Methods

After obtaining IRB approval and informed consent from every patient, Twenty-four ASA I- II patients undergoing general anesthesia were studied. Twenty patients underwent abdominal surgery. Anesthesia was induced by a bolus of 1.0 mg/kg propofol and 0.6 mg/kg rocuronium. RF infusion at 0.3 or 0.4 γ was started 5 min before induction. After operation was started, sevoflurane increased to 0.5% and maintained with 66% nitrous oxide in oxygen. Fifteen min after sevoflurane concentration in expired gas declined to 0.1 vol %, RF was infused at 5 min and RF/HF was calculated using CheckMyHeart® (DailyCare BioMedical Inc., Chungli, Taiwan). Then RF infusion rate was increased to 0.5 γ at increments of 0.1 γ, and LF/HF was determined at every increment 15 min after RF infusion rate was changed. RF was also measured whenever there was a sudden increase in blood pressure. RF infusion rate was not changed after the HRV measurement at 0.5 γ.

Discussion

1) LF/HF increased more than 4 or 5 a little delayed than increases of SBP, HR, and BIS.

Reference

Tetzlaff et al (1) reported that LF/HF remained less than 1 when tourniquet-induced hypertension (T-HTN) did not develop, however it increased above 1.5 when T-HTN developed under general anesthesia. Spinal N-methyl-D-aspartic acid (NMDA) receptor activation via ‘wind-up’ is involved in T-HTN (2). Therefore it is reasonable to consider that LF/HF above 5 is a sign of activation of NMDA receptors. In four patients in this series, we suspect that RF tolerance to RF developed, because LF/HF reached a level observed when NMDA receptors were activated in T-HTN and one patient in this series, we suspect that RF tolerance to RF developed, because LF/HF was observed at a level observed when NMDA receptors were activated in T-HTN. From the results of cases 3, 4, and 5, even after RF tolerance to RF has developed, ket can attenuate the acute tolerance.

Hultzer-Petsche et al (3) reported that tachyphylaxis of the mesentry was an acute visceral nociceptive reflex. RF-induced increases in LF/HF were observed in a subset of patients, increased in blood pressure and decrease in intraganglionic flow rates. Thus, we observed the same type of reflexes in our patients, however the duration of these reflexes was short, so it is suspected that NMDA receptor activation was not involved in these reflexes.

Discussion (2)

Luginbuhl M et al. (4) reported that RF does not discriminate between different levels of haemodynamic responsiveness during surgery and Jeanne M et al. (5) reported that normalized HF power (HF / total power) is related with analgesia-noceception balance more specifically than HR variations. However in our study, RF-induced increases in SBP, HR, and BIS when it was supposed that acute tolerance was developing. We suspect that there is an early phase of development to acute tolerance to RF. Ji RR et al. (6) reported that there is the first phase that is short term functional (non-transcriptional) changes in the nervous system that transduce extracellular stimuli into intracellular post-translational and transcriptional responses via extracellular signal-regulated protein kinases (ERKs). The peak increase in ERK phosphorylation in the dorsal horn of THTN in rats is followed by a slow decline over tens of minutes, although levels remain elevated above baseline for beyond 30 minutes. We supposed that RF/HF is an effective parameter of predicting a development of RF tolerance to RF during anesthesia. We could not measure LF/HF/RF continuously, because the lack of ability of CheckMyHeart®. A continuous monitoring of LF/HF during anesthesia is strongly recommended.

Bis is another candidate for predicting a development of tolerance to RF, however we could observe a case in which no increase of BIS when SBP, HR, and LF/HF increased. Therefore, BIS is not a suitable parameter for predicting a development of acute tolerance to RF during anesthesia.

Ket could attenuate a development of acute tolerance to RF in our study. However, a further study is required to clarify the results of our study, because the number of cases is very small in this study.

Reference

(2) Davies SN., Lodge D. Evidence for involvement of N-methylaspartate receptors in "wind-up" of class 2 neurons in the dorsal horn of the rat. Brain Research 1987; 424: 402-6
(3) Hultzer-Petsche U., Brodacz B. Traction on the mesentery as a model of visceral nociception. Pain 1999; 80: 319-28
(7) Ru-Rong Ji et al (6) explained the mechanisms that are involved in pain hypersensitivity. The mechanism of pain hypersensitivity consists of two phases. The first phase is short term functional (non-transcriptional) changes in the nervous system that transmit extracellular stimuli into intracellular post-translational and transcriptional responses by ERK1 and 2. ERKs are mitogen-activated protein kinases. The ERKs are activated (phosphorylated) rapidly by stimulation of C fibers, heat (>45°C), and cold (4°C). This begins after one minute of stimulation, reached a peak level at two minutes, with a return toward basal level at two hours. Calcium entry into neurons via ionotropic glutamate receptors (NMDA receptors) may initiate the ERK signaling cascade. The second phase is interpreted as an expression of use-dependent changes in spinal neurons, initiated by activity generated during the first phase. This use-dependent regulation of neuronal excitability, known as central sensitization, giving the similarities between synaptic plasticity in the hippocampal and central sensitization in the spinal cord, is involved in the heightened pain sensitivity. The mechanisms responsible for central sensitization include activation of threoenine/serine and tyrosine kinases with subsequent phosphorylation of membrane bound receptors, particularly the NMDA receptor. The ERK have also been shown, via Rsk activation and subsequent CREB phosphorylation, in transcriptional regulation, and this is important for long-term facilitation depending gene expression in Aplysia and for LTP in the hippocampus. ERK signaling cascade induces phosphorylation of CREB and transcriptional activation of many genes, NK-1, TrkB12, 21, 26, 47, 48, 49, 50. ERK activation in the spinal cord after nociceptive stimulation may regulate the expression of some of these genes via CREB-mediated transcription and contribute to the establishment of persistent pain as well as acute pain hypersensitivity.