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Effect of three anaesthetic techniques on isometric skeletal muscle strength

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Background. Our aim was to quantify human involuntary isometric skeletal muscle strength during anaesthesia with propofol, sevoflurane, or spinal anaesthesia using bupivacaine.

Methods. Thirty-three healthy patients undergoing anaesthesia for elective lower limb surgery were investigated. Twenty-two patients received a general anaesthetic with either propofol (n=12) or sevoflurane (n=10); for the remaining 11 patients spinal anaesthesia with bupivacaine was used. We used a non-invasive muscle force assessment system before and during anaesthesia to determine the contractile properties of the ankle dorsiflexor muscles after peroneal nerve stimulation (single, double, triple, and quadruple stimulation). We measured peak torques; contraction times; peak rates of torque development and decay; times to peak torque development and decay; half-relaxation times; torque latencies.

Results. Males elicited greater peak torques than females, medians 6.3 *vs* 4.4 Nm, respectively (P=0.0002, Mann-Whitney rank-sum test). During sevoflurane and propofol anaesthesia, muscle strength did not differ from pre-anaesthetic values. During spinal anaesthesia, torques were diminished for single-pulse stimulation from 3.5 to 2.0 Nm (P=0.002, Wilcoxon signed rank test), and for double-pulse from 7.6 to 5.6 Nm (P=0.02). Peak rates of torque development decreased for single-pulse stimulation from 113 to 53 Nm s^{-1} and for double pulse from 195 to 105 Nm s^{-1}. Torque latencies were increased during spinal anaesthesia.

Conclusions. At clinically relevant concentrations, propofol and sevoflurane did not influence involuntary isometric skeletal muscle strength in adults, whereas spinal anaesthesia reduced strength by about 20%. Muscle strength assessment using a device such as described here provided reliable results and should be considered for use in other scientific investigations to identify potential effects of anaesthetic agents.

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Anaesthetics influence voltage-gated ion channels in the nervous system as well as in skeletal and cardiac muscle. By enhancing sodium current decay in the muscle cell they change signal transduction and may have neuromuscular blocking agent properties; propofol, local anaesthetics, and inhaled anaesthetics have this ability.[1 2] Moreover, anaesthetic agents may alter contractile function by inhibition of cholinergic neurotransmission.[3] Such altered activities could influence recovery from anaesthesia.

To determine muscle strength, isometric assessment tools have to be distinguished from dynamic tools. The measured values are strongly influenced by an investigator's experience and the patient's voluntary efforts, so results are not always objective and reproducible.[4] To improve objectivity, fixed devices have been developed. By using electrical nerve stimulation and electronic data acquisition, it is now possible to get quantitative, non-invasive muscle force assessment results, independent of a subject's voluntary efforts.[5–8]

We used a muscle force assessment system, which was originally developed for neurological trials, to investigate the influence of propofol, sevoflurane, or spinal anaesthesia

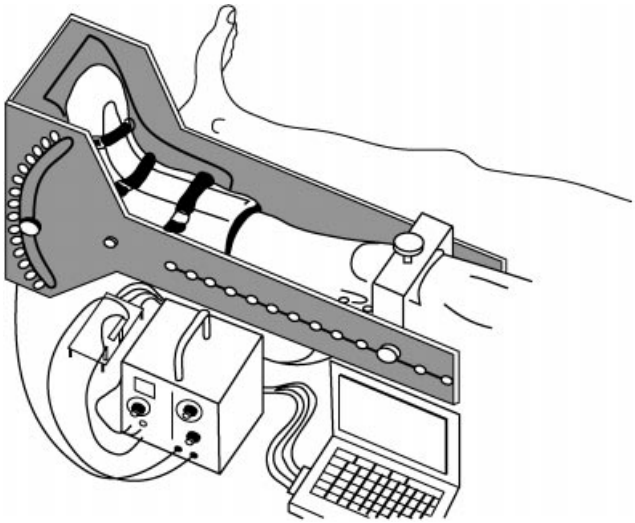

Fig 1 Muscle-force assessment system to determine involuntary isometric torque in humans.[5–8] It is composed of four main components: (i) a stabilizing device consisting of two metal bars, straps and a boot. The boot is fixed on a foot plate that can be rotated and fixed at any position between –40 and 40°. (ii) A strain gauge system with a Wheatstone bridge circuit that detects the evoked torque produced by the stimulated ankle dorsiflexor muscles. (iii) A stimulator/amplifier unit that can supply variable stimulus pulse amplitudes and pulse durations and can amplify the voltage changes, evoked by the torque of the stimulated muscle. (iv) A computer with data acquisition software for recording, analysing and displaying all signals simultaneously.

with bupivacaine on human involuntary isometric skeletal muscle strength following electrical stimulation.

Methods

Before and during anaesthesia, the involuntary isometric skeletal muscle strength of the ankle dorsiflexor muscles after peroneal nerve stimulation in humans was investigated.

Patients

All 33 patients gave their written informed consent, and the Human Ethics Committee of the University of Basel, Switzerland approved the experimental protocol. All patients were ASA I and were to undergo orthopaedic or venous surgery to the lower limb. The patients chose whether to receive either spinal anaesthesia or general anaesthesia. Those patients who chose to receive general anaesthesia were allocated randomly to receive either propofol or sevoflurane for induction and maintenance of anaesthesia.

Muscle force assessment system

For nerve stimulation, a Grass S11 stimulator (Grass Medical Instruments, Quincy, MA) was used. A special device that securely held the subject's leg was used for quantification of muscle torque (Fig. 1).[5–8] The torque was measured by a strain gauge (SG-2/350-LY41 Strain Gauges, OMEGA Engineering, Inc., Stamford, CT) attached to an aluminium bar that restrained movement of the footplate. The output of the strain gauge was amplified (amplifier: Grass Medical Instruments); voltage changes proportional to the muscle torque were digitized through a data acquisition card (DAQCard™-1200, National Instruments, Austin, TX), converted into force and then stored on a personal computer. All data acquisition and analysis programs were written with LabVIEW 2 (National Instruments, Austin, TX).

Experimental protocol

All patients received midazolam 0.1 mg kg^{-1} orally 1 h before the experiments. A sample of blood was analysed for Na^+, K^+, Ca^{2+}, phosphate, urea, creatine kinase, glucose, and haemoglobin concentrations, and a coagulation screen was done. The circumference and skin fold thickness of the lower leg were measured.

After arrival in the operating theatre, an i.v. catheter was sited and an infusion of Ringer lactate solution (500 ml) was started. Standard monitoring was attached and a surface temperature probe was used to determine the temperature over the tibialis anterior muscle (Genius™, infrared thermometer, Sherwood-Davis & Geck, Gosport, UK): for patients receiving general anaesthesia, the Bispectral Index™ was monitored also.

The muscle force assessment system was attached to each patient as follows: the patient was laid on the surgical table with one leg strapped in a stabilizing device that was fitted with a force measuring boot into which the foot was placed. A convective warm-air system was used to minimize variability in dorsiflexor muscle temperature; the skin temperature of the leg was maintained between 31 and 32°C. After cleaning the skin with an alcoholic wipe, a pair of small ball-shaped electrodes was pressed tightly against the skin behind the head of the fibula for transcutaneous common peroneal nerve stimulation. An electromyogram (EMG) of the tibialis anterior muscle was recorded with surface patch electrodes.[10]

The supramaximal voltage (approximately 50–90 V with 0.3 ms duration) was used for stimulation and this was determined by increasing the voltage until no further increases in muscle twitch torque and in the EMG signal of the ankle dorsiflexors were detected. The optimal muscle length for isometric contraction (in this case, the ankle joint position) was determined by moving the torque plate until twitch torques reached a maximum.[9] This position of the torque plate was then fixed and kept unchanged during the experiment. Baseline measurements were then performed. The protocol included single, double, triple, and quadruple-pulse peroneal nerve stimulation.[5–8] These were unidirectional depolarizing pulse stimuli with a pulse duration of 0.3 ms. The pulse interval for the multiple pulse stimula-

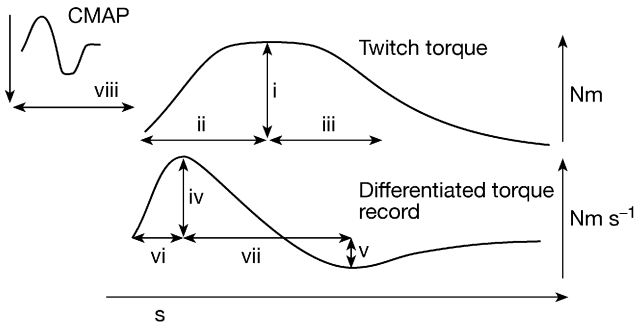

Fig 2 Record of the twitch torque and differentiated torque of the ankle dorsiflexor muscles. Compound muscle action potential is schematic, the stimulus is indicated by the dashed arrow. (i) Peak torque (PT); (ii) contraction time; (iii) half-relaxation time; (iv) peak rate of torque development; (v) peak rate of torque decay; (vi) time to PT development; (vii) time to PT decay; (viii) torque latency; Nm: newtonmeter; s: seconds.

tions was 5 ms. Between each set of stimuli there was a 2 min rest period. After baseline measurements were finished, general or spinal anaesthesia was administered.

One of two general anaesthetic regimens was used: (i) a target controlled infusion (TCI) of propofol with the target concentration set at 5 μg ml^{-1}; (ii) inhalation induction with sevoflurane 6–8 vol%, in oxygen 100%, followed by maintenance with sevoflurane at an end-tidal concentration of 3–3.5 vol%. A laryngeal mask was used in both groups for airway maintenance and ventilation of the lungs was controlled to keep the E'_{CO_2} at 4.5–5 kPa. After a 20 min stabilization period, the measurements were repeated. During this measurement period, the Bispectral Index™ was between 40 and 50. In the propofol group, blood was taken and the plasma obtained was used to determine the concentration of propofol by high performance liquid chromatography with fluorescence detection.

Spinal anaesthesia was performed with hyperbaric bupivacaine 0.5%, 0.2 mg kg^{-1}. When a stable sensory level was reached (upper level between the 6th and 9th thoracic dermatome), the second set of measurements was performed. Completion of both sets of measurements took about 1 h for each subject.

Data analysis

The following indices of isometric skeletal muscle performance were determined: (i) peak torque (Nm): the maximum amount of developed involuntary isometric muscle torque; (ii) contraction time (ms): time from the onset of torque development to peak torque; (iii) half-relaxation time (ms): time for the torque to decay from its peak to 50% of peak torque; (iv) peak rate of torque development (Nm s^{-1}): the maximum rate (first derivative) of torque development; (v) peak rate of torque decay (Nm s^{-1}): the maximum rate of torque decay; (vi) time to peak torque development (ms): the time from the onset of torque development to the peak rate of torque development; (vii) time to peak torque decay (ms): the time from the peak rate of torque development to the peak rate of torque decay; (viii) torque latency (ms): the time from the stimulus to the onset of torque development (Fig. 2).

Statistical analysis

The StatView program (ADEPT®, Hertfordshire, UK) was used. Pre-anaesthetic and anaesthetic muscle force measurements for each group were compared with the Wilcoxon signed rank test. The values between the different anaesthetic groups were analysed with the Kruskal–Wallis test. Measurements in men and women were compared with the Mann–Whitney rank-sum test. P-values <0.05 were considered to be significant.

Results

Thirty-three patients were recruited and their characteristics are shown in Table 1. A total of 376 measurements were performed. The same physician performed the measurements for all patients.

The within-session test–retest reliability for peak torque was 6%. The peak torque development (for all stimulus protocols combined) of male patients from all groups combined was greater than that of female patients, medians 6.3 (range 1.2–24.9) *vs* 4.4 (0.8–12.0) Nm, respectively (P=0.0002, Mann-Whitney rank-sum test). Male patients also had a greater peak torque development during anaesthesia, 8.9 (range 0.5–25.9) *vs* 5.0 (0.5–18.0) Nm (P<0.0001).

During spinal anaesthesia, peak torque values were diminished for single- and double-pulse stimulation but not for the other stimulation modalities (Table 2). The peak rates of torque development decreased for single- and double-pulse stimulation and the torque latency period for single-pulse stimulation only was increased (Table 2).

During spinal anaesthesia with bupivacaine, the peak torque values for single- and double-pulse stimulation were decreased compared with the corresponding values from the groups treated with propofol or sevoflurane (see Table 2). In the propofol and sevoflurane groups, pre-anaesthetic and anaesthetic values were not significantly different (Wilcoxon signed rank test, Table 2).

Discussion

We have demonstrated that clinical concentrations of propofol or sevoflurane did not influence isometric skeletal muscle strength in healthy adults, but spinal anaesthesia did have a small effect.

Propofol blocks voltage-gated channels and thus has a neuromuscular blocking agent effect. This occurs especially in pathological conditions that result in a higher fraction of inactivated channels, such as hypoxia, myotonia, or

Table 1 Patient characteristics and anaesthetic data. Data are mean (SD) or number. **P*=0.02 sevoflurane *vs* bupivacaine

Characteristics	Propofol 1% (*n*=12)	Sevoflurane (*n*=10)	Bupivacaine 0.5% (*n*=11)
Age (yr) (range)	38.3 (17–61)	28.3 (16–60)*	42.4 (28–68)
Gender (male/female)	5/7	6/4	7/4
Weight (kg)	70.8 (14.3)	66.8 (13.3)	77.3 (15.6)
Height (cm)	170 (8)	174 (10)	171 (8)
Lower leg circumference (cm)	36 (2)	34 (3)	35 (6)
Lower leg skin fold (mm)	8 (7)	9 (7)	12 (11)
Plasma propofol concentration ($\mu g\ ml^{-1}$)	3.9 (0.7)	–	–
Dose of bupivacaine (mg)	–	–	15 (3)
End-tidal sevoflurane concentration (vol%)	–	3.6 (0.6)	–

Table 2 Parameters of involuntary isometric strength measurements of the ankle dorsiflexors in humans. Peak torque (PT): the maximum amount of developed involuntary isometric muscle torque; contraction time: time from onset of torque to time of PT; peak rate of torque development: the maximum rate of torque development; peak rate of torque decay: the maximum rate of torque decay; half-relaxation time: time from PT to time when torque decays to half of PT; torque latency: the time from stimulus to the onset of torque development. 1=single pulse; 2=double pulse; 3=triple pulse; 4=quadruple pulse. Data are median (range). **P*=0.002; ***P*=0.02; ****P*=0.01; †*P*=0.005 with bupivacaine anaesthesia *vs* pre-anaesthesia, Wilcoxon signed rank test. ††*P*=0.004; †††*P*=0.02 with bupivacaine anaesthesia *vs* propofol and sevoflurane anaesthesia, Kruskal–Wallis test

Characteristics	Propofol 1% (*n*=12)		Sevoflurane (*n*=10)		Bupivacaine 0.5% (*n*=11)	
	Pre-anaesthesia	With anaesthesia	Pre-anaesthesia	With anaesthesia	Pre-anaesthesia	With anaesthesia
PT 1 (Nm)	4.4 (0.9 to 9.2)	4.7 (0.5 to 8.6)	5.7 (1.5 to 9.4)	5.1 (1.4 to 9.9)	3.5 (0.8 to 9.4)	2.0 (0.5 to 10.1)* ††
PT 2 (Nm)	8.5 (4.4 to 13.0)	10.2 (0.8 to 15.3)	10.4 (2.8 to 14.4)	9.3 (2.9 to 13.6)	7.6 (1.8 to 17.6)	5.6 (1.6 to 19.4)** †††
PT 3 (Nm)	14.3 (6.5 to 17.9)	15.8 (1.1 to 19.0)	9.9 (2.6 to 17.6)	8.7 (4.3 to 16.0)	9.9 (0.8 to 22.4)	8.5 (0.8 to 22.9)
PT 4 (Nm)	17.7 (16.3 to 20.9)	20.0 (17 to 21.5)	9.8 (3.6 to 18.5)	10.1 (5.5 to 17.3)	11.6 (2.6 to 24.9)	10.1 (3.6 to 25.1)
Contraction time 1 (ms)	94 (37 to 134)	97 (68 to 227)	93 (67 to 184)	86 (34 to 191)	84 (41 to 156)	82 (36 to 190)
Peak rate of torque 1 development ($Nm\ s^{-1}$)	113 (15 to 188)	86 (15 to 203)	120 (38 to 158)	116 (30 to 173)	113 (15 to 203)	53 (15 to 225)*** †††
Peak rate of torque 2 development ($Nm\ s^{-1}$)	199 (30 to 465)	188 (23 to 945)	251 (60 to 307)	199 (90 to 322)	195 (38 to 382)	105 (38 to 382)**
Peak rate of torque 1 decay ($Nm\ s^{-1}$)	–49 (–68 to –8)	–41 (–75 to –15)	–45 (–300 to –15)	–45 (–90 to –23)	–30 (–97 to –15)	–23 (–83 to –8)
Half-relaxation time 1 (ms)	115 (70 to 170)	105 (45 to 205)	115 (55 to 145)	105 (60 to 135)	125 (80 to 185)	120 (75 to 185)
Torque latency 1 (ms)	23 (–3 to 27)	25 (–92 to 36)	22 (18 to 26)	23 (20 to 33)	21 (19 to 24)	23 (18 to 31)†

ischaemia.[11 12] Thus, propofol might be the drug of choice for induction of anaesthesia in patients with myotonia. Propofol also exerts a direct negative inotropic effect on failing and non-failing human myocardium, although only at concentrations exceeding the clinical-dose range.[13]

Volatile anaesthetics inhibit skeletal muscle sodium channels. Mountsey and colleagues describe a dose-dependent enhancement of the rate of sodium current decay and a small reduction in sodium current amplitude in rat skeletal muscle for halothane.[1] In animals, the compound muscle action potentials are significantly lower during application of volatile anaesthetics.[14 15] Bouhemad and colleagues describe a moderate negative inotropic effect in rat diaphragm muscle *in vitro* during application of isoflurane (at 2× MAC).[16] In an *in vitro* study using animal tissue, sevoflurane did not enhance the reduction of tension induced by diaphragmatic fatigue but enhanced the prolongation of contraction time and half-relaxation time.[17] Halothane causes a decreased calcium sensitivity and decreased isometric tension in human type I, but not type II skeletal muscle fibres.[18] On the other hand, there is an increased maximal skeletal muscle Ca^{2+}-activated force in the presence of volatile anaesthetics.[19] Moreover, volatile anaesthetics have a direct action on neuromuscular transmission.[3 20] Thus, the effects on striated muscles remain controversial.

We found no influences of sevoflurane or propofol on human isometric skeletal muscle strength *in vivo*. The short-

term effect-site equilibration time of propofol and its high drug transfer rate to the peripheral compartment enable us to assume that propofol concentrations in skeletal muscle and plasma were similar. The plasma concentration of propofol was in the range of the half-maximum blocking concentration of skeletal muscle sodium channels; thus, the effects were too small to be measured in our clinical setting.[11 21]

Since volatile agents reduce isometric force values by about 10% of baseline values *in vitro*,[16] their effects again could have been too small to be measured *in vivo*. Moreover effects of volatile agents are supposed to be more pronounced during muscle fatigue.[17] The distribution of muscle fibre types with their different susceptibility towards volatile anaesthetics can also vary between subjects.[22]

Spinal anaesthesia blocks the roots of the nerve fibres and the superficial layers of the spinal cord.[23] This results in a flaccid paralysis of the muscles and block of the sympathetic outflow. Whereas the main part of this central sympathetic outflow innervates organs such as the heart, lungs, sweat glands, and skin, only a minor component reaches the skeletal muscle and has no measurable influence on muscle tone, as was demonstrated by Smith during spinal anaesthesia.[24] Moreover, during static exercise in humans, central command was found to contribute very little to the activation of sympathetic outflow in skeletal muscle.[25] However, peripheral afferent impulses from muscle mechanoreceptors (muscle spindles), Golgi tendon organs, and chemosensitive endings in muscles influence sympathetic nerve activity and skeletal muscle tension by reflex mechanisms. During static handgrip, an increased sympathetic discharge to muscle was measured, and muscle sympathetic nerve activity returned to control values during relaxation.[26 27] Electrically evoked involuntary biceps flexion also results in increased muscle sympathetic nerve activity.[26] During spinal anaesthesia, these afferent impulses are blocked, which could explain the lower values for evoked torque and peak rate development. Direct actions of local anaesthetics on the pre-synaptic, post-junctional, and muscle membranes are only relevant for i.v. application with a moderate to high drug-plasma level and not for spinal application, thus excluding this effect from contributing to our findings.[28]

The following points must be considered when assessing the relevance of our results. First, for a complete assessment of muscle function it is desirable to study strength variables on the load continuum from isotonic (with low loads) to isometric (with high loads) conditions. In our setting, only isometric measurements were performed. However, negative inotropic effects of anaesthetics typically are found under isometric and not isotonic conditions.[16] Secondly, completely standardized conditions are only possible in *in vitro* studies; for example, inter-subject variability in perfusion, tissue temperature, and muscle cross-sectional area may have influenced the test results. However, clinical trials are required to confirm *in vitro* results under clinical conditions and such variability can be minimized using appropriate study groups.

Our study is the first to use the described muscle-force assessment system during anaesthesia. This new system made it possible to obtain objective and reliable results, independent of a subject's voluntary effort.[5–8] The system is versatile, enabling the examination of different muscle groups.[7] Thus, we recommend such a system to investigate skeletal muscle strength, for example, in patients with potential muscle atrophy, critical illness polyneuropathy, or myopathy.

In conclusion, we evaluated the isometric skeletal muscle strength of the lower leg under different anaesthetic regimens in humans. At clinically relevant concentrations, neither sevoflurane nor propofol changed muscle strength, whereas during spinal anaesthesia there was a small impairment of strength. The skeletal neuromuscular blocking agent properties of anaesthetics do not seem to have a profound effect on isometric skeletal muscle strength in humans *in vivo*.

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