Different Pulse Shapes to Obtain Small Fiber Selective Activation by Anodal Blocking—A Simulation Study

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***Abstract*—The aim of this study was to investigate whether it is possible to reduce a charge per pulse, which is needed for selective nerve stimulation. Simulation is performed using a two-part simulation model: a volume conductor model to calculate the electrical potential distribution inside a tripolar cuff electrode and a human fiber model to simulate the fiber response to simulation. Selective stimulation is obtained by anodal block. To obtain anodal block of large fibers, long square pulses ($> 350\ \mu$s) with a relatively high currents (1–2.5 mA) are usually required. These pulses might not be safe for a long-term application because of a high charge per pulse. In this study, several pulse shapes are proposed that have less charge per pulse compared with the conventional square pulse and would therefore be safer in a chronic application. Compared with the conventional square pulse, it was possible to reduce the charge with all proposed pulse shapes, but the best results are obtained with a combination of a square depolarizing pulse and a blocking pulse. The charge per pulse was up to 32% less with that pulse shape than with a square pulse. Using a hyperpolarizing anodal prepulse preceding a square pulse, it was not possible to block nerve fibers in a whole nerve bundle and to obtain reduction of a charge per phase. Reduction of the charge could be achieved only with spatially selective blocking. The charge per phase was larger for the combination of a hyperpolarizing anodal prepulse and a two-step pulse than for the two-step pulse alone.**

***Index Terms*—Anodal blocking, charge reduction, selective stimulation, two-step pulse.**

I. Introduction

FUNCTIONAL electrical stimulation (FES) is a technique used to restore functions in neurologically impaired individuals. When electrical stimulation is applied to a nerve, large diameter nerve fibers need a lower external stimulus for their activation than small fibers. However, there are some applications in urology, gastroenterology, and skeletal muscle activation, which require selective activation of small fibers without activating larger ones [1], [2]. Several attempts have been made to accomplish this and a large number of pulse shapes have been used in different applications. Zimmerman [3] used very long pulses ($\approx$1 s) to obtain selective membrane accommodation in large fibers. In that way he blocked the myelinated fibers, while unmyelinated fibers remained unblocked. Attempts were made to achieve both spatial and fiber diameter selective activation by applying depolarizing prepulses [4]–[6]. However, selective activation of small fibers was achieved only in a limited region of a nerve bundle.

Another method for selective activation of small nerve fibers is the use of a selective anodal block [2], [7]–[12]. For anodal blocking, a tripolar cuff electrode is most often used. The electrode consists of a cathode, flanked by two anodes. When stimulation is applied, the nerve membrane is depolarized near the cathode and hyperpolarized near the anodes. If the membrane is sufficiently hyperpolarized, an action potential (AP) that travels into the depolarized zone cannot pass the hyperpolarized zone and is arrested. As with excitation, a lower external stimulus is needed for blocking large diameter fibers than for blocking smaller ones. Therefore, by applying a current above the blocking threshold for the large fibers but below the blocking threshold for the smaller ones, selective activation of the small fibers can be obtained. A drawback of this method is that relatively long pulses ($\geq 350\ \mu$s) and a relatively high current (1–2.5 mA) [10] are required. This may cause neural damage and can induce contact corrosion even when the pulses are charge balanced [13]–[16]. In long-term use, neural injury may be caused by the high charge per pulse [13]. A lower charge per pulse could make this technique safer for long-term clinical applications. This may be possible with a modified pulse shape.

Modification might be possible because of the following: an AP is generated close to the cathode and some time is needed for the AP to propagate from the cathode to the anode. Therefore, it is not necessary to apply a high blocking current at the beginning of the pulse. At the beginning of the pulse, the cathodal current should depolarize the membrane. In the second part of the pulse, it is necessary to apply a high anodal current in order to block the generated AP. By using a lower current in the first than in the second part of the pulse it is possible to obtain a lower charge per pulse than with a square pulse of the same duration.

In this paper, we present the results of computer simulations in which different pulse shapes were investigated to determine which one results in the lowest charge per pulse, while still being capable of selective small fiber activation. In addition, a square cathodal pulse is combined with an anodal pulse in order to investigate the influence of the anodal pulse on the blocking threshold of large fibers. We investigated which of these pulse

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shapes contains the least charge per pulse. We also examined whether a combination of a square anodal pulse with a step cathodal pulse could further reduce the charge per pulse.

II. Materials and Methods

A two-part simulation model was used to simulate sacral root stimulation. The first part was a volume conductor model to calculate the electrical potential distribution inside the cuff electrode and the second part was a human nerve fiber model to simulate the fiber response to stimulation.

Two different fiber diameters were simulated: a large diameter fiber of 12 $\mu\mathrm{m}$ and a small diameter fiber of 5 $\mu\mathrm{m}$ corresponding to nerve fibers innervating the external urethral sphincter and the detrusor muscle, respectively. The external urethral sphincter is innervated by nerve fiber diameters in the range of 9.5–12 $\mu\mathrm{m}$ [17] and the smooth detrusor muscle of the bladder is innervated by nerve fibers with a diameter of 2–4 $\mu\mathrm{m}$ [17]. The small fiber diameter of 5 $\mu\mathrm{m}$ was chosen because Wesselink's model [18] cannot be used for fiber diameters under 5 $\mu\mathrm{m}$ [19]. This fiber diameters were chosen because experimental results [2], [10] showed that selective detrusor activation without activation of external urethral sphincter is achievable with the technique of anodal blocking.

A. Volume Conductor Model

The model was rotationally symmetrical, the axis of the cuff electrode and the nerve being the axis of symmetry of the model. The smallest grid spacing in the axial direction was 0.1 mm and in the radial direction was 0.01 mm. The cuff electrode was tripolar and symmetrical, with the central contact placed 3 mm from the lateral contacts. A contact separation of 3 mm was chosen because it was shown by using a rabbit model [9] that for a smaller contact separation, for nerve fibers of 4 and 12 $\mu\mathrm{m}$ on the border of a nerve bundle of 1.4-mm diameter, the operating window for selective activation of small nerve fibers becomes too small. Larger contact separation would increase the length of the cuff. The distance from the lateral contacts to the edge of the cuff was 1 mm. The cuff inner diameter was 2 mm.

In all results, current is expressed as the current of the central contact. Currents of the lateral contacts are half of the current of the central contact. The dimensions of the contacts, cuff thickness and conductivity values were adopted from [9]. The model consisted of a nerve root, diameter 1.4 mm (Fig. 1, compartment 1), an insulating part of the cuff (compartment 2), metal contacts (compartment 3), the surrounding fluid (compartment 4) and the border of the model (compartment 5). The conductivity values are given in Table I.

B. Nerve Fiber Model

A human nerve fiber model was adopted from [18], which is based on data obtained from sensory human fibers [20]–[22]. All constants were calculated for a temperature of 37 °C [18]. The relation between the axon diameter d and the fiber diameter D, $d = 0.8\ D - 1.8 \times 10^{-6}$ [m], and the relation between the fiber diameter D and the internodal distance L, $L = 7.9 \times 10 - 4 \times ln(\mathrm{D}/3.4 \times 10^{-6})$ [m] are novel compared with previous models [23]–[26]. Ionic current consists of sodium, potassium, and leakage currents in contrast to rabbit model, where potassium current is not included. The sodium current is proportional to m^3h, (m activation parameter, h inactivation parameter) instead to m^2h like in previous models [23]–[26]. The model does not include the electrical properties of the internode membrane.

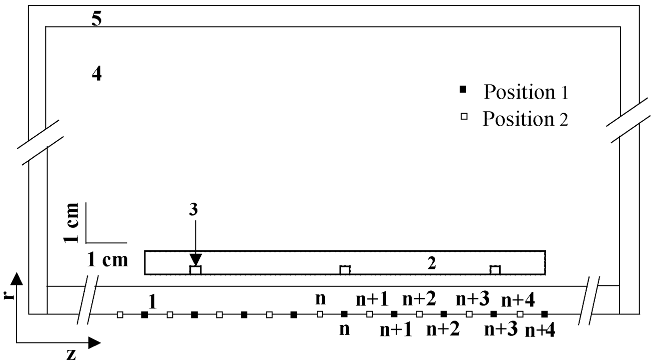

Fig. 1. Rotationally symmetrical volume conductor model. 1: nerve. 2: cuff. 3: metal contact. 4: cerebrospinal fluid. 5: boundary layer. Contact separation: 3 mm. Cuff diameter: 2 mm. Nerve diameter: 1.4 mm. Internodal distance for 12-μs fiber is 0.996 mm. Positions 1 and 2 refer to different positions of nodes to the anodes. n is the node near the cathode, and $\mathrm{n}+3, \mathrm{n}-3$ are the nodes near the anodes. z: axial direction. r: radial direction.

TABLE I
Conductivities of the Media in the Compartments of the Volume Conductor Model

Tissue	Conductivity [S/m]	
	σ_r	σ_z
Nerve	0.083	0.6
Cuff	0.0017	0.0017
Contact	6	6
CSF	1.7	1.7
Boundary	0.01	0.01

The total number of nodes in the fiber model was 35. If, for a 12-$\mu\mathrm{m}$ nerve fiber, the central node of Ranvier n is in the plane of the middle of the central contact, nodes $n + 3$ and $n - 3$ (three nodes from the central node) are in the plane of the middle of the lateral contacts (Fig. 1). A fiber in that position will be referred to as a fiber in position 1. If the fiber is moved by half of the internodal distance, the lateral contacts of the electrode are located between two nodes. A fiber in that position will be referred to as a fiber in position 2. An AP was considered to be blocked if the transmembrane potential Vm did not exceed -30 mV outside of the cuff on the nodes $n + 5$, $n - 5$. Simulations were performed for large nerve fibers at the axis and on the border of the nerve bundle (0.3 mm from the cuff electrode).

A small fiber (5 $\mu\mathrm{m}$) has a smaller internodal distance than larger ones, and when its central node is in position 1, there is no node in the plane of the middle of the lateral contacts. Small fibers have to be excited but not blocked when the large fibers are blocked. In all simulations, the central node was in the plane of the middle of the central contact.

The excitation threshold was examined for a small fiber at the axis because reducing the charge per pulse may affect excitation of that fiber. Blocking threshold was examined for a small fiber on the border, because blocking threshold of the large fibers at

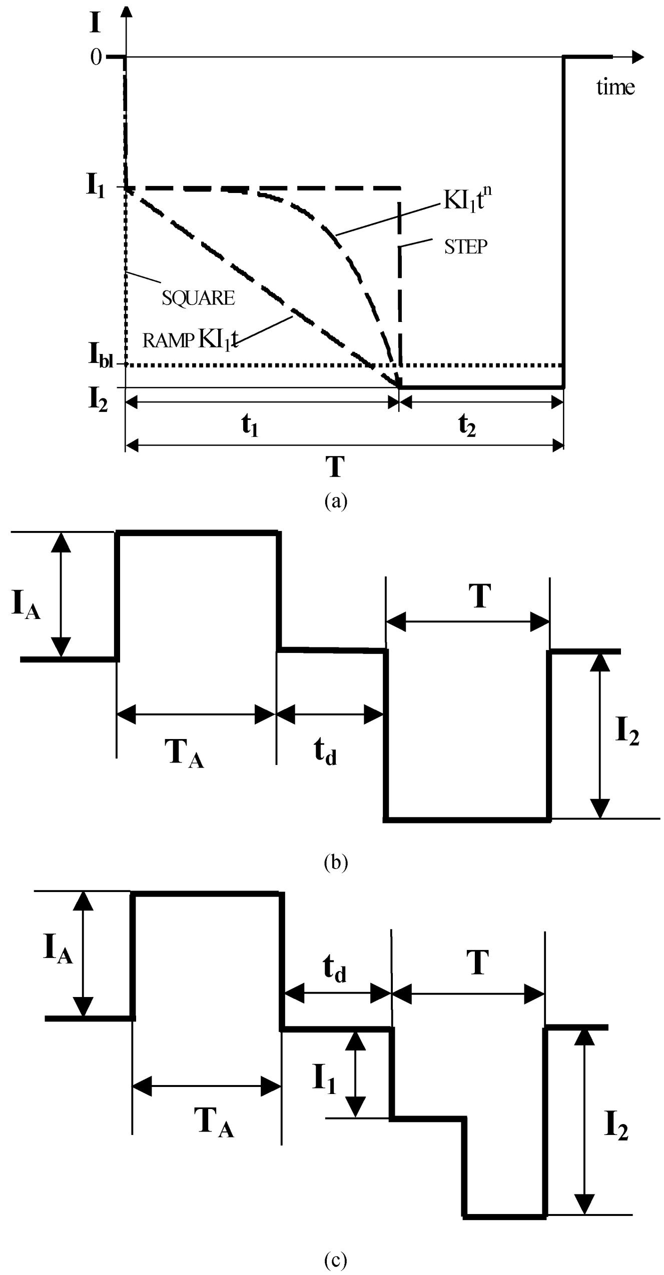

Fig. 2. Different pulse shapes for selective activation of small fibers: square pulse, step pulse, pulses of the form KI_1t^n (with the ramp pulse for $n = 1$). (a) I_1: the prepulse amplitude. I_2: the blocking pulse amplitude. t_1: the duration of the prepulse. t_2: the duration of a blocking pulse. T: the duration of the whole pulse. In this figure, for all pulse shapes: $I_1 = 0.4\ I_2$ and $t_1 = 0.6\ T$. (b) Combination of a HAP and a square pulse. I_A: amplitude of the HAP. T_A: duration of the HAP. t_d: delay. I_2: the blocking pulse amplitude. T: duration of the cathodal pulse. (c) A HAP followed by a step pulse—notation as in (a) and (b).

the axis might exceed blocking threshold of the small fibers on the border.

The measure of charge reduction was defined as the difference between the charge of a square pulse and of several alternative pulse shapes [Fig. 2]. These pulse shapes are described below. When a cathodal pulse was applied, the central contact was the cathode, and the lateral contacts were anodes. When an anodal pulse was applied, the central contact was the anode and the lateral contacts were cathodes.

C. Pulse Shapes

1) Step Cathodal Pulse: A square pulse [Fig. 2(a)] was defined by its duration T and the current amplitude $I_{\rm bl}$ being the minimum current to excite and subsequently block an AP. A step pulse [Fig. 2(a)] consisted of a cathodal prepulse (the first step of duration t_1 and amplitude I_1) immediately followed by a blocking pulse (the second step of duration t_2 and amplitude I_2). The duration of the whole pulse was $T = t_1 + t_2$.

In order to determine the optimal parameters of the step pulse with respect to minimum charge, the following procedure was adopted: I_2 and T were fixed. The amplitude of the prepulse I_1 varied from 0.1 I_2 to 0.9 I_2 in steps of 0.1 I_2. For each constant I_1, the duration of the prepulse t_1 was increased, starting from 10 μs, until the blocking disappeared. Simulations showed that it was not possible to obtain charge reduction if $I_2 = I_{\rm bl}$, but only if $I_2 > I_{\rm bl}$. In all simulations, I_2 was set at 10 μA above $I_{\rm bl}$ for a square pulse of the same duration. Simulation results showed that this was a good compromise between two opposite requirements—to keep the blocking current as low as possible and to reduce the charge per pulse.

2) Cathodal Pulse Shapes of the Form $I_0 = I_1 + KI_1t^n$: Apart from the step pulse, another pulse shape consisted of two parts, with the second part constant $I = I_2$ and with the first part of the form $I_0 = I_1 + KI_1t^n$ were also examined [Fig. 2(a)]. I_1 is the amplitude of the current at the beginning of the first part of the pulse, Io is the current of the first part, $t \in [0 - t_1]$, t_1 is duration of the first part of the pulse, n =1–15 and is constant for a given pulse, $K = (I_2 - I_1)/(I_1 t_1^n)$. The pulse consisted of a cathodal prepulse (duration t_1 and amplitude I_0) immediately followed by a blocking pulse (duration t_2 and amplitude I_2). The duration of the whole pulse was $T = t_1 + t_2$. I_2 and T were fixed. The amplitude of the current at the beginning of the pulse I_1, varied from 0.1 I_2 to 0.9 I_2 in steps of 0.1 I_2. For each I_1 the duration of the prepulse was increased starting from 10 μs, until the blocking disappeared. This was repeated for different values of n.

3) Anodal Pulse Preceding Cathodal Square Pulse: A biphasic pulse consisting of a hyperpolarizing anodal pulse (HAP), preceding a cathodal pulse is shown in Fig. 2(b). The anodal pulse was defined by a duration T_A and amplitude I_A. The delay between the anodal and the cathodal pulse was t_d. The HAP pulse durations T_A were 200, 300, and 400 μs. For each T_A, the excitation threshold $I_{A\rm ex}$ was found. I_A was varied from 1 to 10 μA under $I_{A\rm ex}$. The delay t_d was varied from 10 to 350 μs. For different combinations of T_A, I_A, and t_d, the blocking threshold of a square pulse of duration T was determined and compared with the blocking threshold of the square pulse alone.

4) Anodal Pulse Preceding Cathodal Step Pulse: A biphasic pulse consisting of an anodal pulse preceding a step cathodal pulse is shown in Fig. 2(c). The parameters of the HAP were determined as in *3)*. For different values of I_A, T_A and t_d, the current I_1 of the step pulse was varied from 0.1 I_2 to 0.9 I_2 in steps of 0.1 I_2. Starting from 10 μs, the duration of the prepulse t_1 was increased (and t_2 decreased) until the blocking disappeared. A biphasic pulse consisting of an anodal pulse preceding

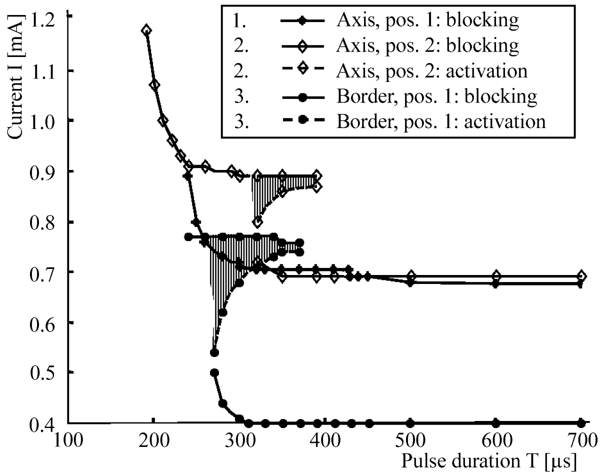

Fig. 3. Blocking and activation thresholds of 12-μm fibers as functions of pulse duration T. Three different situations are shown: 1) fiber on the axis nodes of Ranvier in position 1; 2) fiber on the axis, nodes of Ranvier in position 2; and 3) fiber at the border, nodes of Ranvier in position 1. For situations 2) and 3), three lines are shown—two solid lines and a dashed line between the solid lines. The lower solid line under the dashed line is the "lower" blocking threshold and corresponds to blocking on node $n+4$ for a fiber at the axis in position 2, and on node $n+3$ for a fiber at the border in position 1. The dashed line is an activation threshold. The upper solid line above the shaded region is a "higher" blocking threshold and corresponds to blocking on the node $n+3$ for a fiber at the axis in position 2, and to the node $n+2$ for a fiber at the border in position 1. No blocking occurs in the shaded regions.

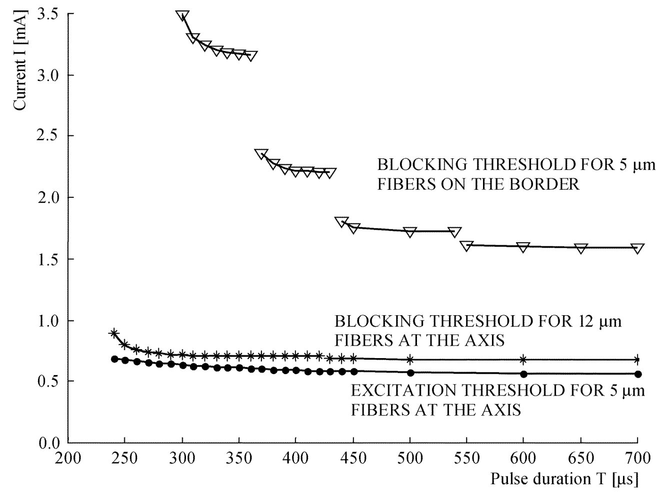

Fig. 4. Blocking threshold of a 12-μm fiber at the axis ($*$) and excitation threshold of a 5-μm fiber at the axis ($\bullet$) as functions of pulse duration. Blocking threshold of a 5-μm fiber on the border (∇) as a function of pulse duration. Blocking threshold of the 12-μm fiber at the axis is higher than the excitation threshold of the 5-μm fiber at the axis and lower than the blocking threshold of the 5-μm fiber on the border.

a step cathodal pulse is shown in Fig. 2(c). The parameters of the HAP were determined as in 3). For different values of I_A, T_A, and t_d, the current I_1 of the step pulse was varied from 0.1 I_2 to 0.9 I_2 in steps of 0.1 I_2. Starting from 10 μs, the duration of the prepulse t_1 was increased (and t_2 decreased) until the blocking disappeared.

III. Results

A. Square Pulse

1) 12-μm Fiber in the Middle of the Nerve Bundle: The relation between the blocking threshold and the pulse duration of a square pulse is shown in Fig. 3. With the fiber in position 1, the blocking threshold decreases with increasing pulse duration for pulse durations under 300 μs. For pulse durations above 300 μs, no further changes of I_{bl} occur until 430 μs, where a plateau occurs at the lower blocking current.

With the fiber in position 2, the minimum pulse duration for which the lowest $I_{\rm bl}$ is achieved is 110 μs less than the minimum pulse duration for the fiber in position 1. The lowest $I_{\rm bl}$ is higher than in the previous case because the anode is farther from the node on which the AP is blocked, and the node is therefore not in the region of the highest hyperpolarization.

For pulse durations between 320 and 390 μs, there are current windows in which blocking occurs. For these pulse durations there is a "low" blocking threshold and a "high" blocking threshold. An AP is blocked in a current window above the "low" blocking threshold at node farther from the cathode $(n+4)$ and in a current window above the "high" blocking threshold at the node closer to the cathode $(n+3)$. Between these two current windows, no blocking is present.

2) 12-μm Fiber at the Border of a Nerve Bundle: The relation between the blocking threshold and the pulse duration of a square pulse is shown in Fig. 3. Like in the previous case for the nerve fibers at the axis, there is a "low" blocking threshold and a "high" blocking threshold. As a consequence, for pulse durations between 240 and 300 μs, a fiber at position 1 at the border of the nerve bundle cannot be blocked with $I_{\rm bl}$ for nerves at the axis (Fig. 3). To block fibers at both locations, a current above the "high" blocking threshold for the fiber at the border must be applied.

3) Excitation and Blocking of Small Fibers: The excitation and blocking thresholds of 5-μm fibers are the highest for the fibers at the axis and the lowest for the fibers at the border of the nerve bundle. During selective blocking of large fibers, small fibers need to be activated. Therefore, it is important to check whether the small fibers at the border are not blocked when $I_{\rm bl}$ for large nerves at the axis is applied. The blocking thresholds of both small and large nerve fibers decrease with increasing pulse duration (Fig. 4). Every time blocking starts at a new node, farther from the cathode, there is a discontinuity in the curve and a drop in the blocking threshold. The ration between the blocking threshold of large fibers at the axis and small fibers on the border is between 2.3 and 4.5. The highest blocking current for small fibers on the border is lower than the lowest blocking current for large fibers at the axis. Therefore, there is no risk that 5-μm fibers on the border will be blocked when 12-μm fibers on the axis are blocked.

B. Charge per Pulse With the Step Pulse

The charge of the step pulse decreases if the duration of the prepulse t_1 increases. To obtain minimum charge per pulse of the step pulse it is necessary that the square pulse that has the same T as the step pulse has parameters close to the one with the minimum charge per pulse. Parameters of the square pulse are determined in the following way: minimum blocking threshold is determined and for that $I_{\rm bl}$ minimum T is found.

1) The Relation Between the Duration and the Amplitude of the Cathodal Prepulse: The duration t_1 and the amplitude I_1

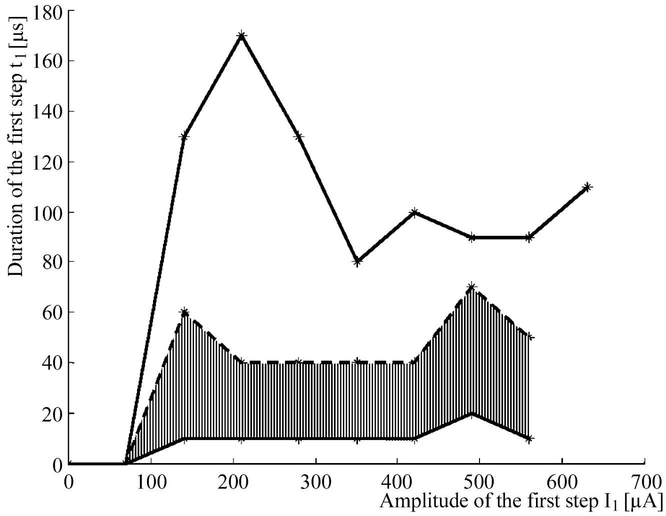

Fig. 5. Duration of the prepulse t_1 of a step pulse as a function of the amplitude of the prepulse I_1. Fiber is on the axis, nodes are in position 1, fiber diameter is 12 $\mu\mathrm{m}$. Duration of the whole pulse is $T = 450$ μs and the amplitude of the blocking pulse is $I_2 = 700$ μA. Blocking occurs for t_1 under and above the shaded region. For $I_1 \leq 0.3$ I_{bl}, the prepulse is subthreshold and for $I_1 \geq 0.4$ I_{bl} the prepulse is suprathreshold. Maximum t_1 is achieved for $I_1 = 0.3$ I_{bl} close to the excitation threshold. For suprathreshold current I_1, maximum t_1 is achieved for $I_1 = 0.9$ I_{bl} close to the blocking threshold.

of the prepulse determine the level of hyperpolarization of the fiber membrane near the anode at the beginning of the blocking pulse.

Fig. 5 shows relation between t_1 and I_1. The longest duration of t_1 is achieved for I_1 that is just under the excitation threshold for the given t_1 (Fig. 5, $I_1 = 0.3$ I_2). For that I_1, the charge per pulse is reduced by 30% compared with the square pulse. An AP cannot be blocked for t_1 in the shaded region (Fig. 5). The duration of the first step t_1 also increases near the blocking threshold, for $I_1 = 0.9$ I_2, because the AP is delayed in the hyperpolarized zone.

2) Blocking of 12 μm *Nerve Fibers at the Axis and at the Border of the Nerve Bundle:* To block the large nerve fibers throughout the nerve bundle, the current should exceed the current needed to block the fiber with the highest blocking threshold. For pulse duration $T > 380$ μm, these are the nerve fibers on the axis. Therefore, minimum T and I_{bl} should be the same as for fibers on the axis.

3) Excitation of 5-μm *Nerve Fibers at the Axis and Blocking of 12-*μm *Nerve Fibers at the Axis:* 5-μm nerve fibers at the axis have to be excited while 12-μm nerve fibers at the axis are blocked. When a step pulse is applied, excitation of a 5-μm nerve fiber with I_{ex} may occur during the first or the second step. It has to be checked if excitation threshold I_{ex} for some pulse durations $t < T$ is higher than I_{bl} for pulse duration T. The ratio between the blocking threshold for 12-μm fibers and the excitation threshold of 5-μm fibers is between 1.1 and 1.3. Therefore, small fibers will always be excited when large fibers are blocked with a step pulse.

C. Charge per Pulse With the Pulse Shapes $I_o = I_1 + KI_1t^n$

For the 12-μm nerve fiber at the axis, at position 1, propagation of an AP can be blocked with the pulse shape $I_0 = I_1 + KI_1t^n$, $n = $ 1–15 [Fig. 2(a)]. In all cases, $T = 450$ μs

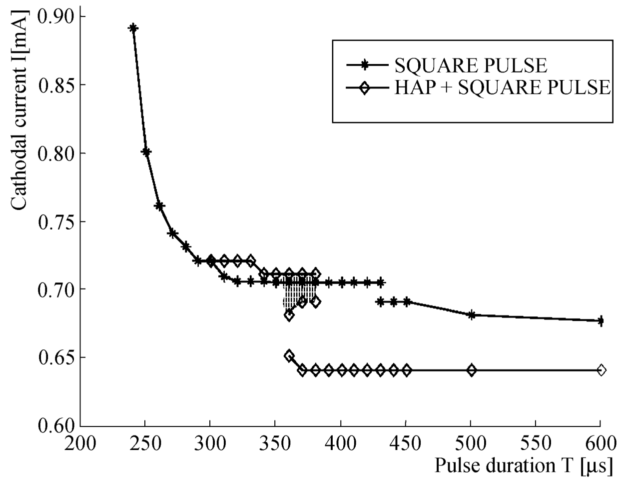

Fig. 6. Blocking and activation thresholds as a function of the pulse duration of a square pulse ($*$) and of combination of a HAP and a square pulse ($\diamond$). Parameters of the HAP—Duration of the HAP T_A: 300 μs. Amplitude I_A: 524 μA. Delay between cathodal and anodal pulses t_d: 100 μs. For the pulse with a HAP, there is a "low" blocking threshold (lower solid line) and "high" blocking threshold (upper solid line). It is not possible to obtain blocking in the shaded region.

and $I_2 = 700$ μA. The charge per pulse decreased when n was increased, but for $n = 15$, this charge was 2.7% larger than the charge of the step pulse with the same T and I_2. The charge per pulse decreased by 15.5% when n increased from 1 to 15.

D. Charge per Pulse With an Anodal Pulse Preceding a Cathodal Pulse

When an anodal pulse is applied before a cathodal pulse, the membrane is hyperpolarized near the central contact and depolarized near the lateral contacts. To prevent excitation with the anodal pulse, depolarization should be under the excitation threshold. Depolarization of the membrane near the lateral contacts prior to the cathodal pulse influences the level of hyperpolarization needed to block an AP during the cathodal pulse.

The relation between the blocking threshold and the pulse duration of cathodal square pulses, with and without a HAP, is shown in Fig. 6. A 12-μm fiber was at the axis, the nodes were in position 1. The HAP amplitude was 10-μA below the anodal excitation threshold ($I_{A\mathrm{ex}} = 534$ μA) and the delay between the pulses was 100 μs. The duration of the HAP was 300 μs. When the HAP precedes a cathodal pulse, there was a "lower" blocking threshold for blocking an AP on node farther from the cathode and a "higher" blocking threshold for blocking an AP on the node closer to the cathode. Blocking of an AP with the "lower" threshold started 100 μs earlier when a HAP precedes a cathodal pulse then with the cathodal pulse alone, because the HAP reduces activation delay. This blocking threshold is also lower than the blocking threshold of the square pulse alone.

1) Relation Between Blocking Threshold of a 12-μm *Fiber at the Axis and the HAP Amplitude:* The blocking threshold decreases if the anodal current increases. If the anodal current is high enough, the current at the lateral electrodes (which in this case are cathodes) causes excitation. Therefore, the amplitude of the HAP has to be below the anodal excitation threshold $I_{A\mathrm{ex}}$. Fig. 7, graphs 2 and 3, shows the blocking threshold for two anodal currents as a function of a delay t_d. The first anodal current

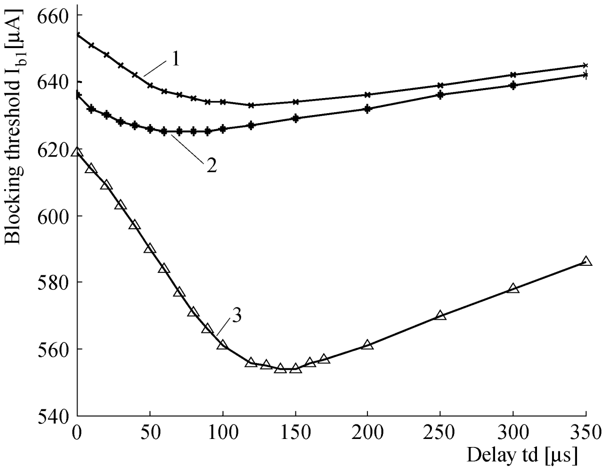

Fig. 7. Blocking threshold (I_{bl}) as a function of delay (t_d) between a HAP and a cathodal pulse. The duration of the cathodal pulse is $T = 450\ \mu s$. The 12-μm fiber was at the axis, at position 1. Curves 1 and 2 are for a HAP amplitude I_A which is 10 μA under the anodal excitation threshold $I_{A\mathrm{ex}}$ for 12-μm fiber for two different pulse durations T_A (Curve 1: $T_A = 200\ \mu s$, $I_A = 545\ \mu A$, $I_{A\mathrm{ex}} = 555\ \mu A$. Curve 2: $T_A = 300\ \mu s$, $I_A = 524\ \mu A$, $I_{A\mathrm{ex}} = 534\ \mu A$). Curves 2 and 3 are for the same pulse duration $T_A = 300\ \mu s$, and two different HAP amplitudes which are 10 μA and 1 μA under $I_{A\mathrm{ex}}$ (Curve 2: $I_A = 524\ \mu A$. Curve 3: $I_A = 533\ \mu A$; $I_{A\mathrm{ex}} = 534\ \mu A$).

is 10 μA under $I_{A\mathrm{ex}}$ (graph 2) and the second anodal current is 1 μA under $I_{A\mathrm{ex}}$ (graph 3). For lower I_A, blocking current I_{bl} is reduced up to 9.5% compared to the I_{bl} of the cathodal pulse alone and for higher I_A, blocking current I_{bl} is reduced up to 21%. Charge per phase for the cathodal pulse is reduced by the same percentage as I_{bl}.

2) Relation Between Blocking Threshold of a 12-μm Fiber at the Axis and a HAP Duration: The blocking threshold decreases when anodal pulse duration increases. Fig. 7 shows the blocking threshold for two HAP durations ($T_A = 200\ \mu s$, graph 1 and $T_A = 300\ \mu s$, graph 2) as a function of a delay t_d. For shorter T_A, I_{bl} is reduced up to 8% compared to the I_{bl} of the cathodal pulse alone and for longer T_A, I_{bl} is reduced up to 9.5%. The difference in I_{bl} for two different T_A is largest when $t_d = 0$ and decreases as t_d increases. The decrease of I_{bl} affected by increase of T_A is limited with the longest T_A in charge-balanced pulses.

3) Relation Between Blocking Threshold of a 12 μm Fiber at the Axis and Time Delay: A decrease of the blocking threshold is possible even if the cathodal pulse follows the HAP without delay. I_{bl} decreases when t_d increases until I_{bl} reaches a minimum. With a further increase of t_d, I_{bl} will increase, toward the level without a HAP. Delay on which I_{bl} has the minimum depends on a duration and the amplitude of the HAP.

4) 12-μm Fibers at the Axis and on the Border of a Nerve Bundle: Fibers on the border have a lower anodal excitation threshold $I_{A\mathrm{ex}}$ than fibers at the axis. The difference between $I_{A\mathrm{ex}}$ for these two fiber positions increases with increasing nerve bundle diameter. For a nerve bundle diameter of 1.4 mm, and a HAP duration of 300 μs, the excitation threshold for a fiber on the border is 0.69 $I_{A\mathrm{ex}}$ of fibers at the axis.

When a HAP is applied on a whole nerve bundle, two situations may occur.

1) The anodal current is close to the excitation threshold of the large nerve fibers at the border, which is lower than the excitation threshold of the large nerve fibers at the axis. HAP has only an influence on reducing I_{bl} of fibers at the border.
2) The anodal current is close to the excitation threshold of the large nerve fibers at the axis. The excitation threshold $I_{A\mathrm{ex}}$ of large nerve fibers on the border is lower than the excitation threshold of large nerve fibers at the axis, so fibers at the border will be excited. In this way, only spatially selective blocking of large nerve fibers at the axis will be achieved. Blocking threshold and consequentially charge per phase can be reduced up to 21% for large fibers at the axis ($T_A = 300\ \mu s$, I_A was 1 μA under $I_{A\mathrm{ex}}$). If reduction of a charge per phase is achieved with a HAP, it can be only spatially selective.

E. Hyperpolarizing Anodal Pulse Preceding a Step Pulse

The HAP changes the transmembrane potential before applying a step cathodal pulse. The blocking threshold is lower than for the step pulse alone, due to the HAP. However, the charge per pulse is higher than with a step pulse alone. The reason for this is that for a combination of HAP and a step pulse, the longest duration of the first step t_1 is achieved for I_1 above excitation threshold while for a step pulse alone, the longest t_1 is achieved for I_1 below excitation threshold. Combination of a HAP with a square or a step cathodal pulse is not decreasing a charge per pulse compared to the step pulse alone.

IV. Discussion

This paper presents how, for the purpose of selective activation of small nerve fibers by anodal blocking, different cathodal pulse shapes and combinations of an anodal and a cathodal pulse can reduce the charge per pulse compared with the square pulse. A two-step pulse decreases the charge per pulse by decreasing the current amplitude during the first step. The HAP decreases the blocking threshold of the cathodal square pulse and in that way also decreases the charge per pulse. When a step pulse is combined with a HAP, the charge per pulse of a step pulse is not additionally reduced, compared to the step pulse alone.

In this study, the fiber model was based on sensory human nerve fibers. It was shown [27] that human sensory nerve fibers have the time constant three to five times longer than the motor fibers. That means that a propagation velocity of an AP in a motor fiber is significantly higher than in a sensory fiber, and that consequently, duration of the first step in a step pulse will be shorter and charge reduction will be smaller. Similar simulation study based on a rabbit fiber model, adopted for dorsal column fibers [28], using the same volume conductor model like in this study, has shown that it was possible to obtain charge reduction up to 13% when a step instead of a square pulse is applied [29]. As dorsal colon fibers consists mostly of sensory fibers, a significant difference in results could be explained by different equations and constants describing the models. Preliminary experimental results [30] obtained on ventral sacral roots in pigs (stimulation with a tripolar cuff electrode, inner cuff diameter 1–1.4 mm, contact separation 3 mm) have shown that it was possible to reduce the charge per pulse up to 13% when a step instead of a square pulse is applied. In these experiments, selective activation of rectum, innervated by parasympathetic fibers, without co-activation of the anal sphincter, innervated by somatic fibers, was achieved. The highest charge reduction was achieved for $I_1 = 25\% \, I_{\rm bl}$ and the longest duration of the first step t_1 was achieved for $I_1 = 75\% \, I_{\rm bl}$. Simulation and experimental results are not directly comparable, not only because sensory fibers are modeled and motor fibers are stimulated in experiments, but also because in simulation study results are obtained for a nerve fiber on one specific position in a nerve bundle and in the experiments large nerve fibers in a whole nerve have to be blocked. Therefore, parameters of a two-step pulse might not be optimal for all large nerve fibers and worse results should be expected in experiments that in simulations.

When a square pulse is applied, there are two main phenomena that determine the relation between the blocking threshold and the pulse duration. The first is the level of depolarization of the membrane near the cathode, which causes excitation of the membrane and increases the propagation velocity of an AP when the cathodal current is increased. The second is the level of membrane hyperpolarization near the anodes, which has the effect of decreasing the AP amplitude and slowing the AP down in the hyperpolarized region [31]. The combination of these two phenomena and the distance between the cathode and the anodes influence the time an AP needs to propagate from the cathode to the anode and determines the node on which the AP is blocked. A combination of these two phenomena causes that lower blocking current is needed to block an AP on a node that is in the zone of the lower hyperpolarization ("low" blocking threshold) than to block an AP on a node that is in the zone of the higher hyperpolarization ("high" blocking threshold). When an AP propagates too fast, it may reach the node close to the anode before the membrane is hyperpolarized enough to block the AP. By the time it reaches the next node that is farther away from the cathode the amplitude of the AP becomes lower and the membrane becomes sufficiently hyperpolarized to block the AP. Therefore, an AP is blocked with "the low" blocking threshold on the node that is farther away from the cathode than the node with "the high" blocking threshold. For some values of the cathodal and anodal currents, the amplitude of an AP can be still too high when it reaches the node farther away from the cathode and it can escape blocking. In that case, there is a region under "the high" blocking threshold where an AP cannot be blocked.

The charge per pulse with the step pulse decreases when the duration of the prepulse increases and/or the amplitude decreases. The transmembrane potential at the beginning of the blocking pulse together with the duration of the blocking pulse determine whether or not an AP will be blocked. If the prepulse is suprathreshold and last sufficiently enough, the membrane close to the anode might be depolarized at the beginning of the blocking pulse. If the prepulse is subthreshold, the membrane close to the anode will be hyperpolarized at the beginning of the blocking pulse and shorter blocking pulse (i.e., longer t_1 for a constant T) will be needed than when the prepulse is suprathreshold. However, for very short prepulses, depending on I_1 that can be either sub- or suprathreshold, hyperpolarization on the node close to the anode will be very high at the beginning of the blocking pulse. That would decrease the propagation velocity of an AP so much that longer blocking pulse would be needed than the square pulse of duration T (Fig. 5, shaded region). The influences of the duration and amplitude of the prepulse on the blocking threshold were not investigated. In the previous study [32] the blocking current was determined for predefined values of the amplitude and the duration of a prepulse. It was shown that the subthreshold prepulses increase the blocking current less than the suprathreshold pulses.

Cathodal pulses of the form $I_0 = I_1 + KI_1t^n$ have a gradual increase from the prepulse to the blocking pulse. Due to the gradual change of the activation parameter m and the inactivation parameter h of the membrane, a longer prepulse duration is obtained. However, due to the shape of these pulses, the charge per pulse is higher than with the step pulse of the same duration.

When an anodal pulse (HAP) is applied before a cathodal pulse, it hyperpolarizes the membrane close to the central contact of the electrode, but after the end of the anodal pulse, the membrane is transiently depolarized. During this "overshoot," the activation parameter m increases, and the inactivation parameter h decreases. At the beginning of the cathodal pulse, m is higher and h is lower than the resting values. A HAP reduces the activation delay. A smaller activation delay means that less time is needed for the AP to reach its maximum amplitude. If, in the presence of a HAP, the duration of the blocking pulse is long enough ($> 360 \, \mu$s), the AP will already reach its maximum amplitude before the end of the pulse. Therefore, the transmembrane potential will be low enough to block the AP after the end of the blocking pulse. This transmembrane potential will be lower than without a HAP, so lower $I_{\rm bl}$ should be applied. For shorter blocking pulses ($< 360 \, \mu$s) in the presence of a HAP, the AP will not reach its maximum amplitude at the end of the blocking pulse and the transmembrane potential will still increase. Therefore, a higher $I_{\rm bl}$ should be applied to block the AP than without a HAP.

The simulation results show that for the fiber at the axis, the blocking threshold and the charge per pulse can be reduced by 20% if the HAP is applied. The minimum blocking threshold is obtained if the HAP amplitude is close to the anodal excitation threshold. Since a fiber at the border of the nerve bundle has lower excitation thresholds than a fiber at the axis, it is not possible to obtain charge reduction for nerves at both positions. These results would be hard to check in experiments, because the HAP amplitude should be several μA under the excitation threshold.

In the simulation and experimental study of Grill and Mortimer [4], as well as in the simulation studies of Deurloo *et al.* [5], [6], spatially and diameter selective stimulation was achieved by applying depolarizing prepulses. Fiber diameter selective activation was obtained in the following way. The current of the stimulating pulse was set high enough to excite both large and small nerve fibers. By applying a prepulse with the amplitude just under the excitation threshold of large nerve fibers, excitation threshold of large fibers was increased so much that only small nerve fibers were activated during the stimulating pulse. Charge per pulse was lower than when anodal block was applied because excitation threshold of small nerve fibers is lower than the blocking threshold of large nerve fibers. If applied for selective small fiber activation, this method would have several limitations: first, fiber diameter selectivity is in general not possible to obtain in the whole nerve, but only spatial selectively. Second, the amplitude of the prepulse has to be very close to the excitation threshold of large nerve fibers, typically 0.95% I_{ex}. When anodal block is applied, a current window in which selective activation of small nerve fibers can be obtained is much larger than in the case of depolarizing prepulse. When sufficiently long pulses with sufficiently high currents are applied, large nerve fibers in a whole nerve bundle can be blocked.

Charge balanced pulses, which have to be applied in chronic stimulation, were not used in this study. This study mostly shows results related to fiber diameter selective activation. However, when using square pulses with the pulse duration between 250 μs and 310 μs it is possible to selectively activate fibers farther away from the electrode. A combination of a HAP and a cathodal pulse could enable both charge reduction and selective blocking of fibers farther from the electrode and activation of the fiber closer to the electrode.

V. Conclusion

This paper shows that it is possible to reduce the charge per pulse up to 30% when anodal blocking is applied. The reduction is achieved either by applying a pulse shape different from a conventional square cathodal pulse or by combining an anodal pulse preceding a cathodal square pulse. It was also shown that, by applying these pulse shapes, it is possible to obtain fiber diameter selective stimulation and/or spatially selective stimulation. Reduction of a charge for fibers in a whole nerve bundle is possible only with two-step pulses, but not for a combination of cathodal and HAP pulses.

The results indicate that the technique of anodal blocking would be safer for long-term applications if a standard square pulse is replaced with a step pulse.

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