High-Frequency Heart Rate Variability Index: A Prospective, Observational Trial Assessing Utility as a Marker for the Balance Between Analgesia and Nociception Under General Anesthesia

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BACKGROUND: Maintaining a balance between nociception and analgesia perioperatively reduces morbidity and improves outcomes. Current intraoperative analgesic strategies are based on subjective and nonspecific parameters. The high-frequency heart rate (HR) variability index is purported to assess the balance between nociception and analgesia in patients under general anesthesia. This prospective observational study investigated whether intraoperative changes in the high-frequency HR variability index correlate with clinically relevant nociceptive stimulation and the addition of analgesics.

METHODS: Instantaneous and mean high-frequency HR variability indexes were measured continuously in 79 adult subjects undergoing general anesthesia for laparoscopic cholecystectomy. The indexes were compared just before and 2 minutes after direct laryngoscopy, orogastric tube placement, first skin incision, and abdominal insufflation and just before and 6 minutes after the administration of IV hydromorphone.

RESULTS: Data from 65 subjects were included in the final analysis. The instantaneous index decreased after skin incision ([SEM], 58.7 [2.0] vs 47.5 [2.0]; $P < .001$) and abdominal insufflation (54.0 [2.0] vs 46.3 [2.0]; $P = .002$). There was no change in the instantaneous index after laryngoscopy (47.2 [2.2] vs 40.3 [2.3]; $P = .026$) and orogastric tube placement (49.8 [2.3] vs 45.4 [2.0]; $P = .109$). The instantaneous index increased after hydromorphone administration (58.2 [1.9] vs 64.8 [1.8]; $P = .003$).

CONCLUSIONS: In adult subjects under general anesthesia for laparoscopic cholecystectomy, changes in the high-frequency HR variability index reflect alterations in the balance between nociception and analgesia. This index might be used intraoperatively to titrate analgesia for individual patients. Further testing is necessary to determine whether the intraoperative use of the index affects patient outcomes. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Do changes in the heart rate (HR) variability index correlate with the balance between nociceptive events and analgesia intraoperatively?
- **Findings:** The HR variability index decreased after direct laryngoscopy, skin incision, and abdominal insufflation and increased after hydromorphone administration.
- **Meaning:** In adult subjects under general anesthesia for laparoscopic cholecystectomy, changes in the high-frequency HR variability index reflect alterations in the balance between nociception and analgesia.

Perioperatively, it is important to maintain a balance between nociception and analgesia for each patient because both too much[1–4] and not enough[5–11] analgesic have negative consequences. Yet, current intraoperative treatment strategies for paralyzed patients under general anesthesia rely almost entirely on anesthetist experience and changes in hemodynamic variables, namely blood pressure and heart rate (HR). There is variability in both patient analgesic requirements for a given nociceptive stimuli and response to a given analgesic dose.[12] In addition, vital sign changes are a nonspecific indicator of patient analgesic requirements as HR, and blood pressure changes occur intraoperatively for many reasons.

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Several parameters have been proposed to assess the balance between nociception and analgesia including skin conductance,[13] peripheral pulse wave plethysmography,[14] pupillary dilation reflex,[15] and HR variability.[16] Controversy exists over the accuracy of these methods, and no analgesia monitor is widely and routinely used intraoperatively.

High-frequency HR variability appears to be altered solely by changes in the parasympathetic nervous system.[17,18] In awake individuals, the analgesia/nociception balance and mood affect the parasympathetic nervous system. Under general anesthesia, the analgesia/nociception balance and some medications and stimuli affect the parasympathetic nervous system and thus, high-frequency HR variability. (Note: the analgesia nociception index and high-frequency HR variability index are identical. The US Food and Drug Administration required Mdoloris to change the index name for the US market.) Previous studies have assessed changes in high-frequency HR variability index after the application of experimentally induced nociceptive stimuli to patients under general anesthesia,[16,19] the correlation of intraoperative high-frequency HR variability index with postoperative pain in adult and pediatric patients,[20–23] the correlation between postoperative high-frequency HR variability index and postoperative pain,[24] and the effect of intraoperative high-frequency HR variability index–guided opioid administration on perioperative measures.[25–27] However, few studies have investigated high-frequency HR variability index changes in patients during surgery to determine whether or not high-frequency HR variability index correlates with normal clinical intraoperative events.[28] Previous studies have found that high-frequency HR variability index values ≥50 corresponded to visual analog scores ≤30 (range, 0–100).[21,29]

We hypothesized that high-frequency HR variability index would change intraoperatively when the analgesia/nociception balance was altered by clinically relevant nociceptive events and the addition of analgesics. Our primary hypothesis was that high-frequency HR variability index would decrease due to direct laryngoscopy in adult subjects under general anesthesia for laparoscopic cholecystectomy. Our secondary hypotheses were that high-frequency HR variability index would decrease due to orogastric tube placement, skin incision, and abdominal insufflation and increase due to the administration of IV hydromorphone in the same subjects.

METHODS

This study was approved by the Partners Healthcare (Boston, MA) Institutional Review Board (Protocol No. 002734).

Demographics and Inclusion/Exclusion Criteria

Inclusion criteria were as follows: ≥18 years of age; scheduled to undergo general anesthesia for elective laparoscopic cholecystectomy at Massachusetts General Hospital (Boston, MA); male and female; American Society of Anesthesiologists (ASA) physical status classification I or II; and able to consent for self. Exclusion criteria were as follows: major cardiovascular disease, arrhythmia, respiratory disease, cerebral vascular disease, or ASA physical status classification III or greater; documented or self-reported history of chronic pain; acute or chronic opioid analgesic use; dysautonomia; diabetes mellitus with evidence of neuropathy; emergency cases; and intraoperative muscarinic anticholinergic administration during the time of monitoring.

Study Protocol

The surgical schedule at the Massachusetts General Hospital was assessed daily to determine subjects who met criteria for study enrollment. More than 24 hours before surgery, a surgical care team member asked patients if they were amendable to be approached on the day of surgery about participation in a research study. On the day of surgery, the study protocol was described to patients who gave verbal consent to be approached, and written consent was obtained by the study principal investigator or a coinvestigator from those who agreed to participate. A research assistant was present in the operating room with a timer and a copy of the study protocol, reminded anesthesia providers of study times and analgesic (fentanyl and hydromorphone) doses, and recorded intraoperative event times.

HR variability monitor (High-Frequency HR Variability Index Monitor, Software Version 1.1.3.0; Mdoloris Medical Systems, SAS, Loos, France) skin electrodes were placed on each subject before preoxygenation. After preoxygenation, 2–3 μg/kg IV fentanyl was administered. One minute later, general anesthesia was induced. General anesthesia induction and maintenance medications were at the discretion of the operating room anesthesia team. Three minutes after the induction of general anesthesia, direct laryngoscopy occurred. At least 3 minutes occurred after placement of the endotracheal tube before the orogastric tube was placed. The time of initial skin incision was noted. To determine the effect of opioid administration on the high-frequency HR variability index during a time of relatively homogenous surgical stimulation, 0.5 mg of IV hydromorphone was given ≥5 minutes after all laparoscopic instrument ports were introduced into the abdomen. At the completion of surgery and before emergence from general anesthesia, HR variability monitoring was stopped, and skin electrodes were removed (Figure 1). Anesthesia providers did not make changes to the anesthetic based on high-frequency HR variability index values. No changes to the study protocol were made after trial commencement.

If the subject's body mass index was ≥30 kg/m^2, an adjusted body weight was calculated and used for fentanyl dosing.[30]

Data Collection

Intraoperative data collection included instantaneous and mean high-frequency HR variability indexes, HR, noninvasive blood pressure, all medications including dose and time of administration, and inhaled and exhaled gas concentrations. High-frequency HR variability index values before fentanyl administration and induction of general anesthesia were not used in analyses because high-frequency HR variability index values in awake patients are confounded by mood.

Data Analysis

The computation method has been described elsewhere.[31] Briefly, it consists of computing the time interval between 2 heart beats (R–R interval) to analyze the R–R series (R–R

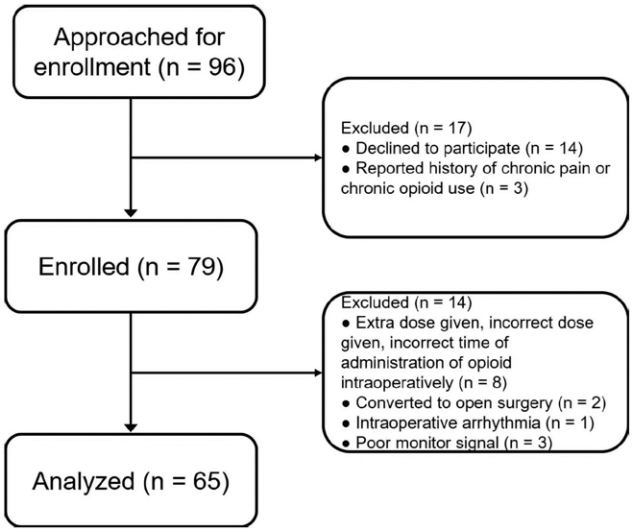

Figure 1. The study procedure timeline is shown from placement of monitor electrodes until the end of surgery. ASA indicates American Society of Anesthesiologists; ECG, electrocardiogram; GA, general anesthesia; OG, orogastric tube placement.

interval evolution over time) variability. The R–R series is then resampled at 8 Hz, normalized, and band-pass filtered between 0.15 and 0.4 Hz. Local minima and maxima are detected, and the resulting envelope is divided into 4 subareas: A1, A2, A3, and A4. The minimum area under the curve is defined as the minimum of the 4 subareas.[16]

High-frequency HR variability index is then computed as follows: $\mathrm{HFVI} = 100\times(a\times \mathrm{AUC}_{\mathrm{min}} + b)/12.8$, where $a = 5.1$ and $b = 1.2$ have been determined using a prior patient dataset; HFVI, high-frequency HR variability index; $\mathrm{AUC}_{\mathrm{min}}$, minimum area under the curve. As maximum values of high-frequency HR variability index are limited to 100, high-frequency HR variability index is further calculated as follows: if high-frequency HR variability index ≥80, then $\mathrm{HFVI} = 80 + (\mathrm{HFVI}-80)\times 20/80$, else HFVI = HFVI. High-frequency HR variability index is computed every second. High-frequency HR variability index is averaged over 1 minute to smooth the signal and to obtain the instantaneous high-frequency HR variability index. High-frequency HR variability index is averaged over 3 minutes to obtain the mean high-frequency HR variability index.

In clinical practice, mean high-frequency HR variability index is related to the imbalance between analgesia and nociception, whereas instantaneous high-frequency HR variability index is related to the instantaneous response of the autonomic nervous system to a particular noxious stimulus (eg, skin incision). Instantaneous high-frequency HR variability index and mean high-frequency HR variability index are scaled indexes from 0 to 100. Higher values indicate greater parasympathetic tone (less nociception, greater analgesia), and lower values indicate lower parasympathetic tone (less analgesia, greater nociception).

To study the intraoperative response to a noxious stimulus in patients under general anesthesia, we compared high-frequency HR variability index, mean high-frequency HR variability index, and HR values before and 2 minutes after the stimulus to take into account the possible delay in instantaneous high-frequency HR variability index and mean high-frequency HR variability index induced by the averaging process. Because mean arterial pressure (MAP) was reported every 3 minutes, we also compared the last MAP value before the stimulus to the first MAP value after the stimulus. To study the response to opioid injections, we compared instantaneous high-frequency HR variability index, mean high-frequency HR variability index, HR, and MAP values before and 6 minutes after injection to consider both the opioid pharmacokinetic response and the averaging process. The mean expired minimum alveolar concentration (MAC) at skin incision, abdominal insufflation, and the time of hydromorphone administration were determined[32–34] because depth of anesthesia can affect the high-frequency HR variability index.

Power Analyses

High-frequency HR variability index variations were studied after (1) direct laryngoscopy, (2) orogastric tube placement, (3) skin incision, (4) abdominal insufflation, and (5) administration of IV hydromorphone. There was a priori power calculation to guide our sample size. Sample size was computed for a 2-tailed paired t test and assumed a missing data rate of 15%. Assuming an $\alpha = .0125$ (Bonferroni correction, number of comparisons among 5 time phases = 4), a total sample size of 56 will achieve a power = 80% to detect an effect size as small as 0.48. This effect size equates to a mean difference of high-frequency HR variability index = 7 between before and after phases assuming SD = 14.7.[35]

Statistical Methods

Patients' continuous demographic data are presented as medians and interquartile range. Categorical data are expressed as percentage. The analyses of instantaneous high-frequency HR variability index, mean high-frequency HR variability index, HR, and MAP over time were performed using linear mixed models including the measuring time as a fixed effect and the individual patient number as a random effect. Post hoc comparison between measures before and after (1)–(5) (above) were performed. Data are presented as mean (standard error). According to the Bonferroni correction, the difference between before and after was considered significant when $P < .0125$. To test the relationship between high-frequency HR variability index variation (Δ instantaneous high-frequency HR variability index, Δ mean high-frequency HR variability index) and age, body mass index, and the baseline high-frequency HR variability index (ie, high-frequency HR variability index before each stimulus), we used a Pearson test. A P value of <.0125 was considered significant. To test the relationship between high-frequency HR variability index variations and gender, we used a Student t test. We compared Δ instantaneous high-frequency HR variability index and Δ mean high-frequency HR variability index in males and females for each procedure. A P value of < .0125 was considered significant. Statistical analyses were performed using IBM SPSS statistics 20.0 (IBM; Armonk, New York).

RESULTS

From January 2017 to July 2017, 96 subjects were approached for enrollment. Fourteen subjects declined to participate,

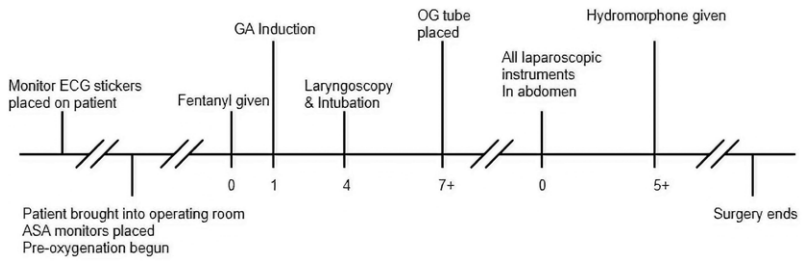

Figure 2. Flowchart of the number of subjects approached, enrolled, and included in the final data analyses.

Table 1. Patient Demographics

Demographics	Median (1st–3rd Quartile)
Age (y)	48 (36.5–58.5)
Weight (kg)	85.3 (70.3 + 97.1)
Height (m)	1.65 (1.58–1.74)
Body mass index (kg/m^2)	29.3 (25.6–35.6)
Sex (% male)	35.4%
Fentanyl dose (μg)	200 (150–200)
$Time_{fentanyl–hydromorphone}$ (min)	32.0 (27.5–39.5)
$MAC_{incision}$	0.97 (0.8–1.1)
$MAC_{insufflation}$	1.04 (0.9–1.2)
$MAC_{hydromorphone}$	1.1 (0.9–1.25)

Continuous data are presented as median (1st–3rd quartile). Categorical data are presented as a percentage.
Abbreviation: MAC, minimum alveolar concentration.

and 3 subjects reported a history of chronic pain or chronic opioid. Seventy-nine subjects were enrolled in the study. Fourteen subjects were excluded. Eight patients received an extra dose of opioid for clinical need as determined by the intraoperative anesthesia team, the doses of fentanyl or hydromorphone given were not compliant with the study protocol, or the incorrect timing of opioid administration occurred; 2 surgeries were converted from laparoscopic to open; 1 subject had continuous intraoperative arrhythmia; and too little useable data were collected from 3 subjects due to poor signal transmission. Data from 65 subjects were included in the final analysis (Figure 2). Subject demographics are shown in Table 1. Enrollment was ended when enough patients were enrolled to meet analyses requirements.

High-Frequency HR Variability Index

Instantaneous high-frequency HR variability index decreased after first skin incision (58.7 [2.0] vs 47.5 [2.0]; $P < .001$) and abdominal insufflation (54.0 [2.0] vs 46.3 [2.0]; $P = .002$) (Tables 2–3). Instantaneous high-frequency HR variability index did not change significantly after laryngoscopy (47.2 [2.2] vs 40.3 [2.3]; $P = .026$) and orogastric tube placement (49.8 [2.3] vs 45.4 [2.2]; $P = .109$). Instantaneous high-frequency HR variability index increased after hydromorphone administration (58.2 [1.9] vs 64.8 [1.8]; $P = .003$). Mean high-frequency HR variability index decreased after laryngoscopy (49.2 [1.6] vs 45.2 [1.6]; $P = 0.002$), first skin incision (57.9 [1.6] vs 53.4 [1.7]; $P = .004$), and abdominal insufflation (56.2 [1.6] vs 48.9 [1.5]; $P < .001$). Mean high-frequency HR variability index did not change after orogastric tube placement (45.5 [1.8] vs 48.4 [1.7]; $P = 0.038$). Mean high-frequency HR variability index increased after hydromorphone administration (57.7 [1.7] vs 63.5 [1.7]; $P < .001$). No relationship was found between Δ instantaneous high-frequency HR variability index and Δ mean high-frequency HR variability index with age, body mass index, or gender (data not shown). We found a significant correlation between Δ instantaneous high-frequency HR variability index and the baseline instantaneous high-frequency HR variability index ($r = 0.53$; $P < .001$) and between Δ mean high-frequency HR variability index and the baseline mean high-frequency HR variability index ($r = 0.389$; $P < .001$). Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C792, shows the mean ± SD instantaneous high-frequency HR variability index and mean high-frequency HR variability index over the time course of the study for the patient cohort.

Heart Rate

HR increased after direct laryngoscopy (69.1 [1.8] vs 77.6 [2.0]; $P < .001$), first skin incision (68.7 [1.8] vs 71.7 [1.8]; $P = .004$), and abdominal insufflation (69.8 [1.7] vs 73.6 [1.7]; $P < .001$) (Tables 2 and 3). HR did not change after orogastric tube placement (76.2 [1.6] vs 76.9 [1.4]; $P = .335$) or hydromorphone administration (71.2 [1.9] vs 69.3 [1.8]; $P = .081$).

Mean Arterial Pressure

MAP did not change after direct laryngoscopy (87.8 [2.5] vs 86.6 [2.8]; $P = .700$) or first skin incision (75.9 [1.3] vs 79.9 [1.6]; $P = .013$) (Tables 2 and 3). MAP decreased after orogastric tube placement (90.6 [2.8] vs 81.7 [2.1]; $P < .001$) and hydromorphone administration (95.9 [2.7] vs 89.5 [2.1]; $P = .003$). MAP increased after abdominal insufflation (77.1 [1.6] vs 85.1 [2.0]; $P < .001$).

Mean Expired MAC Sevoflurane

Results are shown in Table 1. The mean expired MAC of sevoflurane at first skin incision, abdominal insufflation, and IV hydromorphone administration ranged from 1.0 to 1.1. Values were not calculated at the time of direct laryngoscopy and orogastric tube placement as the inspired and expired sevoflurane concentrations were lower given their temporal proximity to anesthesia induction.

No adverse events occurred as a result of this study in any of the study subjects.

DISCUSSION

An important goal of perioperative anesthesia care is to provide adequate analgesia for each patient. However, current methods for the intraoperative assessment of the balance between nociception and analgesia are nonspecific. The results of this study indicate that in adult patients undergoing general anesthesia during laparoscopic cholecystectomy, the high-frequency HR variability index changes with clinically relevant nociceptive events (direct laryngoscopy,

Table 2. High-Frequency HR Variability Index, HR, and MAP Before and After Painful Stimulations

	Instantaneous High-Frequency HR Variability Index					Mean High-Frequency HR Variability Index				
	Before	+2 min	Mean Difference	CI	*P* Value	Before	+ 2 min	Mean Difference	CI	*P* Value
Direct laryngoscopy (n = 52/63)	47.2 (2.2)	40.3 (2.3)	−6.9	−12 to −0.85	.026	49.2 (1.6)	45.2 (1.6)	−4.0	−6.6 to 1.4	.002
Orogastric tube placement (n = 57/65)	49.8 (2.3)	45.4 (2.2)	−4.4	−9.9 to 1.0	.109	45.5 (1.8)	48.4 (1.7)	2.9	0.2 to 5.6	.038
Skin incision (n = 59/63)	58.7 (2.0)	47.5 (2.0)	−11.2	−15.4 to −6.9	<.001	57.9 (1.6)	53.4 (1.7)	−4.4	−13.2 to −5.8	.004
Abdominal insufflation (n = 63/65)	54.0 (2.0)	46.3 (2.0)	−7.8	−12.7 to −2.9	.002	56.2 (1.6)	48.9 (1.5)	−7.3	−10 to −4.5	<.001
	HR					MAP				
	Before	+2 min	Mean Difference	CI	*P* Value	Before	+3 min	Mean Difference	CI	*P* Value
Direct laryngoscopy (n = 58/63) (n = 53/63)	69.1 (1.8)	77.6 (2)	8.5	5.2–11.9	<.001	87.8(2.5)	86.6(2.8)	−1.2	−7.5 to 5.1	.700
Orogastric tube placement (n = 62/65) (n = 54/65)	76.2 (1.6)	76.9 (1.4)	0.7	−0.8 to 2.3	.335	90.6(2.8)	81.7(2.1)	−8.9	−13.1 to −4.7	<.001
Skin incision (n = 58/63) (n = 51/63)	68.7 (1.8)	71.7 (1.8)	3.0	1.0–5.0	.004	75.9(1.3)	79.9(1.6)	4.1	0.9–7.2	.013
Abdominal insufflation (n = 62/65) (n = 54/65)	69.8 (1.7)	73.6 (1.7)	3.8	2.0–5.6	<.001	77.1(1.6)	85.1(2.0)	8.1	4.1–12	<.001

Data are presented as mean (standard error), the mean difference, and 95% CI for the difference. Comparisons between before and after events were made using a Student *t* test for repeated measures. Differences are considered significant if $P < .0125$.

Abbreviations: HR, heart rate; MAP, mean arterial pressure.

Table 3. High-Frequency HR Variability Index, HR, and MAP Before and 6 Minutes After Opioid Injection

	Instantaneous High-Frequency HR Variability Index					Mean High-Frequency HR Variability Index				
	Before	+6 min	Mean Difference	CI	*P* Value	Before	+6 min	Mean Difference	CI	*P* Value
Hydromorphone (n = 61/64)	58.2 (1.9)	64.8 (1.8)	6.6	2.4–10.8	.003	57.7 (1.7)	63.5 (1.7)	5.8	2.7–8.8	<.001
	HR					MAP				
	Before	+6 min	Mean Difference	CI	*P* Value	Before	+6 min	Mean Difference	CI	*P* Value
Hydromorphone (n = 60/64) (n = 50/64)	71.2 (1.9)	69.3 (1.8)	1.8	−0.2 to 3.9	.081	95.9 (2.7)	89.5 (2.1)	−6.5	−10.6 to −2.3	.003

Data are presented as mean (standard error), the mean difference, and 95% CI for the difference. Comparisons between before and after events were made using a Student *t* test for repeated measures. Differences are considered significant if $P < .0125$.
Abbreviations: HR, heart rate; MAP, mean arterial pressure.

skin incision, and abdominal insufflation) and the addition of opioid analgesia (0.5 mg IV hydromorphone).

This is the largest and first North American study assessing changes in HR variability during clinically relevant intraoperative events. Diverse anesthesia practices in different geographic regions may affect results. This is also the first study to assess intraoperative high-frequency HR variability index changes after the administration of hydromorphone. The results presented here are in keeping with several previous smaller studies (15–25 subjects per study) assessing the relationship of changes in high-frequency HR variability with nonclinical (tetanic stimulation) and/or clinical nociceptive events (laryngeal mask airway insertion, intubation, skin incision, and abdominal insufflation) during laparoscopic abdominal surgery, craniotomy, or undefined elective surgeries.[16,19,28] In 2 of these studies, HR and blood pressure did not change during these events, while in one, both HR and blood pressure changed inversely to the change in the high-frequency HR variability index. Results from the study described here are similar to those in the latter study; HR changed inversely to the change in high-frequency HR variability index during direct laryngoscopy, incision, and insufflation, and blood pressure changed inversely to the change in high-frequency HR variability index during skin incision and insufflation.

While stimulation of the parasympathetic nervous system may occur from peritoneal stretch during abdominal insufflation, in this study, HR increased after insufflation indicating that insufflation may not have had a dramatic effect on the parasympathetic nervous system and thus high-frequency HR variability index.

More recent studies have assessed how the intraoperative use of high-frequency HR variability index may affect outcomes. Intraoperative opioid analgesic titration based on high-frequency HR variability index (maintained ≥50) was found to decrease intra- or postoperative opioid use. In one study, adult patients undergoing lumbar discectomy or laminectomy were randomly assigned to intraoperative groups, a standard clinical control group, and a high-frequency HR variability index maintenance group. Those patients receiving intraoperative high-frequency HR variability index–guided (maintained between 50 and 70) opioid administration had decreased pain scores and opioid requirements in the postanesthesia care unit.[25] In the other study, patients undergoing bariatric surgery were randomly assigned to similar groups. Patients receiving intraoperative high-frequency HR variability index–guided opioid administration received less intraoperative opioid but had no differences in postoperative outcomes (pain medication use, pain scores, nausea, and vomiting).[26]

We speculate that mean high-frequency HR variability index values that change by small amounts (<10%) after transient clinical events (direct laryngoscopy) may not be clinically relevant. However, instantaneous high-frequency HR variability index (skin incision, insufflation, hydromorphone administration) and mean high-frequency HR variability index (insufflation) values that change by greater amounts (>10%) and cross an index value of 50 (skin incision, insufflation) may be clinically relevant. High-frequency HR variability index is an HR variability analysis method that evaluates the respiratory sinus arrhythmia component of the parasympathetic activity. Its evaluation, therefore, requires ventilation (spontaneous or mechanical), and high-frequency HR variability index analysis during apnea phases is questionable. The lack of pH before intubation may explain the high-frequency HR variability index changes from direct laryngoscopy.

This study has several limitations. While there were statistically significant changes in high-frequency HR variability index with intraoperative nociceptive events, it is not yet clear what absolute or percent change is clinically relevant. A representative graph of instantaneous high-frequency HR variability index and mean high-frequency HR variability index is shown in Figure 3. Fluctuations in values occurred intraoperatively at times when it was not apparent that clinically relevant interventions occurred. Thus, while our study shows statistical correlation with nociceptive events and the administration of opioid analgesic, it is not clear that it would always be straightforward to determine when a patient requires intervention based on this monitor. This study was not designed to investigate whether intraoperative intervention based on high-frequency HR variability index values alter patient outcomes. While a small number of studies have assessed the value of intraoperative high-frequency HR variability index, even if changes correspond to intraoperative events, it remains to be seen whether interventions based on these values alter patient outcomes in a clinically meaningful manner. The intraoperative anesthetic

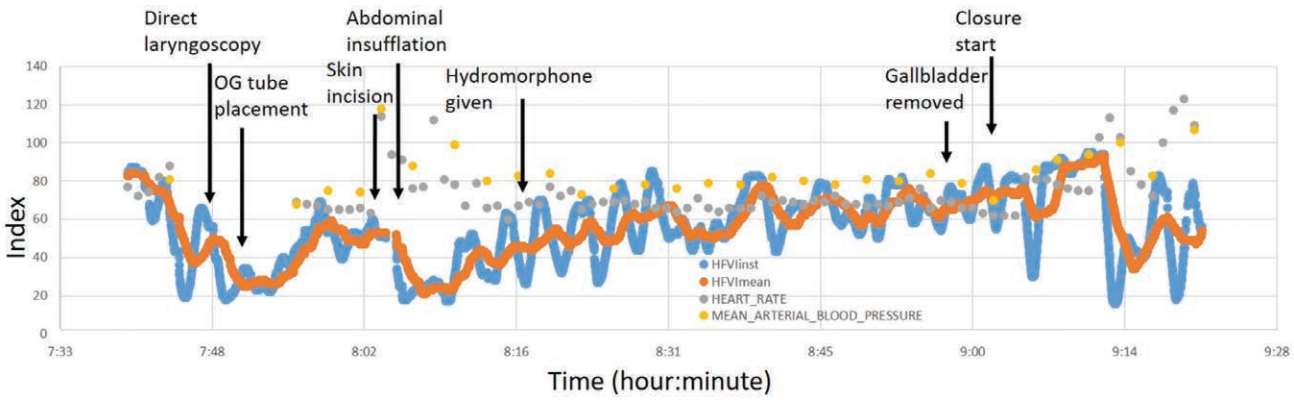

Figure 3. Example graph of the $HFVI_{inst}$, $HFVI_{mean}$, heart rate, and mean arterial pressure over the course of laparoscopic cholecystectomy from a single subject. $HFVI_{inst}$ indicates instantaneous high-frequency heart rate variability index; $HFVI_{mean}$, mean high-frequency heart rate variability index; OG, orogastric tube placement.

management was not controlled because this study was designed to be as clinically relevant as possible. It is conceivable that small changes in the anesthetic management from provider to provider affected the study results. Depth of anesthesia may affect high-frequency HR variability index values; intraoperative, electroencephalogram-based depth of anesthesia data were not collected for this study. However, MAC values were 1.0–1.1 during incision, insufflation, and hydromorphone administration suggesting adequate depth of anesthesia.

While high-frequency HR variability index could potentially be used to attain accuracy in determining the balance between nociception and analgesia in patients under general anesthesia during virtually any type of surgery, it remains to be seen if intraoperative high-frequency HR variability index use affects patient outcomes. If its intraoperative use is found to improve postoperative pain parameters (pain scores and analgesic use), it might be best utilized for surgeries with higher risk of poorly controlled postoperative pain (ie, obstetric, orthopedic, and general surgeries).[36]

CONCLUSIONS

This study shows that in adult patients undergoing general anesthesia during laparoscopic cholecystectomy, changes in high-frequency HR variability index reflect alterations in the balance between nociception and analgesia. High-frequency HR variability index might be used intraoperatively to appropriately titrate analgesia for individual patients. Further testing is necessary to determine if the intraoperative use of high-frequency HR variability index changes patient outcomes.

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DISCLOSURES

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Conflicts of Interest: Mdoloris Medical Systems provided heart rate variability index monitors and skin electrodes.
Name: Joshua R. Segaran.
Contribution: This author helped with patient recruitment, data collection, writing, and final approval of the manuscript.
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