Bayesian Analysis Supports Use of Ambulatory Blood Pressure Monitors for Screening

Fernando Elijovich and Cheryl L. Laffer

To assess whether there is a role for ambulatory blood pressure monitoring (ABPM) in screening for hypertension, we conducted Bayesian analysis of office blood pressure (OBP) as a diagnostic “test” in populations with different prior probabilities (PP) of hypertension. OBP was considered a positive test if systolic blood pressure was greater than 140 mm Hg or diastolic pressure was greater than 90 mm Hg. Chosen daytime ABPM cutoffs for a “gold standard” diagnosis of hypertension were systolic pressure of 139 and diastolic pressure of 88 mm Hg. Sensitivity and specificity of OBP were determined in 72 patients with established hypertension (PP=1). After 3 weeks off therapy, OBP was 168±3/101±1 and ABPM was 151±2/94±1 mm Hg. Systolic ABPM was in the normotensive range in 17 patients and diastolic in 15 patients. OBP was falsely positive in 14 and 15 of these patients, respectively. Thus, sensitivity and specificity of OBP were 0.8909 and 0.1765 (systolic) and 0.9825 and 0 (diastolic). These data cannot be extrapolated to populations with lower PPs for use of Bayes’ theorem. Hence, we calculated sensitivity and specificity for PP=0 from published series of ABPM in normotensive subjects and used our measurements and these calculations in arithmetic interpolations for populations with PP 0.1-0.9. Sigmoid relations between PP and predictability of hypertension by a positive OBP were disclosed by use of Bayes’ theorem. Their best-fit cubic polynomials predict that an elevated OBP will misdiagnose hypertension 46-50% of the time in a general population (PP=0.2) but only 8-9% in a specialty practice (PP=0.9). In conclusion, we confirm that the diagnostic accuracy of OBP worsens when prevalence of hypertension decreases. This suggests a role for ABPM in screening for hypertension, with the potential for reduction of overdiagnosis, mislabeling, and cost. (Hypertension 1992;19[suppl II]:II-268-II-272)

Clinical use of ambulatory blood pressure monitoring (ABPM) has been reviewed by policy boards and committees of experts. Present indications include the study of certain diagnostic issues in essential hypertension (e.g., “white coat hypertension” and refractoriness to treatment), workup of secondary forms of hypertension (e.g., analysis of circadian rhythms or episodic blood pressure [BP] elevation), and research (e.g., evaluation of drug therapy and estimation of prognosis). In contrast to these established indications, the Coordinating Committee of the National High Blood Pressure Education Program has recently stated that, pending further research, ABPM should not be routinely used for diagnosis of hypertension in patients with “mild sustained” elevation of BP in the office. Hence, ABPM is presently recommended for use in patients with an established diagnosis of hypertension only.

Office blood pressure (OBP) measurement has been the “test” with which physicians traditionally make a diagnosis of hypertension. Estimation of “true” BP by OBP is subject to three sources of error, however: 1) the methodological error inherent to all biological measurements, 2) the large variability of BP throughout the day, and 3) the pressor effect of the recording maneuver itself. Furthermore, Bayesian theory states that the diagnostic power of a test will be lower in populations with lower prevalence (prior probability) of the disease. Therefore, the diagnostic accuracy of OBP is bound to be worse in screening or epidemiological surveys than in a referral population. If this is true, diagnosis of hypertension in populations with low prevalence of the disease should be made by ABPM, a technique that allows for a closer estimate of true BP. To investigate this issue, we used Bayesian analysis to assess the diagnostic power of OBP in populations with high and low prior probabilities of essential hypertension.
Blood Pressure in Essential Hypertensive Patients

Rationale

OBP, a continuous variable, is used as a diagnostic test for a dichotomous classification (normotension/hypertension). It is well known, however, that the diagnostic sensitivity and specificity of a continuous variable used in this fashion will depend on its measured value. This issue has been addressed by complex mathematical modeling, which supports the intuitive contention that an OBP of 250/150 mm Hg, for example, will be a more accurate predictor of hypertension than one of 141/91 mm Hg. Because populations with different prevalences of hypertension have different average OBP values, the sensitivity and specificity of OBP is also dependent on prior probability. Thus, to conduct Bayesian analyses we 1) measured sensitivity and specificity of OBP in a referred population of patients with established essential hypertension (i.e., prior probability of hypertension of 1), 2) calculated sensitivity and specificity of OBP in normotensive subjects (i.e., prior probability of 0) from data published in the literature, 3) estimated sensitivity and specificity of OBP for populations of intermediate prior probability by arithmetic interpolation of the values from the previous two groups, and 4) applied Bayes' theorem to these data.

Measurement of Sensitivity and Specificity of Office Blood Pressure in Essential Hypertensive Patients

We studied 72 patients in whom secondary forms of hypertension were excluded by history, physical examination, and appropriate laboratory determinations. They underwent measurements of OBP (mercury sphygmomanometer) and 24-hour ABPM (Spacelabs 5200, Redmond, Wash.) on the same day. Therapy was discontinued 3 weeks before study. All patients gave informed consent, and the study was approved by the Institutional Review Board. Reported OBP values are the mean ±SEM, range) of three measurements with patients in the sitting position, obtained after 5 minutes' rest, at 2-minute intervals. Patients had their backs and arms supported throughout this period. The fifth phase of the Korotkoff sounds was recorded as the diastolic BP. ABPM was carried out as previously described in detail by our laboratory. In brief, each procedure was validated by sphygmomanometric BPs obtained in the contralateral arm simultaneously with the first and last readings of the monitor. Studies were excluded if diastolic BPs by these two methods differed by more than 5 mm Hg. The monitor recorded BPs every 30 minutes from 6 AM to midnight and every 60 minutes from midnight to 6 AM. Errors were edited out electronically or by a commonly used algorithm. Data were electronically transferred to the mainframe computer of the City University of New York, where calculations were performed with a statistical package (SAS Institute Inc., Cary, N.C.). Sleep readings were excluded from analyses on the basis of information in patients' diaries. Reported ambulatory BPs are the average of all daytime readings.

Ambulatory BPs of 139 mm Hg systolic and 88 mm Hg diastolic were used as the cutoffs for "gold standard" diagnosis of hypertension. These are the 90% upper confidence limits derived from the published weighted mean and variance of daytime ABPM in a meta-analysis of 2,638 normotensive subjects. OBP, the diagnostic test to be evaluated, was considered positive if systolic pressure was greater than 140 mm Hg or diastolic pressure was greater than 90 mm Hg. Two-by-two tables and calculations of sensitivity and specificity were done by conventional techniques.

Calculation of Sensitivity and Specificity of Office Blood Pressure in Normotensive Subjects

In patients with documented lack of hypertension by ABPM, sensitivity of OBP is 1 (0/0), because by definition there is no patient with the disease. Specificity of OBP in this setting is the percentage of subjects who have "negative" tests (i.e., who are normotensive by OBP). This was calculated from three studies in the literature involving 126 subjects deemed to be normotensive for recruitment and confirmed to be normotensive by ABPM. These subjects were somewhat younger and more commonly male than our hypertensive patients. These studies did not provide the number of subjects with OBPs above and below 140 mm Hg systolic or 90 mm Hg diastolic. Hence, we derived these data from the reported means and standard deviations, assuming a normal distribution for BP in their populations. The weighted average of the three specificity values of these series (i.e., the percentages of patients with normotensive OBPs) was used as the specificity value for OBP in normotensive subjects.

Arithmetic Interpolation of Sensitivity and Specificity Values for Populations With Intermediate Prior Probabilities of Hypertension

To carry out these calculations, we assumed that the prevalence of hypertension in a given population would approximate its estimated prior probability. For example, in a population with a prior probability of 0.5, the sensitivity and specificity of OBP were calculated as the average of those observed in normotensive and hypertensive individuals, assuming that half the population would actually fall in each of these categories. In an analogous manner, we calculated sensitivities and specificities for systolic and diastolic OBPs for theoretical populations in each decile of prior probabilities, from 0.1 to 0.9.

Bayes' Theorem Calculations

The probability of having the disease when the test is positive (i.e., the conditional Bayes' probability or the diagnostic power of OBP) was calculated by

\[
P(D|+) = \frac{PP \cdot S}{(PP \cdot S) + ([1 - PP] \cdot [1 - Sp])}
\]
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TABLE 1. Office and Daytime Ambulatory Systolic Blood Pressures in 72 Subjects Referred With a Diagnosis of Essential Hypertension

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease present (ABPM&gt;139 mm Hg)</th>
<th>Disease absent (ABPM≤139 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (OBP&gt;140 mm Hg)</td>
<td>49</td>
<td>14</td>
</tr>
<tr>
<td>Negative (OBP≤140 mm Hg)</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

ABPM, daytime ambulatory blood pressure; OBP, office blood pressure.

where PD+ is the conditional Bayes' probability, PP is prior probability, S is sensitivity, and Sp is specificity.

Results

Our patients were predominantly middle-aged (58.5±1.6 years), Hispanic (82%) women (84%) with a history of 12±1 years of hypertension. At the time of study, OBPs averaged 168±3 (130–210/101±1 (90–110) mm Hg and daytime ABPMs 151±2 (112–213)/94±1 (74–131) mm Hg. Table 1 shows the distribution of our patients according to their systolic OBPs (the test) and ABPMs (presence or absence of hypertension, see “Methods”). Only 76% of the patients referred to us as hypertensive had systolic ABPMs in the hypertensive range, and six of these had a negative test. Therefore, sensitivity of systolic OBP was 49/55=0.8909. Of the 24% of patients with systolic ABPMs in the normotensive range, three had a negative test (specificity, 3/17=0.1765), whereas most had “false-positive” systolic OBPs. Similarly, two-by-two analysis of diastolic OBPs and ABPMs (not shown) resulted in a sensitivity value of 0.9825 and a specificity value of zero (all patients with diastolic ABPMs in the normotensive range had false-positive diastolic OBPs).

The three left columns of Table 2 show the bibliographic source, number of participants, and mean±SD of systolic OBP in three published studies of normotensive subjects (confirmed by ABPM). The calculated number of standard deviations above the mean required to encompass all patients with a systolic OBP of 140 or less (i.e., a negative test) is given in the fourth column. The area under the curve of a normal distribution up to this value represents the proportion of normotensive subjects who had systolic OBPs in the normotensive range (i.e., the specificity of systolic OBP). These data were derived from tables of the normal distribution and are shown in the rightmost column. Similar calculations were made for diastolic OBPs (not shown). The resulting specificities for systolic and diastolic OBPs (the weighted averages of the three studies) are 0.9505 and 0.9517, respectively.

Bayes' conditional probabilities (i.e., the likelihood of having hypertension if systolic OBP is greater than 140 or diastolic OBP is greater than 90 mm Hg) and their dependence on the prior probability in a given population are shown in Figure 1. Data points were obtained with Bayes' theorem using the calculated sensitivities and specificities for OBP in each decile of prior probability, as described in “Methods.” Regression of conditional probability on prior probability was best fit by the cubic polynomials shown in the figure legend. The dashed arrows point to the conditional probabilities obtained from these polynomials for populations with prior probabilities of 0.2 and 0.9 (examples representing the general population and a referral population, respectively). In the former, conditional probabilities are 0.538 systolic and 0.505 diastolic, whereas in the latter, the respective values are 0.918 and 0.909. In other words, these data predict that in the general population, a systolic OBP of greater than 140 mm Hg would misdiagnose hypertension 46.2% of the time, whereas this will occur in only 8.2% of referrals to a specialty practice. The respective predicted values for diastolic OBP of greater than 90 mm Hg are 49.5% and 9.1%. The ratio between these percentages (46.2/8.2=5.6 and 49.5/9.1=5.4) is an estimate of how manyfold less powerful OBP is as a diagnostic test in a sample of the general population than in a referral population.

Discussion

Prospective epidemiological studies and therapeutic trials using usual recordings of BP in the office are the basis for current assessment of risk and management of hypertension. Notwithstanding the importance of these data, it is accepted that OBP is worse than ABPM in estimating true BP, because the relation between BP and target organ damage (e.g., left ventricular mass) is stronger for ABPM than for OBP.11 Hence, ABPM should also be better for diagnosis of hypertension in patients with “borderline” elevation of OBP. Caution against this assumption has been raised by a recent review3 on the basis of the lack of appropriate normative data for ABPM.

In screening for hypertension in the general population, there is an additional reason to question the

TABLE 2. Specificity of Office Systolic Blood Pressure in Normotensive Subjects From Reports in the Literature

<table>
<thead>
<tr>
<th>Report</th>
<th>n</th>
<th>OBP±SD (mm Hg)</th>
<th>140–OBP SD</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drayer (Reference 8)</td>
<td>29</td>
<td>121±11</td>
<td>1.73</td>
<td>0.9580</td>
</tr>
<tr>
<td>Pickering (Reference 9)</td>
<td>37</td>
<td>117±14</td>
<td>1.64</td>
<td>0.9498</td>
</tr>
<tr>
<td>Palatini (Reference 10)</td>
<td>60</td>
<td>123±11</td>
<td>1.62</td>
<td>0.9473</td>
</tr>
</tbody>
</table>

OBP, average office systolic blood pressure.

*Area under the normal distribution curve that encompasses all patients with OBP≤140 mm Hg.
validity of using OBP. Bayes' theorem states that the lower the prevalence of a disease, the lower the power of any test to diagnose it. We provide confirmation for this statement using Bayesian analysis of OBP as a test and ABPM as a gold standard for hypertension. Our numerical estimates indicate that for diagnosis of hypertension in the general population, an elevated OBP is only slightly more accurate than the toss of a coin. In contrast, OBP is 5.5-fold more powerful for hypertension in the general population than in a referral population (unpublished data from our laboratory). The second issue is the choice of the cutoffs themselves. Using 140/90 mm Hg for OBP as a test reflects the current standard in the practice of medicine. Running our analyses with a more permissive cutoff, such as 160/95 mm Hg (formerly used as the limit between borderline and established hypertension), or with a stricter one, such as 140/85 mm Hg (the high-normal range defined by the 1988 Joint National Committee report), results in OBP being 5.4- to 6.3-fold less powerful in a sample of the general population than in a referral population (unpublished data from our laboratory).

Defining a cutoff for daytime ABPM as a gold standard for diagnosis of hypertension is even more problematic, because large-scale prognostic studies have not been carried out with this methodology. Our choice of the 90% upper confidence limit from a meta-analysis of ABPM in normotensive subjects is a conservative estimate because of the usually skewed distribution of ABPM in normal subjects. In addition, the 95% upper confidence limit for this meta-analysis, 143/91 mm Hg, generally would not be acceptable to clinicians as the upper limit for normal BP. Others have proposed that the upper limit of normal daytime ABPM is 130/85 mm Hg, because below this level, none of their patients exhibited target organ damage (i.e., left ventricular diastolic dysfunction by Doppler echocardiography). Using this cutoff in our analysis did not substantially modify our results. OBP was still 5.4- to 7.6-fold less powerful in a sample of the general population than in a referral population (unpublished data). The two cutoffs above do not take into consideration that the magnitude of the reduction of BP during sleep may have prognostic implications in essential hypertensive patients. Reanalyzing the data with the gold standard being the 90% upper confidence limit for 24-hour BP (i.e., including sleep values from the meta-analysis) resulted in OBP being 5.4- to 6.1-fold less powerful in a sample of the general population than in a referral population (unpublished data from our laboratory).

Finally, our assumption that prior probability of hypertension is equatable to its prevalence (for arithmetic interpolation of OBP sensitivities and specificities) is merely an approximation. Except in the hypothetical case of a Bayes' conditional probability of 1 (i.e., a perfect test), prevalence of a disease is less than its estimated prior probability. To quantify the effect of this assumption on our results, we conducted iterative analyses in which the conditional Bayes' probability of the preceding calculation was used as the prior probability for the next. Estimates of prevalence corrected by the first iteration enhanced conditional Bayes' probabilities for OBP in a...
referral population, whereas the effect in a general population was negligible. Overall, an elevated OBP would still have been 8.2- to 8.8-fold less powerful for diagnosis of hypertension in a sample of the general population than in a referral population (unpublished data from our laboratory).

In summary, modifying our cutoffs or conservative assumptions either has no major effect on our results or alters them in the direction of further supporting a role for ABPM in hypertension screening.

We have not addressed issues of cost. Expenditures for equipment, skilled technicians, and worktime allocation for use of ABPM in screening would be considerable. However, the potential for savings due to reduced overdiagnosis and mislabeling is greatest in these large populations. Cost-effectiveness of ABPM for screening will have to be properly evaluated by use of economic models, as others have done for use of ABPM in the diagnosis of mild hypertension.13

References


Key Words • ambulatory blood pressure monitoring • essential hypertension • diagnostic tests
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