Reproducibility of the Hyperbaric Index as a Measure of Blood Pressure Excess

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Abstract—The approach of establishing a time-specified tolerance limit reflecting the circadian variability in blood pressure and then determining the hyperbaric index, the area of blood pressure excess above the upper limit of the tolerance interval, has been proposed for diagnosing hypertension as well as for evaluating the patient’s response to treatment. The retrospective evaluation of this test provided high sensitivity and specificity in the diagnosis of hypertension, with a threshold value for the hyperbaric index of 15 mm Hg · h. To evaluate the stability and reproducibility of this tolerance-hyperbaric test, we studied 332 previously untreated subjects (218 men) who underwent sequential 48-hour ambulatory blood pressure monitoring for 2 years, providing a total of 1337 blood pressure profiles. Diagnosis of hypertension was established for each subject on the restricted basis of presenting at least 1 blood pressure profile with a hyperbaric index above the previously defined threshold. Sensitivity of this tolerance-hyperbaric test was 98.6%, with a negative predictive value of 99.7%. For the same subjects, the blood pressure load (percentage of values >140/110/90 mm Hg for systolic/mean arterial/diastolic blood pressure during activity or >120/95/80 mm Hg during resting hours) had a sensitivity of 49% and specificity of 25%. The 24-hour mean, still the most common approach for diagnosing hypertension on the basis of ambulatory monitoring, had sensitivities of 40% and 31% for systolic and diastolic blood pressure, respectively. Despite the limitations of ambulatory blood pressure monitoring, the tolerance-hyperbaric test represents a reproducible, noninvasive, and high-sensitivity test for the identification of subjects in need of prophylactic or therapeutic intervention. (Hypertension. 2000;35:118-125.)

Key Words: blood pressure ■ hyperbaric index ■ normotension ■ hypertension

Blood pressure (BP) determined casually in the examiner’s office has been commonly used to diagnose hypertension and evaluate treatment efficacy.1,2 These conventional time-unspecified single measurements may be misleading because BP and heart rate (HR) vary according to a spectrum of rhythms with several frequencies (the circadian in particular) and because measurements may be influenced by external and internal stimuli that include, among other factors, the patient’s sleeping or waking schedule, physical activity, diet, and emotional state.3,4 Self-measurement, if done systematically, offers an alternative, but it interferes with daytime activities and is not feasible during sleep. The development of automatic instrumentation for indirect noninvasive ambulatory BP monitoring (ABPM) makes it possible to follow the time course of BP variation around the clock in large groups of subjects. The use of such monitors has provided a method for BP assessment that may compensate for some of the limitations of office and even self-measurements.5

To recognize that most of the circadian variability in BP is predictable, inasmuch as it is part of a rhythmic structure, is to admit that the diagnosis of hypertension should be based not just on whether a casual BP measurement is too high or too low, but rather on more pertinent questions: How long are pressures elevated above a given time-varying threshold? What is the excess BP? When does most of the excess occur? These considerations can easily be adapted for the case of low BP. Answers to these questions may be obtained by first establishing an adequate time-varying reference threshold and then establishing a proper measurement of BP elevation.5

The construction of a time-specified reference limit reflecting the circadian BP variability has been proposed as a substitute for the constant limits now used (140/90 mm Hg for systolic [SBP]/diastolic [DBP] BP6). A proper reference limit could be constructed, for instance, as a model-independent 90% tolerance interval determined within a short interval (in which no appreciable changes in population characteristics, namely mean and variance, take place), which is progressively displaced throughout 1 cycle of the periodicity investigated.4,7 Once the threshold (given by the upper limit of the tolerance interval) is available, the hyperbaric index (HBI), as a measure of the total load exerted on the arterial walls,5,8 can be calculated by numerical integration as the total area (within 1 cycle) of any given patient’s BP above the threshold.5,9 The HBI has been defined as a better determinant of BP excess than the BP load (percentage of...
The retrospective evaluation of this test provided high sensitivity and specificity in the diagnosis of hypertension with a threshold value for the maximum HBI (defined as the maximum of 3 values of HBI: those determined for SBP, mean arterial BP [MAP], and DBP, respectively) of 15 mm Hg · h. An equivalent approach was also tested retrospectively and validated prospectively for the very early identification of gestational hypertension and preclampsia, providing sensitivity, specificity, relative risk, and positive and negative predictive values consistently larger than values obtained from other parameters also calculated from ABPM, such as the BP load, the 24-hour mean, or the nocturnal mean of BP. The purpose of this study was to evaluate the stability and reproducibility of this tolerance-hyperbaric test on previously untreated and apparently healthy men and women who underwent sequential 48-hour ABPM on several occasions within 2 years.

Methods

Subjects

In this prospective trial, we studied 332 white, apparently healthy, young subjects (218 men and 114 women matched in age, ethnic origin, and, to a great extent, physical characteristics such as weight and height; Table 1), aged 22.9±4.0 years, who completed the study and provided the minimum required information (see below). Inclusion criteria were the absence of any condition requiring the use of antihypertensive medication. Exclusion criteria were, among others, chronic hypertension, chronic liver disease, any disease requiring the use of anti-inflammatory medication, diabetes, and any other endocrine disease such as hyperthyroidism, as well as the impossibility to tolerate the use of an ambulatory BP monitor. The Ethical Committee of Clinical Research approved the study. All volunteers signed consent forms before entering the study. We also used information previously sampled from 148 volunteers (96 men and 52 women), aged 22.6±2.8 years, without medical history of hypertension and with mean BP from ambulatory profiles always <135/85 mm Hg for SBP/DBP. Data from this independent reference population were used to determine tolerance intervals for the circadian variability in BP as a function of gender.

BP Assessment

The SBP, MAP, DBP, and HR of each subject in the validation sample were automatically monitored every 30 minutes for 48 hours with an ABPM-630 Colin device on different occasions within 2 years. All subjects included in this study provided at least 3 BP profiles. Volunteers were scheduled to have consecutive sessions of ABPM differing by at least 1 month. A total of 107 BP series were eliminated from analysis because they showed an irregular schedule during the 2 days of sampling, an odd sampling with spans of >3 hours without BP measurements, or a night resting span <6 hours or >12 hours. The total number of valid BP series provided by the subjects under investigation fulfilling all mentioned requirements set a priori was 1337. Additionally, we also analyzed data from 266 BP profiles previously obtained following the same sampling protocol from the reference population of 148 normotensive men and women (Table 1). During sampling, all subjects were living according to their usual diurnal waking (8 AM to midnight for most subjects) and nocturnal resting routine, following everyday life conditions with minimal restrictions. They were told to follow a similar schedule during the days of sampling and to avoid the use of medication during ABPM as well as for at least 2 weeks before the days of BP monitoring. The clinical evaluation of the monitor according to the standards published by the Association for Advancement of Medical Instrumentation has been previously established. The BP cuff was worn on the nondominant arm. Cuff size was determined by upper arm circumference at the time of each visit. ABPM started between 9 AM and 1 PM. During monitoring, each subject maintained their usual diurnal waking (8 AM to midnight for most subjects) and nocturnal resting span, following everyday life conditions with minimal restrictions. 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reference threshold in the calculation of HBI. Those limits were derived separately for men and women, in keeping with the statistically significant differences between genders in BP and HR previously documented, and also were corroborated for the reference population at hand. Other factors potentially affecting BP such as age, body mass index, or seasonal variation were not taken into account in deriving reference thresholds for this study. On the one hand, age and physical characteristics were mostly matched for the subjects in this protocol, as indicated above (Table 1). On the other hand, a circannual rhythm of variation in BP could not be demonstrated in this trial for either the reference or the validation sample of subjects. Moreover, since most subjects included in the present study were studied in different seasons, stability in the diagnosis would provide further evidence on the minimal influence of seasonal changes on the computation of the reference threshold used here.

The method for the determination of tolerance intervals, derived on the basis of bootstrap techniques, does not need to assume normality or symmetry in the data. It is therefore highly appropriate to describe the circadian pattern of BP. A detailed explanation of the mathematical development of nonparametric tolerance intervals for hybrid time series has been provided previously. Results will rely on model-independent smoothed tolerance intervals obtained by taking into account only among-subjects variance and determined for 2-hour time classes with 1-hour overlap between consecutive time classes. Advantages of these smoothed tolerance intervals with respect to any other tolerance or prediction intervals have been already documented. Once the tolerance intervals are obtained, both the PTE and the HBI for any given subject can be obtained by numerical integration. Details of the mathematical procedure for determining these parameters have also been previously described.

Since the conventional assessment of hypertension relies on absolute casual values >140 or 90 mm Hg for SBP or DBP, results based on the determination of BP excess will be expressed as a function of the maximum HBI, as defined above. Analysis of the HBI obtained separately for any of the 3 cardiovascular variables provided lower sensitivity and specificity than results based on the maximum HBI. Diagnosis of hypertension was established in this trial for each subject in the validation sample on the highly restricted basis of presenting at least 1 BP profile with an HBI above the previously defined threshold for diagnosis. While it seems reasonable to show stability and reproducibility.

Results obtained for the tolerance-hyperbaric test were compared with those obtained by the use of other parameters calculated from the BP series sampled by ABPM, including the BP load (defined as the percentage of all individual BP readings >140/110/90 mm Hg for SBP/MAP/DBP during diurnal active hours or 120/95/80 mm Hg during nocturnal resting hours); the daily (24-hour), diurnal, and nocturnal means of BP; and the circadian midline estimating statistic of rhythm (MESOR), a rhythm-adjusted mean here obtained by the least-squares fitting of a multiple component curve with periods of 24 and 12 hours to the data from each BP series. This model has been shown to describe sufficiently well the circadian pattern of BP variability at the specified sampling rate, despite the fact that other ultradian rhythms can be demonstrated as statistically significant in some but not all individuals sampled by 48-hour ABPM. The BP load, diurnal mean, and nocturnal mean were calculated for each individual BP profile according to the actual rest-activity cycle of each subject obtained from the subject’s diary. Sensitivity and specificity of all those parameters, including the HBI, were calculated by comparing distributions of values obtained for normotensive and hypertensive subjects, without assuming an a priori threshold for diagnosis of hypertension on the basis of that particular parameter. Additionally, we also computed the positive and negative predictive values, as well as the relative risk, defined as the proportion of subjects with a positive test that really have the disease divided by the proportion of subjects with a negative test that really have the disease. A good clinical test should have values for sensitivity, specificity, and positive and negative predictive values close to 100%, while the relative risk is markedly >1. If the relative risk is, for instance, 10, then persons with a positive test are 10 times as likely to have the disease than persons with a negative test.

Results
Figure 1 shows the distributions of the maximum HBI, maximum PTE, and maximum BP load (maximum of the

Figure 1. Frequency distribution of maximum HBI, PTE, and BP load for normotensive (top; 1115 BP series) and hypertensive (bottom; 222 BP series) subjects of both genders, sampled by 48-hour ambulatory monitoring.
values obtained for SBP, MAP, and DBP) determined from the BP series sampled by ABPM in the validation population. The top graph on the left of Figure 1 indicates that, according to the criteria set a priori for diagnosis, none of the BP profiles from the defined group of normotensive subjects were \( 15 \text{ mm Hg} \) for HBI. The bottom graph on the left of Figure 1 indicates that subjects with at least 1 BP profile exceeding the threshold for diagnosis are consistently characterized by a maximum HBI above the threshold. Moreover, most of the BP series from these subjects have a maximum HBI \( 105 \text{ mm Hg} \), a value chosen here only to keep the length of the horizontal axis of the histogram below a reasonable size. The mean HBI was \( 1.72 \pm 0.08 \text{ mm Hg} \) for the normotensive subjects and \( 97.70 \pm 6.58 \text{ mm Hg} \) for the hypertensive volunteers (\( P < 0.001 \)).

The distributions of the maximum PTE (center of Figure 1) show a slightly larger overlap between normotensive and hypertensive subjects than the overlap shown for HBI or PTE.

The histograms on the right of Figure 1 further indicate a larger overlap between the distributions of maximum BP load for normotensive and hypertensive subjects than the overlap shown for HBI or PTE.

Using results from Figures 1 to 3, we determined and compared sensitivity and specificity for diagnosing hypertension on the basis of each of the parameters calculated from ABPM. For all the cardiovascular parameters included in Table 2, sensitivity corresponds to the largest possible value found for an assumed maximum specificity of 100%. Correspondingly, the values of specificity provided in Table 2 were calculated assuming a possible sensitivity of 100%. A similar approach was also used to calculate positive and negative predictive values. Results from Table 2 indicate a sensitivity for the tolerance-hyperbaric test of 98%, with a negative predictive value of 99%. The relative risk was several orders of magnitude larger than for any other cardiovascular parameter. Sensitivity of the PTE was lower, mainly because of the larger overlap between the distributions for normotensive and hypertensive subjects obtained for this parameter, as represented in the center of Figure 1. Both the maximum and the mean BP load (defined as the average of the 3 values obtained for SBP, MAP, and DBP) had sensitivity \( \geq 50\% \) and very low specificity and positive predictive value. Table 2 also includes results obtained for the daily, diurnal, and nocturnal means as well as for the circadian MESOR of SBP and DBP. Sensitivity, specificity, and positive and negative predictive values were always lower for DBP than for SBP. The worst results were consistently obtained for the nocturnal mean of both SBP and DBP. The circadian MESOR provides slightly better results than the daily mean. In general, the MESOR

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**Figure 2.** Frequency distribution of daily, diurnal, and nocturnal means of SBP for normotensive (top; 1115 BP series) and hypertensive (bottom; 222 BP series) subjects of both genders, sampled by 48-hour ambulatory monitoring.
provides a better estimation of the true 24-hour mean than the average of all BP values. Results were similar for the circadian MESOR of SBP and the BP load. The relative risk was <1 for all parameters in Table 2 except for HBI and PTE.

The characteristics of the test for diagnosing hypertension on the basis of some of the parameters included in Table 2 are described in Figure 4. The graphs in Figure 4 represent sensitivity and specificity determined as a function of different threshold values for the maximum HBI, maximum BP load, and daily, diurnal, and nocturnal means of SBP. The top graph on the left of Figure 4 indicates that, as we increase the threshold value for the maximum HBI, specificity will increase very rapidly. Sensitivity, on the contrary, will smoothly decrease for higher values of HBI. The slopes for increasing specificity and decreasing sensitivity are markedly different. Moreover, this graph also indicates that the range for a threshold value of HBI providing both sensitivity and specificity >90% is very high. These results characterize a highly stable diagnostic test. For the other parameters represented in Figure 4, sensitivity decreases as we increase the threshold value for diagnosis. Specificity, on the contrary, increases very rapidly since, as indicated in Figures 1 and 2, there is a considerable amount of overlap between the distributions on those parameters obtained for normotensive and hypertensive subjects. The values shown in Table 2 somehow represent an average result indicating how much sensitivity can be improved and how much specificity will be lost by increasing sensitivity. Figure 4 shows that the slopes for increasing sensitivity and decreasing specificity while lowering the threshold values of BP load and mean SBP are quite similar and very pronounced. This indicates that a small change in the optimal threshold would result in an important loss in either sensitivity or specificity. These results characterize an unstable and thus poor diagnostic test. The graph on the right bottom of Figure 4 provides the receiver operating characteristic curves for the 5 parameters with sensitivity and specificity also represented in the other graphs of Figure 4. Results from the receiver operating characteristic curves further indicate the advantages of the tolerance-hyperbaric test compared with other parameters obtained from ABPM. The area under the curve is similar for the BP load, the daily mean of SBP, and the diurnal mean of SBP. The poorest results, as also corroborated by Table 2, were obtained for the nocturnal mean of BP.

**Discussion**

The use of a set of new end points in addition to the BP values themselves and the rhythm characteristics derived therefrom has been advocated to improve sensitivity and specificity in diagnosing hypertension and the evaluation of a given subject’s response to treatment. This approach has also been recently extended for the early identification of gestational hypertension and preeclampsia. These hyperbaric end points are the percentage of time an individual’s profile lies above the upper reference limit during 24 hours; the extent of excess, defined as the area delineated by the reference limit and the individual’s profile when it lies outside the reference range; and the time when most of the excess occurs within 24 hours. The HBI represents a better determinant of BP load than the current definition given above and used in most reports on ABPM. Advantages of these end points compared with the BP load or with parameters derived from the use of fixed limits have been previously documented and are also corroborated here by the results in Table 2. Following the previously provided definition for the tolerance-hyperbaric test, we computed the HBI assuming a 24-hour periodicity for BP. While the separate study of nighttime and daytime values for the HBI could also be of interest, previous results...
have indicated that a proper diagnosis of hypertension based on the HBI should include evaluation of the 24-hour span.\(^5,7\) Within the context of pregnant women, it has been shown before\(^21\) that in women with a confirmed diagnosis of gestational hypertension, the HBI was equivalently distributed in each of the three 8-hour intervals in which the 24-hour span was divided. In all trimesters, subjects were found with either 0% or 100% of their BP elevations in each of the 3 time intervals. Moreover, the mean HBI for those 3 time intervals was not different in any trimester of pregnancy.\(^21\) Although further research along these lines should be performed prospectively, those results suggested that ABPM, at least for the early identification of gestational hypertension or preeclampsia, should be extended to include the 24-hour span. Along these lines, a nighttime value for the HBI could be most pertinent when analyzing potentially nondipping subjects. In the present study, the percentages of BP series in the validation sample showing a nondipping status were 11% among those subjects considered normotensives and 13% among those considered hypertensives according to the criteria mentioned above. That is, the percentage of dippers and nondippers was similar in both groups. The results from Table 2 further indicate that the nondippers among those subjects considered normotensives still had no HBI above the threshold value for diagnosis.

The ideal predictive or diagnostic test should be simple and easy to perform, reproducible, and noninvasive, with high sensitivity and a high positive predictive value. The tolerance-hyperbaric test is easy to perform and is noninvasive, since it basically relies on ABPM for 48 hours (instead of the most common span of 24 hours\(^20\)). Advantages of sampling over 48 hours have already been established.\(^5,15\) The test’s sampling requirements are not very demanding. Results in Table 2 were obtained with BP series sampled at half-hour intervals, without apparent loss in sensitivity or specificity. Even though 15-minute sampling has been advocated previously,\(^22\) a larger sampling interval increases compliance and patient acceptability. Moreover, a minimum number of BP measurements is guaranteed by sampling over 2 days instead of only 1 day. Sampling requirements for estimating stable

<table>
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<th>Diagnostic End Point</th>
<th>Max HBI</th>
<th>Max PTE</th>
<th>Max BP Load</th>
<th>Mean BP Load</th>
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<tr>
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HBI indicates hyperbaric index, the area of BP excess (obtained by numerical integration) above a given threshold, here a 95% upper circadian tolerance limit computed (separately for men and women) from data sampled for 48 hours by ambulatory monitoring on a reference population of 148 clinically healthy, normotensive subjects. PTE indicates the percent time of BP excess, within a cycle (here, 24 hours), above the 95% upper circadian tolerance limit. Max HBI and Max PTE indicate the maximum of 3 values, those obtained for SBP, MAP, and DBP, respectively, for each individual BP profile. BP load indicates the percentage of all individual BP readings 140/110/90 mm Hg in SBP/MAP/DBP during the active hours or 120/95/80 mm Hg during the resting hours. Max BP load indicates the maximum of the values obtained for each of the 3 cardiovascular variables. Mean BP load indicates the average of the values obtained for each of the 3 cardiovascular variables. MESOR indicates the midline estimating statistic of rhythm, defined as the 24-hour rhythm-adjusted mean, here obtained by the least-squares fitting of a multiple component curve with periods of 24 and 12 hours to the data from each BP series.
Tolerance intervals are also low. As an indication of reproducibility, results from Table 2 corroborate prospectively those obtained from previous studies. Finally, the diagnostic test provides both a high sensitivity and high positive predictive value, as concluded from the results in Table 2. In summary, the method here described represents a reproducible, noninvasive, and high-sensitivity test for the identification of subjects in need of prophylactic or therapeutic intervention. Limitations of this approach stem from the fact that instrumentation for ABPM, although advanced, is not perfect and still quite expensive. This claim may be true when the analysis of the data provided by these recorders remains limited to the computation of a mean and SD and their inspection by the naked eye. Because of this apparent increase in cost, the use of such monitors has been limited to solving special problems in small groups of patients.

The values of sensitivity and specificity provided in Table 2 need to be considered carefully. If one uses a high constant value for diagnosis of hypertension based, for instance, on the 24-hour mean (135/85 mm Hg for SBP/DBP has been recently established), sensitivity will be very low, as indicated in Figure 4, since just a few of the BP series sampled from young apparently healthy subjects in our study actually exceeded that threshold (Figures 2 and 3). Specificity, on the contrary, will be very high, reflecting the fact that the criteria will identify practically all subjects as normotensive. This situation is graphically displayed in Figure 4, which represents sensitivity and specificity for some of the parameters studied as a function of different threshold values for each endpoint. As indicated above, the pronounced slopes presented in Figure 4 for all parameters except HBI indicate that a small change in the optimal threshold would result in an important loss in either sensitivity or specificity. Moreover, it is important to note that, when relying for diagnosis on the daily average BP, the combination of sensitivity and specificity reaches the highest possible value for 120 mm Hg for SBP (Figure 4) and 68 mm Hg for DBP (not shown). These values are markedly below those currently used for defining hypertension with regard to ABPM. While individuals with BP above those values but could hardly be considered hypertensive, Figure 1 indicates that most of those subjects consistently showed an HBI above the previously established maximum acceptable range of physiological BP excess. By using this threshold for the HBI and the highly restricted criterion of diagnosing hypertension on the basis of only 1 BP series with an HBI above the threshold, Figure 1 indicates a very small overlap between the distributions of maximum HBI obtained for the 2 groups of young volunteers. The lack of overlap results in a test for diagnosing hypertension with high sensitivity and specificity, as indicated in Table 2. Moreover, the changes in sensitivity and specificity as a function of threshold value for the HBI represented in Figure 4 characterize a highly stable diagnostic test. The stability and reproducibility of the HBI as a measure of BP excess can be directly extrapolated from these results.

One may wonder what could really happen with subjects with a consistent HBI above the threshold for diagnosis and mean BP <135/85 mm Hg. In a parallel study using the same approach on pregnant women, the combination of sensitivity and specificity reached the highest possible value for a daily
SBP mean of 108 mm Hg in the first and second trimesters of pregnancy and of 112 mm Hg in the third trimester. The question was then raised as follows: What happens to pregnant women with BP values in the rather extensive area between, for example, 70 and 90 mm Hg for DBP or between 115 and 140 mm Hg for SBP during the second trimester of pregnancy? Results from a prospective study, corroborating an earlier retrospective evaluation of the tolerance-hyperbaric test in pregnancy, indicated that BP elevations above the upper limit of the time-specified tolerance interval exceeding an acceptable physiological amount of excess were consistently associated with a subsequent development of gestational hypertension or even preeclampsia later in pregnancy. Results also indicated that, once a given amount of excess allowing early diagnosis was obtained for any given women, the diagnosis could be maintained on the basis of subsequent evaluations of maximum HBI determined from BP sampled by ABPM at a later gestational age. Moreover, values of maximum HBI below the critical threshold from normotensive pregnant women were consistently associated with uncomplicated pregnancies. The results provided in Table 2 are, however, qualified by the lack of a proper follow-up of the subjects in this study or correlation with target organ damage, and therefore they await further investigation.

Along these lines, increases in BP have already been associated with overt pathology, as in the cases of severe preeclampsia and of increased risk of cardiovascular disease. Correlations have been also described between the HBI and interventricular septal thickness, posterior wall thickness, left ventricular mass (with or without correction for body surface area), and relative wall thickness. The tolerance-hyperbaric test, a combined approach of establishing time-qualified tolerance limits and then assessing the extent and timing of BP elevation, may serve to help in prognosis and diagnosis with a better assessment of health status, to initiate treatment if needed, to time treatment when it is most desirable and least harmful in terms of undesired effects, and to gauge the subject’s response to treatment.

Acknowledgments

This research was supported by grants from Conselleria de Educació e Ordenación Universitaria, Xunta de Galicia (XUGA-32202B97 and PGIDT99PX132202B); Dirección General de Enseñanza Superior, DGES (PM98-0106); and Vicerrectorado de Investigación, University of Vigo.

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Reproducibility of the Hyperbaric Index as a Measure of Blood Pressure Excess
Ramón C. Hermida, José R. Fernández, Artemio Mojón and Diana E. Ayala

Hypertension. 2000;35:118-125
doi: 10.1161/01.HYP.35.1.118

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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