The Italian Multicenter Study of Reversible Cerebral Ischemic Attacks: IV-Blood Pressure Components and Atherosclerotic Lesions


SUMMARY Utilizing the initial BP assessment in the 462 patients who entered the Italian Multicenter Study of reversible cerebral ischemia, an analysis of the effect of each BP component in respect of presence, extent and severity of atherosclerotic lesions, as displayed by angiography, was carried out separately for lesions located at either intra- or extracranial level.

In a multivariate statistical model, among the following variables: sex, age, systolic BP, diastolic BP, cholesterol and smoking, systolic BP was found the best predictor of extent and severity of atherosclerotic lesions at extracranial level. None of the same variables was predictive of the severity of intracranial atherosclerosis.

The results of this clinical study may confirm the indication, coming from physiopathologic observations, of a predominant role of systolic hypertension in the process of maintenance and acceleration of atherosclerosis in the large pre-cerebral arteries.

A NUMBER OF STUDIES1, 2 have demonstrated that hypertension is an important risk factor in stroke. The Framingham Study, confirmed by other population studies,3, 4 determined that systolic BP is a better predictor than diastolic BP of the risk of atherothrombotic brain infarction. On this basis, the concept, widely accepted in clinical practice, that diastolic pressure was the BP component more directly involved in all the clinical manifestations of cerebral vascular disease was criticized and the necessity of carefully treating systolic hypertension firmly stressed.

Although a few pathological studies5 have indicated a positive correlation between systolic BP values and severity of atherosclerotic (AS) lesions in the cerebral vessels, the site of action as well as the mechanism by which systolic hypertension may play a role in increasing the risk of ischemic stroke remains to be clarified. Moreover, rather than being a causative factor, increased systolic values could simply be an epiphenomenon of arterial damage. If so, therapeutic implications might be quite different.

The protocol of the Italian Multicenter Study of reversible cerebral ischemic attacks (RIA) provided the opportunity to contribute to the understanding of these problems for the following reasons: 1) careful and standardized BP data, obtained by means of a series of BP registrations throughout the baseline period of observation, were available; 2) patients with RIA conduct normal daily activities and therefore in such patients BP recordings are more closely representative of the real individual BP values than in restricted stroke patients; 3) all of the patients had undergone a thorough assessment of other risk factors for atherosclerosis; 4) all of the patients were studied by means of angiography: the extent and severity of the angiographic lesions were determined in a standardised manner and expressed by a score-index which can be used as a continuous variable.

On the basis of these considerations and utilizing some of the available data, we examined each BP component’s relative contribution to the presence, se-

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Received February 19, 1985; revision #1 accepted June 12, 1985.
verity and extent of AS lesions in the cerebral arteries. This represents, in effect, an in vivo study on a symptomatic population.

We further investigated the role of BP components in relation to presenting clinical manifestations of reversible cerebral ischemia and to cerebral and cardiac events in the follow-up period.

Methods

Study Population, Clinical Presentation and Follow-up Data

From January 1976 through December 1978, the eight centers participating in the Italian Study on RIA enrolled 462 patients (mean age 52.3, standard deviation 10.0) to be studied by means of a large set of standardised clinical and laboratory investigations and followed-up during the successive years. The population characteristics and methodology have been described in more detail in a previous publication.6

Presenting symptoms were categorized as follows: 1) number of events: one; more than one; 2) time of the last event; within the preceding three months; more than three months ago; 3) duration of events: less than 1h; between 1 and 24hs; more than 24hs; 4) reversibility of events: transient ischemic attacks (TIAs); subjective duration less than 24hs, neurological examination completely normal; prolonged transient ischemic attacks (PTTAs); subjective duration more than 24hs, neurological examination absolutely normal within 4 weeks; transient ischemic attacks with incomplete recovery (TIAs-IR); subjective duration more or less than 24hs with minimal residual symptoms after 4 weeks; 5) territory of events: carotid (right or left) territory; vertebrobasilar territory; mixed territory (including bilateral carotid territory); undefined territory.

The events occurred in the follow-up period were grouped as follows: no event, cerebral events, cerebral plus cardiac events.

BP Registrations

Criteria for BP assessment followed the recommendation of the Framingham Study Group;7 the average of a series of pressures should be used to determine the risk of cardiovascular diseases.

During the period of baseline observation the patients had a mean of 7 BP recordings on different days. BP was registered twice each day, in the morning and afternoon. The average (systolic and diastolic) of all recordings in the lying position, using the higher value obtained from the two arms, was considered the BP specific for each patient. The disappearance of sounds was the criterion for determining diastolic pressure.

Out of 462 patients only 62 (13.4%) were under antihypertensive treatment at entry. The distribution of those patients among the different BP classes (as defined in the "statistical analysis" section) showed a high concentration in the elevated BP classes (25.8% in the non hypertensive group; 12.9% in the isolated systolic group; 19.4% in the isolated diastolic group; 41.9% in the systodiastolic group), thus providing indirect evidence of its poor regulation. Moreover all the analyses, whether carried out with or without these cases, yielded substantially similar results. Therefore we decided to present the data obtained using the BP values from the entire study population.

Angiography Data

All the patients were submitted to cerebral angiography of at least the symptomatic territory. The X-rays were read by two neuroradiologists and the pathologic findings coded in a standardized manner.

A score-index was elaborated in order to have a quantitative measure of the extent and severity of AS lesions. The extracranial circulation was subdivided into 11 arterial segments and the intracranial circulation into 21 arterial segments. The score used to grade the atherosclerotic process in each abnormal segment, was the following: grade 0.5: irregularity and tortuosities of the vessel without lumen narrowing; grade 1: localized plaque with minimal lumen narrowing; grade 1.5: diffuse or localized 25–50% lumen narrowing; grade 2: diffuse or localized 50–70% lumen narrowing; grade 2.5: diffuse or localized 70–90% lumen narrowing; grade 3: diffused or localized lumen narrowing of more than 90%. A numerical value for the degree of the atherosclerotic process was obtained by adding the score of all graded segments. There were two separated indices: the Extra-Cranial Atherosclerotic Score (ECAS) and the Intra-Cranial Atherosclerotic Score (ICAS), each expressing extent and severity of the AS lesions at the extra- or intra-cranial level, respectively. The criteria for the score-index determination are reported in more detail elsewhere.6 The values for ECAS and ICAS used in this work are the percentages of the maximum theoretical degree of lesion.

Age, Sex and Other Risk Factors for AS

Age and sex were taken into account in all statistical analyses and were used as covariate variables.

Among risk factors for AS other than hypertension we decided to study only cholesterol and smoking, because in a preliminary analysis of the effect of all possible cardiovascular risk factors, only those variables were found to be significantly correlated with presence or severity of AS lesions (these data are the object of a paper in preparation).

Serum cholesterol level was used as a continuous variable. Subjects were divided into four classes on the basis of their smoking habits: 1) non smokers; 2) smokers of less than 10 cigs/day; 3) smokers of 10 to 20 cigs/day; 4) smokers of more than 20 cigs/day.

Statistical Analyses

The distribution of systolic and diastolic BP values according to sex and age classes (44; 45–64; 65) and between subpopulations with and without angiographic signs of AS was first analyzed. The differences among groups were tested by means of the analysis of the variance.9

The relative contribution of each BP component as well as that of each of the other considered variables to prevalence and severity of AS lesions was assessed by means of multivariate analyses.
For the following variables: age, sex, systolic BP, diastolic BP, cholesterol, smoking, multiple logistic regression function analyses were used in order to select those variables which showed the best discrimination between patients with and without angiographic signs of AS. Dependent variables for the logistic function were defined as presence/absence of AS lesions. The analysis was carried out between the following groups: a) patients without AS lesions vs. all the other cases; b) patients without AS lesions vs. cases with extracranial AS lesions (i.e., excluding cases with only intracranial lesions); c) patients without AS lesions vs. cases with intracranial AS lesions (i.e., excluding cases with only extracranial lesions).

The net and joint effect of each selected factor was determined by means of the subtractive selection method of variables, and employing the maximum likelihood method of analysis.10-12 The formula utilized was the usual one:

\[ p = 1/[1 + \exp(-\alpha - \Sigma \beta x_i)] \]

where \( p \) is the probability of showing signs of AS lesions, and \( x_i \) are the independent variables. The parameters of the equation, \( \alpha \) and \( \beta \), were estimated by using the maximum likelihood method.13 The ratio of the coefficient/standard error of the characteristic, affords a measure of the association between risk of the event and levels of the characteristic, and is distributed as a t-Student statistic. In order to estimate the goodness of fit of model to data, the appropriate \( \chi^2 \) value (\( G^2 \)) was reported. Stepwise discriminant analysis15 was also carried out with substantially similar results.

Multiple linear regression analysis16,17 was used to determine the net contribution of the above indicated variables to the severity of the angiographic lesion as expressed by the score-index. This analysis was carried out separately for the ECAS and the ICAS.

The mean values of ECAS and ICAS were then compared among subpopulations with different BP patterns defined as follows: normotension: BP values < 150 - < 90; systolic hypertension: BP values > 150 - < 90; diastolic hypertension: BP values < 150 - > 90; systodiastolic hypertension: BP values > 150 - > 90.

An a-posteriori contrast test was performed for comparing all possible pairs of group means.

Finally the distribution of patients with different clinical presentations as well as with different outcome in the follow-up period among these classes of BP was examined.

Results

In our population of RIA cases the systolic BP values increased significantly with age among both males and females. However the difference among age classes was more marked for females than for males (fig. 1). As regard the diastolic BP, the analysis of variance showed a significant effect for the sex-age interaction; the increase of diastolic BP values among age classes was significant for females only (\( F = 4.07; \) \( dF = 2; p < 0.025 \)).
Systolic BP and smoking appeared to be the variables most highly correlated with severity of arterial lesion as expressed by ECAS. Diastolic BP was also predictive, although at a lower level of significance. None of the variables considered contributed significantly to the severity of the intracranial lesion as expressed by ICAS.

The distribution of mean values of ECAS and ICAS among classes with different BP patterns confirmed the close relationship between systolic PB and the severity of AS lesions at the extracranial level and the secondary role of the diastolic component (fig. 4). Mean values of ECAS were definitely higher in the class of isolated systolic hypertension. Duncan's multiple range test showed a statistical difference ($\alpha = 0.01$) between mean ECAS in the group of isolated systolic hypertensives vs. the isolated diastolic group, and in the isolated systolic group vs. the normotensive group. Mean ECAS in the isolated systolic group was even higher than in the systodiastolic group. However, the difference was not significant. Moreover mean sys-

### Table 1

<table>
<thead>
<tr>
<th>$X_i$</th>
<th>Variables</th>
<th>Level</th>
<th>Presence/absence of any type of lesion (447 cases, 15 missing)$^\dagger$</th>
<th>Presence/absence of extra-cranial lesions (340 cases, 8 missing)$^\dagger$</th>
<th>Presence/absence of intra-cranial lesions (373 cases, 12 missing)$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$</td>
<td>Age</td>
<td>years</td>
<td>Unstandardized coefficient</td>
<td>$T$</td>
<td>Unstandardized coefficient</td>
</tr>
<tr>
<td>$X_2$</td>
<td>Sex</td>
<td>1 = male; 2 = female</td>
<td>-0.348</td>
<td>-2.733$^\dagger$</td>
<td>-0.351</td>
</tr>
<tr>
<td>$X_3$</td>
<td>Systolic BP</td>
<td>mm Hg</td>
<td>0.014</td>
<td>1.994$^*$</td>
<td>0.013</td>
</tr>
<tr>
<td>$X_4$</td>
<td>Diastolic BP</td>
<td>mm Hg</td>
<td>0.006</td>
<td>1.920</td>
<td>0.006</td>
</tr>
<tr>
<td>$X_5$</td>
<td>Cholesterol</td>
<td>mg/100 ml</td>
<td>0 = no; 1 = &lt;10; 2 = 10-20; 3 = &gt;20 cigarettes/day</td>
<td>3.730</td>
<td>4.907</td>
</tr>
</tbody>
</table>

$k$ Constant

$G^2$ 431.10

DF 442

$P$ 0.64

$T = \frac{\text{Unstandardized coefficient}}{\text{Standard error}}$; $^*p < 0.01$; $^\dagger p < 0.05$.

$^\dagger$Cases missed due to the lack of information about one of the considered variables.

Goodness of fit of multiple-by maximum-likelihood test.
TABLE 2  Unstandardized Coefficient of Multiple Linear Regression of AS Severity Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Level</th>
<th>Regression coefficient</th>
<th>F°</th>
<th>R²</th>
<th>F</th>
<th>DF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>X₁ Age</td>
<td>years</td>
<td>-0.0064</td>
<td>0.003</td>
<td>0.0389</td>
<td>0.464</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₂ Sex</td>
<td>1 = male; 2 = female</td>
<td>1.9383</td>
<td>0.537</td>
<td>0.7724</td>
<td>0.294</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₃ Systolic BP</td>
<td>mm Hg</td>
<td>0.2909</td>
<td>15.258*</td>
<td>0.0249</td>
<td>0.336</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₄ Diastolic BP</td>
<td>mm Hg</td>
<td>-0.2936</td>
<td>4.745*</td>
<td>0.6662</td>
<td>0.738</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₅ Cholesterol</td>
<td>mg/100 ml</td>
<td>0.0029</td>
<td>0.021</td>
<td>0.0014</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X₆ Smoking</td>
<td>0 = no; 1 = 10; 2 = 10-20; 3 = 20 cigarettes/day</td>
<td>3.5979</td>
<td>12.258†</td>
<td>0.5151</td>
<td>0.979</td>
<td></td>
<td></td>
</tr>
<tr>
<td>k Constant</td>
<td></td>
<td>-6.6443</td>
<td>10.0197</td>
<td>0.13</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td>4.946</td>
<td>0.381</td>
<td>6.237</td>
<td>0.270</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DF</td>
<td></td>
<td>0.05</td>
<td>n.s.</td>
<td>0.0014</td>
<td>0.013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DF for F-test = 1 and 237; + DF for F-test = 1 and 270; °p < 0.05; †p < 0.01.

Discussion

In a previous publication of our Study Group, a history of hypertension was found to be not correlated with severity of angiographic signs of AS. In the present study, using the BP registered values on admission and analyzing separately the effect of each BP component we obtained substantially different results.

The analysis of the effect of BP components as well as of other considered risk factors with respect to the presence of AS signs at angiography showed a definite role of cholesterol in discriminating positive from negative AS cases. However, this effect is more apparent when cases with only intracranial lesions are omitted from the analysis. This finding may confirm a set of experimental observation of the crucial role of cholesterol in initiating the AS process, and at the same time indicates a selective site of action of this risk factor among the different segments of the cerebral arterial tree. The specific role of cholesterol in the pathogenesis of the AS lesion in the large extracranial arteries has already been suggested on the basis of epidemiological and clinical evidence.

In the total population, the distribution of the values of each BP component by sex and age shows a positive correlation between systolic BP and increasing age, particularly among females. This result appears in line with the information coming from population studies. However, the increase of systolic values with age...
becomes more apparent among both males and females when only the subpopulation with AS signs at angiography is considered. Sex and age were significantly discriminating factors with regard to the presence/absence of AS, either at the extracranial or intracranial level or in the total population.

On the other hand, sex and age do not appear to be significantly involved in the extent and severity of AS lesions when multiple regression analysis of the effect of risk factors on the severity of the AS lesions (as expressed by the score-index) was carried out in the positive AS subpopulation only. On the contrary, data from this kind of analysis show a strong association between systolic BP values and the severity of AS lesions, although, in this case too, the relationship is evident only at the extracranial level. At this level, smoking as well as diastolic BP appear to be significant contributors, although the contribution of the latter is definitely smaller.

Due to their selective effect on the severity of AS lesions, systolic BP, smoking and, to a lesser extent, diastolic BP might be considered as factors predominantly involved in the mechanism of the maintenance and acceleration of the AS process.

The analysis of the distribution of the mean values of ECAS and ICAS among classes with different BP patterns, shows that the ECAS values were significantly higher in the class with isolated systolic hypertension. Pathological studies have indicated that cerebral atherosclerosis increases with systolic BP values. However, the cause-effect relationship between systolic hypertension and damage of the large arteries remains to be elucidated. Isolated systolic hypertension may be the consequence of the reduced arterial compliance due to either age-dependent degenerative changes and loss of elastic components of the arterial wall (atherosclerosis) or to diffuse atheroma in the main arteries. Therefore isolated systolic hypertension would merely reflect the degree of vascular deterioration, whereas the pathogenic potential would reside in diastolic hypertension.

The Framingham Study, by assessing the risk of cardiovascular events in groups of individuals with different pulse-wave recordings, excluded the possibility that the increased risk of such events in systolic hypertension was related to arterial rigidity. However, recent physiopathological studies have indicated that different hemodynamic mechanisms are involved in systolic hypertension at different ages. In young people, it is linked to increased cardiac output and heart rate, in old people to the reduction of arterial compliance. In the young there is also hyperdynamic circulation that, according to hemodynamic studies, may have a role in maintaining or accelerating the AS lesions, particularly at bifurcation sites, through mechanical forces linked with the increased blood velocity.

Our data, showing that the net contribution of systolic BP is much more important than that of age in relation to the severity of the AS lesions (particularly at the level of the carotid bifurcation), may support the hypothesis of a causative effect of increased systolic BP on AS of the large arteries.

<table>
<thead>
<tr>
<th>Classes of hypertension</th>
<th>No events</th>
<th>Length attacks</th>
<th>Reversibility of events</th>
<th>Territory of events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>events</td>
<td>1H</td>
<td>2H-2H</td>
<td>2H-2H</td>
</tr>
<tr>
<td>No</td>
<td>58</td>
<td>173</td>
<td>66</td>
<td>47</td>
</tr>
<tr>
<td>Isolated diastolic</td>
<td>20</td>
<td>43</td>
<td>53.1</td>
<td>51.6</td>
</tr>
<tr>
<td>Isolated systolic</td>
<td>14</td>
<td>26</td>
<td>110</td>
<td>5</td>
</tr>
<tr>
<td>Systo-diastolic</td>
<td>34</td>
<td>89</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Subtotal</td>
<td>126</td>
<td>331</td>
<td>128</td>
<td>91</td>
</tr>
</tbody>
</table>

*5 cases had systolic or diastolic BP missing values.
†Percentage on sub-total number of cases.
Chi-square test, for each contingency table is reported.
Clinical studies have indicated that AS lesions located in the main intracranial trunks may be associated with different risk factors from those associated with extracranial lesions.

Harrison and Marshall reported on the results of carotid angiography in 304 cases with cerebral hemisphere infarction. They found that the prevalence of carotid occlusion was significantly lower in those patients with a diastolic pressure of 110 or more and the chance of finding a normal angiogram was significantly greater in this hypertensive group.

Prineas and Marshall had found that patients afflicted with stroke who had a diastolic BP above 110 mm Hg tended to have less severe and less persistent clinical deficits, and had EEG abnormalities suggesting deep-seated lesions.

In these studies the systolic component had not been taken into account. However their results suggest that deep infarctions, conceivably linked with the hypertensive changes in the penetrating arteries, are more strongly associated with the diastolic BP component and that other risk factors are possibly linked to the occlusive lesions in the large extracranial arteries.

Our data in a RIA population showed that systolic BP and diastolic BP were equally predictive of the severity of the lesions in the extracranial arteries, but systolic BP seems to play a predominant role in the pathogenesis of those lesions.

The higher values detected for the mean intracranial score in the non-hypertensive group and the lack of any correlation between the BP components (as well as the other risk factors) and the severity of the intracranial AS lesions in multivariate analysis, may be due to the peculiarities of this study (relatively young population, high proportion of patients with short attacks, lack of information about the status of penetrating arteries). It is also possible that in some of the patients the intracranial abnormalities were of cardiac embolic origin. However, the role of still obscure risk factors (possibly constitutional) in the pathogenesis of occlusive lesions at this level cannot be excluded.

Components of BP, Presenting Symptoms of Reversible Cerebral Ischemia and Follow-up Events

It appeared of interest to study the possible influence of BP patterns on the clinical features of presenting symptoms of reversible cerebral ischemia in our population.

Patients with different clinical presentation were homogeneously distributed among classes with the different BP patterns. This result does not allow any conclusion other than that the variations of BP components do not affect the features of clinical presentation of reversible cerebral ischemia.

Moreover no difference was found in the outcome among the different BP classes according to the occurrence of cerebral or cardiac events. This result may be either due to the low number of follow-up events in our population with the consequent very low number of events in each BP class, or due to the effect of the accurate BP monitoring and treatment of hypertension in the follow-up period.

A further study of these factors may be of interest.

References

Holter Monitoring in Patients With Transient and Focal Ischemic Attacks of the Brain

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SUMMARY The results of Holter monitoring in 100 patients with transient and focal cerebral ischemia were studied retrospectively. Atrial fibrillation (AF) was found in five patients compared with two from a group of 100 age and sex-matched control patients. Four of these had a previous history of AF or showed AF on the standard electrocardiogram. Episodic forms of sick sinus syndrome, which have also been related to cerebral embolism, were found in 32 of the TIA patients against 13 of the controls (p < 0.0025). Sick sinus syndrome was of the bradyarrhythmia-tachyarrhythmia type in 14 of the TIA patients and in three of the controls (p < 0.01). The relationship between TIA and the mentioned node dysfunction could not be explained by concomitant heart disease. It is not yet clear whether the relationship is causal or indirect.

Stroke Vol 17, No 2, 1986

CARDIAC DYSRHYTHMIAS may cause transient neurological symptoms in two ways: (1) by diminishing cardiac output, which may lead to generalized cerebral symptoms, such as dizziness, syncope, etc., and (2) by predisposing to thrombus formation in the heart, with subsequent embolism and focal cerebral dysfunction. The importance of continuous ECG recording in cerebral infarction in normotensive and hypertensive subjects.


Appendix

Special Project Ischemic Brain Disease OD2

Participant Units

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Received January 5, 1984; revision #2 accepted August 29, 1985.
The Italian Multicenter Study of reversible cerebral ischemic attacks: IV--Blood pressure components and atherosclerotic lesions.
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Stroke. 1986;17:185-192
doi: 10.1161/01.STR.17.2.185

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