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# A consistent reference frame for ambulatory blood pressure monitoring is found in different populations

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## Summary:

**This study investigated the consistency of a reference frame for ambulatory pressure monitoring, which using various approaches was determined in two different populations. The two reference groups were 718 subjects randomly selected from the population and 895 bank employees. The reference values derived in these two groups were subsequently tested in 591 untreated hypertensive patients. The ambulatory pressures equivalent to a conventional pressure of 140 mmHg systolic and 90 mmHg diastolic were calculated by regression analysis in all subjects. In addition, in subjects who were normotensive by conventional sphygmomanometry, the mean +2 and +3 standard deviations and the 90th, 95th and 99th percentiles of the ambulatory measurements were determined. The distributions of the ambulatory measurements were similar in the two reference groups and the aforementioned parameters therefore agreed within 4 mmHg in the two populations. There was considerable overlap in the ambulatory pressures between the two reference groups and the hypertensive patients. Classification of the patients according to the means +3 standard deviations and the regression limits gave the same results because in both reference groups these boundaries approximated to each other within 1 mmHg. For the 24h pressures in the population sample these boundaries were 140 mmHg systolic and 88 mmHg diastolic. Of the patients with systolic hypertension (≥ 160 mmHg on conventional measurement), 39% had a 24h systolic pressure of < 140 mmHg and of those with diastolic hypertension (≥ 95 mmHg), 44% had a 24h diastolic pressure of < 88 mmHg; if the corresponding boundaries derived in the bank employees (143/90 mmHg) were applied, these proportions were 47% and 44%, respectively. In conclusion, there was considerable consistency: (1) between two different populations in the distribution of the ambulatory pressures and in the derived reference frames for ambulatory monitoring, and (2) between the mean +3 standard deviations and the limits derived by regression in classifying hypertensive patients. Thus, arbitrary methods can achieve consistent results in determining a reference frame for ambulatory monitoring. The prognostic significance of such reference values nonetheless needs to be further validated in longitudinal studies and clinical trials.**

**Keywords:** *ambulatory BP, BP measurement, conventional BP, reference values*

## Introduction

An operational threshold for making clinical decisions based on ambulatory BP monitoring must be defined.[1–3] Although there is evidence that ambulatory monitoring is better than conventional BP measurement in predicting morbidity,[4,5] the relationship between ambulatory measurements and the incidence of cardiovascular complications must be further clarified.[1–3] Moreover, the benefits of using ambulatory monitoring in addition to conventional sphygmomanometry needs also to be established in prospective clinical trials.[6]

Because many years will evolve before a generally accepted operational threshold for ambulatory monitoring will become available to clinicians, several preliminary proposals have been published.[7–14] Most of these proposals[7,9–11,13] considered the distribution of the ambulatory pressure in normotensive persons as a starting point but some investigators regressed ambulatory on conventional pressures to determine equivalent pressure levels.[8] There

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may be substantial incoherence between these preliminary proposals.[7,9–14] Thus, the purpose of the present study was to compare the reference values determined by various approaches in two different reference populations, i.e. a Belgian population sample[11,14–16] and the employees enrolled in the Allied Irish Bank Study.[9] These reference values were subsequently tested in a group of untreated hypertensive patients.

## Subjects and methods

### Study population

In the ongoing Belgian survey, the participants (minimum age 20 years) were randomly selected from the population of a geographically defined area.[11,14–16] The subjects included in this report were recruited starting from the last trimester of 1989 through to the first semester of 1992. The sample comprised 1414 subjects. Subjects were excluded from further participation when they did not live on the address listed in the population registry ($n = 128$, of whom 19 had died) or when they were bedridden or confined to a wheelchair ($n = 4$). During the first year of the survey,[11] but not thereafter,[14] subjects taking antihypertensive drugs, diuretics or nitrates were also excluded ($n = 131$). Of the remaining 1151 subjects, 70% ($n = 807$) consented to participate and 68% ($n = 786$) had their ambulatory BP measured.

A second independent data set was analysed to investigate if the findings in the Belgian population sample were reproducible. It consisted of 918 bank employees and their spouses, who volunteered for a study on ambulatory BP monitoring.[9] In the Belgian and Irish studies a self-administered questionnaire was used to determine each participant's personal and familial medical history and intake of medications.

The reference values identified in the present study were subsequently tested in a sample of 591 untreated hypertensive patients who had been referred to the Blood Pressure Unit (Dublin). All these patients were hypertensive according to the criteria of the World Health Organization,[17] i.e. two or more measurements of their pressure obtained after five minutes rest in the sitting position at the outpatient clinic, averaged at least 160 mmHg systolic or 95 mmHg diastolic.

### Conventional BP measurement

In the Belgian and Irish studies cuff size was adjusted according to arm circumference not only for the conventional but also for the ambulatory pressure measurements. In the Belgian survey[11,14–16] all conventional readings were obtained between 10 am and 8 pm by trained nurses. They measured each participant's sitting pressure five times consecutively on each of two separate home visits. A film showing a falling mercury column with Korotkoff sounds (Blood Pressure Measurement, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK) was used to test the accuracy of the nurses' measurements at intervals of three months. Their readings were within 5 mmHg compared with those of experienced medical staff. Because in many published epidemiological studies the BP is measured on only one occasion, only the five readings recorded at the first home visit were used to calculate the conventionally measured BP in the Belgian study but the present results were not materially altered if the average of all conventional readings was used.

In the Allied Irish Bank Study[9] the BP was measured during regular working hours. After the subjects had rested for a few minutes in the sitting position, a trained nurse obtained two readings, according to the recommendations of the British Hypertension Society.[18] The mean of the two office measurements was used in the present analysis.

### Ambulatory BP measurement

In both the Belgian and Irish studies the ambulatory BP was measured with SpaceLabs 90202 and 90207 devices[19–21] (SpaceLabs Inc., Redmond, Washington, USA). The recorders were calibrated before use in the studies and the calibration was checked at least at intervals of three months. In the Belgian study the recordings were started at the occasion of one of the home visits; the recorders were programmed to obtain measurements with an interval of 20 minutes from 8 am until 10 pm and every 45 minutes from 10 pm to 8 am.[11,14] In the Irish studies the ambulatory readings were programmed at 30 minute intervals.[9]

The ambulatory BP recordings were truncated so that their total duration did not exceed 24 hours. Intra-individual ambulatory BP means were weighted by the time interval between successive readings. Daytime and nighttime were defined as the intervals from 10 am to 8 pm and from midnight to 6 am because previous studies[11,13–15] have shown that these conventions exclude the rapid BP changes in the morning and evening.

Applying previously published editing criteria[11] excluded < 1% of the ambulatory readings and did not affect the averages of the ambulatory pressures or the characteristics of the distributions; therefore, only the results for unedited recordings will be presented. Subjects were removed from analysis if the ambulatory recording covered < 20 hours, if less than ten readings were available for computing the daytime BP means or less than five for the nighttime means.[13] These criteria excluded 68 participants from the Belgian population survey and 23 from the Allied Irish Bank Study.

### Statistical methods

Database management and statistical analyses were performed with the SAS software (The SAS Institute Inc., Cary, NC). The central tendency and spread of the data were reported as the mean ± standard deviation. Departure from normality was

evaluated by the Shapiro–Wilk statistic[22] and skewness by the computation of the coefficient of skewness (the third moment about the mean) and its error term.[23] The distributions of the ambulatory measurements in the two reference populations were compared with use of a chi-square statistic.

Various approaches were applied to construct a reference frame for ambulatory monitoring. The first involved all available subjects. The ambulatory measurements were correlated with the conventional readings using linear regression analysis and the ambulatory pressures that would be equivalent to a conventional pressure of 140 mmHg systolic or 90 mmHg diastolic were determined.[8]

Further analyses identified the upper limits of the ambulatory BP in persons whose conventional pressure did not exceed the generally accepted limits of normotension, i.e. a pressure of 140 mmHg systolic and 90 mmHg diastolic.[17] A nonparametric approach, which did not imply any assumption concerning the distributions of their ambulatory measurements, consisted of the determination of the 90th, 95th and 99th percentiles of the ambulatory measurements. In addition, on the assumption that in normotensive subjects the distributions of the ambulatory pressures would not largely depart from normality, the mean ambulatory pressures +2 and +3 standard deviations were calculated. For some analyses the normotensive subjects were stratified by sex and age (< 50 years and ≥ 50 years).

## Results

### Charactertistics of the participants

The study population included 718 subjects from the Belgian population survey (age range 20–88 years), 895 participants from the Allied Irish Bank Study (29–51 years) and 591 hypertensive patients (18–87 years). Their main characteristics are listed in Table I. The distributions of their 24h ambulatory pressures are presented in Figure 1. There were no differences in the distributions of the ambulatory measurements between the population sample and the Irish bank workers (Figure 1). Of the hypertensive patients, 515 had an elevated SBP (≥ 160 mmHg) and 352 had diastolic hypertension (≥ 95 mmHg).

In the Belgian population sample 88 subjects were on antihypertensive drug treatment. By contrast, all Irish bank workers and hypertensive patients were free of antihypertensive medication.

### Daytime BP in the population sample used as an example to illustrate the various statistical approaches

As an example, the methods for determining a reference frame were first applied to the daytime pressures in the 718 subjects drawn from the population. A conventional pressure of 140 mmHg systolic was equivalent to daytime pressure of 131 mmHg, while a conventional pressure of 90 mmHg diastolic corresponded with 82 mmHg (Figure 2). The 95% confidence intervals for the mean daytime pressures equivalent to a conventional pressure of 140 mmHg systolic and 90 mmHg diastolic, ranged from 130 to 132 mmHg and from 81 to 83 mmHg, respectively. The 95% confidence intervals for the prediction of a single individual's daytime pressure ranged from 114 to 147 mmHg and from 68 to 95 mmHg (Figure 2).

The Belgian population sample included 574 normotensive persons, in whom the 90th, 95th and 99th percentiles were 134, 137 and 145 mmHg for

**Table I** Characteristic of the subjects

| | *Population study* | *Allied Bank study* | *Hypertensive patients* |
|---|---|---|---|
| Number | 718 | 895 | 591 |
| Men (%) | 48.2 | 48.4 | 47.5 |
| Age (years) | 50 ± 14 | 46 ± 4 | 51 ± 14 |
| Body mass index (kg/m²) | 25.9 ± 4.3 | 23.5 ± 3.1 | 26.4 ± 4.1 |
| Systolic pressure | | | |
| Conventional (mmHg) | 126 ± 17 | 120 ± 16 | 176 ± 21 |
| 24h (mmHg) | 119 ± 11 | 118 ± 11 | 145 ± 16 |
| Daytime (mmHg) | 125 ± 11 | 124 ± 12 | 152 ± 17 |
| Nighttime (mmHg) | 105 ± 11 | 106 ± 11 | 131 ± 19 |
| Diastolic pressure | | | |
| Conventional (mmHg) | 76 ± 10 | 76 ± 11 | 97 ± 13 |
| 24h (mmHg) | 71 ± 7 | 72 ± 8 | 88 ± 12 |
| Daytime (mmHg) | 76 ± 8 | 78 ± 8 | 93 ± 12 |
| Nighttime (mmHg) | 62 ± 8 | 61 ± 8 | 78 ± 13 |
| WHO classification* | | | |
| Normotensive (%) | 73.8 | 90.1 | 0.0 |
| Borderline (%) | 10.9 | 4.1 | 0.0 |
| Hypertensive (%)# | 15.3 | 5.8 | 100.0 |
| Antihypertensive treatment (%) | 12.3 | 0.0 | 0.0 |

*Values are means ± standard deviation or percentages*
**Normotension and hypertension were defined on the basis of the conventional pressure. Normotension was a pressure not exceeding 140 mmHg systolic and 90 mmHg diastolic. Hypertension was defined as a systolic pressure of at least 160 mmHg or a diastolic pressure of ≥ 95 mmHg*
*# Includes subjects on antihypertensive treatment, regardless of their conventional BP level*

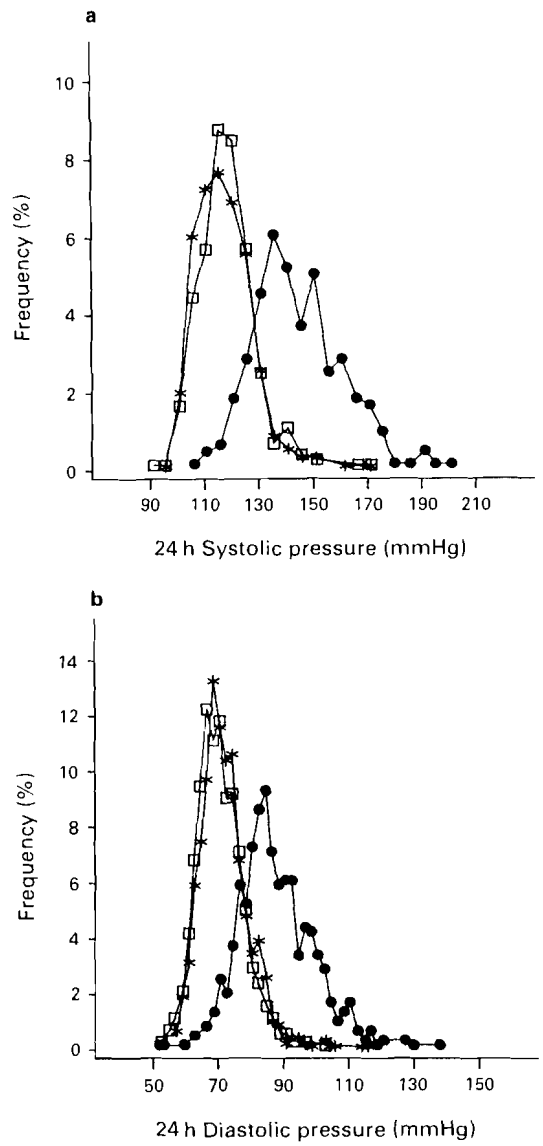


**Figure 1** Distribution of the 24h systolic (**a**) and diastolic (**b**) pressures in 718 subjects drawn from the general population (Belgium, □), 895 participants from the Irish Allied Bank Study (⋆) and 591 hypertensive patients (●). The vertical axis shows the frequency and the horizontal axis the mean pressure level in 5 mmHg intervals for the 24h SBP and in 2 mmHg intervals for the 24h DBP.

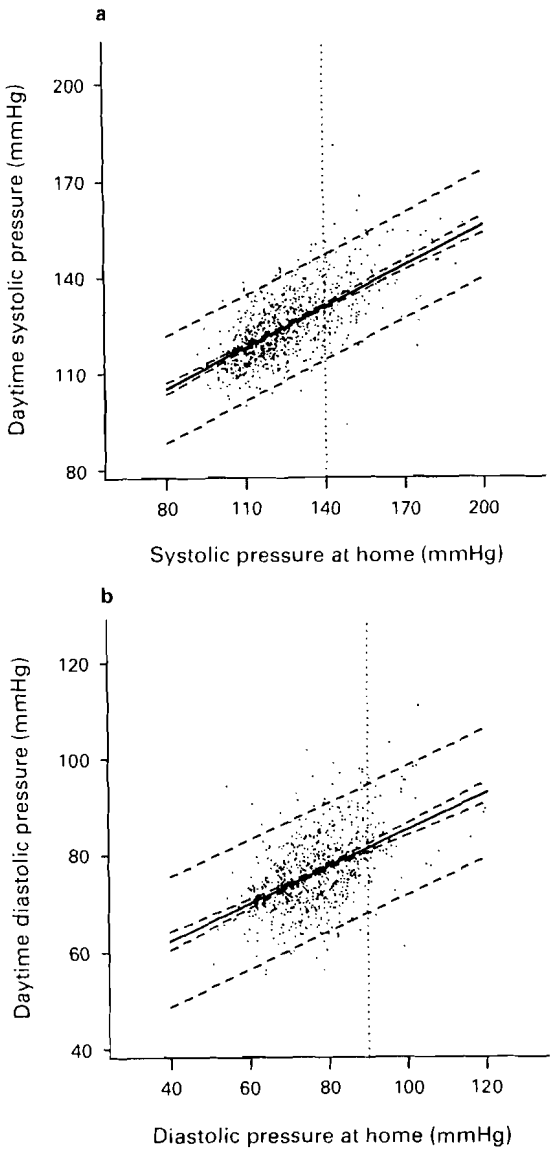


**Figure 2** Relationship between daytime and conventional pressures in 718 subjects randomly selected from the population. **a** SBP. **b** DBP. (····) 95% confidence intervals for the mean daytime pressure corresponding with a given conventional pressure (smaller interval) and for the prediction of a single individual's daytime pressure (larger interval).

the daytime SBP and 84, 87 and 94 mmHg for the daytime DBP. The mean daytime pressures +2 and +3 standard deviations were 140 and 147 mmHg for SBP and 81 and 89 mmHg for DBP.

## Determination of a reference frame

The distributions of the 24h and the day- and nighttime time SBPs and DPBs in the Belgian population survey ($n = 718$) and in the Irish bank employees ($n = 895$) were positively skewed ($P < 0.01$) and departed from normality ($P < 0.01$). However, when only the normotensive subjects (≤ 140/90 mmHg on conventional BP measurement) were considered, the coefficients of skewness of the ambulatory measurements on average decreased from 0.96 (range 0.54–1.37) to 0.47 (range 0.21–0.88).

The approaches illustrated above for the daytime ambulatory pressure were applied to the 24h and the day- and nighttime pressures for the Belgian population sample, in the Irish bank workers and in six strata delineated by sex and age: younger Belgian ($n = 182$) and Irish ($n = 391$) men, younger Belgian ($n = 164$) and Irish ($n = 433$) women and older Belgian men ($n = 198$) and women ($n = 174$). Only 71 Irish bank workers were ≥ 50 years and they were therefore not considered as separate male and female strata.

The 95% confidence limits for predicting a single individual's ambulatory pressures equivalent to a conventional pressure of 140 mmHg SBP or 90 mmHg DBP (regression limits) are shown in Figures 3 and 4. These regression limits were superimposed on the parameters determined in normotensive subjects, i.e. the 95th and 99th percentiles and the means +2 and +3 standard deviations. For

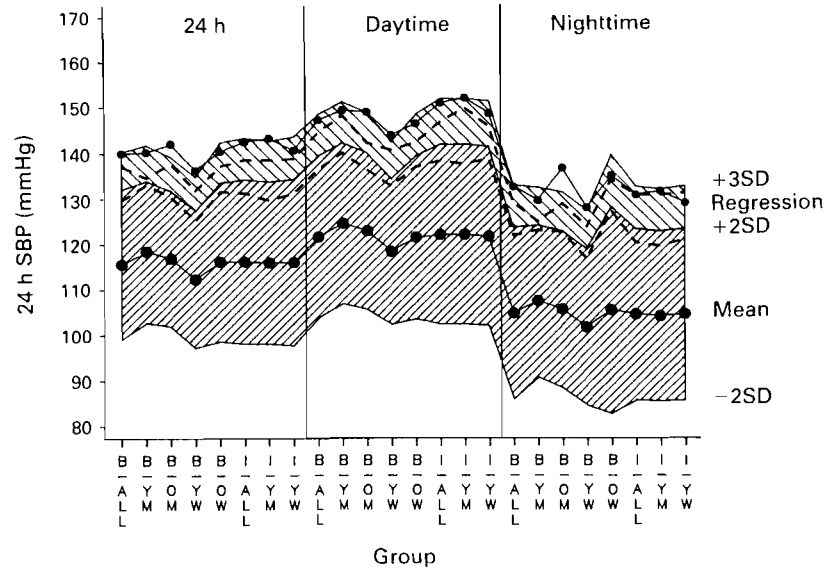


**Figure 3** The 95% confidence limits of the ambulatory pressures equivalent to a conventional SBP of 140 mmHg were calculated by regression analysis in 718 Belgian subjects (B-ALL), in 895 Irish bank employees (I-ALL) and in 6 subgroups delineated by nationality (B = Belgium, I = Ireland), sex (M = men, W = women) and age (Y = < 50 years, O = ≥ 50 years). The 95th and 99th percentiles (dotted lines) and the mean +2 and +3 standard deviations were determined in the normotensive subjects from each group.

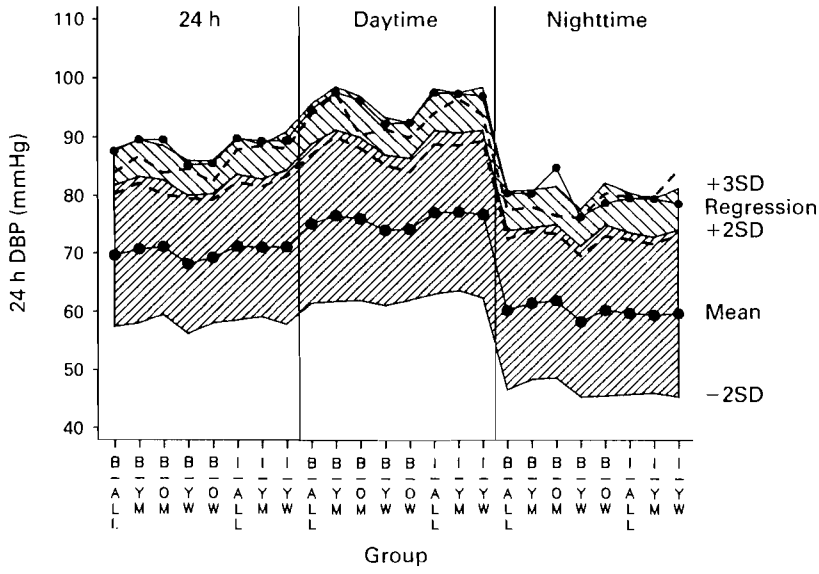


**Figure 4** Reference frame for the diastolic ambulatory pressures. For further explanation see Figure 3.

the Belgian study population as a whole these statistics also appear in Table II and for the Irish Bank Study in Table III.

In general, there was close agreement between the boundaries derived by regression and the means +3 standard deviations. For the 24h and the daytime and nighttime SBPs across various groups (Figure 3), the regression limits were on average only 0.7 mmHg lower than the means +3 standard deviations, while the 99th and 95th percentiles were, respectively, 4.0 and 11.4 mmHg lower. Similarly, for the DBPs (Figure 4), the regression limits were only 0.6 mmHg lower than the means +3 standard deviations, while the percentiles were, respectively, 2.4 and 8.1 mmHg lower.

## Classification of hypertensive patients with respect to the reference frame determined in the population sample

As expected, the ambulatory BP was on average higher in the hypertensive patients than in the mainly normotensive population sample and in the cohort of bank employees (Table I). Nevertheless, there was considerable overlap between the hypertensive patients and the two reference groups when the distributions of their ambulatory pressures were compared (Figure 1).

For instance, the mean +3 standard deviations of the 24h SBP in the normotensives drawn from the Belgian population sample was 140 mmHg, a

**Table II** Percentage of hypertensive patients with an ambulatory pressure below specified thresholds

| | *24h* | | *Daytime* | | *Nighttime* | |
|---|---|---|---|---|---|---|
| | $T^{\S}$ | $< T^{*}$ | $T^{\S}$ | $< T^{*}$ | $T^{\S}$ | $< T^{*}$ |
| Systolic pressure# | | | | | | |
| $P_{90}$ | 126 | 7.4 | 134 | 10.5 | 118 | 24.7 |
| $P_{95}$ | 130 | 13.8 | 137 | 16.1 | 122 | 30.9 |
| $P_{99}$ | 137 | 30.1 | 145 | 34.6 | 129 | 46.0 |
| Mean +2 SD | 132 | 17.9 | 140 | 23.3 | 124 | 35.0 |
| Mean +3 SD | 140 | 38.8 | 148 | 41.4 | 133 | 53.6 |
| Regression limit | 140 | 38.8 | 147 | 38.8 | 133 | 53.6 |
| Diastolic pressure## | | | | | | |
| $P_{90}$ | 78 | 10.9 | 84 | 15.1 | 69 | 15.7 |
| $P_{95}$ | 80 | 16.2 | 87 | 22.7 | 72 | 27.6 |
| $P_{99}$ | 84 | 27.8 | 94 | 44.0 | 77 | 45.7 |
| Mean +2 SD | 82 | 22.2 | 89 | 25.6 | 74 | 33.5 |
| Mean +3 SD | 88 | 43.8 | 95 | 48.9 | 81 | 55.4 |
| Regression limit | 88 | 43.8 | 95 | 48.9 | 80 | 53.1 |

**Percentage of hypertensive patients with an ambulatory pressure below the specified thresholds*
*§Threshold ambulatory pressure level (mmHg) determined in the Belgian population sample: $P_{95}$, $P_{99}$ = 95th, 99th percentiles; SD = standard deviation; regression limit = the ambulatory pressures that would be equivalent to a conventional pressure of 140 mmHg systolic or 90 mmHg diastolic*
*#Analyses including 515 patients with a conventional systolic pressure of ≥ 160 mmHg; ##Analyses including 352 patients with a conventional diastolic pressure of ≥ 95 mmHg*

**Table III** Percentage of hypertensive patients with an ambulatory pressure below specified thresholds

| | *24h* | | *Daytime* | | *Nighttime* | |
|---|---|---|---|---|---|---|
| | $T^{\S}$ | $< T^{*}$ | $T^{\S}$ | $< T^{*}$ | $T^{\S}$ | $< T^{*}$ |
| Systolic pressure# | | | | | | |
| $P_{90}$ | 127 | 8.5 | 134 | 10.5 | 116 | 20.9 |
| $P_{95}$ | 131 | 15.3 | 137 | 18.1 | 120 | 27.8 |
| $P_{99}$ | 139 | 35.5 | 147 | 38.8 | 131 | 50.1 |
| Mean +2 SD | 134 | 22.1 | 142 | 28.7 | 123 | 32.8 |
| Mean +3 SD | 143 | 46.6 | 152 | 52.0 | 133 | 53.6 |
| Regression limit | 143 | 46.6 | 151 | 48.3 | 131 | 49.9 |
| Diastolic pressure## | | | | | | |
| $P_{90}$ | 79 | 12.5 | 86 | 20.2 | 67 | 9.6 |
| $P_{95}$ | 82 | 22.2 | 89 | 25.6 | 72 | 27.6 |
| $P_{99}$ | 88 | 43.8 | 94 | 44.0 | 80 | 53.1 |
| Mean +2 SD | 84 | 27.8 | 91 | 33.0 | 73 | 32.4 |
| Mean +3 SD | 90 | 49.4 | 98 | 58.8 | 80 | 53.1 |
| Regression limit | 90 | 49.4 | 97 | 57.4 | 79 | 49.7 |

*§Threshold ambulatory pressure level (mmHg) determined in the Irish bank employees; $P_{95}$, $P_{99}$ = 95th, 99th percentiles; SD = standard deviation; regression limit = the ambulatory pressures that would be equivalent to a conventional pressure of 140 mmHg systolic or 90 mmHg diastolic*
**Percentage of hypertensive patients with an ambulatory pressure below the specified thresholds*
*#Analyses including 515 patients with a conventional systolic pressure of ≥ 160 mmHg. ##Analyses including 352 patients with a conventional diastolic pressure of ≥ 95 mmHg*

threshold which was not exceeded by 38.8% of the 515 patients who on conventional sphygmomanometry had a SBP of > 160 mmHg (Table II). Similarly, of the 352 patients with a conventional DBP of > 95 mmHg, 43.8% had a 24h DBP below the mean +3 standard deviations (88 mmHg) (Table II).

Compared with 24h measurements, the day- and nighttime pressures showed similar degrees of overlap between the population sample and the hypertension patients (Table II). Classification of the hypertensive patients with reference to the mean +3 standard deviations or the regression boundaries gave the same results in terms of the overlap of the distributions (Table II).

### Classification of hypertensive patients with respect to the reference frame determined in the bank employees

Classification of the hypertensive patients according to the reference frame determined in the bank employees gave results which were largely comparable to those obtained on the basis of the Belgian population sample (Table III). This was the case because the statistical parameters used as a reference frame were within 4 mmHg concordant in the two reference populations.

## Discussion

Comparison of the Belgian population sample and the Irish bank employees demonstrated considerable consistency both in the distribution of the ambulatory BPs (Figure 1) and in the reference frame derived for ambulatory monitoring (Tables II and III). Furthermore, there was also close agreement between the mean +3 standard deviations and the boundaries derived by regression analysis in classifying hypertensive patients (Tables II and III).

The present study tried to determine a reference frame for ambulatory monitoring by identifying the upper limits of the ambulatory pressures in normotensive subjects. This approach offers the advantage that it builds on the large experience which has accumulated since the turn of this century with the use of conventional sphygmomanometry. It is indeed known from observational studies and clinical outcome trials that normotensive compared with hypertensive subjects, in the absence of other risk factors, have a lower cardiovascular risk profile.

The regression analyses involved all available subjects regardless of their conventional BP and treatment status (Figure 2). Truncation of the conventional pressure distribution at 140 mmHg systolic or 90 mmHg diastolic may indeed influence the position of the regression line, the estimate of the mean ambulatory pressure corresponding with a given conventional pressure and the width of the confidence intervals. Based on the regression approach, the upper normal limits of the daytime pressure have been reported to be 137 mmHg systolic and 87 mmHg diastolic.[8] These levels were the mean daytime pressures, respectively, corresponding with a clinic pressure of 140 and 90 mmHg.[8] In the latter study,[8] in which the participants were not randomly selected from the population or from a well-defined group, the 95% confidence boundaries for predicting a single individual's daytime pressure, were 154 mmHg SBP and 99 mmHg DBP.

**Table IV** Mean and standard deviation of BP in normotensive# subjects in various studies

| | *Number* | *Conventional pressure* | *Ambulatory pressure* | | |
|---|---|---|---|---|---|
| | | | *24h* | *Day* | *Night* |
| Systolic pressure (mmHg) | | | | | |
| Population sample | 574 | 119 ± 10 | 116 ± 8 | 122 ± 9 | 105 ± 9 |
| Bank employees | 806 | 117 ± 11 | 116 ± 8 | 122 ± 10 | 105 ± 9 |
| Meta-analysis## | 3414 | NA | 118 ± 11 | 123 ± 11 | 106 ± 10 |
| Large database§ | 4577 | 119 ± 12 | 116 ± 10 | 122 ± 11 | 106 ± 11 |
| Diastolic pressure (mmHg) | | | | | |
| Population sample | 574 | 74 ± 8 | 70 ± 6 | 75 ± 7 | 60 ± 7 |
| Bank employees | 806 | 75 ± 8 | 71 ± 6 | 77 ± 7 | 60 ± 7 |
| Meta-analysis## | 3414 | NA | 72 ± 8 | 76 ± 8 | 64 ± 9 |
| Large database§ | 4577 | 73 ± 9 | 70 ± 7 | 75 ± 8 | 61 ± 8 |

*Values are means ± standard deviation*
*#Normotension was a conventional pressure not exceeding 140 mmHg systolic and 90 mmHg diastolic; ##see ref. 10, NA = mean and standard deviation of the conventional blood pressures not available in all reviewed papers; §Large international database (see ref. 13)*

In a study on the prevalence of white coat hypertension[7] the 90th percentiles of the daytime pressures in normotensive volunteers were used as arbitrary cut-off points, i.e. a pressure level of 134 mmHg systolic and 90 mmHg diastolic. Also other investigators relied on percentiles of the ambulatory measurements.[9,11,13,14] Remarkably, the definition of normality on the basis of the 5th to 95th percentile interval was judged to be acceptable for tightly distributed variables, such as serum sodium, but not for skewed measurements, such as BP.[3] However, by contrast to what has been suggested,[3] percentiles are nonparametric statistics which only require that a set of data be arranged in order of magnitude without implying any assumption on the shape of the underlying distribution. Thus, whether applied to serum sodium or BP, percentiles have exactly the same meaning.

The use of the 95th percentile for defining normality has also been criticised[3] because if it is applied to the general population, by definition 5% of all individuals must have an abnormally elevated BP. However, in the present study and in other reports[9,10,13,14] the 95th and 99th percentiles and the mean +2 and +3 standard deviations were not determined in the totality of the reference population but only in subjects with a normal conventional pressure. This approach therefore does not lead to an artificial 5% prevalence of hypertension on ambulatory measurement in the population at large. Conversely, < 95% of the hypertensive patients appear to have ambulatory pressures within the normal range (Tables II and III).

One possible drawback of using percentiles results from the fact that they may be meaningless if the sample size is too small or if sampling from the reference population is biased in a systematic way, for instance by the preferential inclusion of subjects with white coat hypertension. A first publication[11] on the Belgian population study was criticised[24] because it had excluded patients on antihypertensive treatment and involved only 328 normotensive and untreated hypertensive subjects. In this first publication[11] the following 95th percentiles for the 24h BP were reported: 134/87 mmHg in 85 younger (20–49 years) men, 147/87 mmHg in 74 older (≥ 50 years) men, 125/80 mmHg in 96 younger women and 150/83 mmHg in 73 older women. Although the Belgian reference population in the present report did include patients on antihypertensive treatment, and although its sample size had been increased to 718 subjects, the 95th percentiles of the 24h BP (Table II) were within a few mmHg comparable to those reported earlier.[11]

The use of the mean +2 and +3 standard deviations requires that the ambulatory pressure distributions do not deviate too much from normality. Whereas this assumption was obviously violated in the totality of the reference populations (Figure 1), this occurred to a much lesser extent when only persons with a normal conventional pressure were considered. This may have contributed to the high degree of concordance between the means +3 standard deviations, which were exclusively derived in the normotensive subjects and the regression boundaries, which were derived in all subjects regardless of their conventional pressure and treatment status.

Some investigators have proposed to define normality of the ambulatory pressure based on the discrepancy between conventional and ambulatory measurements.[25] In a group of mainly hypertensive (88%) subjects, the conventional pressures were demonstrated to be on average 18/10 mmHg higher than the 24h pressures and 14/7 mmHg higher than the daytime pressures. However, the discrepancy between the ambulatory and the conventional pressure is to a large extent dependent on the height of the conventional pressure[11,16] and on the age and the body mass index of the subjects.[16] Moreover, from a mathematical point of view there is no real difference between this new approach[25] and the regression method. Indeed, plotting the difference between two variables versus one of these variables must inevitably lead to the same conclusions as a direct plot of one variable versus the other.[26]

The present database provided the means to compare the ambulatory measurements among subjects who were either normotensive or hypertensive according to conventional sphygmomanometry.[17] One-tenth to over one-third of the hypertensive patients appeared to have ambulatory pressures below the 95th percentiles of the ambulatory pressures in the normotensive subjects. These findings

have recently been corroborated by an international group of researchers.[13] The latter study also demonstrated that the overlap tended to be greater in women and increased with advancing age. By contrast, the overlap diminished if the patients had shown higher pressures on conventional sphygmomanometry and if the diagnosis of hypertension had been reached after a greater number of visits and conventional BP readings. Nevertheless, even if these confounders were considered, the overlap remained substantial.[13] The fundamental question which still remains to be resolved is how the risk profile of hypertensive patients with a normal ambulatory BP differs from that of normotensive subjects and from the prognosis of patients in whom both the conventional and ambulatory pressures are elevated.

Studies available at this moment[27–29] suggest that there is a continuous relationship between the ambulatory pressure and the incidence of cardiovascular complications. Thus, defining an operational threshold for ambulatory monitoring[3] will necessitate concensus on arbitrary pressure limits for use in clinical practice, exactly as has been the case for conventional sphygmomanometry.[17] In this context, the present study demonstrated that across different populations consistent results can be achieved regardless of whether the thresholds were based on regressing the ambulatory on the conventional pressure in unselected subjects or on the distribution of the ambulatory BP in normotensive people. In addition, these thresholds approximated to earlier proposals.[1,10,13] However, the reference values presented in this and other[7–14] studies cannot yet be recommented for general use as their prognostic significance needs validation in longitudinal studies[30,31] and clinical trials.[6] Until this has been achieved, one should rely on conservative estimates to define normality of the ambulatory pressure.[32]

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