A Beat-by-Beat Cardiovascular Index, CARDEAN: A Prospective Randomized Assessment of Its Utility for the Reduction of Movement During Colonoscopy

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BACKGROUND: We sought to determine whether online use of a beat-by-beat cardiovascular index, CARDEAN® (Alpha-2, Lyon, France), modifies the incidence of patient movement during colonoscopy under anesthesia.

METHODS: Monitoring included an electrocardiogram, oscillometric and noninvasive beat-by-beat arterial blood pressure, O_2 saturation, bispectral index (BIS), and CARDEAN. CARDEAN consists of beat-by-beat Finapres® (Ohmeda, Madison, WI) combined with an algorithm that detects hypertension followed by tachycardia and produces an index scaled 0 to 100. The anesthesiologist was denied access to Finapres and CARDEAN. Propofol was adjusted to keep $40<BIS<60$. Alfentanil 3.5 $\mu g \cdot kg^{-1}$ was administered according to conventional signs (tachycardia, hypertension, and movement), unless the patient had signs of brady/apnea or Spo_2 $<95\%$. One hundred fifty-nine patients presenting for colonoscopy under propofol anesthesia were prospectively randomized to (i) control: no other intervention, or (ii) CARDEAN: in addition to conventional signs, an observer instructed the anesthesiologist to administer alfentanil when CARDEAN was >60. The primary outcome was the number of observed movements.

RESULTS: Data were analyzed in 146 patients (control: 75; CARDEAN: 71). The doses of propofol and alfentanil were similar in both groups. When BIS was <60, movements were less frequent in the CARDEAN group (3.3 movements/100 min [2.3–4.8]) than in the control group (6.7 [5.3–8.5]) (odds ratio: 0.5 [0.32; 0.76], $P = 0.001$). During the first 10 minutes of the procedure, the incidence of movements was 38% and 59% in the CARDEAN and control groups, respectively ($P = 0.04$).

CONCLUSION: With BIS <60, CARDEAN-guided opioid administration is associated with a reduction of 51% of clinically unpredictable movements in unparalyzed patients undergoing colonoscopy. More studies are required to refine the role of CARDEAN in surgical settings. (Anesth Analg 2010;110:765–72)

In guiding drug dosing to provide optimal anesthetic conditions, intraoperative recall appears reduced when bispectral index (BIS) is used.[1–3] Neuromuscular blockade is adequately monitored using a neuromuscular twitch monitor and the train-of-four technique. By contrast, currently available cerebral function monitors have not demonstrated an ability to successfully monitor the third component of anesthesia, intraoperative nociception.[4] Conventional sympathetically mediated signs (i.e., hypertension measured every few minutes and tachycardia assessed continuously) as a measure of intraoperative nociception have not been shown to be an adequate monitor for the titration of opioid analgesics for the prevention of movement on a second-by-second basis. This lack of a monitor to determine adequate therapeutic intervention for the management of intraoperative nociception potentially increases the use of neuromuscular blockade to avoid movement linked to intraoperative nociception or may result in the overdosing of opioid analgesics.

A cardiovascular depth of anesthesia index, CARDEAN® (Alpha-2, Lyon, France), is an algorithm based on beat-by-beat arterial blood pressure (BP) changes followed by tachycardia, which estimates online the intraoperative nociception. CARDEAN 1.0 was written through the retrospective analysis of a database including 40 unparalyzed patients undergoing orthopedic surgery to achieve

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100% sensitivity for movement prediction.[5] The present prospective randomized controlled clinical trial was designed to assess the possibility of predicting online movement during surgery using this prototype software, CARDEAN 2.0 (Appendix, see Supplemental Digital Content 1, http://links.lww.com/AA/A73).[6] After performing a pilot study to confirm its potential utility,[7] we designed a larger study with patients undergoing colonoscopy, alone or combined with gastroscopy. Because movements are not a concern for the endoscopist in this setting and because it would be important to establish the utility of this index where movement is not critical to the outcome, we chose these procedures for our initial large-scale utility trial. Thus, the main outcome measure was not the clinical usefulness per se but testing the software under real-life conditions. The primary end point was the possible reduction of movement in the CARDEAN group after the administration of alfentanil when CARDEAN crossed a threshold.

METHODS

Patients

After receiving approval from our IRB and written informed consent, 159 ASA physical status I or II patients (aged 20–75 years), presenting for endoscopy (colonoscopy ± gastroscopy) in a strictly supine position, under general anesthesia, were enrolled. No patient had any history of cardiovascular (including nonsinus rhythm), endocrinologic, neurologic, and autonomic diseases or was taking any drug for the treatment or management of such pathologies. No patient included in previous studies[5,7] was included. Patients were monitored with an electrocardiogram, oscillometric BP, pulse oximeter (Spo_2), and capnograph (end-tidal CO_2 through an anesthesia mask; Siemens SC 7000, Erlangen, Germany). Respiratory rate (Biopac RSP 100B, Goleta, CA), BIS (XP4.0, Aspect, Newton, MA; refreshment of display set at 30 seconds), noninvasive beat-by-beat BP[8] (Finapres 2300, Ohmeda, Madison, WI), and CARDEAN 2.0[5] were recorded for all patients. The Finapres was levelled to the heart on one arm, which was warmed throughout surgery using an air warmer device (Bair Hugger®, Arizant Healthcare, Eden Prairie, MN) and a blanket.

Anesthesia

Patients were not premedicated. Induction of anesthesia was performed with propofol (initial effect-site concentration = 4 $\mu g \cdot mL^{-1}$; Master TCI Diprifusor®-Zeneca, Fresenius-Kabi, Bad Homburg, Germany).[9] Later, the effect-site concentration was adjusted to achieve $40 < BIS < 60$ and stable circulatory variables (systolic BP [SBP] assessed on oscillometric BP measured every 5 minutes and continuous heart rate [HR] observed on the monitor to be maintained both within ±20% of perioperative values). Patients were allowed to breathe spontaneously. Spo_2 >95% was maintained with oxygen supplementation and/or jaw lift, insertion of an airway cannula, or positive pressure ventilation of the lungs via a facemask, as needed. Endotracheal intubation was not performed, and when clinically indicated, patients were excluded from the study. The end of induction was defined as the combination of BIS <60 and immobility lasting >1 minute after forceful jaw lift by the same 2 anesthesiologists (PFW and CL). After induction, if propofol alone was not sufficient to reach immobility after jaw lift, an alfentanil bolus (3.5 $\mu g \cdot kg^{-1}$) was administered. The study duration was defined as the interval between the beginning of the procedure (gastroscopy: introduction of the probe into the mouth after completion of induction according to set criteria; colonoscopy: lubrication of the anal margin) and the beginning of the withdrawal of the colonoscope from the right colon. To accelerate emergence, propofol infusion was discontinued immediately after the beginning of the withdrawal of the colonoscope. Patients were randomized to 2 groups:

1. Control: (i) Propofol was titrated to achieve a $40 < BIS < 60$. Given the brevity of the procedure, sometimes BIS reached values between 25 and 40 or >60. When hypotension or bradycardia occurred (20% decrease below presurgical baseline), the propofol concentration was reduced as long as BIS was maintained ($40 < BIS < 60$). When tachycardia or hypertension (20% above presurgical baseline) occurred, the propofol concentration was increased, maintaining BIS >40 and <60. (ii) When the propofol increase failed, after 5 minutes, to maintain HR and SBP within 20% of the baseline value, alfentanil (3.5 $\mu g \cdot kg^{-1}$) was administered. If any movement occurred, alfentanil (3.5 $\mu g \cdot kg^{-1}$) was also administered. Additional boluses of alfentanil were administered if movement persisted after 1 minute. When repeated movements occurred, a movement was considered distinct from the previous movement when it occurred at least 1 minute after the end of the previous movement. Alfentanil was administered only if ventilation was deemed adequate (respiratory rate ≥5 breaths/min, Spo_2 >95%). The procedure was not stopped if a movement occurred. When ventilation was inadequate, while BIS <60, movement was tolerated without any increase in propofol concentration or alfentanil administration.
2. CARDEAN: (i) Propofol was administered as in the control group. (ii) Alfentanil 3.5 $\mu g \cdot kg^{-1}$ was administered if conventional signs occurred as in the control group or if an observer (AC) warned the anesthesiologist that the CARDEAN index crossed a predefined threshold (≥60). The anesthesiologist, the gastroenterologist, and his nurse were all blinded to both the Finapres and the CARDEAN readings throughout the study. Only the observer not involved in anesthesia administration or in the procedure had access to the CARDEAN and Finapres data. Thus, the anesthesiologist was double blinded to group assignment up to the study end in the control group and until the first notified CARDEAN ≥60 in the CARDEAN group, and the gastroenterologist and his nurse were double blinded from assignment up to the end of study in both groups. First, the observer discreetly touched the shoulder of the anesthesiologist when CARDEAN crossed the threshold. Second, the room was darkened as is common in the endoscopy setting. Third, the gastroenterology team concentrated on the video screen to perform the

procedure. A movement was defined as a head, limb, or finger movement, grimacing, or a groan. Swallowing, cough, hiccup, and yawn were not considered movements. The gastroenterologist, his nurse, the anesthesiologist, and the observer were all instructed to look for the patient's movements from the start of endoscopy until 2 minutes after propofol discontinuation. When any of these 4 individuals observed any movement, the anesthesiologist was warned. The anesthesiologist made the final determination whether or not this was an actual movement. All movements were immediately collected on a data sheet by the observer. The total number of movements was verified and recorded by the anesthesiologist immediately after the end of procedure. Adverse events were defined as follows: (i) tachycardia: HR >90 bpm; (ii) bradycardia: HR <40 bpm; (iii) hypertension: SBP >140 mm Hg measured by oscillometric method; (iv) hypotension: SBP <90 mm Hg; (v) hypoventilation: respiratory rate <5 breaths/min with the jaw lifted; (vi) apnea: no observed breathing for >20 seconds even if the jaw was lifted; and (vii) desaturation: Spo_2 <95%.

Data Analysis

The maximal BIS value was calculated on 1-minute analysis periods. In the absence of movements or alfentanil boluses, the 1-minute periods started 2 minutes before the start of endoscopy and were adjacent to each other until not >2 minutes after propofol discontinuation. If an event such as movement or alfentanil bolus occurred, the 1-minute periods were all adjacent and occurred before each event and after the last event. Three types of movements were excluded from analysis (Fig. 1): (i) when cardiovascular and/or BIS signals were interrupted or of poor quality 2 minutes before a movement; (ii) when a movement occurred spontaneously before the start of endoscopy compatible with incomplete induction; or (iii) when the administration of an alfentanil bolus was not performed before the movement despite CARDEAN warning because of apnea, slow respiratory rate, or desaturation. The remaining movements were counted separately as a function of BIS: (i) movements with BIS ≥60 <1 minute before movement could be linked to cortical arousal, not to nociception. The normalized incidence of these movements per time unit was calculated for each patient by dividing the number of these movements by the total number of 1-minute periods with BIS ≥60; (ii) movements with BIS <60 >1 minute before the movement was considered a withdrawal movement linked to nociception. The normalized incidence of these movements per time unit was calculated for each patient by dividing the number of these movements by the total period when BIS <60; (iii) among movements preceded by BIS <60 for >1 minute, 2 categories of movements were distinguished: movements followed by an increase of the BIS ≥60 within 1 minute and movements followed by the BIS <60 within 1 minute; and (iv) the beginning of colonoscopy was considered a standardized stimulus: among movements preceded by BIS <60 for >1 minute, the normalized incidence of movements occurring within 10 minutes after the beginning of the colonoscopy was also calculated.

Receiver Operating Characteristic Analysis

Because CARDEAN patients were injected with alfentanil, after following observation of CARDEAN ≥60, the ability of CARDEAN to predict movement could not be tested using a receiver operating characteristic (ROC) in CARDEAN patients. Thus, ROC analysis was restricted to the control group. Given the large number of events and/or cortical arousals (BIS ≥60) over a short procedure, the following periods were excluded from analysis: (i) periods ≤5 minutes if any event (induction of anesthesia, movement, cough, etc.) occurred before a cough, and all the adjacent 1-minute periods during the cough; (ii) periods ≤5 minutes if any event occurred before a movement preceded by BIS ≥60 and all the adjacent 1-minute periods during this movement; (iii) periods ≤5 minutes if any event occurred before a propofol bolus or an increase by >10% of the propofol concentration imposed by an increase of the BIS ≥60, 1 minute during and 1 minute after the propofol bolus, or concentration increase. In the remaining periods, the maximum of the CARDEAN index was computed on 5-minute periods or at least 2-minute periods if any event occurred before a movement, and on 2-minute periods when no movement was observed. All the periods lasting <2 minutes were discarded. A positive event was considered the occurrence of movement. A negative event was considered the absence of movement. The delay between the CARDEAN ≥60 and the movement was measured in the control group for the 12 movements without any interfering event (induction of anesthesia, movement, cough, etc.) 5 minutes before the movement. Apneas after administration of propofol alone were counted separately from apneas immediately after alfentanil. The doses of propofol and alfentanil (only for those patients having received alfentanil) were normalized to the study duration and patient's weight.

Sample Size

The number of patients needed was calculated according to the result of a pilot study[7] (n = 22 patients) showing a reduction of 65% of the incidence rate of movements in the CARDEAN group. Control group: incidence rate (normalized to duration of procedure; Poisson model; 95% confidence interval [CI]; number/100 min; raw data) 5.4 movements per 100 patient × minutes; CARDEAN group: 1.9 movements per 100 patient × minutes. For an α risk of 5% and a statistical power of 90%, 73 patients were to be included in each group. Secondary end points (propofol or alfentanil dose, brady/tachycardia, hypo/hypertension, apnea/hypoventilation, and duration to emergence) were not considered. The alfentanil dose was optimized to 3.5 $\mu g \cdot kg^{-1}$ to suppress movement with minimal respiratory and circulatory side effects.

Statistical Analysis

Patients at inclusion were compared between groups using the Student t test or a Mann-Whitney nonparametric test when the distribution was Gaussian or non-Gaussian, respectively (Stata 10.0, StataCorp LP, College Station, TX).

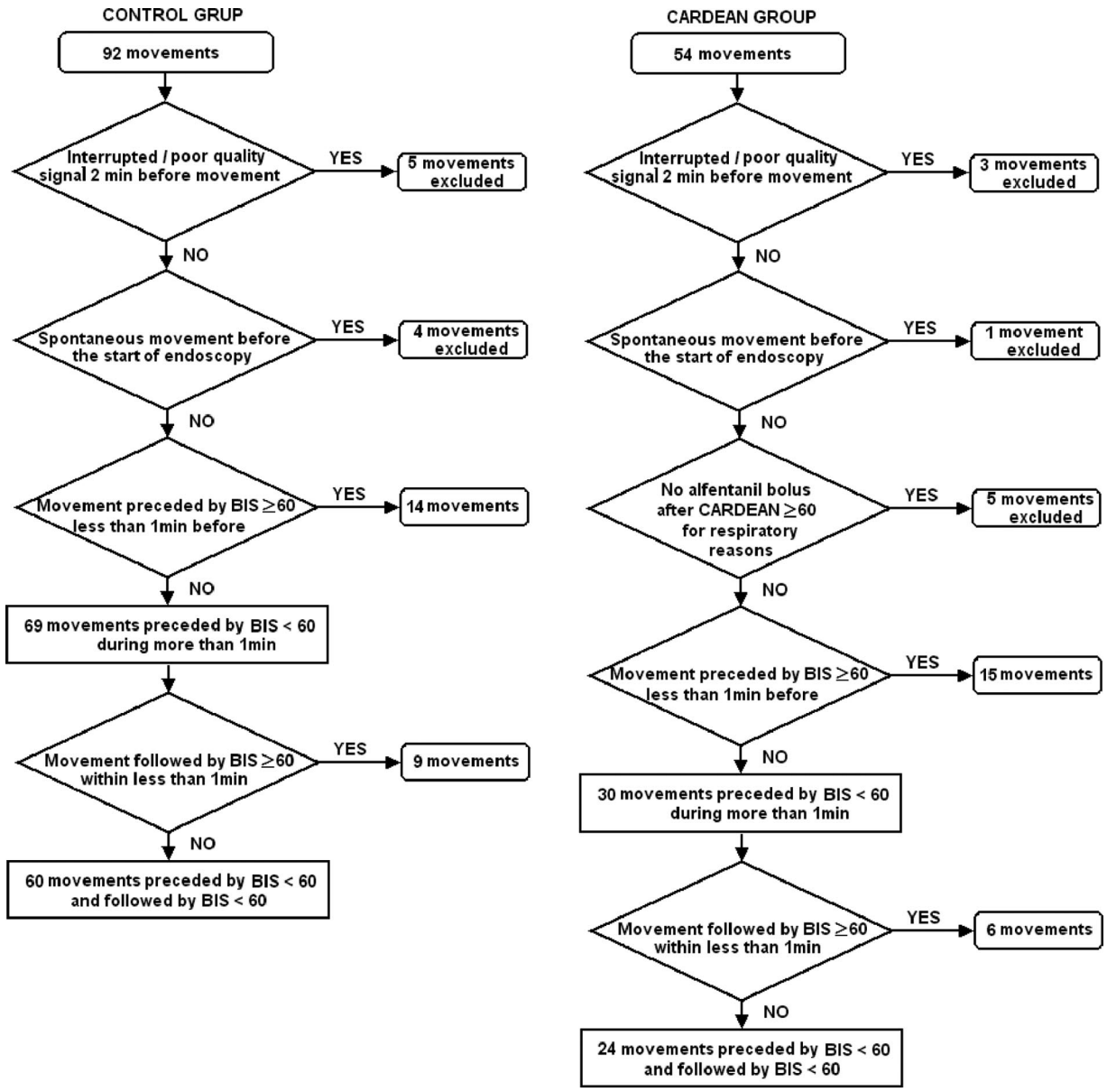

Figure 1. Flow chart for inclusion and exclusion criteria for movements observed upon endoscopy in control and CARDEAN (cardiovascular depth of anesthesia) groups.

Skewness was determined by observation of raw data.[10] χ^2 test was used for categorical characteristics. The number of movements occurring during the procedure (total number, movements after exclusions, movements preceded by BIS ≥60, movements preceded by BIS <60, movements preceded by BIS <60 and occurring within 10 minutes after beginning of colonoscopy [standardized stimulus]) was compared between groups using a Poisson regression, considering the duration of the procedure for each patient. The odds ratio with its 95% CI was used to quantify the CARDEAN effect on the risk of occurrence of movement. Side effects were analyzed as binary variables (at least 1 event versus no event) and compared between groups using a logistic regression adjusted on duration of the study period. ROC analysis was performed using SPSS 17.0 (SPSS, Chicago, IL). The area under the ROC curve and its 95% CI were computed to quantify the ability of CARDEAN to predict movement. Data are expressed as mean ± SD or median (range) where appropriate. $P < 0.05$ was considered significant.

RESULTS

Thirteen patients were excluded for the following reasons: broncho- or laryngospasm or severe desaturation leading to endotracheal intubation (2 patients); severe desaturation in a tracheotomized patient (1 patient); intestinal perforation and endotracheal intubation (1 patient); poor cardiovascular signals (2 patients); dose of alfentanil not in agreement with preset dose (2 patients); and technical difficulties with the online display of the CARDEAN 2.0 version led us to exclude 5 patients in the CARDEAN group, which had erroneously received alfentanil without

Table 1. Demographics		
	Control	CARDEAN
Demographics		
n	75	71
Age (y)	52.1 ± 12.6	51 ± 12.4
Weight (kg)	72.8 ± 14.8	69.8 ± 15.1
Body mass index (kg/m^2)	24.8 ± 3.4	24.6 ± 4.0
Gender (male/female), % (*n*)	60/40 (45/30)	45/55 (32/39)
Combined gastroscopy and colonoscopy, *n* (%)	23 (30.7%)	14 (19.7%)

CARDEAN ≥60. Thus, 146 patients underwent final analysis (control: $n = 75$; CARDEAN: $n = 71$; Fig. 1). No differences were observed with respect to age, weight, body mass index, gender, colonoscopy alone versus gastroscopy combined with colonoscopy, duration of endoscopy, normalized doses of propofol or alfentanil, hypoventilation, hypoxia, hypo/hypertension, brady/tachycardia, and duration of emergence (Tables 1 and 2). In most patients, a 25 < BIS < 40 was observed at some intervals (duration not significant [NS] between groups).

Movements

The number of movements was lower in the CARDEAN group (details for raw data; data after excluded movements; BIS <60 before movement; and movement after standardized stimulus; Table 3 and Fig. 2A). When only data in which BIS <60 before movement (i.e., adequate hypnosis) were considered, a 51% reduction was observed in the CARDEAN group ($P = 0.001$; Fig. 2A and Table 3). When the 10 minutes after the beginning of colonoscopy are considered as a standardized stimulus, a 40% reduction in movements was observed ($P = 0.04$; Table 3). In the control group, CARDEAN threshold (>60) was crossed 96 ± 77 seconds (range: 12–297 seconds, $n = 12$ movements) before the movement actually occurred. For CARDEAN = 60, a ROC curve (Fig. 2D) for the control group showed a sensitivity = 30% (19%–43%), specificity = 86% (82%–90%), positive predictive value = 26% (17%–37%), and negative predictive value = 88% (83%–91%). The area under the ROC curve was 0.68 (0.61–0.75) ($P < 0.001$).

Opioid Analgesics

During induction, 14 patients received alfentanil (NS between groups). The normalized doses for propofol and alfentanil were not different. During the procedure, the number of patients having received at least 1 bolus of alfentanil was significantly higher in the CARDEAN group (control: 61.3%; CARDEAN: 83.1%, $P = 0.003$; Table 2). In the CARDEAN group, only 3 movements occurred within 5 minutes after CARDEAN-guided alfentanil administration as opposed to 14 movements occurring in the control group (CARDEAN: 62 boluses, recurrence rate = 3 of 62 = 4.8%; control: 78 boluses, recurrence rate = 14 of 78 = 17.9%; $P = 0.015$).

DISCUSSION

We tested the utility of the CARDEAN index to guide alfentanil administration to prevent movement during colonoscopy/gastroscopy when BIS was maintained between 40 and 60 using target-controlled infusion propofol. The use of the CARDEAN index reduced the number of movements by 51% during endoscopy (Table 3; Fig. 2, A and D). This confirms previous retrospective[5] and pilot prospective[7] studies. In the CARDEAN group, more patients presented no movement at all, and fewer patients presented many movements (Fig. 2, B and C). Movements occurring with a BIS ≥60 are differentiated from movements occurring with a BIS <60. Thus, CARDEAN in combination with the BIS may be able to differentiate between inadequate intraoperative antinociception and cortical arousal. The CARDEAN threshold was crossed at intervals allowing sufficient time for an effective intervention to abort movement (present data: 12–297 seconds; previous data: 15–274 seconds[5]).

More patients received alfentanil in the CARDEAN group. However, the normalized dose of alfentanil administered did not reach significance between groups; the difference does not lie in the total amount of opioid analgesics administered but rather in its administration only when and if needed before movement. The recurrence of movement was 5% in the CARDEAN group versus 18% in the control group. Thus, preemptive administration of opioid analgesics seems superior to administration after movement. Although the normalized dose of alfentanil administered did not reach significance between groups, a trend to a higher incidence of apnea was observed in the CARDEAN group ($P = 0.06$, Table 2), a result of reducing the incidence of movement when patients' lungs are not ventilated. However, the aim of this study was not to increase immobility per se in the endoscopy setting but rather to refine CARDEAN for further application in the setting of patients under mechanical ventilation presenting for operations with more intense noxious stimuli.

Does absence of movement imply analgesia? Minimal alveolar concentration was defined on the basis of the absence of a withdrawal movement upon a standardized stimulus in unparalyzed animals.[11] Thus, absence of movement should be restricted to infer absence of intraoperative nociception. By contrast, proper analgesia requires addressing the subjective experience of an awake patient. When BIS was <60, the reduction in movement suggests that these movements were not attributable to cortical arousal but to nociception. If the analysis excludes movements preceded by BIS <60 and followed by BIS >60, the reduction of movement observed in the CARDEAN group was still observed (Table 3). Besides, these movements followed by BIS ≥60 are not necessarily linked to a late detection of a cortical arousal: the electromyogram may affect BIS.[12]

Limitations

In the CARDEAN group, the anesthesiologist was double blinded only up to the first CARDEAN-guided injection of alfentanil. Further administration of alfentanil was guided both by CARDEAN and movement. By contrast, the gastroenterologist remained totally blinded throughout the study in both groups. The only possible biases in the CARDEAN group were (i) underestimation of the number

Table 2. Anesthesia

	Control	CARDEAN	$P < 0.05$	Odds ratio (95% CI)[a]
n	75	71		
Anesthesia				
Duration of endoscopy, median (min–max)	13.9 (4–44)	12 (4–56)		
Propofol (normalized dose, $mg \cdot kg^{-1} \cdot min^{-1}$)	0.54 ± 0.31	0.48 ± 0.22		
Alfentanil during endoscopy (yes/no)	46/29	59/12	*	
Alfentanil (normalized dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.42 ± 0.23	0.50 ± 0.25		
Side effects, *n* (%)				
Apnea	6 (10)	13 (22.4)		2.7 (0.9–7.9)
Apnea associated with propofol	2 (3.3)	3 (5.2)		
Hypoventilation	26 (43)	32 (55)		1.6 (0.8–3.3)
Desaturation ($SpO_2 < 95\%$)	19 (28.4)	13 (20.3)		0.7 (0.3–1.6)
Hypotension	8 (11.9)	7 (10.9)		1.2 (0.4–3.8)
Hypertension	2 (3)	1 (1.6)		0.5 (0.04–5.8)
Bradycardia	1 (1.5)	0		
Tachycardia	2 (3)	3 (4.7)		4.8 (0.4–53.6)

CI = confidence interval.
[a] Control group as reference.

Table 3. Movements

	Control	CARDEAN	$P < 0.05$	Odds ratio[a]
n	75	71		
Number of patients presenting at least 1 movement, *n* (%)	50 (66.7%)	38 (53.5%)		
Incidence rate[b] (number/100 min; raw data)	7.52 (6.13–9.21)	5.0 (3.8–6.5)	*	0.67 (0.48–0.91)
Incidence rate[b] (number/100 min; data after excluded movements)[d]	6.8 (5.5–8.4)	4.2 (3.1–5.6)	*	0.61 (0.42–0.88)
Duration of endoscopy with BIS <60 (min)	13.3 (1.8–53)[c]	9.4 (2–37)[c]		
Number of movements with BIS <60 before movement	69	30		
Incidence rate[b] (number/100 min with BIS <60 before movement)	6.7 (5.3–8.5)	3.3 (2.3–4.8)	*	0.5 (0.32–0.76)
Number of movements with BIS <60 before movement and BIS ≥60 after movement (% of the movements)	9 (13%)	6 (20%)		
Number of movements with BIS <60 before movement and occurring within the first 10 min of colonoscopy	44	27		
Incidence rate[b] (number/100 min with BIS <60 before movement within the first 10 min of colonoscopy)	8.6 (6.4–11)	5.2 (3.6–7.6)	*	0.61 (0.36–0.98)

BIS = bispectral index.
[a] Control as a reference; odds ratio (95% confidence interval).
[b] Normalized to duration of procedure (Poisson model; [95% confidence interval]).
[c] Median [min–max].
Movement: head, limb, or finger movement, grimacing, groan.
[d] Excluded movements: (i) poor quality signals, (ii) spontaneous movements before beginning of procedure, (iii) alfentanil not injected due to ventilatory reason.

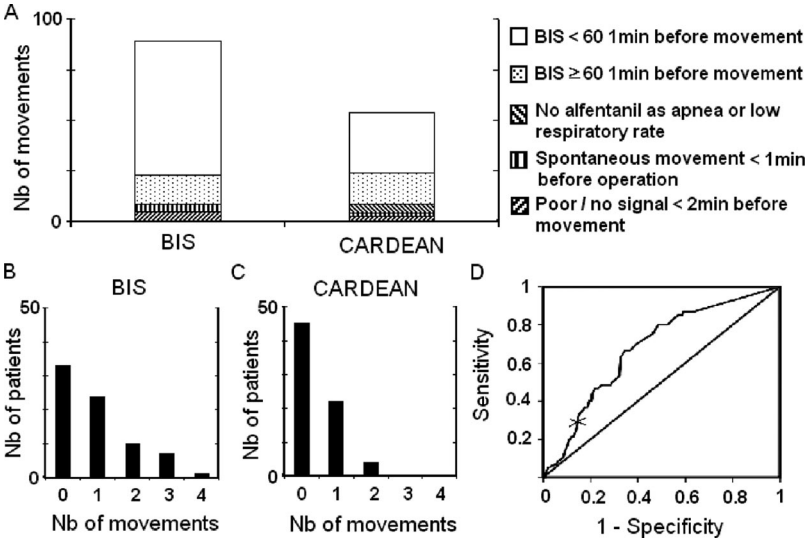

Figure 2. Movements. A, Distribution of movements. Movements preceded by a bispectral index (BIS) <60 at least 1 minute before the movement (no hatching) were presumably linked to nociception (control: 69 movements; CARDEAN: 30 movements). When BIS was <60, movements normalized to the duration of procedure were reduced by 51% (control: 6.7 [95% confidence interval, 5.3–8.5]; CARDEAN: 3.3 [2.3–4.8]). B and C, Movements preceded by a BIS <60 at least 1 minute before the movement for each patient throughout study (B) and within 10 minutes after beginning of colonoscopy considered a standardized stimulus (C). D, Receiver operating characteristic curve for the prediction of movement by CARDEAN in the control group. The cross indicates the sensitivity (*y* axis) and specificity (*x* axis) for CARDEAN = 60.

of movements (however, the gastroenterologist was totally double-blinded), and (ii) increase in the propofol doses in the CARDEAN group (however, the doses were similar). A truly double-blind prospective trial will be possible only when CARDEAN will automatically guide the administration of the opioid analgesics. Other trials dealing with BIS

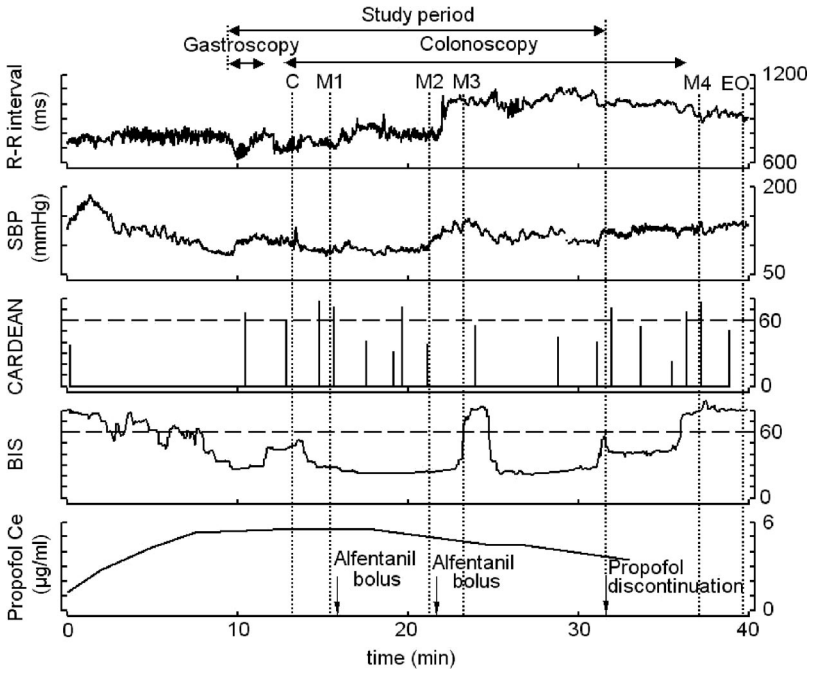

Figure 3. CARDEAN and bispectral index (BIS) in a control patient during colonoscopy. Top to bottom: R-R interval, noninvasive beat-by-beat systolic blood pressure (SBP), CARDEAN and BIS (threshold = 60), and propofol effect-site concentration (Propofol Ce). C = cough; M1 to M4 = unexpected movements, EO = eyes opening to command. M3 was not followed by an alfentanil bolus; alfentanil had been administered approximately 1 minute before M3. M1 and M2 were preceded by BIS <60 during the 1-minute period before the movement, which stopped after the alfentanil bolus. M1 and M2 were associated with CARDEAN >60 (presumed intraoperative nociception). M3 was preceded by BIS ≥60 (presumed cortical arousal) during the 1-minute period before M3 and occurred despite an alfentanil bolus approximately 1 minute before. Neither increased SBP nor heart rate was apparent before M1 and M2. Increased BIS variability was not apparent before M2. CARDEAN may predict movements not predicted by BIS or by conventional signs. M4 occurred after the end of study and was not included in the analysis.

were not truly double-blind.[1–3,13] This did not invalidate their results. Given the technological limitations, the design is reasonably valid. Hypnosis was set to 40 < BIS < 60. Given the highly unstable procedure, 25 < BIS < 40 was observed (NS between groups). Further trials should use automated procedures[14] to drive propofol administration within set BIS limits during longer procedures. A pilot study[7] allowed the calculation of a sample to show only a reduction in intraoperative movement. Thus, no inference can be drawn beyond movement. We only looked for intraoperative movements under real-life conditions. Thus, further studies should evaluate the performance of CARDEAN during a standardized stimuli, as in a minimal alveolar concentration study.[11] However, if the beginning of colonoscopy is considered a standardized stimulus similar to incision, movements under real-life conditions and standardized stimuli were reduced by CARDEAN (51% and 40%, respectively). To assess the clinical usefulness of CARDEAN will require more intense stimuli, e.g., during orthopedic or intraabdominal surgery. CARDEAN needs refinement because it offers no value between consecutive pillars (Fig. 3). Another unsolved problem is that after an increase of CARDEAN ≥60, a value <60 could be observed (see immediately before movement M2 in Fig. 3). If this value <60 is within 5 minutes after a CARDEAN ≥60, this value <60 does not invalidate the predictive power for movement of the CARDEAN value ≥60. Movements could be preceded by sympathetic bursts, leading to CARDEAN ≥60. However, after a sympathetic surge that indicates nociception and generates CARDEAN ≥60, sympathetic nervous activity may recede leading to CARDEAN <60 just before movement. Our subset of patients was highly homogeneous, in sinus rhythm, and without hypovolemia, hypothermia, or any elderly/coronary patient or patient treated with β-blockers or α-2 agonists. Obviously, CARDEAN needs further validation. CARDEAN works only in operating rooms equipped with a continuous noninvasive or invasive beat-by-beat BP monitor; the algorithm should be adapted to use existing sensors in the operating room. Finally, sensitivity needs to be much improved to allow for daily clinical use.

CARDEAN scrutinizes the small changes in SBP and HR occurring before hypertension and tachycardia conventionally observed by the clinician. The pressure increase followed by a bradycardia (baroreflex coupling) is transformed, by the somato-sympathetic reflex, into hypertension followed by tachycardia observed on line on a beat-by-beat basis.[15] CARDEAN is based anatomically and functionally on the projection of the pain pathways on the core circuitry of the sympathetic cardiac and vasomotor baroreflex.[16,17] Will CARDEAN detect 100% of intraoperative nociception? No, the hypertension-tachycardia underlying CARDEAN occurs only before 80% to 85% of observed movements (Cividjian, unpublished data). Will CARDEAN alone offer total monitoring of movement and intraoperative antinociception? No, movements M1 and M2 were predicted by CARDEAN ≥60 increases but not by BIS ≥60 (Fig. 3). Conventional signs do not allow assessment of depth of anesthesia as early as CARDEAN. By contrast, M3 was predicted by BIS ≥60 (i.e., cortical arousal) but not by CARDEAN ≥60. Thus, both BIS and CARDEAN need to be used in conjunction to predict movement.

In conclusion, when alfentanil administration was guided by an online beat-by-beat cardiovascular index, CARDEAN, in a prospective randomized manner during colonoscopy/gastroscopy, a 51% reduction of movements was observed in patients (n = 146) receiving similar doses of propofol and alfentanil. These data are encouraging and suggest improvement in the sensitivity of CARDEAN and its validation to guide opiate administration in patients receiving mechanical ventilation under a standardized surgical stimulus and operations with more intense noxious stimuli.

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DISCLOSURE

JYM and LQ received travel fees from Hôpital Desgenettes and CNRS. AC and LQ are shareholders in Alpha-2 Ltd. and hold the patent for CARDEAN. AC is a paid consultant of Alpha-2 Ltd.

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