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Variations in propagation velocity of muscle-fiber action potentials in individual motor units during voluntary contractions

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MUSCLE-FIBER CONDUCTION VELOCITY can be measured in humans in vivo during either voluntary or electrically elicited contractions. Its measure provides a window into the membrane electrophysiological properties of the muscle fibers, which cannot be directly measured, because the velocity of propagation of action potentials depends on the polarization state of the membrane. Measures of conduction velocity can be obtained from fibers innervated by individual motoneurons to characterize the membrane properties of fibers in single motor units during natural muscular contractions (9).

Conduction velocity in individual motor units has been shown to vary, depending on the time separation between discharge times (10). A potential explanation for this observation is the variation in potassium concentration in the t-tubule system, although other mechanisms have also been proposed (3). The dependence of conduction velocity on the time interval between two discharges has been termed the velocity recovery function and has been investigated classically by paired electrical stimuli. In addition to variations due to the instantaneous discharge rate, conduction velocity shows a relatively slow decreasing trend over time during sustained contractions. This trend is not necessarily associated with fiber activation, but rather to the activity of the whole muscle, and is probably due to variations in the extracellular concentration of potassium.

Changes in muscle-fiber conduction velocity, either fast or slow, can, in principle, be predicted and explained by modeling the ion exchanges across the fiber membrane. Nevertheless, because the parameters that describe human ion channels are not known, not all experimental observations on changes in conduction velocity have a simple explanation based on the current fiber membrane modeling approaches. Indeed, one single measure (conduction velocity) is not sufficient to identify several model parameters, so that multiple solutions exist, and an inverse modeling approach is not possible. In addition, there is a lack of data on changes in motor unit conduction velocity under a variety of conditions, which further hinders the possibility of using a biophysical model identification approach. This scarcity of data also limits the opportunity to build realistic models of electromyogram (EMG) generation (1).

In this issue of the *Journal of Applied Physiology*, McGill and Lateva (8) fill some of the gaps in our understanding of the determinants of conduction velocity during voluntary motor unit activation. The authors measured interspike intervals and conduction velocity from action potentials of fibers of single

motor units in several conditions, to identify associations between conduction velocity and discharge rate or time. Although their main findings are in agreement with observations reported in previous studies, this is the first study that provides, with a single experimental approach and in a comprehensive manner, an overview of variations in conduction velocity for individual motor units in a very broad range of conditions. By doing so, the authors were also able to fit their results to a descriptive model, which aimed at the precise prediction of the experimental observations with simple equations and few parameters. Among the several well-documented results in this comprehensive study, I will comment on a few that may be of broad interest.

McGill and Lateva (8) show that conduction velocity decreases over time, even during intervals in which the tested fibers are not active. This conclusion is in agreement with the observation by Gazzoni et al. (4) that, during ischemic conditions, inactive muscle fibers undergo progressive changes in conduction velocity, similar to those of the active fibers. The present results, however, are shown for normal conditions and for relatively low levels of muscle activity. Taken together, these data indicate that fiber activation is not a necessary condition for a reduction in conduction velocity during muscle activity. All fibers during a muscle contraction likely vary their baseline conduction velocity, partly independent of their activity. A similar behavior has been included in recent attempts to describe the fatigue-induced changes of muscle properties by computational modeling (1). Interestingly, this result indicates that the extracellular environment is the main determinant of changes of the membrane muscle-fiber properties. This observation, which exemplifies the gap between the study of membrane electrophysiology in in vitro fiber preparations and in vivo, has direct implications for the interpretation of changes in the surface EMG during sustained contractions (2). For example, additional recruitment of motor units during a contraction does not necessarily correspond to an increase in the average muscle-fiber conduction velocity, since the baseline conduction velocity of the newly recruited motor units would have also decreased with respect to the beginning of the contraction.

McGill and Lateva (8) further proceed by characterizing the relation between discharge rate and conduction velocity in individual motor units. It is relevant at this point to add a note on the complexity and the sophistication of such in vivo measures. This characterization requires an accurate identification of all action potentials discharged by a motor unit (EMG decomposition) and an estimate of conduction velocity for each of these action potentials with minimal estimation error. Since the fluctuations in conduction velocity due to discharge rate are in the order of 10%, the variance of estimation should be substantially lower than 0.5 m/s. It is not necessary here to

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discuss in detail the methodological aspects involved in achieving such measures; however, it is worth stating that the authors solved these issues using state-of-the-art approaches and, as a result, provide an extremely solid set of data that can be used as a reference for future studies.

The relation between discharge rate and conduction velocity is reported by the authors as directly proportional in most cases, with the exception of a few cases in which, interestingly, the association is reversed. The direct proportionality of conduction velocity and discharge rate is related to the second supernormal region of the velocity recovery function (10, 11). In this region, the firing rate is indeed almost linearly related to conduction velocity. This region extends to most of the range of discharge rates observed during voluntary motor unit activation. However, although the velocity recovery function broadly justifies the findings of a history dependence of conduction velocity on discharge rate, the authors correctly point out that it is not possible to precisely characterize the variations in conduction velocity for a train of action potentials during voluntary contractions from the findings on the velocity recovery function obtained by paired activations only. The velocity recovery function indeed explains the changes in conduction velocity of an action potential discharged after a previous action potential whose velocity of propagation corresponds to the baseline velocity. However, when using pairs of stimulations, the baseline value for conduction velocity is reached only for intervals that are between 250 ms and 1 s (10), so that a further activation at a shorter interval, as occurs in voluntary contractions, would not correspond to the membrane in the same condition as for paired activations. A direct indication that the velocity recovery function measured from pairs of stimuli is insufficient to explain the history dependence of conduction velocity on discharge rate is exemplified by a recent study in which a conditioning activation was delivered before the pair of activations used to determine the velocity recovery function (i.e., when a triplet of activation rather than a doublet was used) (6). In that study, the velocity recovery function measured after the conditioning activation was substantially different than that measured for a single pair of activations. This effect was observed for time intervals separating the conditioning stimulus from the pair of stimuli within the range of the voluntary discharge rates of motor units and, therefore, indicates that the entire pattern of discharge may, in principle, influence the conduction velocity of each action potential. Therefore, studies on the velocity recovery function that have included only two or few activations cannot explain the behavior of the muscle fiber for several discharges. The study by McGill and Lateva provides this information.

Despite confirming the observation of a direct association between discharge rate and conduction velocity, the authors also report an inverse association in two of the investigated subjects. In these cases, the association was direct during recruitment (i.e., at low discharge rate) and inversed during a steady activation (at higher discharge rate). This observation is the first that documents a change in the association between the discharge rate and conduction velocity for the same motor unit in normal conditions. A change in association between interspike interval and conduction velocity could be explained for double stimulation pulses (velocity recovery function) as a passage from one to the other supernormal region, in which the association is reversed. The turning point between these two

regions varies greatly across subjects and, presumably, across muscle fibers. For example, in a recent study (6), the peak in velocity was observed to vary between 4 and 75 ms of the interstimulus interval. Therefore, in principle, both supernormal regions can be crossed within the physiological range of discharge rates of a motor unit. Nevertheless, as discussed above, the velocity recovery function measured in double pulse stimulation does not provide the full information to predict conduction velocity behavior during steady-state firing, when the conduction velocity is affected by the entire discharge history going back to ~ 1 s. Therefore, the reasons for the inversion of the association between discharge rate and conduction velocity during voluntary activation remain to be fully explained.

One of the main contributions of this study is the fitting of a descriptive model to estimate a few parameters that are sufficient to explain the data. This model provides several interesting observations. The model quantifies the above discussed problems in predicting changes in conduction velocity from instantaneous changes in discharge rate. A perfect association is indeed obtained only by a causal smoothing of the discharge rate, which models the history and not only the instantaneous variations. The time constant for this smoothing is associated with the time interval after which the recovery function returns to baseline, and is also in the same range of values as the time interval after which a conditioning stimulus has an effect on the velocity recovery function (6). The model provides a concise description of the data, which can be used to summarize observed behaviors by a few parameters. Indeed, it would not be possible to explain the observed behavior by providing values of conduction velocity for all of the combinations of a series of interspike intervals, as it is done for the case of two discharges in the velocity recovery function. Moreover, interestingly, the descriptive model also allows inferences on potential mechanisms. For example, the authors note that the model proposed by Lf (7), which they modified, can be seen as a simple diffusion model, which may fit with the actual dynamics of the potassium concentration in the t-tubule system. The fact that this model accurately explains the data, in such a large data set, supports the notion that the history dependence of conduction velocity may be a consequence of the accumulation of potassium in the t-tubule system. Although this inference may seem speculative, alternative explanations based on complex biophysical models are equally difficult to prove due to the uncertainty of most model parameters.

Many of the observations and results of this study will generate subsequent work. The issue of variability in the association between discharge rate and conduction velocity across fibers and subjects is an aspect that needs further investigation, specifically in the context of the observed inversion of the relation between discharge rate and conduction velocity during the activity of the same fiber. Another aspect to be further analyzed is the association between the velocity recovery function and the history dependence of conduction velocity on discharge rate. The velocity recovery function appears to change when more pulses are added in the stimulation train (11), and these changes can be explained by linear combinations of the recovery functions for paired stimulations in some conditions only (5). The model applied by the authors can provide the values of conduction velocity for any discharge sequence, including those not directly observed. Therefore, the

model can provide a characterization of the velocity recovery function, given any baseline value of conduction velocity. It may be interesting to verify if this approach can explain the velocity recovery functions experimentally measured for different baseline conduction velocity values, as well as during longer stimulation trains. This would not only provide further evidence for the validity of the descriptive model used and its parameter values, but would also offer more information on the electrophysiological mechanisms. Finally, a relevant aspect not addressed in the present paper is the influence of changes in conduction velocity on the generated twitch force. It is likely that a history-dependent change in conduction velocity underlies a history dependence of twitch force on discharge rate. Indeed, a recovery function can also be observed for twitch forces, although with some characteristics different from that of conduction velocity (6).

With this study, McGill and Lateva have provided the most detailed analysis of conduction velocity in individual motor units to date. They also provide a concise and precise description of their data based on few parameters. This description is necessary for other modeling approaches that describe changes in extracellular action potentials during sustained activity (e.g., Ref. 1). Moreover, the data of this study allow inferences to be made on the potential underlying mechanisms that explain the variations in conduction velocity with discharge rate as an alternative to the investigation of these mechanisms through complex biophysical membrane models, for which most parameters are unknown. Measures of muscle-fiber conduction velocity provide a means to assess the membrane electrophysiology in vivo in humans during natural muscular contractions. Understanding the mechanisms that underlie the measured values of conduction velocity provides a unique window of

opportunity to examine the fiber membrane properties in vivo in individual motor units.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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