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Non-esterified Fatty Acids and Risk of Sudden Cardiac Death in Older Adults

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Abstract

Background—While non-esterified fatty acids (NEFA) have been positively associated with coronary heart disease risk factors, limited and inconsistent data are available on the relation between NEFA and sudden cardiac death.

Methods and Results—Using a prospective design, we studied 4,657 older men and women (mean age 75 y) from the Cardiovascular Health Study (1992-2006) to evaluate the association between plasma NEFA and the risk of sudden cardiac death in older adults. Plasma concentrations of NEFA were measured using established enzymatic methods and sudden death was adjudicated using medical records, death certificates, proxy interview, and autopsy reports. We used Cox proportional hazard models to estimate multivariable-adjusted relative risks. During a median follow-up of 10.0 years, 221 new cases of sudden cardiac death occurred. In a multivariable model adjusting for age, sex, race, clinic site, alcohol intake, smoking, prevalent coronary heart disease and heart failure, and self-reported health status, relative risks (95% CI) for sudden cardiac death were 1.0 (ref), 1.15 (0.81-1.64), 1.06 (0.72-1.55), and 0.91 (0.60-1.38) across consecutive quartiles of NEFA concentration. In secondary analyses restricted to the first five years of follow up, we

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Conflict of Interest Disclosures: None

also did not observe a statistically significant association between plasma NEFA and sudden cardiac death.

Conclusions—Our data do not provide evidence for an association between plasma NEFA measured late in life and the risk of sudden cardiac death in older adults.

Keywords

epidemiology; sudden death; fatty acid binding protein 4; risk factors

Each year, about 450,000 Americans die from sudden cardiac death (SCD)[1,2]. Coronary heart disease (CHD) accounts for a large proportion of SCD cases and consequently, major risk factors for CHD are also associated with SCD[3]. Indeed, SCD is the first manifestation of CHD in about 50% of cases[4], setting a daunting task to prevent its occurrence among patients without overt CHD. This underscores the importance of identifying novel biomarkers for SCD that might help in risk stratification and perhaps offer new opportunities for pharmacological or other targeted interventions.

Non-esterified fatty acids (NEFA) are metabolic byproducts of lipolysis[5,6] and have been associated with abnormal glucose metabolism and diabetes, a major CHD risk factor. In the fasting state, NEFA are largely derived from adipose tissue lipolysis. Whereas insulin resistance promotes greater lipolysis, higher levels of circulating NEFA in turn may further impair insulin signaling and secretion from pancreatic β-cells, and promote hepatic gluconeogenesis[7-10]. In experimental models, higher plasma NEFA concentrations induce peripheral insulin resistance in vivo[11,12]. Epidemiologic studies have reported positive associations between NEFA and the risk of diabetes[13-16] and other CHD risk factors[17].

Potential effects of NEFA on the heart are less established. Under physiologic conditions, the heart preferentially utilizes NEFA for energy, providing 60-70% of the adenosine triphosphate required by myocardial metabolism[18]. Given a higher oxygen demand for beta-oxidation of NEFA than glucose utilization, greater availability and utilization of NEFA might predispose to severe arrhythmia[18-20] and perhaps SCD. However, limited data exist on the association between NEFA and SCD in humans[1721]. We sought to test the hypothesis that plasma levels of NEFA are positively associated with incident SCD in older adults.

Materials and Methods

Study population

The Cardiovascular Health Study (CHS) is a prospective, population-based cohort study of cardiovascular disease in older adults. In 1989-1990, 5,201 people aged 65 years and older were recruited from a random sample of Medicare-eligible residents in four U.S. communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania. An additional cohort of 687 predominantly African-Americans was recruited during 1992 and 1993 from three of the same communities (except for Washington County) using the same sampling and recruitment methods. Each center's institutional review board approved the study and all participants gave informed written consent. Description of the design, sampling, and recruitment in the Cardiovascular Health Study has been published[22].

The 1992-93 examination served as the baseline for this analysis. Of the 5,265 participants who were alive and participated in the 1992-1993 examination, we excluded 493 subjects without a blood sample; 57 with missing NEFA measurements; and 58 individuals with missing covariates. The final analysis sample included 4,657 participants.

Measurement of NEFA

Plasma samples collected at the 1992-1993 examination were stored at -70° C until analyzed at the Central Laboratory at the University of Vermont in 2010. NEFA concentration in plasma was measured in duplicate by the Wako enzymatic method and the average of the two measurements was used in current analyses. This technique utilizes the acylation of coenzyme A by the fatty acids in the presence of added acyl-CoA synthetase. Acyl-CoA produced is oxidized by added acyl-CoA oxidase with generation of hydrogen peroxide, which in the presence of peroxidase permits the oxidative condensation of 3-methy-N-ethyl-N(β-hydroxyethyl)-aniline with 4-aminoantipyrine to form a purple colored adduct. The latter is then measured colorimetrically at 550 nm. Intra-assay coefficient of variation was 5%.

Ascertainment of sudden cardiac death in CHS

Details of the procedures used in CHS to identify and classify cardiovascular events and deaths have been published[23,24]. Information on vital status was available for 100% of participants. Cause of death is adjudicated by the CHS Events Subcommittee following review of death certificates, inpatient medical records, nursing home or hospice records, physician questionnaires, interviews with next-of-kin and autopsy records where available. This analysis included events occurring by June 2006. SCD is defined as a sudden pulseless condition, presumed due to cardiac arrhythmia, in a previously stable individual that occurred out of the hospital or in the emergency room. For unwitnessed deaths, the participant must have been seen within 24 hours of the arrest in a stable condition and without evidence of a noncardiac cause of cardiac arrest. By definition, SCD cases could not be under hospice or nursing home care or have a life-threatening noncardiac comorbidity. SCD cases were identified and classified by a cardiologist's record review of all CHS Events Subcommittee adjudicated cardiac deaths. A blinded second physician review of a random sample of 70 of these death records showed an 88% inter-reviewer agreement and κ=0.74 for SCD.

Other risk factors

Information on age, sex, race, educational attainment, physical activity, smoking status, alcohol consumption, and dietary habits were based on self-report at baseline. Leisure-time activity (kcal/week) was assessed using a modified Minnesota Leisure-Time Activities questionnaire[25]. Usual dietary habits were assessed using a picture-sort food frequency questionnaire[26] in 1989-90 and a Willett food frequency questionnaire in 1995-1996. Weight, height, and waist circumference were measured using standardized protocols. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Diabetes was defined as a use of insulin or oral hypoglycemic agents; a fasting glucose level of ≥ 7 mmol/L (126 mg/dL); or a non-fasting glucose level of ≥ 11.1 mmol/L (200 mg/dl). Coronary heart disease endpoints and congestive heart failure were adjudicated by an endpoint committee. Detailed descriptions of cardiovascular adjudication in the Cardiovascular Health Study have been published previously[23,27]. Prevalent coronary heart disease and heart failure was based on status at baseline (1992-1993 examination).

Statistical analysis

We categorized participants into quartiles based on the distribution of NEFA concentrations in the study sample. P values for trends were calculated using linear regression for continuous variables and a non-parametric test across ordered groups for categorical variables. To compute p values for difference between SCD and non-SCD groups, we used t-test for normally distributed continuous variables, theWilcoxon rank-sum test for continuous variables with skewed distributions, and the chi-square test for categorical

variables. To estimate the risk of sudden cardiac death associated with NEFA categories, we used Cox proportional hazards regression to estimate relative risks, with the lowest quartile serving as the reference group. An initial multivariable model adjusted for age, sex, race, and clinic site, and a second model additionally adjusted for smoking status (never, former, current), alcohol consumption (0, <7, ≥7 drinks/week), prevalent CHD, prevalent CHF, and self-reported health status (excellent, very good, good, fair, poor). Additional adjustment for body mass index, diabetes, HDL-cholesterol, hypertension, hormone replacement therapy, broiled or baked fish consumption, and physical activity did not appreciably alter the results.

We evaluated potential heterogeneity in the association of NEFA with SCD by comparing stratified hazard ratio estimates by sex, body mass index (<255 vs. 25+ kg/m^2), and age (<75 vs. 75+ y). In sensitivity analyses, we stratified by presence of CHD, ECG abnormality, or prevalent diabetes. Because a single measurement of NEFA may not capture changes over a long period of follow up, we repeated the main analysis while restricting follow-up to the first five years. Lastly, we repeated main analyses restricted to the first five years of follow-up (n=95 SCD cases) in a minimally adjusted model (age, sex, race, and clinic site) as well as a full adjusted model (with additional inclusion of smoking, alcohol use, coronary heart disease, heart failure, and self-reported health status). We used Schoenfeld residuals to evaluate proportional hazards assumptions and found no appreciable evidence of violations. All analyses were conducted using Stata, version 11.2 (StataCorp LP, College Station, Texas).

Results

Of the 4657 participants, 58% were women and 16% were African-Americans. The mean age was 74.9±5.3 years (range 65-98 y). Table 1 shows the baseline characteristics according to plasma NEFA. Higher levels of plasma NEFA were associated with older age, higher measures of adiposity, female sex, lower levels of physical activity, poor self-reported health status, lower prevalence of smoking, higher concentration of triglycerides and HDL-cholesterol, higher prevalence of diabetes and hypertension, and lower prevalence of coronary heart disease. Table 2 presents baseline characteristics of participants who experienced SCD compared to those who did not. People in which SCD occurred were older, more likely to be male, and have higher waist circumference, low HDL-cholesterol, and a higher prevalence of diabetes, hypertension, coronary disease, and heart failure.

During an average follow up of 10.0 years (maximum of 13.5 y), 221 cases of sudden cardiac death occurred. Crude incidence rate of sudden cardiac death were 5.15, 5.45, 4.56, and 3.78 cases per 1,000 person-years from the lowest to the highest quartile of plasma NEFA. In a multivariable model adjusting for age, sex, race, and clinic site, there was no significant association between NEFA and sudden cardiac death (Table 3). Additional control for smoking, alcohol consumption, self-reported health status, prevalent coronary heart disease and heart failure did not alter these findings (Table 3). Additional adjustment for lipid lowering drugs, beta-blockers, body mass index, diabetes, hypertension, exercise, hormone replacement therapy, and serum albumin did not change the results (data not shown). The association between NEFA and SCD did not differ by sex [fully adjusted relative risk (95% CI): 1.0 (ref), 1.27 (0.84-1.92), 0.75 (0.44-1.31), 1.05 (0.59-1.85) from the lowest to the highest quartile of NEFA in men; corresponding values for women were 1.0 (ref), 0.99 (0.50-1.93), 1.43 (0.77-2.63), and 0.89 (0.46-1.72)]. Stratification by body mass, age, prevalent diabetes, ECG abnormality, or coronary heart disease did not show any association between NEFA and SCD (data not shown). The relative risk (95% CI) per unit change in plasma NEFA modeled continuously was 0.66 (0.31-1.40) for a model adjusted for age, race, gender, and clinic, and 0.72 (0.33-1.54) for a model additionally adjusted for smoking status, alcohol consumption, CHD, CHF, and health status.

In a sensitivity analysis restricted to the first five years of follow up, plasma NEFA was not associated with SCD (n=95 events) in a model adjusted for age, race, gender, and clinic site [relative risks: 1.0 (ref), 1.06 (0.62-1.78), 0.75 (0.41-1.37), and 0.82 (0.45-1.51)] or fully adjusted model [relative risk (95% CI) of 1.0 (ref), 1.10 (0.65-1.86), 0.82 (0.45-1.49), and 0.88 (0.47-1.62) across consecutive quartiles of plasma NEFA]. Exclusion of participants with prevalent coronary heart disease or heart failure did not alter the findings [multivariable adjusted relative risk for SCD 1.0 (ref), 1.09 (0.65-1.81), 1.35 (0.81-2.24), and 0.96 (0.54-1.70) across consecutive quartiles of NEFA.

Discussion

In this large prospective study of older adults with long-term follow up and adjudicated incidence of SCD, plasma concentration of NEFA measured late in life was not associated with the risk of sudden cardiac death. Considering only participants with or without prevalent diabetes or coronary heart disease at baseline or restricting follow-up to the first five years did not alter the results. Contrary to our results, the Paris Prospective Study[28] reported a 70% increased risk of SCD per each standard deviation increase in NEFA in a multivariable model among French men [RR; 1.70 (1.21-2.13)]. The participants in the Paris prospective study[28] were all men and were younger (age 42-53 y at baseline) than subjects in our study (mean age 75 y). Of note is that when we stratified our data by sex and age (<75 vs 75+ y), we did not observe any association between NEFA and SCD in any stratum. In another prospective study, Pilz et al[17] observed a 76% increased risk of SCD comparing the fourth to the first quartile of NEFA in patients referred for coronary angiography [HR: 1.76 (1.03-3.00)]. Findings from these two prospective studies are supported by the pro-arrhythmic effects of NEFA[29-31]. The discordance of these two studies with our results merits some comments.

It is possible that a lack of an association between NEFA and SCD in our cohort may be partially explained by the relatively older age in our cohort (75 y on average) and a relatively high prevalence of subclinical cardiovascular disease, making all subjects at a higher risk of SCD than those in the Paris Prospective study (42-53 y)[28] or the LURIC study (51-75 y) in Germany[17]. With a higher background rate of SCD in the reference group, greater statistical power is required to detect a modest increase in SCD risk with higher NEFA levels. Such a conjecture is supported by the relatively higher proportion of subjects with major risk factors for SCD in our cohort including diabetes, hypertension, heart failure, and coronary heart disease. We had 80% power to detect a 70% increase risk of SCD and 59% power to detect a 50% increase in SCD risk in our study when comparing the fourth to the first quartile of NEFA. It is also possible that people at higher risk of SCD (i.e. subjects with prevalent coronary heart disease) were more likely to have lower plasma NEFA concentration due to aggressive dietary and pharmacological treatment for comorbidities. Such a scenario would have led to a depletion of susceptible pool of SCD in the highest quartile of NEFA and to a paradoxical lower risk of SCD with higher concentration of plasma NEFA. This hypothesis of confounding by indication is partly supported in our data by a higher prevalence of coronary heart disease in the lowest (26%) compared to the highest quartile of NEFA (20%). Furthermore, the fact that we observed a decrease in crude incidence rate of SCD across consecutive also lend support to the above hypothesis. In an animal experiment, injection of saturated fatty acids[30] led to ventricular arrhythmia, suggesting that the composition of NEFA may be important. In our study, we were not able to examine the role of fatty acid type as we measured total NEFA.

As an observational study, we cannot exclude the possibility that unmeasured or residual confounding accounted for our results. NEFA concentrations were measured late in life in our study and we were not able to account for changes in plasma NEFA over time in our

analyses as we had only a single baseline measurement of NEFA. The limited number of SCD events in our study precluded the ability to detect small yet clinically relevant association between NEFA and SCD. Lastly, our sample consisted mostly of European-American individuals with an average age of 75 years at baseline, thereby limiting the generalizability of our results to other ethnic groups or younger adults. Nonetheless, our study has several strengths including a centralized and standardized approach to adjudicated SCD, a relatively large sample size of older adults from four geographic locations across the US, 13.5 years of follow-up, robustness of the findings in stratified analyses (sex, age, body mass, comorbidity, etc) and a large number of covariates to assess confounding.

In conclusion, our data do not support a major association between plasma NEFA measured late in life and the risk of sudden cardiac death in older adults. Further investigation in other cohorts and experimental models is needed to clarify the role of NEFA in the development of SCD.

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Table 1

Baseline characteristics of 4657 participants by category of non-esterified fatty acid concentration

	Non-esterified fatty acids (mEq/L)				
Range	**≤0.35**	**>0.35-0.47**	**>0.47-0.61**	**>0.61**	
Mean	**0.27**	**0.41**	**0.54**	**0.76**	
N	**1168**	**1166**	**1161**	**1162**	
Characteristics					**P_{trend}***
Age (Y)	74.11±4.85	74.70±5.26	75.25±5.38	75.38±5.55	<0.001
Body mass index (kg/m^2)	26.19±3.94	26.82±4.60	27.13±4.99	27.37±5.30	<0.001
Waist circumference (cm)	96.32±11.26	97.20±13.39	98.02±13.60	98.44±14.33	0.002
Male	713 (61.0%)	539 (46.2%)	401 (34.5%)	287 (24.7%)	<0.001
African-American	172 (14.7%)	196 (16.8%)	198 (17.1%)	201 (17.3%)	0.10
Physical activity (kcal/week)	1642±1924	1455±1763	1318±1601	1278±1669	<0.001
HDL-cholesterol (mg/dl)	49.44±12.81	52.12±13.75	54.26±14.37	56.99±15.47	<0.001
LDL-cholesterol (mg/dl)	126.75±32.40	128.26±32.80	128.69±34.86	126.06±35.74	0.28
Triglycerides (mg/dl)	131.58±72.93	142.12±79.88	148.67±95.13	155.73±90.96	<0.001
Prevalent diabetes	138 (12.0%)	149 (13.0%)	166 (14.6%)	247 (21.7%)	<0.001
Hypertension	568 (54.9%)	619 (59.8%)	679 (64.9%)	777 (74.2%)	<0.001
Hypertension medication	549 (47.0%)	564 (48.4%)	583 (50.3%)	667 (57.5%)	<0.001
Lipid-lowering medication	97 (8.3%)	96 (8.2%)	72 (6.2%)	87 (7.5%)	0.20
Statin use	62 (5.3%)	65 (5.6%)	39 (3.4%)	51 (4.4%)	0.07
Diabetes medication	91 (7.8%)	82 (7.0%)	96 (8.3%)	155 (13.4%)	<0.001
Prevalent CHD	309 (26.5%)	239 (20.5%)	235 (20.2%)	231 (19.9%)	<0.001
Prevalent CHF	75 (6.4%)	63 (5.4%)	64 (5.5%)	78 (6.7%)	0.75
Health status					
Excellent	105 (9.0%)	88 (7.5%)	56 (4.8%)	56 (4.8%)	
Very good	415 (35.5%)	382 (32.8%)	346 (29.8%)	298 (25.6%)	
Good	435 (37.2%)	477 (40.9%)	522 (45.0%)	508 (43.7%)	
Fair	191 (16.4%)	201 (17.2%)	211 (18.2%)	262 (22.5%)	
Poor	22 (1.9%)	18 (1.5%)	26 (2.2%)	38 (3.3%)	<0.001
Smoking status					

	Non-esterified fatty acids (mEq/L)				
Range	**≤0.35**	**>0.35-0.47**	**>0.47-0.61**	**>0.61**	
Mean	**0.27**	**0.41**	**0.54**	**0.76**	
N	**1168**	**1166**	**1161**	**1162**	
Characteristics					**p_{trend}***
Never smoker	444 (38.0%)	514 (44.1%)	546 (47.0%)	610 (52.5%)	
Former smoker	595 (50.9%)	520 (44.6%)	507 (43.7%)	454 (39.1%)	
Current smoker	129 (11.0%)	132 (11.3%)	108 (9.3%)	98 (8.4%)	<0.001
Alcohol consumption					
None	592 (50.7%)	634 (54.4%)	640 (55.1%)	684 (58.9%)	
<7 drinks/week	427 (36.6%)	391 (33.5%)	394 (33.9%)	316 (27.2%)	
7+ drinks/week	149 (12.8%)	141 (12.1%)	127 (10.9%)	162 (13.9%)	0.05

*Test for trends were conducted using linear regression for continuous variables and a nonparametric test for trend across ordered groups for categorical variables.

Table 2

Baseline characteristics of 4657 participants by sudden cardiac death status.

Characteristic	No SCD (n=4,436)	SCD (n=221)	p-value*
Age (Y)	74.8±5.3	75.8±5.5	0.005
Body mass index (kg/m^2)	26.9±4.8	27.2±4.3	0.37
Waist circumference (cm)	97.4±13.3	99.4±12.1	0.03
Male	1813 (40.9)	127 (57.5)	<0.001
African-American	724 (16.3)	43 (19.5)	0.22
Physical activity (kcal/week)	1423.6±1736.8	1425.1±1986.4	0.99
HDL-cholesterol (mg/dl)	53.4±14.4	49.9±48.1	<0.001
LDL-cholesterol (mg/dl)	127.3±33.9	129.5±35.9	0.36
Triglycerides (mg/dl)	144.2±85.2	149.7±93.6	0.36
Prevalent diabetes	642 (14.7)	58 (26.6)	<0.001
Hypertension	2504 (62.9)	139 (76.8)	<0.001
Hypertension medication	2219 (50.1)	144 (65.2)	<0.001
Lipid-lowering medication	334 (7.5)	18 (8.1)	0.74
Statin	207 (4.7)	10 (4.5)	0.92
Diabetes medication	390 (8.8)	34 (15.4)	0.001
Prevalent CHD	924 (20.8)	90 (40.7)	<0.001
Prevalent CHF	246 (5.6)	34 (15.4)	<0.001
Health status			
Excellent	292 (6.6)	13 (5.9)	
Very good	1392 (31.4)	49 (22.2)	
Good	1838 (41.4)	104 (47.1)	
Fair	817 (18.4)	48 (21.7)	
Poor	97 (2.2)	7 (3.2)	0.05
Smoking status			
Never smoker	2034 (45.9)	80 (36.2)	
Former smoker	1964 (44.3)	112 (50.7)	
Current smoker	438 (9.9)	29 (13.1)	0.01
Alcohol consumption			

Characteristic	No SCD (n=4,436)	SCD (n=221)	p-value*
None	2425 (54.7)	125 (56.6)	
<7 drinks/week	1456 (32.8)	72 (32.6)	
7+ drinks/week	555 (12.5)	24 (10.9)	0.60

* Differences in characteristics between SCD and non-SCD groups were tested using a t-test for normally distributed continuous variables; the Wilcoxon rank-sum test for continuous variables with skewed distributions; and the chi-square test for categorical variables.

Table 3
Hazard ratio of sudden cardiac death by serum concentration of non-esterified fatty acids

	Quartiles of non-esterified fatty acids (mEq/L)			
Range	**≤0.35**	**>0.35-0.47**	**>0.47-0.61**	**>0.61**
N	**1168**	**1166**	**1161**	**1162**
Cases of SCD	62	65	52	42
Person-years of follow-up	12033	11927	11395	11113
Hazard ratio (95% CI) [1]	1.00 (Ref.)	1.11 (0.78, 1.58) p=0.56	1.00 (0.69, 1.46) p=1.00	0.89 (0.59, 1.34) p=0.58
Hazard ratio (95% CI) [2]	1.00 (Ref.)	1.15 (0.81, 1.64) p=0.42	1.06 (0.72, 1.55) p=0.77	0.91 (0.60, 1.38) p=0.65

[1] adjusted for age, gender, race, and clinic site

[2] adjusted for age, gender, race, clinic site, smoking status (never, former, current), alcohol consumption (0, <7, ≥7 drinks/wk), prevalent CHD, prevalent CHF, self-reported health status (excellent, very good, good, fair, poor)