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Compound action potentials (CAPs) were recorded from the sural nerve of healthy volunteers. A mathematical technique (inverse modeling) was used to compute conduction velocity (CV) histograms from the data. Results were compared to the morphology of age-matched normal sural nerve biopsies. Coefficients of variation (CoVs) revealed the statistical relationship between morphological data (diameter histograms) and electrophysiological data (CV histograms and conventional CAP parameters). No differences were found for the thick fiber group when comparing the CoVs of the diameter histogram parameters with the corresponding CV histogram parameters. Apparently, the same inherent biological interindividual variability is encountered. The CoVs of the CVs of the CAP's main phases are in good agreement with the CoVs of the estimated mean velocity of the thick fiber group. Inverse modeling increases the reliability of the estimation of the number of active fibers as compared to direct CAP amplitude interpretation. © 1995 John Wiley & Sons, Inc.

Key words: sural nerve CAPs • normal data • morphology • electrophysiology

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## CONDUCTION VELOCITY DISTRIBUTIONS COMPARED TO FIBER SIZE DISTRIBUTIONS IN NORMAL HUMAN SURAL NERVE

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It is well established that the diagnosis of pathological processes in polyneuropathy occasionally requires a morphological investigation of a nerve biopsy.<sup>2,5,11</sup> Behse and Buchthal<sup>2</sup> and Tackmann et al.<sup>18</sup> related electrophysiology and morphology in the same nerve by comparing latencies and amplitudes in the recorded nerve compound action potential (CAP) components with nerve biopsy observations. However, interpretation of conventional CAP parameters in terms of nerve morphology is not self-evident due to the complex way by which the different single-fiber action potentials

(SFAPs) summate to the compound signal.<sup>12</sup> To facilitate this interpretation, some theoretical models describing the genesis of SFAPs have been described.<sup>1,4,13,14,15,16,17,19</sup>

The ultimate objective in using such models is the production of a reliable conduction velocity distribution from measured CAPs. This distribution can be directly related to the diameter distribution since the relation between fiber diameter and velocity is roughly a proportional one.<sup>3,8,10</sup> These studies usually pertain to the main complex of the CAP, being associated with the fast conducting fibers in the nerve (conduction velocity, CV > 25 m/s). The estimation procedure introduced by Schoonhoven et al.<sup>14</sup> and Stegeman et al.<sup>17</sup> accounts for the thick and fast (25–70 m/s; 5–14  $\mu\text{m}$ ) as well as the thin and slow (<25 m/s; <5  $\mu\text{m}$ ) myelinated fiber group. The procedure was validated in a model study.<sup>17</sup> van Veen et al.<sup>19</sup> further elaborated on the above procedure which led to successfully relating fiber diameter histograms obtained from biopsies to conduction velocity histograms from the same nerve.

Studies which directly relate morphological data to electrophysiological data of the same hu-

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man nerve are obviously based on pathophysiological patient data. Normal morphological data of human nerve have been scarcely collected.<sup>6</sup> Schellens et al.<sup>11</sup> report on the morphology of the normal human sural nerve and its age-related changes. They collected their normal biopsy data from 51 patients which were finally diagnosed as suffering from diffuse cerebral degenerative disorders or system degenerations. Their biopsies can be considered as normal.

The present study intends to relate normal electrophysiological CAP data obtained from the human sural nerve to these normal morphological findings presented by Schellens et al.<sup>11</sup> To this end, CAPs were recorded from 11 healthy volunteers between 20 and 35 years of age. From the data of Ref. 11, we selected the morphological characteristics of 15 subjects who were age-matched to the above group of volunteers.

Electrophysiological data were recalculated in terms of conduction velocity histograms according to the procedure of van Veen et al.<sup>19</sup> and also judged in the conventional way, i.e., by measuring CAP amplitudes and conduction velocities. The relations between the conventional CAP parameters and estimated conduction velocity distributions and between conduction velocity distributions and the morphologically observed diameter distributions were studied.

## METHODS

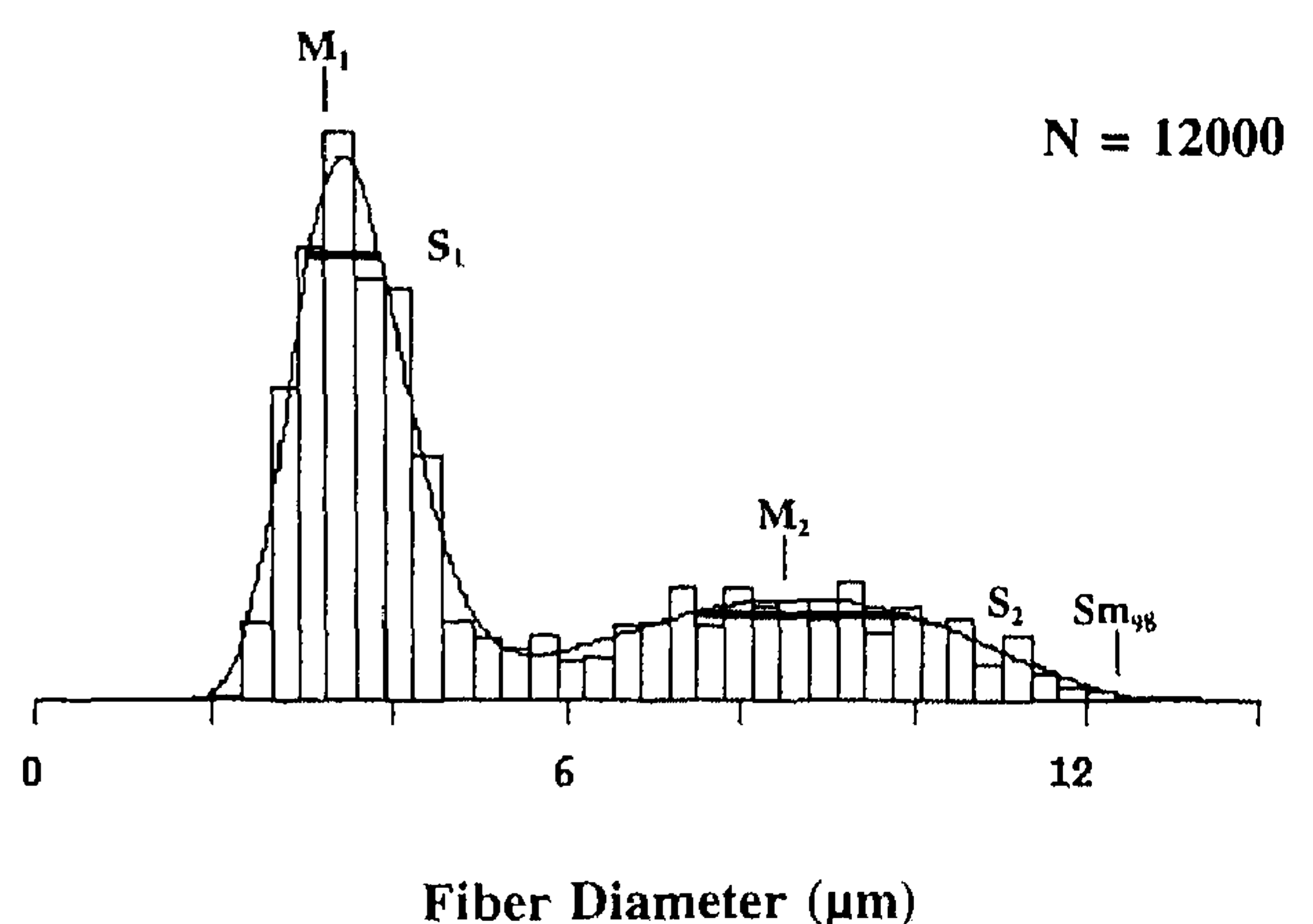
**Morphological Data.** The methods in obtaining fiber diameter distributions from the human sural nerve have been described before.<sup>11</sup> For clarity, the most important aspects are summarized below. Between 1970 and 1982, about 800 diagnostic sural nerves biopsies were performed at the Nijmegen institute. Fifty-one biopsies obtained from patients with diffuse cerebral disorders or system degenerations were indicated as normal. Among these, 15 patients were in the age category to be considered (between 20 and 35 years). Biopsies were prepared using standard techniques.<sup>7</sup> Fiber diameter histograms were generated to graphically represent the number of fibers per micrometer. So-called beta distribution functions were used to individually describe the two peaks in each histogram using a least squares curve fitting technique.<sup>11</sup> A beta distribution function can be skew in contrast to, e.g., the Gaussian distribution. The sum of two beta functions was used to describe the diameter histogram: function 1 described the distinct peak of the smaller fibers while function 2 was used to describe the peak of the larger fibers. From

these beta distributions a number of parameters was derived:

- $Sm_{98}$ : 98 percentile, indicating an upper limit of the myelinated fiber diameter.
- $M_1$ : mean of beta-function 1 (group of thin fibers).
- $M_2$ : mean of beta-function 2 (group of thick fibers).
- $S_1$ : width of the thin fiber population (standard deviation of beta-function 1).
- $S_2$ : width of the thick fiber population (standard deviation of beta-function 2).
- $N_{thick}$ : the total number of thicker fibers, defined as the area under beta-function 2.

The most representative diameter histogram out of this group, as determined by a statistical clustering technique,<sup>11</sup> is depicted in Figure 1.

**Conventional Electrophysiological Data.** Compound action potentials were obtained from the sural nerve in a group of 11 healthy volunteers between 20 and 35 years of age. CAPs were recorded orthodromically after supramaximal stimulation of the nerve. Both for recording and stimulation, near-nerve stainless steel needle electrodes, teflon-coated with 3 mm bare tip (DISA 13L64) were used. CAPs were recorded at mid-calf level using two different recording distances,  $l_1$  and  $l_2$ . The difference between  $l_1$  and  $l_2$  was realized by changing the stimulation site instead of the recording site. Typically  $l_2$  was about 15 cm by stimulating just distal to the malleolus lateralis, and



**FIGURE 1.** A typical example of a nerve diameter histogram, obtained from morphological data. The total number of fibers ( $N$ ) as well as the estimation by beta distribution functions is indicated. This histogram is the most representative one (see the main text) for the age category to be considered. Histogram parameters  $M_1$ ,  $S_1$ ,  $M_2$ ,  $S_2$ , and  $Sm_{98}$  are indicated.

$l_1$  was about 6 cm. Details concerning the recording procedure have been presented before.<sup>12</sup> Guided by observation of the peak-to-peak amplitude of the CAP the recording electrode was placed as close as possible to the sural nerve.

As a first approach to characterize the CAPs, their peak-to-peak amplitudes ( $V_{pp}$ ) and the conduction velocities of the first positive ( $u_1$ ), first negative ( $u_2$ ), and second positive peak ( $u_3$ ) were determined. We observed that on average  $V_{pp}$  changes linearly with negative slope to the recording distance  $l$ . So, in order to reduce this cause of amplitude variability all  $V_{pp}$  values were normalized to a longitudinal recording distance  $l_n = 10$  cm, yielding  $V_{pp,N}$  according to:

$$V_{pp,N} = V_{pp} \cdot \left( \frac{1}{l_n} - c_n \right) / \left( \frac{1}{l} - c_n \right) \quad (1)$$

with  $c_n = 0.0342 \text{ cm}^{-1}$ , an empirical normalization constant based on our data. An example of a set of CAPs, recorded from the same subject at two different longitudinal recording distances, is depicted in Figure 2.

**Conduction Velocity Histograms.** In the quantification of the conduction velocity histogram also two beta distribution functions were used to individually describe the two peaks in each histogram, also yielding the set of parameters  $Sm_{98}$ ,  $M_1$ ,  $M_2$ ,  $S_1$ , and  $S_2$ , introduced before now for conduction velocity.

In the velocity estimation procedure parameters used to compute SFAPs were either estimated (radial recording distance between nerve and recording electrode<sup>19</sup>), chosen in accordance with the experimental situation (longitudinal recording distance, temperature), or chosen according to literature values (conductivities).<sup>12,15,17</sup> The sural nerve was assumed to lie at a depth of 8 mm below the skin, in a layer of subcutaneous fat tissue with a thickness of 10 mm. Intracellular conductivity  $\sigma_i$  was taken  $0.25 (\Omega\text{m})^{-1}$ , nerve trunk conductivity in radial direction  $\sigma_r = 0.01 (\Omega\text{m})^{-1}$ , nerve trunk conductivity in longitudinal direction  $\sigma_l = 1.0 (\Omega\text{m})^{-1}$ , conductivity of fat  $\sigma_f = 0.04 (\Omega\text{m})^{-1}$ , muscle tissue conductivity  $\sigma_m = 0.25 (\Omega\text{m})^{-1}$ . The intracellular action potential was assumed equal for all fibers, with a duration adapted to the skin temperature measured at the recording site.<sup>9</sup> Conduction velocity distributions were computed from the estimated arrival time distributions.<sup>14</sup> Parameter  $N_{fast}$  defined as the area under beta function 2, denotes the total number of fast conducting fibers.

As an example, the estimated conduction velocity distribution histogram based on the set of CAPs of Figure 2 is given in Figure 3.

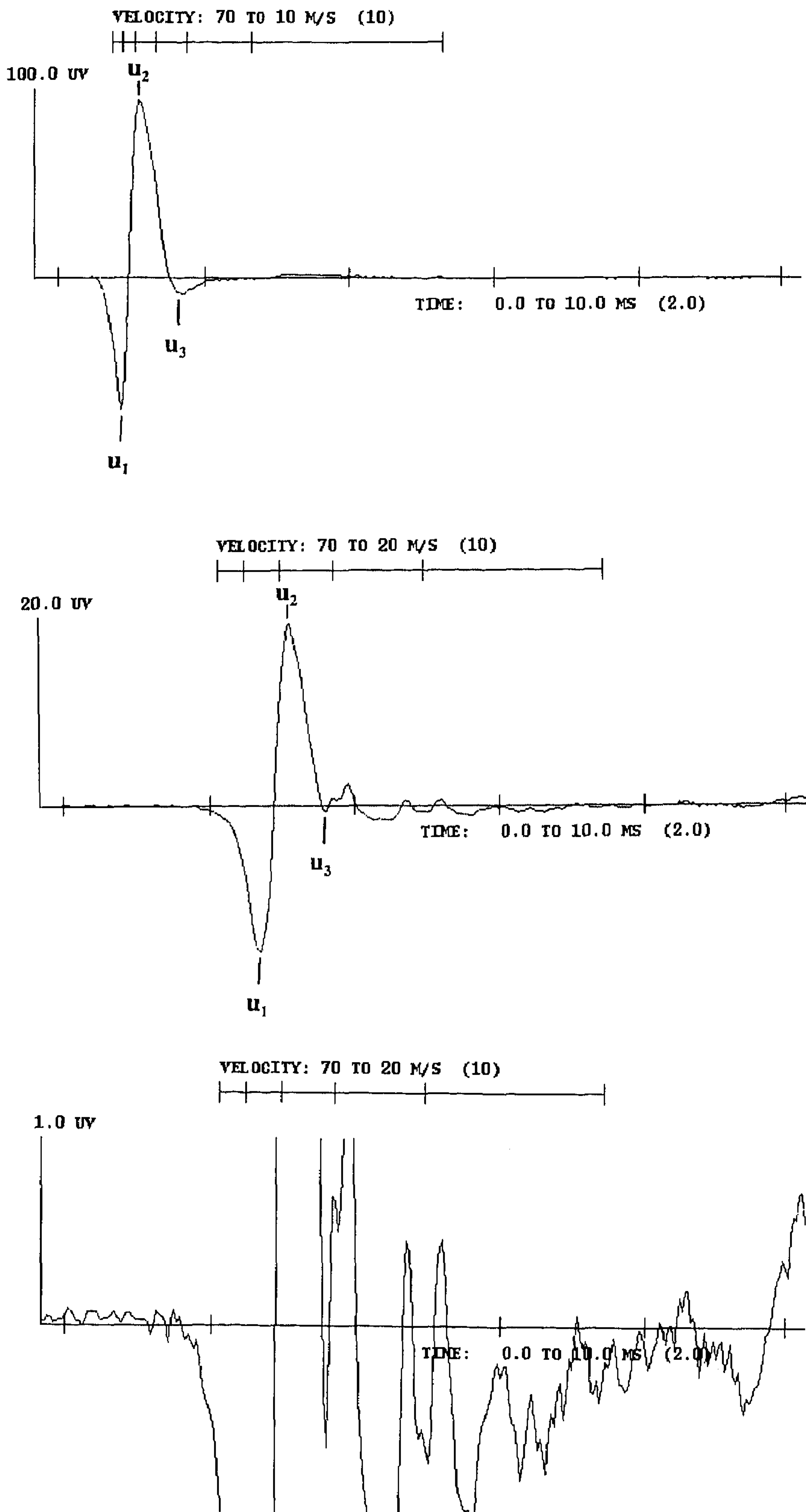
**Relation between Morphological Data and Electrophysiological Data.** For obvious reasons, the presentation of nerve electrophysiological data (conventional CAP parameters and conduction velocity histograms) in comparison with morphological data cannot be made at a one-to-one level. We use coefficients of variation (CoV) of a number of parameters to make such a comparison between both groups feasible. The rationale behind this choice is found in the assumption that in first approximation the values of a number of parameters, obtained from morphology and electrophysiology respectively, are expected to be proportionally related. This applies to the number of thick fibers found in the biopsy ( $N_{thick}$ ) and the CAP amplitude ( $V_{pp,N}$ ), to the mean velocity of the fastest fiber group ( $M_2$ ) and the conventional CAP parameters ( $u_1, u_2, u_3$ ), and to the relation between fiber diameter and fiber conduction velocity.<sup>3,13</sup> Therefore, the relation between a number of morphological parameters  $y_m$  and their electrophysiological counter parameters  $y_e$  can be expressed as:

$$y_e + \epsilon_e = \alpha \cdot y_m + \epsilon_m \quad (2)$$

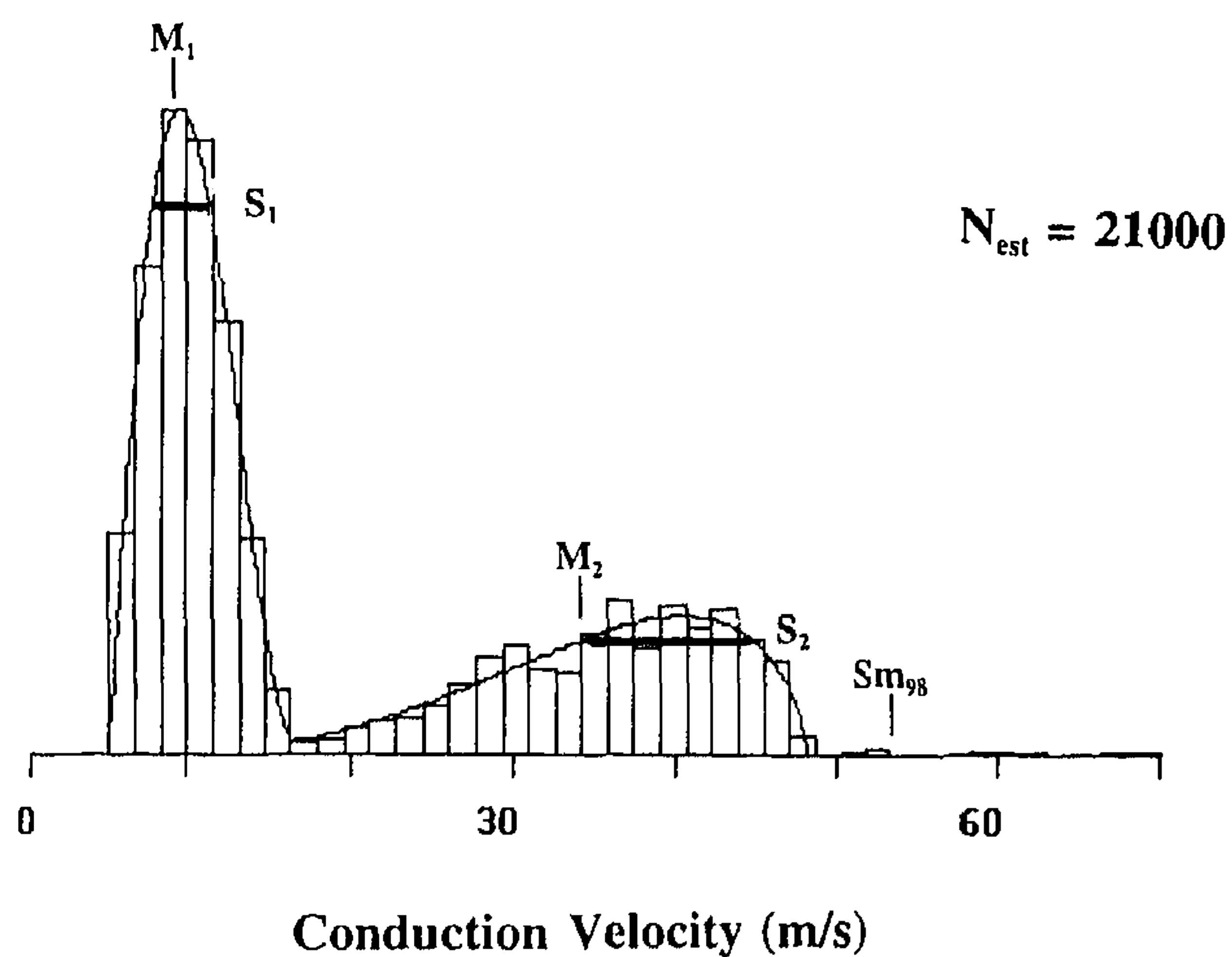
where  $\epsilon_e$  denotes a summary of all experimental errors made in the electrophysiological measurement and  $\epsilon_m$  the same for the morphological measurement. On the basis of eq. (2) parameter  $p$  can be judged by comparing the interindividual coefficients of variation ( $CoV_p$ ), defined as  $\sigma_p/\mu_p$ , where  $\sigma_p$  is the standard deviation of parameter  $p$  and  $\mu_p$  its mean.  $p$  denotes either an electrophysiological parameter ( $p = e$ ) or its morphological counterpart ( $p = m$ ). A measure  $D_{e,m}$  to quantify differences between interindividual variabilities of electrophysiological data with corresponding morphological data can then be defined as:

$$D_{e,m} = \sqrt{(CoV_e)^2 - (CoV_m)^2} \quad (3)$$

Note that eq. (3) requires that  $CoV_m (= \sigma_m/\mu_m)$  is smaller than  $CoV_e (= \sigma_e/\mu_e)$ . The background here is that morphological parameters  $y_m$  are derived in a more straightforward manner from the underlying data than electrophysiological parameters  $y_e$ . The latter are more indirect and subject to a number of experimental and model inaccuracies inevitable in electrophysiological observations. A coefficient of variation of a morphological parameter  $CoV_m$  is assumed to reflect mainly the inherent bi-



**FIGURE 2.** Compound action potential, recorded from a healthy volunteer. The upper trace shows the CAP recorded at a recording distance  $l_1 = 8$  cm, the middle one shows the CAP recorded at  $l_2 = 16$  cm. The lower trace is an enlargement of the CAP recorded at  $l_2$ . The slow components of the signal are clearly visible. The conduction velocities associated with the signal components are indicated. Also electrophysiological parameters  $u_1$ ,  $u_2$ , and  $u_3$  are indicated.



**FIGURE 3.** A conduction velocity histogram as estimated from the CAPs depicted in Figure 2. The estimated number of fibers  $N_{est}$  is indicated. Similar to the diameter histogram, this histogram is described by two beta distribution functions. Histogram parameters  $M_1$ ,  $S_1$ ,  $M_2$ ,  $S_2$ , and  $Sm_{98}$  are indicated.

ological variability, whereas the electrophysiological countermeasurement also contains other uncertainties as mentioned. So,  $|\epsilon_m| \ll |\epsilon_e|$ . Furthermore, it is assumed that the error in the electrophysiological estimation may not exceed the estimation itself ( $|\epsilon_e| < |y_e|$ ). Finally, it is assumed that  $y_m$ ,  $y_e$ , and  $\epsilon_e$  are Gaussian distributed and mutually independent. Straightforward calculation, combining eq. (2) and (3) then yields:

$$D_{e,m} = \sigma_{\epsilon_e} / \mu_{y_e} \quad (4)$$

where  $\sigma_{\epsilon_e}$  is the standard deviation associated with the measurement error of an electrophysiological parameter, and  $\mu_{y_e}$  the mean value of the same parameter.  $D_{e,m}$  can thus be regarded as measuring the normalized measurement error in an electrophysiological parameter. Significance was judged with an  $F$ -test,  $p < 0.05$ . This is allowed, as long as the expected values of the parameters to be considered are constant.

## RESULTS

Fifteen patients who fulfilled the criteria for our present study had an indication for a sural nerve biopsy.<sup>11</sup> The two peaks in each diameter histogram were described by the beta function parameters  $Sm_{98}$ ,  $M_1$ ,  $M_2$ ,  $S_1$ ,  $S_2$ , and  $N_{thick}$  for each patient. Mean  $\mu$ , standard deviation  $\sigma$ , and coefficient of variation  $CoV_m$  were calculated for all parameters. Results are listed in the upper left part of Table 1.

Compound action potentials (CAPs), recorded from the 11 healthy volunteers, were characterized by their normalized peak-to-peak amplitudes  $V_{pp,N}$  [see eq. (1)] and conduction velocities  $u_1$ ,  $u_2$ , and  $u_3$ , associated with the main peaks in the triphasic signal (see Fig. 2). Values for  $\mu$ ,  $\sigma$ , and  $CoV_e$  of  $V_{pp,N}$ ,  $u_1$ ,  $u_2$ , and  $u_3$  were computed. These results are listed in the lower right part of Table 1.

From the recorded CAPs conduction velocity histograms were estimated. The two peaks in the conduction velocity histograms, as described by means of two beta distribution functions, also yield

**Table 1.** Group means ( $\mu$ ), standard deviations ( $\sigma$ ), and coefficients of variation (CoV) of histogram parameters.

Parameter	Morphology: diameter histograms ( $N = 15$ )				Electrophysiology: conduction velocity histograms ( $N = 11$ )			
	Unit	$\mu$	$\sigma$	$CoV_m$	Unit	$\mu$	$\sigma$	$CoV_e$
$M_1$	$\mu\text{m}$	3.11	0.40	0.129	m/s	9.20	2.95	0.321
$M_2$	$\mu\text{m}$	8.46	0.80	0.095	m/s	33.75	2.45	0.073
$S_1$	$\mu\text{m}$	0.86	0.19	0.221	m/s	3.00	0.305	0.102
$S_2$	$\mu\text{m}$	2.26	0.63	0.279	m/s	8.10	1.50	0.185
$Sm_{98}$	$\mu\text{m}$	12.7	1.2	0.094	m/s	55.3	4.2	0.076
$N_{thick}$		3809	624	0.164				
$N_{fast}$						5664	1536	0.271
					Electrophysiology: CAPs ( $N = 11$ )			
	Unit	$\mu$	$\sigma$	$CoV_e$				
$V_{pp,N}$	$\mu\text{V}$	84.9	37.6	0.44				
$u_1$	m/s	56.9	3.6	0.063				
$u_2$	m/s	48.9	2.6	0.053				
$u_3$	m/s	39.4	3.3	0.084				

For definition of the parameters see the Methods section.

histogram parameters  $Sm_{98}$ ,  $M_1$ ,  $M_2$ ,  $S_1$ ,  $S_2$ , and  $N_{fast}$ . The characteristics of all these parameters are listed in the upper right part of Table 1.

The difference between  $CoV_m$  of the morphological estimate  $N_{thick}$  and  $CoV_e$  of the electrophysiological estimate  $N_{fast}$  was significant [ $D_{e,m} = \sqrt{((0.271)^2 - (0.164)^2)} = 0.22$ ]. It can be expected that  $V_{pp,N}$  also primarily depends on the number of thick, fast conducting fibers. The difference between  $CoV_e$  of  $V_{pp,N}$  and  $CoV_m$  of  $N_{thick}$  was significantly larger [ $D_{e,m} = \sqrt{((0.44)^2 - (0.164)^2)} = 0.41$ ]. The significant difference between these  $D_{e,m}$  values, both estimating the total number of fast conducting fibers, shows that application of inverse modeling better approaches the inherent biological interindividual variability.

Parameter  $Sm_{98}$ , indicating the upper limit of the histogram, is a measure for the thickest (and thus the fastest conducting) fibers. Its electrophysiological counterpart is parameter  $u_1$ , being the conduction velocity of the first (positive) peak in the CAP (see Fig. 2). Differences between  $CoV_e$  of  $u_1$  and CoV values of  $Sm_{98}$  (obtained from both morphology and electrophysiology) were not significant either. Differences between  $CoV_m$  of  $Sm_{98}$  obtained from electrophysiology were not significant. This implies that with respect to the conduction velocity, distribution  $u_1$  is as reliable as  $Sm_{98}$  as a measure of the fastest conducting fibers and that the measured morphological and electrophysiological variability might both be close to the inherent biological variability.

$D_{e,m}$  of the  $M_1$  and the  $S_1$  parameters ( $p < 0.05$ ), being the mean and standard deviation of the beta function describing the thin, slow conducting fiber group, appeared to be significant. Because the morphological variability comes out as larger than the electrophysiological, it is impossible to handle  $S_1$  in terms of the defined  $D_{e,m}$  parameter. In connection with this result, it should be kept in mind that the slow fiber estimates were derived from the variance of the CAP, yielding a typical uncertainty of 50% per bin and an uncertainty of 25% for the total number of slow fibers.<sup>14</sup> The same applies for the  $N_{thin}$  vs.  $N_{slow}$ , the number of fibers in the slow and thin fiber group, which is therefore not listed. No significant difference was found between relative deviations of the  $M_2$  and the  $S_2$  parameters, obtained from morphology and electrophysiology.

## DISCUSSION

In the present study conduction velocity histograms of the human sural nerve were computed from CAP signals, using an inverse procedure in-

troduced by Schoonhoven et al.<sup>14</sup> and elaborated by van Veen et al.<sup>19</sup> The latter authors presented an experimental validation of the inverse procedure, by comparing their computed conduction velocity histograms to diameter histograms obtained from biopsies from the same patients in which CAPs were measured. In those experiments and subsequent analysis, a good agreement was found between conduction velocity and diameter from the same patients. Differences could be explained from pathology.

Obviously, no biopsies from the healthy volunteers were available in the present study, preventing a one-to-one comparison of conduction velocity and diameter histograms. Therefore, normal fiber diameter histograms presented in an earlier study<sup>11</sup> were compared to the estimated conduction velocity histograms. The raw CAP data, the diameter histograms, and the conduction velocity histograms were compared using coefficients of variation (CoV) of their descriptive parameters. The differences between the CoV values were significant for the mean and width ( $M_1$  and  $S_1$ ) of the distribution of the smaller and slower group of fibers and for  $N_{fast}$  vs.  $N_{thick}$ , the two estimates of the total number of fibers. For all other parameters differences were not significant. The relatively low accuracy of the slow fiber estimates prevented a comparison of the total number of slow with the number of thin fibers, as actually appeared to be the problem for  $S_1$  as well.

The two electrophysiological measures for the total number of thick fibers are  $V_{pp,N}$  and  $N_{fast}$ . The differences between interindividual variabilities in the  $N_{thick}$  (obtained from morphology) versus the  $N_{fast}$  (obtained from the conduction velocity histogram) parameters on one side and the difference  $V_{pp,N}$  versus  $N_{thick}$  on the other side yields a significantly larger value  $D_{e,m}$  for the latter difference (0.41 compared to 0.22). Applying the inverse procedure apparently reduces the errors made in straightforward CAP amplitude interpretation, which is the main achievement of using this inverse procedure. This error reduction is based on the fact that the inverse procedure uses an adequate model description. A crucial parameter in the procedure is how close the recording electrode is positioned to the nerve (the radial recording distance). In our inverse procedure, this parameter was estimated from the data.<sup>19</sup> When straightforwardly interpreting CAP amplitudes, no information considering this recording distance can be used. The result underlines that amplitude measurements of CAPs are rather unreliable without

additional a priori knowledge about measurement conditions.

Our present study also illustrates that direct interpretation of peak conduction velocities gives a rather reliable reflection of the underlying biological variation. No significant difference was found between CoV values of  $u_1$ ,  $u_2$ , and  $u_3$  and that of  $Sm_{98}$  obtained from morphology. The calculation of  $Sm_{98}$  from the velocity distribution seems not to increase the precision of a fast velocity estimate. This illustrates that no profit can be gained from the inverse procedure for the determination of "simple" conduction velocity parameters. From the chosen point of view, the lack of a significant difference between pairs of  $M_2$  and  $S_2$  nicely illustrates that the velocity distribution of the group of fast conducting fibers reflects the biological variability which is also found in describing the thick fiber distribution.

In summary, using a statistical error analysis on conventional CAP parameters, estimating conduction velocity histograms and morphologically determined diameter distributions, we have made plausible that information regarding maximum conduction velocities can reliably be assessed from CAP component latencies and that the velocity distribution of the fast fibers can reliably be estimated by using the inverse modeling procedure. The CAP amplitude is not a reliable parameter for the number of thick, fast conducting fibers. Here the inverse modeling increases the reliability of the estimation.

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