Labile Hypertension: A Faulty Concept?
The Framingham Study

W. B. Kannel, M.D., Paul Sorlie, M.S., and Tavia Gordon

SUMMARY. Labile blood pressure elevation is believed to have less clinical significance than "fixed hypertension." This assertion was examined in the Framingham cohort of 5209 men and women followed for 20 years for the development of cardiovascular events in relation to three routinely measured blood pressures at each of 10 biennial examinations.

Variability of pressure judged from the standard deviation about the mean of three pressures was not a consistent characteristic of subjects from one examination to the next \( r = 0.07 \). Higher pressures were more labile than low ones, so that "fixed hypertensives" actually had more labile pressures than did so-called labile hypertensives. Lability also increased with age.

Labile hypertension, determined during a 1-hour period of observation, adds nothing to the ability of the mean blood pressure to predict cardiovascular disease. The mean, minimum and maximum of three pressures measured during an examination were equally efficient predictors of cardiovascular disease. In multivariate analysis, for any given average pressure, risk of cardiovascular events was unaffected by the degree of variability of the pressure. It is recommended that the average of a series of pressures be used to determine risk, preferably over more than one examination.

LABILE HYPERTENSION is regarded as a relatively innocuous antecedent of "fixed" hypertension. As such, it is common clinical practice to consider labile hypertension unworthy of treatment.

The purpose of this report is to examine the concept of labile hypertension and its role in the development of cardiovascular disease in the Framingham Study. This cohort has been followed over 20 years for the development of cardiovascular disease in relation to three routinely obtained biennial blood pressures. The lability of pressure is calculated from these readings and its net effect on risk of cardiovascular disease, taking the average level of pressure into account, is ascertained.

Methods

The Framingham cohort consists of 2336 men and 2873 women ages 30–62 years at entry to the study in 1948–1952. They received a standardized, routine reexamination for the development of cardiovascular disease every 2 years. Cardiovascular events and mortality that occurred in the 20 years of follow-up were ascertained by means of these biennial cardiovascular examinations and surveillance of hospital admissions and deaths. Criteria for cardiovascular end points have been given elsewhere.

The examination procedures, sampling, type of follow-up and response rates have been described in detail previously. The examination procedure includes blood pressure measurements, an ECG, a cardiovascular physical examination and history, a cigarette history and a variety of blood chemistries, including cholesterol, lipoproteins and blood sugar.

Systolic and diastolic pressures were obtained using a mercury sphygmomanometer with a 14-cm cuff long enough to fit the most obese arm. The subject was seated and the left arm was used. Recommendations of the American and British Heart Associations were followed. Palpation was used to check auscultatory findings. Diastolic pressure was read at the fifth Korotkoff phase. Readings were made to the nearest even number. Beginning in 1950, three pressures were obtained routinely on each subject: one by the nurse and two by the examining physician — one at the start of the exam, the other at the end of the interview after the blood specimen was obtained.

The relation of the various components of pressure under consideration — the mean, minimum, maximum and variability — to subsequent appearance of cardiovascular disease was evaluated by estimating a logistic function using the methods of Walker-Duncan and Truett-Cornfield. These evaluations use a person-exams approach in which blood pressures at all 10 exams are considered. Thus, the assessment of cardiovascular risk is based on all available blood pressures and not on a single initial reading.

The within-person standard deviation was used to assess the variability of the pressure. Because only two or three blood pressures were used to estimate this variability, the standard deviation was adjusted for the bias caused by small numbers. When two blood pressures are available, the standard deviation is the absolute difference of the two measurements multiplied by a constant. Thus, in some analyses, the absolute difference between the blood pressures is used as a description of within-person variability.

Hypertension was designated when two pressure determinations exceeded 160/95 mm Hg, normotension was indicated by pressures consistently below 140/90 mm Hg, and intermediate pressures were designated "borderline."
Results

Variability

Blood pressure is acknowledged to be a measurement that fluctuates physiologically in response to changes in physical activity, emotion, mood, wakefulness and other demands for greater tissue perfusion. Therefore, pressures under office conditions are sometimes variable. This has engendered skepticism about the value of a single blood pressure reading.

However, it is difficult to discern what most physicians or texts mean by the term “labile hypertension.” Presumably it means that, using some arbitrary definition of “hypertension,” the pressure measurement, when repeated, is below this arbitrary level and in the borderline or normal range.

When examined in this way, 35% of male and 27% of female hypertensives on one biennial examination were borderline or normotensive on the next (table 1). By this criterion, those subsequently found to be normotensive might be judged very labile, and those borderline moderately so.

However, this concept of “lability” is confounded by the statistical phenomenon of regression toward the mean. A subgroup selected because it is above average pressure and then remeasured, will be closer to the mean for the entire sample and hence lower on the second measurement.

One indication of the lability of the blood pressure is the standard deviation about the mean of a series of pressures obtained over an hour on a particular biennial examination. An approximation of this standard deviation for two measurements is the absolute difference between the measurements. About 65% of those examined had differences in two systolic measurements, made by a physician, of less than 10 mm Hg; for diastolic, 81% had a difference less than 10 mm Hg. Differences greater than 20 mm Hg occurred in less than 10% of persons for systolic and in only 2% for diastolic (table 2).

The variation of blood pressure during the 1-hour exam did not appear to be a repeatable characteristic of a subject. The variation at one moment was unrelated to variation at another. While the blood pressures themselves were highly correlated in a subject from one exam to the next (table 3), the correlation of standard deviations of blood pressure from one examination to another is extremely low whether 2 years or 18 years apart (0.08 and 0.04, respectively).

Analysis of subjects who had all 10 examinations shows that extreme variability of systolic blood pres-

<table>
<thead>
<tr>
<th>TABLE 1. Hypertensive Status at Examination 3 vs Examination 4: Men and Women Ages 30-62 Years at Entry. Framingham Study</th>
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<tbody>
<tr>
<td>Pressure status at exam 3</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Normotensive</td>
</tr>
<tr>
<td>Borderline</td>
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<tr>
<td>High</td>
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</tbody>
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<thead>
<tr>
<th>TABLE 2. Distribution of Differences Between Two Physician-measured Blood Pressures at One Examination: Framingham Study, Examination 3, Men and Women Ages 34-68 Years</th>
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<tbody>
<tr>
<td>Differences (mm Hg)</td>
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<tr>
<td>---------------------</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>0-9</td>
</tr>
<tr>
<td>10-19</td>
</tr>
<tr>
<td>20-29</td>
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<tr>
<td>≥ 30</td>
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<tr>
<th>TABLE 3. Correlation of Blood Pressures Between Initial and Later Examinations: Framingham Study, Men and Women Ages 30-62 Years at Entry</th>
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<tbody>
<tr>
<td>Later exam</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Exam 2 (2 yrs later)</td>
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<tr>
<td>Exam 10 (18 yrs later)</td>
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</table>

sure repeated on many examinations is a rare finding (table 4). In comparing the number of persons with high variability with that expected from the binomial function, there are slightly more subjects observed than expected in those categories with the more frequent occurrences (three or more exams with high variability). This is consistent with the small but positive correlation coefficient described earlier. However, the magnitude is very small. If four or more occurrences of high variability may be thought to indicate an individual with “characteristically high variability,” there are only 12 more individuals so observed than expected out of a population of 1785.

Thus, although pressures do vary some during an office examination (table 1), there is little evidence to support the contention that there are actually identifiable persons in a population who characteristically

<table>
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<th>TABLE 4. Number of Subjects with High Variability (HV)* of Systolic Blood Pressure on 10 Framingham Examinations: Observed and Expected</th>
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<tbody>
<tr>
<td>Number of Framingham exams with high within-person variability</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>No. of exams with HV</td>
</tr>
<tr>
<td>1 of 10</td>
</tr>
<tr>
<td>2 of 10</td>
</tr>
<tr>
<td>3 of 10</td>
</tr>
<tr>
<td>4 of 10</td>
</tr>
<tr>
<td>5 of 10</td>
</tr>
<tr>
<td>6 of 10</td>
</tr>
<tr>
<td>7 or more</td>
</tr>
<tr>
<td>1785</td>
</tr>
</tbody>
</table>

*High variability means difference > 20 mm Hg between systolic pressures taken by two examiners.
†Expected is based on binomial function with an overall probability of HV of 0.07983.
have unusually labile pressures on a number of examinations. However, systolic blood pressure variability is related to age, with the older subjects having higher variability, at least in the age range 35–64 years (table 5). Furthermore, all pressures are to some extent labile, and high pressures are actually more labile than low ones. Even after adjusting for age, within-person variability increases with increasing systolic pressure (fig. 1). Hence, pressures far above the arbitrary dividing line between “hypertension” and normal or borderline pressures, commonly regarded as “fixed hypertension,” are actually more labile than those close to this arbitrary boundary and usually regarded as labile.

Lability and Risk

“Basal” pressures have been considered the best basis for judging the need for treatment.1,2 Those not elevated under basal conditions were often in the past judged innocuous and thought not to require treatment. As an extension of this concept, physicians have tended to use the lowest pressure recorded on a patient as the most valid for evaluating risk.

In the Framingham cohort, the lowest pressure recorded during an office visit was not a better predictor than the average pressure. The mean, minimum and maximum of three pressures taken during an office examination are, judging from the regression of incidence of cardiovascular disease on them, virtually indistinguishable predictors of cardiovascular disease (table 6). The similarity of the regression coefficients in table 6 indicates that the relative risk is similar for the three measures of blood pressure. For example, if the blood pressure were to differ by 20 mm Hg, the approximate relative risk for the minimum, mean and maximum would be, respectively, 1.43, 1.43 and 1.39 for men.

However, because of the relationship among the minimum, the mean and the maximum pressures, the absolute risks are different (table 7). If only the maximum of three readings is over 140 mm Hg, the other readings will be lower, resulting in a lower risk of cardiovascular disease in this group. This risk is still 42% higher than that for normotensives. If the minimum is high, this reflects a higher average pressure, which results in a higher risk — more than twice that of normotensives.

Thus, there is no question that persistently elevated basal pressures are associated with a high risk of cardiovascular disease. The lowest pressure obtained in the office is, when elevated, clearly associated with a high risk (fig. 2). Also, at any level of pressure the risk is greater when it is the lowest than when it is the highest of a series of pressures. This is merely a reflection of the higher average pressure of the former. In any event, the converse is not true. It is not safe to disregard patients whose pressures fail to be persistently
elevated on every determination if the average pressure is high.

It would seem that the best indicator of risk is the average of a series of office pressures rather than the lowest reading. Though all measures demonstrate nearly equal relative risks, the average of a series would yield a more precise estimate of a person's blood pressure.

Whereas the risk of cardiovascular disease is best judged from the average of a series of pressures, the risk is unaffected by the variability of these pressures about the mean. Patients whose pressures are more "labile" have no lower risk of cardiovascular events than those whose pressures were less variable. In fact, taken alone, the risk of cardiovascular disease actually increases with the degree of variability in pressure (table 8). However, this reflects only the higher average pressure of those with more variable values. When this is adjusted for the mean level of pressure by computing coefficients of variation, there is no relation of variability to risk.

Table 8. Cardiovascular Disease by Pressure Variability in Men Ages 45-74 Years: Framingham Study 20-year Follow-up

<table>
<thead>
<tr>
<th>Standard deviation of pressure (mm Hg)</th>
<th>2-year incidence rate (%)</th>
<th>Coefficient of variation (%)</th>
<th>2-year incidence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>3.7</td>
<td>0-0.9</td>
<td>4.2</td>
</tr>
<tr>
<td>5-9</td>
<td>4.0</td>
<td>1.0-1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>10-14</td>
<td>4.5</td>
<td>2.0-2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>15+</td>
<td>5.7</td>
<td>3.0+</td>
<td>4.5</td>
</tr>
<tr>
<td>Standardized slope</td>
<td>0.129</td>
<td></td>
<td>0.051</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>2.74</td>
<td></td>
<td>1.02</td>
</tr>
</tbody>
</table>

*Coefficient of variation is the within-person standard deviation of pressure divided by within-person mean pressure.

Table 9. Cardiovascular Disease vs Systolic Level, Lability and Age: Framingham Study 20-year Follow-up, Ages 45-74 Years

<table>
<thead>
<tr>
<th>Standardized multiple logistic coefficients</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP lability</td>
<td>0.027</td>
<td>0.080</td>
</tr>
<tr>
<td>SBP level</td>
<td>0.357*</td>
<td>0.420*</td>
</tr>
<tr>
<td>Age</td>
<td>0.303*</td>
<td>0.458*</td>
</tr>
</tbody>
</table>

*p < 0.001.

Abbreviation: SBP = systolic blood pressure.

A surer way of disentangling the effects of lability from the pressure level is to compute multivariate regression coefficients, allowing an interpretation of the net effect of each component of the pressure. This shows coefficients for lability that are neither substantial nor statistically significant and they are not negative (table 9). Thus, there is no indication of a lesser risk in relation to lability, taking the level of pressure into account. In fact, there is no suggestion of any influence of lability, one way or the other, on risk of cardiovascular sequelae of hypertension.

Discussion

Blood pressure is a dominant contributor to the major cardiovascular diseases, particularly for stroke and cardiac failure. Epidemiologic data have clearly shown that casual office pressures are highly predictive of subsequent incidence of cardiovascular disease. Physicians appear convinced that they can improve on this by attention to the lability, systolic and diastolic components, repeated measurements over a period of observation and basal pressures.

Casual pressures can be obtained more reproducibly by standardizing the measurement situation, making sure that the subject is tranquil and rested, and by acclimatization through repeated measurements. Whether this is a more appropriate measurement for evaluating risk is uncertain. It can be argued that a casual measurement is more representative and relevant. The initial examination blood pressure measurement at Framingham was somewhat higher on average than on later exams, presumably due to the novelty of the procedure, and predicted cardiovascular disease at least as well as pressures on later exams.

Variation in blood pressure has been examined previously, but its significance in evaluating risk has not been clearly determined. The lack of precision in the diagnosis of "hypertension" is surprising, considering that it is a prevalent and powerful contributor to cardiovascular disease. Over the years, hypertension has been subdivided into malignant and benign and labile and fixed varieties in an attempt to distinguish severe from mild forms of the disease process.

The malignant or accelerated variety appears to be a distinct entity with a unique vascular pathology — a necrotizing, fibrinoid arteriolar process. Labile hypertension has no such distinguishing features. In fact, almost all normotensive persons occasionally...
have pressures above the arbitrary normal limits.\textsuperscript{16, 17} Likewise, almost all patients with so called fixed hypertension occasionally have pressures below the conventionally designated hypertensive limits. Perhaps a useful characterization of lability could be arrived at by responses to standard stimuli or by analysis of long-term chronobiological fluctuations.\textsuperscript{18}

By current definitions, however, and by short-term observations, the entity does not appear to be a persistent individual characteristic or to have clinical significance.

**Clinical Implications**

As assessed by repeated 1-hour clinic visits, no support can be found for the concept that there is a discrete subgroup of the population with characteristically labile pressures. However, there are other definitions and descriptions of labile blood pressures.

Many distraught patients will have an elevated pressure in the physician’s office but will later exhibit what is considered a nonhypertensive pressure. Recognition of this appears to be responsible for the traditional concept of fixed and labile hypertension.\textsuperscript{19, 20} Those who accept this distinction as valid have concluded that “basal” blood pressures are more reliable determinants of the prognosis in hypertension than are casual pressures.\textsuperscript{21, 22} While this may seem reasonable on a priori grounds, given the known variability of blood pressure, casual pressures predict outcomes surprisingly well. In regard to cardiovascular sequelae, it appears that the only reason that fixed hypertension is associated with a higher risk than labile hypertension and basal pressure elevations carry a higher risk is that the average pressure of basal or fixed hypertension is higher. It would therefore appear more logical to rely on the average pressure rather than on such ambiguous indicators as basal or fixed states of hypertension. It is not safe to rely on the lowest pressure recorded on a patient as an indicator of the need for treatment.

Caldwell et al.\textsuperscript{23} found that near-basal pressures were no more accurate as indicators of cardiorenal manifestations of hypertension than were casual pressures.

It may be unwise to label a patient hypertensive on the basis of a single office blood pressure. It does not appear to be good practice to place such patients, who may have been transiently emotionally upset, on a lifetime of antihypertensive therapy on the basis of one office blood pressure reading. However, it would appear equally unwise to conclude that the patient who occasionally has a nonhypertensive blood pressure is in no jeopardy.

Greater attention to diastolic than systolic casual office pressures, contrary to widely held belief, adds nothing to the precision of risk estimates.\textsuperscript{10, 11} Disregarding those with isolated systolic elevations is also a mistake.\textsuperscript{10} More important in assessing the gravity of the average blood pressure is the height of the systolic pressure, the number of associated cardiovascular risk factors and whether or not there is target organ involvement.\textsuperscript{10} This is true whether the pressure elevation is labile or fixed.

**References**

5. Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland: Standardization of blood pressure readings. Am Heart J 18: 95, 1939
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