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Modulation of heart rate and heart rate variability by *n*-3 long chain polyunsaturated fatty acids: Speculation on mechanism(s)

Merritt L. Drewery [a,*], Steven B. Spedale [b], Carol J. Lammi-Keefe [a,c]

[a] School of Nutrition and Food Sciences, Louisiana State University, Baton Rouge, LA 70803, USA
[b] InfaMedics, Woman's Hospital, Baton Rouge, LA 70817, USA
[c] Louisiana State University Agricultural Center, Baton Rouge, LA 70803, USA

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ABSTRACT

Heart rate (HR) and heart rate variability (HRV) are valuable markers of health. Although the underlying mechanism(s) are controversial, it is well documented that *n*-3 long chain polyunsaturated fatty acid (LCPUFA) intake improves HR and HRV in various populations. Autonomic modulation and/or alterations in cardiac electrophysiology are commonly cited as potential mechanisms responsible for these effects. This article reviews existing evidence for each and explores a separate mechanism which has not received much attention but has scientific merit. Based on presented evidence, it is proposed that *n*-3 LCPUFAs affect HR and HRV directly by autonomic modulation and indirectly by altering circulating factors, both dependently and independently of the autonomic nervous system. The evidence for changes in cardiac electrophysiology as the mechanism by which *n*-3 LCPUFAs affect HR and HRV needs strengthening.

Role of the autonomic nervous system in determining heart rate and heart rate variability

The autonomic nervous system contains two antagonistic divisions, the sympathetic and parasympathetic (vagal) nervous systems [1]. Autonomic output is mediated through preganglionic sympathetic and parasympathetic neurons which innervate the heart via the stellate ganglia and vagus nerve, respectively [2]. The interaction between these inputs and the sinoatrial (SA) node reflect spontaneous changes in autonomic activity which are apparent in heart rate (HR) and heart rate variability (HRV) measures [3].

Autonomic innervation of the sinoatrial node

Autonomic innervation lowers resting HR by 30% of its intrinsic value [4]. Greater parasympathetic influence further reduces HR with the opposite occurring for greater sympathetic influence [4]. Sympathetic stimulation, via β-adrenergic receptors and release of norepinephrine, increases SA node automaticity and atrioventricular (AV) node conduction, increasing HR [1,4,5]. Sympathetic stimulation increases the probability pacemaker channels will be open, allowing greater ion flow, increasing the steepness of the slope required for depolarization [4,6]. As a result, nodal cells reach threshold and spontaneously depolarize earlier than normal. With greater sympathetic influence, there is also a greater probability that Ca channels will be open; this shifts the threshold required for an action potential to a more negative voltage, resulting in a lower threshold potential for diastolic depolarization [6,7].

Parasympathetic stimulation, via muscarinic cholinergic receptors and release of acetylcholine (ACh), the primary parasympathetic neurotransmitter, reduces intrinsic firing rate of the SA node and slows conduction in the AV node, reducing intrinsic HR [1,4,5]. Parasympathetic influence decreases the probability pacemaker channels will be open, reducing flow and the slope of depolarization. Further, the probability of Ca channels being open decreases with parasympathetic stimulation, increasing the action potential threshold to a more positive voltage [8]. Parasympathetic stimulation also increases the probability transmembrane ACh-sensitive K channels will be open at rest, resulting in a more negative maximum diastolic potential [6,9].

Autonomic influence on circulating cytokines and catecholamines

Innervation of the SA node is a direct mechanism by which the autonomic nervous system controls HR and HRV. A separate,

* Corresponding author at: 202G Knapp Hall, Louisiana State University, Baton Rouge, LA 70803, USA.
E-mail address: merrittdrewery@gmail.com (M.L. Drewery).

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indirect autonomic mechanism also exists. By modulating circulating inflammatory factors (i.e., cytokines) and catecholamines, the autonomic nervous system indirectly affects HR and HRV.

Electrical or mechanical stimulation of the vagus nerve and the resulting increase in parasympathetic tone reduces cytokine production [10]. Further, peripheral release of pro-inflammatory cytokines (tumor necrosis factor [TNF], interleukin [IL]-1β, IL-6, IL-18), but not anti-inflammatory cytokines (IL-10), is attenuated by ACh [11]. The interaction between ACh and the α-7 nicotinic ACh receptor subunit, expressed on cytokine-producing cells, is the molecular basis for this anti-inflammatory circuit [12]. This relationship has been observed *in vivo*; C-reactive protein concentrations are inversely related to surrogate measures of vagus nerve activity in healthy adults [13,14] and adults with coronary heart disease [15]. Further, IL-6 concentrations in adults with coronary heart disease are inversely related to HRV measures before covariate adjustment [15].

The sympathetic nervous system also indirectly modulates HR by increased catecholamine release and pro-inflammatory cytokine production [6,16]. Stimulation of β-adrenoreceptor (a target of sympathetically-derived catecholamines) increases gene expression and protein production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) in myocardial cells [17] and β-blockade reduces plasma IL-6 in patients with congestive heart failure [18]. Further, stress-induced activation of nuclear factor (NF)-κB, a mediator of TNF-α responses [19], is dependent on the primary sympathetic neurotransmitter, norepinephrine, and this activation can be abrogated by α1-adrenoreceptor blockade [20].

Autonomic maturation and age-dependence of heart rate and heart rate variability

Age affects autonomic control; age-related autonomic changes are characterized by changes in the sympathetic and parasympathetic (sympatho-vagal) balance [3,21]. The sympathetic nervous system matures before the parasympathetic and predominates in early fetal life [21–23]. Fetal HR peaks around 10 gestational weeks then decreases with advancing gestational age [24]; this decline continues throughout life [25,26]. Variability in fetal HR begins to emerge around 32–34 gestational weeks, a reflection of increasing parasympathetic influence and the resulting inhibitory effect on the sympathetic nervous system [27]. Accordingly, group differences in time- and frequency-domain metrics of fetal HRV are especially pronounced during the third trimester; increased HRV and frequency-domain metrics specific to parasympathetic tone are associated with advancing gestational age [28]. Significant autonomic maturation continues throughout infancy [3] and is accompanied by profound, progressive changes in HR and HRV [25]. Fetal HRV patterns observed *in utero* persist postnatally [29] suggesting individual differences in autonomic control are established during gestation and this developmental trajectory continues after birth. As in the perinatal period, HRV changes in aging populations are profound. Time-domain metrics of HRV evidence a linear decrease in autonomic regulation (overall HRV) with advancing age and a U-shaped pattern for metrics related to parasympathetic influence such that there are progressive decreases from 40 to 69 years of age then an increase to 80+ years of age [30].

Heart rate and HRV are easily assessed across the age continuum [3] and may indirectly reflect cardiac health and cardiac-autonomic integration. In general, low HR and high metrics of overall HRV or metrics representing parasympathetic tone are hallmarks of health [31], although there is a threshold beyond which greater decreases in HR and/or increases in HRV would indicate abnormal functioning and populations for whom this interpretation is inappropriate [32].

Relationship between *n*-3 LCPUFAs, heart rate, and heart rate variability in different populations

Dietary fats are ubiquitous components of cell membranes, including those of the cardiovascular system [33]. Fatty acid composition of cell membranes reflects that of the diet [33], implying that dietary interventions may affect cardiac health, reflected as alterations in HR and HRV. Further, HR and HRV are modulated by the autonomic nervous system, which may also be impacted by dietary fat intake.

The long chain polyunsaturated fatty acids (LCPUFA) of the *n*-3 family, eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:6*n*-3) have been studied extensively with regard to human health. There is interest in exploring if these fatty acids affect HR and HRV. Similar to the age-dependence of HR and HRV [25], which is largely dictated by autonomic control, the effect(s) of *n*-3 LCPUFA supplementation depends on the population.

Effect of n-3 LCPUFAs on heart rate and heart rate variability: early life

The perinatal period is a sensitive time during which nutrition may have programming effects on later infant health and outcome [34,35]. In fetuses and infants, HRV is a developmental expression of maturation, thought to be linked to parasympathetic activity and integrity of the developing autonomic nervous system [3,28,36,37]. The autonomic nervous system matures significantly during perinatal life [3]; therefore, provision or deficits of nutrients during this time may exert long-term programming effects [38].

Gustafson et al. [28] explored if maternal supplementation with *n*-3 LCPUFA during pregnancy affected the developing fetus. Pregnant women were supplemented with 600 mg DHA per day or a placebo from gestational week 14.4 to term delivery. Fetal HR and HRV were assessed at 24, 32, and 36 weeks of gestation with magnetocardiography. There was a statistical trend for lower fetal HR and significantly higher indices of HRV, assessed as time- and frequency-domain metrics, in fetuses whose mothers received supplemental DHA. Colombo et al. [39] administered 4 levels of DHA (0.0, 0.32, 0.64, and 0.92% of fatty acids as DHA) to term infants from birth to 12 months of age and measured HR at 4, 6, and 9 months. Groups receiving supplemental DHA had lower HR than the control group; this effect was not dose-dependent. Similarly, term infants who were breast-fed, fed DHA-enriched milk formula, or fed DHA-enriched soy formula had lower HR and higher HRV than infants fed a DHA-deficient soy formula [40]. These effects were documented from 4 to 12 months of age. In another study [41], male infants receiving 924 mg fish oil (a source of *n*-3 LCPUFA) per day from 9 to 12 months of age had lower HR than those not receiving supplemental fish oil; no effect was observed for females. There was a positive association between the changes in HR and red blood cell *n*-3 PUFA content, regardless of gender [41]

Effect of n-3 LCPUFAs on heart rate and heart rate variability: healthy adults

In healthy adults, HR and HRV are prognostic markers for later cardiovascular morbidity and mortality [42–47]. Low HRV in adult life indicates the autonomic nervous system has been chronically strained by excessive sympathetic tone and/or diminishment of parasympathetic tone [47]. Interventions that shift autonomic balance to favor parasympathetic dominance and/or minimize sympathetic regulation improve disease prognosis [47].

In a meta-analysis of intervention trials including healthy adult populations ($n = 16$) and populations of adults with at least 1