Hiroshima J. Med. Sci.
Vol.42, No.2, 73~81, June, 1993
HIJM 42-9

Distribution of Serum Lipoprotein(a) Levels — A Non-Parametric Analysis —

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ABSTRACT

The distribution of serum lipoprotein(a) [Lp(a)] concentration among Japanese male adults was evaluated using non-parametric methods. The following results were obtained.

1) Among healthy male adults undergoing a medical checkup, Lp(a) showed a highly skewed distribution towards the low level. The distribution could be regarded as a power normal distribution with the power order of 1/2. The median of Lp(a) level was 14.1 mg/dl (the 25th percentile was 6.2 mg/dl and the 75th percentile was 26.7 mg/dl).
2) The values of serum Lp(a) in subjects with vasospastic angina distributed at a higher level than for subjects with normal coronary arteries as diagnosed by coronary angiography.
3) The observed serum Lp(a) concentration moved to a higher range as the number of branches with significant stenosis on the coronary angiography increased.
4) Serum Lp(a) was one of the risk factors for ischemic heart disease. Its odds ratio when the cut-off value was set at 26.7 mg/dl or 30 mg/dl was 2.52 and 2.94, respectively.

Information on the distribution of serum Lp(a) concentration is useful for estimating the coronary atherogenic factor.

Key words: *Lipoprotein(a), Non-parametric analysis, Coronary atherosclerosis, Odds ratio*

Recently, various laboratory tests have made striking advances and have proved extremely valuable for diagnosis and treatment in numerous fields of clinical medicine. However, since laboratory tests provide numerical data and are therefore often mistakenly considered to be absolute indicators, their "normal ranges" and "standard ranges" are generally established empirically from the mean and standard deviation (SD) of a putatively normal population rather than derived on a theoretical or physiological basis.

For example, the normal serum total cholesterol level was set at less than 240-250 mg/dl in the past, but has recently been revised to less than 180-200 mg/dl because the roles of low density lipoprotein (LDL) and high density lipoprotein (HDL) have been clarified on the basis of long-term epidemiological research[17,18]. In the case of diseases such as arteriosclerosis which only develop after the persistence of pathological hypercholesteremia for a long period, the effects of various other factors make the establishment of normal values more difficult, although there is no doubting a positive relationship between a high total cholesterol level and arteriosclerosis.

Indicators such as mean and SD are frequently used for the establishment of normal ranges and they are sometimes used even when the normal distribution cannot be assumed. However, with recent advances in computers, the non-parametric definition of distributions using quantile indicators has become possible.

Lipoprotein(a) [Lp(a)] was first reported by Berg et al[1] in 1963 and was presumed to be a genetic variant of a specific part of the LDL fraction. It contains specific apolipoprotein which is called apolipoprotein(a)[14]. Since the study of Dahlén et al[4] in 1972, various reports on the relationship between Lp(a) and arteriosclerosis have been published, and this lipoprotein has recently come to be considered one of the risk factors for atherosclerotic disease[12,13]. The distribution of serum Lp(a) concentrations varies among the different races, with Caucasians showing a distribution biased towards low levels[12] while Negroes show a bell-shaped distribution that approximates to a normal distribution[7]. However, there have been no detailed investigations of the distribution of serum Lp(a) concentrations in the Japanese including ischemic heart disease cases. In this study, the distribution of serum Lp(a) concentrations was evaluated using quantile indicators in healthy individuals and patients undergoing coronary angiography among Japanese male adults living in and around Hiroshima city. The data was investigated using box-and-whisker plots (boxplots)[19] and

quantile-quantile plots (Q-Q plots)[2,10]. Moreover, a cut-off value of the serum Lp(a) concentration was set and its significance was assessed using odds ratios.

MATERIALS AND METHODS

Subjects

To determine the normal range of Lp(a), 271 healthy individuals(healthy group) were selected from those undergoing medical checkup between October 1990 and February 1991. In the selection, individuals were excluded if they had ischemic heart disease, hepatic disease, renal disease, diabetes, severe hyperlipidemia, or other diseases with inflammation, as determined by interview, physical examination, biochemistry tests, and ECG. Individuals on drug therapy were also excluded. In addition, 241 patients undergoing coronary angiography for suspected ischemic heart disease from March 1990 to December 1991 were selected, excluding those with acute myocardial infarction less than one month earlier, those with hepatic or renal disease, and those taking antihyperlipidemic drugs. All the subjects were Japanese male adults living in and around Hiroshima city. The subjects undergoing coronary angiography included 94 not having more than 75% stenosis of a major coronary artery (non-stenosis group) and 147 with significant stenosis of at least one branch (stenosis group). Of the non-stenosis group, 59 with neither coronary vasospasm nor significant stenosis were designated as the non-stenosis without vasospasm group and 35 were diagnosed as having vasospastic angina (non-stenosis with vasospasm group). The stenosis group consisted of 87 patients with old myocardial infarction and 60 with effort angina. Eighty-one patients had significant stenosis in only one branch (single-vessel disease), 43 in two branches (double-vessel disease), and 23 in three branches (triple-vessel disease).

Methods for measurements

Blood was drawn after fasting for 12 hours. Patients undergoing coronary angiography received blood sampling on the morning of the day when angiography was performed. Total cholesterol (TCHO) and triglycerides (TG) were determined by enzymatic methods, HDL cholesterol (HDL-C) by the dextran sulfate method, and apolipoprotein A-I(Apo A-I) and apolipoprotein B (Apo B) by turbidimetric immunoassay (Apo A-I Auto and Apo B Auto, Daiichi Kagaku, Tokyo). Serum Lp(a) concentrations were determined using samples stored frozen at -80°C until assayed, and an enzyme-linked immunosorbent assay (Tint Elize™, Biopool, Sweden) was employed. The obesity index (OI) was calculated according to the following equation:

$$OI\ (\%) = 100 \times \text{body weight (kg)} / \{(\text{height (cm)} - 100) \times 0.9\}.$$

The LDL-cholesterol (LDL-C) level was determined using the following equation[5]:

$$\text{LDL-C (mg/dl)} = \text{TCHO (mg/dl)} - \text{HDL-C (mg/dl)} - 0.2 \times \text{TG (mg/dl)} - 0.3 \times \text{Lp(a) (mg/dl)}.$$

Data analysis

The distributions of the serum Lp (a) and LDL-C concentrations was evaluated using a Q-Q plot instead of a histogram. A Q-Q plot is used to determine visually whether or not the data follow some theoretical distribution. In brief, quantiles of actual data or their converted values were plotted on the Y axis whereas calculated quantiles based on normal distribution, a special case of empirical distribution function, were plotted on the X axis. Whether or not the distribution of the actual data or the converted values followed a normal distribution was then evaluated by determining the distance of the plotted points from the linear regression line. Moreover, data such as the median value could be obtained from the plots.

Comparison of the distributions of serum Lp(a) concentration and other factors among the groups was done by the Kruskal-Wallis test with $p < 0.05$ being taken to indicate a significant difference. In addition, indices of arteriosclerosis such as the LDL-C/HDL-C ratio and the Apo B/Apo A-I ratio were plotted against the distribution of serum Lp(a) concentrations in each group on a boxplot. With the boxplot method, a box is formed by using the 25th percentile and 75th percentile values that enclose the median, and the distribution is expressed by widening the box to 1.5 times the 75th percentile and the 25th percentile values, respectively.

Using the cut-off value for Lp(a) calculated from these data and the value of 30 mg/dl proposed from a national survey[9] in which the author participated, the odds ratios for the presence or absence of coronary artery stenosis were obtained by multiple logistic analysis[3]. In this analysis, age was regarded as a continuous variable and the LDL-C/HDL-C ratio and the Apo B/Apo A-I ratio as discrete variables, with age and the Apo B/Apo A-I ratio being used as confounding factors. These parameter estimates were obtained by the maximum likelihood method. With a logistic model, odds ratios can be obtained not only by a cohort study but also by a case control study, so this method is commonly used in epidemiological research.

All statistical analyses were performed using PC-SAS software (ver. 6 and appendix).

Table 1. Characteristics of the subjects

	No. of subjects	Age (y.o.)	Obesity index (%)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
Healthy group	271	43 (38-50)	108 (100-116)	194 (175-213)	108 (82-139)	51 (41-60)	112 (92-131)
Non-stenosis group	94						
without vasospasm	59	60 (53-69)	111 (102-118)	173 (155-205)	120 (83-171)	37 (29-44)	109 (88-123)
with vasospasm	35	57 (52-66)	106 (99-118)	205 (179-235)	123 (86-196)	34 (30-46)	129 (97-156)
Stenosis group	147						
1-vessel disease	81	61 (55-69)	109 (101-117)	199 (175-219)	128 (100-128)	33 (27-39)	134 (112-144)
2-vessel disease	43	66 (60-72)	111 (100-115)	194 (173-225)	125 (103-184)	29 (24-39)	120 97-156)
3-vessel disease	23	65 (57-69)	106 (100-114)	214 (184-240)	107 (91-174)	40 (29-46)	132 (109-172)

Values are expressed as follows: median (25th percentile-75th percentile).
HDL-C: high density lipoprotein cholesterol
LDL-C: low density lipoprotein cholesterol

RESULTS

1) Distribution of serum Lp(a) concentrations in healthy group

The background factors of the healthy group and the patients undergoing coronary arteriography are shown in Table 1. As compared with the non-stenosis group, the healthy group were younger and had higher HDL-C levels ($p<0.05$, Kruskal-Wallis test). The distribution of serum Lp(a) concentrations and the distribution of LDL-C levels in the healthy group are shown in Fig. 1 and Fig. 2 respectively, using Q-Q plots in which the theoretical distribution was a normal distribution. The median, the 25th percentile value, and the 75th percentile value of serum Lp(a) was respectively 14.1 mg/dl, 6.2 mg/dl, and 26.7 mg/dl, showing no linearity. On the other hand, the median, the 25th percentile, and the 75th percen-

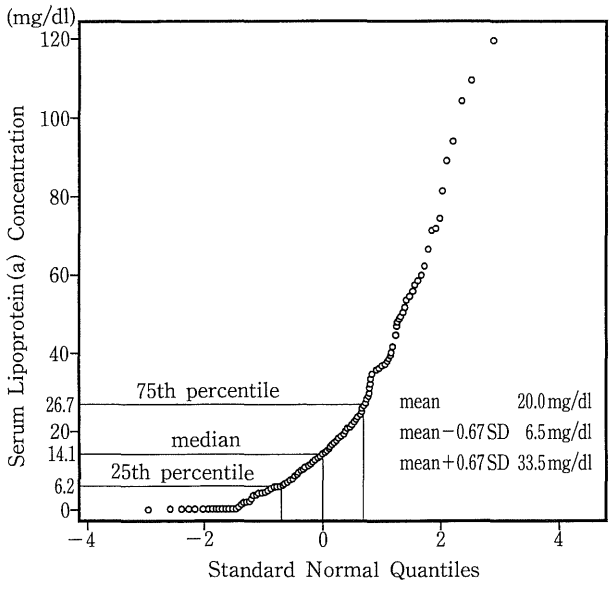

Fig. 1. Distribution of serum lipoprotein(a) concentrations in healthy subjects (Q-Q plot).

Y axis: serum lipoprotein(a) concentration (mg/dl)
X axis: standard normal quantiles

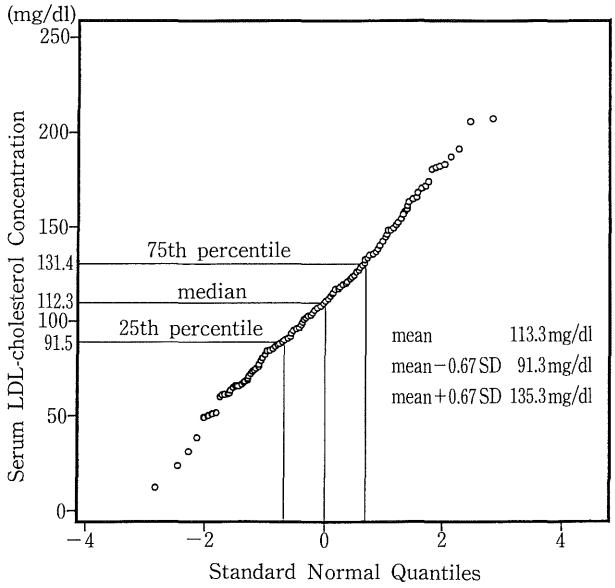

Fig. 2. Distribution of LDL-cholesterol in healthy subjects (Q-Q plot).

Y axis: LDL-cholesterol (mg/dl)
X axis: standard normal quantiles

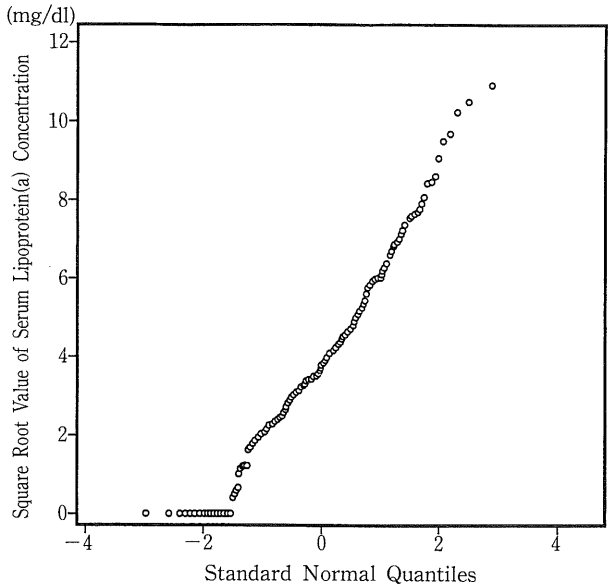

Fig. 3. Distribution of the square root values of serum lipoprotein(a) concentrations in healthy subjects (Q-Q plot).

Y axis: square root values of serum lipoprotein(a) concentrations
X axis: standard normal quantiles

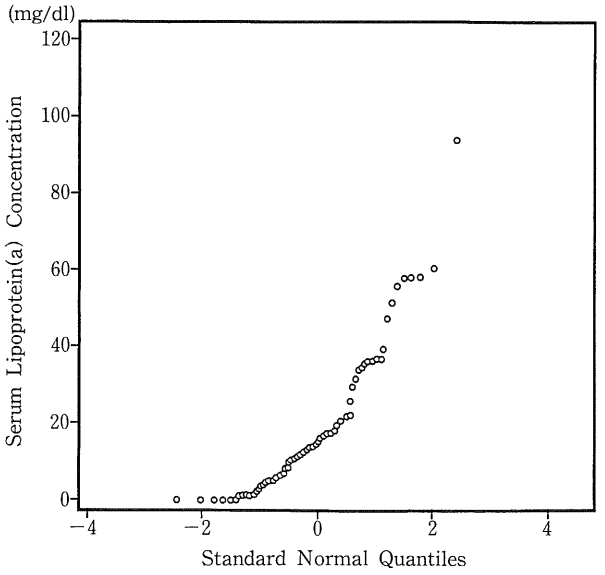

Fig. 5. Distribution of serum lipoprotein(a) concentrations in healthy subjects over 50 years old (Q-Q plot).

Y axis: serum lipoprotein(a) concentration (mg/dl)
X axis: standard normal quantiles

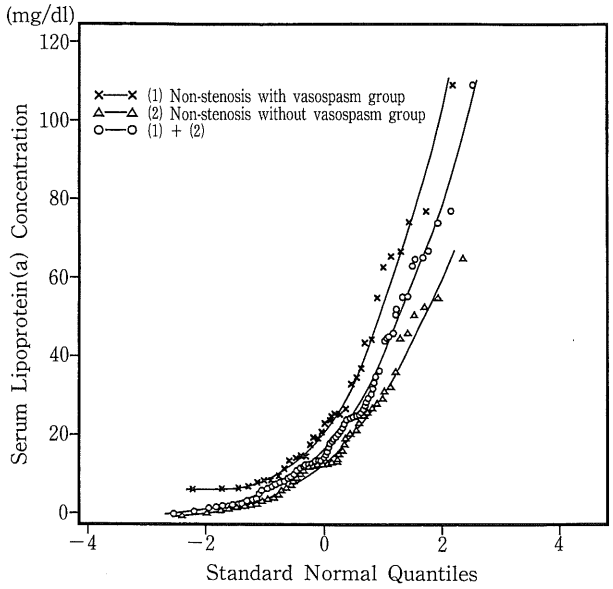

Fig. 4. Distribution of serum lipoprotein(a) concentrations in the non-stenosis group (Q-Q plot).

(1): non-stenosis with vasospasm group
(2): non-stenosis without vasospasm group
(3): (1) plus (2)
Y axis: serum lipoprotein(a) concentration (mg/dl)
X axis: standard normal quantiles

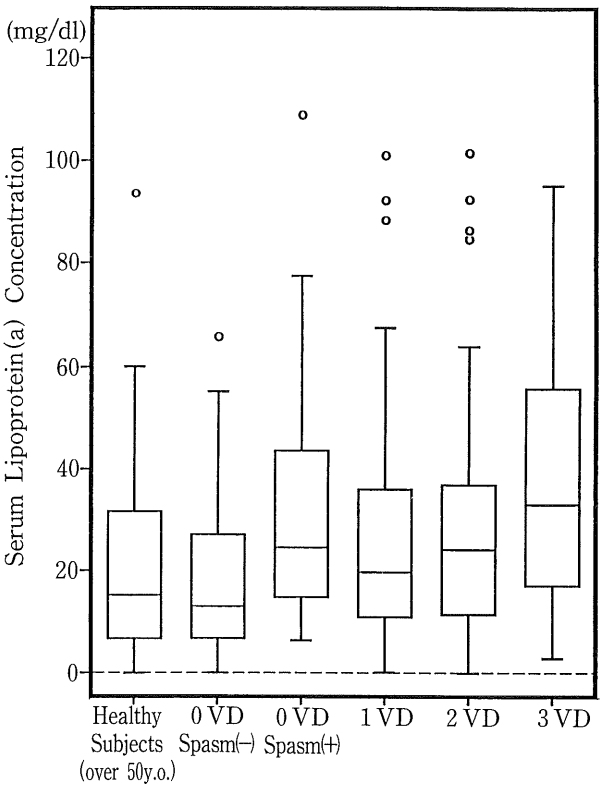

Fig. 6. Boxplots of the distribution of serum lipoprotein(a) concentrations in healthy subjects over 50 years old and subjects with 0-(non-stenosis group), 1-, 2- and 3-vessel disease(VD). The non-stenosis group was divided into the subjects without vasospasm group[0 VD spasm(-)] and the subjects with vasospasm group[0 VD spasm(+)].

Y axis: serum lipoprotein(a) concentration (mg/dl)

tile value of LDL-C was respectively 112.3 mg/dl, 91.5 mg/dl, and 131.4 mg/dl, showing an approximate linearity which suggested agreement with a normal distribution in contrast to Lp(a). However, when the Lp(a) concentrations ware transformed by square root function, the distribution almost exhibited linearity as shown in Fig. 3. It did not follow a log-normal distribution with the power order of 0.

2) Distribution of serum Lp(a) concentrations in the groups without significant stenosis on coronary angiography

Q-Q plots of the serum Lp(a) concentrations for the subjects without significant stenosis on coronary angiography, the non-stenosis group, is illustrated in Fig. 4. The patients with vasospasm had higher Lp(a) levels than those without vasospasm.

Because of the difference in age between the healthy group and the non-stenosis group, a comparison of subjects over 50 years old was made. This demonstrated that the distributions of serum Lp(a) concentrations were extremely close in both groups (Figs. 4 and 5), with the median being 15.5 mg/dl for the healthy group over 50 years old and 12.7 mg/dl for the non-stenosis without vasospasm group. Moreover, there was one person with a high Lp(a) value in the healthy group over 50 years old.

3) Distribution of serum Lp(a) concentrations in the stenosis group

Using the non-stenosis without vasospasm group as a control and stratifying the stenosis group by the number of coronary vessels involved, the distributions of Lp(a) and of the LDL-C/HDL-C and Apo B/Apo A-I ratios, conventional indicators of the risk of arteriosclerosis, were compared. The median age was 60 in the non-stenosis without vasospasm group, 61 for the patients with single-vessel disease, 66 for those with double-vessel disease, and 64.5 for those with triple-vessel disease (Table 1). The Lp(a) data are presented in Fig. 6, while the LDL-C/HDL-C and Apo B/Apo A-I ratios are presented by boxplot in Figs. 7 and 8. Serum Lp(a) concentrations were significantly higher in the steno-

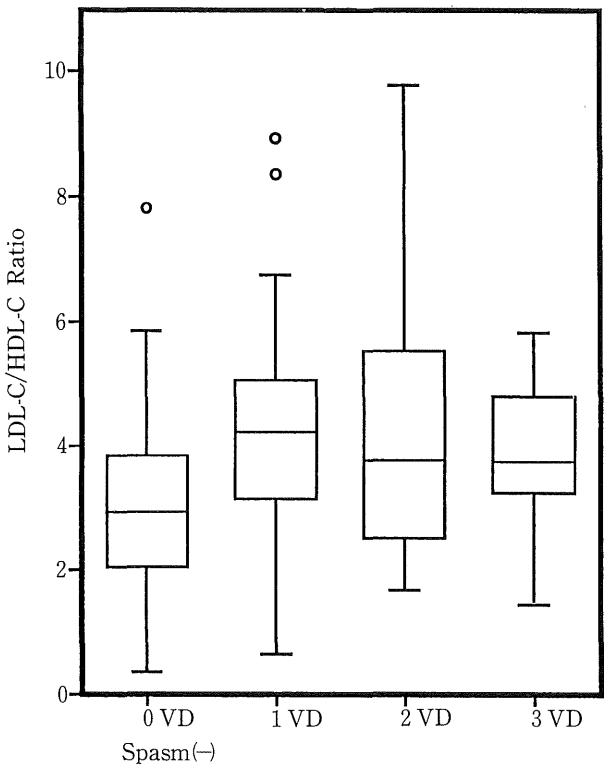

Fig. 7. Boxplots of the distribution of the LDL-cholesterol/HDL-cholesterol ratio in subjects with 0-(non-stenosis group), 1-, 2- and 3-vessel disease(VD). The non-stenosis group was divided into the subjects without vasospasm group[0 VD spasm(-)] and the subjects with vasospasm group[0 VD spasm(+)].

Y axis: LDL-cholesterol/HDL-cholesterol ratio

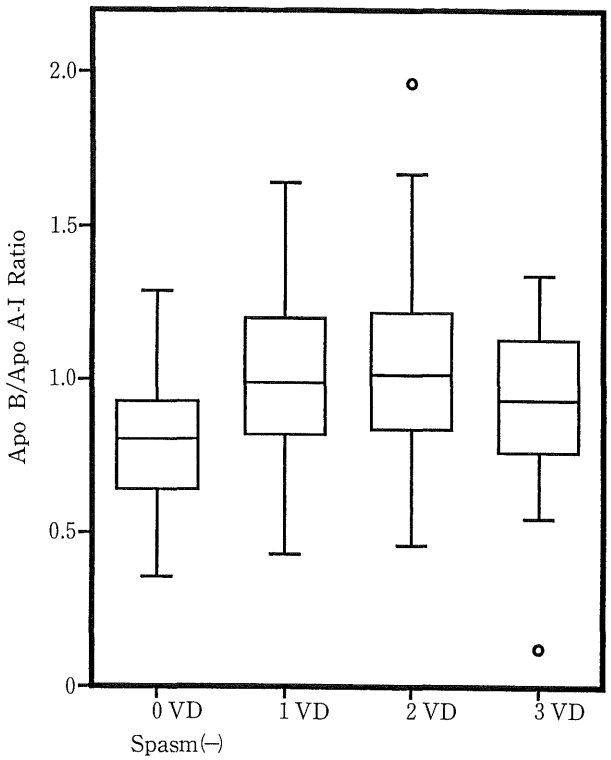

Fig. 8. Boxplots of the distribution of the apolipoprotein B/apolipoprotein A-I ratio in subjects with 0-(non-stenosis group), 1-, 2- and 3-vessel disease(VD). The non-stenosis group was divided into the subjects without vasospasm group[0 VD spasm(-)] and the subjects with vasospasm group[0 VD spasm(+)].

Y axis: apolipoprotein B/apolipoprotein A-I ratio

sis group as compared with the control group. The median value was 12.7 mg/dl in the non-stenosis without vasospasm group, 19.6 mg/dl in the single-vessel disease group, 24.2 mg/dl in the double-vessel disease group, and 32.8 mg/dl in the triple-vessel disease group, indicating that the serum Lp(a) concentrations rose as the number of vessels with stenosis increased. The LDL-C/HDL-C ratio and the Apo B/Apo A-I ratio also showed significant increases in the stenosis groups, but there was little difference in relation to the number of vessels involved.

4) Odds ratio of serum Lp(a) concentrations for coronary arteriosclerosis

In the multiple logistic analysis using age as a confounding factor, 26.7 mg/dl, 3.85, and 0.92, which were the 75th percentile values in the healthy group, were respectively adopted as the standard serum Lp(a) concentration, LDL-C/HDL-C ratio, and Apo B/Apo A-I ratio. For the serum Lp(a) concentration, a cut-off value of 30 mg/dl, as advocated by the national survey[7], was also studied. The odds ratio for Lp (a) was 2.91 at a cut-off of 26.7 mg/dl and 3.81 at a cut-off of 30 mg/dl. The odds ratios for the LDL-C/HDL-C and Apo B/Apo A-I ratios were 3.53 and 5.22, respectively, both being significant (Table 2). Also, analysis using age and Apo B/Apo A-I ratio as confounding factors demonstrated that the serum Lp(a) concentration was a significant risk for coronary arteriosclerosis (Table 3), with the odds ratio being 2.52 at a cut-off value of 26.7 mg/dl and 2.94 at a cut-off value of 30 mg/dl (95% confidential interval of 1.24-5.11 and 1.29-6.68, respectively). At the cut-off value of 26.7 mg/dl, the sensitivity was 44.2 % and the specificity was 81.4 %, while the sensitivity was 39.5 % and the specificity was 86.2 %t at a cut-off value of 30 mg/dl.

Table 2. Results of multiple logistic analysis adjusted for age

	Cut-off value	Odds Ratio	95% Confidential Interval	P value
Lipoprotein(a)	26.7 mg/dl	2.91	1.49- 5.72	0.0019
Age		1.02	0.99- 1.05	0.1192
Lipoprotein(a)	30 mg/dl	3.81	1.73- 8.37	0.0009
Age		1.02	1.00- 1.05	0.1099
LDL-C/HDL-C	3.85	3.53	1.78- 6.99	0.0003
Age		1.03	1.00- 1.06	0.0346
Apo B/Apo A-I	0.92	5.22	2.61-10.43	0.0001
Age		1.04	1.01- 1.07	0.0153

LDL-C: high density lipoprotein cholesterol
HDL-C: low density lipoprotein cholesterol
Apo B: apolipoprotein B
Apo A-I: apolipoprotein A-I

Table 3. Results of multiple logistic analysis adjusted for age and the apolipoprotein B/apolipoprotein A-I ratio

	Cut-off value	Odds Ratio	95% Confidential Interval	P value
Lipoprotein(a)	26.7 mg/dl	2.52	1.24-5.11	0.0106
Apo B/Apo A-I	3.85	4.80	2.37-9.73	0.0001
Age		1.03	1.00-1.07	0.0287
Lipoprotein(a)	30 mg/dl	2.94	1.29-6.68	0.0100
Apo B/Apo A-I	3.85	4.49	2.21-9.11	0.0001
Age		1.03	1.00-1.07	0.0290

LDL-C: high density lipoprotein cholesterol
HDL-C: low density lipoprotein cholesterol
Apo B: apolipoprotein B
Apo A-I: apolipoprotein A-I

DISCUSSION

When establishing normal range, it is the general procedure to clarify the distribution of the data between the control and patient group. Although Hoffman's method[8] is applied to the establishment of normal range, this method is based on the assumption that the central part of the data shows a normal distribution. Thus, it has the shortcoming that the only central part of the distribution of data contributes to determin-

ing the distribution, and the permanent assumption of normality may also cause bias. In the present study, the LDL-C level in the healthy group was assessed and its distribution was evaluated. The Q-Q plot of LDL-C was almost linear (Fig. 2), and little possibility of the inclusion of outliers was suggested. The median was 112.3 mg/dl, which was almost equal to the mean of 113.3 mg/dl. In addition, the 25th percentile value of 91.5 mg/dl and the 75th percentile value of 131.4 mg/dl were also respectively almost consistent with the corresponding mean−0.67SD of 91.3 mg/dl and mean+0.67SD of 135.3 mg/dl, which also suggested that the distribution of the population may be a normal distribution. If outliers are not present, the moment indicators and quantile indicators are almost consistent and the standard derived from these indicators is also consistent if the distribution is close to a normal distribution. Thus, no problems will arise if either method is used. However, the distribution of serum Lp(a) concentrations showed no linearity on the Q-Q plot, and some markedly high values, possibly due to outliers, were observed. The mean was 20.0 mg/dl and the median was 14.1 mg/dl. The mean−0.67SD and the mean+0.67SD were respectively 6.5 mg/dl and 33.5 mg/dl, while the 25th and 75th percentile values were respectively 6.2 mg/dl and 26.7 mg/dl, which were not consistent. Thus, establishment of normal range by applying moment indicators to the distribution of serum Lp(a) concentrations is presumed to be invalid. Tango[16] has attempted to establish normal values using Akaike's information criteria (AIC) and power normal distribution. However, this method involves the necessity of assuming a theoretical distribution (power normal distribution). In the present study, the distribution of serum Lp(a) concentrations in healthy individuals actually conformed to a power normal distribution with the power order of 1/2 when the assumption of a power normal distribution was used. However, there is no physiological basis for this distribution, and the possibility of inclusion of outliers cannot be denied. Thus, it seems valid to assess the distribution of serum Lp(a) concentrations using quantile indicators, even though some outliers are included. In the present study, representative values with little influence by outliers could be obtained by using percentiles as quantile indicators, and the author was able to obtain a useful index that was marginally affected by the determination of the distribution.

Hiroshima city is an average city in Japan from the viewpoint of age distribution, and the food intake of its population, so the subjects of this study should provide a representative sample of the Japanese population. The present study revealed the distribution of serum Lp(a) concentrations was biased towards low values in healthy individuals. This is the same pattern as seen in Caucasians[12] and in the Chinese[21], and is clearly different from that in Negroes[7]. Concerning the skewed distribution of blood Lp(a) concentrations towards low values, Utermann[20] has hypothesized that each phenotype of Lp(a) has a symmetrical distribution and that skewing occurs owing to the polymorphism of Lp(a). The differences in the distribution of blood Lp(a) concentrations between the races may also be due to differences in the frequency of each phenotype. The significance of phenotype is now widely under discussion.

The subjects without stenosis on coronary angiograms had a distribution markedly biased towards low values similar to that in healthy individuals. Since there are various hypotheses on the etiology of vasospastic angina[6,15], these subjects were divided into a non-stenosis with vasospasm group and a non-stenosis without vasospasm group to observe the relation with Lp(a). The non-stenosis with vasospasm group had higher Lp(a) values than the non-stenosis without vasospasm group, suggesting that it might be incorrect to consider these subjects as the same. Since different groups should not be included together when assessing distributions like this, the vasospasm group was excluded from the subjects when assessing the relationship of Lp(a) with coronary arteriosclerosis.

The patients with coronary arteriosclerosis and the healthy subjects in this study differed greatly in age, so only those over 50 years old were sampled from the healthy group. They still had a distribution of serum Lp(a) concentrations similar that in the non-stenosis without vasospasm group. Thus, to evaluate the relationship of the LDL-C/HDL-C ratio and the Apo B/Apo A-I ratio, which are conventional indicators of atherogenesis as well as the serum Lp(a) concentration to coronary arteriosclerosis, the non-stenosis without vasospasm group and the patients with stenosis were compared. Consequently, and compatible with the findings of Kawanishi et al.[11], the LDL-C/HDL-C ratio and the Apo B/Apo A-I ratio were found to be significantly higher in the stenosis group, but showed no clear relationship to the number of vessels with stenosis. On the other hand, the serum Lp(a) concentrations were significantly higher in the stenosis group, and increased further as there was an increase in the number of vessels with stenosis. This suggested that Lp(a) is not only a risk factor for coronary arteriosclerosis but may also be related to the progression of arteriosclelosis in Japanese male adults.

The national survey advocated 30 mg/dl as a cut-off value of serum Lp(a) concentration. One of the reasons for this recommendation was that the value of 30 mg/dl was approximately the 90th

percentile of the distribution among healthy volunteers in the national survey. Another reason was that the value of 30 mg/dl did not conflict with the values of foreign studies. But the subjects of the survey were younger than the author's control and thus the data may have much measurement bias because they were collected from many facilities. Therefore the distribution of serum Lp(a) concentrations between the control of the national survey and the author's control was different.

As patients with ischemic heart disease were also investigated in the author's study, the odds ratios could be calculated. The author used 26.7 mg/dl as a cut-off value in order to calculate the odds ratios. The value of 26.7 mg/dl was the 75th percentile of the distribution of serum Lp(a) concentration of the healthy group in the author's study. The 75th percentile of controls has commonly been used as a cut-off value in foreign studies. The author also used 30.0 mg/dl as a cut-off value because of the recommendation of the national survey. The multiple logistic evaluation using the value of 26.7 mg/dl and the value of 30 mg/dl demonstrated that Lp(a) was an independent risk factor for coronary arteriosclerosis. The odds ratio was 2.52 at a cut-off value of 26.7 mg/dl and 2.94 at a cut-off value of 30 mg/dl (95% confidential interval of 1.24-5.11 and 1.29-6.68, respectively). At the cut-off value of 26.7 mg/dl, the sensitivity was 44.2 % and the specificity was 81.4 %, while sensitivity was 39.5 % and specificity was 86.2 %t at the cut-off value of 30 mg/dl. In general, increasing sensitivity causes a decrease in specificity. Therefore, both cut-off values were useful. It is a further problem to determining which cut-off value is better. But it is important to estimate serum Lp(a) concentration as a continuous value and not just as a cut-off value. In order to establish the cut-off value of serum Lp(a) concentration, it will be necessary too to take into account the questions of cost and benefit.

Compared with the other atherogenic indexes, the odds ratio of serum Lp(a) concentration was lower than that of the Apo B/Apo A-I ratio but was higher than that of the LDL-C/HDL-C ratio. Determining the serum Lp(a) concentration is thought to be important in estimating the coronary atherogenic factor.

ACKNOWLEDGEMENTS

I am grateful to Dr. Goro Kajiyama, Professor of our laboratory, and Dr. Masaki Munaka, Professor of the Department of Biometrics, for their helpful discussion. I would also like to thank Dr. Masahiro Kawanishi, Dr. Itaru Horiuchi, Dr. Hideo Matsuura and my colleagues in the laboratory for their advice.

(Received November 10, 1992)
(Accepted February 10, 1993)

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