Non-invasive ambulatory blood pressure variability and cardiac baroreflex sensitivity

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Aim: The objective of this study was to evaluate the relationship between non-invasive ambulatory blood pressure variability and cardiac baroreflex sensitivity in hypertensive patients.

Subjects and methods: Ambulatory blood pressure measurements (15-min intervals for 24 h) and continuous blood pressure measurements (Finapres, 20 min at rest after a 10-min resting period) were performed in 123 untreated hypertensives (resting diastolic blood pressure ≥90 mmHg; 80 males, 43 females; mean ± SD age 49 ± 12 years, range 19–73). Fourier series were used to model 24-h blood pressure profiles (four harmonics). Ambulatory blood pressure variability was assessed by determination of the residuals in each 24-h blood pressure profile (measured minus predicted pressures). Resting blood pressure variability was defined as the SD of the mean Finapres value. Baroreflex sensitivity was evaluated by automatic detection of blood pressure and pulse interval sequences of ≥3 beats when systolic blood pressure and pulse interval sequences changed in the same direction (increase or decrease: 1 mmHg for systolic blood pressure and 4 ms for RR interval), and was assessed as the slope of the regression line for each sequence.

Results: Ambulatory systolic blood pressure variability increased with age ($r = 0.28$*) and systolic pressure ($r = 0.44$**). Baroreflex sensitivity (increasing systolic pressure/pulse interval) decreased significantly with age ($r = -0.48$**) and systolic pressure ($r = -0.23$**), and was significantly related to increased ambulatory blood pressure variability ($r = -0.33$**). In a multivariate stepwise analysis the relationship between ambulatory blood pressure variability and baroreflex sensitivity (increasing systolic pressure/pulse interval) was statistically independent of age and systolic pressure ($R = 0.55$, $P < 0.001$); this relationship was not observed with the corresponding decreasing sequence.

Conclusions: This study shows that in uncomplicated hypertension, ambulatory blood pressure variability is related to baroreflex sensitivity independently of the blood pressure level. This finding has prognostic implications for this non-invasive measurement, which needs to be confirmed by large longitudinal studies.

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Introduction

The level of blood pressure measured at rest in the physician's office is an undoubted risk factor in terms of morbidity and mortality. The ability to record blood pressure during activity by means of ambulatory recordings has allowed refinement of these prognostic data [1–3]. However, until recently, little account had been taken of the variability in blood pressure [4–6]. This variability can now be examined by intermittent blood pressure measurements during normal activity over a 24-h period or by continuous measurements using finger

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photophlethysmographic method by Finapres (Ohmeda, Englewood, Colorada, USA). It has been shown that blood pressure variability is a prognostic factor both in the short and in the long term, independently of age and the level of blood pressure [5,6]. We therefore set out to examine the relationships likely to exist between these two approaches to the study of variability in blood pressure.

Subjects and methods

The study comprised 123 patients with untreated mild or moderate hypertension in a multicenter French study (Grenoble, Lille, Paris, Poitiers). Mild to moderate hypertension was defined as a supine diastolic blood pressure of 95–114 mmHg on three consecutive visits in the absence of treatment or after withdrawal of treatment for at least 2 weeks. No subject showed any evidence of diabetic, neurological, coronary or valvular heart disease or heart failure, based on biological, clinical and ECG examinations. The mean age of these patients was 49 ± 12 years (range 19–73), there were 80 males and 43 females and the mean body mass index was 26 ± 6 kg/m^2.

Experimental procedures and analysis of blood pressure

Basal supine and standing blood pressure levels were measured after 10 min of rest using the World Health Organisation criteria. Left ventricular hypertrophy was measured by echocardiography (Hewlett–Packard model 77030A, Sonos 1500; Palo Alto, California, USA) following the recommendations of the American Society of Echocardiography (Penn Convention). The index of left ventricular mass was calculated according to Devereux *et al.* [7].

Ambulatory blood pressure measurements were recorded using the fully automatic monitor SpaceLabs (model 90207; Redmond, Washington, USA) set to record measurements every 15 min. Measurements showing diastolic pressure higher than systolic pressure were rejected, and also, if two successive pressure recordings (diastolic or systolic) differed by more than 50% without a concomitant increase in the heart rate, the second measurement was rejected. The 24-h profile was also rejected for the analysis if less than four recordings per hour were available for analysis [8,9]. About 10% of the data were discarded by this method.

Ambulatory blood pressure variability was evaluated by two methods, a simple daytime blood pressure variability calculated as the SD of the mean, and the predicted ambulatory blood pressure monitoring variability was calculated by a modeling method. Fourier series were used to model the 24-h blood pressure profiles [8]. Four harmonics were necessary to describe the data accurately. The ambulatory systolic and diastolic pressure variability was individually determined by calculating the residuals (measured minus predicted pressures) in each 24-h blood pressure profile.

Continuous measurement of blood pressure was performed over 20 min with the patient lying at rest after an initial 10-min resting period. This was done using a finger plethysmographic device (Finapres 2300) and also via dedicated software after 12-bit digitalization of the blood pressure signal at 200 Hz (PC Labcard 712; Advantech Co. Ltd, Lexington, MA, USA), the beat to beat systolic and diastolic and the interbeat pulse intervals were calculated. The resting blood pressure variability and Finapres diastolic variability were determined as SD of the mean resting blood pressure values.

The baroreflex sensitivity was examined according to Parati *et al.* [10], using dedicated software that identified the systolic blood pressure and pulse interval sequences which either increased progressively or decreased progressively over three or more consecutive beats. The threshold for change was set at 1 mmHg for systolic pressure and 4 ms for the pulse interval. If the correlation coefficient between systolic pressure and the pulse interval for each sequence was ≥0.95, then the slope was taken as a measure of the sensitivity of the baroreceptor heart rate reflex. Data from sets of sequences were averaged in order to obtain a mean value of baroreflex sensitivity.

Data were compared by Pearson correlation coefficients. Multiple linear regression analysis was used to assess the independent effects of age and 24-h mean systolic blood pressure on blood pressure variability and baroreflex sensitivity with significance at $^*P<0.05$ and $^{**}P<0.01$.

Results

The clinical characteristics of the subjects (mean age, sex ratio, body mass index, office, Finapres and ambulatory blood pressure) did not differ significantly between the groups from the four centers.

Office resting blood pressure values (162 ± 16/101 ± 9 mmHg) were significantly ($P<0.05$) higher than Finapres values (155 ± 21/84 ± 13 mmHg) and ambulatory blood pressure values (144 ± 14/92 ± 11 mmHg). Table 1 shows the ambulatory and short-term Finapres blood pressure variability.

Table 1. Ambulatory monitoring (ABPM) and short-term Finapres (F) systolic and diastolic blood pressure variability.

Variability	Systolic	Diastolic
ABPM	6.3 ± 1.4 (3.3–11.0)	7.7 ± 2.0 (94.7–16.2)
ABPM (SD)	13.8 ± 4.1 (7–30)	11.4 ± 3.2 (6.1–20)
F (SD)	7.6 ± 2.9 (1.7–14)	3.2 ± 1.4 (2.4–14)*
F–ABPM (p)	–0.07 ± 3.2	–3.1 ± 1.8*
F–ABPM) (SD)	7.8 ± 4.5**	8.1 ± 3.6**

Values are expressed as means ± SD (range). ABPM predicted (p): 24-h ambulatory systolic and diastolic blood pressure variability obtained by determination of the residual; SD, variability determined by SD of the mean. Finapres–ABPM, mean paired difference between Finapres and ABPM. *$P<0.05$, **$P<0.01$.

The simple daytime ambulatory blood pressure monitoring variability (SD of the mean) was related to the 24-h ambulatory blood pressure monitoring level (r=0.31* between systolic blood pressure variability and mean ambulatory blood pressure, r=0.19* for diastolic blood pressure). The simple daytime ambulatory pressure variability was not related to age (systolic blood pressure, r=0.12; diastolic blood pressure, r=–0.16) or to the left ventricular mass index (r=0.10 and r=–0.07, respectively).

Predicted ambulatory blood pressure variability was related to the 24-h ambulatory blood pressure level. Ambulatory systolic and diastolic blood pressure variability increased with 24-h ambulatory blood pressure levels (r=0.42** between mean systolic blood pressure and variability and r=0.28* for diastolic blood pressure). The predicted ambulatory systolic blood pressure variability increased with age (0.28**), but not diastolic blood pressure variability. The predicted ambulatory blood pressure variability increased with the left ventricular mass index (systolic, r=0.34**; diastolic, r=0.29**). No relationship between variability and sex or the body mass index was found by either method.

According to these results and because of the theoretic advantage of the modeling method for measurements of ambulatory blood pressure variability, we present only the results from the modeling method.

With the Finapres, systolic but not diastolic variability increased with age (r=0.22* and r=0.12, respectively). Systolic and diastolic Finapres variability was higher in female subjects (0.29**, 0.22*) but there was no relationship to the body mass index. The systolic and diastolic Finapres variability was positively related to the systolic and diastolic ambulatory variability (r=0.22*, r=0.21*). The diastolic Finapres variability was significantly lower than the diastolic ambulatory variability ($P<0.05$), but systolic Finapres and systolic ambulatory blood pressure variability were not significantly different (Table 1). The agreement between the two methods of measurement is represented on Fig. 1.

The baroreflex sensitivity was 7.7 ± 3.5 ms/mmHg (range 1.7–20.0) for increasing and 8.8 ± 4.8 ms/mmHg (range 2.2–31.7) for decreasing systolic pressure/pulse interval sequences. The corresponding number of sequences per recording was 31 ± 29 (range 1–152) and 27 ± 26 (range 1–185), respectively. The analysis of the distribution of the number of sequences showed that 95% of the subjects had over three sequences per recording of two different types.

The baroreflex sensitivity sequences decreased with age (increasing: r=–0.48**; decreasing, r=–0.44**). No relationship was observed with sex or the body mass index. Increasing sequences were significantly related to mean ambulatory systolic blood pressure (r=–0.23*), but not to Finapres or resting blood pressure values. Decreasing sequences were not related to ambulatory, Finapres or resting blood pressure values.

There was a significant negative relationship between baroreflex sensitivity (both increasing and decreasing sequences) and Finapres systolic (r=–0.26*, r=–0.23**, respectively) but not Finapres diastolic variability. There was also a significant negative relationship between increasing sequences and ambulatory systolic and diastolic blood pressure variability (r=–0.35** and r=–0.21*, respectively), but not decreasing sequences (Fig. 2). A multivariate stepwise analysis showed that the relationship between increasing sequences and ambulatory systolic variability was statistically independent of the systolic blood pressure level (Fig. 2).

The mean left ventricular mass index was 113.5 ± 32.8 g/m^2 (range 44.2–242.2). This index was significantly related to age (r=0.19, $P=0.03$) and 24-h ambulatory blood pressure (systolic: r=0.40**; diastolic r=0.36**). The left ventricular mass index was not significantly correlated with short-term Finapres blood pressure variability (systolic: r=–0.01, NS; diastolic: r=0.02, NS), but was significantly correlated with predicted ambulatory blood pressure variability. The multivariate stepwise regression analysis showed that the left ventricular mass index and ambulatory systolic blood pressure variability were statistically related (R=0.45; left ventricular mass index = 0.71(24-h systolic blood pressure) + 27.8(ln ambulatory systolic blood pressure variability) – 44; F=14, $P<0.0001$; Table 2).

Discussion

The present study confirms previous findings of a relationship between baroreflex sensitivity and blood pressure variability, both in ambulatory recordings [10,11] and at rest [12]. The previous studies used pharmacological methods [11] and recorded spontaneous variability in blood pressure by invasive [10] and non-invasive techniques [12]. The present study further demonstrates that (1) daytime blood pressure variability can be evaluated by ambulatory monitoring using discontinuous non-invasive recordings, (2) daytime blood pressure variability is related to short-term blood

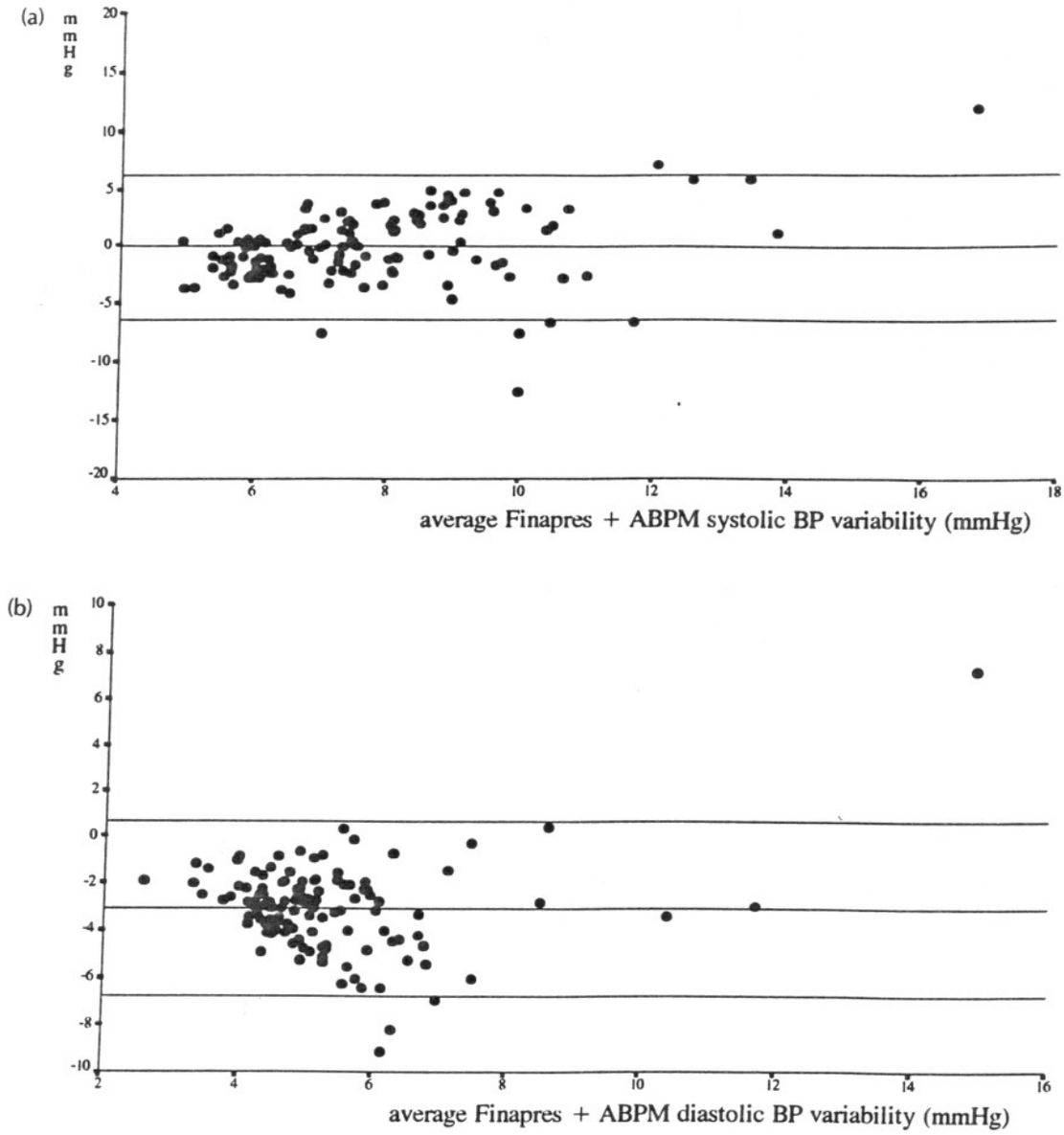

Fig. 1. Agreement between Finapres and ambulatory monitoring (ABPM) measurements of (a) systolic and (b) diastolic blood pressure (BP) variability. The two estimates of variability were significantly correlated, and only Finapres diastolic variability was significantly lower than ambulatory diastolic blood pressure variability ($P<0.05$) with a mean paired difference of -3.1 ± 1.85 mmHg.

pressure variability and (3) ambulatory and resting variability are related to baroreflex sensitivity.

Ambulatory blood pressure monitoring has become the focus of much research because there is some evidence that this method gives more prognostic information than casual measurements [5,6].

A number of definitions have been formulated to express the variability of ambulatory recordings. Mancia *et al.* [11] defined variability from short-term recordings of less than half an hour and long-term variability from studies of over half an hour. Thus the use of intermittent 15-min ambulatory measurements will not give the same definition of variability. It is known that blood pressure measurements taken every 15 min give a good estimate of the mean blood pressure over 24-h compared to invasive measurements, but the use of such measurements to assess blood pressure variability is debatable. Gerin *et al.* [13] claim that a more frequent sampling interval with measures every 5 min may give a more reliable estimate of variability. Di Rienzo *et al.* [14] demonstrated that the difference in variability between an invasive reference value and intermittent readings was larger than 10% with a sampling interval of up to 15 min [14]. Thus it seems that sampling at 15-min intervals is a reasonable compromise

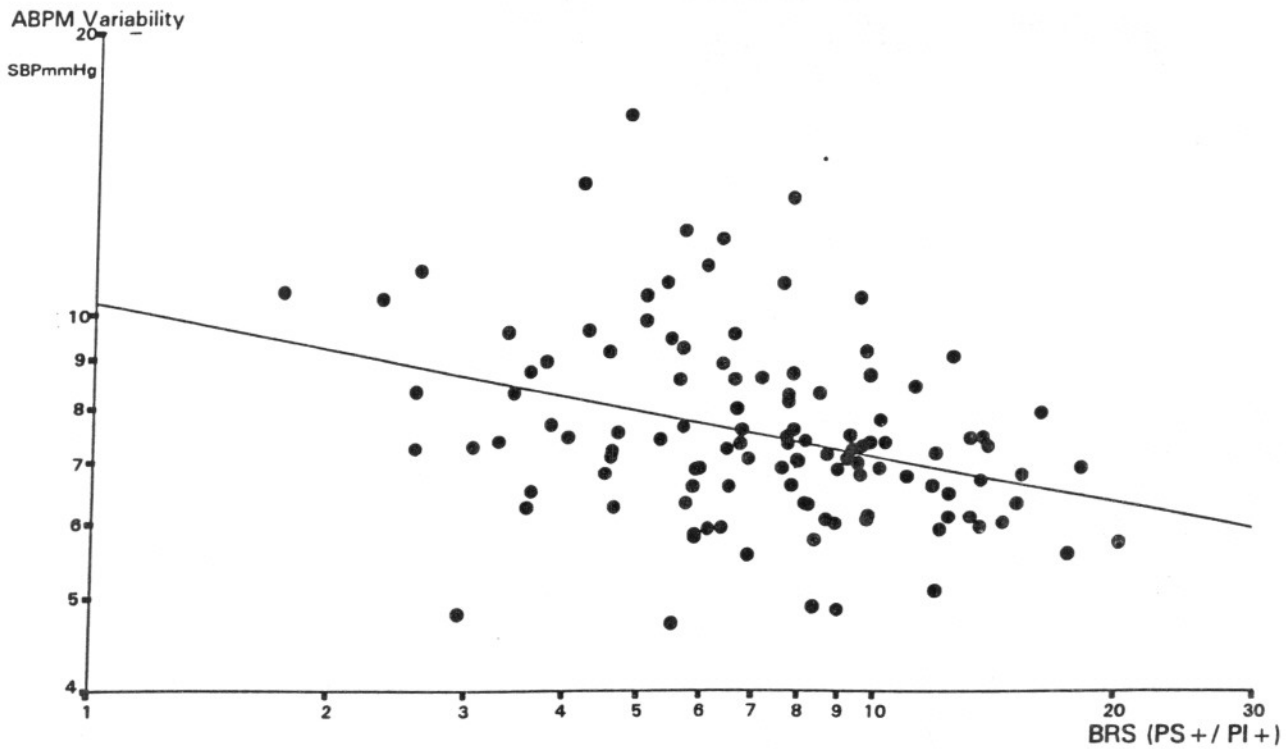

Fig. 2. Scatterplot shows correlation between ambulatory blood pressure (ABPM) systolic blood pressure (SBP) variability and baroreflex sensitivity (BRS) to sequences of increasing systolic pressure/pulse interval (PS+/PI+; ms/mmHg). Univariate relationship between ambulatory blood pressure and baroreflex sensitivity: $r = -0.35$, $P < 0.001$. Multivariate stepwise analysis (systolic blood pressure level as related variable): $R = 0.51$; ln(ABPM systolic variability] $= -0.145 \cdot \ln(\text{BRS PS+/PI+}) + 0.006$ 24-h SBP + 1.45; $F = 21.6$, $P < 0.0001$.

Table 2. Stepwise regression analysis for left ventricular mass index (LVMI) as dependent variable and related variables.

LVMI	r	R	β	SEβ	*P*
24-h SBP	0.40**	0.40	0.71	0.20	0.0007
SBP var. ABPM p	0.37**	0.45	27.8	12.9	0.0335
Age	0.22*	–			0.208

r, Pearson value for univariate relationship; R, multiple model value; SBP, systolic blood pressure; SBP var. ABPM p, ambulatory systolic blood pressure variability predicted by determination of the residual.

between methodological constraints and the technical limits of repeated, frequent, mechanical, non-invasive measurements which are unlikely to be acceptable over a long period [15]. Indeed, in the present investigation, up to 10% of samplings were discarded because of missing values.

By using four measurements an hour to model the ambulatory blood pressure profile, the mean 24-h blood pressure profile can be evaluated [8]. Evaluation of the residual, which is defined as the spread of the measured values compared to those predicted by the model, allowed us to construct individual profiles for a global examination of the relationship between blood pressure variability and different 24-h blood pressure values. This method of analysis confirmed previous findings of increased variability with age, blood pressure and the left ventricular mass index, and revealed relationships between ambulatory blood pressure variability and baroreflex sensitivity measured at rest. This work further confirms the relationships demonstrated by Mancia *et al.* [11] using invasive measurements, and our relationships were also close to those obtained by the neck chamber technique and pharmacological methods.

In the present study, only increasing systolic pressure/pulse interval sequences (baroreflex sensitivity) were significantly related to blood pressure variability measured by ambulatory monitoring, but both increasing and decreasing sequences have been related to blood pressure variability by using pharmacological techniques. However, these relationships were weak, suggesting that in addition to the different types of baroreflex sensitivity explored by the two methods, diurnal variation also contributes to baroreflex sensitivity as indicated by Parati *et al.* [10] in ambulatory studies. Thus it appears that other parameters should to be evaluated, such as the effect of daily activity on variability [16].

To our knowledge there have been no studies on the practical usefulness of short-term blood pressure variability evaluated at rest. We have shown a correlation between the two modes of evaluation of blood pressure variability, but the fluctuations in blood pressure described by the two techniques were not superimposable. It is obviously difficult to compare continuous measures made at rest by Finapres with discontinuous ambulatory measures. It is likely that these two measures of variability depend on different mechanisms which are,

however, both related to baroreflex sensitivity. In the present study, when baroreflex sensitivity fell, short-term variability (Finapres) and long-term ambulatory blood pressure variability increased, and vice versa. Thus we have confirmed the relationship between baroreflex and blood pressure variability by both continuous and ambulatory measurements.

We know of no studies showing a pronostic significance for short-term blood pressure variability measured at rest. We have examined the relationship between short-term variability and left ventricular hypertrophy, but did not find a significant effect [17]. This was also the case for the relationship between the left ventricular mass index and a simple measurement of blood pressure variability such as the SD of 24-h ambulatory blood pressure. This is in contrast to our present findings: we observed a significant relationship only with the modeled measure of blood pressure variability. This finding emphasizes the limited evidence available on the correspondence between data obtained by modeling 24-h blood pressure profiles and the 'raw' assessment of blood pressure variability obtained without mathematical modeling. Futhermore, this predicted ambulatory blood pressure variability was related to two prognostic indices, baroreflex sensitivity and the left ventricular mass index. Similar findings have been reported previously. Parati *et al.* [5] were the first to find a correlation between the variability in blood pressure measured intra-arterially and the development of lesions in target organs. More recently, Verdecchia *et al.* [18] used an intermittent auscultatory method to study the effect of variability on morbidity and mortality. However, intermittent ambulatory blood pressure values allow only a very crude estimate of variability.

Our demonstration of a close relationship between resting blood pressure measurements (which allow an evaluation of baroreflex sensitivity and discontinuous ambulatory blood pressure variability seems to indicate that analysis of short-term variability may give some pronostic information. If this is indeed the case, short-term measurements of blood pressure obtained by the Finapres and long-term predicted ambulatory blood pressure variability have the great advantage of simplicity and ease of use. The possible prognostic value of those measurements needs to be confirmed by large longitudinal studies.

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