Creatine kinase is associated with failure of hypertension treatment

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ABSTRACT

**Background** Failure of hypertension treatment is a major clinical issue because of the high prevalence and the associated mortality risk. We have reported evidence that creatine kinase (CK) increases blood pressure through greater sodium retention and cardiovascular contractility, by rapidly providing ATP for these functions. Therefore, we hypothesized that high CK is associated with failure of antihypertensive treatment.

**Method** We analyzed a cross-sectional, random multi-ethnic sample of the general population (N=1444), aged 34-60y. The primary outcome was the independent association between resting serum CK and treated uncontrolled hypertension in the population, using multinomial logistic regression analysis.

**Results** Hypertension prevalence was respectively 26.8; 30.8, and 41.2% for the lowest (<88 IU/L) through the highest population CK tertile (>145 IU/L); (p<0.001). Treatment failed in 72.9% of subjects within the highest CK tertile vs 46.7% with low CK (p=0.004). In logistic regression analysis, CK was the main predictor of treatment failure (adjusted OR 3.7; 95% CI 1.2 to 10.9), independent of age, sex, BMI, fasting glucose, ethnicity, or education level.

**Conclusion** CK is associated with failure of antihypertensive therapy. Further investigations concerning the causal relationship for CK in hypertension might help improve treatment strategies for difficult to treat hypertension.
**BACKGROUND**

A substantial proportion of treated hypertensive patients does not achieve blood pressure control.\(^1\)-\(^4\) In general, these subjects tend to be obese, older, or have diabetes and end organ damage. However, many patients have uncomplicated, primary hypertension, and it is not well explained why these subjects respond poorly to drug therapy, even when patients’ adherence and physicians’ therapeutic inertia are taken into account.\(^1\)-\(^4\)

The enzyme creatine kinase (CK) is thought to enhance pressor responses through rapid regeneration of ATP, as the enzyme catalyses the reversible transfer of the high-energy phosphate moiety (P) between creatine and ADP:

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

The rate of transfer of the phosphoryl group by CK is greater than the maximum rate of ATP generation by oxidative phosphorylation and glycolysis together, ensuring rapid resynthesis of ATP.\(^4\)-\(^11\) Cytosolic CK is tightly bound in the immediate proximity of ATP-utilizing enzymes such as Na\(^+\)/K\(^+\)-ATPase and Ca\(^{2+}\)-ATPase, and myosin light chain kinase and myosin ATPase at the contractile proteins. Here, ATP synthesized by CK is preferentially used to fuel highly energy-demanding processes such as sodium retention, cardiovascular contractility, as well as remodeling of arteries.\(^3\),\(^5\)-\(^13\)

Serum CK was found to be a main independent predictor of blood pressure in the general population, independent of age, sex, body mass index (BMI), or ethnicity, with a crude systolic blood pressure increase of 14 mm Hg per log CK increase, without evidence of muscle damage.\(^3\),\(^5\),\(^14\),\(^15\) Importantly, high tissue CK precedes hypertension,\(^11\),\(^16\),\(^17\) and antihypertensive therapy lowers high tissue CK in animal models,\(^16\),\(^17\) while incubation of human resistance arteries with a CK inhibitor reduces vascular contractility.\(^18\) Finally, tissue CK is high in population subgroups with high hypertension risk,\(^5\),\(^19\),\(^20\) including in skeletal muscle, cardiac muscle, and vascular muscle.\(^20\) Taking this evidence on enhanced pressor responses with high CK into account, we proposed that serum CK activity after rest is associated with failure of hypertension treatment in the general population.
METHOD

Study population
The study population has been previously analysed for the association between serum CK and blood pressure, but in that report, treated hypertensives were excluded from the analyses.5 This group of treated hypertensives is the focus of the current report. The institutional review committee approved the study and the participants gave written informed consent. Further methods have been previously described in detail.5 In brief, we included random population sample of 1444 subjects aged 34 to 60 years, and living in Amsterdam. Cardiovascular risk factors, the use of antihypertensive drugs, socioeconomic status, and self-defined ethnicity were assessed through a questionnaire.

We instructed participants to abstain from heavy exercise for 3 days before visiting our hospital for a physical examination. Walking, driving a car, and normal daily activities were allowed. Physical examination included height, weight, and blood pressure levels. Blood pressure was measured by a trained observer with an Omron M4 oscillometric device (Omron Healthcare Europe BV, Hoofddorp, the Netherlands) in a quiet room with the subject seated. An appropriately adjusted cuff size was used on the nondominant arm, which was supported at heart level.

To account for blood pressure variability, blood pressure was calculated as the mean of the first 2 consecutive readings, with a maximum of 5 mm Hg difference, as recommended by the Dutch Institute for Healthcare Improvement.21 This method results in lower blood pressure readings with smaller standard deviations.22 Laboratory studies included serum CK activity after 3 days of rest,5 estimated with automated analyzers (Roche/Hitachi Systems, Roche Diagnostics, Indianapolis, Ind) according to procedures recommended by the International Federation of Clinical Chemistry.23

Definitions
Subjects were classified as follows: treated controlled hypertension (taking antihypertensive drugs and blood pressure <140 mm Hg systolic and <90 mm Hg diastolic); treated uncontrolled hypertension (taking antihypertensive drugs and blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic); untreated high blood pressure (no antihypertensive drugs and blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic); and normal blood pressure (no antihypertensive drugs and blood pressure <140 mm Hg systolic and <90 mm Hg diastolic).
Primary outcome measure
The primary outcome was the independent association of resting serum CK with failure of hypertension treatment in the general population.

Statistical analyses
We used the sample size calculation method for multinomial logistic regression of Peduzzi et al.,24 and calculated that with 8 predictors planned (age, sex, BMI, ethnicity, CK, fasting glucose, cholesterol, and education level), and for the response variable, hypertension categories, 25%-30% hypertensives expected, of which half would be treated (12.5% of the population), and half adequately treated (6.5% of the population), the minimum number of cases required was 1333.

Since the distribution of serum CK was known to be skewed to the right,25 we planned to exclude outliers and establish the empirical 97.5 percentile point of CK, to discard values that were abnormally high.5,25 We also planned to exclude subjects without data on blood pressure levels or CK activity.

To assess whether treated uncontrolled hypertension was associated with serum CK, we first calculated the difference in mean CK between normotension, treated controlled hypertension, and treated uncontrolled hypertension. After testing the assumption of a normal distribution, we used one-way analyses of variance (ANOVA) statistics to establish differences in CK between these blood pressure categories, with a Tukey HSD post test. Furthermore, to assess a potential dose-effect relationship, we used the Kruskal-Wallis test to assess differences between low to high CK tertiles within these blood pressure categories.

We used multinomial, multivariable logistic regression analysis to assess whether an increase in serum CK levels increased the likelihood to be categorized as treated uncontrolled, independent of other known predictors of blood pressure or treatment status. In a parsimonious approach, we first analyzed known predictors of blood pressure treatment status in a univariable multinomial logistic regression model, before including those predictor variables that were significant at \( p<0.05 \) for at least one blood pressure category in multivariable multinomial logistic regression analysis, using the backward procedure when needed to formulate the best model. Blood pressure categories of normotension, treated controlled, treated uncontrolled, and untreated blood pressures were entered in the analysis as a four-group categorical outcome variable. Using these four categories, we defined normotension as the comparison category and determined separate relative risk ratios for predictor variables for each
category of the blood pressure status, except the comparison category. Relative risk ratios, the exponential beta coefficient, represented the change in the odds of being in the blood pressure category of treated-controlled, treated-uncontrolled, and untreated, versus the normotension associated with a one unit change on the predictor variable.

We ensured that the following assumptions were met for the multivariable multinomial logistic regression, adequate sample size related to the number of predictors, independent cases in the sample (no repeated observations in one individual, no paired or clustered individuals), no strongly correlated independent variables (multicollinearity), and linearity of predictor variables and log odds.\textsuperscript{26} To meet the assumption of linearity of independent variables and log odds, we reanalyzed the data, and categorized all the continuous independent variables to ordinal levels before including them in the model.

Finally, we addressed the question whether altering the inclusion criteria had a major effect on the results of the analyses. We reanalyzed the data, excluding participants using statins, because these drugs may cause an increase in CK activity; and excluding those with renal failure, because this condition has been associated with higher serum CK activities.\textsuperscript{5,27} Where applicable, we considered a two-sided $p$ value of <0.05 to be significant. Data within parentheses are standard errors, and within square brackets are 95% confidence intervals, unless otherwise specified. Statistical analyses were performed with SPSS statistical software package for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

Table 1 summarizes the characteristics of the participants stratified for blood pressure status. Blood pressure was normally distributed. Crude CK activity ranged from 14 to 5783 IU/L (median 111 IU/L), with a distribution highly skewed to the right ($z$ score for skewness 228.5), as previously reported.\textsuperscript{20} We excluded 3 outliers and 36 participants with CK activities above the 97.5 percentile.\textsuperscript{5,25} The data were still skewed to a significant degree ($z$-score for skewness: 22.3). Subsequent log transformation of the data to the base of 10 reduced the non-Gaussian distribution characteristics of positive skewness to a $z$-score of 1.5.
Creatine kinase is associated with failure of hypertension treatment

Table 1. Estimations of parameters within treatment groups.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Hypertension</th>
<th>Treated</th>
<th>Controlled</th>
<th>Uncontrolled</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>942</td>
<td>62</td>
<td>94</td>
<td>307</td>
</tr>
<tr>
<td>Male, %</td>
<td></td>
<td>36.9</td>
<td>25.8</td>
<td>40.4</td>
<td>53.1*</td>
</tr>
<tr>
<td>Black people, %</td>
<td></td>
<td>37.7</td>
<td>48.3</td>
<td>50.0*</td>
<td>48.1*</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>44.2 (0.2)</td>
<td>47.0 (0.9)*</td>
<td>49.0 (0.6)*</td>
<td>47.9 (0.4)*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td>116.1 (0.4)</td>
<td>124.6 (1.2)</td>
<td>154.7 (1.8)</td>
<td>148.8 (0.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td>76.0 (0.2)</td>
<td>81.4 (0.7)</td>
<td>97.9 (1.0)</td>
<td>95.0 (0.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>26.4 (0.2)</td>
<td>29.4 (0.8)*</td>
<td>30.1 (0.5)*</td>
<td>28.5 (0.3)*</td>
</tr>
<tr>
<td>CK, IU/L†</td>
<td></td>
<td>126.8 (2.5)</td>
<td>124.3 (10.9)</td>
<td>159.7 (9.4)*</td>
<td>144.7 (4.7)*</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td></td>
<td>5.6 (0.1)</td>
<td>6.8 (0.4)*</td>
<td>6.1 (0.2)*</td>
<td>5.8 (0.1)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td>5.4 (&lt;0.1)</td>
<td>5.4 (0.1)</td>
<td>5.3 (0.1)</td>
<td>5.4 (0.1)</td>
</tr>
<tr>
<td>University degree (%)</td>
<td></td>
<td>26.0</td>
<td>20.7</td>
<td>16.1*</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Data are mean (SE) unless indicated otherwise; *Significant predictor of hypertension category (as compared to normotension) in univariable multinomial logistic regression. †after exclusion of outliers.

Table 2. Multivariable predictors of hypertension categories.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hypertension Categories</th>
<th>Treated</th>
<th>Controlled</th>
<th>Treated Uncontrolled</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log CK</td>
<td></td>
<td>0.28 [0.08 to 1.00]</td>
<td>3.67 [1.23 to 10.91]*</td>
<td>1.36 [0.70 to 2.65]</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.06 [1.01 to 1.11]*</td>
<td>1.14 [1.10 to 1.19]*</td>
<td>1.11 [1.08 to 1.13]*</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>1.08 [1.01 to 1.13]*</td>
<td>1.15 [1.11 to 1.20]*</td>
<td>1.09 [1.06 to 1.12]*</td>
<td></td>
</tr>
<tr>
<td>Black ethnicity</td>
<td></td>
<td>2.26 [1.17 to 3.38]*</td>
<td>1.85 [1.04 to 3.30]*</td>
<td>2.21 [1.57 to 3.12]*</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td>1.18 [1.08 to 1.30]*</td>
<td>1.12 [1.01 to 1.24]*</td>
<td>1.04 [0.96 to 1.13]</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td>0.96 [0.49 to 1.89]</td>
<td>1.70 [0.99 to 2.93]</td>
<td>2.52 [1.81 to 3.50]*</td>
<td></td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td>1.51 [0.91 to 3.77]</td>
<td>1.62 [0.71 to 3.70]</td>
<td>1.31 [0.79 to 2.18]</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable, multinomial logistic regression analysis. Creatine kinase (CK) was the main and only specific predictor of treatment failure in the general population. Other predictors did not discriminate between treated controlled and treated uncontrolled hypertension. Data are the odds ratios (95% CI) of being classified in one hypertension category in the population, compared to the reference category normotension. Black ethnicity was compared to non-black ethnicity, and results on education level represent primary education vs tertiary education (university degree). *p<0.05. CK, creatine kinase. BMI, body mass index. Glucose, fasting serum glucose. Model goodness-of-fit: Pearson 3702.887, df 3873, p=0.96; Deviance 2109.062, df 3873, p=1.00; Nagelkerke’s pseudo R square 0.23; Model chi square (24) 272.59 (p<0.001)
Hypertension risk was the highest with high CK, respectively 26.8; 30.8; and 41.2% of the subjects within the first (CK<88 IU/L) through the third (CK>145 IU/L) population CK tertile were hypertensive ($p<0.001$ for differences between all groups). In addition, subjects with treated, but uncontrolled hypertension, had significantly higher CK, 157.9 IU/L (9.4), vs 124.3 (10.9) IU/L in controlled hypertension, and 126.8 (2.5) in normotensives. ($p<0.001$ for differences between groups; and in the post test, between treated uncontrolled vs controlled and vs normotension, Figure 1).

There was no significant difference in the treatment rates between low and high CK tertiles (respectively 34.1 and 30.1%; $p>0.05$). However, importantly, treatment failed in 72.9% of subjects within the highest CK tertile vs 46.7% within the lowest CK tertile ($p<0.004$ for differences between CK tertiles; Figure 2).

Using univariable multinomial logistic regression analysis, we assessed the association of age, BMI, sex, ethnicity, fasting glucose, CK, cholesterol, and education level with the blood pressure categories of normotension, treated controlled hypertension, treated uncontrolled hypertension, and untreated hypertension. Except for serum total

![Figure 1. Population mean CK levels in normotension and treated hypertension.](image)

Values depict mean creatine kinase (CK) activity (SE) in serum after rest in a random population sample, with significant differences between groups in ANOVA ($p<0.001$). Treated Controlled, and Treated Uncontrolled refer to hypertensive subjects. *In the post test, CK levels in Normotension and Controlled Hypertension did not significantly differ. †‡CK in Treated Uncontrolled Hypertension was significantly higher than Normotension and Treated Controlled Hypertension ($p<0.001$).
Creatine kinase is associated with failure of hypertension treatment.

cholesterol, these predictors showed a significant association (at $p<0.05$) with at least one hypertension category.

![Figure 2. Hypertension control rates within CK tertiles.](image)

Members of the population with high creatine kinase (CK) had the highest hypertension rates. Treatment failed in the majority of hypertensive subjects with high CK (>70%), while it was successful in the majority of hypertensive subjects with low CK. Hypertens, hypertensive subjects in the population (%); Contr. HT., Controlled hypertension, as a percentage of all hypertensive subjects; Contr.Tr., Controlled hypertension, as a percentage of treated hypertensives (Control defined as systolic <140 and diastolic <90 mm Hg). Low, Med. and High CK are the lowest (<88 IU/L) through the highest (>145 IU/L) serum CK tertile after 3 days of rest ($p<0.001$ differences between tertiles).

The univariable odds ratio for log CK in the categories treated controlled, treated uncontrolled, and untreated hypertension, was respectively 0.62 [0.21 to 1.80], 5.06 [2.12 to 12.10], and 2.85 [1.67 to 4.84]. We further quantified these results in multivariable multinomial logistic regression analysis. CK was the only specific, independent predictor of treatment failure (OR 3.67 [1.23 to 10.91]). Age, BMI, and black ethnicity were not useful to discriminate among hypertension treatment categories, neither were fasting glucose (which increased the odds of being treated), or male sex (which increased the odds of receiving no treatment; Table 2). The model had a good overall fit with an overall accuracy rate of 68.9%, and a -2 Log Likelihood of 2109.06 in the final model.
with a model chi-square of 272.6 (df 24; \( p < 0.001 \)), supporting a significant relationship between the predictor variables and blood pressure treatment status in this model.

Reanalyzing the data, categorizing all the continuous independent variables to ordinal levels before including them in the model to assess the assumption of linearity of independent variables and log odds, did not change the direction of the outcomes. We also reanalyzed the data excluding participants using statins, and those with renal failure, which did not change the outcomes (data not shown).

![Creatine kinase enhances vascular contractility](image)

**Figure 3. Creatine kinase enhances vascular contractility.**

This is a schematic representation of the main intracellular regulatory pathways of vascular smooth muscle contraction, based on Brewster et al.\(^3\,5\) Creatine and nitric oxide (NO) share a common precursor in L-arginine. Creatine kinase (CK) is colocalized with Ca\(^{2+}\)-ATPase and myosin ATPase, and evidence suggests the enzyme is also colocalized with myosin light chain (LC) kinase, to rapidly supply these enzymes with ATP using creatinephosphate (Creatine\(\sim\)P)\(^3\,5\,12\,15\,18\). NO, RhoA/Rho kinase, and calcium-dependent pathways are intracellular effectors of blood pressure-regulating systems that converge on metabolic processes fueled by CK.\(^3\,5\) Thus, high CK activity might lead to greater vascular contractility, partly through a lack of bioavailability of L-arginine for nitric oxide synthesis.\(^5\) cGMP, guanosine cyclic 3',5'- (hydrogen phosphate); MLCP, myosin light chain phosphatase. SER, sarcoendoplasmic reticulum.
**DISCUSSION**

Creatine kinase was the main and only specific variable associated with treatment failure in the general population, independent of age, sex, BMI, fasting glucose, or ethnicity. To our knowledge, this is the first report linking CK with treatment failure.

There are several possible explanations for this association between CK and treated uncontrolled hypertension. Creatine kinase activity in tissue and serum is known to be higher in men, in obese people, and in the black subpopulation, and has been associated with blood pressure.\(^5,14,15\) Since patients with higher mean blood pressure levels are often more difficult to treat, the results could merely reflect the association of serum CK with high blood pressure reported earlier.\(^3,5\) In the Dutch setting, according to national guidelines treatment of uncomplicated hypertension is only imperative at systolic pressure levels \(\geq 180\text{ mm Hg}\).\(^28\) This selection is probably related to the finding of higher mean blood pressures in participants from our population study with treated hypertension, than those with untreated hypertension (Table 1). However, since treatment failure was independently, strongly, and specifically associated with serum CK, with a clear dose-dependency, a causal relationship between CK and resistance to treatment cannot be excluded.

There is no evidence that hypertension directly increases serum CK. Clearance of serum CK is not altered with higher blood pressure levels,\(^29\) and there is no evidence that circulating CK is derived from the luminal surface of vascular endothelial cells, or that higher blood pressure levels causes cardiovascular muscle damage and increased serum CK activity.\(^5\) Importantly, normal CK isoenzymes are reported in subjects with relatively high serum CK activity and uncomplicated hypertension.\(^15,30\) A common cause of elevated serum CK activity levels is exercise,\(^31\) but participants were instructed to refrain from exercise for 3 days before the test. This period of 3 days used in this study should have substantially reduced the effect of exercise on serum CK, but CK activity can be elevated up to 3 weeks after eccentric muscular activity (where muscle contracts and lengthens at the same time).\(^31\) None of the participants stated to have been involved in such vigorous exercise, and if so, this would have led to an underestimation of the association between serum CK activity and treatment failure in this study.

In the absence of overt muscle damage, serum CK at rest is thought to be derived from tissue.\(^5\) Proportional to the level of tissue CK activity, normal tissue loses a small fraction of cytosolic CK into the interstitial space, which is transported through
lymphatic vessels into the blood stream. Hence, in resting subjects without muscle damage, serum CK is considered a measure of tissue CK levels. Existing evidence indicate that an association between the level of tissue CK and treatment failure is biologically plausible. CK functions to rapidly regenerate ATP at subcellular locations of high energy demands. The enzyme is reported to enhance vascular contractility (Figure 3), and there is evidence CK facilitates renal salt retention, through providing ATP to basolateral Na+/K+-ATPase as a final common and rate limiting step. High tissue CK activity, which may be constitutive, induced, or both, might thus attenuate responses to antihypertensive therapy through enhanced contractile responses and salt retention. Experimental evidence shows that the activity of the enzyme is already elevated in relatively young spontaneously hypertensive rat’s myocardium and aorta, before the development of hypertension in the early normotensive phase, and increases further after hypertension occurs. Increasing CK is also seen in cardiac tissue of animal models of acute pressure overload of the left ventricle. This high tissue CK activity might enhance ATP buffer capacity and contribute to the greater cardiovascular contractility.

Our data are also in consensus with experimental evidence of lowering of the high tissue CK levels upon blood pressure lowering in the spontaneously hypertensive rat, and reduction of human vascular contractility with inhibition of CK. On the other hand, in heart failure in humans and animals, decreased total cardiac CK activity, and a reduction in the flux through the CK reaction are typical findings. Thus, the aggregated data provide evidence that the level of tissue CK activity modulates the function and dysfunction of cardiovascular system, with elevated CK associated with hyperfunction and decreased CK with hypofunction of the cardiovascular system.

The main strength of this study is the finding that CK shows a dose-dependent association with treatment failure, in accord with existing data on CK enhancing pressor responses. However, the cross-sectional design precludes causal inferences, for which prospective studies are needed. Furthermore, in this study we focussed on the real world outcome of the likelihood of hypertension treatment failure in the general population, with high CK as the hitherto unknown factor that enhances pressor responses. Details of medication type, dose, participants’ compliance, or physicians’ therapeutic inertia, well known to affect blood pressure control, were not available. But these factors are unlikely to have explained the strong independent association of treatment failure with CK, a hidden factor increasing the propensity toward higher blood pressures. Also, we cannot exclude that subclinical cardiovascular damage contributed
to the results. However, we consider this option unlikely as both normotensive and hypertensive people with relatively high CK activities are shown by us and others to have normal isoenzyme patterns.\textsuperscript{15,30,37}

Studies on the pathophysiology of failing hypertension treatment are scarce.\textsuperscript{38} To our knowledge, this paper is the first showing that creatine kinase, the enzyme that regenerates ATP for pressor responses, significantly increases the likelihood of being classified as hypertension treatment failure in a real-world setting of a multi-ethnic population, independent of age, sex, BMI, fasting glucose, or ethnicity. CK was the main and only specific independent predictor of failure of antihypertensive treatment. Prospective analysis on this association between CK and treatment failure is needed for causal inferences, and to decide whether CK could serve as a new, clinically useful biomarker for difficult to treat hypertension.
Chapter 6

REFERENCES

Creatine kinase is associated with failure of hypertension treatment


