Creatine Kinase and the Correlates of Blood Pressure in a Random Population Sample

To the Editor:

We hypothesized that creatine kinase (CK), the central regulatory enzyme of energy metabolism, amplifies blood pressure responses, and subsequently showed that CK activity is independently associated with blood pressure.\(^1\) CK catalyzes the reversible transfer of the high-energy phosphate moiety (P) between creatine and ADP:

\[
\text{MgADP + PCreatine + H}^+ \rightarrow \text{MgATP + Creatine}
\]

CK is tightly bound near Na\(^+/\)K\(^-\) and Ca\(^{2+}\)-ATPase, as well as near myosin light chain kinase and myosine ATPase, where it rapidly generates ATP in situ for sodium retention and cardiovascular contractile activity.\(^1\) Hence, high activity of the enzyme is thought to augment pressure responses rather directly.\(^1,3\)

High tissue CK activity has been reported in the obese, in blacks, and in men.\(^1,3,4\) We therefore assessed to which extent CK explained the effect of body mass index (BMI), ethnicity, and sex on systolic (SBP) and diastolic blood pressure (DBP),\(^5\) using partial correlation, which is commonly used in “causal” modeling of small models, with 3 to 5 variables.

We analyzed a stratified random sample of the population of Amsterdam, The Netherlands, consisting of 1444 citizens (503 self-defined White Europeans, 292 South Asians, 580 blacks, and 69 of other ethnicity), aged 34 to 60 years.\(^1\) The institutional review committee approved the study, and the participants gave written informed consent. Clinical examination included blood pressure measured in the sitting position with an Omron M4 oscillometric device (Omron Healthcare Europe B.V.), using an appropriately adjusted cuff size around the nondominant arm supported at heart level. Serum CK activity was estimated after 3 days of rest, with an automated analyzer (Roche/Hitachi Systems, Roche Diagnostics). In the absence of muscle damage, serum CK at rest may be used as a measure of proportionally released tissue CK as previously described.\(^1\)

We calculated we needed 765 subjects to assess the association between CK activity and blood pressure with a 2-tailed \(\alpha=0.05\) and \(1-\beta=0.80.\)\(^1\) We performed a logarithmic transformation to base 10 for the CK data to achieve a more symmetric distribution and computed the squared zero-order Spearman rank-order correlation coefficient for SBP and DBP versus log CK, age, BMI, black ethnicity, and sex. The difference with the squared first-order partial correlation while controlling for log CK was the primary outcome. In addition, we calculated the contribution of CK when controlling for all other variables. Finally, we assessed the contribution of CK as semipartial correlations in multivariable linear regression analysis. Statistical analyses were performed with SPSS statistical software for Windows, version 14.0 (SPSS Inc.). We considered a 1-tailed probability value of \(<0.05\) to be statistically significant.

As shown in the Table, the squared zero-order correlations were between 0.61 and 11.42%, with the highest correlations for age and the lowest for ethnicity in this predominantly normoten-sive population. Controlling for CK in first order correlations reduced the variance in SBP and DBP accounted for by BMI, ethnicity, and sex, with an absolute reduction of 0.27 to 3.29%, and a relative reduction of 32% to 100% (Table). When controlling for the aforementioned risk factors, adding CK to the model reduced the variance by 9% to 72% (Table). Finally, assessment of the added value of CK above the established risk factors in multivariable regression analysis resulted in relative changes (%) in the regression coefficients for SBP/DBP of \(+2/0\) for age, \(-6/6\) for BMI, \(-27/-21\) for ethnicity, and \(-21/-18\) for sex. The difference in mean SBP between black and non-black people was 3.3 mm Hg before and 0.8 mm Hg after adjusting for CK only. When adjusting for the established risk factors age, BMI, and sex, the difference in SBP was 5.8 mm Hg before and 4.3 mm Hg after adding CK to the model.\(^1\) The assumptions of correlation and regression analysis, including normality, linearity, and homoscedasticity were met.

Cellular metabolism and protein interactions are regaining scientific attention. In the cardiovascular system, cellular energetics, with a lack of ATP buffer capacity and a reduced flux through the CK reaction in heart failure, have raised considerable interest.\(^6\) We developed a hypothesis at the other end of the energy spectrum, that relatively high tissue CK activity and ATP buffer capacity enhance cardiovascular contractility and the ability to retain salt and thereby increase hypertension risk.\(^1\)–\(^3\) CK is the single cellular enzyme that has the capacity to regenerate ATP at a faster rate than oxidative phosphorylation and glycolysis together. The enzyme is localized near ATPas to execute pressor responses. It provides ATP to these enzymes as a final step in the intracellular signaling cascade.\(^1\) Studies in the spontaneously hypertensive rat showed that high cardiovascular CK activity precedes the development of hypertension,\(^2\) and we previously showed that CK is independently associated with blood pressure using regression analysis.\(^1\) Further data from our group and others indicated that contractility of resistance vessels depends on CK, with higher activities of the enzyme reported in the obese, blacks, and men.\(^1,3,4\) We therefore analyzed whether CK altered the association between obesity, black ethnicity, male gender, and blood pressure.

Our present analysis indicates that controlling for CK reduces the effect of these established risk factors on blood pressure. This statistical analysis cannot be considered proof of a causal role for CK in hypertension, but the analysis presented here fits our hypothesis that the high CK activity levels found in the obese, in blacks, and in men may enhance pressor responses and contribute to the higher blood pressure levels found in these population subgroups.\(^1,3,4\)

Disclosures

None.

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Table. Creatine Kinase and Partial Correlates of Blood Pressure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Zero-Order</th>
<th>Log CK</th>
<th>[AR (RR)]‡</th>
<th>Variables Except Log CK</th>
<th>Variables Adding Log CK</th>
<th>[AR (RR)]¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>11.42</td>
<td>11.83</td>
<td>+0.41 (+4%)</td>
<td>11.29</td>
<td>11.42</td>
<td>+0.13 (+1%)</td>
</tr>
<tr>
<td>BMI</td>
<td>8.18</td>
<td>5.57</td>
<td>−2.61 (−32%)</td>
<td>5.06</td>
<td>4.62</td>
<td>−0.44 (−9%)</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td>0.61</td>
<td>0.006</td>
<td>−0.61 (−100%)</td>
<td>2.19</td>
<td>1.08</td>
<td>−1.08 (−51%)</td>
</tr>
<tr>
<td>Sex†</td>
<td>3.72</td>
<td>1.21</td>
<td>−2.51 (−68%)</td>
<td>3.92</td>
<td>2.40</td>
<td>−1.52 (−39%)</td>
</tr>
<tr>
<td>Log CK</td>
<td>3.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>7.29</td>
<td>7.02</td>
<td>−0.27 (−4%)</td>
<td>6.81</td>
<td>6.92</td>
<td>+0.11 (+2%)</td>
</tr>
<tr>
<td>BMI</td>
<td>9.00</td>
<td>5.71</td>
<td>−3.29 (−37%)</td>
<td>5.24</td>
<td>4.68</td>
<td>−0.36 (−7%)</td>
</tr>
<tr>
<td>Ethnicity*</td>
<td>1.39</td>
<td>0.46</td>
<td>−0.93 (−67%)</td>
<td>3.27</td>
<td>1.96</td>
<td>−1.31 (−40%)</td>
</tr>
<tr>
<td>Sex†</td>
<td>3.35</td>
<td>1.35</td>
<td>−2.00 (−60%)</td>
<td>4.84</td>
<td>1.35</td>
<td>−3.49 (−72%)</td>
</tr>
<tr>
<td>Log CK</td>
<td>4.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S(D)BP indicates systolic (diastolic) blood pressure; BMI, body mass index; CK, creatine kinase.
*Black vs white and South Asian people.
†Men vs women.
‡One-tailed Spearman rank-order correlation \( P < 0.05 \), except the correlation between ethnicity and SBP when controlling for CK§, with \( P = 0.49 \). Percentages and \( P \) values are based on unrounded data.
¶AR, RR, absolute and relative reduction in zero order squared correlation coefficients after controlling for log CK only; ¶absolute and relative reduction in squared correlation coefficients after adding CK to the other risk factors in the model (age, BMI, black ethnicity, and sex).

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