# Ambulatory blood pressure in normotensive and hypertensive subjects: results from an international database

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**Objective:** To delineate more precisely an operational threshold for making clinical decisions based on ambulatory blood pressure (ABP) measurement by studying the ABP in subjects who were diagnosed as either normotensive or hypertensive by conventional blood pressure (CBP) measurement.

**Subjects:** Twenty-four research groups recruited 7069 subjects. Of these, 4577 were normotensive (CBP ≤140/90 mmHg), 719 were borderline hypertensive (systolic CBP 141–159 mmHg or diastolic CBP 91–94 mmHg) and 1773 were definitely hypertensive. Of the subjects in the last of these categories, 1324 had systolic

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hypertension (systolic CBP ≥160 mmHg) and 1310 had diastolic hypertension (diastolic CBP ≥95 mmHg). Combined systolic and diastolic hypertension was present in 861 subjects. Hypertension had been diagnosed from the mean of two to nine (median two) CBP measurements obtained at one to three (median two) visits.

**Results:** The 95th centiles of the ABP distributions in the normotensive subjects were (systolic and diastolic, respectively) 133 and 82 mmHg for 24-h ABP, 140 and 88 mmHg for daytime ABP and 125 and 76 mmHg for night-time ABP, respectively. Of the subjects with systolic hypertension, 24% had 24-h systolic ABP <133 mmHg. Similarly, 30% of those with diastolic hypertension had 24-h diastolic ABP <82 mmHg. The probability that hypertensive subjects had 24-h ABP below these thresholds tended to increase with age and was two- to fourfold greater if the CBP of the subject had been measured at only one visit and if fewer than three CBP measurements had been averaged for establishing the diagnosis of hypertension. By contrast, for each 10-mmHg increment in systolic CBP, this probability decreased by 54% for 24-h systolic ABP and by 26% for 24-h diastolic ABP, and for each 5-mmHg increment in diastolic CBP it decreased by 6 and 9%, respectively. In comparison with 24-h ABP, the overlap in the daytime and night-time ABP between normotensive and hypertensive subjects was of similar magnitude and was influenced by the same factors.

**Conclusions:** The ABP distributions of the normotensive subjects included in the present international database were not materially different from those in previous reports in the literature. One-fifth to more than one-third of hypertensive subjects had an ABP which was below the 95th centile of the ABP of normotensive subjects, but this proportion decreased if the hypertensive subjects had shown a higher CBP upon repeated measurement. The prognostic implications of elevated CBP in the presence of normal ABP remain to be determined.

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## Introduction

Auscultatory blood pressure measurements made by an observer using a sphygmomanometer are part of the clinical routine worldwide. The relationship of conventional blood pressure (CBP) measurements to the incidence of cardiovascular complications is well established, as they have guided patient recruitment and experimental therapy in all outcome trials on the treatment of hypertension [1]. In spite of their proven record, CBP readings are subject to the so-called white-coat effect [2,3] and are characterized by a high variability [4], limiting their reproducibility. CBP measurements are often made in an artificial medical environment and do not necessarily reflect the habitual blood pressure of a subject. Ambulatory blood pressure (ABP) measurements, by contrast to CBP readings, provide an estimate of the blood pressure of the subject throughout the day [5–9]. They are free of the white-coat effect [2,3] and of observer bias, and are therefore more reproducible [10,11]. However, the widespread clinical application of ABP monitoring requires the definition of operational thresholds [12]. Preliminary proposals [13–19] have been published, but continuing research has not yet reached a widely endorsed consensus [9].

A recent meta-analysis [16] pooled statistics from 23 published studies of 3476 normotensive subjects. The ABP measurements in those studies had been processed using different mathematical techniques, various definitions of day and night and different editing criteria for the exclusion of invalid readings. In an attempt to delineate more precisely an operational threshold for ABP monitoring, the objective of the present study was to constitute and analyse an international database of ABP recordings. The perceived advantage of studying recordings from individual subjects, rather than the summary statistics of published reports, was that the same mathematical approach [20], the same quality standards and a uniform definition of day and night could be applied to 7069 recordings from 24 clinical research units. The database also provided the means to contrast the distributions of the ABP measurements from subjects who were either normotensive or hypertensive according to conventional sphygmomanometry [21,22] and to examine how many hypertensive subjects would have ABP within the normotensive range if certain thresholds were applied.

## Methods

Experts in ABP monitoring were identified from the list of attendants of the Second International Consensus Meeting on 24-Hour Ambulatory Blood Pressure Measurement (Dublin, 23 September 1991; organized by Professor E.T. O'Brien), from computer searches of the English, French and German literature from January 1980 to June 1991 using the Medical Literature Analysis and Retrieval System, and through contacts at international meetings. A total of 33 research groups were invited to make available for analysis ABP recordings and relevant clinical information. Twenty-four centres co-operated, six units did not have suitable data and three either did not reply or decided not to take part.

Unedited ABP recordings were available from 7595 people. Of these, 526 subjects were excluded because there was no record of their CBP, because their ABP recording covered <20 h, because fewer than 10 readings were available for the computation of average daytime blood pressure or because fewer than five readings were available for night-time blood pressure.The study group thus totalled 7069 subjects.

In agreement with current medical practice [21,22], normotension and hypertension were defined solely on the basis of CBP measurements. Normotension was defined as CBP ≤140/90 mmHg. Borderline hypertension was present if either systolic CBP was 141–159 mmHg or diastolic CBP was 91–94 mmHg, or both. Definite hypertension was defined as systolic CBP ≥160 mmHg or diastolic CBP ≥95 mmHg, or both.

The vast majority of the hypertensive subjects had been examined on several occasions. However, the number of visits for which CBP readings could be made available for the present analysis varied from one to three. The CBP was the average of at least two measurements in all subjects with borderline or definite hypertension. By contrast, some normotensive subjects had been examined once only and, in a few normotensive subjects, one blood pressure reading within the normotensive range had been deemed sufficient to exclude hypertension.

In all subjects ABP had been recorded non-invasively either with auscultatory (Accutracker II [23], Del Mar Avionics Pressurometer P4 [24], Novacor Diasys 200R [25], Oxford Medilog [26], SpaceLabs 5200 [27] or Takeda A & D TM-2420 [28]) or oscillometric (SpaceLabs 90202 [29] or 90207 [29]) devices. Whenever the ABP had been recorded with both techniques (using the Colin Medical ABPM-630 [30]) only the oscillometric measurements were used for the present analysis. All ABP recordings were truncated so that their total duration did not exceed 24 h. In order to eliminate the transition periods between daytime activity and sleep, during which blood pressure often changes rapidly, daytime was defined as 1000–2000 h and night-time as 0000–0600 h [15,20]. To contrast the distributions of ABP among normotensive and hypertensive subjects, subjects with definite hypertension were subdivided into two partially overlapping groups: subjects with systolic hypertension (systolic CBP ≥160 mmHg) and subjects with diastolic hypertension (diastolic CBP ≥95 mmHg).

DBMS/COPY (Conceptual Software Inc., Houston, Texas, USA) was used to convert the available data to a database compatible with the SAS format (SAS Institute Inc., Cary, North Carolina, USA). After conversion all ABP recordings were processed by the same computer program, using SAS software. The ABP recordings were not edited. Within-subject means of the ABP measurements were weighted for the interval between successive blood pressure readings [20]. Exact confidence intervals for proportions were computed using STATXACT software (CYTEL Software Corporation, Cambridge, Massachusetts, USA). Group means were compared using Student's t-test, and proportions were compared using a standardized normal deviate [31]. Multiple logistic regression [31,32] was used to identify the factors determining the probability that hypertensive subjects had ABP below the 95th centile of the corresponding distribution in normotensive subjects.

## Results

### Characteristics of the study population

The study population included 7069 subjects (3600 male, 3469 female; mean ± SD age 48 ± 16 years, range 10–99). The age distribution was similar among men and women: 2.7% were aged 10–19 years, 13.1% were 20–29, 14.5% were 30–39, 27.4% were 40–49, 17.8% were 50–59, 15.3% were 60–69 and 9.2% were ≥70.

Body mass index was available in 5052 subjects (mean ± SD 24.6 ± 4.1 kg/m$^2$, range 14.0–52.7). The number of subjects for whom data were contributed by each investigator, the criteria by which these participants had been recruited, and their age and sex distributions are summarized in Table 1.

### Blood pressure measurements

The median number of visits for which CBP readings had been made available for the present analysis was two throughout the database and two among the 1776 subjects with definite hypertension (Table 1). CBP was the average of two readings in 2519 persons, three readings in 3551, four in 262, five in 396 and nine in 110 subjects (Table 1). In 231 subjects only one sphygmomanometric blood pressure reading had been obtained, which was found to be normal. The median number of CBP readings averaged for the present analysis was three in all 7069 subjects, and two in the 1776 subjects with definite hypertension.

**Table 1.** Characteristics of the study population.

| Investigator | n | Subjects | Age (years) | Men (%) | NBP (%) | Device(s) used | Visits | CBP |
|---|---|---|---|---|---|---|---|---|
| Baumgart | 103 | S (r) | 24 (20–29) | 50 | 92 | $S_2$, $S_7$ | C 2 (6) | S (4) |
| De Gaudemaris | 158 | E (v,d,n) | 41 (15–75) | 49 | 100 | $S_5$, $ND_2$ | S 1 (3) | S (3) |
| De Cort | 352 | P (v) | 72 (59–97) | 42 | 49 | $S_7$ | P 2 (12) | S (3) |
| Degaute | 45 | E,S (v) | 35 (19–72) | 100 | 76 | OM | C 1 (3) | S (3) |
| Enström | 159 | C (r,d) | 52 (40–64) | 100 | 45 | $S_5$ | P 3 (1) | R (3) |
| Fagard | 37 | P (v,h) | 41 (26–56) | 62 | 3 | $S_5$ | C 2 (10) | R (5) |
| Gosse | 231 | E (v,n) | 39 (21–74) | 61 | 79 | $S_5$, $ND_2$ | S 1 (1) | S (1) |
| Gourlay | 76 | C (r) | 47 (21–68) | 59 | 64 | $A_{II}$ | S 1 (2) | S (2) |
| Hayashi | 311 | ? (v,d,n) | 40 (15–86) | 60 | 87 | $CM_6$ | S 3 (1) | S (3) |
| Imai | 429 | C (r) | 55 (12–72) | 31 | 77 | $CM_6$ | S 1 (2) | S (2) |
| James | 80 | E (v,d,n) | 30 (21–50) | 0 | 100 | $S_5$, $S_7$ | S 1 (5) | S (5) |
| Kawasaki | 700 | ? (v,d) | 54 (12–72) | 57 | 78 | $CM_6$ | S 2 (6) | S (3) |
| Kuschnir | 110 | P (h) | 55 (39–74) | 45 | 0 | T | C 3 (9) | S (9) |
| Kuwajima | 99 | P (v) | 78 (62–99) | 56 | 43 | $CM_6$ | S 1 (3) | S (3) |
| Liu Lisheng | 26 | E (v,d,n) | 65 (44–76) | 85 | 100 | $S_2$ | C 3 (1) | S (3) |
| Middeke | 82 | P (v) | 39 (16–77) | 46 | 50 | $S_2$, $S_7$ | C 1 (5) | S (5) |
| O'Brien | 896 | E (v) | 46 (29–51) | 48 | 90 | $S_2$, $S_7$ | S 2 (2) | S (2) |
| O'Brien | 938 | P (v,h) | 50 (16–81) | 49 | 0 | $S_2$, $S_7$ | C 2 (2) | S (2) |
| Omboni | 9 | P (v) | 43 (21–64) | 44 | 100 | $S_7$ | C 1 (3) | S (3) |
| Otsuka | 321 | C (v,d,n) | 38 (16–89) | 41 | 90 | $CM_6$ | S 1 (3) | S (3) |
| Otsuka | 151 | S (v,d,n) | 20 (18–27) | 0 | 99 | $CM_6$ | S 1 (3) | S (3) |
| Otsuka | 122 | P (v) | 52 (15–81) | 45 | 0 | $CM_6$ | C 1 (3) | S (3) |
| Palatini | 214 | P (v) | 31 (10–81) | 86 | 17 | $S_5$, D, T | C 1 (3) | S (3) |
| Pieper | 159 | E (v) | 43 (30–60) | 89 | 99 | $S_5$ | S 2 (6) | S (4) |
| Staessen | 739 | C (r) | 50 (20–87) | 48 | 79 | $S_2$ | H 2 (10) | S (3) |
| Staessen | 36 | P (v,h) | 50 (19–69) | 58 | 14 | $S_2$, $S_7$ | C 2 (10) | S (5) |
| Staessen | 161 | E,S (v,d) | 34 (19–62) | 52 | 76 | $S_2$, $S_7$ | C 2 (10) | S (5) |
| Verdecchia | 145 | E (v,d,n) | 46 (16–91) | 53 | 100 | $S_2$, $S_5$, $S_7$ | C 1 (3) | S (3) |
| Weizhong Zhang | 54 | E (v,d,n) | 47 (22–76) | 50 | 100 | $S_2$ | C 1 (2) | S (2) |
| Zachariah | 126 | C (v,d,n) | 49 (21–84) | 44 | 95 | D | S 2 (2) | S (2) |

**Subjects:** C, community; E, employees (white- or blue-collar); P, patients; S, students. Selection criteria are given in parentheses: d, subjects with concomitant disease excluded; h, borderline hypertension, i.e. 140<systolic blood pressure<160 mmHg or 90<diastolic blood pressure<95 mmHg or definite hypertension, i.e. systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg; n, normotension, i.e. systolic blood pressure ≤140 mmHg and diastolic blood pressure ≤90 mmHg; r, random sample; v, volunteers. **Age:** mean (range). **NBP**, percentage of subjects with normal blood pressure upon conventional measurement. **Devices:** $A_{II}$, Accutracker II; $CM_6$, Colin Medical ABPM-630; D, Del Mar Avionics Pressurometer P4; OM, Oxford Medilog; $ND_2$, Novacor DIASYS 200R; $S_5$, $S_2$ and $S_7$, SpaceLabs 5200, 90202 and 90207; T, Takeda A & D TM-2420. **Visits:** the number of visits (total number of conventional blood pressure readings) available for analysis for each subject. The letter indicates where the blood pressure readings were obtained: S, special centre; C, clinic; H, home; P, surgery of general practitioner. **CBP**, conventional blood pressure readings (number of readings averaged for the present analysis): R, recumbent, S, sitting.

**Table 2.** Blood pressure in normotensive subjects and in those with borderline and definite hypertension.

| | Normotensive | Borderline hypertensive | Definite hypertensive |
|---|---|---|---|
| n | 4577 | 719 | 1773 |
| Men (%) | 48.6 | 61.6 | 52.7 |
| Age (years) | 45±15* | 53±18 | 52±15 |
| Systolic blood pressure (mmHg) | | | |
| Conventional | 119±12* | 146±7 | 169±18 |
| 24-h Ambulatory | 116±10* | 128±11 | 143±17 |
| Daytime | 122±11* | 134±12 | 149±18 |
| Night-time | 106±11* | 117±14 | 130±19 |
| Diastolic blood pressure (mmHg) | | | |
| Conventional | 73±9* | 83±9 | 102±15 |
| 24-h Ambulatory | 70±7* | 76±8 | 86±11 |
| Daytime | 75±8* | 81±9 | 91±12 |
| Night-time | 61±8* | 68±9 | 77±12 |

Age and blood pressure are expressed as means±SD. *$P<0.05$, versus borderline and definite hypertensive.

The technique of ABP measurement used was oscillometric in 5572 subjects, auscultatory in 1417 and either auscultatory (using the SpaceLabs 5200) or oscillometric (using the SpaceLabs 90202) in 80 (those data contributed by James G; Table 1).

A total of 4577 subjects had CBP within the normotensive range (Table 2), 582 of whom (Staessen JA, Table 1) had had their CBP measured in the relaxed home environment. However, excluding these subjects from the database did not substantially alter the distributions of ABP measurements among the normotensive subjects (Table 3). These distributions were also unchanged by the exclusion of 44 adolescents (aged <18 years).

The database included 2492 hypertensive subjects, of whom 719 had a borderline elevation of systolic or diastolic CBP, or both, and 1773 were definitely hypertensive (Table 2). Of the latter, 1324 had systolic and 1310 had diastolic hypertension. Both systolic and diastolic

**Table 3.** Ambulatory blood pressure in normotensive subjects, including and excluding 582 subjects in whom conventional blood pressure had been measured at home.

| | Blood pressure (mmHg) | |
|---|---|---|
| | Systolic | Diastolic |
| All subjects (n = 4577) | | |
| 24-h Ambulatory | 116±10 (133, 142) | 70±7 (82, 88) |
| Daytime | 122±11 (140, 149) | 75±8 (88, 94) |
| Night-time | 106±11 (125, 140) | 61±8 (76, 83) |
| Excluding subjects examined at home (n = 3995) | | |
| 24-h Ambulatory | 116±10 (133, 143) | 70±7 (82, 88) |
| Daytime | 122±11 (140, 149) | 75±8 (88, 94) |
| Night-time | 106±12 (126, 142) | 62±8 (77, 83) |

Values are expressed as means±SD (95th, 99th centiles).

**Table 4.** Blood pressure measurements in three subgroups of subjects with definite hypertension.

| | Hypertensive | | |
|---|---|---|---|
| | Isolated systolic | Isolated diastolic | Systolic and diastolic |
| n | 463 | 449 | 861 |
| Men (%) | 50.3 | 65.3 | 47.4 |
| Age (years) | 58±18 | 43±13 | 52±13 |
| Systolic blood pressure (mmHg) | | | |
| Conventional | 173±13 | 148±8 | 178±16 |
| 24-h Ambulatory | 141±14 | 135±17 | 147±17 |
| Daytime | 147±15 | 141±18 | 154±18 |
| Night-time | 130±18 | 122±18 | 135±19 |
| Diastolic blood pressure (mmHg) | | | |
| Conventional | 83±10 | 104±7 | 111±11 |
| 24-h Ambulatory | 80±10 | 85±10 | 90±11 |
| Daytime | 85±12 | 91±11 | 95±12 |
| Night-time | 72±11 | 75±11 | 81±12 |

Values are expressed as means±SD. Hypertension was defined as blood pressure ≥160/95 mmHg upon conventional blood pressure measurement.

hypertension were present in 861 subjects, 463 subjects had isolated systolic hypertension and 449 had isolated diastolic hypertension (Table 4).

As expected, ABP was, on average, higher in the hypertensive than in the normotensive subjects (Table 2). The mean ABP throughout the day and the corresponding 95% confidence interval and SD are shown for the normotensive subjects, by country, in Figs 1 and 2. The 95th centiles of the ABP distributions in the normotensive subjects were (systolic and diastolic, respectively) 133 and 82 mmHg for 24-h blood pressures, 140 and 88 mmHg for daytime blood pressures and 125 and 76 mmHg for night-time blood pressures (Table 5).

## Ambulatory blood pressure in normotensive compared with hypertensive subjects

By definition there was a difference of ≥20 mmHg in systolic CBP between the 4577 normotensive subjects and the 1324 subjects with systolic hypertension. Indeed, in the former the distribution had been truncated at 140 mmHg and in the latter at 160 mmHg (Fig. 3). Similarly, diastolic CBP was ≥5 mmHg higher in the subjects with diastolic hypertension (n =1310) than in the normotensive subjects. Nevertheless, there was considerable overlap between the normotensives and hypertensives when their ABP distributions were analysed (Fig. 3, Table 5). For instance, the 95th centile of 24-h systolic ABP in normotensive subjects (133 mmHg) was not exceeded by 24% of the subjects with systolic hypertension

**Table 5.** Percentages of hypertensive subjects with conventional blood pressure above and ambulatory blood pressure below specified thresholds.

| | | Hypertensive subjects (%) | |
|---|---|---|---|
| | Threshold (mmHg) | Conventional systolic blood pressure ≥160 mmHg (n = 1324) | Conventional diastolic blood pressure ≥95 mmHg (n = 1310) |
| 24-h Ambulatory blood pressure | | | |
| Systolic | | | |
| 90th Centile | <129 | 15 | 23 |
| 95th Centile | <133 | 24 | 32 |
| 99th Centile | <142 | 47 | 54 |
| Mean + 2SD | <136 | 31 | 39 |
| Mean + 3SD | <146 | 57 | 62 |
| Diastolic | | | |
| 90th Centile | <79 | 27 | 21 |
| 95th Centile | <82 | 37 | 30 |
| 99th Centile | <88 | 57 | 44 |
| Mean + 2SD | <84 | 44 | 38 |
| Mean + 3SD | <91 | 66 | 61 |
| Daytime ambulatory blood pressure | | | |
| Systolic | | | |
| 90th Centile | <136 | 18 | 24 |
| 95th Centile | <140 | 26 | 34 |
| 99th Centile | <149 | 46 | 53 |
| Mean + 2SD | <143 | 34 | 42 |
| Mean + 3SD | <154 | 59 | 62 |
| Diastolic | | | |
| 90th Centile | <85 | 32 | 25 |
| 95th Centile | <88 | 41 | 34 |
| 99th Centile | <94 | 57 | 51 |
| Mean + 2SD | <91 | 47 | 40 |
| Mean + 3SD | <98 | 70 | 65 |
| Night-time ambulatory blood pressure | | | |
| Systolic | | | |
| 90th Centile | <120 | 27 | 35 |
| 95th Centile | <125 | 37 | 46 |
| 99th Centile | <140 | 68 | 72 |
| Mean + 2SD | <128 | 44 | 53 |
| Mean + 3SD | <140 | 67 | 71 |
| Diastolic | | | |
| 90th Centile | <72 | 36 | 32 |
| 95th Centile | <76 | 47 | 45 |
| 99th Centile | <83 | 66 | 63 |
| Mean + 2SD | <78 | 52 | 49 |
| Mean + 3SD | <86 | 73 | 69 |

Thresholds were determined from ambulatory blood pressure in 4577 normotensive subjects.

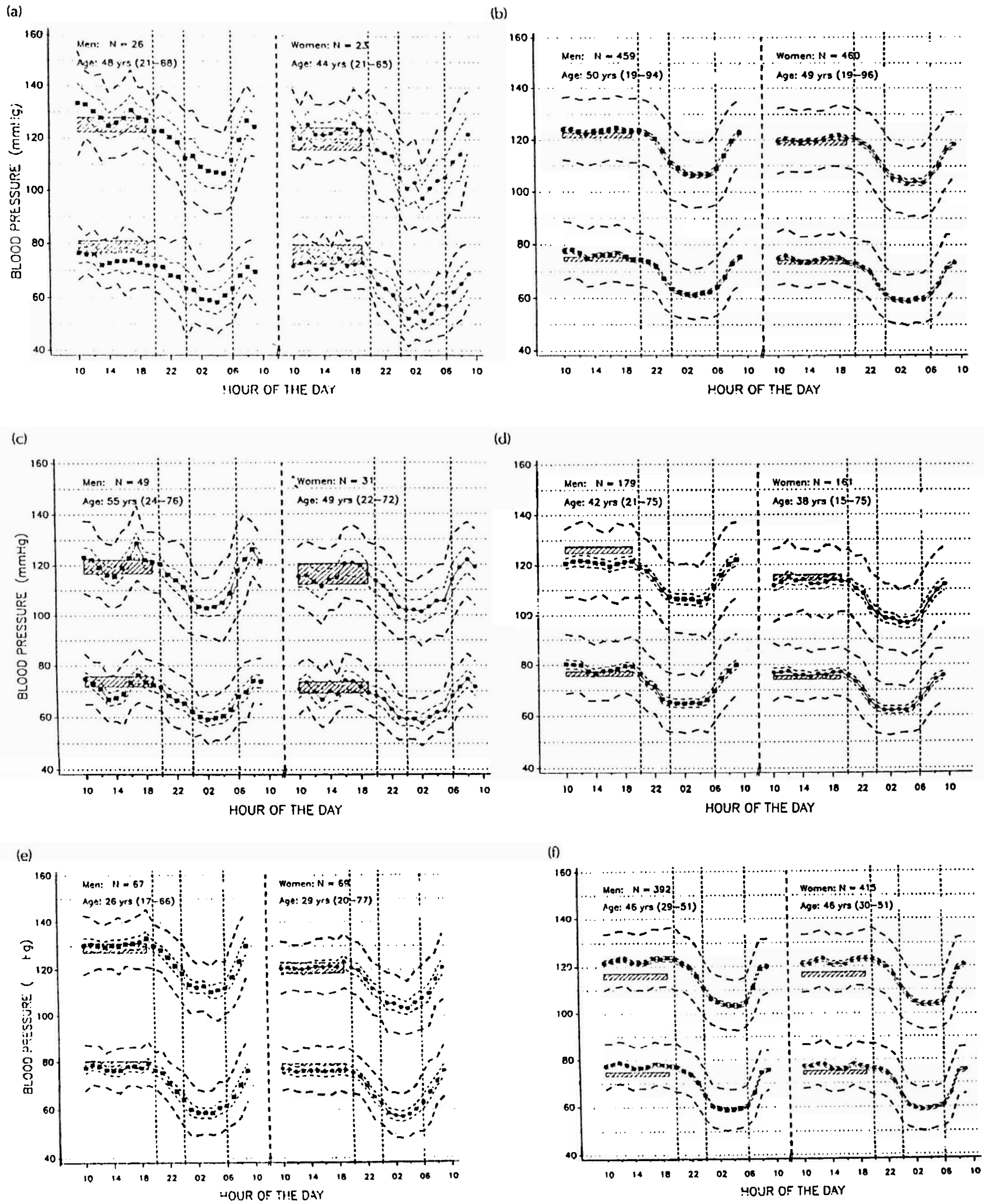


**Fig. 1.** Ambulatory blood pressure in normotensive subjects recruited in (a) Australia, (b) Belgium, (c) the People's Republic of China, (d) France, (e) Germany and (f) Ireland. Values are expressed as hourly means (with 95% confidence interval)±SD, for systolic and diastolic blood pressure in men (■) and women (●) separately. The shaded bands indicate the 95% confidence interval of the mean conventional blood pressure.

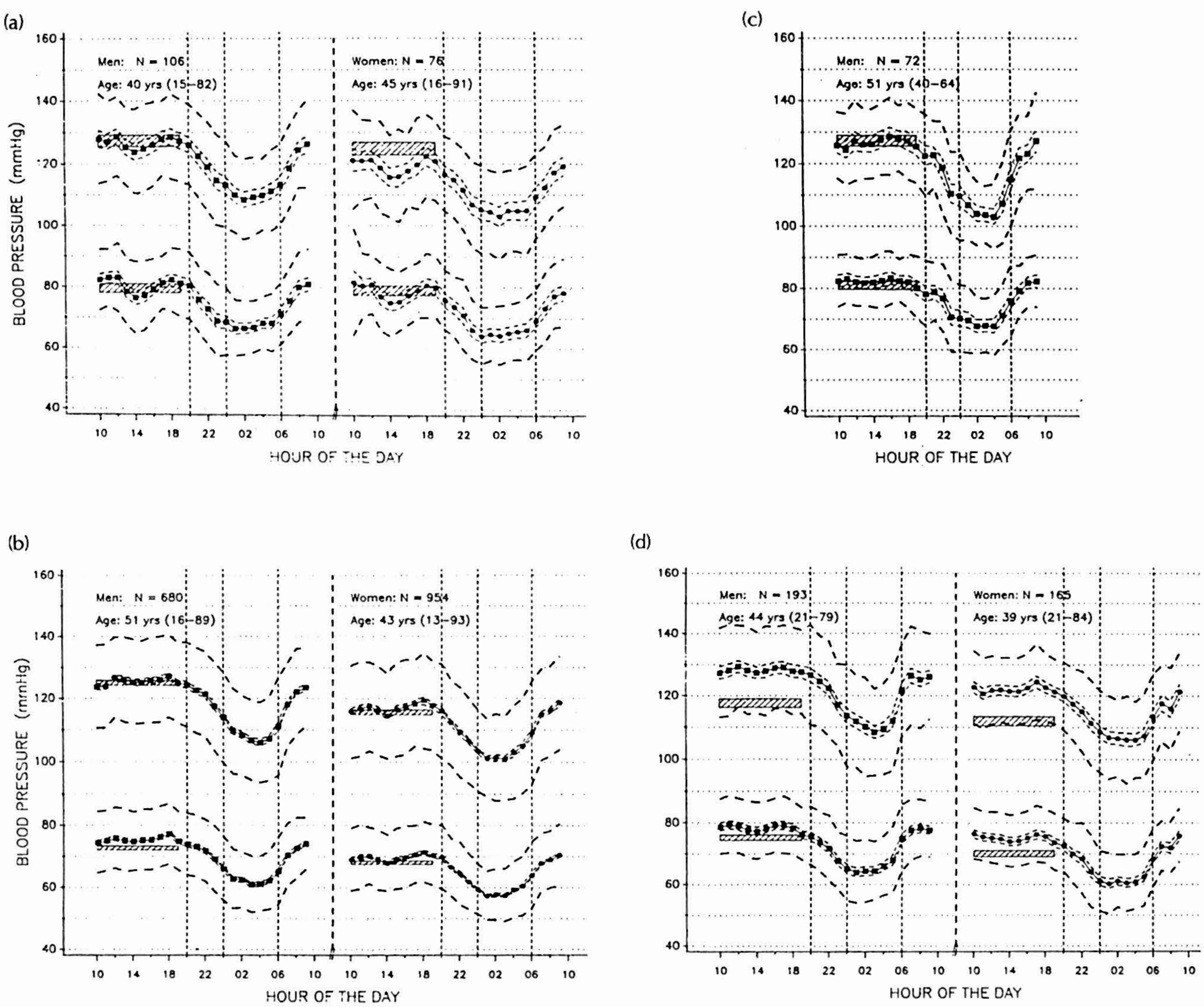


**Fig. 2.** Ambulatory blood pressure in normotensive subjects recruited in (a) Italy, (b) Japan, (c) Sweden and (d) the USA. Values are expressed as hourly means (with 95% confidence interval)±SD, for systolic and diastolic blood pressure in men (■) and women (●) separately. The shaded bands indicate the 95% confidence interval of the mean conventional blood pressure.

upon conventional sphygmomanometry (Fig. 3, Table 5). Similarly, 30% of the subjects with diastolic hypertension upon conventional measurement had 24-h diastolic ABP below the 95th centile (82 mmHg) of the subjects with normal CBP.

In univariate analyses the overlap in ABP measurements between normotensive and hypertensive subjects decreased if the CBP measurements of hypertensive subjects had been obtained repeatedly (more than one visit), if more than two CBP readings had been made available and averaged for analysis, and if both systolic and diastolic CBP had been elevated (Table 6). The probability that hypertensive subjects would have a 24-h ABP below the 95th centile of normotensive subjects also decreased considerably with increasing CBP (Fig. 4). In univariate analyses the overlap of diastolic blood pressure between normotensive and hypertensive subjects was also less when an auscultatory rather than an oscillometric technique had been used to measure ABP (Table 6).

Using a multivariate approach, logistic regression was subsequently employed to identify the factors determining the overlap in ABP measurements between the normotensive and the hypertensive subjects. The probability that the hypertensive subjects had 24-h systolic ABP below the 95th centile of ABP in the normotensive subjects was described by the following logistic function:

$$12.1 + (0.65 \times \text{sex}) + (0.0092 \times \text{age}) - (0.078 \times \text{systolic CBP}) - (0.013 \times \text{diastolic CBP}) + (0.82 \times n_v) + (0.78 \times n_{CBP})$$

where the sex term is scored as 1 for women and 0 for men, $n_v$ is the number of visits (one visit scored as 1, more than one scored as 0) and $n_{CBP}$ is the number of CBP readings (two readings scored as 1, more than two scored as 0).

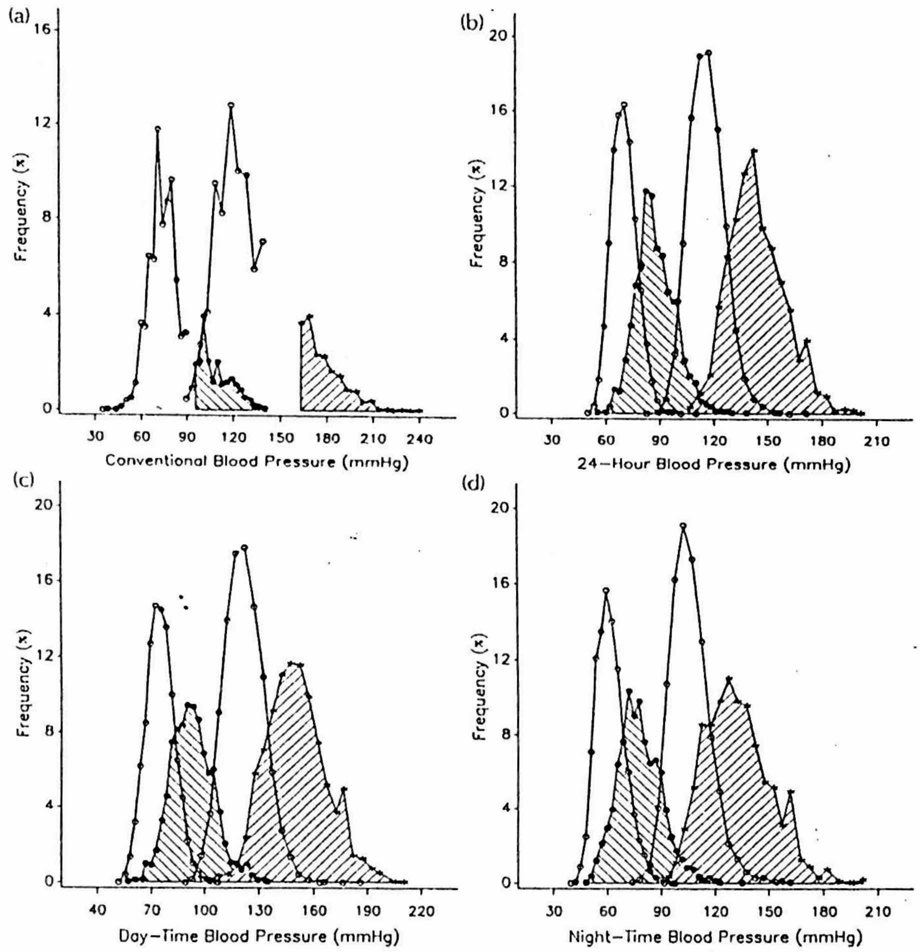


**Fig. 3.** The distributions of (a) conventional blood pressure and (b) 24-h, (c) daytime and (d) night-time ambulatory blood pressure. Systolic and diastolic blood pressure is shown in the normotensive subjects (O, n = 4577), systolic pressure in the subjects with systolic hypertension (*, n = 1324) and diastolic pressure in those with diastolic hypertension (●, n = 1310). The distribution of ambulatory blood pressures overlapped considerably among normotensive and hypertensive subjects, although the conventional blood pressures (a) were, by definition, completely separated. Subjects with borderline hypertension (n = 719) were excluded from this analysis.

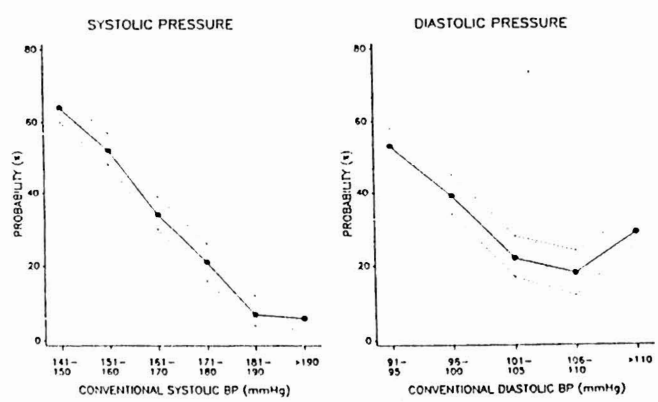


**Fig. 4.** The probability that hypertensive subjects would have 24-h ambulatory blood pressure (BP) below the 95th centile of that of the normotensive subjects is shown as a function of their conventional blood pressure. This analysis includes 719 subjects with borderline hypertension and 1773 with definite hypertension. Probabilities are unadjusted for other confounding variables. ----, 95% Confidence interval.

For 24-h diastolic ABP the equivalent logistic function was:

$$4.2 + (0.32 \times \text{sex}) + (0.0109 \times \text{age}) - (0.030 \times \text{systolic CBP}) - (0.018 \times \text{diastolic CBP}) + (1.36 \times n_v) + (1.41 \times n_{CBP})$$

Thus, multiple logistic regression demonstrated that the probability that the subjects with definite hypertension upon conventional sphygmomanometry had 24-h systolic ABP below the 95th centile of the normotensive subjects was nearly 90% greater in women than in men. For both 24-h systolic and diastolic ABP this probability rose by approximately 10% for each 10-year increase in age. By contrast, for each 10-mmHg increment in systolic CBP this probability decreased by 54% for 24-h systolic ABP and by 26% for 24-h diastolic ABP, and for each 5-mmHg increment in diastolic CBP this probability decreased by 6 and 9%, respectively (Table 7). If a blood pressure record of only one visit (rather than two or three visits) had been made available, and if the subjects had been classified on the basis of two CBP

**Table 6.** Hypertensive subjects with ambulatory blood pressure below the 95th centile of that in the normotensive subjects.

| | Systolic blood pressure (%) | | | Diastolic blood pressure (%) | | |
|---|---|---|---|---|---|---|
| | Group A | Group B | Difference (95% confidence limits) | Group A | Group B | Difference (95% confidence limits) |
| Conventional blood pressure measurements | | | | | | |
| One (A) versus more (B) visits | | | | | | |
| n | 235 | 1089 | | 243 | 1067 | |
| 24-h | 34 | 22 | −12 (−19, −6) | 44 | 27 | −17 (−24, −10) |
| Daytime | 32 | 25 | −7 (−14, −1) | 50 | 30 | −20 (−27, −13) |
| Night-time | 39 | 37 | 0 (−9, 4) | 55 | 43 | −12 (−19, −5) |
| Two (A) versus more (B) readings | | | | | | |
| n | 855 | 469 | | 777 | 533 | |
| 24-h | 24 | 23 | −1 (−6, 4) | 33 | 25 | −8 (−13, −3) |
| Daytime | 26 | 25 | −1 (−6, 4) | 36 | 30 | −6 (−11, −1) |
| Night-time | 41 | 29 | −12 (−17, −7) | 52 | 35 | −17 (−22, −11) |
| Supine (A) versus sitting (B) position | | | | | | |
| n | 38 | 1286 | | 77 | 1233 | |
| 24-h | 21 | 24 | 3 (−10, 16) | 9 | 31 | 22 (15, 29) |
| Daytime | 16 | 26 | 10 (−2, 22) | 23 | 35 | 12 (1, 21) |
| Night-time | 37 | 37 | 0 (−15, 16) | 22 | 46 | 24 (15, 34) |
| Isolated (A) versus non-isolated (B) blood pressure elevation | | | | | | |
| n | 463 | 861 | | 449 | 861 | |
| 24-h | 30 | 21 | −9 (−14, −4) | 39 | 25 | −14 (−19, −8) |
| Daytime | 31 | 23 | −8 (−13, −3) | 43 | 29 | −14 (−20, −9) |
| Night-time | 42 | 34 | −8 (−14, −3) | 59 | 38 | −21 (−26, −15) |
| Other factors | | | | | | |
| Men (A) versus women (B) | | | | | | |
| n | 641 | 683 | | 701 | 609 | |
| 24-h | 21 | 27 | 6 (1, 10) | 28 | 31 | 3 (−2, 8) |
| Daytime | 22 | 30 | 8 (3, 13) | 34 | 34 | 0 (−5, 5) |
| Night-time | 35 | 39 | 4 (−1, 9) | 43 | 47 | 4 (−1, 9) |
| Oscillometric (A) versus auscultatory (B) recordings | | | | | | |
| n | 1157 | 167 | | 1233 | 77 | |
| 24-h | 25 | 19 | −6 (−12, 1) | 33 | 14 | −14 (−20, −9) |
| Daytime | 37 | 14 | −13 (−19, −7) | 36 | 26 | −10 (−16, −4) |
| Night-time | 38 | 31 | −7 (−15, 1) | 50 | 21 | −21 (−27, −15) |

Values are expressed as percentages. The results for each entry are unadjusted for possible confounding by all other entries in the table.

readings only (rather than three or more), the probability that hypertensive subjects had 24-h systolic or diastolic ABP below the 95th centile of the normotensive subjects rose by between two- and fourfold (Table 7).

In comparison with 24-h ABP, the overlap in the daytime and night-time blood pressures between the normotensive and the hypertensive subjects was of similar magnitude (Table 5) and was influenced by the same factors (Table 6).

## Discussion

### Ambulatory blood pressure in normotensive subjects

An operational threshold for making clinical decisions based on ABP measurements is urgently needed [12]. This requires that the relationship between these measurements and the incidence of cardiovascular complications be clarified further [33]. Moreover, the benefits of using ABP monitoring as an accessory to conventional sphygmomanometry must be established in prospective clinical trials [34–36], although prospective studies alone are unlikely to establish an operational threshold for ABP monitoring. Indeed, studies of intermediate endpoints, such as left ventricular hypertrophy [37–39], and a previous study of daytime blood pressure only [33] have shown that the relationship between ABP measurements and cardiovascular complications is continuous, without a threshold level at which the risk rises suddenly.

It is becoming increasingly evident that to define an operational threshold for ABP monitoring an arbitrary judgement is inevitable, as it has proved to be for conventional sphygmomanometry [21,22]. Although arbitrary, an operational threshold must be based on factual observations and at least two other approaches are likely to be helpful: insight into the distributions of ABP measurements in subjects who are normotensive or hypertensive according to the current definitions of these conditions [21,22], and a description of the distributions of ABP measurements in unselected populations [15,40]. The former approach, followed in the present study, constitutes a link between ABP monitoring and the vast experience accrued in the past using conventional sphygmomanometry. Indeed, observational studies and clinical outcome trials have established unequivo-

Table 7. Probabilities that hypertensive subjects had a 24-h ambulatory blood pressure below the 95th centile of that of the normotensive subjects.

| | Systolic blood pressure (n = 1324) | Diastolic blood pressure (n = 1310) |
|---|---|---|
| Female versus male | 1.92 (1.45, 2.54) | 1.38 (1.06, 1.79) |
| 10 years older | 1.10 (0.99, 1.21) | 1.12 (1.01, 1.24) |
| 10-mmHg higher conventional systolic blood pressure | 0.46 (0.39, 0.54) | 0.74 (0.68, 0.81) |
| 5-mmHg higher conventional diastolic blood pressure | 0.94 (0.89, 0.98) | 0.91 (0.85, 0.98) |
| One versus more visits | 2.29 (1.55, 3.38) | 3.89 (2.65, 5.70) |
| Two versus more conventional pressure readings | 2.19 (1.55, 3.09) | 4.11 (2.91, 5.81) |

Values are expressed as odds ratio (95% confidence limits), determined by multiple logistic regression; the odds ratio for each variable is adjusted for possible confounding by all other variables in the table.

cally that normotensive subjects, in the absence of other risk factors, have a lower cardiovascular risk profile than hypertensive subjects [1].

Preliminary proposals for an operational threshold for ABP monitoring have been published [13–19]. In a meta-analysis of 23 studies the pooled estimate of the average 24-h ABP + 2SD in 3476 normotensive people was 139/87 mmHg [16]. The ABP measurements in the studies referenced for this meta-analysis had been processed using different mathematical techniques, various definitions of daytime and night-time and different editing criteria for the exclusion of invalid readings. In the present study 7069 individual recordings contributed by 24 clinical research groups were pooled and analysed. The advantage of analysing recordings from individuals rather than the summary statistics of published reports was that the same mathematical approach [15,20], the same quality standards and uniform definitions of daytime and night-time could be applied. Both the present study and the previously published meta-analysis [16], despite differences in the databases and statistical approaches used, found very similar distributions of ABP in normotensive subjects.

## Comparison of normotensive and hypertensive subjects

The present database provided the means to compare ABP measurements among subjects who were either normotensive or hypertensive according to conventional sphygmomanometry [21,22]. If no confounding variables were considered, one-fifth to more than one-third of the hypertensive subjects appeared to have ABP below the 95th centiles of ABP in the normotensive subjects. However, further analyses showed that for systolic blood pressure this overlap tended to be greater in women than in men. The overlap also increased with advancing age. By contrast, the overlap diminished if the subjects had shown higher blood pressure upon conventional sphygmomanometry or if the diagnosis of hypertension had been reached after a greater number of visits and CBP measurements, or both. Nevertheless, even if these confounding variables were considered, the overlap remained substantial. For instance, the multiple logistic model derived in the present study predicted that a 70-year-old man who, upon repeated measurements at two or more visits, maintained a CBP of 180/100 mmHg, had a 7% chance of having a 24-h systolic ABP below the 95th centile of that of the normotensive subjects, whereas for diastolic blood pressure the probability would be 22%. On the assumption that in the same man only two blood pressure readings had been obtained at a single visit, a CBP of 180/100 mmHg would be associated with a 27% chance of the 24-h systolic ABP being below the 95th centile of that of the normotensive subjects, the probability rising to 82% for 24-h diastolic ABP.

The prevalence of white-coat hypertension has been evaluated in a few smaller cohorts of selected patients [13,17,39,41–44] and has been reported to be approximately 40% in some studies [41,42,44], although, in keeping with the present findings, estimates varied from as low as 5% [13] to more than 70% [43], depending on how the patients had been selected, how the blood pressure had been measured and which thresholds had been applied to diagnose hypertension based on CBP and ABP measurements. Many experts would agree that ABP measurements reflect the true blood pressure of a subject more closely than CBP readings [5–9]. Thus, both the present study and previous reports [13,17,39,41–44] suggest that the current practice of CBP measurement may lead to the misclassification of subjects if only the CBP level is considered.

At present, the definitions of normotension and hypertension are based entirely on conventional sphygmomanometry [21,22]. The present findings do not suggest that this standard procedure, long established in clinical practice, should be abandoned. However, practising physicians need additional guidelines to maximize the reproducibility of their CBP measurements, to minimize the white-coat effect [2,3] and to diagnose white-coat hypertension. ABP monitoring could be a very useful accessory to conventional sphygmomanometry in these respects.

A fundamental question which remains is how the risk profile of white-coat hypertensive patients [2,3] differs from that of normotensive subjects and from the prognosis of patients in whom both CBP and ABP are elevated. Normotensive subjects were recently compared with hypertensive patients with concentric left ventricular hypertrophy [45] (the left ventricular pattern most commonly associated with hypertension [46,47] and, possibly, with the worst prognosis). The findings suggested that awake ABP <139/86 mmHg might be considered normal, whereas values >149/95 mmHg might be regarded as being elevated [45]. By comparison, the 95th centile of the daytime ABP in the present study was 140/88 mmHg, whereas in the previously published meta-analysis [16] the average daytime ABP + 2SD was 146/91 mmHg. However, even at the latter level of daytime ABP, the late-diastolic transmitral peak flow velocity and its ratio to the early peak flow velocity may be abnormally increased in 9% of subjects [18]. Thus, it has been suggested that until these issues are clarified further by prospective studies, conservative estimates should be used to define normality of ABP [18].

Most hypertensive subjects in the present study had been examined on several occasions, but the CBP readings made available for the present analysis had been obtained at one to three (median two) visits. Such readings may differ from the usual CBP [48] determined by repeated measurements during several years' follow-up. Thus, the overlap in ABP between the normotensives and the hypertensives in the present study might have been lower if the hypertensive subjects had been followed for several years. However, repeating the blood pressure readings over lengthy periods entails considerable cost and is unlikely to abolish completely this overlap in ABP between normotensives and hypertensives. Moreover, in clinical practice and in employment and insurance examinations subjects are often classified on the basis of repeated measurements taken at a single or at a few visits only. In this respect the present paper reflects common practice.

### Worldwide experience

For practical reasons the diurnal blood pressure profiles in the normotensive subjects were categorized by country. This does not mean that these profiles were representative for each country. Indeed, in only a few studies has a random population sample been examined. The most prominent feature when all profiles were compared was the great similarity in shape and blood pressure level, although the profiles did reflect some national characteristics, such as the dip associated with the siesta in Italy (Fig. 2a). The blood pressure levels were also influenced by the age and sex distributions of the normotensive subjects, although to a much lesser extent than might have been expected on the basis of CBP [49].

Normotensive subjects do not experience a white-coat effect [2,3] as, by definition, they have normal CBP. By contrast with hypertensive patients [13,19], the daytime ABP of normotensives is usually higher than their CBP [14,15]. In the present study there was considerable variability in the difference between CBP and daytime ABP of the normotensive subjects across countries. These differences reflected the circumstances in which the CBP readings had been obtained and the level of physical activity during the ABP recordings. CBP readings taken after a longer period of rest or in a relaxed environment, and heavy manual work during ABP recordings (e.g. in blue-collar workers), predisposed the subjects to a higher daytime ABP than CBP.

## Conclusions

The ABP distributions of the normotensive subjects included in the present international database were not materially different from those reported in the literature [14–16]. One-fifth to more than one-third of hypertensive subjects had ABP within the normotensive range. The latter was arbitrarily defined as ABP below the 95th centile of the ABP of normotensive subjects. In agreement with current clinical experience, the overlap in ABP among normotensive and hypertensive subjects decreased if CBP was more elevated or if the hypertensive subject had repeatedly shown an elevated CBP, or both. The prognostic implications of elevated CBP in the presence of normal ABP remain to be elucidated.

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