failure was present, obesity and overweight were associated with lower all-cause and cardiovascular mortality and that underweight patients consistently had a higher risk of death (Oreopoulos and others 2008). The benefit of obesity in heart failure appears due to a *lack* of cachexia, rather than to the obesity *per se*, given the adverse effects associated with cachexia. Typically, excess weight is comprised of 75% adipose and 25% lean tissue. Therefore, obese people also have more lean body mass and this extra lean body mass may provide a greater reserve during the catabolic state of heart failure. The obesity paradox has also been demonstrated in dogs and cats with naturally occurring heart failure (Slupe and others 2008, unpublished data). These human and canine data emphasise the importance of avoiding weight (and muscle) loss in patients with heart failure.

Cachexia of all types is associated with increased inflammation and heart failure is no exception (Ross and others 1999, Freeman 2009, von Haehling and others 2009). While heart failure is known to be an inflammatory condition, cardiac cachexia is associated with an even greater degree of inflammation than heart failure alone (Anker and others 1997a, Anker and others 1997b, von Haehling and others 2009). Therefore, the anti-inflammatory effects of omega-3 fatty acids have made these compounds of interest in cachexia for many years. The mechanisms of inflammation and the resultant muscle loss that occurs in heart failure is now an area of great interest due to the large number of people with cardiac disease and the important detrimental effects of cachexia. The inflammatory cytokines, especially TNF and IL-1, are primary mediators of cachexia as they inhibit appetite, increase energy metabolism and accelerate the breakdown of muscle protein (catabolism) of lean body mass via the NF-κB pathway, myoD and myogenin downregulation, reduced muscle regeneration and inhibition of muscle differentiation (Moresi and others 2008). It has been known for many years that omega-3 fatty acids reduce protein catabolism by blocking the effects of TNF and IL-1 (Hirschberg and others 1990). Complete blockade of TNF or other inflammatory mediators may have adverse effects but other anti-inflammatory agents, such as certain cardiovascular drugs (e.g. angiotensin converting enzyme inhibitors, beta blockers; Gullestad and others 1999; Tatli and others 2008), antioxidants and omega-3 fatty acids may be more successful in combating cachexia. This may be strictly via anti-inflammatory effects of reducing TNF, IL-1 and inflammatory eicosanoids, but also may involve other mechanisms (Freeman 2009).

Despite a large body of research in other forms of cachexia (e.g. cancer cachexia), little research has been published on the effects of omega-3 fatty acids in heart failure. In a study of dogs with dilated cardiomyopathy (DCM) and heart failure, Freeman and others (1998) showed that omega-3 fatty acid supplementation (25 mg/kg EPA and 18 mg/kg DHA) significantly reduced IL-1 and prostaglandin E_2 production, and reduced muscle loss compared with placebo. In addition, there was a significant negative correlation between a reduction in IL-1 and survival time. In people with heart failure, omega-3 fatty acid supplementation (61 mg/kg/day EPA and 33 mg/kg/day DHA) reduced TNF and IL-1, and was associated with an increase in body fat (Mehra and others 2006). Not all human studies of omega-3 fatty acids in other forms of cachexia (e.g. cancer, AIDS) have had positive results (Dewey and others 2007). However, newer research in human cancer patients has begun to successfully combine omega-3 fatty acids for their anti-inflammatory effects with calorie and protein supplementation (to ensure adequate substrates) (Fearon and others 2006, Fearon 2008, Bayram and others 2009). This underscores the importance of ensuring adequate calorie and protein intake in combination with omega-3 fatty acid supplementation in animals with cardiac disease.

Decreased intake of calories is a major problem for any species with heart failure and can be a significant contributor to cardiac cachexia (Freeman and Roubenoff 1994, Freeman and others 1998, Freeman 2009). Anorexia, either a complete or partial loss of appetite, is extremely common in cardiac disease, particularly in dogs with congestive heart failure (CHF), with prevalence between 34 and 84% of dogs and cats with cardiac disease (Mallery and others 1999, Freeman and others 2003, Torin and others 2007). Animals may not develop complete anorexia but instead have reductions in food intake, changes in food preferences or "cyclical" appetite (i.e. the animal will eat one food well for several days and then refuse it). In cachexia, there is altered neural control of appetite such that normal factors that trigger a person to eat are reduced and satiety factors are elevated (Laviano and others 2008). This imbalance is primarily the result of an elevated inflammatory state, especially the inflammatory cytokines TNF and IL-1 (Laviano and others 2008). While a critical issue for managing anorexia is to optimise medical therapy including dietary modifications, modulation of cytokine production also can help to improve appetite (Freeman and Rush 2010). Omega-3 fatty acid supplementation, by decreasing production of inflammatory cytokines, can improve food intake which may aid in minimising loss of lean body mass in animals with heart failure (Freeman and others 1998).

Preventing deficiencies

Dogs with heart failure have been shown to have a relative deficiency of plasma EPA and DHA compared with normal dogs (Freeman and others 1998). One study of dogs with heart failure secondary to DCM showed that 8 weeks of fish oil supplementation normalised these plasma fatty acid abnormalities (Freeman and others 1998). Another canine study showed multiple differences in plasma fatty acids between Boxers and Doberman pinschers (Smith and others 2008). For example, Boxers had higher plasma concentrations of γ-linolenic acid but lower concentrations of arachidonic acid and total omega-6 fatty acids compared with Doberman pinschers (Smith and others 2008).

While more research is needed to delineate the fatty acid changes in various breeds and underlying forms of heart disease in dogs, alterations in plasma fatty acid also may have important implications for the heart. Prenatally, glucose is the main source of energy for cardiomyocytes, but there is a postnatal switch that allows fatty acids to become the major energy source in the adult heart (Stanley and others 2005, Neubauer 2007). When heart failure develops, however, the heart reverts to a fetal metabolic phenotype such that glucose once again becomes the major myocyte fuel, but the capacity for glucose utilisation in heart failure is limited. Thus, a myocardial energy deficit can result (Stanley and others 2005, Neubauer 2007). One promising approach to improving myocardial energy metabolism and mitochondrial function is to use omega-3 fatty acids (Duda and others 2009). Therefore, supplementation of omega-3 fatty acids may benefit energy metabolism via correction of a deficiency or through effects that are more pharmacologic in nature.

"Pharmacologic" effects of omega-3 fatty acids

Arrhythmia Many human studies, including a recent meta-analysis, have shown a benefit of fish consumption in reducing risk of coronary heart disease and death from myocardial infarction (Kromhout and others 1985, Ascherio and others 1995, Daviglus and others 1997, Albert and others 2002, He and others 2004, Iso and others 2006). Intake of omega-3 fatty acids from supplementation, rather than fish intake, has also been studied in a variety of human populations, such as people with implantable defibrillators (Leaf and others 2005, Raitt and others 2005, Brouwer and others 2006, London and others 2007, Brouwer and others 2009) and those with DCM (Nodari and others 2009), with mixed results. For example, a meta-analysis of people with defibrillators showed no benefit of omega-3 fatty acids (Brouwer and others 2009). However, the GISSI-HF Trial of nearly 7000 people with heart failure followed for a median of 3·9 years showed that omega-3 fatty acids (1 g/day) reduced mortality and hospital admission for cardiovascular reasons compared with placebo (Tavazzi and others 2008). Most of the human studies have evaluated effects on ventricular arrhythmias but recent publications also have shown benefits of omega-3 fatty acids on atrial fibrillation (Mozaffarian and others 2004, Calo and others 2005, London and others 2007, Sakabe and others 2007, Virtanen and others 2009). One of these, an induced canine model of atrial tachypacing (Sakabe and others 2007), suggested that omega-3 fatty acids reduced atrial fibrillation. Two epidemiologic studies showed that higher fish intake or circulating omega-3 fatty acid concentrations were associated with a lower incidence of atrial fibrillation (Mozaffarian and others 2004; Virtanen and others 2009). Finally, a randomised, controlled trial of omega-3 fatty acids after coronary artery bypass surgery in 160 people showed a significant reduction in postoperative atrial fibrillation (Calo and others 2005). A large study evaluating the effects of omega-3 fatty acids in people with recurrent atrial fibrillation currently is ongoing (Pratt and others 2009).

Although dogs have sometimes been used in experimentally induced conditions to study the effect of omega-3 fatty acids on arrhythmia, only one study has been published evaluating their effect in dogs with naturally occurring disease. Smith and others (2007) reported the results of a study in Boxers with ventricular arrhythmias which showed a reduction in arrhythmia number after 6 weeks of fish oil supplementation compared with control (sunflower oil). This effect was not found with supplementation of a similar dose of flax oil although the sample size may have been insufficient. As this study was conducted only in Boxers, further research is needed to determine whether these effects are consistent in a larger population of dogs and also in dogs of other breeds. As previously mentioned, Boxers and Doberman pinschers have some differences in plasma fatty acids and may have different relationships between arrhythmias and fatty acid concentrations (Smith and others 2008). Despite positive results, the effects of omega-3 fatty acids on arrhythmias appear to be modest and omega-3 fatty acids should only be viewed as an adjunct to medical therapy for dogs with significant arrhythmias.

While most studies of cardiac arrhythmias have evaluated the long-term effects of omega-3 fatty acids consistent with incorporation of fatty acids into the cell membrane, studies also have shown acute beneficial effects in multiple species including humans (Billman and others 1994, Billman and others 1999, Schrepf and others 2004, Den Ruijter and others 2008). For example, in laboratory dogs with experimentally induced ventricular arrhythmias, infusion of EPA, DHA or ALA protected dogs against ventricular fibrillation (Billman and others 1994, Billman and others 1999). The anti-arrhythmic effects of omega-3 fatty acids appear to be multifactorial and include significant effects on sodium, potassium and calcium channels (London and others 2007).

Other cardiovascular effects of omega-3 fatty acids Most of the beneficial effects of omega-3 fatty acids in people with heart failure have been presumed to be the result of reduced arrhythmias. However, more recent studies are beginning to delineate additional positive effects. For example, one study showed that fish intake was associated with a reduced incidence of heart failure (Mozaffarian and others 2005a), although a recent large study, while showing similar patterns, was not significant (Levitan and others 2009). Omega-3 fatty acids have been associated with improved survival in some studies of human (Tavazzi and others 2008) and canine (Slupe and others 2008) heart failure. For example, a retrospective study of 108 dogs with heart failure secondary to

DCM or chronic valvular disease (CVD) showed a significant effect of omega-3 fatty acids on survival (P=0·009; Slupe and others 2008). These associations may be related to the aforementioned anti-inflammatory effects, prevention of cachexia, improved appetite or anti-arrhythmic effects. However, omega-3 fatty acids also have a number of other effects that may also play a role and warrant further research. For example, omega-3 fatty acids reduce cardiac remodelling and subsequent dysfunction, reduce heart rate and blood pressure, improve endothelial function, and enhances baroreceptor function and heart rate variability (Geleijnse and others 2002, Mozaffarian and others 2005b, Morgan and others 2006, Radaelli and others 2006). Omega-3 fatty acids can alter immune function (Kearns and others 1999, Hall and others 2003, Farabaugh and others 2004, Freeman and Rush 2005) which may contribute to the cardiovascular effects of omega-3 fatty acids. Finally, omega-3 fatty acids reduce platelet aggregation as a result of production of the less potent thromboxane B_5 (Bright and others 1994). This latter effect might be particularly useful in cats with cardiac disease at risk for thrombus formation but also is an important effect to consider with the use of omega-3 fatty acids in animals with coagulopathies (see below).

Current American Heart Association recommendations for people are to include 0·5 to 1·8 g/day either as fatty fish or supplements for primary prevention of cardiovascular disease (Kris-Etherton and others 2003). As coronary heart disease is not a concern in veterinary patients, there is less potential for a preventive role for dogs and cats. However, the author believes that there is adequate evidence to warrant the use of omega-3 fatty acids in dogs, and likely cats, with heart failure or certain arrhythmias for secondary prevention. In addition, omega-3 fatty acids may have benefits in earlier stages of cardiac disease (e.g. DCM, CVD, hypertrophic cardiomyopathy (HCM)) due to their numerous positive effects on the cardiovascular system but this requires further research. Despite their promise, many questions about the use of omega-3 fatty acids in animals with cardiac disease remain, such as patient selection, when to initiate omega-3 fatty acids, and whether they have similar benefits in cats. Therefore, further research is required to determine the optimal use of omega-3 fatty acids in animals with cardiac disease.

GENERAL ISSUES WITH OMEGA-3 FATTY ACID SUPPLEMENTATION

A challenge in comparing any of the omega-3 fatty acid studies is that there are tremendous differences in study design including species, naturally occurring disease *versus* induced experimental model, underlying disease, total dose of omega-3 fatty acids, type of omega-3 fatty acids (e.g. ALA *versus* EPA + DHA) and ratio of EPA to DHA. These are all important factors to consider when evaluating published studies of omega-3 fatty acids but also in designing the much-needed studies of these supplements in dogs and cats with cardiac diseases. Although much additional research is required, there are currently many dogs and cats with cardiac disease that might benefit from omega-3 fatty acids supplementation. For these animals, clinicians should consider a number of important issues.

Dose

The optimal dose of omega-3 fatty acids is not yet known for people or for dogs and cats. Our group's recommendations that have been developed are based on our studies in dogs using two doses of omega-3 fatty acids: 25 mg/kg EPA+18 mg/kg DHA and 40 mg/kg EPA+25 mg/kg DHA (Freeman and others 1998, Freeman and others 2006, Smith and others 2007). While some significant benefits have been shown for these doses, it is not yet clear whether these are the optimal doses for all animals with cardiac disease, for all stages of cardiac disease or for cats as well as dogs. Studies in other species using lower and higher doses also have been conducted with variable results. Therefore, further research is needed to determine the optimal dose for all stages and types of cardiac disease. While some authors discuss the "optimal" omega-6: omega-3 ratio, studies have shown that it is the total omega-3 dose that determines plasma omega-3 fatty acids, independent of n-6:n-3 ratio (Hall and others 2006). Until further information is available, the author currently recommends a dose of 40 mg/kg EPA and 25 mg/kg DHA for both dogs and cats with cardiac disease.

Timing

While omega-3 fatty acids may have some acute effects in certain conditions (Billman and others 1999, Schrepf and others 2004, Den Ruijter and others 2008), most of the benefits of omega-3 fatty acid supplementation occur only after peak plasma and tissue concentrations have been achieved. Plasma concentrations increase significantly within 1 week of initiating omega-3 fatty acid supplementation but 4 to 6 weeks are required to reach peak plasma concentrations (Hansen and others 1998, Hall and others 2006). Clinically, this means that peak effects will not occur immediately after beginning omega-3 fatty acid supplementation.

Forms of omega-3 fatty acids

The omega-3 fatty acids, EPA and DHA, can be provided via the diet or as a dietary supplement. With the exception of a few specially designed therapeutic pet foods, commercial diets generally do not achieve the high level of EPA and DHA recommended. To achieve a dose of 40 mg/kg EPA + 25 mg/kg DHA, a food would need to contain between 80 and 150 mg/100 kcal EPA+DHA, depending on the size of the animal and the amount of food eaten. If the diet is not sufficiently high in EPA and DHA, the author recommends supplementation of fish oil which is typically found in the form of a capsule or a liquid. It is important to be aware that commercial fish oil supplements vary widely in the amount of EPA and DHA they contain. Therefore, a clinician must recommend a specific brand of omega-3 fatty acid supplement for which he or she knows the exact concentration of EPA and DHA. A common formulation of fish oil is one gram capsules that contain approximately 180 mg EPA and 120 mg DHA and can be purchased over the counter at most human pharmacies or health food stores. At this concentration, fish oil can be administered at a dose of one capsule

per 4·5 kg of bodyweight to achieve the author's recommended EPA and DHA dosage. However, products with higher concentrations are becoming available and are advantageous as they require administration of fewer capsules or less liquid/day.

Cod liver oil is sometimes administered to provide omega-3 fatty acids. However, compared with fish oil, it is a lower concentration and different ratio of EPA and DHA. Instead of ratio of 1·5:1 EPA:DHA found in most fish oils, 1 g of cod liver oil contains only 69 mg EPA and 110 mg DHA and results in an EPA:DHA ratio of 0·6:1. More importantly, cod liver oil is high in vitamins A and D (1 g contains 1000 IU vitamin A and 100 IU vitamin D) so toxicity can be an issue at the recommended EPA and DHA dose.

Flax and flaxseed oil is a product promoted for its high content of omega-3 fatty acids but its omega-3 fatty acids are in the form of ALA. As previously mentioned, the conversion of the shorter-chain omega-3 fatty acid, ALA, to EPA and DHA, is inefficient at best (in dogs and people) to nearly non-existent (in cats). Therefore, using flax or flaxseed oil to provide the omega-3 fatty acids, EPA and DHA, either in the diet or as a supplement, is not recommended in dogs or cats.

Potential adverse effects of omega-3 fatty acids

While this article has concentrated on the beneficial effects of omega-3 fatty acids, clinicians must also be aware of its potential adverse effects. These can include hemostatic alterations due to anti-aggregatory effects on platelets, vitamin E deficiency and lipid peroxidation, and mild diarrhoea (Hall 1996). Most studies have not identified these issues to be of clinical relevance (Bright and others 1994, McNiel and others 1999, LeBlanc and others 2008) but it is important to consider the individual animal before recommending omega-3 fatty acid supplementation. For example, animals with thrombocytopenia may not be ideal candidates for omega-3 fatty acid supplementation. Animals receiving high doses of omega-3 fatty acid supplementation should be monitored for adverse effects.

For animals receiving large amounts of omega-3 fatty acids in dry pet food, it is important to be aware that diets high in the long-chain fatty acids are more susceptible to oxidation so owners (particularly of cats or small dogs which take longer to finish a bag of dry food) should be cautioned to purchase small enough bags so that the bag is finished within 4 to 6 weeks and to store the unused food properly (e.g. purchased and opened by the expiration date, storing food in the original bag with extra air expressed).

While many dogs and cats appear to enjoy the taste of fish oil and will willingly eat it in the diet or as a supplement, others appear to dislike the taste. Because of the strong flavour of fish oil, one must be careful to avoid the stress of giving a supplement if the animal dislikes it or causing food aversions by feeding a food containing fish oil or by administering fish oil in the food.

Finally, an important issue related to the safety of omega-3 fatty acid supplements is quality control. In the USA and in many other countries, dietary supplements currently do not require proof of safety, efficacy or quality control to be marketed (Coppens and others 2006, FDA 2010). Because dietary supplements are regulated very differently than drugs, poor-quality control of these products can be a significant problem in that the amount in the product may be much less (or more) than stated on the label or may contain contaminants.

Clinical recommendations

Because of the wide variation in concentrations and quality control, without specific recommendations, owners may end up administering too much or too little omega-3 fatty acids to an animal or may provide a poor-quality product. Clinicians must obtain a careful diet history to determine the type of food an animal is eating and whether it contains any omega-3 fatty acids, as well as any dietary supplements the animal is receiving. Based on this information, a plan for increasing omega-3 fatty acids can be developed and specific recommendations can be made for the individual animal (Table 1).

Conclusions

Omega-3 fatty acids appear to have many potential benefits in dogs and cats with cardiac disease. If omega-3 fatty acids are used, clinicians should be careful to provide specific recommendations for their patients. Additional research is needed and warranted to determine optimal indications, doses and formulations for the large canine and feline population with cardiac disease.

Conflict of interest

Dr. Freeman received remuneration from Boehringer Ingleheim for this article.

References

Ad Hoc Committee on Dog and Cat Nutrition, National Research Council. (2006) Fats and fatty acids. In: Nutrient Requirements of Dogs And Cats. The National Academies Press, Washington, D.C. pp 81-110

Table 1. Clinical recommendations for omega-3 fatty acid supplementation in dogs and cats with cardiac disease

- Decide if omega-3 fatty acids will be provided via diet or supplements.
  - If using diet, ensure that the diet contains 80 to 150 mg/100 kcal EPA + DHA. If the diet is enriched in EPA and DHA but not at this concentration, consider additional supplementation but at lower doses.
  - If using a supplement, recommend a specific product that the clinician has researched to have good quality control and knows the specific concentration of EPA and DHA, as well as any other ingredients.
    - Recommend a specific dose of that brand appropriate for the patient.
      - 40 mg/kg eicosapentaenoic acid (EPA) and 25 mg/kg docosahexaenoic acid (DHA).
      - A ratio of EPA:DHA of approximately 1·5:1.
  - Vitamin E (α-tocopherol) should be included in the product (diet or supplement) to help prevent oxidation.
  - Products (diets or supplements) which include other nutrients in addition to EPA and DHA should be carefully evaluated on an individual basis to ensure that the dose of the other ingredient(s) is optimal for that individual patient.
- Ensure palatability of product for the individual animal.

Albert, C. M., Campos, H., Stampfer, M. J., Ridker, P. M., Manson, J. E., Willett, W. C. & Ma, J. (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *New England Journal of Medicine* **346**, 1113-1118

Anker, S. D., Chua, T. P., Ponikowski, P., Harrington, D., Swan, J. W., Kox, W. J., Poole-Wilson, P. A. & Coats, A. J. (1997a) Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* **96**, 526-534

Anker, S. D., Ponikowski, P., Varney, S., Chua, T. P., Clark, A. L., Webb-Peploe, K. M., Harrington, D., Kox, W. J., Poole-Wilson, P. A. & Coats, A. J. (1997b) Wasting as independent risk factor for mortality in chronic heart failure. *Lancet* **349**, 1050-1053

Anker, S. D., Negassa, A., Coats, A. J. S., Afzal, R., Poole-Wilson, P. A., Cohn, J. N. & Yusuf, S. (2003) Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* **361**, 1077-1083

Ascherio, A., Rimm, E. B., Stampfer, M. J., Giovannucci, E. L. & Willett, W. C. (1995) Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *New England Journal of Medicine* **332**, 977-982

Bauer, J. E. (2007) Responses of dogs to dietary omega-3 fatty acids. *Journal of American Veterinary Medical Association* **231**, 1657-1661

Bayram, I., Erbey, F., Celik, N., Nelson, J. L. & Tanyeli, A. (2009) The use of a protein and energy dense eicosapentaenoic acid containing supplement for malignancy-related weight loss in children. *Pediatric Blood Cancer* **52**, 571-574

Billman, G. E., Hallaq, H. & Leaf, A. (1994) Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids. *Proceedings of National Academy of Sciences USA* **91**, 4427-4430

Billman, G. E., Kang, J. X. & Leaf, A. (1999) Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation* **99**, 2452-2457

Brenna, J. T. (2002) Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. *Current Opinion in Clinical Nutrition & Metabolic Care* **5**, 127-132

Bright, J. M., Sullivan, P. S., Melton, S. L., Schneider, J. F. & McDonald, T. P. (1994) The effects of n-3 fatty acid supplementation on bleeding time, plasma fatty acid composition, and in vitro platelet aggregation in cats. *Journal of Veterinary Internal Medicine* **8**, 247-252

Brouwer, I. A., Zock, P. L., Camm, A. J., Bocker, D., Hauer, R. N., Wever, E. F., Dullemeijer, C., Ronden, J. E., Katan, M. B., Lubinski, A., Buschler, H. & Schouten, E. G. (2006) Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *Journal of the American Medical Association* **295**, 2613-2619

Brouwer, I. A., Raitt, M. H., Dullemeijer, C., Kraemer, D. F., Zock, P. L., Morris, C., Katan, M. B., Connor, W. E., Camm, J. A., Schouten, E. G. & McAnulty, J. (2009) Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *European Heart Journal* **30**, 820-826

Buchanan, J. W. (1999) Prevalence of cardiovascular disorders. In: Textbook of Canine and Feline Cardiology. 2nd edn. Eds P. R. Fox, D. Sisson and N. S. Moise. W. B. Saunders, Philadelphia, PA, USA. pp 457-470

Calder, P. C. (2008) The relationship between the fatty acid composition of immune cells and their function. *Prostaglandins Leukotrienes & Essential Fatty Acids* **79**, 101-108

Calo, L., Bianconi, L., Colivicchi, F., Lamberti, F., Loricchio, M. L., de Ruvo, E., Meo, A., Pandozi, C., Staibano, M. & Santini, M. (2005) N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of American College of Cardiology* **45**, 1723-1728

Caughey, G. E., Mantzioris, E., Gibson, R. A., Cleland, L. G. & James, M. J. (1996) The effect on human tumor necrosis factor alpha and interleukin 1 beta production of diets enriched in n-3 fatty acids from vegetable oil or fish oil. *American Journal of Clinical Nutrition* **63**, 116-122

Coppens, P., da Silva, M. F. & Pettman, S. (2006) European regulations on nutraceuticals, dietary supplements and functional foods: a framework based on safety. *Toxicology* **221**, 69-74

Cote, E., Manning, A. M. & Emerson, D. (2004) Assessment of the prevalence of heart murmurs in overtly healthy cats. *Journal of American Veterinary Medical Association* **225**, 384-388

Daviglus, M. L., Stamler, J., Orencia, A. J., Dyer, A. R., Liu, K., Greenland, P., Walsh, M. K., Morris, D. & Shekelle, R. B. (1997) Fish consumption and the 30-year risk of fatal myocardial infarction. *New England Journal of Medicine* **336**, 1046-1053

Den Ruijter, H. M., Berecki, G., Verkerk, A. O., Bakker, D., Baartscheer, A., Schumacher, C. A., Belterman, C. N., de Jonge, N., Fiolet, J. W., Brouwer, I. A. & Coronel, R. (2008) Acute administration of fish oil inhibits triggered activity in isolated myocytes from rabbits and patients with heart failure. *Circulation* **117**, 536-544

Dewey, A., Baughan, C., Dean, T., Higgins, B. & Johnson, I. (2007) Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database of Systematic Reviews* **CD004597**

Duda, M. K., O'Shea, K. M. & Stanley, W. C. (2009) Omega-3 polyunsaturated fatty acid supplementation for the treatment of heart failure: Mechanisms and clinical potential. *Cardiovascular Research* **84**, 33-41

Endres, S., Ghorbani, R., Kelley, V. E., Georgilis, K., Lonnemann, G., van der Meer, J. W., Cannon, J. G., Rogers, T. S., Klempner, M. S. & Weber, P. C. (1989) The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *New England Journal of Medicine* **320**, 265-271

Farabaugh, A. E., Freeman, L. M., Rush, J. E. & George, K. L. (2004) Lymphocyte subpopulations and hematologic parameters in dogs with congestive heart failure. *Journal of Veterinary Internal Medicine* **18**, 505-509

Food and Drug Administration (FDA). (2010). Dietary supplements. http://www.fda.gov/Food/DietarySupplements/default.htm. Accessed January 25, 2010.

Fearon, K. C. (2008) Cancer cachexia: developing multimodal therapy for a multidimensional problem. *European Journal of Cancer* **44**, 1124-1132

Fearon, K. C., Barber, M. D., Moses, A. G., Ahmedzai, S. H., Taylor, G. S., Tisdale, M. J. & Murray, G. D. (2006) Double-blind, placebo-controlled, randomized study of eicosapentaenoic acid diester in patients with cancer cachexia. *Journal of Clinical Oncology* **24**, 3401-3407

Freeman, L. M. (2009) The pathophysiology of cardiac cachexia. *Current Opinion in Supportive and Palliative Care* **3**, 276-281

Freeman, L. M. & Roubenoff, R. (1994) The nutrition implications of cardiac cachexia. *Nutrition Reviews* **52**, 340-347

Freeman, L. M. & Rush, J. E. (2010) Nutritional modulation of heart disease. In: Textbook of Veterinary Internal Medicine. 7th edn. Eds S. J. Ettinger and E. C. Feldman. Saunders Elsevier, St Louis, MO. pp 691-696

Freeman, L. M. & Rush, J. E. (2005) Relationship between cachexia and lymphocyte subpopulations and hematologic parameters in dogs with spontaneously-occurring congestive heart failure. Third Cachexia Conference, Rome, Italy. p 82

Freeman, L. M., Rush, J. E., Cahalane, A. K., Kaplan, P. M. & Markwell, P. J. (2003) Dietary patterns in dogs with cardiac disease. *Journal of American Veterinary Medical Association* **223**, 1301-1305

Freeman, L. M., Rush, J. E., Kehayias, J. J., Ross, J. N. Jr., Meydani, S. N., Brown, D. J., Dolnikowski, G. G., Marmor, B. N., White, M. E., Dinarello, C. A. & Roubenoff, R. (1998) Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. *Journal of Veterinary Internal Medicine* **12**, 440-448

Freeman, L. M., Rush, J. E. & Markwell, P. J. (2006) Effects of dietary modification in dogs with early chronic valvular disease. *Journal of Veterinary Internal Medicine* **20**, 1116-1126

Geleijnse, J. M., Giltay, E. J., Grobbee, D. E., Donders, A. R. & Kok, F. J. (2002) Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *Journal of Hypertension* **20**, 1493-1499

Gullestad, L., Aukrust, P., Ueland, T., Espevik, T., Yee, G., Vagelos, R., Froland, S. S., Fowler, M. (1999). Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. *Journal of the American College of Cardiology* **34**, 2061-2067

Hall, J. A. (1996) Potential adverse effects of long-term consumption of (n-3) fatty acids. *Compendium on Continuing Education for the Practicing Veterinarian* **18**, 879-895

Hall, J. A., Tooley, K. A., Gradin, J. L., Jewell, D. E. & Wander, R. C. (2003) Effects of dietary n-6 and n-3 fatty acids and vitamin E on the immune response of healthy geriatric dogs. *American Journal of Veterinary Research* **64**, 762-772

Hall, J. A., Picton, R. A., Skinner, M. M., Jewell, D. E. & Wander, R. C. (2006) The (n-3) fatty acid dose, independent of the (n-6) to (n-3) fatty acid ratio, affects the plasma fatty acid profile of normal dogs. *Journal of Nutrition* **136**, 2338-2344

Hansen, R. A., Ogilvie, G. K., Davenport, D. J., Gross, K. L., Walton, J. A., Richardson, K. L., Mallinckrodt, C. H., Hand, M. S. & Fettman, M. J. (1998) Duration of effects of dietary fish oil supplementation on serum eicosapentaenoic acid and docosahexaenoic acid concentrations in dogs. *American Journal of Veterinary Research* **59**, 864-868

He, K., Song, Y., Daviglus, M. L., Liu, K., Van Horn, L., Dyer, A. R. & Greenland, P. (2004) Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* **109**, 2705-2711

Hirschberg, Y., Pomposelli, J. J., Blackburn, G. L., Istfan, N. W., Babayan, V. & Bistrian, B. R. (1990) The effects of chronic fish oil feeding in rats on protein catabolism induced by recombinant mediators. *Metabolism* **39**, 397-402

Iso, H., Kobayashi, M., Ishihara, J., Sasaki, S., Okada, K., Kita, Y., Kokubo, Y. & Tsugane, S. (2006) 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* **113**, 195-202

Kang, J. X. & Weylandt, K. H. (2008) Modulation of inflammatory cytokines by omega-3 fatty acids. *Subcellular Biochemistry* **49**, 133-143

Kearns, R. J., Hayek, M. G., Turek, J. J., Meydani, M., Burr, J. R., Greene, R. J., Marshall, C. A., Adams, S. M., Borgert, R. C. & Reinhart, G. A. (1999) Effect of age, breed and dietary omega-6 (n-6): omega-3 (n-3) fatty acid ratio on immune function, eicosanoid production, and lipid peroxidation in young and aged dogs. *Veterinary Immunology and Immunopathology* **69**, 165-183

Kris-Etherton, P. M., Harris, W. S. & Appel, L. J. (2003) Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, e20-e30

Kromhout, D., Bosschieter, E. B. & de Lezenne Coulander, C. (1985) The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *New England Journal of Medicine* **312**, 1205-1209

Laviano, A., Inui, A. & Marks, D. L. (2008) Neural control of the anorexia-cachexia syndrome. *American Journal of Physiology – Endocrinology and Metabolism* **295**, E1000-E1008

Leaf, A., Albert, C. M., Josephson, M., Steinhaus, D., Kluger, J., Kang, J. X., Cox, B., Zhang, H. & Schoenfeld, D. (2005) Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* **112**, 2762-2768

LeBlanc, C. J., Horohov, D. W., Bauer, J. E., Hosgood, G. & Mauldin, G. E. (2008) Effects of dietary supplementation with fish oil on in vivo production of inflammatory mediators in clinically normal dogs. *American Journal of Veterinary Research* **69**, 486-493

Levitan, E. B., Wolk, A. & Mittleman, M. A. (2009) Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: a population-based prospective study of middle-aged and elderly men. *European Heart Journal* **30**, 1495-1500

London, B., Albert, C. M., Anderson, M. E., Giles, W. R., Van Wagoner, D. R. & Balk, E. (2007) Omega-3 fatty acids and cardiac arrhythmias: prior studies and recommendations for future research: a report from the National Heart, Lung, and Blood Institute and Office Of Dietary Supplements Omega-3 Fatty Acids and their Role in Cardiac Arrhythmogenesis Workshop. *Circulation* **116**, e320-e335

Mallery, K. F., Freeman, L. M., Harpster, N. K. & Rush, J. E. (1999) Factors contributing to the euthanasia decision in dogs with congestive heart failure. *Journal of American Veterinary Medical Association* **214**, 1201-1204

McNiel, E. A., Ogilvie, G. K., Mallinckrodt, C., Richardson, K. & Fettman, M. J. (1999) Platelet function in dogs treated for lymphoma and hemangiosarcoma and supplemented with dietary n-3 fatty acids. *Journal of Veterinary Internal Medicine* **13**, 574-580

Mehra, M. R., Lavie, C. J., Ventura, H. O. & Milani, R. V. (2006) Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. *Journal of Heart and Lung Transplantation* **25**, 834-838

Moresi, V., Pristera, A. & Scicchitano, B. M. (2008) Tumor necrosis factor-α inhibition of skeletal muscle regeneration is mediated by a caspase-dependent stem cell response. *Stem Cells* **26**, 997-1008

Morgan, D. R., Dixon, L. J., Hanratty, C. G., El-Sherbeeny, N., Hamilton, P. B., McGrath, L. T., Leahey, W. J., Johnston, G. D. & McVeigh, G. E. (2006) Effects of dietary omega-3 fatty acid supplementation on endothelium-dependent vasodilation in patients with chronic heart failure. *American Journal of Cardiology* **97**, 547-551

Mozaffarian, D., Psaty, B. M., Rimm, E. B., Lemaitre, R. N., Burke, G. L., Lyles, M. F., Lefkowitz, D. & Siscovick, D. S. (2004) Fish intake and risk of incident atrial fibrillation. *Circulation* **110**, 368-373

Mozaffarian, D., Bryson, C. L., Lemaitre, R. N., Burke, G. L. & Siscovick, D. S. (2005a) Fish intake and risk of incident heart failure. *Journal of the American College of Cardiology* **45**, 2015-2021

Mozaffarian, D., Geelen, A., Brouwer, I. A., Geleijnse, J. M., Zock, P. L. & Katan, M. B. (2005b) Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* **112**, 1945-1952

Neubauer, S. (2007) The failing heart – an engine out of fuel. *New England Journal of Medicine* **356**, 1140-1151

Nodari, S., Metra, M., Milesi, G., Manerba, A., Cesana, B. M., Gheorghiade, M. & Dei Cas, L. (2009) The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. *Cardiovascular Drugs and Therapy* **23**, 5-15

Oreopoulos, A., Padwal, R. & Kalantar-Zadeh, K. (2008) Body mass index and mortality in heart failure: a meta-analysis. *American Heart Journal* **156**, 13-22

Oyama, M. A., Rush, J. E. & O'Sullivan, M. L. (2008) Perceptions and priorities of owners of dogs with heart disease regarding quality versus quantity of life for their pets. *Journal of American Veterinary Medical Association* **233**, 104-108

Paige, C. F., Abbott, J. A., Elvinger, F. & Pyle, R. L. (2009) Prevalence of cardiomyopathy in apparently healthy cats. *Journal of American Veterinary Medical Association* **234**, 1398-1403

Pratt, C. M., Reiffel, J. A., Ellenbogen, K. A., Naccarelli, G. V. & Kowey, P. R. (2009) Efficacy and safety of prescription omega-3-acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. *American Heart Journal* **158**, 163-169, e161-e163

Radaelli, A., Cazzaniga, M., Viola, A., Balestri, G., Janetti, M. B., Signorini, M. G., Castiglioni, P., Azzellino, A., Mancia, G. & Ferrari, A. U. (2006) Enhanced baroreceptor control of the cardiovascular system by polyunsaturated Fatty acids in heart failure patients. *Journal of the American College of Cardiology* **48**, 1600-1606

Raitt, M. H., Connor, W. E., Morris, C., Kron, J., Halperin, B., Chugh, S. S., McClelland, J., Cook, J., MacMurdy, K., Swenson, R., Connor, S. L., Gerhard, G., Kraemer, D. F., Oseran, D., Marchant, C., Calhoun, D., Shnider, R. & McAnulty, J. (2005) Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *Journal of the American Medical Association* **293**, 2884-2891

Ross, J. A., Moses, A. G. & Fearon, K. C. (1999) The anti-catabolic effects of n-3 fatty acids. *Current Opinion Clinical Nutrition and Metabolic Care* **2**, 219-226

Sakabe, M., Shiroshita-Takeshita, A., Maguy, A., Dumesnil, C., Nigam, A., Leung, T. K. & Nattel, S. (2007) Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. *Circulation* **116**, 2101-2109

Schrepf, R., Limmert, T., Claus Weber, P., Theisen, K. & Sellmayer, A. (2004) Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia. *Lancet* **363**, 1441-1442

Slupe, J. L., Freeman, L. M. & Rush, J. E. (2008) Association of body weight and body condition with survival in dogs with heart failure. *Journal of Veterinary Internal Medicine* **22**, 561-565

Smith, C. E., Freeman, L. M., Rush, J. E., Cunningham, S. M. & Biourge, V. (2007) Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *Journal of Veterinary Internal Medicine* **21**, 265-273

Smith, C. E., Freeman, L. M., Meurs, K. M., Rush, J. E. & Lamb, A. (2008) Plasma fatty acid concentrations in Boxers and Doberman Pinschers. *American Journal of Veterinary Research* **69**, 195-198

Stanley, W. C., Recchia, F. A. & Lopaschuk, G. D. (2005) Myocardial substrate metabolism in the normal and failing heart. *Physiological Reviews* **85**, 1093-1129

Tatli, E., Kurum T, Aktoz M, Buyuklu M (2008). Effects of carvedilol on right ventricular ejection fraction and cytokine levels in patients with systolic heart failure. *International Journal of Cardiology* **125**, 273-276

Tavazzi, L., Maggioni, A. P., Marchioli, R., Barlera, S., Franzosi, M. G., Latini, R., Lucci, D., Nicolosi, G. L., Porcu, M. & Tognoni, G. (2008) Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* **372**, 1223-1230

Torin, D. S., Freeman, L. M. & Rush, J. E. (2007) Dietary patterns of cats with cardiac disease. *Journal of the American Veterinary Medical Association* **230**, 862-867

Torrejon, C., Jung, U. J. & Deckelbaum, R. J. (2007) n-3 Fatty acids and cardiovascular disease: actions and molecular mechanisms. *Prostaglandins Leukotrienes & Essential Fatty Acids* **77**, 319-326

Virtanen, J. K., Mursu, J., Voutilainen, S. & Tuomainen, T. P. (2009) Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation* **120**, 2315-2321

von Haehling, S., Lainscak, M., Springer, J. & Anker, S. D. (2009) Cardiac cachexia: a systematic overview. *Pharmacology & Therapeutics* **121**, 227-252