Increase of low- to high-frequency ratio of heart rate variability spectra to above 5 predicts acute tolerance to remifentanil during anesthesia.

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Background

In power spectral analysis of heart rate variability (HRV), the ratio of low-frequency component (LF) to high-frequency component (HF) (LF/HF) provides a noninvasive quantitative evaluation of the sympathovagal balance. When acute tolerance to remifentanil (Rf) develops during anesthesia, it should lead to activation of sympathetic nerve and result in a continuous increase of LF/HF.

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 µg/kg/min (γ) was started 5 min before induction. After operation was started, sevoflurane inhalation was stopped to avoid the vasodilating effect, and anesthesia was maintained with 66% nitrous oxide in oxygen. Fifteen min after sevoflurane concentration in expired gas declined to 0.1 vol%, HRV was measured for 5 min and LF/HF was calculated using CheckMy Heart® (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 the Rf infusion rate was changed. HRV 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. In most patients, bispectral index (BIS) was monitored by using BIS monitor A-2000TM (Aspect Medical Systems, Newton, MA, USA) and electroencephalogram (EEG) was monitored by BIS monitor. Rocuronium at 20 mg/h was infused during anesthesia. In 3 patients who had a sudden increase of SBP, a bolus of 0.5 mg/kg ketamine (Ket) was given and we measured LF/HF after 15 min of its infusion.

Results (1)

In 19 patients, LF/HF, sympathetic nerve activity and HR decreased depending on Rf infusion rate. SBP and DBP increased depending on Rf infusion rate. After the beginning of N_2O, EEG became sign wave-like (δ and θ wave), BIS decreased to nearly 30 and the suppression ratio number began to appear on the BIS apparatus in most cases. There was no awakening during anesthesia in all patients. In 4 patients case (1-4), LF / HF increased more than 5 when Rf infusion rate was 4 or 5γ, and in one patient (case 5), LF/HF increased nearly to 5 when Rf infusion rate was 0.5γ.

Results (2)

1) LF/HF increased more than 4 or 5 a little delayed than increases of SBP, HR, and BIS.
2) LF/HF increased more than 2 earlier than increases of SBP, HR, and BIS.
3) Time between LF/HF more than 4 or 5 and LF/HF more than 2 was 35 ± 25 min (mean ± standard deviation).
4) SBP, HR, and BIS increased almost simultaneously, however BIS did not increased in case 3 and BIS increase in case 5 was mild. We did not measure BIS in case 4. The increase of HR in case 4 was mild.
5) Ket (0.5 mg/kg) could attenuate increases of LF/HF, SBP, HR, and BIS. However, in case 5, 0.5 mg/kg ket was not effectively attenuate these increases and two bolus infusions of ket (total 1.0 mg/kg ket) could attenuate these increses.

Discussion (1)

Tetzlaff et al (1) reported that LF/HF remained less than 1 when tourniquet-induced hypertension (T-HTN) did not develop, however it increased to above 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 acute 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 acute tolerance to Rf developed, because LF/HF reached nearly a level observed when NMDA receptors were activated in T-HTN. From the results of cases 3, 4, and 5, even after acute tolerance to Rf has developed, Ket can attenuate the acute tolerance.

U Holtzer-Petsche et al (3) reported that traction of the mesentery was an acute visceral nociception and evoked pseudaffective reflexes that resulted in a sudden increase in blood pressure and decrease in intragastric pressure in rats. We could observe the same type of reflexes in our patients, however the duration of these reflexes were short, so it is suspected that NMDA receptor activation was not involved in these reflexes.

Discussion (2)

Luginbuhl M et al. (4) reported that HRV dose not discriminate between different levels of haemodynamic responsiveness during surgical anaesthesia and Jeanne M et al. (5) reported that normalized HF power (HF / total power) are related with analgesia-nociception balance more specifically than HR variations. However, we could observe LF/HF increased earlier than increases of 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-transcrptional) 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 posphorylation in the dorsal horn is relatively transient, activated maximally within 2 minutes followed by a slow decline over tens of minutes, although levels remain elevated above baseline for beyond 30 minutes.

We suppose that LF/HF is an effective parameter of predicting a development of tolerance to Rf during anesthesia. We could not measure LF/HF 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.

Discussion (3)

Ru-Rong Ji et al (6) explained the mechanisms that are involved in pain hypersensitibity. The mechanism of pain hypersensitivity consists of two phases. The first phase is short term functional (non-transcrptional) changes in the nervous system that transduce extracellular stimuli into intracellular post-translational and transcriptional responses by ERK1 and 2. ERKs are mitogen-activated protein kinases. The ERKs are activated (phospolylated) rapidly by stimulation of C fibers, heat (>45˚C), and cold (4˚C). This began after one minutes of stimulations, reached a peak level at two minutes, with a return toward basal level at two hours. Calcium entry into nurons 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 hippocamous and central sensitization in the spinal cord, is involved in the heightened pain sensitivity. The mechanisms responsible for C-fiber-induced plasticity in the spinal cord include activation of threonine/serine and tyrosine kinases with subsequent phosporylation of membrane bound receptors, particularly the NMDA receptor. The ERKs have a major role, via Rsk activation and subsequent CREB phospolylation, in transcriptional regulation, and this is important for long-term facilitation depending gene expression in Aplysia and for LTP in the hippocamous. ERK sigmaling cascade induces phosphorylation of CREB and trnascriptional activation of many genes, NK-1, TrkB12, 21, 46, 47, 48, 49, 50. ERK activation in the spinal cord after noxious stimulation may regulate the expression of some of these genes via CRE-mediated trnascription and contribute to the establishment of persistent pain as well as acute pain hypersensitivity.

References

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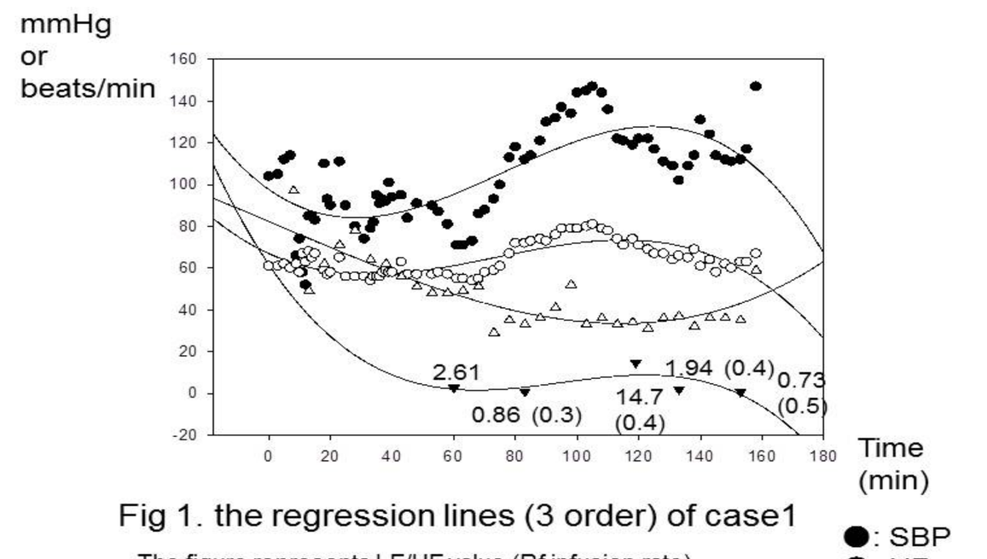

Fig 1. the regression lines (3 order) of case1
The figure represents LF/HF value (Rf infusion rate)

●: SBP
○: HR
△: BIS
▼: LF/HF

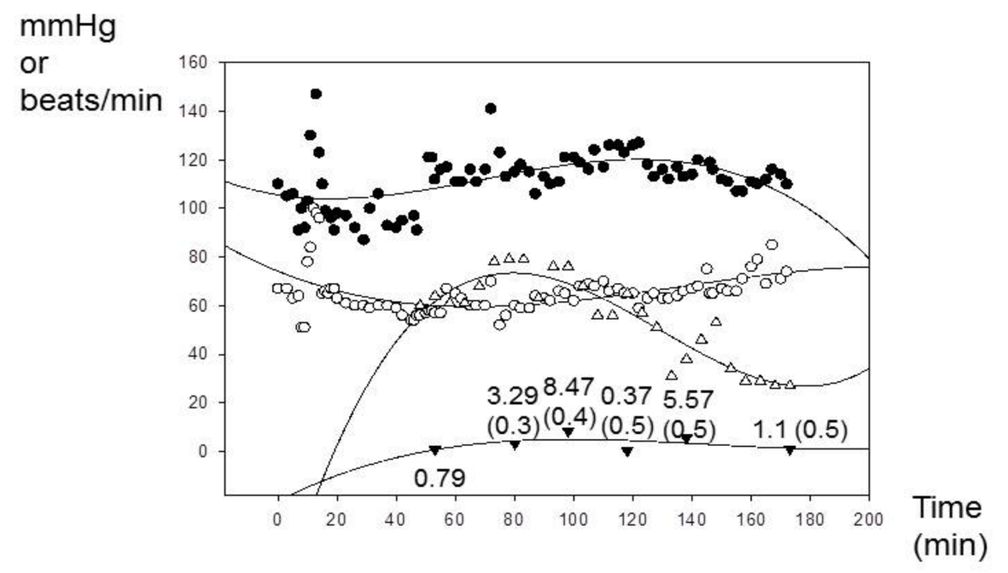

Fig. 2 the regression lines (3 order) of case 2

●: SBP
○: HR
△: BIS
▼: LF/HF

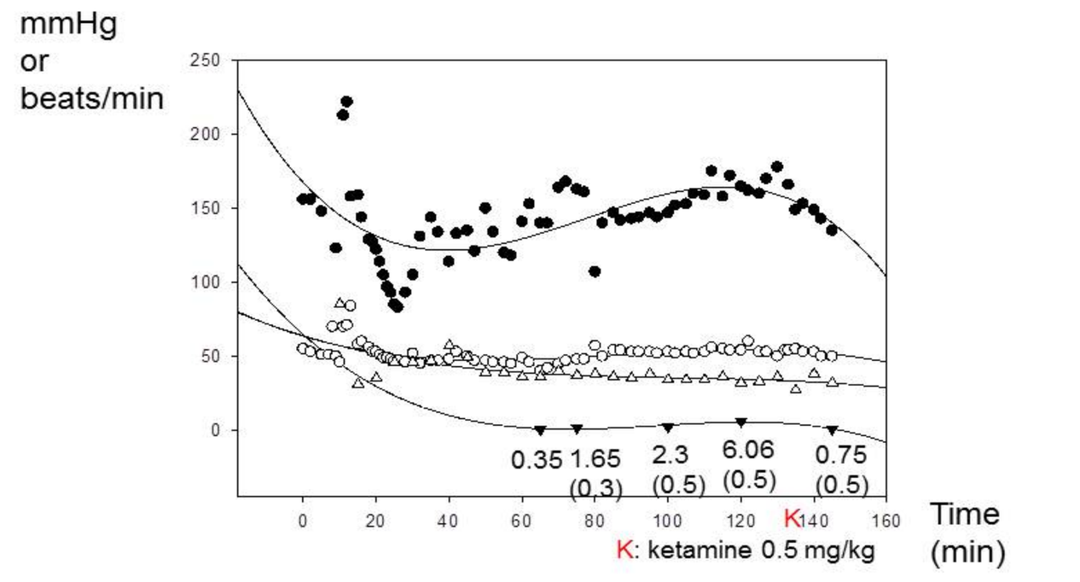

Fig. 3 the regression lines (3 order) of case 3

●: SBP
○: HR
▼: LF/HF

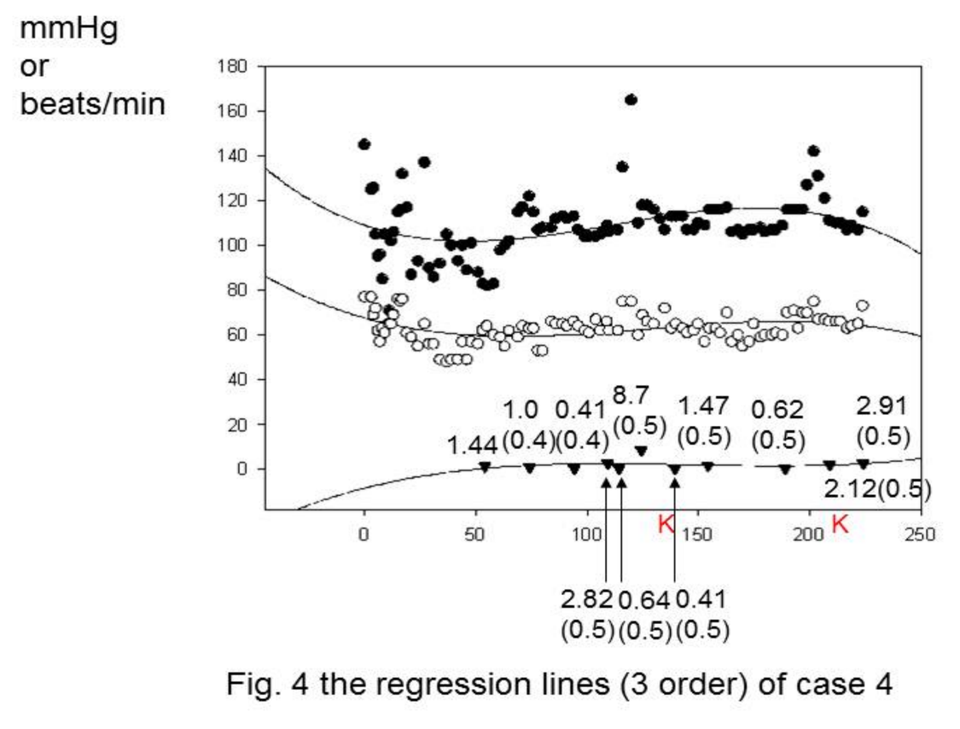

Fig. 4 the regression lines (3 order) of case 4

●: SBP
○: HR
▼: LF/HF

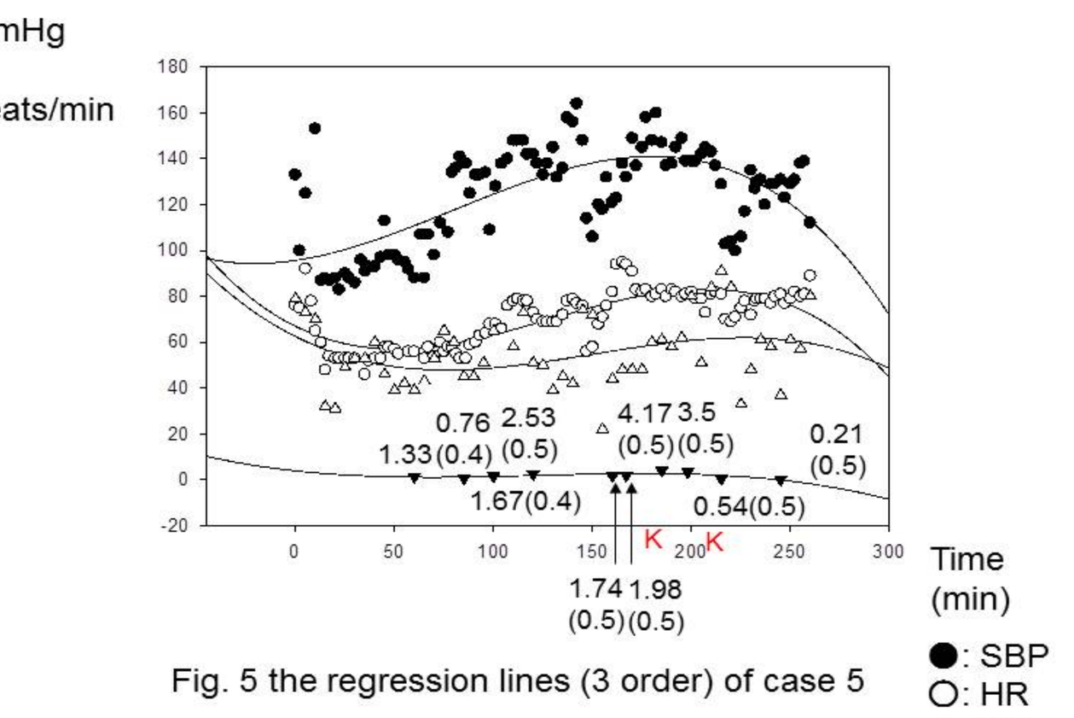

Fig. 5 the regression lines (3 order) of case 5

●: SBP
○: HR
△: BIS
▼: LF/HF

Table 1 summarization of case 1-5

	case1		case2		case3		case4		case5	
SBP	↑		↑		↑		↑		↑	
HR	↑		↑		↑		↑*		↑	
BIS	↑		↑		→		×		↑*	
LF/HF										
>4 or 5 (min)	118	delayed	95	delayed	120	delyed	125	delayed	185	delayed
>2 (min)	60	earlier	80	same time	100	earlier	109	earlier	120	earlier
	58		15		20		16		65	
							*: mild		*mild	

Time between LF/HF >2 and LF/HF>4 or 5 was 35 ± 25 min.