Elevated plasma free fatty acids predict sudden cardiac death: a 6.85-year follow-up of 3315 patients after coronary angiography

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Aims
Sudden cardiac death (SCD) is the most common fatal cardiovascular event. Free fatty acids (FFAs) exert several harmful effects on the myocardium and may therefore contribute to SCD. We examined whether fasting FFA predict SCD in patients who had undergone coronary angiography.

Methods and results
FFAs were measured at baseline (1997–2000) in 3315 patients scheduled for coronary angiography. Angiographic coronary artery disease was found in 2231 study participants. After a median time of follow-up of 6.85 years, 165 SCD occurred in the entire study population. In a Cox proportional hazards model, the unadjusted hazard ratio (HR) for SCD in the fourth when compared with the first FFA quartile was 2.95 (95% CI 1.84–4.73; \(P = 0.001\)). After adjustment for common and emerging cardiovascular risk factors, the HR remained significant at 1.76 (1.03–3.00; \(P = 0.038\)). High FFA levels were also significantly associated with all-cause and cardiovascular mortality, even after exclusion of patients with SCD.

Conclusion
Our study shows that elevated plasma FFAs are an independent risk factor for future SCD in patients referred to coronary angiography. These results may suggest that modulation of myocardial fatty acid uptake and/or metabolism are a possible target of treatment, but it still remains to be clarified whether high FFA levels are a cause or a consequence of pathological processes that underlie the association between FFA and SCD.

KEYWORDS
Free fatty acids; NEFA; Sudden cardiac death; Epidemiology; Mortality

Introduction
Sudden cardiac death (SCD) accounts for \(\sim 50\%\) of all fatal coronary heart disease events.\(^1\) Patients die unexpectedly and shortly after the onset of a change in clinical status that usually begins with an abrupt loss of consciousness.\(^1\) Ventricular tachyarrhythmias are most often recorded in subjects with SCD but the underlying pathological processes that lead to an electrically unstable myocardium remain to be further clarified.\(^1\) Hence, there is still a great need to identify risk factors for SCD so that preventive strategies may be applied to this significant public health problem. Epidemiological studies have shown that the incidence of SCD is highest in patients already afflicted with coronary artery disease (CAD) but every second SCD occurs in persons of relatively low cardiovascular risk.\(^1\) This suggests that apart from common cardiovascular risk factors, other aetiological factors may exist in the pathogenesis of SCD. There is growing evidence that free fatty acids (FFAs), also named non-esterified fatty acids (NEFAs), contribute to SCD.\(^2\)

Circulating FFAs are mainly released from triglyceride stores of the adipose tissue and serve as physiologically important energy substrates. An excess of FFA has been implicated in insulin resistance and hepatic steatosis.\(^3,4\) Furthermore, elevated FFAs are associated with atherosclerosis\(^5\) and hypertension.\(^6\) Fatty acid oxidation supplies the heart with \(\sim 70\%\) of its energy but an overwhelming delivery of plasma FFA to the heart, as it is observed in acute coronary syndromes (ACS) and heart failure, may contribute to myocardial dysfunction.\(^2,7,8\) High FFA and subsequent increased utilization of fatty acids for energy generation in the ischaemic myocardium may cause a ‘metabolic crisis’ in patients with CAD because fatty acid oxidation requires more oxygen when compared with the use of glucose.\(^2,7\) Apart from this, high concentrations of FFA have been shown to exert pro-arrhythmic actions.\(^2,9,10\) The population-based Paris Prospective study has already...
shown that elevated levels of FFA are predictive for SCD but not for overall cardiovascular mortality or fatal myocardial infarction, suggesting that FFAs are specifically related to SCD.\textsuperscript{11,12} We have previously demonstrated in the LUdwigshafen RIsk and Cardiovascular Health (LURIC) study that FFA predict all-cause and even more pronounced cardiovascular mortality in patients scheduled for coronary angiography.\textsuperscript{13} In the present work, we report about data from an extended follow-up examination of LURIC. We aimed to address the role of FFA as an independent risk factor for SCD.

Methods
Study population

The LURIC study is a prospective cohort study that is designed to investigate cardiovascular risk factors.\textsuperscript{14} Between July 1997 and January 2000, baseline measurements were performed in 3316 Caucasians who were scheduled for coronary angiography at the Herzzentrum Ludwigshafen in South-West Germany. Inclusion criteria were German ancestry and clinical stability with the exception of ACS. Patients with any acute illness other than ACS, any non-cardiac chronic disease, or a history of malignancy within the past 5 years were excluded. Written informed consent was obtained from all the participants and the Institutional Review Board at the Ärztekammer Rheinland-Pfalz approved the study.

Our study cohort comprises patients in whom coronary angiography was clinically indicated which was most commonly the case in patients with chest pain or results of non-invasive tests in which myocardial ischaemia was suspected. CAD was defined as the occurrence of one stenosis of 50% or more in at least one of 15 coronary segments by using the maximal luminal narrowing. In 3194 study probands, left ventricular (LV) function had been graded semiquantitatively by contrast ventriculography into normal, minimally, moderately, or severely impaired. LV ejection fraction, calculated from the right anterior oblique was available in 1360 of these patients and correlated highly significantly with the semiquantitatively assessed LV function (Spearman’s correlation coefficient = 0.84; P < 0.001) suggesting that the semiquantitative grading provides a reliable estimate of LV function.

Patients with a fasting plasma glucose level >1.25 g/L or with a 2 h value greater than 2.00 g/L in an oral glucose tolerance test were classified as having type 2 diabetes as well as patients who were already treated with oral antidiabetics or insulin. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as the product of the fasting insulin value (in $\mu$U/mL) and the fasting glucose value (in mmol/L) divided by 22.5.\textsuperscript{15} Hypertension was diagnosed if the systolic and/or diastolic blood pressure exceeded 140 and/or 90 mmHg or if there was a clinically significant history of hypertension.

Laboratory analysis

Baseline laboratory measurements in LURIC have been described previously.\textsuperscript{16} Blood collection was done after an overnight fast, in the morning before coronary angiography and samples were snap frozen and stored at \textendash 80°C until analysis. FFAs were measured enzymatically (ACS-ACOD method) with an NEFA C kit (Wako Chemicals GmbH, Neuss, Germany) on a Wako 30R analyzer. Inter- and intra-assay coefficients of variations for the FFA assay were 3.0 and 1.6%, respectively. N-terminal pro-B type natriuretic peptide (NT-pro-BNP) was measured by electrochemiluminescence on an Elesys 2010 (Roche Diagnostics, Mannheim, Germany). Noradrenaline was determined by HPLC (electrochemical detection) with a Chromsystem HPLC Noradrenaline kit (Chromsystems Instruments and Chemical GmbH, Martinsried, Germany).

Follow-up

Information on vital status was obtained from local person registries. Medical records of local hospitals, death certificates, and autopsy data were used for the classification of the causes of death. The deceased were classified into those who died from cardiovascular and non-cardiovascular causes. Death from cardiovascular causes was further subdivided into SCD, fatal myocardial infarction, death due to congestive heart failure, death immediately after intervention to treat CAD, fatal stroke, and other deaths due to cardiac causes. SCD was defined as sudden unexpected death either within 1 h of symptom onset or within 24 h of having been observed alive and symptom free.\textsuperscript{16} Patients who suffered from any non-cardiac chronic and terminal disease (e.g. cancer) so that their death was not unexpected and persons whose sudden death was most likely attributed to a non-cardiac cause were not coded as an SCD. Three experienced clinicians who were blinded to any data of the study patients independently classified the causes of death. In cases of a disagreement or uncertainty concerning the coding of a specific cause of death, classification was based on majority opinion.

Statistical analysis

We established quartiles of FFA from the values of all study participants. Distributions of continuous variables were examined for skewness and kurtosis and were logarithmically transformed, where appropriate. Baseline characteristics according to quartiles of FFA are presented as percentages for categorical data and as means ± standard deviations or as medians with inter-quartile range for continuous data depending on whether or not their distribution was Gaussian. Comparisons between groups were performed with $\chi^2$ test for categorical data and with analysis of variance (ANOVA) for continuous variables. Kruskal–Wallis test was applied for group comparisons of continuous variables that followed a skewed distribution even after being logarithmically transformed and that violated the ANOVA assumption of equality of error variances. Differences in survival without SCD between the quartiles of FFA were analysed using the Kaplan–Meier method followed by a log-rank test. To further examine the impact of FFA on mortality, we calculated hazard ratios (HRs) and 95% CI using the Cox proportional hazards model. HRs are presented for FFA quartiles using the first quartile as the reference and are also shown per increase of one FFA quartile with multivariate adjustments as indicated. Backward stepwise LR selection method was used and the results of the final step are shown. We tested for plausible interactions between the covariates by adding product terms to our models and we also tested for collinearity. The assumptions underlying the proportional-hazards model were further evaluated with log-minus-log survival and partial (Schoenfeld) residuals vs. survival time plots and found valid. All statistical tests were two-sided and a $P < 0.05$ was considered statistically significant. The SPSS 14.0 statistical package (SPSS Inc., Chicago, IL, USA) was used.

Results

Baseline FFA concentrations were measured in 3315 (99.97%) of our study patients. Angiographic CAD was found in 2231 of the study participants and was ruled out in 1035 participants, whereas the information about angiography was not available in 49 cases. Baseline characteristics of our study participants according to FFA quartiles are shown in Table 1. High levels of FFA levels were significantly associated with age, body mass index, HOMA-IR, triglycerides, systolic and diastolic blood pressure, homocysteine, C-reactive protein, creatinine, NT-pro-BNP, and noradrenaline concentrations. Type 2 diabetes, female gender, systemic hypertension, reduced LV function, and bundle branch block
Elevated plasma FFAs predict SCD

Table 1 Baseline characteristics of the study population stratified by free fatty acid quartiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>FFA quartile (&lt;0.44 mmol/L)</th>
<th>FFA quartile (0.44–0.62)</th>
<th>FFA quartile (0.63–0.89)</th>
<th>FFA quartile (&gt;0.89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFAs (mmol/L)</td>
<td>0.34 (0.27–0.40)</td>
<td>0.53 (0.49–0.58)</td>
<td>0.74 (0.68–0.81)</td>
<td>1.15 (1.01–1.48)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.2 (51.5–67.2)</td>
<td>63.3 (56.2–70.4)</td>
<td>65.0 (57.6–71.7)</td>
<td>66.0 (59.1–72.1)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>81.7</td>
<td>70.4</td>
<td>63.0</td>
<td>62.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 (24.5–28.8)</td>
<td>27.1 (24.8–29.6)</td>
<td>27.4 (24.8–30.0)</td>
<td>27.4 (24.8–30.7)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>16.6</td>
<td>24.2</td>
<td>33.6</td>
<td>43.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.86 (1.17–3.11)</td>
<td>1.98 (1.29–3.02)</td>
<td>2.28 (1.36–3.64)</td>
<td>2.69 (1.54–4.62)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Plasma lipids (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>2.93 (2.43–3.50)</td>
<td>2.93 (2.43–3.60)</td>
<td>3.00 (2.49–3.60)</td>
<td>2.98 (2.41–3.60)</td>
<td>0.469p</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.96 (0.80–1.14)</td>
<td>0.96 (0.80–1.17)</td>
<td>0.98 (0.80–1.17)</td>
<td>0.96 (0.83–1.19)</td>
<td>0.061b</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.62 (1.20–2.21)</td>
<td>1.58 (1.19–2.17)</td>
<td>1.65 (1.25–2.27)</td>
<td>1.84 (1.36–2.61)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>135 (120–151)</td>
<td>141 (123–157)</td>
<td>142 (125–160)</td>
<td>143 (125–160)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>79 (71–88)</td>
<td>81 (74–89)</td>
<td>81 (72–90)</td>
<td>80 (73–89)</td>
<td>0.001a</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63.2</td>
<td>72.6</td>
<td>77.4</td>
<td>78.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>69.0</td>
<td>67.7</td>
<td>69.2</td>
<td>68.3</td>
<td>0.802</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (%)</td>
<td>73.8</td>
<td>73.6</td>
<td>69.6</td>
<td>64.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimally impaired (%)</td>
<td>11.0</td>
<td>10.2</td>
<td>11.2</td>
<td>13.7</td>
<td>13.7</td>
</tr>
<tr>
<td>Moderately impaired (%)</td>
<td>10.0</td>
<td>10.8</td>
<td>13.6</td>
<td>14.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Severely impaired (%)</td>
<td>5.2</td>
<td>5.8</td>
<td>5.6</td>
<td>9.8</td>
<td>0.029</td>
</tr>
<tr>
<td>Left bundle branch block (%)</td>
<td>3.4</td>
<td>2.8</td>
<td>4.6</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, ex-smokers and active smokers (%)</td>
<td>72.6</td>
<td>62.9</td>
<td>61.1</td>
<td>58.9</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>12.2 (9.9–15.2)</td>
<td>11.7 (9.6–14.6)</td>
<td>12.4 (9.7–15.7)</td>
<td>13.0 (10.4–16.6)</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>2.5 (1.0–6.5)</td>
<td>3.3 (1.2–8.1)</td>
<td>3.8 (1.5–9.2)</td>
<td>4.5 (1.7–9.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>0.004a</td>
</tr>
<tr>
<td>NT-pro-BNP (ng/mL)</td>
<td>224 (89–574)</td>
<td>231 (98–696)</td>
<td>329 (109–961)</td>
<td>481 (163–1286)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Noradrenaline (ng/L)</td>
<td>281 (196–399)</td>
<td>289 (209–406)</td>
<td>324 (225–461)</td>
<td>344 (230–500)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>Beta-blocker medication (%)</td>
<td>65.8</td>
<td>64.1</td>
<td>63.0</td>
<td>60.1</td>
<td>0.109</td>
</tr>
<tr>
<td>Statin medication (%)</td>
<td>50.8</td>
<td>48.3</td>
<td>44.5</td>
<td>43.7</td>
<td>0.012</td>
</tr>
<tr>
<td>ACE-inhibitor medication (%)</td>
<td>48.4</td>
<td>51.7</td>
<td>53.2</td>
<td>60.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as median with inter-quartile range and percentages of study patients. Differences between tertiles of FFAs were analysed with ANOVA and Kruskal–Wallis test for continuous variables and with χ² test for categorical variables. FFAs, free fatty acids; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

*Kruskal-Wallis test.

†ANOVA of logarithmically transformed values with P-value for trend.

were associated with increased and smoking with decreased FFA concentrations.

During a median follow-up time of 6.85 years, 639 persons (19% of the study population) have died, including 416 (12.5%) cardiovascular deaths. SCD, as defined, occurred in 165 of these persons accounting for every fourth (25.8%) case of death. Information about causes of death were not available for 49 deceased persons, whose dates of death were classified as censoring dates. The Kaplan–Meier curves of SCD-free survival according to quartiles of FFA are depicted in Figure 1. The log-rank test showed that the risk for SCD significantly increases across the FFA quartiles (P < 0.001). The Unadjusted HR (and 95% CI) for SCD in the fourth when compared with the first FFA quartile was 2.95 (1.84–4.73; P < 0.001) (Table 2). This HR remained significant after adjustments for several cardiovascular risk factors and the use of medication. In detail, we adjusted for age, sex, body mass index, systolic and diastolic blood pressure, hypertension, HOMA-IR, type 2 diabetes, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, homocysteine, creatinine, smoking status (current and active smoker: yes/no), CAD, left bundle branch block, C-reactive protein, use of beta-blockers, ACE-inhibitors and statins, NT-pro-BNP, noradrenaline, and LV function. In patients with significant CAD, unadjusted and fully adjusted HRs (according to model 5 in Table 2) for SCD were 3.25 (1.84–5.67; P < 0.001) and 1.72 (0.92–3.22; P = 0.088), and the unadjusted and fully adjusted HRs for SCD per increase of one FFA quartile were 1.48 (2.29–4.19; P < 0.001) and 1.24 (1.02–1.50; P = 0.007), respectively. FFA were also significantly predictive for all-cause and overall cardiovascular mortality. Unadjusted and fully adjusted HRs for all-cause mortality in the fourth when compared with the first FFA quartile were 2.70 (2.14–3.39; P < 0.001) and 1.54 (1.19–2.00; P = 0.001). Unadjusted and fully adjusted HRs for cardiovascular mortality were 3.09 (2.29–4.19; P < 0.001) and 1.61 (1.14–2.26; P = 0.007). After exclusion of patients with SCD, unadjusted and fully adjusted HRs for cardiovascular death were 3.28 (2.22–4.85; P < 0.001) and 1.78 (1.14–2.78; P = 0.011). Unadjusted and fully adjusted HRs for all deaths other than SCD were 2.68 (2.06–3.49; P < 0.001) and 1.58 (1.17–2.13; P = 0.003). There was no significant collinearity or interaction in the Cox proportional hazards models.
Discussion

Our study shows that high concentrations of fasting blood FFA are an independent risk factor for SCD in patients scheduled for coronary angiography. Furthermore, after exclusion of patients with SCD, high FFA levels remained predictive for all-cause and cardiovascular mortality. These results highlight elevated FFA as a marker for the identification of subjects at high risk for SCD and other fatal cardiovascular events. However, it remains to be determined whether high FFAs are a causal factor in the pathogenesis of these diseases or whether they are elevated in response to other pathological processes that contribute to fatal cardiovascular events.

Several studies support the hypothesis that FFA increase cardiac sympathetic activity and are related to ventricular tachyarrhythmias that are the final common event in SCD. FFAs correlate with the frequency of ventricular premature complexes, a risk factor for SCD, and are associated with ventricular fibrillation in subjects with myocardial infarction. Pro-arrhythmic features of FFA that may explain their close association with SCD involve damaging of membranes, increases in reactive oxygen species (ROS), and disturbances of ion channels with subsequent instability of the membrane potential of the cardiomyocytes. A causal role of FFA in the pathogenesis of SCD is further supported by the fact that FFAs are associated with heart failure that is a significant risk factor for SCD. FFA concentrations are elevated in patients with heart failure because lipolysis is stimulated by high levels of catecholamines in these patients. Natriuretic peptides (e.g., NT-pro-BNP), which are closely related to heart failure, were also recently shown to exert lipolytic activities. Furthermore, it was demonstrated that high concentrations of FFA worsen ventricular function, partially mediated through an increase in mitochondrial uncoupling proteins that impair mitochondrial energy production. In addition, intralipid/heparin infusions that increase FFA concentrations are associated with raised catecholamine levels and enhanced adrenoreceptor reactivity, therefore suggesting a stimulatory effect of FFA on the sympathetic nervous system. Thus, the hypothesis has been raised of a vicious metabolic cycle, in which catecholamines and natriuretic peptides stimulate an increase in FFA that causes myocardial dysfunction and elevation of lipolytic substances. This relationship between high concentrations of FFA and heart failure may partially explain the increased risk for SCD in patients with reduced LV function. Trimetazidine, a drug that inhibits beta-oxidation of fatty acids, was shown to reduce ROS generation in the myocardium and improved LV function in patients with heart failure. It remains to be clarified whether the inhibition of fatty acid oxidation with drugs such as trimetazidine could also reduce the incidence of SCD. Considering the significant association between high FFA and SCD in our study, it may be speculated that the protective effect of beta-blockers on SCD may in part be mediated by their ability to reduce FFA levels.

Common cardiovascular risk factors that contribute to the development of CAD are associated with an increased risk for SCD. FFAs were also shown to contribute to insulin resistance and hypertension. This relationship between FFA and cardiovascular risk factors (Table 1) may in part explain the link between FFA and SCD but FFA remained a significant predictor for SCD even after adjustments for several cardiovascular risk factors including measures of insulin resistance (HOMA-IR), LV function, or emerging cardiovascular risk factors such as NT-pro-BNP.

Figure 1. The Kaplan–Meier curve for sudden cardiac death according to free fatty acid quartiles in the whole study population.
that was also associated with SCD in our study (data not shown).

Interestingly, the risk for SCD and the risk for non-SCD cardiovascular mortality associated with high FFA were very similar suggesting that FFAs are not specifically related to SCD. Hence, high FFA may also be associated with other fatal cardiovascular diseases such as heart failure or myocardial infarction, which were not separately analysed in this work because of insufficient numbers of precisely classified events. However, FFA may be directly involved in the development of atherosclerosis because it was reported that FFAs are associated with endothelial dysfunction and induce endothelial apoptosis and the expression of endothelial adhesion molecules. Further, pro-atherosclerotic features of FFA involve their contribution to macrophage to foam cell formation and their pro-inflammatory effects. Thus, FFA may not only serve as a risk factor for SCD, but also as a general cardiovascular risk factor.

We want to point out that our results do not prove causality for the association between high FFA concentrations and fatal cardiovascular events. FFA levels are associated with several cardiovascular risk factors but it remains largely unclear whether high FFA levels are mainly a cause or a consequence of these risk factors that are well known to be causally involved in the pathogenesis of cardiovascular diseases including SCD. The established knowledge about the increased lipolysis associated with heart failure, ACS, and other conditions associated with increased sympathetic nervous system activity as well as the impaired ability of insulin to suppress lipolysis in patients with insulin resistance may favour the hypothesis that high FFAs are merely a consequence of other metabolic and cardiovascular disease entities. Taking into account that FFA remained a significant predictor for SCD even after adjustments for these cardiovascular risk factors, it could be speculated that FFA reflect certain aspects of metabolic or cardiovascular pathologies that are crucial for the pathogenesis of SCD but are not adequately considered by the risk factors included in our analysis.

Our results may be limited because FFA levels have a relatively high day-to-day variability that is likely to be non-differential and might bias our results toward the null. Furthermore, fasting FFA may not adequately reflect circadian variations of FFA. FFA concentrations strongly depend on the nutritional state with commonly lower FFA levels in the post-prandial period due to insulin-mediated suppression of lipolysis. Considering that FFAs are raised in subjects with ACS and are associated with severe arrhythmias and increased mortality risk in these patients, it might be a promising diagnostic approach to identify those patients who show a strong increase in FFA in response to a catecholamine stimulus. In this context, it should be mentioned that the incidence of SCD is also significantly increased during physical activity and is related to social stress. Both conditions are associated with a hyperadrenergic state and subsequently increased FFA levels. A ‘FFA tolerance test’ with a lipolytic agent such as, for example, the adrenergic agonist isoproterenol might therefore identify subjects who are prone to an excessive raise of FFA in ACS, but also in daily stress situations or during physical activity. There is bound to be some apprehension in patients scheduled for coronary angiography and those who overreact at this time are likely to do so when an ACS develops. Blood collection in LURIC was done in the morning before coronary angiography and it is therefore conceivable that levels of FFA were particularly high in those patients with a hyperadrenergic response to the stress situation of a coronary angiography.

It should be noted that our results from a study population at intermediate to high risk for cardiovascular disease fit well with the results from the Paris Prospective study that showed an independent association between high FFA and SCD in men free of known ischaemic cardiac disease at baseline. Our results provide important additional information because we are the first to show the association between FFA and SCD in high-risk patients for SCD. In addition, we were able to show that this association remained statistically significant even after multivariable adjustments including several important risk factors for SCD (e.g. LV function) that were not all considered in the Paris Prospective study.

Nevertheless, our results are limited by relatively high CIs (Table 2) warranting confirmation of our findings in further
studies with more cases of SCD. Furthermore, we did not ban smoking before blood sampling, which may limit our results in view of data showing an acute increase of FFA after smoking. In summary, our study shows that elevated plasma FFA are an independent risk factor for SCD in patients referred to coronary angiography. These results point to the need for future investigations that further address the question whether the association between high FFA and future SCD is causal and might therefore provide an epidemiological background for therapeutic approaches aiming to modulate FFA metabolism in the prevention of SCD.

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Conflict of interest: none declared.

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Successful repair of a quadricuspid aortic valve illustrated by transoesophageal echocardiography, 64-slice multidetector computed tomography, and cardiac magnetic resonance

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Case illustration
A 54-year-old man presented with a 6-month history of dyspnoea on exertion. On physical examination, his blood pressure was 120/50 and a diastolic murmur of grade 2/6 was heard at the left parasternal border. Transthoracic echocardiography demonstrated severe aortic regurgitation. Transoesophageal echocardiography showed a quadricuspid aortic valve with four equally sized cusps, which presented a central coaptation defect resulting in a central aortic regurgitation (Panel A). This aspect was confirmed by 64-slice multidetector computed tomography (MDCT, Panel C) and cardiac magnetic resonance imaging (cMR) (Panels D and E). According to phase contrast cMR, pre-operative aortic regurgitant volume was 49 mL (Panel F). According to 64-MDCT, the coronary arteries were calcified but without significant stenosis (Panel B). This was confirmed by cardiac catheterization.

The patient underwent an aortic valve repair that consisted of suturing the two non-coronary cusps to turn the valve from quadricuspid to tricuspid. Six months after the surgery, the patient was asymptomatic. Follow-up cMR showed a functional ‘tricuspid’ aortic valve (Panel G) with minimal aortic regurgitation (Panel H), measured as 9 mL regurgitant volume on phase contrast imaging (Panel I).

Panel A. Pre-operative short-axis colour Doppler TEE shows quadricuspid aortic valve with central regurgitation.

Panel B. Pre-operative MDCT shows calcification of coronary arteries without significant stenosis.

Panel C. Pre-operative MDCT short-axis images through the aortic valve confirms quadricuspid aortic valve.

Panel D. Pre-operative short-axis cardiac MR confirming quadricuspid aortic valve.

Panel E. Pre-operative 3-chamber view cardiac MR shows severe central aortic regurgitation.

Panel F. Pre-operative phase contrast cardiac MR measurement demonstrates severe aortic regurgitation (49 mL).

Panel G. Six months post-operative short-axis cardiac MR shows repaired valve, which is now ‘tricuspid’.

Panel H. Six months post-operative 3-chamber view cardiac MR shows mild aortic regurgitation.

Panel I. Six months post-operative phase contrast cardiac MR measurement demonstrated mild aortic regurgitation (9 mL).