Osteoporos Int (1997) 7:363–369

Osteoporosis International

Original Article

Quantitative Ultrasound Imaging at the Calcaneus Using an Automatic Region of Interest

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Abstract. A new approach to measuring bone properties at the calcaneus using ultrasound parametric imaging has recently emerged. However, an additional source of observer-related error is the substantial regional variations in the pattern of ultrasound parameters. The contribution of intra-observer and inter-observer variability to the coefficient of variation can be eliminated using an algorithm which selects the region of interest (ROI) completely automatically. The objective of the present study was the clinical assessment of an automatic ROI for both broadband ultrasonic attenuation (BUA) and speed of sound (SOS) measurement using ultrasound parametric imaging. The automatic ROI was defined as the circular region of lowest attenuation in the posterior tuberosity of the calcaneus. We have tested this algorithm using clinical images of the calcaneus from 265 women. Mean coefficients of variation were 1.6% (95% confidence interval 1.4%–1.9%) and 0.26% (95% confidence interval 0.23%–0.32%) for BUA and SOS respectively (standardized CV was 2.1% for BUA and 2.6% for SOS). Z-scores in an osteoporotic group were −0.61 and −0.52 for BUA and SOS respectively. In healthy women, the age-related decline was −0.50 dB/MHz per year (0.7%/year) for BUA and −1.2 m/s per year (0.08%/year) for SOS. In the subgroup of healthy postmenopausal women, using stepwise multiple regression, we found that BUA was predicted best by years since menopause (YSM) and weight, with overall model $r^2 = 0.28$; SOS was predicted best by YSM only ($r^2 = 0.21$). Neither the range of biological variation of ultrasound parameters nor the clinical value were affected by the choice of the region of lowest attenuation for measurement. The automatic procedure was totally independent of operator interaction, therefore excluding loss of precision due to intra- or inter-observer variability. The results showed the high precision and robustness of the procedure. These factors make this approach viable for routine clinical use.

Keywords: Automatic ROI; Broadband ultrasonic attenuation; Calcaneus; Osteoporosis; Speed of sound; Ultrasound imaging

Introduction

Quantitative ultrasound reveals relevant information about the status of the appendicular skeleton [1,2] which is related to the risk of osteoporotic fracture [3,4]. Historically, the calcaneus was the first skeletal site to be extensively investigated with ultrasound. Measurements have been made at a fixed location of attenuation [5] (or broadband ultrasonic attenuation, BUA) and speed of sound (SOS) [6] of an ultrasonic pulse after propagating through the heel, immersed in water. Further elaboration of the technique of measuring the calcaneus has recently emerged, including contact measurements [7] and more sophisticated imaging devices [8]. Various alternative interesting approaches have been developed for investigation of other peripheral skeletal sites including patella [9], phalanges [10] and tibia [11,12].

Whereas the measurement with a fixed-location measurement device may fall in different parts of the calcaneus in different individuals (or even partly outside the bone), BUA imaging has the potential to help in the standardization of the region of interest (ROI) and to overcome some of the limitations of the precision of a

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measurement taken at fixed position [13]. A recent clinical study has been reported in which BUA images were analyzed and three distinct manual ROIs [14]. In the case of manual data analysis, an additional source of error related to the observer and his or her level of training is the substantial regional variations in the pattern of BUA demonstrated in several reports [13–16]. Subjectivity in the manual determination of the ROI influences the precision in a negative way. With manual ROI determination, Roux et al. [14] have found inter-observer variability of 1.9% (mean coefficient of variation in percent, based on the arithmetic mean) in normals, and intra-observer variability of 1.1% in normals when data were analyzed by a trained observer; the equivalent figures were 1.4% and 1.5% when data were analyzed by two unskilled observers.

The contribution of the intra-observer and inter-observer variability to the coefficient of variation is eliminated if an algorithm is utilized which selects the ROI completely automatically. By analogy with the automated analysis procedure of bone images produced by dual-energy X-ray absorptiometry, two different classes of methods of automatic ROI determination in ultrasound images of the calcaneus can be anticipated. A first approach, based on an image segmentation, could provide truly anatomical ROI grounded on a contour tracing procedure of the calcaneus. However, the automatic segmentation problem for ultrasound bone images is not a trivial task, because of the low spatial resolution of ultrasound images and the absence of edge signal in some of the boundary region of the calcaneus (Fig. 1), resulting in complexity of the scene, particularly in the vicinity of the upper joint [13]. Furthermore, these procedures are usually time-consuming unless performed on a powerful workstation. For these reasons, an alternative approach was preferred using acoustical features (such as local extremes in the attenuation) rather than anatomical features of the calcaneus, based on the observation in more than 500 subjects that a region of minimum attenuation was consistently found in the posterior region of the great tuberosity.

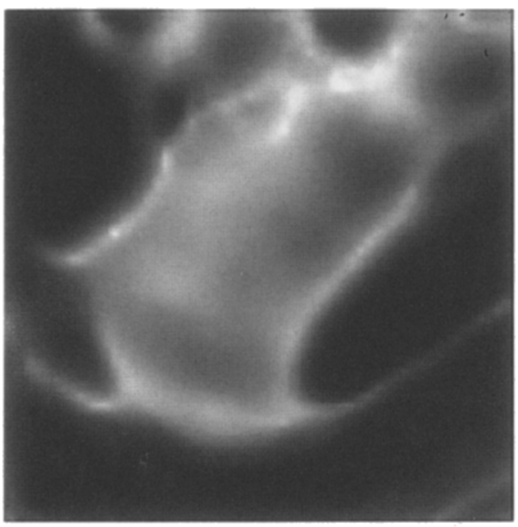

Fig. 1. Typical broadband ultrasonic attenuation (BUA image showing the absence of clear edge signal of the calcaneus in the vicinity of the upper joint.

An automated ROI procedure based on the region of lowest attenuation was implemented on our BUA imaging prototype [13]. The main objective of the present study was the clinical assessment of an automatic ROI for both BUA and SOS measurement using ultrasound parametric imaging, and a secondary objective was to report the clinical value of SOS obtained in this ROI with our BUA imaging prototype since it was not available in the previous report by Roux et al. [14]. The general requirements for the automated method were: (1) that the ROI determination should be fully automatic (i.e. no input from the observer); (2) that the precision errors in the ultrasonic parameter values should be no greater than those resulting from the manual analysis; (3) that the algorithm should be robust enough to succeed in finding the ROI in all cases.

Materials and Methods

Ultrasonic Measurement

Ultrasonic characterization of the calcaneus relies on the measurement of acoustic properties such as the slope of the frequency-dependent attenuation (BUA,dB/MHz) and the speed of sound (SOS, m/s) using an insertion technique in which an ultrasound pulse waveform transmitted through the heel is deconvolved by the system response (reference signal transmitted through water). Ultrasonic data acquisition was performed as previously reported [13] with a prototype developed in our laboratory. Ultrasound images were obtained by scanning the heel, immersed in water (without temperature control), and calculating the ultrasonic parameters at each position in the scan. The pixel size was 1 mm, with a spatial resolution of approximately 5 mm, and the data acquisition procedure duration was 3 min.

The automatic ROI was defined as the circular region of lowest attenuation in the posterior tuberosity of the calcaneus. The method can be divided into four major steps:

1. Ultrasonic data acquisition.
2. Signal processing of the transmitted waveforms to provide a value of the attenuation at each pixel every millimeter in both *XY* directions. In Fig. 2 the attenuation map is represented in the form of a three-dimensional surface where the elevation at each pixel is proportional to the attenuation value.
3. Automatic detection of the circular ROI of lowest attenuation: the initial position of the ROI was set automatically approximately in the center of the scan, the final ROI being identical to that found by a ball

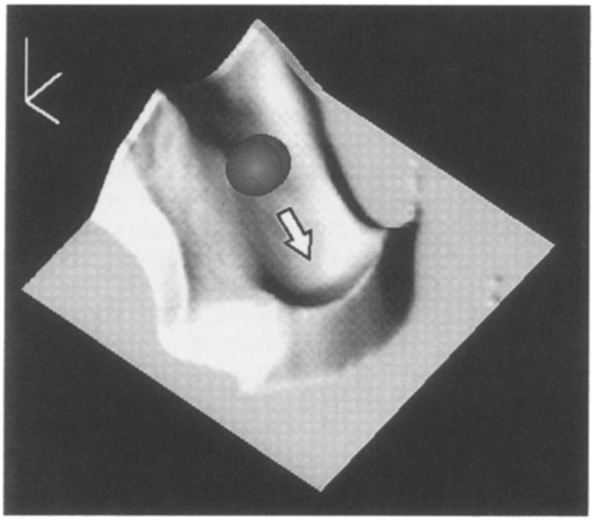

Fig. 2. Illustration of the algorithm used for automatic detection of the ROI of lowest attenuation. The *three-dimensional surface* represents a map in elevation of the ultrasonic attenuation in the calcaneus. The *ball* represents the region of interest (ROI) in its initial position. The *white arrow* indicates the final position of the ROI.

dropped on a three-dimensional surface representing topographical variations of the attenuation as illustrated in Fig. 2.

4. Measurement of BUA and SOS: individual BUA and SOS values are obtained by averaging the values in the automatically determined ROI.

The automatic ROI algorithm requires less than 1 s for analysis of each image on a PC.

Patients

The automatic analysis presented in this paper and manual analysis of images published previously in [14] were performed on BUA images coming from a single database corresponding to an identical study group. Reanalysis of the data obtained in this previous study is the basis of this report. Clear advantages of reanalysis of the data were the ability to compare the precision and natural variability obtained with this new algorithm with those in investigations that were based on manually drawn ROIs from the same subjects, and to complete the previous study by providing new clinical data on SOS using the ultrasound parametric imaging technique.

Short-term reproducibility of ultrasonic parameters was determined by five consecutive measurements with interim repositioning in 29 women (age range 24–77 years). The size of the circular ROI was varied between 12 and 20 mm to determine the optimal size of the ROI in terms of precision; this optimal size was adopted for the rest of the study. In addition, we also measured the precision on the ROI in a fixed location relative to the foot plate (ROI_{fixed}), mimicking the approach used in current ultrasound devices. The circular ROI (19 mm in diameter) was located approximately in the great tuberosity of the calcaneus.

Although described elsewhere in detail [14], we briefly outline here the population that was the subject of the present study. We studied a total of 236 consecutive women, of whom 159 were without osteoporotic fracture, referred to our unit for evaluation of bone density. Three separate subgroups were identified. Group I consisted of 72 healthy women, free of bone disease, with a negative history for inflammatory or neoplastic disease and for premature menopause, without past or current use of anti-osteoporotic drugs (mean age $\pm$ SD 57.9 $\pm$ 11.8 years; range 36–91 years), of whom 67 were healthy postmenopausal women. Group II comprised 77 patients (71.2 $\pm$ 9.9 years; range 49–92 years) with osteoporotic fracture (vertebral fractures in 58, hip fracture in 14, Colles' fracture in 5). All these women were selected by the same physician (C.R.), who determined that the fractures were due to bone fragility on the basis of the circumstances in which they occurred. Group III was a subgroup of the 67 healthy postmenopausal women, consisting of 64 women with a mean age similar to the mean age (SD) of the osteoporotic group (group II). Weight and height were not significantly different in controls and osteoporotic patients. Bone mineral density (BMD, g/cm^2) was measured in all patients on antero-posterior spine and proximal femur scans using dual-energy X-ray absorptiometry (DXA, Hologic QDR).

Each subject gave informed consent to their participation to the study, which has been approved by the ethical review board of Cochin Hospital (Paris).

Data Analysis

Descriptive data utilize mean and standard deviation.

Precision for each subject was calculated using the coefficient on variation (CV%) as usual: CV_i = $mean_i$/SD_i, where subscript *i* refers to patient *i*. Reproducibility is the root mean square (RMS) CV of the patient-specific CVs. The 95% confidence intervals (CI) were calculated according to the method recommended in [17]. To compare the reproducibility of various parameters (BUA and SOS), a standardized CV was derived by normalizing the CV to the variability found in the group according to the relationship

$$Standardized\,CV = \frac{CV\%}{4SD/mean}$$

where mean and 4 SD represent the average and range of variation in the group [11].

The association between BUA and SOS was determined by the calculation of the Pearson coefficient (significant if $p < 0.05$).

We compared the differences between group II (osteoporotics) and group III (age-matched controls) using independent *t*-tests. The percentage decrement (percentage of the mean value of controls) between osteoporotic and controls, and *t*-values for *t*-test served as a first indicators of group separate. The two groups were also compared using the conventional Z-score, defined as follows: Z-score = $(\text{mean}_{III} - \text{value})/\text{SD}_{III}$, where subscript III refers to the age-matched control group and 'value' refers to the osteoporotic-patient-specific BUA and SOS values. The patients' individual Z-scores were averaged.

Simple regression analysis was used to examine the relationship between ultrasound parameters and age in group I, and stepwise multiple linear regressions were used to determine the relative importance of age, years since menopause (YSM), weight and height on BUA and SOS in the subgroup of $n = 67$ healthy postmenopausal women in group I. The level of significance for including a variable in the model was set to 0.10. Models were optimized with respect to overall model r^2 using stepwise backward and forward regression.

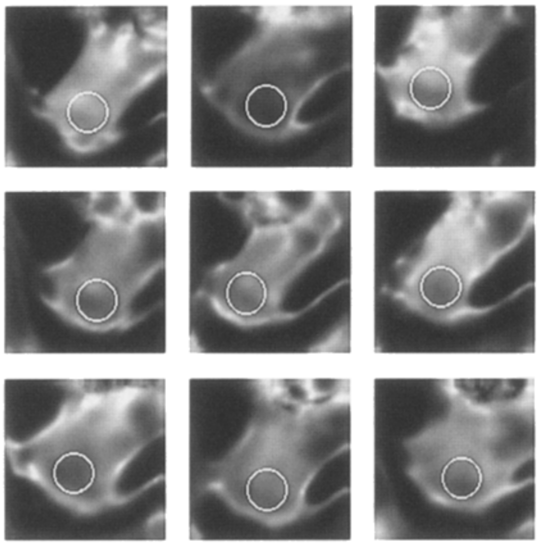

Fig. 3. Nine typical BUA images of the calcaneus from nine different subjects showing the final location of the automatic ROI.

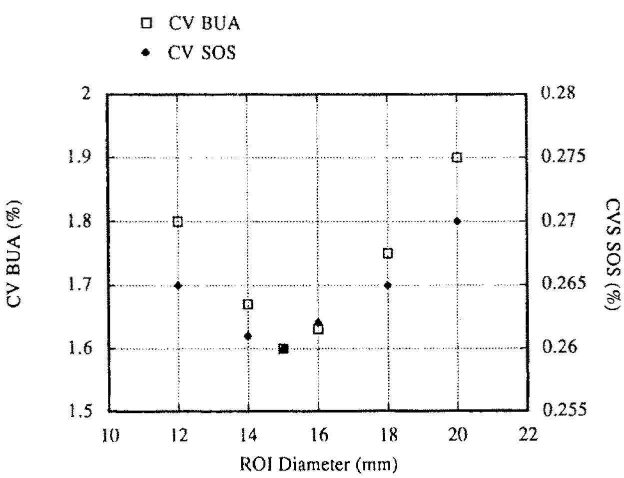

Fig. 4. Variation of BUA and speed of sound (SOS) precision as a function of ROI size.

Results

Typical BUA images of the calcaneus from nine different subjects showing the final location of the automatic ROI are depicted in Fig. 3. We have tested this algorithm using clinical images of the calcaneus from 265 subjects included in the study. In all cases the automatic ROI was found in the posterior part of the great tuberosity of the calcaneus. The anatomical position of the ROI could differ slightly from subject to subject as illustrated in Fig. 3.

In Fig. 4 the precision of BUA and SOS have been plotted versus ROI size, showing that the best precision of BUA and SOS was reached for a circular ROI 15 mm in diameter. The short-term reproducibility values for that optimal ROI (circular with a diameter of 15 mm) are shown in Table 1. Mean coefficient of variation of 1.6% (95% CI 1.4%–1.9%) and 0.26% (95% CI: 0.23%–0.32%) were found for BUA and SOS respectively. The standardized CV of BUA was 2.1% (95% CI 1.9%–2.5%) and that of SOS was 2.6% (95% CI 2.3%–3.1%), indicating comparable precision for the two measurements. In $\text{ROI}_{\text{fixed}}$, mean CVs of 2.9% (95% CI 2.6%–3.4%) and 0.43% (95% CI 0.38%–0.50%) were found for BUA and SOS respectively. For $\text{ROI}_{\text{fixed}}$ the standardized CV of BUA was 4.3% (95% CI 3.9%–5.1%) and that of SOS was 3.0% (95% CI 2.6%–3.4%).

The correlation between BUA and SOS was $r = 0.77$ for the total population and $r = 0.67$ for the group of healthy women. These values were similar to those reported recently by Schott et al. [18].

Simple descriptive statistics for groups I, II and III are summarized in Table 2. The percentage decrement

Table 1. Coefficient of variation (CV) and standardized CV for broadband ultrasonic attenuation (BUA) and speed of sound (SOS) in an automatic region of interest (ROI) and fixed ROI in 29 women

	Automatic ROI		Fixed ROI	
	BUA	SOS	BUA	SOS
Mean ± SD (dB/MHz)	71 ± 12	1528 ± 39	81 ± 14	1541 ± 56
CV% (95% CI)	1.6 (1.4–1.9)	0.26 (0.23–0.32)	2.9 (2.6–3.4)	0.43 (0.38–0.50)
Standardized CV% (95% CI)	2.1 (1.9–2.5)	2.6 (2.3–3.1)	4.3 (3.9–5.1)	3.0 (2.6–3.4)

Table 2. Group average BUA, SOS and densitometric measurements

Group	Age (years)	Weight (kg)	Height (cm)	BUA (dB/MHz)	SOS (m/s)	Spine BMD[a] (g/cm^2)	Femur BMD[a] (g/cm^2)
I. Healthy (*n*=72)	57.9±11.8	57.7±9.7	157.6±8.6	66.1±17.5	1524±31	0.888±0.148	0.792±0.144
II. Osteoporotic (*n*=77)	71.2±9.9	57.5±9.6	154.9±6.0	48.1±11.8	1494±28	0.727±0.113	0.654±0.127
III. Age-matched control (*n*=64)	70±10	57.1±10.1	156.4±8.8	57.1±14.8[b]	1517±42[b]	0.799±0.132[c]	0.719±0.123[c]
Total population	63.5±11.8	58.0±9.4	156.8±7.5	58.9±17.5	1514±34	0.811±0.150	0.739±0.142

[a]Data from [14].
[b]BUA and SOS are significantly different ($p<0.0005$) between groups II and III.
[c]Spine and femur BMD are significantly different ($p<0.005$) between groups II and III.

Table 3. Stepwise multiple regression analysis between ultrasound parameters and age, years since menopause (YSM), weight and height in a group of n = 67 healthy postmenopausal women: coefficient (±SEE) of the model and r^2 values

	Intercept	Age	YSM	Weight	Height	r^2
BUA	36.5 (12.3)	NS	−0.53 (0.17)	0.60 (0.20)	NS	0.28 (p>0.005)
SOS	1533 (46)	NS	−1.17 (0.29)	NS	NS	0.22 (p>0.001)

NS, non-significant.

between osteoporotic patients and controls was −15.8% for BUA and −1.5% for SOS. The t values were −3.9 for BUA and −3.7 for SOS. The Z-scores were found to be respectively −0.61 for BUA and −0.52 for SOS. All values were highly significant. BUA and SOS were lower in the osteoporotics compared with the age-matched controls ($p<0.0005$) and could discriminate the two groups similarly. For BMD at the spine and total femur, the percentage decrement between osteoporotics and controls was −9%. The Z-scores were found to be respectively −0.54 for spine BMD and −0.53 for total femur BMD.

In group I of healthy women there was a significant decrease in ultrasound parameters with age (BUA: r^2 = 0.12, $p<0.005$; SOS: r^2 = 0.19, $p<0.001$). The age-related decline was −0.50 dB/MHz per year for BUA and −1.2 m/s per year for SOS. The age-related decline in dB/MHz per year for BUA (respectively in m/s for SOS) was divided by the young adult value measured between 36 and 45 years to obtain the annual percentage decrease. Annual percentage decreases of 0.7%/year and 0.08%/year were found for BUA and SOS respectively. The results of the linear regression analysis and stepwise multiple regression analysis in the subgroup of healthy postmenopausal women are shown in Table 3. BUA was significantly associated with YSM (r^2 = 0.17, $p<0.001$), weight (r^2 = 0.15, $p<0.002$) and height (r^2 = 0.11, $p<0.01$), whereas SOS was significantly associated only with YSM (r^2 = 0.21, $p<0.0001$) and height (r^2 = 0.12, $p<0.01$). The correlation between SOS and weight was not significant. In stepwise forward and backward multiple regression BUA was predicted best by YSM and weight, the overall model r^2 = 0.28; SOS was predicted best by YSM only (r^2 = 0.21).

Discussion

This study has been designed to address the reliability of an algorithm of automatic ROI tracing for quantitative ultrasound measurements using parametric imaging. Manual positioning of the ROI on BUA images entails large variation between operators in precision of the technique [14]. To avoid these problems a fast automated ROI detection algorithm was proposed. A simple acoustic criterion was used to define the ROI. We have adopted the convention of averaging BUA and SOS values over a circular ROI of the lowest attenuation in the posterior part of the calcaneus. The method could be easily expanded to the detection of other local minimal or maximal values of the attenuation or of the SOS, or even to the detection of the total calcaneal area. It could be interesting to define automatically the ROI with the largest sensitivity to changes during therapeutic follow-up. However, the criteria chosen to define the ROI must fulfill the requirements in term of precision and reliability. If one were to make measurements on a limited volume of the calcaneus, different answers could be obtained depending upon where the measurements were made. It has been suggested that different areas in the calcaneus lose mineral at different rates and that the area of the lowest mineral content in the central calcaneus appears to exhibit a somewhat greater liability [19]. Our choice of the region of the lowest attenuation was based upon our recent data showing that BUA and calcaneal BMD were strongly correlated [20], and upon the resulting assumption that the area of lowest attenuation should also be approximately the area of the lowest mineral content. One possible drawback of an acoustically rather than anatomically defined ROI might be that, due to inhomogeneous response to therapy, the ROI of a follow-up scan could be located in an anatomically different region of the calcaneus compared with the baseline. If so, cross-correlation techniques might prove useful to relocate the ROI on the follow-up scan in an identical location compared with baseline.

The algorithm performs without requiring any input from an operator. It resulted in a substantial saving in operator time and an improvement in the reliability of ROI tracing. No case of failure of the algorithm was encountered. Our approach yielded a ROI located in all cases approximately in the same position – in the posterior part of the great tuberosity – yet moderate variations in the location of the ROIs could be seen in different individuals (Fig. 3). To counter the variability in the anatomical position of the ROI based on detection of a specific acoustic feature, it might be necessary to use also true anatomical image features in the definition of the ROI such as those based on contour tracing procedures.

Results regarding precision demonstrated that ROI size could influence slightly, yet not critically, the precision of BUA and SOS which is best for a ROI size of 15 mm (Fig. 4). Averaging the parameters in small ROIs might be too sensitive to small variations (of the order of a fraction of pixel) due to imperfect positioning of the foot. On the other hand, if a large ROI is used it might result in the inclusion of spurious edge artifacts that will ultimately increase the variability of the measurements. In this study an identical size of ROI was used to analyze images from all subjects. However, substantial differences exist in the size and shape of the calcaneus among individuals. In future development, ROI size might well be adapted to the size of the bone.

The precision of the automatic algorithm was found to be consistent with that obtained from manual ROI tracing of the same data [14]. Reproducibility of BUA and SOS was worse for ROI_{fixed} than for the automatic ROI. This can be easily explained by small displacements of the heel on the foot plate between successive measurements. Automatic ROI can be properly relocated on the image, while a measurement at fixed coordinates may be located in different regions of the calcaneus. Due to the heterogeneity of the calcaneus, such variations in the placement of ROI_{fixed} between repeated measurements increase measurement errors.

In fact, high precision can be reached with a fixed-location measuring device if there is painstaking control of experimental conditions. However, such systems provide parameter values in an anatomically undefined site. As recently outlined, a measurement at fixed coordinates can give results in different ROIs of the calcaneus in different individuals [13,14]. In some cases the ROI can even fall partly outside the bone. The key feature of quantitative ultrasound imaging lies in the possibility of acoustical or anatomical standardization of the ROI. ROI standardization with the new algorithm proposed here is based on a very simple acoustical feature of the ultrasound image. Furthermore, the method is fully automatic, without any input from the operator, which ensures optimal measurement precision independently of experimental conditions.

The standardized CV was defined to relate the precision of the technique to the variability of the parameter in a given population. This is particularly useful if the precision of various parameters with different scales of physiological variations have to be compared – such as BUA or SOS measured at different skeletal sites. Our results indicate that standardized CVs are similar for BUA and SOS. The concept of a standardized CV has not been widely used in the literature, and the new ultrasound technologies cannot be fully appreciated in comparison with current technologies. Compared with comparable information from the literature, our findings suggest that the performance characteristics of the automatic ROI are similar or superior to those previously estimated for ultrasound measurements at the tibia (standardized CV 1.8% [11]) or calcaneus (standardized CV 6–10% for BUA, and 12% for SOS [16]).

This paper focuses on ultrasound measurements in the automatic ROI. Data regarding BUA values in ROIs located elsewhere in the calcaneus (ROI1, largest ROI that can be fitted in the posterior tuberosity; ROI2, 15 mm in diameter in the center of ROI1; ROI3, located in the postero-inferior part, adjacent to the cortices) using manual data analysis of an identical database have been published elsewhere [14]. Our BUA findings confirm previous results provided by manual analysis: equivalent percentage decrements (−15.7% compared with −12.6%, −16.1% and −13.7% for manual ROIs), equivalent Z-scores (0.61 compared with 0.59, 0.66 and 0.54 for manual ROIs) and equivalent age-related decreases (0.7%/year compared with 0.71, 0.74 and 0.63%/year for manual ROIs). The closest results yielded by manual data analysis were those found in ROI3. This result can be explained by the fact that ROI3 was placed manually close to the area of lowest attenuation (Fig. 3).

As in previous studies, SOS assessed in the automatic ROI was found to be significantly lower in osteoporotic patients versus controls [4,21,22]. Group separation was identical for BUA and SOS, albeit the percentage decrement and the age-related decline were apparently lower for SOS than BUA. This was the effect of the small biological variation of SOS (1450–1600 m/s approximately) compared with the mean value (1500 m/s). If the decrement between osteoporotics and controls, and the age-related-decline, were standardized by the biological variability (defined as between the 5th and 95th percentiles of normal women, or 4 SD), identical values would be found for BUA and SOS (percentage decrement 15.2% for BUA and 13.7% for SOS; age-related decline 0.8% for BUA and 0.7% for SOS). Our age-related decline fell in the range of the annual decrease in the values of ultrasonic parameters as recently reviewed by Schott et al. [18]. The percentage decrement between osteoporotics and controls compared favorably with those found by Krieg et al. [22]. The relationships found in this study between anthropomorphic parameters (weight, height) and BUA or SOS were also comparable to those found by Hans et al. [23]. Both BUA and SOS in the automatic ROI performed as well as DXA of spine and femur [14] for discriminating osteoporotics from controls. An interesting outcome of these findings what that the biological variation of quantitative ultrasound, compared with previous findings with manual analysis, did not seem to be influenced by the location of the region of measurement.

In, summary, a new approach to measure the calcaneus using ultrasound parametric imaging has recently emerged. Advantages of this technique have been clearly shown previously. As this instrument produces bone images, the automatic ROI detection described in this paper can be applied to patient data obtained with this new instrument. The automatic procedure was totally independent of the operator, and therefore avoided the loss of precision due to intra- or inter-observer variability. The results showed the high precision and robustness of the procedure. Neither the range of biological variation of ultrasound parameters nor the clinical values were affected by the choice of the region of lowest attenuation for measurement. These factors make this approach viable for routine clinical use.

Acknowledgements. This study was supported by ANVAR grant no. A 94 10 501 QAT. C.C. would like to acknowledge the financial support of the GRIO (Groupe de Recherche et d'Information sur les Ostéoporoses).

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