FACTORs AFFECTING MAGNITUDE AND TIME COURSE OF NEUROMUSCULAR BLOCK PRODUCED BY SUXAMETHONIUM


SUMMARY
This study was designed to identify factors that significantly affect the magnitude and duration of suxamethonium-induced neuromuscular block in patients with an apparently normal genotype for pseudocholinesterase. One hundred and fifty-six adults (ages 18-65 yr) were allocated to thirteen subgroups. Patients in each subgroup received suxamethonium 50-2000 μg kg⁻¹. The mechanographic response of the adductor pollicis brevis muscle to ulnar nerve stimulation was recorded. The ED₅₀ was found to be 167 μg kg⁻¹. ED₉₅ was 316 μg kg⁻¹ and ED₉₉ was 392 μg kg⁻¹. The duration of action (Δt) was in agreement with earlier published results. The magnitude of block was dose-related and decreased with increasing onset time (ton) and pseudocholinesterase activity (PChA). Neither age nor gender affected the degree of suxamethonium-induced block. Δt was dose-related, decreased with increasing PChA, and was shorter for women. Age and ton had no effect on Δt.

KEY WORDS
Neuromuscular relaxants: suxamethonium.
70% nitrous oxide in oxygen. End-tidal carbon dioxide concentration was maintained at 4–5% (Multicap, Datex, Helsinki, Finland) for the entire procedure. Inhalation anaesthetics were not used during the study.

A single twitch of the thumb was evoked at a frequency of 0.15 Hz, using rectangular pulses of 0.2 ms duration and supramaximal intensity. The stimulating current, generated by a Grass S44 stimulator, was applied to the ulnar nerve at the wrist using subcutaneous 27-gauge steel needle electrodes, placed 30 mm apart. The hand and forearm were immobilized in supination and abduction on a splint and the fingers were strapped in extension. The transducer was mounted so that the thumb was exposed to a tension of 200 g, measured continuously and recorded. During the study, a preload of 100–300 g was accepted. In patients who exhibited changes outside the range 100–300 g (that is, after gross fasciculations), the preload was readjusted. The mechanomyogram (MMG) of isometric thumb adduction was measured using a Grass FT10 force-displacement transducer and recorded on a strip chart recorder.

Baseline was regarded as stable when, on the mechanographic recordings, the change in twitch height over 20 consecutive twitches was < 1% of the amplitude of the last twitch. This occurred usually after 10–12 min of baseline recording. When the baseline recording was stable, suxamethonium (concentration 20 mg ml⁻¹, kept refrigerated at 4 °C from manufacture to the time of administration) was injected i.v. as a bolus over 5 s and flushed with 0.9% sodium chloride 10 ml. After twitch height had recovered to the control value, additional thiopentone and suxamethonium were given to facilitate tracheal intubation. The remainder of the anaesthetic management was left to the discretion of the attending anaesthetist.

The twitch responses recorded were expressed as percentage changes from the baseline control period. The following events were selected:

1. the degree of maximal twitch depression;
2. the time from injection of suxamethonium until the first depressed twitch (ton) if maximal twitch depression > 0%;
3. the times from injection to 10% (t10), 50% (t50) and 90% (t90) recovery of twitch height.

In order to compare our results with those of other authors, duration of effect was calculated also as the time from the first depressed twitch to 10% (t10), 50% (t50) and 90% (t90) recovery of twitch height.

Measurements of PChA and dibucaine number were made at 30°C with butyrylthiocholine as a substrate using a reagent set (Test-Combination Cholinesterase, Boehringer, Mannheim, Germany) [10]. The results from patients with an abnormal dibucaine number were not taken into consideration.

**Data analysis**

Body surface area (BSA) was calculated from the height and weight using the formula of Dubois and Dubois [11]. Percentage of ideal weight for height was calculated using life insurance tables [12]. The age, weight, percentage of ideal weight for height, BSA and PChA of the 13 groups were compared using one-way analysis of variance. PChA values of males and females were compared by Student's t test.

The relationship between dose of suxamethonium (expressed as μg kg⁻¹ or μg m⁻²) and effect was examined by fitting the standard Hill equation to the patient data by non-linear least squares regression:

\[ \frac{E}{E_{\text{max}}} = \frac{D}{D_{\text{50}} + D} \]  

where \( E = \) depression of twitch as % of control; \( E_{\text{max}} = \) control value (100%); \( D = \) dose; \( D_{\text{50}} = \) dose producing 50% block; \( \gamma = \) steepness factor.

In order to examine if the remaining variability in \( E/E_{\text{max}} \) could be explained by invoking additional variables other than the dose, we used the logistic function:

\[ \frac{E}{E_{\text{max}}} = \frac{e^{\logit(E/Emax)}}{1 + e^{\logit(E/Emax)}} \]

where \( X_1, X_2, \ldots, X_m = \) m independent variables, and \( a_0, a_1, a_2, \ldots, a_m = \) the coefficients to be estimated. This can be restated as a linear model in the logit \( (E/E_{\text{max}}) \):

\[ \logit \left( \frac{E}{E_{\text{max}}} \right) = a_0 + a_1 \cdot X_1 + a_2 \cdot X_2 + \ldots + a_m \cdot X_m \]  

As the logit for \( E/E_{\text{max}} = 0 \) and \( E/E_{\text{max}} = 1 \) do not exist, these values were transformed into \( E/E_{\text{max}} = 0.001 \) and \( E/E_{\text{max}} = 0.999 \), respectively.

The duration of the suxamethonium block (\( \Delta t \)) was described as a linear combination of independent variables:

\[ \Delta t = b_0 + b_1 \cdot Y_1 + b_2 \cdot Y_2 + \ldots + b_n \cdot Y_n \]

where \( \Delta t = t90 \). If the maximal depression of twitch was < 10% of the pre-block control value (i.e. for \( E/E_{\text{max}} < 0.1 \), \( t90 \) was considered as a missing value. \( Y_1, Y_2, \ldots, Y_n \) are a set of \( n \) independent variables and \( b_0, b_1, b_2, \ldots, b_n \) are the coefficients to be estimated. Both the logit of \( E/E_{\text{max}} \) and \( \Delta t \) were assumed to be approximately normally distributed.

The variables Log(dose), PChA, age, ton and gender were investigated as possible causes of variation in \( E/E_{\text{max}} \) and \( \Delta t \). The first four of these variables are continuous, whereas the fifth was scored 0 for males and 1 for females. For doses that produced no measurable effect (i.e. \( E/E_{\text{max}} = 0 \), it was considered as a missing value. Stepwise regression analysis by the statistical software package SAS/STAT (Release 6.03, SAS Institute Inc., Cary, U.S.A.) [13] was used on the experimental data to select a predictor set from the above five variables for logit \( (E/E_{\text{max}}) \) and \( \Delta t \). In this study \( P < 0.05 \) was considered significant.

Fitting the logistic function (equation (2)) to the untransformed data by non-linear least squares regression allowed the estimate of the coefficients \( a_0, a_1, a_2, \ldots, a_m \) presented in this paper.
FACTORS AFFECTING SUXAMETHONIUM BLOCK

Table I. Patient characteristics (mean (SD) [range] or number). Twelve patients in each dose group. Ideal weight = percentage of ideal weight for height; BSA = body surface area; PChA = pseudocholinesterase activity

<table>
<thead>
<tr>
<th>Dose (µg kg⁻¹)</th>
<th>Sex (M/F)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Ideal weight (%)</th>
<th>BSA (m²)</th>
<th>PChA (u. litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>8/4</td>
<td>44</td>
<td>71 (11)</td>
<td>98 (10)</td>
<td>1.86 (0.15)</td>
<td>7706 (1857)</td>
</tr>
<tr>
<td>100</td>
<td>8/4</td>
<td>44</td>
<td>66 (9)</td>
<td>100 (13)</td>
<td>1.74 (0.15)</td>
<td>7441 (1951)</td>
</tr>
<tr>
<td>150</td>
<td>9/3</td>
<td>56</td>
<td>73 (12)</td>
<td>96 (11)</td>
<td>1.91 (0.17)</td>
<td>8566 (1216)</td>
</tr>
<tr>
<td>200</td>
<td>10/2</td>
<td>35</td>
<td>72 (9)</td>
<td>99 (11)</td>
<td>1.88 (0.17)</td>
<td>7009 (1846)</td>
</tr>
<tr>
<td>250</td>
<td>8/4</td>
<td>41</td>
<td>73 (13)</td>
<td>99 (11)</td>
<td>1.88 (0.14)</td>
<td>7589 (1527)</td>
</tr>
<tr>
<td>300</td>
<td>5/7</td>
<td>32</td>
<td>71 (11)</td>
<td>100 (11)</td>
<td>1.85 (0.16)</td>
<td>7384 (1548)</td>
</tr>
<tr>
<td>350</td>
<td>7/5</td>
<td>32</td>
<td>68 (13)</td>
<td>99 (7)</td>
<td>1.79 (0.19)</td>
<td>7225 (1580)</td>
</tr>
<tr>
<td>400</td>
<td>6/6</td>
<td>35</td>
<td>64 (9)</td>
<td>97 (13)</td>
<td>1.74 (0.14)</td>
<td>8074 (2137)</td>
</tr>
<tr>
<td>450</td>
<td>7/5</td>
<td>37</td>
<td>68 (12)</td>
<td>99 (9)</td>
<td>1.83 (0.17)</td>
<td>7589 (1410)</td>
</tr>
<tr>
<td>500</td>
<td>6/6</td>
<td>39</td>
<td>64 (10)</td>
<td>99 (6)</td>
<td>1.73 (0.18)</td>
<td>6788 (1903)</td>
</tr>
<tr>
<td>600</td>
<td>7/5</td>
<td>44</td>
<td>72 (12)</td>
<td>95 (10)</td>
<td>1.86 (0.16)</td>
<td>8477 (1826)</td>
</tr>
<tr>
<td>1000</td>
<td>7/5</td>
<td>33</td>
<td>73 (13)</td>
<td>97 (14)</td>
<td>1.89 (0.16)</td>
<td>8383 (1174)</td>
</tr>
<tr>
<td>2000</td>
<td>8/4</td>
<td>34</td>
<td>70 (16)</td>
<td>98 (11)</td>
<td>1.84 (0.18)</td>
<td>7944 (1801)</td>
</tr>
</tbody>
</table>

RESULTS

We studied 167 patients, but results from 11 were excluded because they had an abnormal dibucaine number. In the final study population, comprising 156 eligible patients, there were 96 men and 60 women. There were no significant differences between patient characteristics measured in the 13 treatment groups in age, weight, percentage of ideal weight for height, BSA and PChA (table I). PChA ranged from 2790 to 37377 u. litre⁻¹. Eight patients had a maximum twitch depression of 0% (i.e., E/Emax = 0) after administration of suxamethonium. In these patients, ton could not be determined and was considered as a missing value. ton in the remaining 148 patients ranged from 13 to 81 s.

There were no significant differences in mean PChA between the males (7840 (sd 1600) u. litre⁻¹) and females (7450 (1800) u. litre⁻¹).

Because virtually every dose of suxamethonium exceeding 500 µg kg⁻¹ prevented a response, the relationship between dose and effect was calculated for doses up to and including 500 µg kg⁻¹ (n = 120). The results calculated by fitting the standard Hill equation to the patient data are presented in table II. The dose–response curve is shown in figure 1. The coefficient of determination (R²) was not different when the dose was in µg kg⁻¹ (R² = 0.69) or in µg m⁻² (R² = 0.69). As a consequence, the fit was not improved by expressing dose on a surface area basis. Dose–duration data are shown in table III.

The identification of factors affecting magnitude of the neuromuscular block produced by suxamethonium was performed on the patients belonging to the dosage groups up to and including 500 µg kg⁻¹ (n = 120). In eight patients from the smallest dosage groups, ton could not be determined because there was no measurable response after administration of suxamethonium. In these patients, ton was considered as a missing value. In the remaining patients (n = 112), stepwise regression demonstrated significant contribution to the maximal intensity of block, not only by the dose (P < 0.001), but also by ton (P < 0.001) and PChA (P < 0.05). The dose, ton and PChA explained 64.7, 6.7 and 3.5%, respectively, of the total variation in E/Emax (table IV). Neither age nor gender affected the degree of suxamethonium-induced block. The regression model for E/Emax may be written as:

\[
\frac{E}{E_{\text{max}}} = \frac{e^{(\gamma \cdot \text{ton})}}{1 + e^{(\gamma \cdot \text{ton})}}
\]
TABLE III. Times to recover from neuromuscular block produced by suxamethonium (mean (SD) [range]). \( t_{100} \), \( t_{50} \) and \( t_{90} \) = times from first evidence of twitch suppression to 10%, 50%, and 90% recovery of twitch height, respectively.

<table>
<thead>
<tr>
<th>Dose and source</th>
<th>( t_{100} ) (min)</th>
<th>( t_{50} ) (min)</th>
<th>( t_{90} ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 ( \mu \text{g kg}^{-1} ) Present study (( n = 12 ))</td>
<td>4.8 (1.3)</td>
<td>6.3 (1.6)</td>
<td>8.3 (2.5)</td>
</tr>
<tr>
<td>([26] ) (( n = 13 ))</td>
<td>4.6 (1.4)</td>
<td>5.9 (1.6)</td>
<td>7.4 (2.1)</td>
</tr>
<tr>
<td>([2] ) (( n = 20 ))</td>
<td>5.5 [1.5-9.4]</td>
<td>6.7 [2.0-10.6]</td>
<td>10.1 [4.2-16.0]</td>
</tr>
<tr>
<td>1000 ( \mu \text{g kg}^{-1} ) Present study (( n = 12 ))</td>
<td>8.5 (2.2)</td>
<td>10.6 (2.5)</td>
<td>13.2 (3.2)</td>
</tr>
<tr>
<td>([26] ) (( n = 13 ))</td>
<td>8.1 (3.0)</td>
<td>10.1 (3.1)</td>
<td>12.1 (3.4)</td>
</tr>
<tr>
<td>2000 ( \mu \text{g kg}^{-1} ) Present study (( n = 12 ))</td>
<td>13.0 (2.4)</td>
<td>15.7 (3.2)</td>
<td>18.6 (4.2)</td>
</tr>
<tr>
<td>([26] ) (( n = 13 ))</td>
<td>10.7 [18.0]</td>
<td>12.1 [23.3]</td>
<td>13.5 [28.6]</td>
</tr>
</tbody>
</table>

where:

\[
A(x) = -11.8 + 3.10 \cdot \log e D - 3.22 \cdot 10^{-4} \cdot \text{ton} - 3.69 \cdot 10^{-4} \cdot \text{PChA}
\]

with units \( D = \mu \text{g kg}^{-1} \), \( \text{ton} = \text{s} \) and \( \text{PChA} = \text{u. litre}^{-1} \).

The identification of factors affecting the duration of the neuromuscular block produced by suxamethonium was investigated in patients from all dose groups. In 16 patients \( E/Emax \) was < 0.1 and, as a consequence, in these patients \( \Delta t (= \tau_{90}) \) could not be determined. In eight of these patients, \( \text{ton} \) was considered as a missing value because the maximum twitch depression after suxamethonium administration was 0%. In the remaining patients (\( n = 140 \)), the duration of action was shown to be affected significantly not only by the dose (\( P < 0.001 \)), but also by the gender (\( P < 0.001 \)) and PChA (\( P < 0.001 \)). The dose, gender and PChA explained 59.0, 7.8 and 2.9 %, respectively, of the total variation in \( \Delta t \) (table V).

The linear regression model for \( \Delta t \) was:

\[
\Delta t = -933 + 279 \cdot \log e D - 0.031 \cdot \text{PChA} - 163 \cdot \text{gender}
\]

where \( \Delta t = \tau_{90} \) and with units \( D = \mu \text{g kg}^{-1} \), PChA = u. litre\(^{-1} \) and gender = 0 for males and 1 for females.

DISCUSSION

In the current study, depolarizing block was monitored using the evoked MMG of the adductor pollicis brevis muscle. Mechanical and electrical evoked responses represent physiological events different from, but related to, nerve stimulation [14]. Unlike the EMG, which measures only electrical responses of the muscle endplate and sarcolemma to
cholinergic transmission in those fibres that are near enough to the recording electrodes, the MMG reflects the overall performance of a whole muscle in response to nerve stimulation [14, 15]. Because the clinically relevant outcome of the use of a neuromuscular blocking agent is its effect on the capability of muscle to contract when the nerve is stimulated, the MMG was preferred as a measure to evaluate depolarizing block. Because a reliable assay for suxamethonium is lacking, methods of studying inter-individual differences in drug responses (simultaneous pharmacokinetic and pharmacodynamic modelling or population pharmacokinetic studies) could not be applied. We therefore used multiple regression functions with stepwise selection of variables throughout the study. These functions are flexible expressions that are capable of describing much of the between-patient variation [16].

Factors affecting maximum intensity of neuromuscular block produced by suxamethonium

The potency estimates (table II) of the current study are in agreement with previously reported values from studies which used i.v. anaesthesia and one single bolus of suxamethonium and quantified neuromuscular transmission by MMG [4, 17].

The difference in magnitude of response between otherwise comparable individuals given the same dose of drug was considerable, particularly in the dose range 50–350 μg kg⁻¹ (fig. 1). Our observations are consistent with those of other investigators [1, 18].

The current study shows that PChA and ton contribute significantly to the total variation in magnitude of block. The susceptibility of an individual to suxamethonium increases with decreasing PChA and ton becoming shorter.

These results appear to be at variance with previous work of Chesnut and co-authors [1], who concluded that the degree of block was not related to PChA and ton. In this investigation, the contribution of PChA to the variation in magnitude of block was studied in 14 patients, presumably heterozygous for abnormal pseudocholinesterase. Sensitivity to suxamethonium in such patients can be normal or only slightly increased [19]. In addition, their conclusion about ton were based on a population of 16 patients with only minor variation in ton (15–35 s). In contrast, our study used the ton values (range 13–81 s) from 112 patients.

Several case reports have suggested a role for PChA in the sensitivity of individuals to suxamethonium [4, 20–25]. Reduced enzymatic activities were associated with lower potency estimates [4, 20–22], whereas greater PChA resulted in resistance to the neuromuscular blocking activity of suxamethonium [23–25]. However, these patients were homozygous for abnormal pseudocholinesterase. In our study, all patients had an apparently normal genotype, but still there was a significant relationship between PChA and sensitivity to suxamethonium. Similar findings have been reported previously [3].

The results of the current study are in keeping with the work of Harrison and co-authors who suggested that the degree of neuromuscular block for a given dose of suxamethonium would be less with ton becoming longer [5, 6].

Neither age nor gender contributed to the dose–response relationship in the adult population.

Pseudocholinesterase has a great capacity to hydrolyse suxamethonium at a very rapid rate. It seems reasonable, therefore, to assume that the greater the PChA, the longer ton (i.e. the longer the exposure to the enzyme in blood before reaching the endplates), or both, the smaller the fraction of the injected dose that is ultimately available for the endplates. This might lead to a lower suxamethonium concentration at the receptors and, as a consequence, to a less intense neuromuscular block for a given dose of drug.

In this study, the dose contributed 64.7 % of the variation in magnitude of neuromuscular block. PChA and ton together accounted for 10.2 % of the variation. Ton still leaves 25.1 % of the variation in response unexplained. Consideration must be given to other influences (initial volume of distribution and target organ sensitivity) as additional factors to explain the biological variation in the degree of suxamethonium-induced block.

Factors affecting duration of action of suxamethonium

Our results for the duration of effect are consistent with previously reported results [2, 26] (table III), despite the fact that methoxyflurane [26], trichloroethylene and halothane [2] were used to maintain anaesthesia. This suggests that, in contrast with non-depolarizing agents, the duration of action of suxamethonium is not affected by these anaesthetics. This is supported by previous work [27] demonstrating that administration of halothane had no influence on the duration of suxamethonium-induced block.

The current investigation shows that duration of action was consistently determined not only by dose, but also by PChA and the gender of the patients. The recovery time increased with decreasing PChA. These observations are supported by the findings of other authors [7, 8, 28]. Blitt and co-authors [9] did not show a correlation between PChA and duration of paralysis from suxamethonium. This is probably because their patients had only minor variation in enzymatic activity. We agree with Viby-Mogensen that even reduced PChA of the qualitatively normal enzyme prolongs only slightly the duration of paralysis with suxamethonium [7].

In this study, a consistent, gender-related difference in duration of action was found. We have no explanation for the significantly shorter recovery time in females. In the present population there was no significant, sex-related difference in enzymatic activity. Gender-related differences in extracellular volume [29] and muscle mass, normalized per kg body weight, may explain the shorter duration of action in females.

Age in the adult population had no influence on the duration of action.

There was no relationship between ton and duration of suxamethonium-induced block. Similar
findings have been reported previously [5, 6]. Inability to give an indication of the arm-to-arm circulation time [6] and muscle blood flow [30]. Our results suggest that circulation time or muscle perfusion are not important factors in determining the duration of the neuromuscular block produced by suxamethonium. This is consistent with the work of Argent, Dinnick and Hobbiger, who demonstrated that recovery from suxamethonium was unaltered despite stoppage of blood flow at the peak of muscle paralysis [31].

Both distribution volume (Vd) (the extracellular fluid [32]) and clearance (Cl) are independent factors that control half-life (T½): T½ = 0.693 * Vd/Cl. Clearance of suxamethonium depends upon hydrolysis by pseudocholinesterase. In the PCHA range studied, variation in enzymatic hydrolysis accounts for only a small part (2.9%) of the total variability in duration of action. Therefore, differences in distribution volume must be implicated to explain inter-individual differences in recovery from suxamethonium-induced paralysis. Other factors that may play a role in termination of drug action are the steepness of the individual concentration–response relationship (γ') and the concentration at half-maximal effect (C0.5) as a measure of the target organ sensitivity [33]. Vd, γ' and C0.5 were not determined in this study.

Although the proposed models do not include all sources of variability, they may explain a considerable part of the variation in magnitude (74.9%) and duration (69.7%) of the neuromuscular block produced by suxamethonium. The dose of suxamethonium is, not unexpectedly, the most important factor in determining the magnitude and duration of neuromuscular block. Aon and PCHA contribute to the variability in neuromuscular block after suxamethonium. PCHA also affects the duration of neuromuscular block, but PCHA of the qualitatively normal enzyme must be reduced dramatically before clinical relevant prolongation of neuromuscular block is observed. Women, with PCHA similar to that of men, have a shorter duration of paralysis after suxamethonium than men.

**APPENDIX**

The standard Hill equation:

\[
\frac{E}{E_{\text{max}}} = \frac{D}{D_{\text{max}} + D}
\]

(3)

can be transformed into a logistic function:

\[
\frac{E}{E_{\text{max}}} = \frac{e^{b_0 + b_1 X_1}}{1 + e^{b_0 + b_1 X_1}}
\]

(4)
or:

\[
\frac{E}{E_{\text{max}}} = \frac{e^{b_0 + b_1 X_1}}{1 + e^{b_0 + b_1 X_1}}
\]

(5)

Equation (5) can be restated as a linear model in the logit (E/Emax):

\[
\text{logit}(E/E_{\text{max}}) = a_0 + a_1 X_1
\]

(6)

where logit (E/Emax) = log(E/(Emax−E)); a0 = −γ * log(Dmax); a1 = γ; X1 = log(D).

Assuming a monoe-xponential drug disposition function for suxamethonium, Levy [34] showed that:

\[
\Delta t = (\log D - \log D_0)/k
\]

(7)

where Δt = duration of action; D = dose injected (µg kg−1); D0 = minimum effective dose (µg kg−1); k = apparent first order rate constant for elimination (s−1);

or

\[
\Delta t = b_0 + b_1 X_1
\]

(8)

where b0 = −(log(Dmax))/k; b1 = 1/k; Y1 = log(D).

An obvious question to ask is, when the independent variables X1 and Y1 can explain part of the variability in logit (E/Emax) (equation (6)) and Δt (equation (8)) respectively, may more of the variability be explained by invoking additional variables? This leads us to consider linear multiple regression models as:

\[
\text{logit}(E/E_{\text{max}}) = a_0 + a_1 X_1 + a_2 X_2 + ... + a_m X_m
\]

(9)

\[
\Delta t = b_0 + b_1 Y_1 + b_2 Y_2 + ... + b_n Y_n
\]

(10)

where X1, X2, ..., Xm and Y1, Y2, ..., Yn are independent variables with X1 = log(D) and Y1 = log(D).

Equation (9) can be transformed into the logistic function:

\[
\frac{E}{E_{\text{max}}} = \frac{e^{b_0 + b_1 Y_1}}{1 + e^{b_0 + b_1 Y_1}}
\]

(11)

where: A(x) = a0 + a1 X1 + a2 X2 + ... + am Xm.

**ACKNOWLEDGEMENT**

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**REFERENCES**


15. Lam HS, Morgan DL, Lampard DG. Derivation of reliable electromyograms and their relation to tension in mammalian
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