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Comparison between invasive and non-invasive measurements of baroreflex sensitivity

Implications for studies on risk stratification after a myocardial infarction

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Aims The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study has proved the independent prognostic value of baroreflex sensitivity. A limitation of the traditional method of estimating baroreflex sensitivity by phenylephrine, is the need to monitor intra-arterial blood pressure. Our objective was to establish whether this invasive method of monitoring could be superseded by non-invasive methods, such as the Finapres device.

Methods and Results Patients with three repeated invasive and non-invasive baroreflex sensitivity measurements were selected from the ATRAMI database (n=454). The mean of these measurements was taken as the baroreflex sensitivity estimate. The repeatability of both methods (standard deviation of the three measurements) decreased with increasing baroreflex sensitivity. There was no constant bias between invasive and non-invasive measurements ($0{\cdot}22 \pm 2{\cdot}2$ ms . mmHg^{-1}, $P=0{\cdot}42$). The linear correlation was very high (r=0·91, $P<0{\cdot}01$). The normalized 95% limits of agreement were $-0{\cdot}5$ and 0·52. On survival analysis, invasive and non-invasive baroreflex sensitivity gave similar prognostic information (likelihood ratio: 155·6 ($P=0{\cdot}007$) and 155·0 ($P=0{\cdot}006$); risk ratio: 0·79 and 0·81, respectively). According to the ATRAMI cut-off points, 85% of patients were classified concordantly by the two methods. None of the patients at high (low) risk with the invasive method were classified as low (high) risk class by the non-invasive method.

Conclusion Despite wide limits of agreement, invasive and non-invasive baroreflex sensitivity measurements are highly correlated and provide equivalent prognostic information.
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Key Words: Baroreflex sensitivity, myocardial infarction, risk stratification, Finapres.

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Introduction

Control of the heart rate by arterial baroreceptors is mainly studied by analysing the response of the heart rate to changes in blood pressure induced by a vasoactive drug[1]. Usually, an intravenous bolus of the alpha-adrenoreceptor stimulant phenylephrine is administered to the subject while monitoring beat-to-beat changes in the systolic arterial pressure and RR interval. The slope of the linear regression line fitting the relationship between these changes quantifies the strength of the baroreceptor reflex, i.e. baroreflex sensitivity. Besides its intrinsic value in cardiovascular research, measurement of baroreflex sensitivity has gained considerable interest as a new clinical tool, since alterations in the baroreflex control of heart rate have been associated with an increased propensity for cardiac mortality and sudden cardiac death[2]. Recently, the multicentre study ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction), which enrolled 1284 patients with a

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recent myocardial infarction who were followed for a mean of 21 months, has provided definitive evidence of the prognostic value of baroreflex sensitivity, by showing that low baroreflex sensitivity (<3 ms . mmHg^{-1}) yields a 2·8-fold risk for cardiac mortality, independent of well established risk stratifiers such as depressed left ventricular function and frequent ventricular arrhythmias[3,4].

Beat-to-beat recording of arterial pressure during the phenylephrine test has traditionally been performed through cannulation of the radial or brachial artery[1,5]. This invasive technique, however, represents a major limitation to the widespread application of the phenylephrine test in the clinical setting. The development of a well validated device for non-invasive recording of blood pressure based on the volume–clamp method (Finapres) has overcome this limitation. However, the accuracy of non-invasive baroreflex sensitivity measurements, which has been evaluated only in small samples of hypertensive[6] or suspected coronary artery disease[7] patients, remains unclear.

The purpose of the present study was to compare the two methods in a large sample of post myocardial infarction patients enrolled in the ATRAMI study in order to establish whether or not the non-invasive measurement of baroreflex sensitivity can supersede those done invasively, thus facilitating the routine clinical use of baroreflex sensitivity.

Methods

Study subjects

The study was based on data collected within the ATRAMI multicentre study. The enrolment procedures, clinical follow-up, and results have been described previously[3]. Systolic arterial pressure was obtained directly in 70% of patients from the brachial or radial artery, or non-invasively by the Finapres in 30%. Both methods were used in 614 patients. For the purpose of assessing not only the agreement between the two methods but also their repeatability, the present study required patients in whom at least three repeated estimates of baroreflex sensitivity, both invasive and non-invasive, using the same dosage were available. These criteria and the exclusion of patients with one unreliable test (see below) reduced the final sample of the study to 454 subjects.

Protocol

After instrumentation, calibration and signal stabilization (≥ 10 min) the phenylephrine test was administered to each subject according to the Oxford technique[5]. Briefly, phenylephrine (2–4 μg . kg^{-1}) was given as an intravenous bolus to raise systolic arterial pressure by 15–40 mmHg. If the blood pressure increase was not sufficient, additional injections were made with increments of 25 μg of phenylephrine. At least three bolus injections were made at 10 min intervals at the dosage that caused the desired increase in systolic pressure. Besides the ECG, the arterial blood pressure was simultaneously recorded from the same arm both invasively, via brachial or radial artery cannulation, and non-invasively, via the finger blood pressure monitor Finapres 2300 (Ohmeda Corp.).

Signal acquisition and processing

All analog signals were digitized at 250 Hz on a personal computer and processed in order to obtain RR interval and systolic arterial pressure time series. Data files were then sent to the coordinating centre to be analysed by two investigators well acquainted with the technique (M.T. L.R. and A.M.).

The time series of RR interval and systolic pressure changes with respect to their median values during the pre-injection phase (30 s) were plotted together and the analysis window was selected as the interval between the beginning and the end of the first significant increase (≥ 15 mmHg) in systolic pressure. Recordings containing artifacts were discarded. The slope of the regression line relating RR interval changes to systolic pressure changes in the analysis window (i.e. the baroreflex sensitivity) was then automatically computed. Regression lines with a non-significant slope ($P>0{\cdot}05$) were not accepted. The average value of the three measurements was conventionally considered the final baroreflex sensitivity estimate for each subject[1]. Henceforth, it will be referred to as invasive and non-invasive baroreflex sensitivity.

Statistical analysis

Statistical analysis aimed: (1) at investigating the repeatability of each of the two methods, (2) at assessing the strength of association and the agreement between them, and (3) at testing the equivalence of their prognostic value.

To reach the first goal we tested for the presence of a systematic change between successive measurements by the Wilcoxon matched paired test, and verified whether the repeatability was dependent on the magnitude of the baroreflex sensitivity by analysing the regression between the standard deviation of the three baroreflex sensitivity measurements and the corresponding average. Standard deviations obtained by the two methods were finally compared by the Wilcoxon matched paired test.

The second goal was reached by analysing (1) the correlation between invasive and non-invasive baroreflex sensitivity and the relationship between their difference (i.e. invasive–non-invasive) vs invasive

Table 1 Baseline clinical characteristics (n=454)

Age (years)	58 ± 10
Male sex (%)	89
Site of MI	
Anterior (%)	47
Inferior (%)	49
Other (%)	4
Thrombolytic therapy (%)	64
LVEF (%)	49 ± 11

MI=myocardial infarction, LVEF=left ventricular ejection fraction.
Age, LVEF are mean ± SD.

baroreflex sensitivity (Bland–Altman method)[8]. The latter procedure was also carried out using the normalized difference, as this enabled computation of the limits of agreement between the two measurements[8]. We used invasive baroreflex sensitivity as a reference because we assumed that it would represent the gold standard.

To test for the equivalence of the prognostic value of invasive and non-invasive measurements, a Cox proportional hazards model was fitted to survival data, using cardiac mortality as the primary end-point[3]. As explanatory variables we first used the non-invasive baroreflex sensitivity measurement and its difference with respect to that done invasively, namely the measurement error due to Finapres monitoring of arterial pressure. We tested whether this error contains independent prognostic information. Survival analysis was then repeated using invasive and non-invasive baroreflex sensitivity separately as explanatory variables, and the two prediction models were compared by the likelihood ratio statistic and the hazard ratio.

Patients were also classified according to the three baroreflex sensitivity risk stratification ranges identified in the ATRAMI study: <3 ms . mmHg^{-1}, 3–6·1 ms . mmHg^{-1} and $>6{\cdot}1$ ms . mmHg^{-1}[3] using both measurement methods of baroreflex sensitivity. We tested for the presence of an association between these categorized measurements of baroreflex sensitivity by the Mantel–Haenszel chi-square test. The strength of the association was assessed by the Pearson coefficient.

Descriptive results are expressed as mean ± SD. In case of a marked violation of the assumption of normality in the distribution of data (Shapiro–Wilk's W test), results are expressed as median (interquartile range). The level of significance was set at 0·05.

Results

The clinical characteristics of the patients included in the study are given in Table 1. These data are very similar to those of the entire population of the ATRAMI study[3], indicating that the sample of patients considered in our study was truly representative of that population. Descriptive statistics of baroreflex sensitivity measurements obtained by both methods are given in Table 2. Median values are remarkably similar in the two methods and there is no trend between successive measurements ($P>0{\cdot}63$ for all comparisons). Of note, expressing baroreflex sensitivity data as mean ± SD instead of as median (interquartile range), yields $7{\cdot}3 \pm 4{\cdot}8$ ms . mmHg^{-1}, which is almost the same as that in the entire ATRAMI sample ($7{\cdot}2 \pm 4{\cdot}6$ ms . mmHg^{-1})[3].

Scatterplots and regression lines of the standard deviation of the three measurements against their mean are shown in Fig. 1(a) and (b) for invasive and non-invasive measurements, respectively. In both cases, the standard deviation is dependent on the baroreflex sensitivity magnitude ($R^2=0{\cdot}44$ for invasive and $R^2=0{\cdot}52$ for non-invasive, $P<0{\cdot}01$), indicating that the repeatability of the phenylephrine test measurements tends to decrease as baroreflex sensitivity increases. The median difference between the standard deviation of the two methods was 0·16 (1·2) ms . mmHg^{-1} ($P<0{\cdot}01$).

The scatterplot of non-invasive vs invasive baroreflex sensitivity represented in Fig. 2 shows a very high linear association between them ($r=0{\cdot}91$). The Bland–Altman[8] plot of the difference between the two measurements against invasive baroreflex sensitivity (Fig. 3) clearly demonstrates that the disagreement between the two methods increases as the baroreflex sensitivity increases. The mean difference between invasive and non-invasive baroreflex sensitivity was $0{\cdot}22 \pm 2{\cdot}2$ ms . mmHg^{-1} ($P=0{\cdot}42$), indicating that there was no constant bias between the two measurements.

In the Bland–Altman plot of the normalized difference between invasive and non-invasive measurements vs invasive baroreflex sensitivity shown in Fig. 4, the distribution of data as baroreflex sensitivity increases is

Table 2 Baroreflex sensitivity (BRS) measured in the three successive phenylephrine tests

	BRS 1	BRS 2	BRS 3	Average BRS	SD BRS
Invasive (ms . mmHg^{-1})	6·1 (5·2)	6·1 (5·3)	6·2 (4·8)	6·2 (5·2)	1·2 (1·4)
Non-invasive (ms . mmHg^{-1})	6·2 (5·8)	5·9 (6·1)	6·1 (5·6)	6·2 (6·0)	1·3 (1·7)

BRS 1, BRS 2 and BRS 3 are, respectively, the first, second and third baroreflex sensitivity measurement. The average value of these measurements (Average BRS) was conventionally considered the final baroreflex sensitivity estimate for each subject. SD BRS is the standard deviation across the three tests. Due to their skewed distribution, data are expressed as median (interquartile range).

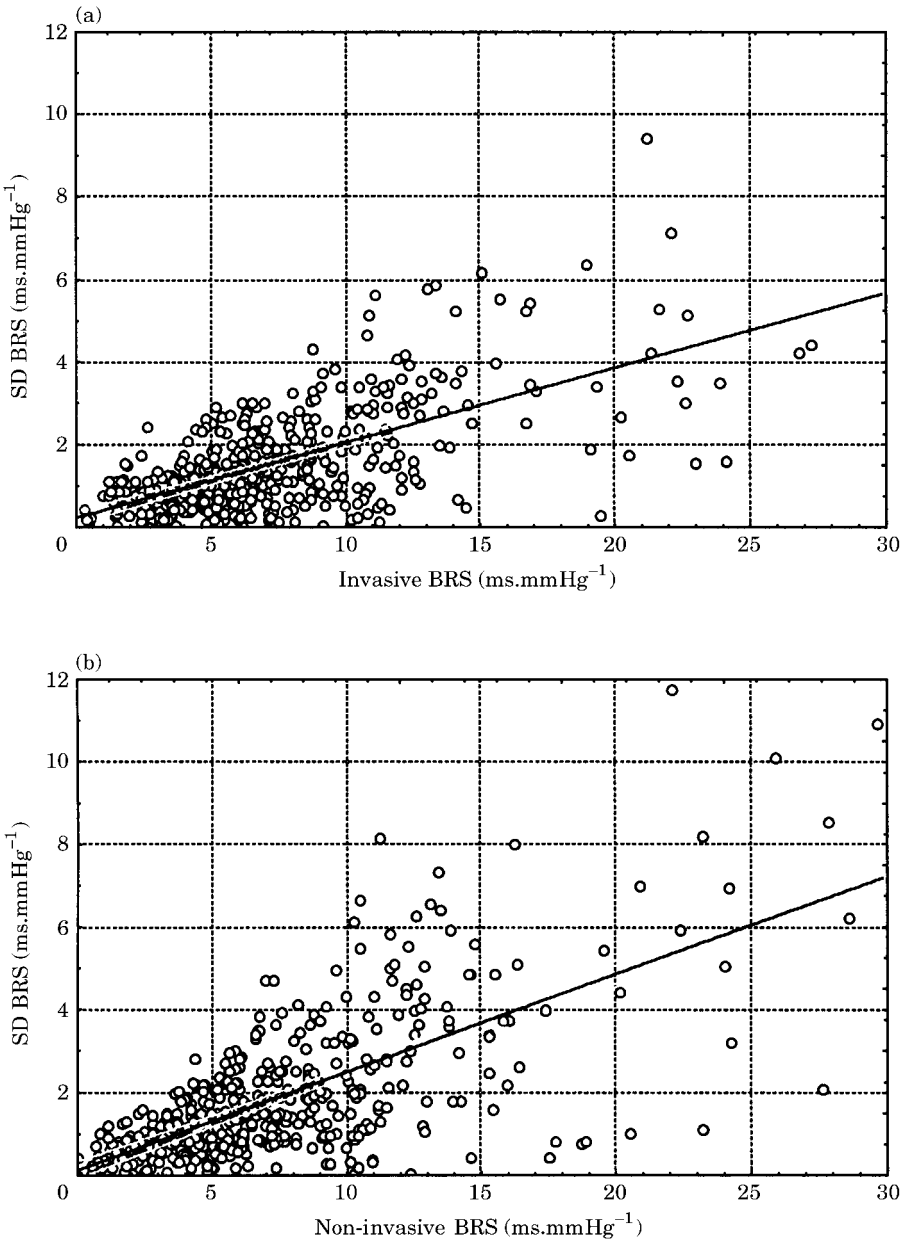

Figure 1 **Scatterplot and least squares regression line for the relationship between the SD of the three baroreflex sensitivity measurements performed in each subject and their mean using (a) invasive and (b) Finapres monitoring of arterial pressure. Invasive baroreflex sensitivity: mean value of the three invasive baroreflex sensitivity measurements. Non-invasive baroreflex sensitivity: mean value of the three non-invasive baroreflex sensitivity measurements.**

much more uniform. The limits of agreement were $-0{\cdot}5$ and 0·52, indicating that 95% of non-invasive measurements will lie between 0·5 and 1·52 times the simultaneous invasive measurement; 50% of the non-invasive measurements will lie between 0·84 and 1·18 times the simultaneous invasive measurement.

Cardiac mortality occurred in 14 out of the 454 (3·1%) patients. Analysis of survival data showed that no additional independent prognostic information was contained in the measurement error ($P=0{\cdot}42$). The likelihood ratio statistic for the invasive and non-invasive prediction models was, respectively, 155·6 ($P=0{\cdot}007$) and 155·0 ($P=0{\cdot}006$), indicating that the two models equally explain the variation, i.e. equally fit the data. Risk ratios were 0·79 (95% confidence limits: $0{\cdot}64 \div 0{\cdot}96$) and 0.81 (95% confidence limits: $0{\cdot}67 \div 0{\cdot}97$), respectively, for the invasive and the non-invasive measurement.

The contingency table relating invasive and non-invasive categorized baroreflex sensitivity data accord-

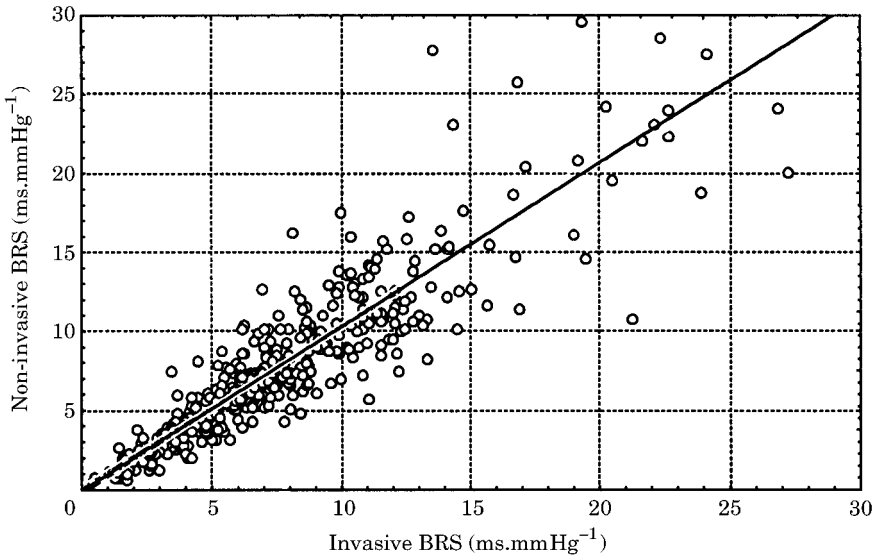

Figure 2 **Scatterplot and least squares regression line for the relationship between baroreflex sensitivity estimates using invasive and Finapres monitoring of arterial pressure. Invasive baroreflex sensitivity: mean value of the three invasive baroreflex sensitivity measurements. Non-invasive baroreflex sensitivity: mean value of the three non-invasive baroreflex sensitivity measurements.**

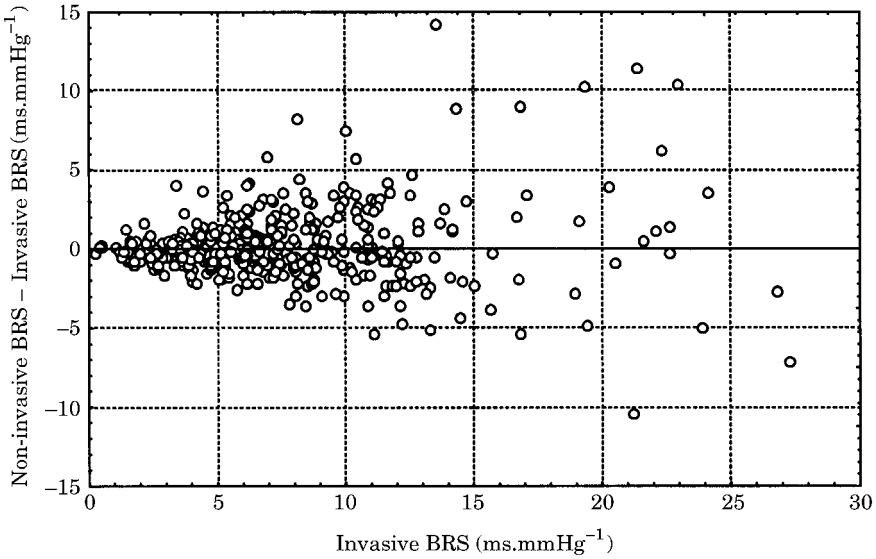

Figure 3 **Bland–Altman scatterplot and zero line of the difference between non-invasive and invasive baroreflex sensitivity against invasive baroreflex sensitivity. Invasive baroreflex sensitivity: mean value of the three invasive baroreflex sensitivity measurements. Non-invasive baroreflex sensitivity: mean value of the three non-invasive baroreflex sensitivity measurements.**

ing to the ATRAMI risk stratification cut-off points, is given in Table 3. About 85% of the patients in the study were classified concordantly by the two measurement methods (Mantel–Haenszel chi-square=329, P=0·001). The Pearson correlation coefficient was 0·85 (P<0·01), indicating a high linear association between the two categorized variables. Importantly, none of the patients at high risk according to the invasive measurement (baroreflex sensitivity <3) was classified in the low risk class with the non-invasive method; similarly, none of those in the low risk class (baroreflex sensitivity >6·1) was classified as high risk by the other method.

Discussion

The present study demonstrates that invasive and non-invasive measurements of baroreflex sensitivity have

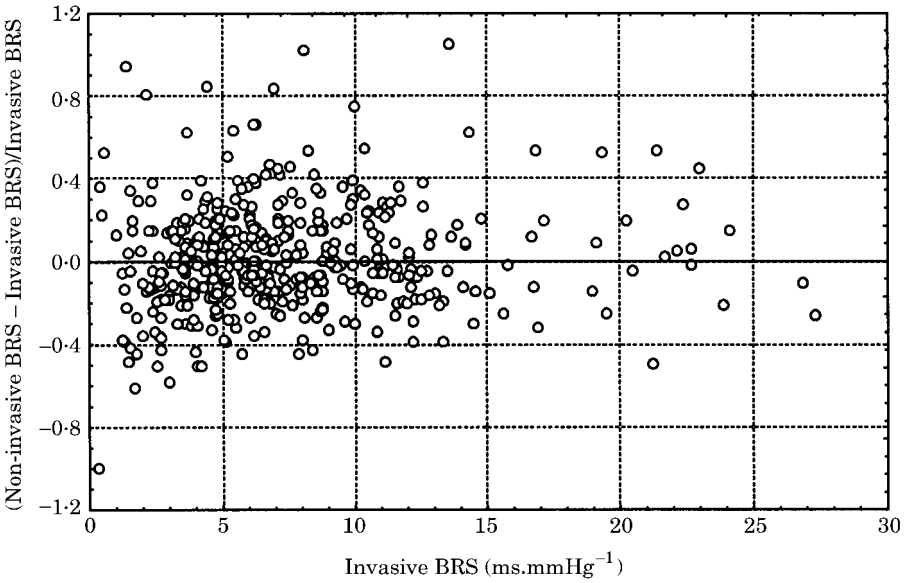

Figure 4 **Bland–Altman scatterplot and zero line of the normalized difference between non-invasive and invasive baroreflex sensitivity against invasive baroreflex sensitivity. Invasive baroreflex sensitivity: mean value of the three invasive baroreflex sensitivity measurements. Non-invasive baroreflex sensitivity: mean value of the three non-invasive baroreflex sensitivity measurements.**

Table 3 Contingency table relating invasive and non-invasive categorized baroreflex sensitivity data according to the risk stratification cut-off points proposed in the ATRAMI study

	Non-invasive BRS <3 ms . mmHg^{-1}	Non-invasive BRS 3÷6·1 ms . mmHg^{-1}	Non-invasive BRS >6·1 ms . mmHg^{-1}
Invasive BRS <3 ms . mmHg^{-1}	55	4	0
Invasive BRS 3÷6·1 ms . mmHg^{-1}	12	123	23
Invasive BRS >6·1 ms . mmHg^{-1}	0	31	207

similar short-term repeatability, are strongly correlated, and have no constant relative bias. Moreover, the two methods provide equivalent prognostic information and are equally effective in identifying high risk patients.

The practical importance of this information lies in the fact that interest in the clinical use of baroreflex sensitivity has grown since the demonstration by ATRAMI of its independent prognostic value in patients after myocardial infarction[3,4]. It is evident that widespread clinical use requires the availability of reliable non-invasive monitoring of arterial blood pressure.

Methodological considerations

The absence of any systematic trend between consecutive bolus injections of phenylephrine, both in invasive and non-invasive baroreflex sensitivity measurements, shows that there is no carry-over effect of the drug. However, the dispersion of baroreflex sensitivity measurements within each subject showed a clear trend towards an increase, in parallel with larger values of baroreflex sensitivity. Two factors may contribute to this phenomenon. First, the higher variability in the response observed in patients with a valid baroreflex is a common feature of all control systems whose stability tends to decrease as the gain increases. Second, small changes in the angle of the regression line relating changes in the RR interval to changes in systolic pressure occur often, due to either the effect of noise or physiological perturbations such as respiration or intra-rater variability in the selection of the analysis window. These small changes have a greater impact on high than low values of baroreflex sensitivity because the slope of the regression line is a non-linear function of the angle itself.

Non-invasive estimates of baroreflex sensitivity did not show any systematic offset with respect to those performed intra-arterially, as the error was evenly

distributed over positive and negative values (Fig. 3). This is apparently in contrast with the positive bias observed by other investigators using either constant infusion[9] or bolus injection of phenylephrine[7]. However, the difference reported by Hartikainen *et al.* between the two methodologies was largely dependent on the absolute value of baroreflex sensitivity, being almost evenly distributed around zero for low baroreflex sensitivity values and largely positive for higher baroreflex sensitivity values. Furthermore, the difference in our respective conclusions is probably due to the small sample size burdened by a few outliers in their study.

Two studies have indicated a strong linear association between non-invasive and invasive baroreflex sensitivity independent of the population considered[6,7]. However, to evaluate the agreement between the two methods it is far more appropriate to analyse the difference between the two measurements vs the invasive baroreflex sensitivity. We found that the dispersion of this difference increased with increasing values of invasive baroreflex sensitivity, a phenomenon which simply reflects the increase in variability between repeated baroreflex sensitivity measurements (Fig. 1(a) and (b)). This has the advantage of making the relative error of non-invasive baroreflex sensitivity fairly constant within the physiological range of the population of the study (0·5–27 ms . mmHg^{-1}), yielding 95% confidence limits for this error of approximately $\pm 50\%$ of the invasive baroreflex sensitivity. Even though this error may appear large, it has to be noted that half of the non-invasive measurements will actually lie between -16% and $+18\%$ of the corresponding invasive ones. Although in the studies by Parati and Hartikainen the limits of agreement were not computed, similar[7] or slightly lower errors[6] than those found in our study can be derived from their plots.

Several factors contribute to the differences in measurements by the two methods. Indeed, beat-to-beat discrepancies in blood pressure values are not only due to the different site of blood pressure detection (i.e. more distal for Finapres compared to intra-arterial) but also to the interfering effect of smooth muscle tone of the small finger arteries under the cuff during Finapres measurements[10,11]. It is therefore conceivable that under conditions of phenylephrine-induced constriction of these small arteries, the resulting physiological changes of the pulse pressure at the periphery and the interfering effect of smooth muscle tone could affect Finapres blood pressure measurements and hence baroreflex sensitivity estimates.

Clinical implications

Although the estimated normalized limits of agreement between non-invasive and invasive baroreflex sensitivity clearly indicate the likelihood of a substantial error in the measurement by Finapres, this error does not play a significant role when considering the practical implications of baroreflex sensitivity measurement in the clinical setting. Three arguments support this concept.

First, there is nothing to suggest that, within the range representing normal values, a given value of baroreflex sensitivity might carry a specific physiological implication different from that of another value. For example, we cannot attach a different significance to a baroreflex sensitivity of 12 vs a baroreflex sensitivity of 16 ms . mmHg^{-1}. In this regard, the non-invasive measurement is quite sufficient to correctly identify whether baroreflex sensitivity is within the physiological range of variation of the population under study, due to the close linear relationship between invasive and non-invasive baroreflex sensitivity (Fig. 2).

The second point concerns the major clinical implication of baroreflex sensitivity assessment, namely its prognostic information in post-myocardial infarction patients. In this regard, we found a substantial identity between the two measurements, as indicated by the closeness of both model fitting and hazard ratios.

Third, using the ATRAMI cut-off points to define the classes of risk for patients after myocardial infarction, 85% of the subjects were correctly classified using the Finapres. It is important to emphasize that misclassification occurred only between contiguous classes (high risk and intermediate, and low risk and intermediate) and that not a single patient identified as at high risk according to the invasive measurement was classified as at low risk by the non-invasive method.

Conclusions

Although the non-invasive measurements were highly correlated to intra-arterial measurements and did not show any systematic offset, the limits of agreement were wide. Nonetheless, the practical implication of this error in the clinical use of baroreflex sensitivity as an indicator of the strength of the reflex and as a prognostic index is negligible. Thus, non-invasive measurements of baroreflex sensitivity can replace invasive measurements for risk stratification in clinical practice.

References

[1] La Rovere MT, Pinna GD, Mortara A. Assessment of baroreflex sensitivity. In: Malik M, ed. Clinical guide to cardiac autonomic tests. Dordrecht, The Netherlands: Kluwer Academic Publishers, 1998: 257–81.
[2] Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death: experimental basis and clinical observations for post-myocardial infarction risk stratification. Circulation 1992; 85 (Suppl 1): 177–91.
[3] La Rovere MT, Bigger JT, Marcus FI, Mortara A, Schwartz PJ for the ATRAMI Investigators. Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. Lancet 1998; 351: 478–84.
[4] Schwartz PJ, La Rovere MT. ATRAMI: a mark in the quest for the prognostic value of autonomic markers. Autonomic Tone and Reflexes After Myocardial Infarction. Eur Heart J 1998; 19: 1593–5.
[5] Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. Circ Res 1969; 24: 109–21.

[6] Parati G, Casadei R, Groppelli A, Di Rienzo M, Mancia G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension 1989; 13: 647–55.
[7] Hartikainen JEK, Tahvanainen KUO, Mantysaari MJ, Tikkanen PE, Lansimies EA, Airaksinen KEJ. Simultaneous invasive and noninvasive evaluations of baroreflex sensitivity with bolus phenylephrine technique. Am Heart J 1995; 130: 296–301.
[8] Bland MJ, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 8: 307–10.
[9] Imholz BPM, Parati G, Mancia G, Wesseling KH. Effects of graded vasoconstriction upon the measurement of finger arterial pressure. J Hypertens 1992; 10: 979–84.
[10] Wesseling KH, Settels JJ, Van Der Hoeven GMA *et al*. Effects of peripheral vasoconstriction on the measurement of blood pressure in a finger. Cardiovasc Res 1985; 19: 139–45.
[11] Pinna GD, Maestri R, Mortara A. Estimation of arterial blood pressure variability by spectral analysis: comparison between Finapres and invasive measurements. Physiol Meas 1996; 17: 147–69.