ORIGINAL COMMUNICATIONS

CREATINE KINASE: RACE-GENDER DIFFERENCES IN PATIENTS HOSPITALIZED FOR SUSPECTED MYOCARDIAL INFARCTION

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Race-gender differences in creatine kinase values were studied in 647 consecutive patients admitted for suspected myocardial infarction. The lowest value in a serial set for each patient was used for group comparisons. Significant differences were found between Hispanic females and black males, using standard values. Using log creatine kinase values, significant differences were found among blacks, Caucasians, and Hispanics. Males had higher log creatine kinase values than females, but no differences were found between sexes within racial groups. Body surface area differences (significant between males and females) did not explain all of the racial-gender differences found. Reexamination of ranges of normality, taking into account race-gender differences, is strongly supported by these data.

Key words • creatine kinase • laboratory normals • myocardial infarction • enzyme diagnosis

The diagnosis of myocardial infarction and muscle disorders often hinges on the laboratory values obtained for creatine kinase (CK). Normal values have been established for the general population without reference to age, sex, race, or body habitus. Meltzer and Holy[1] studied psychiatric inpatients and found significant differences in CK levels according to race and sex. Others, seeking to define values consistent with the carrier state of Duchenne muscular dystrophy, have noted that CK values are also influenced by nonpathological factors (vide infra).

Data from our medical center has revealed significant differences in total CK values between nonhospitalized, apparently healthy subjects based on sex and ethnic groupings.[2] This study was undertaken to document whether total CK levels in a population suspected of having acute myocardial injury would exhibit similar group variations. Marked variations in total CK values based on sex or ethnic factors would modify the interpretation of this test when used in estimating degrees of tissue damage and for diagnosing myocardial infarction (MI).

METHODS

The study population consisted of 647 consecutive patients admitted to the coronary care unit of the Los Angeles County/University of Southern California Medical Center. For each patient, information regarding age, race, sex, body surface area, MI diagnosis, and total CK levels was obtained and retained in a database. Serum CK levels were obtained serially according to a standard coronary care protocol for evaluating patients for possible MI, with a minimum of two values on consecutive days recorded for each patient. Total CK was determined using standard laboratory methods and instrumentation (Technichon Procedures).[2] The lowest CK value

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TABLE 1. CHARACTERISTICS OF STUDY POPULATION

Variable	N	%
Sex		
Male	400	61.7
Female	248	38.3
Racial Origin		
Black	234	36.1
Caucasian	201	31.0
Hispanic	163	25.2
Oriental	11	1.7
Other	39	6.0
Acute Myocardial Infarction	246	38.0
Age (years)	Mean 57.9	Range 19-92
Body Surface Area	Mean 1.80 m^2	Range 1.22-2.81 m^2

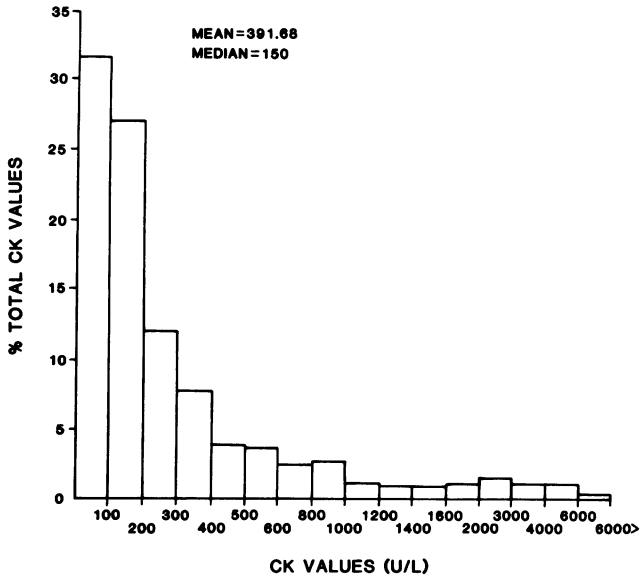

Figure 1. Raw total creatine kinase data are displayed. The distribution of values is skewed to the left, similar to values obtained from normal outpatients in an earlier study.

obtained during each patient's stay was used for evaluating differences between groups. The diagnosis of acute MI was based on criteria previously established.[3]

Of the 647 patients, 246 were shown to have acute MI; for the purpose of this investigation, the data from all 647 patients were included because no significant differences were noted in the MI versus non-MI groups in regard to lowest CK values. The study population was divided into groups according to sex and the following ethnic classifications: black, Caucasian, Hispanic, Oriental, and others. As the latter two groups consisted of only 11 and 39 patients, respectively, the small number as well as the heterogeneity was thought to preclude meaningful interpretation of the group data obtained; the information from these two groups was, therefore, used only for the male-female statistical comparison.

Data were collected using protocols approved by the Human Subjects Committee with appropriate informed consent, according to the principles of the Declaration of Helsinki. Data analysis was carried out using the student's *t* test for group comparisons.

RESULTS

The largest ethnic group was black (234 patients), followed by Caucasian (201), Hispanic (163), others (39), and Oriental (11) (Table 1).

The 647 patients had a mean age of 59 years, with a range of 19 to 92 years. The only significant mean age difference between race-sex groups occurred in black males versus black females (56 vs 60 years, $P < .04$) and black males versus Hispanic females (56 vs 61 years, $P < .02$).

Males constituted 62% of the total population and females 38%. Body surface area ranged from 1.22 to 2.81 m^2, with a mean of 1.80 m^2 and a median of 1.79 m^2. In all comparisons of race-sex groups, males had significantly larger body surface area than females ($P < .001$). There was no significant difference in body surface area between Caucasian males and black males.

Two hundred forty-six patients (38%) had documented acute myocardial infarction; the remaining 402 patients (62%) did not. The incidence of acute MI did not vary significantly between race-sex groups. Interestingly, the group with the smallest percentage of acute MI (Caucasian males, 33%) had the highest mean CK value. The overall sample population had CK values that were nongaussian in distribution (Figure 1) The range of values obtained were 7.5 to 15 800 U/L, with a mean of 392 U/L and a median of 150 U/L. Seventy-nine percent of the patients had CK values below the mean. However, when log CK transformations were used, the distribution of values appeared to be more gaussian (Figure 2). Blacks had mean CK (396 U/L) and median CK (216 U/L) values above those of the overall population. Caucasians had the highest mean CK values at 425 U/L, with a median

of 140 U/L. Hispanics had the lowest values, with a mean of 299 U/L and a median of 130.

Because of the wide range of CK values obtained, there was a statistically significant difference observed only between Hispanic females and black males. This was not the case when log CK was examined between race-sex groups.

In the whole population, males had a mean CK of 427 U/L and females 331 U/L ($P < .01$). The mean log CK for males was 2.30 ± 0.48 and for females 2.19 ± 0.48, a difference that was significant at $P < .006$.

Caucasian males constituted 23% of the total population and 73% of the Caucasian group. Their CK values ranged from 10 to 15 800 U/L, with a mean of 442 ± 1454. The log CK for this group ranged from 1.0 to 4.2, with a mean of 2.23 ± 0.49. The Caucasian females made up 27% of the Caucasian group and 8.5% of the population. The CK values for Caucasian females ranged from 7.5 to 5300 U/L, with a mean of 381 ± 779. Log CK values ranged from 0.88 to 3.72, with a mean of 2.22 ± 0.52. There were no significant differences in mean CK or mean log CK values between Caucasian males and Caucasian females (Table 2).

Black males numbered 134, 21% of the total population and 57% of the black group. Black males had a CK range of 18 to 4400 U/L, with a mean of 430 ± 612. The log CK ranged from 1.26 to 3.64 with a mean of 2.41 ± 0.42. Black females constituted 15% of the total population and 43% of the black population. Their CK values ranged from 15 to 5950 U/L, with a mean of 320 ± 829, and log CK values from 1.18 to 3.77, with a mean of 2.21 ± 0.44. There was no significant difference between mean CK values of black males and black females, but mean log CK was significantly higher in black males ($P < .001$) (Table 2).

There was also a significant difference between the mean log CK values of Caucasians and blacks, with the blacks having higher values ($P < .03$). This difference can be accounted for by lower mean log CK values between Caucasian males ($P < .001$) and Caucasian females ($P < .002$) compared with black males. There were no significant differences between black females and Caucasian males or Caucasian females.

Hispanic males numbered 80 patients, 12% of the total population and 49% of the Hispanic group. Their mean CK values were 360 ± 623 U/L, with mean log CK values of 2.24 ± 0.49. The CK values ranged from 7.5 to 3925 U/L and the log CK values ranged from 0.88 to 3.50. Hispanic females had CK values from 7.5 to 1548, with a mean of 239 ± 331 and log CK values from 0.88 to 3.19, with a mean of 2.13 ± 0.46. No significant differences between Hispanic males and Hispanic females were found (Table 2).

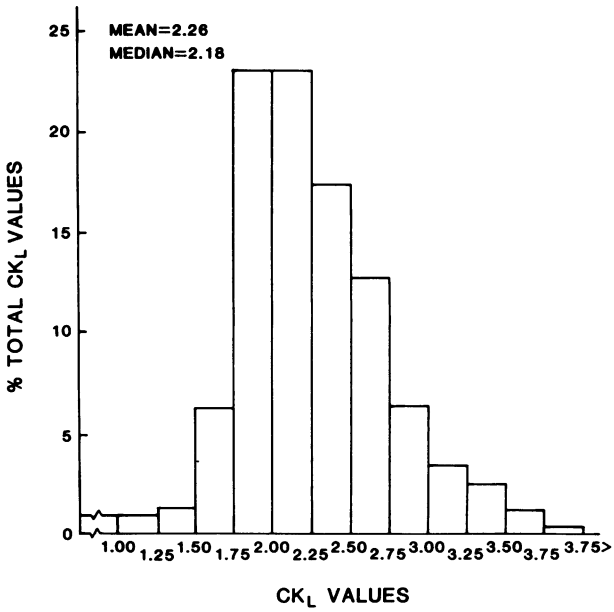

Figure 2. The log of the total creatine kinase values (CK_L) is displayed in this graph, which shows a more gaussian distribution.

When blacks and Hispanics were compared, the former had higher (although not significantly) mean CK values. On the other hand, log CK of blacks was statistically greater than that of Hispanics ($P = .002$. Again the black males showed higher mean log CK values than the Hispanic males ($P = .009$) and Hispanic females ($P < .001$). Interestingly, the Hispanic females provided the only mean CK value differences of statistical significance when compared with the higher value of the black males ($P = .003$). The values for black females were not significantly different from the Hispanic values for either sex (Table 2).

DISCUSSION

The measurement of serum CK and CK-MB (creatine kinase isoenzyme) has become one of the cornerstones in the diagnosis and, to some degree, prognosis of myocardial injury and infarction.[4-11] Pathological conditions other than myocardial injury are known to increase levels of serum CK. The most common of these include Duchenne muscular dystrophy and its carrier state, myopathies, hypothyroidism, acute psychoses, rhabdomyolysis,

TABLE 2. RACE-GENDER SUBGROUP COMPARISONS

Subgroup	N	Range CK	Mean CK (SD)	*P* Value*	Log CK (SD)	*P* Value†
Black Male	134	18-4400	430 (612)	—	2.41 (0.42)	—
Black Female	100	15-5950	350 (829)	NS	2.21 (0.44)	.001
Caucasian Male	146	10-15800	441 (1454)	NS	2.23 (0.49)	.001
Caucasian Female	55	7.5-5300	381 (779)	NS	2.22 (0.52)	.02
Hispanic Male	80	7.5-3925	361 (623)	NS	2.24 (0.49)	.009
Hispanic Female	83	7.5-1548	239 (331)	.003	2.13 (0.46)	<.001

* Column 5 indicates that a significant difference exists only between black males and MA-F for mean CK.
† Column 7 shows that a significant difference was found between black males and all other race-gender groups.

muscle biopsies and injections, pulmonary embolus, and recovery from malnutrition.[4,6,12-25] Increases in muscle cell membrane permeability, as well as primary injury itself, are thought to be contributing factors to the elevation of CK in these circumstances.

In addition, several authors have noted nonpathological factors that affect CK levels when screening for the carrier state of Duchenne muscular dystrophy. These have included age, sex, exercise, time of day, and estrogen status of the female.[6,16,24,25] Siegel et al recently demonstrated, in trained marathon runners, that racing acutely elevated serum CK, often to levels consistent with massive acute MI; their subjects had no signs, symptoms, ECG or myocardial scan evidence of acute MI. Skeletal muscle was the apparent source of the CK-MB release.

Meltzer and Holy,[1] in observing stable hospitalized psychiatric patients, noted significant differences in mean CK levels between black males and black females and between Caucasian males and Caucasian females. They also noted higher CK levels for Caucasian males and black females compared with Caucasian females. A trend toward higher CK levels based on an index of skin color (higher levels with darker skin) in black males was noted. They found no relation to age, height, or weight in CK differences between race-sex subgroups. The authors suspected differences in CK enzyme activity or metabolism or the presence of unique enzymes or enzyme inhibitors between blacks and Caucasians as an explanation of group differences in serum levels.

In our study, serum CK levels for race-sex groups in a hospital coronary care were investigated. For this population, the serum CK ranges were quite large, resulting in poor statistical separation of group means. The distributions of mean CK for each race-sex group paralleled that of the population as a whole, ie., a nongaussian distribution. This was a result of the majority of the values being skewed toward the normal range. On the other hand, log CK transformations appeared to have a more gaussian distribution, and most significant enzyme differences noted between groups were based on log CK values.

Similar distributions of data were observed in our previous study, and our decision to analyze the full data set seems reasonable on this basis. Moreover, our previous data confirmed that black males were responsible for most of the higher values, that most other patients had moderate values, and that nonblack females accounted for a subgroup with low CK values.[2]

Only the lowest CK value obtained was used to compute differences between groups, on the assumption that this value would be the closest to the sedentary norm for each individual. Moreover, our purpose was to determine whether lowest values would reflect the group differences previously discovered in our ambulatory, nonpatient population and, thus, whether group differences in CK would be important to consider in the course of the clinical assessment of such patients.

In all racial groups, the largest percent of CK values were approximately 200 U/L or less: black median 215, Caucasian 140, Hispanic 130. Each group also had a large disparity between the mean and the median, with approximately 80% of patients below the mean: black 78.2%, Caucasian 80.6%, Hispanic 79.1%. Each group also had approximately equivalent numbers of values at the high extremes (> 600 U/L): blacks 11.9%, Caucasian 11.9%, Hispanic 11.7%. The incidence of acute MI between racial groups was not significantly different. It, therefore, appears that the various factors associated with elevated CK had similar occurrence rates among the race-sex groups.

Several investigators have noted that CK values of males are significantly higher than CK values of females and have attributed this finding to the greater

muscle mass in the male.[27-30] Garcia[31] reported that 11 muscular males had elevated CK in the absence of any pathology and postulated that the enzyme elevations were secondary to their unusually large muscle mass. In our study, all male subgroups had significantly larger body surface area than any female subgroup, and males as a whole had a larger log CK value than females. However, excluding the black male subgroup, no other male subgroup had significantly larger CK or log CK values than any female subgroup. Black males had larger body surface area than Hispanic males but not Caucasian males, although both of the latter groups had significantly smaller log CK values than black males. Therefore, body surface area does not appear to be the sole determinant of differences in log CK values between males and females. The possible exception would be the black male subgroup, who had larger body surface area and higher log CK values compared with all subgroups, except Caucasian males. The black male subgroup appears to provide the greatest contribution to male-female log CK differences.

The rate of CK and CK-MB appearance in serum can vary with continued release of enzymes up to 72 to 96 hours following acute MI.[4,7,32] Sobel[33,34] has shown that the disappearance rates (K_d) of injected and endogenous CK fits a two-compartment (intravascular and extravascular) model, with the K_d of endogenous CK less than the K_d of injected CK. These differences affect enzyme-based estimates of infarct size because of the probable contribution of continued and possibly irregular CK release from injured myocardium. Errors from sampling and different methods of CK analysis add to the complexity of defining CK metabolism and time-activity curves. Complete understanding also requires full knowledge of contributing physiologic processes, such as enzyme transport and inactivation, diffusion rates from necrotic myocardium, and variance in regional perfusion.[33] Other contributing factors may include the volume of enzyme distribution, the quantity of myocardial injury, and enzyme activity at the site of infarction.[4,35,36] These various factors may be influenced by race-sex differences, which could contribute to variations in time-activity curves and ultimately CK and log CK values.[37,38]

Strong support for our findings comes from the report of Black, Quallich, and Gareleck,[39] who report similar results in nonhospitalized subjects. Our delineation of similar group differences in hospitalized patients underscores the importance and reliability of both sets of data.[40] The clinical utility of enzyme measurements will likely be enhanced if the subgroup differences noted here are taken into account. It may well be that for the individual patient, the "normal range" will ultimately be defined using frequency distribution curves or regression equations that take into account demographic variables. Prudence would dictate that laboratory normal values be reevaluated to reflect differences in race-sex groups, which may refine the ability to use these tests in the diagnosis and assessment of significant illnesses.

Acknowledgments

Research supported, in part, by grants HM 00651 and HL 15162 from the National Heart, Lung, and Blood Institute; grant MB 00146 from the Human Resources Agency; and contracts PH 108-66-160 from the United States Public Health Services, Heart Disease Control Program and HV 72970 from the National Heart, Lung, and Blood Institute.

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