The Effect of Sevoflurane on Somatically induced Sympathetic Reflexes

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The effects of various inspiratory concentrations of sevoflurane anesthetics on the sympathetic reflex responses evoked in the left inferior cardiac nerve branch following an electrical stimulation to the ipsilateral superficial peroneal nerve were investigated in cats. At a 2.0% inspiratory concentration of sevoflurane, two components of the somato-sympathetic reflexes with two different latencies were recorded. The early component was due to an activation of myelinated A afferent fibers (referred to as the A-reflex), while the late component was due to an activation of unmyelinated C afferent fibers (referred to as the C-reflex). The increase in the concentration of sevoflurane from 2.0 to 3.0% resulted in about 50% attenuation of both the A- and C-reflexes. A further increase in the concentration of sevoflurane to 4.0% resulted in further suppression of both reflexes. (Key words: sevoflurane, sympathetic nerve, cat)

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Sevoflurane is a recently developed inhalational anesthetic which provides rapid induction and recovery processes[1]. It has been reported that sevoflurane causes dose-related depression in cardiac output, stroke volume and mean arterial pressure[2], but it does not markedly influence heart rate[2,3]. Based on the properties of sevoflurane described above and on other evaluations of this agent from pharmacologic[1], toxicologic[1,3] and clinical aspects[3,4], sevoflurane is proposed as a new anesthetic agent of reasonably acceptable quality[1–4].

Since it was found that electrical stimulations of both myelinated (A) and unmyelinated (C) afferent fibers of hindlimb nerves elicited two distinct sympathetic reflexes, the A-reflex having a shorter latency and the C-reflex having a longer latency in anesthetized cats[5,6], it has been proposed that these somatically induced reflexes can be employed as appropriate indicators for analyzing the efficacy of various analgesics[7–9].

The present study was designed to examine how various inspiratory concentrations of sevoflurane influence the two sympathetic reflexes.

The experiments were performed on 6 cats, anesthetized with inspiratory concentrations of sevoflurane (Maruishi Pharmaceutical Co.) between 2.0 and 4.0% (in air), after an initial induction with ketamine hydrochloride (100 mg/cat, i.m.). Sevoflurane MAC has been reported to be between 2.0 and 3.0% of the inspiratory concentration[10]. Animals were ventilated by an artificial respirator via a tracheal cannula following an intravenous injection of gallamine triethiodide. The end-tidal CO_2 level was maintained at approximately 3.5%. Other general

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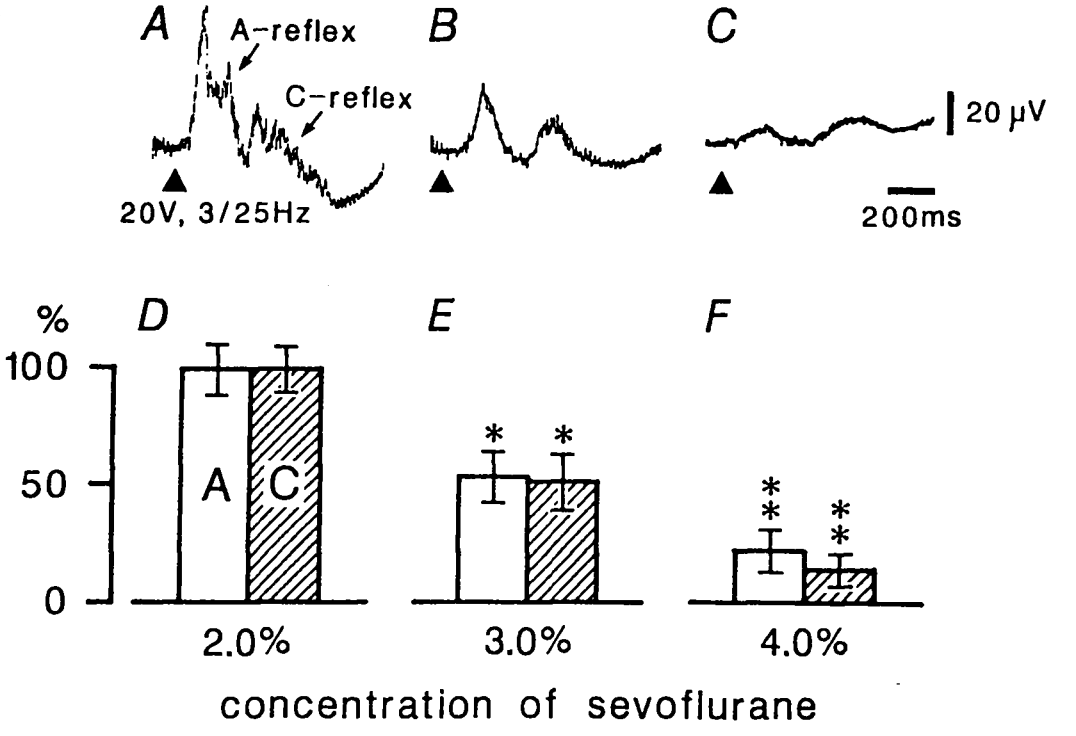

Fig. 1. A-C demonstrate sample recordings of the averaged sympathetic A- and C-reflexes evoked in the left inferior cardiac sympathetic nerve to hindlimb nerve stimulation at supramaximal intensity (0.5 ms duration for each pulse) in 2.0% (A), 3.0% (B) and 4.0% (C) inspiratory concentrations of sevoflurane anesthesia. D-F summarize the data (mean ± S.E.) for A-(open bar) and C-(hatched bar) reflexes in all 6 animals tested at 3.0% (E) and 4.0% (F) comparing the sizes of the A- and C-reflexes at 2.0% expressed as 100%. The columns and vertical lines in E and F represent the mean ± S.E. Asterisks represent significant differences at the $P<0.05$ (*) and $P<0.01$ (**) level tested by Student's t-test.

experimental procedures were performed as previously described[11]. The animals underwent a bilateral vagotomy at the cervical level.

The left superficial peroneal nerve (SP), a hindlimb cutaneous nerve, was surgically isolated from the surrounding tissues and cut at the distal part of the hind leg. Then, the distal segment of the central part of the severed nerve was stimulated electrically to excite afferent fibers. Electrical train pulse stimulations (3 pulses of 0.5 ms duration at 25 Hz) were delivered to the SP, every 3s by an electrical stimulator (Nihon Kohden SEN 7103). Action potentials were recorded from a more proximal (about 3 cm from the stimulating electrode) portion of the SP to categolize the nerve fibers activated by the stimulation.

After removal of the first two left ribs, the left inferior cardiac sympathetic nerve (ICN) was dissected and cut as close to the heart as possible. The reflex nerve activity evoked in the ICN by SP stimulation was recorded from the central segment of the ICN severed, and was amplified by a preamplifier (with a time constant of 0.3s) and averaged 8–16 times for each analysis by an averaging instrument (Nihon Kohden ATAC 450). The averaged response were displayed on an X-Y plotter.

When the inspiratory concentration of sevoflurane was kept at 2.0%, stimulation of SP afferents by electrical train pulses (3

pulses at a frequency of 25 Hz) at an intensity of 20V, which was sufficient to excite both A and C afferent fibers, evoked two different reflex responses, i.e., early and late reflex responses. The early reflex response has been designated as the sympathetic A-reflex, because it was elicited by stimulation of A afferent fibers alone[5]. The late reflex response has been designated as the sympathetic C-reflex, because it was only elicited by additional stimulation of C afferent fibers[5].

The A- and C-reflex responses at 2.0% sevoflurane anesthesia are demonstrated in Fig. 1A. Similar results were observed in 5 other cats tested. Both latencies of these A- and C-reflexes, when evoked by stimulation at supramaximal intensity, in all 6 cats tested under the inspiratory concentration of sevoflurane at 2.0%, ranged between 50–100 ms and 280–370 ms, respectively. Both durations of the A- and C-reflexes ranged between 140–270 ms and 240–420 ms, respectively.

Figure 1 summarizes the effects of different concentrations of sevoflurane (2.0, 3.0 and 4.0%) on the sizes of A- and C-reflexes in the 6 animals. Example records of both reflexes in Figs. 1A, B and C were depicted for 2.0%, 3.0% and 4.0% of sevoflurane concentrations respectively, and Figs. 1D–F summarize the results. Sizes of A- and C-reflexes at 3.0 and 4.0% of sevoflurane were expressed in percentages of those at 2.0%. Both reflexes were depressed significantly with increases in sevoflurane concentration. At 3.0%, the A- and C-reflexes decreased to 53 ± 11% and 51 ± 12% of those at 2.0%, respectively. At 4.0%, both of them further decreased to 22 ± 9% and 14 ± 7% of those at 2.0%.

The sympathetic A- and C-reflexes evoked in inferior cardiac nerve by stimulation of the myelinated and unmyelinated afferent fibers of hindlimb nerves in sevoflurane anesthesia resembled the A- and C-sympathetic reflexes evoked in articular sympathetic nerve branches under halothane (1.0–1.5%) anesthesia[12], and in renal[13] or cardiac sympathetic nerve[7] branches under urethane-chloralose (100 mg/kg and 50 mg/kg) anesthesia, following similar stimulation of the hindlimb afferent nerves. Concerning the latencies of these reflexes, there was no noticeable difference between the urethane-chloralose or halothane anesthetized cats[7] and the sevoflurane anesthetized cats. However, the durations of these reflexes seemed slightly longer in 2.0% sevoflurane anesthetized cats than in urethane-chloralose or halothane anesthetized cats, suggesting a more dominant excitability of sympathetic activity at 2.0% sevoflurane anesthesia than halothane or urethane-chloralose anesthesia.

The present results revealed that the A- and C-sympathetic reflexes were depressed dose-dependently with sevoflurane concentrations of 2.0 and 4.0%. These results suggest that cardiac functions innervated by sympathetic nerves can respond well to various somatic afferent stimuli, including innocuous and noxious mechanical stimuli to the skin, at 2.0% of sevoflurane anesthesia, while at 4.0% of sevoflurane anesthesia these functions cannot respond to the same stimulation.

It is noteworthy that both A- and C-reflexes were depressed in parallel with an increase in the concentration of sevoflurane. Some analgesic agents, for example morphine[7] or Fentanyl[9] depress the C-reflex more than the A-reflex. It seems that sevoflurane has not such specific effect on C-reflex, but general supressive effect on both of A- and C-reflexes. As the A- and C-sympathetic reflexes elicited by hindlimb afferent nerves have been reported to have central reflex arcs through the medulla oblongata[5], it is likely that their depression by sevoflurane at high concentrations occurs at the medullary level. However, the action of sevoflurane at the spinal level cannot be neglected, because morphine can act at the spinal level to depress both the A- and C-sympathetic reflexes in spinalized animals[14]. Further study to examine the effects of different concentrations of sevoflurane on A- and C-sympathetic reflexes in spinalized animals is necessary to verify the exact locations of its central action on the

sympathetic nerve activity.

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