Role of Muscular Strength on the Risk of Sudden Cardiac Death in Men

To the Editor: The effect of cardiopulmonary fitness (CRF) on sudden cardiac death (SCD) has been summarized, with the conclusion that the risk of SCD decreases by 14% to 22% per 1-metabolic equivalent task increase in CRF. Recently, Mayo Clinic Proceedings has not only emphasized articles on CRF but also articles on resistance exercise and muscular strength (MusS). However, there is no study of the effect of MusS on SCD, even though MusS was inversely and independently associated with all-cause mortality in healthy men. Consequently, this report investigated the effect of MusS as a predictor of SCD, independent of several risk factors, and explored the combined influence of MusS and CRF on the risk of SCD.

This report is based on data from the Aerobics Center Longitudinal Study, a prospective observational investigation. For the present analysis, men 18 years or older with data on MusS and potential confounders (eg, medical history and lifestyle behaviors) as well as at least 1 year of mortality follow-up were included. Participants were predominantly white, well-educated, and belonged to the middle and upper socioeconomic strata. We could not include women because of the limited SCD cases (n=2).

Muscular strength was assessed in the upper and lower body by using a standardized bench and leg press strength testing protocol as previously reported. A composite strength score was computed by averaging together the body weight–adjusted then standardized values of bench and leg press. For SCD events, the National Death Index was the primary data source for mortality surveillance, augmented with death certificates. Cox proportional hazards regression was used to compute hazard ratios (HRs; 95% CIs) of SCD for tertiles of MusS (models 1-3 in the Table).

A total of 8116 men were included, and 23 cases of SCD occurred over a mean follow-up of 18.4±2.8 years. Compared with the lower third of MusS, there was a 69% reduced risk of SCD in the middle third of MusS after adjusting for model 3 (Table). Although statistically not substantial, we also observed an approximately 50% reduced risk of mortality in the upper third of MusS in all models. In additional analyses, we further adjusted for CRF in a subsample of men with complete and valid CRF data (n=7669; 21 SCD cases) and found that there was a 58% reduced risk of SCD in the middle third of MusS, although no longer statistically significant (HR, 0.42; 95% CI, 0.13-1.36). Moreover, a 1-SD increase in MusS was associated with a 43% reduced risk of SCD in model 1.

In the subsample with CRF data, men were dichotomized into weak (lower third of MusS) or strong (middle and upper thirds of MusS) and unfit (lower third of CRF) or fit (middle and upper thirds of CRF) groups for a joint analysis, as previously done. Compared with the weak and unfit group as a reference, the HR (95% CI) for the unfit and strong, fit and weak, and fit and strong groups was 0.39 (0.10-1.50), 0.61 (0.17-2.26), and 0.28 (0.08-0.94), respectively, after adjusting for the full set of confounders in model 3, indicating a potential additive benefit of being fit combined with being strong.

Muscular strength was associated with a reduced risk of SCD, independent of several risk factors, including aerobic physical activity. However, the results were attenuated and no longer significant when CRF was included in the model. It is not clear whether this is due to the confounding effects of CRF on the association or due to the reduced sample size and SCD cases. However, we noted that there was a 58% reduced risk of SCD in the middle third of MusS even after adjusting for CRF, although not significant. Moreover, the joint analysis indicated that being both fit and strong may provide the greatest benefit on preventing the risk of SCD significantly by 72% (0.28 [0.08-0.94]). To our knowledge, this is the first study to report the protective effect of MusS on SCD risk, independent of several risk factors, and the first to report the additional value of the combination of high MusS and CRF for the reduction in SCD risk.

These findings offer new insights into the prevention of SCD through increasing MusS in addition to the previously documented protective benefits of CRF. Moreover, this supports previous research indicating that both MusS and CRF predict all-cause mortality risk.

The apparent protective effect of MusS against the risk of SCD might be due to the direct effect of muscle strength, which is considered an index of muscle quality and function that is generally improved by resistance exercise. Resistance exercise is...
### TABLE. Sample Characteristics and Association of MusS With the Risk of SCD\(^a,b,c\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Tertiles of MusS</th>
<th>(\text{P Value})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Middle</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Sample characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>8116</td>
<td>2696</td>
<td>2723</td>
</tr>
<tr>
<td>Age (y)</td>
<td>42.0±9.7</td>
<td>42.5±9.6</td>
<td>42.1±9.7</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>26.1±3.7</td>
<td>27.3±4.4</td>
<td>25.8±3.2</td>
</tr>
<tr>
<td>Meeting aerobic physical activity guidelines(^d)</td>
<td>3056 (38)</td>
<td>840 (31)</td>
<td>992 (36)</td>
</tr>
<tr>
<td>Current smoking status(^e)</td>
<td>1315 (16)</td>
<td>493 (18)</td>
<td>464 (17)</td>
</tr>
<tr>
<td>Heavy alcohol drinking(^f)</td>
<td>1991 (25)</td>
<td>695 (26)</td>
<td>705 (26)</td>
</tr>
<tr>
<td>Parental history of CVD(^g)</td>
<td>2359 (29)</td>
<td>804 (30)</td>
<td>802 (29)</td>
</tr>
<tr>
<td>Abnormal electrocardiogram(^h)</td>
<td>459 (6)</td>
<td>170 (6)</td>
<td>153 (6)</td>
</tr>
<tr>
<td>Hypertension(^i)</td>
<td>2177 (27)</td>
<td>848 (31)</td>
<td>685 (26)</td>
</tr>
<tr>
<td>Diabetes(^j)</td>
<td>226 (3)</td>
<td>106 (4)</td>
<td>64 (2)</td>
</tr>
<tr>
<td>CRF data(MET)(^k)</td>
<td>12.4±2.5</td>
<td>11.3±2.3</td>
<td>12.4±2.4</td>
</tr>
<tr>
<td>Upper body strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kg</td>
<td>72.0 (17.7)</td>
<td>62.0 (12.7)</td>
<td>70.3 (12.9)</td>
</tr>
<tr>
<td>kg/kg of body weight</td>
<td>0.9 (0.2)</td>
<td>0.7 (0.1)</td>
<td>0.9 (0.1)</td>
</tr>
<tr>
<td>Lower body strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kg</td>
<td>138.1 (27.6)</td>
<td>126.2 (26.1)</td>
<td>136.8 (23.7)</td>
</tr>
<tr>
<td>kg/kg of body weight</td>
<td>1.7 (0.3)</td>
<td>1.4 (0.2)</td>
<td>1.7 (0.2)</td>
</tr>
<tr>
<td>Composite strength score</td>
<td>8.6x10(^{-6}) (0.91)</td>
<td>−0.81 (0.48)</td>
<td>−0.05 (0.44)</td>
</tr>
<tr>
<td>Association of MusS with the risk of SCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>2696</td>
<td>2723</td>
<td>2697</td>
</tr>
<tr>
<td>No. of SCD cases</td>
<td>13</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Hazard ratio (95% CI): model 1(^m)</td>
<td>1.00 (reference)</td>
<td>0.28 (0.09-0.87)</td>
<td>0.43 (0.16-1.14)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI): model 2(^n)</td>
<td>1.00 (reference)</td>
<td>0.31 (0.10-0.97)</td>
<td>0.48 (0.17-1.32)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI): model 3(^o)</td>
<td>1.00 (reference)</td>
<td>0.31 (0.10-0.96)</td>
<td>0.52 (0.19-1.44)</td>
</tr>
</tbody>
</table>

\(^a\) CRF = cardiorespiratory fitness; CVD = cardiovascular disease; MET = metabolic equivalent task; MusS = muscular strength; SCD = sudden cardiac death.

\(^b\) Data are presented as mean ± SD or as No. (percentage) unless indicated otherwise. Bold text indicates significant results.

\(^c\) Data were analyzed using the chi-square tests (categorical variables) or F tests (continuous variables).

\(^d\) ≥500 MET-minutes per week.

\(^e\) Current smoking: yes or no.

\(^f\) >14 drinks/wk.

\(^g\) Parental history of CVD: yes or no.

\(^h\) Abnormal electrocardiogram: yes or no from the resting or exercise electrocardiogram.

\(^i\) Hypertension: yes or no from self-report or measured blood pressure ≥140/90 mm Hg.

\(^j\) Diabetes: yes or no from self-report, taking insulin, or measured glucose level ≥126 mg/dL (to convert to mmol/L, multiply by 0.0259).

\(^k\) Only in the subsample with CRF data (n=7669).

\(^m\) Total muscular strength scores were standardized into z scores using the sample’s mean and SD of their standardized total strength (combined with body weight–adjusted leg and chest press) scores. The total muscular strength z scores had a mean of 0 and an SD of 1.

\(^n\) Adjusted for age.

\(^o\) Adjusted for model 1 plus body mass index, meeting aerobic physical activity guidelines (≥500 MET-minutes per week), current smoking, and heavy alcohol drinking (>14 drinks/wk).

\(^p\) Adjusted for model 2 plus parental history of cardiovascular disease, abnormal electrocardiogram, hypertension, and diabetes (all yes or no).
LETTERS TO THE EDITOR

associated with better functional capacity, metabolic and inflammation profiles,9 and recently with better survival.10 In fact, the results of intervention studies indicate that resistance training enhances MusS and endurance, muscle mass, functional capacity, risk profile for cardiovascular disease, and quality of life,9 which are well-known predictors of overall mortality.

This study is limited by the small sample size and SCD cases, which may partially contribute to no significant result in the upper third of MusS. However, the reduction in SCD risk for those with moderate MusS or the combination of both high MusS and CRF was even higher (69% or 72%, respectively) than that previously found for CRF alone (44%-48% risk reduction) in a larger sample of the Aerobics Center Longitudinal Study cohort (n=59,611).3 Further studies are needed to assess the combined effects of MusS and CRF on the prevention of SCD.

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Clinical Activity of Sunitinib and Regorafenib in Endometriosis

To The Editor: Endometriosis is a sex hormone-dependent gynecological disease characterized by the presence and growth of endometrial tissue outside the uterus that affects up to 10% of women of reproductive age.1 Endometriosis lesions harbor dense vascularization, and angiogenesis has been shown to play a critical role in its establishment and progression.2 Hence, targeting the vascular endothelial growth factor (VEGF) signaling pathway is considered a promising approach for the treatment of endometriosis.2

We herein report the case of a patient with concomitant endometriosis and metastatic gastrointestinal stromal tumor (GIST), in whom the anti-VEGF agents sunitinib and regorafenib led to a complete regression of a biopsy-proven endometriosis lesion.

A 37-year-old woman with a history of pelvic endometriosis (documented by laparoscopy, and treated by promegestone 0.5 mg a day) was diagnosed with an ileal GIST with synchronous liver metastases in November 2015.

The primary tumor was resected, and a biopsy was performed on one