AJH 1993; 6:201S–206S

Defining Normal Ambulatory Blood Pressure

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Providing normal reference values and the means to interpret such values in practice is an urgent issue requiring consensus. Five basic approaches to defining normalcy for 24 h blood pressures (BP) are considered: 1) the relationship of ambulatory blood pressure (ABP) to morbidity and mortality, 2) the relationship of ABP to end-organ involvement, 3) ABP levels in normal populations, 4) the relationship of ABP to clinic BP, and 5) the relationship of 24 h indices to risk. Although there now is considerable evidence demonstrating that ambulatory measurement correlates more strongly with end-organ damage, the first two approaches are scientifically the best. It will be some time before levels of normalcy can be derived. There is a large volume of data on population samples permitting derivation of normalcy for clinical practice. Rounded upper limits of normal can be calculated as 140/90 mm Hg for 24 h ambulatory pressure, 150/90 mm Hg for daytime pressure, and 130/80 mm Hg for nighttime pressure. There are, however, considerable differences for age and gender which need to be taken into consideration. Am J Hypertens 1993;6:201S–206S

KEY WORDS: **Ambulatory blood pressure, normal levels, population studies.**

The importance of establishing normal reference values for blood pressure (BP) levels throughout the 24 h period is of paramount importance if the technique of 24 h ambulatory monitoring is to become established in clinical practice. The most fundamental need of the technique is the establishment of normal reference values. Abnormality cannot be defined without first having established normalcy.

It is evident in Europe that the technique of 24 h ambulatory measurement is rapidly moving away from the research arena, to which it had been confined for the past 15 years. Pharmaceutical companies in particular are providing ambulatory systems for use in general practice. There is little point in lamenting the inevitability of this development by claiming it to be premature; market forces often dictate the pace of progress. What is important, however, is for those with expertise in ambulatory blood pressure (ABP) measurement to provide the essential information necessary to ensure that the technique is used in practice to enhance patient management, and not abused for fiscal advantage. Just as important, we want to ensure that the large amount of data provided by 24 h BP measurement is not misinterpreted because of unfamiliarity with a new methodology.

The need, therefore, for providing normal reference values and the means to interpret such values in practice is an urgent issue requiring consensus. It must be recognized that our present state of knowledge may not permit us to provide the reference values to fulfill the precise dictates that scientific methodology requires. It is important for us to use the knowledge we possess (and this is considerable) to establish guidelines for normalcy in clinical practice, recognizing that we may have to adjust these figures slightly as information from longitudinal studies accumulates. We cannot, however, retreat to a position which was once afforded to us when ambulatory measurement was confined solely to research, by opting to tread scientific waters until the information necessary to make a

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0895-7061/93/$6.00

definitive statement on normalcy becomes available. Research has shown us the important contribution that ambulatory measurement may make to managing hypertensive patients. The exigencies of developments in ambulatory measurement, primarily the technological advances in equipment design and research, have made a working definition of normal 24 h BPs mandatory.

REVIEW OF AVAILABLE METHODS

The following are five basic approaches to defining normalcy for 24 h BPs that can be considered.

Relationship of ABP to Morbidity and Mortality First, we can relate BP to risk of heart attack, stroke, and death in longitudinal studies. The classical epidemiological approach, used in studies such as the Framingham[1] and Multiple Risk Factor Intervention Trial[2] studies relating risk to the level of clinic BP, is the ideal one to adopt for ABP. There has been, however, only one such study performed to date. This study was first reported by Dr. Maurice Sokolow's group in 1964,[3] and subsequently in the intervening years.[4] This study showed that the relationship between risk and BP is steeper for ABP than for clinic pressure. The results of the study were consistent with the prediction that true BP would be distinct from clinic BP.[5]

The Office Versus Ambulatory (OvA) trial in Europe is attempting longitudinally to relate the outcome of managing BP on the basis of clinic BP *v* ABP.[6] The assumption, which awaits confirmation, is that hypertensive subjects managed on the basis of ABPs will have at least as good an outcome as those managed on clinic BP. In addition, subjects may have the advantage of needing less antihypertensive medication, and therefore, may enjoy a better quality of life.

In the Syst-Eur trial,[7] another multicenter longitudinal study examining antihypertensive medication in isolated systolic hypertension, a side project on ABP measurement should provide information on the relationship between 24 h ambulatory measurement and the risk in elderly subjects. There is evidence that patients diagnosed as having isolated systolic hypertension by conventional measurement may not experience the phenomenon when BP is measured over the 24 h period.[8] It is hoped that the implications of this observation will be demonstrated in the Syst-Eur trial.

The approach of relating 24 h ABP to outcome is the most ideal one from a scientific viewpoint. This should enable us to relate actual levels of 24 h BP and variations of the pattern of 24 h pressure, such as blunting of the normal nocturnal pattern,[9] to the ultimate cardiovascular consequences of hypertension. The major problem with longitudinal studies is that they take time, usually many decades, before providing answers. Moreover, the interpretation of results is not always as straightforward as it might seem to be; study design, the effects of other risk factors, and management strategies often prove to be confounding factors.

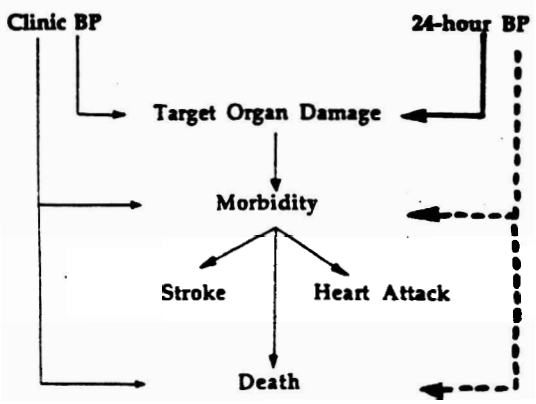

FIGURE 1. *Plan of the relationships of clinic blood pressure and ambulatory BP to target organ damage, morbidity, and mortality. Left-hand arrows indicate the established relationship between clinic BP and target organ damage, and morbidity and mortality. Right-hand arrows indicate the established relationship of 24 h BP with target organ damage and the likely, but not as yet fully proven, relationship with morbidity and mortality.*

Relationship of ABP to End-Organ Involvement Another approach in relating 24 h ABP to risk is to substitute the surrogate end-points of end-organ involvement for the classical end-points of death and morbidity. This technique would establish an association with risk in a shorter period of time.

This approach has been followed in a number of studies in which the relationship of ABP to end-organ involvement as determined in the heart,[10] kidney,[11] blood vessels,[12,13] and brain[14] has been shown to be superior to clinic blood pressure. Indeed, with the increasing development of techniques for assessing end-organ involvement in hypertension, it can only be a matter of time before the evidence becomes irrefutable However, two important issues need to be clarified.

First, one can ask if it is acceptable to substitute surrogate end-points for the more substantial end-points of morbid events and death. In response, we might apply the scheme of reasoning outlined in Figure 1. Clinic BP depicted on the left predicts end-organ involvement in addition to morbidity and death. Therefore, associating end-organ involvement with morbidity and death may be seen as a stepping stone to the ultimate cardiovascular insults of stroke, heart attack and death. If we accept that ABP is a better predictor of end-organ involvement (shown on the right) than clinic BP, it is difficult to escape the conclusion that ABP also must provide us with a sensitive means of predicting outcome in terms of morbidity and death,

TABLE 1. UPPER LIMITS OF NORMAL BPS DERIVED FROM THE ALLIED IRISH BANK (AIB) STUDY AND THE ANALYSIS OF INTERNATIONAL POPULATION STUDIES

	AIB Study (mm Hg)	International Study (mm Hg)
24 h BP	140/86	142/91
Daytime BP	148/92	149/94
Nighttime BP	128/77	133/80
Office BP	149/96	142/91

Data from personal communications with J. Staessen and colleagues and from E. O'Brien et al.[20]

although we have only minor scientific evidence to support this point.

The second issue is to determine which of the many indices of 24 h BP[15,16] is the most sensitive in terms of predicting risk. Our questions might lead us to find that the nocturnal,[17] white-coat,[18] or matinal[19] windows, for example, are more sensitive predictors of risk than the absolute levels of pressure. The answers are, for the moment, out of reach.

ABP Levels in Normal Populations Another alternative to relying on longitudinal studies is to determine the distribution of 24 h BPs in normal population or community samples. Generally, samples will define a distribution according to percentiles or standard deviations above or below the mean values for a given population. This approach has been widely utilized for different nationalities and consequently, reference tables showing normal levels for different ages and gender have been produced.[20–23]

A metaanalysis of data from 19 studies performed in Europe, the United States, the Far East, and Australia has been performed by Staessen et al.[24] Many of the studies included in this analysis were presented at the Second International Consensus Meeting on 24 h ABP Monitoring (ABPM) in Dublin in September 1991.[25] More recently, Staessen et al have reanalyzed unedited ambulatory recordings for 6959 subjects from 23 centers around the world (personal communication). The major disadvantage of such population studies is that the normalcy of the population is dependent on how subjects are included or excluded from the sample. The evidence that has accumulated from a number of well-conducted studies, however, is sufficient to allow at least a good working definition of normal 24 h pressures across age and gender. For example, in the Allied Irish Bank (AIB) study, using mean + 2 SD as the upper limit of normal, values are obtained for a 24 h pressure of 140/86 mm Hg, 148/94 mm Hg for daytime pressure, and 128/77 mm Hg for nighttime pressure in subjects in whom the upper limit of normal for office pressure was 149/96 mm Hg. In 4930 subjects in the recent analysis by Staessen et al, the comparative figures in 4930 normotensive subjects were 142/91, 149/94, and 133/80 mm Hg, respectively for 24 h, daytime, and nighttime pressures (personal communication). The small differences between a relatively homogeneous, unselected national sample and a large sample of different races and nationalities may be accounted for on the basis of the office BP at entry, which is slightly higher in the international sample (Table 1).Data from these studies allow us to produce, with some confidence, a working definition of normalcy which would have 140/90 mm Hg as the upper limit of normal for 24 h pressure, 150/90 mm Hg for daytime pressure, and 130/80 mm Hg for nighttime pressure.

However, in the AIB study in which only hypertensive subjects receiving drug treatment were excluded, it is evident that there are considerable differences for age and gender (Table 2). If we take the extremes for age and gender into consideration, for a woman in the 17 to 29 years old age range, the upper limit of daytime pressure would be 134/86 mm Hg and 120/69 mm Hg for nighttime pressure, whereas for a man in the 50 to 79 years old age range the corresponding values would be 156/102 mm Hg and 139/86 mm Hg, respectively. Clearly, it makes little scientific sense to treat these two groups as if they were the same, although this is what has been done with conventional office measurement. Therefore, it is important to differentiate at least between men and women when making clinical decisions based on the normalcy of 24 h ambulatory pressures.

Relationship of ABP to Clinic BP A further approach is to relate ABP to clinic BP. Because the risk for clinic BP is known, we can extrapolate how ambulatory pressure relates to risk. Calculating the regression lines between daytime ABP and office readings, Baumgart concluded that if 140/90 mm Hg is taken as the upper limit of normal for office BP, the corresponding daytime mean value for ambulatory measurement would be > 135/85 mm Hg.[26] The weakness in this approach is the assumption that the risk of a given clinic pressure holds for the individual measurement. Unlike the risk for groups, the variation in risk for individuals is well established. As stated previously, the relationship within age groups and gender needs to be analyzed carefully.

Palatini and Pessina followed the same line of reasoning, attempting to relate ambulatory levels to WHO recommendations for conventional office measurement of an upper limit of 140/90 mm Hg.[27] Based on the data of this study, the daytime ambulatory equivalent of the WHO upper limit of 140/90 mm Hg was 125.8/83.3 mm Hg for daytime pressure and 121.6/80.4 mm Hg for 24 h pressures. A weakness in

TABLE 2. MEAN ± SD, MEDIAN, AND 95TH PERCENTILES AND COEFFICIENTS OF VARIATION FOR OFFICE AND 24 h AMBULATORY BLOOD PRESSURE IN 815 PEOPLE BY AGE (AIB Study[20])

	Men				All Men	Women				All Women	Both
	17–29 (107)	30–39 (123)	40–49 (109)	50–79 (60)	17–79 (399)	17–29 (174)	30–39 (149)	40–49 (55)	50–79 (35)	17–79 (416)	17–79 (515)
Office measurements											
SBP (mm Hg)											
Mean ± SD	121 ± 12	122 ± 11	125 ± 16	133 ± 15	124 ± 14	110 ± 11	113 ± 10	121 ± 17	130 ± 24	115 ± 15	119 ± 15
Median	121	122	122	130	122	110	113	116	123	114	118
95th percentile	140	142	153	160	150	130	131	154	193	139	145
Coeff. var.	10	9	13	11	11	10	9	14	19	13	13
DBP (mm Hg)											
Mean ± SD	73 ± 9	77 ± 8	81 ± 10	85 ± 11	78 ± 10	71 ± 8	72 ± 8	78 ± 9	81 ± 12	73 ± 9	76 ± 10
Median	73	77	80	84	78	70	72	76	80	72	75
95th percentile	89	90	99	110	96	83	84	96	103	88	93
Coeff. var.	12	10	13	13	13	11	11	12	15	12	13
Ambulatory measurements											
Daytime											
SBP (mm Hg)											
Mean ± SD	129 ± 8	128 ± 9	129 ± 12	132 ± 12	129 ± 10	118 ± 8	117 ± 8	121 ± 12	126 ± 18	118 ± 10	124 ± 12
Median	129	128	127	134	128	118	116	120	122	118	123
95th percentile	144	143	150	155	146	131	132	150	177	135	143
Coeff. var.	6	7	9	9	8	7	7	10	14	9	9
DBP (mm Hg)											
Mean ± SD	77 ± 7	80 ± 6	83 ± 9	84 ± 9	81 ± 8	74 ± 6	75 ± 7	76 ± 9	78 ± 9	75 ± 7	78 ± 7
Median	77	80	82	85	80	73	74	74	76	74	77
95th percentile	88	91	98	103	92	83	85	94	97	88	91
Coeff. var.	8	8	10	11	10	8	9	12	12	10	10
Nighttime											
SBP (mm HG)											
Mean ± SD	110 ± 9	108 ± 8	109 ± 12	113 ± 13	110 ± 10	102 ± 9	101 ± 9	103 ± 11	108 ± 12	102 ± 9	106 ± 11
Median	110	108	107	110	109	101	100	101	106	101	105
95th percentile	125	121	128	140	126	117	116	125	133	120	123
Coeff. var.	8	8	11	11	9	9	8	10	11	9	10
DBP (mm Hg)											
Mean ± SD	59 ± 6	62 ± 6	66 ± 10	68 ± 9	63 ± 8	57 ± 6	58 ± 7	61 ± 8	63 ± 7	58 ± 7	61 ± 8
Median	59	61	65	66	62	56	57	59	63	57	60
95th percentile	70	71	80	90	77	68	71	77	75	72	75
Coeff. var.	10	9	15	14	13	10	11	13	10	12	13
24 h											
SBP (mm Hg)											
Mean ± SD	123 ± 8	121 ± 8	122 ± 11	126 ± 12	122 ± 10	112 ± 7	111 ± 8	114 ± 10	120 ± 15	113 ± 9	118 ± 11
Median	123	120	122	125	122	112	110	112	118	112	117
95th percentile	136	133	136	151	137	125	126	141	160	129	134
Coeff. var.	6	7	9	9	8	7	7	9	13	8	9
DBP (mm Hg)											
Mean ± SD	71 ± 5	74 ± 5	77 ± 8	79 ± 9	75 ± 7	68 ± 5	69 ± 6	71 ± 8	73 ± 8	69 ± 6	72 ± 7
Median	71	74	76	77	74	67	68	69	72	68	71
95th percentile	81	82	89	98	86	78	78	87	87	82	84
Coeff. var.	8	7	11	11	10	8	9	11	10	9	10

Numbers are indicated in parentheses.

SBP, systolic blood pressure; DBP, Diastolic blood pressure; Coeff. var., coefficient of variation.

this study is that the relationship between ambulatory and office measurements is derived from 522 subjects comprised of normotensives, borderline, mild, moderate, and severe hypertensives. Other weaknesses are that the hypertensive subjects greatly outnumber the normotensive subjects, the hypertensive subjects are older than the normotensive subjects, and the ambulatory measurements were performed with three ambulatory systems, at least one of which had not met the current criteria for accuracy.[28] The conclusion that the disparity between office and ABP was unrelated to age and gender would need to be examined more closely.

Relationship of 24 h Indices to Risk It is possible to examine the relationship of a number of indices of 24 h BP to risk. These indices might include measures of BP load on the 24 h pressure profile,[29] or measures of excessive reduction in BP (leese effect[30]), and measures of the variability of 24 h BP, such as standard deviations, coefficients of variation, cumulative sums, Fourier analysis, and spectral analysis. Any of the latter measures may prove to be more sensitive predictors of cardiovascular risk than absolute levels of BP.[15,16,31]

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