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The effects of omega-3 polyunsaturated fatty acids on cardiac rhythm: A critical reassessment

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ABSTRACT

Although epidemiological studies provide strong evidence for an inverse relationship between omega-3 polyunsaturated fatty acids (n−3 PUFAs) and cardiac mortality, inconsistent and often conflicting results have been obtained from both animal studies and clinical prevention trials. Despite these heterogeneous results, some general conclusions can be drawn from these studies: 1) n-PUFAs have potent effects on ion channels and calcium regulatory proteins that vary depending on the route of administration. Circulating (acute administration) n−3 PUFAs affect ion channels directly while incorporation (long-term supplementation) of these lipids into cell membranes indirectly alter cardiac electrical activity via alteration of membrane properties. 2) n−3 PUFAs reduce baseline HR and increase HRV via alterations in intrinsic pacemaker rate rather than from changes in cardiac autonomic neural regulation. 3) n−3 PUFAs may be only effective if given before electrophysiological or structural remodeling has begun and have no efficacy against atrial fibrillation. 5) Despite initial encouraging results, more recent clinical prevention and animal studies have not only failed to reduce sudden cardiac death but actually increased mortality in angina patients and increased rather than decreased malignant arrhythmias in animal models of regional ischemia. 6) Given the inconsistent benefits reported in clinical and experimental studies and the potential adverse actions on cardiac rhythm noted during myocardial ischemia, n−3 PUFA must be prescribed with caution and generalized recommendations to increase fish intake or to take n−3 PUFA supplements need to be reconsidered.

Contents

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; ALA, alpha-linolenic acid; APD, action potential duration; BP, blood pressure; Ca-ATs, calcium aftertransients; CICR, calcium induced calcium release; DADs, delayed afterdepolarizations; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EADs, early afterdepolarizations; EPA, eicosapentaenoic acid; ERP, effective refractory period; HR, heart rate; HRV, heart rate variability; ICDs, implantable cardioverter defibrillators; MI, myocardial infarction; MSNA, muscle sympathetic nerve activity; n−3 PUFAs, omega-3 polyunsaturated fatty acids; n−6 PUFAs, omega-6 polyunsaturated fatty acids; RBC, red blood cell; RYRs, ryanodine receptors; SR, sarcoplasmic reticulum; VF, ventricular fibrillation; VT, ventricular tachycardia.

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1. Introduction

The effective management of cardiac arrhythmias, either of atrial or of ventricular origin, remains a major challenge for the cardiologist. Sudden cardiac death, most frequently due to ventricular tachyarrhythmias (Hinkle & Thaler, 1982; Bayes de Luna et al., 1989; Greene, 1990), remains the leading cause of death in industrially developed countries, accounting for 300,000 to 500,000 deaths each year in the United States (Abildstrom et al., 1999; Zheng et al., 2001). In a similar manner, atrial fibrillation is the most common rhythm disorder, accounting for about 2.6 million cases in the United States and contributes to approximately one quarter of the ischemic strokes in the elderly population (Anonymous, 1998; Kannel et al., 1998; Lakshminarayan et al., 2006; McManus et al., 2012). The emotional and economic consequences associated with the morbidity and mortality resulting from cardiac arrhythmias cannot be understated (the incremental cost per quality-adjusted life-year has been estimated to be as high as US $558,000 (Byrant et al., 2005)).

Despite the enormity of this problem, the development of safe and effective anti-arrhythmic agents remains elusive. Several anti-arrhythmic drugs have actually been shown to increase, rather than to decrease, the risk for arrhythmic death in patients recovering from myocardial infarction (Echt et al., 1991; Waldo et al., 1996), while even "optimal" pharmacological therapy fails to suppress these arrhythmias completely (Buxton et al., 1999). For example, the one-year mortality is 10% or higher, with sudden death accounting for approximately one-third of the deaths, in post-myocardial infarction patients treated with β-adrenergic receptor antagonists (Buxton et al., 1999). Implantable cardioverter defibrillators (ICDs) have been shown to reduce cardiac mortality, providing a better protection from sudden death than current pharmacological therapy in certain high-risk patient populations (Buxton et al., 1999; Connelly et al., 2000; Al-Khatib et al., 2013). However, these devices are expensive to use and maintain (Byrant et al., 2005; Groeneveld et al., 2006), negatively affect the patient's quality of life (Groeneveld et al., 2006), have a significant risk for inappropriate shock delivery (Poole et al., 2008), are ineffective in elderly and female patients (Henyan et al., 2006; Katritsis & Josephson, 2012), and, perhaps most importantly, only extend life by a mean of 4.4 months (Connelly et al., 2000). Given the adverse outcomes associated with ICDs and many anti-arrhythmic medications, as well as the partial protection afforded by even the best agents (e.g., β-adrenergic receptor antagonists and ICDs), it is obvious that more effective anti-arrhythmic therapies must be developed.

Dietary interventions have recently received considerable attention as viable alternatives to the less than effective current therapies. In particular, the cardiovascular benefits of dietary omega-3 polyunsaturated fatty acids (n−3 PUFA) have been actively investigated for nearly 40 years. Epidemiological data provide strong evidence for an inverse relationship between fatty fish consumption and cardiac mortality (Kromhout et al., 1985; Daviglus et al., 1997) while both experimental studies (McLennan et al., 1988; Billman et al., 1994) and clinical secondary preventions trials (Burr et al., 1989; Marchioli et al., 2002) have reported salutary actions of n−3 PUFAs against ventricular arrhythmias and sudden cardiac death. However, more recent studies in patients with heart disease (Burr et al., 2003; Raitt et al., 2005; Brouwer et al., 2006b; Yokoyama et al., 2007; GISSI-HF investigators, 2008; Kromhout et al., 2010; Rauch et al., 2010) or animals (Coronel et al., 2007; Billman et al., 2012) have yielded conflicting results, particularly with regards to the prevention of atrial fibrillation (Kowey et al., 2010; Mozaffarian et al., 2012; Sandesara et al., 2012). Thus, a scientific consensus on the effects of n−3 PUFA on cardiac rhythm has yet to be reached.

It is the purpose of this review to evaluate the putative benefits of n−3 PUFAs on cardiac rhythm. The review will first address the effects of n−3 PUFAs on heart rate variability (i.e., sinus rhythm) and then will provide a critical analysis of the effects of n−3 PUFAs on atrial fibrillation and ventricular arrhythmias/sudden cardiac death.

2. The effects of omega-3 fatty acids on heart rate and heart rate variability

There is a strong association between both heart rate (HR) and heart rate variability (HRV) and cardiovascular mortality. It is now well established that an elevated resting heart rate (>70–90 beats/min) is associated with a greater risk for sudden cardiac death in both individuals with and without pre-existing cardiovascular disease, even after adjusting for other established cardiovascular risk factors (Shaper et al., 1993; Palatini et al., 1999). Indeed, individuals with the lowest resting heart rates also exhibited the lowest long-term (>20 years) mortality rate (Jouven et al., 2009). Among the Framingham study cohort, resting HR was one of the strongest independent predictors of future sudden cardiac death with mortality rates progressively increasing as resting heart rate increased (Kannel et al., 1987). In a similar fashion, a reduced HRV (beat-to-beat variation in either HR or the duration of the R–R interval—the heart period) is associated with a poorer prognosis for a wide range of clinical conditions while, conversely, robust periodic changes in R–R interval are often a hallmark of health (Task Force of the European Society of Cardiology and the North American Society of Pacing & Electrophysiology, 1996; Berntson et al., 1997; Hohnloser et al., 1997; Billman, 2009; Thayler et al., 2010; Billman, 2011). It is now widely accepted that these beat-to-beat variations in HR reflect changes in cardiac autonomic regulation and several time and frequency domain techniques have been developed to quantify HRV, each with strengths and weaknesses (for reviews see: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hohnloser et al., 1997; Berntson et al., 1997; Thayler et al., 2010; Billman, 2011). In general, and at the risk of oversimplification, HRV can be considered to be directly related to cardiac parasympathetic regulation and to a lesser extent inversely related to sympathetic activity. However, it must be emphasized that the exact contributions of the parasympathetic and the sympathetic divisions of the autonomic nervous system to this variability are controversial and remain the subject of active investigation and debate (Parati et al., 2006; Billman, 2013; Reyes del Paso et al., 2013).

It is well established that interventions that decrease cardiac parasympathetic activity and/or enhance cardiac sympathetic decrease both HRV and cardiac electrical stability increasing the risk for life threatening arrhythmias (Billman, 2009). Furthermore a variety of cardiovascular risk factors and disease states have been shown to reduce HRV, including diabetes (Murray et al., 1975; Ewing et al., 1985; Vinik et al., 2003; Rosengard-Barlund et al., 2009), smoking (Mancia et al., 1997; Karakaya et al., 2007), obesity (Skrapari et al., 2007), and work stress (Thayler et al., 2010). Of particular interest, HRV is reduced in patients recovering from a myocardial infarction and, further, those patients with the greatest reduction in this variable also have the greatest risk for sudden death (Myers et al., 1986; Kleiger et al., 1987; La Rovere et al., 1988; Malik et al., 1989; Farrell et al., 1991; Bigger et al., 1992; Mazzuero et al., 1992; Huikuri et al., 1996; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hohnloser et al., 1997; La Rovere et al., 1998; Lanza et al., 1998). Indeed, low HRV is one of the strongest independent predictors of mortality following myocardial infarction. (La Rovere et al., 1988; Malik et al., 1989; Mazzuero et al., 1992; La Rovere et al., 1998). Similar findings have been reported in animals models of human disease (Billman & Hoskins, 1989; Collins & Billman, 1989; Halliwill et al., 1998; Houle & Billman, 1999; Smith et al., 2005; Billman, 2006a,b; Billman & Kukielka, 2006; Billman, 2009).

Heart rate reduction lowers the metabolic demand placed on the heart and could thereby indirectly decrease the risk for adverse cardiac events while HRV increases may reflect increased cardiac parasympathetic regulation which has been shown to protect against ventricular arrhythmias (Billman, 2009, 2011). Thus, interventions that reduce resting HR and improve cardiac autonomic balance as measured by an