Isolated Forearm Test: Replicated, Relevant, and Unexplained

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"…there are states of consciousness that do not fit conveniently into our understanding of being perfectly awake or perfectly asleep."

IT is a natural human tendency to internally construct the world around us largely as we learned to see it while growing up, just as it is our tendency to prefer simplified, intuitive constructs over ambiguous complexity. As anesthesiologists, we largely learned the binary concept that patients were either awake or asleep. Asleep was good, and awake was not so good. This elegant simplicity was both convenient and reassuring and enabled us to summarize the mysteries of anesthesia to patients without delving into the language and nuances of cognitive neuroscience. What our patients heard, and what we mostly intended them to hear, was that they would be asleep. Completely. Every time.

These binary divisions are no longer applicable.[1,2] It is now clear that there are states of consciousness that do not fit conveniently into our understanding of being perfectly awake or perfectly asleep. They are hiding in plain sight, well disguised, in part, because we instinctively assess behaviors as surrogates to decide whether a person is conscious or unconscious. We intuitively assume that a person behaving as though they are conscious actually is conscious and *vice versa*. This interpretation of behavior as signaling cognitive state is mostly reliable, but it is nonetheless flawed, and perhaps no more so than when drugs alter neural function to create states that do not occur naturally.

In this regard, the anesthesiologist's impression of whether patients were awake or asleep is confused because it has characteristically relied on probing their memory—a behavior for which consciousness is necessary but not sufficient. A patient who is under the influence of an amnesic drug such as a benzodiazepine interacts with the world with behaviors that suggest they are awake. However, on the following day, with no recollection of events, their behavior is grossly indistinguishable from what it would be had they been completely unconscious. What exactly is the nature of this state, and where does it fit along the good—not so good spectrum? If a patient is aware of an event but develops no memory of it, is this neutral or rather worse that being unconscious during those same events?

The current issue of Anesthesiology presents a study by Sanders, Gaskell *et al.*[3] that forces us to pointedly confront this question. The authors conducted an international, six-center study of 260 patients to assess responsiveness to command after intubation, using the isolated forearm technique (IFT). It is by no means the first study using the IFT, but it can lay claim to being the most methodologically robust. The incidence they report, using conservative criteria, is 4.6%. This is an order of magnitude less than the estimate of approximately 40% suggested by previous studies[1] and provides reassurance to assuage the uncomfortable prospect that nearly half of our patients possess some level of consciousness at a time when we assume they are distinctly otherwise. But 4.6% still represents a 20- to 50-fold increase over the incidence of *remembered* awareness reported in randomized controlled trials using the Brice protocol[4–6] and is approximately 1,000 times the incidence of spontaneously reported awareness.[7]

If we routinely informed our patients that there was a 1 in 20 chance that they would have some form of connected

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consciousness during their anesthesia, would their initial unease be relieved by next telling them that they would form no memory of it? Could we tell them, with intellectual confidence, that awareness not remembered is effectively the same as no awareness at all? Could we tell them that while they might not be completely unconscious, the state they will be in is not consciousness as they normally experience it?

Controversy arises with this question, in no small part fueled by our incomplete knowledge and misconceptions, which Sanders, Tononi *et al.*[1] captured elegantly in the title of a previous 2012 review: Unresponsiveness ≠ Unconsciousness. As our understanding of the mechanisms of anesthetic-induced unconsciousness unfold, it is not surprising that additional states of being emerge near the borders.[8–10] However, knowing of their existence mostly serves only to heighten the mystery and elusiveness of their nature. It is suggested, for example, that anesthetics can induce a state of being termed dissociated awareness or dysanesthesia.[11] Here, one is for all purposes awake during a period when being otherwise is expected yet unperturbed by this strange state of perception–sensation uncoupling. Dysanesthesia is a nascent construct open to question[12]: an exemplar of how it is expected and appropriate that, as our exploration of multi-modal states evolves, controversy will first surround whether a new entity exists. But as clinical relevance is considered, the question should then evolve into whether such an entity is desirable, or more relevantly does no harm. As new evidence mounts, new entities are finally incorporated in some fashion into an updated model of the world, much as physics continuously reveals to us strange things such as spooky actions at a distance.[13] Neurologists are coursing a similar path, investigating states of consciousness between awake and asleep on the basis of structural and functional changes in the brain.[14,15]

The study that Sanders, Gaskell *et al.*[3] present is an important replication, a milestone in objectively identifying evidence supporting a novel, intermediate state of consciousness, confirming multiple single-site studies from a small number of investigators reporting what some had argued were observations under contrived conditions. The current replication revealed an effect size smaller than that in previous reports, a phenomenon consistently observed across many spheres of research. Perhaps the most prominent discussion of diminishing effect size and nonreproducibility has been focused on the psychology literature,[16,17] which is of special relevance to the current study because the experimental method is in essence probing the neuropsychology of modulated consciousness. As a staggering 60% of well-regarded psychology studies cannot be replicated, the fact that Sanders, Gaskell *et al.*[3] have done so with IFT observations in a multicenter pragmatic trial puts this anesthetic-induced state of being on substantially more solid ground. Nonetheless, it must be noted that even a pragmatic IFT experiment introduces potential effects that may challenge the generalizability of the finding. The very act of informed consent may create an unusual Hawthorne effect, priming the patient for input from the external world during anesthesia. The use of muscle stimulation to test for nonparalysis may represent a priming stimulus infrequently present outside of the experimental setting, and the brain response to salient or primed stimuli can be greater than that to random stimuli.[18–20] The authors have demonstrated that a form of connected consciousness *is able* to occur during the early minutes of a general anesthetic but not that it routinely does. In this sense, the authors' statement that this is a conservative estimate of connected consciousness may not be as conservative as they contend.

If we can now accept that the IFT is a real, replicable phenomenon, it is time to move on to investigating the exact nature and implications of this mysterious state. One can now hope to apply the big hammers of systems neuroscience to understand what is going on in the brain, with the added advantage that, unlike equivalent investigations of the vegetative state,[21] the IFT provides a definitive behavioral response. But our curiosity to understand the neuroscience should not dwarf the need to evaluate the neuropsychology. We must look forward to the next phase of investigations with more objective data to decide whether this state is benign and to be expected in the natural course of anesthesia or whether it retains a potential for harm, at least until proven otherwise, as has been suggested by several investigators.[1,2,22,23] It may also be time to weigh and debate how a loss of the illusion of simplicity should modify the way we describe the anesthetic state to our patients and the expectations that we set.

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Incidence of Connected Consciousness after Tracheal Intubation

A Prospective, International, Multicenter Cohort Study of the Isolated Forearm Technique

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ABSTRACT

Background: The isolated forearm technique allows assessment of consciousness of the external world (connected consciousness) through a verbal command to move the hand (of a tourniquet-isolated arm) during intended general anesthesia. Previous isolated forearm technique data suggest that the incidence of connected consciousness may approach 37% after a noxious stimulus. The authors conducted an international, multicenter, pragmatic study to establish the incidence of isolated forearm technique responsiveness after intubation in routine practice.

Methods: Two hundred sixty adult patients were recruited at six sites into a prospective cohort study of the isolated forearm technique after intubation. Demographic, anesthetic, and intubation data, plus postoperative questionnaires, were collected. Univariate statistics, followed by bivariate logistic regression models for age plus variable, were conducted.

Results: The incidence of isolated forearm technique responsiveness after intubation was 4.6% (12/260); 5 of 12 responders reported pain through a second hand squeeze. Responders were younger than nonresponders (39 ± 17 *vs.* 51 ± 16 yr old; $P = 0.01$) with more frequent signs of sympathetic activation (50% *vs.* 2.4%; $P = 0.03$). No participant had explicit recall of intraoperative events when questioned after surgery (n = 253). Across groups, depth of anesthesia monitoring values showed a wide range; however, values were higher for responders before (54 ± 20 *vs.* 42 ± 14; $P = 0.02$) and after (52 ± 16 *vs.* 43 ± 16; $P = 0.02$) intubation. In patients not receiving total intravenous anesthesia, exposure to volatile anesthetics before intubation reduced the odds of responding (odds ratio, 0.2 [0.1 to 0.8]; $P = 0.02$) after adjustment for age.

Conclusions: Intraoperative connected consciousness occurred frequently, although the rate is up to 10-times lower than anticipated. This should be considered a conservative estimate of intraoperative connected consciousness. (ANESTHESIOLOGY 2017; 126:00-00)

EXPLICIT recall of intraoperative events after intended general anesthesia is rare (0.1 to 0.2%),[1–3] implying that anesthesia is a remarkably effective therapeutic intervention with a number needed to treat approaching 1 (1.002).[4] However, since anesthetics are effective amnesic agents, reliance on postoperative report of intraoperative events is unlikely to capture all events of intraoperative consciousness[4] and thus overestimate anesthesia's therapeutic effectiveness. Indeed, patients expect to be unaware of surgery during general anesthesia. The isolated forearm technique (IFT)[5] does not depend on explicit postoperative recall of events as a surrogate of consciousness,[4] providing real-time information about the presence of consciousness using the best available method: behavioral report.[6] The IFT captures evidence of intraoperative consciousness of sensory stimuli (so-called connected consciousness as the experiences are

What We Already Know about This Topic

- The frequency of intraoperative consciousness of sensory stimuli (connected consciousness) under general anesthesia is not known, but could be as high as 37%
- The isolated forearm technique is an established method for detecting connected consciousness during general anesthesia

What This Article Tells Us That Is New

- In a prospective, multicenter study of the incidence of connected consciousness in response to tracheal intubation in 260 anesthetized surgical patients, 4.6% had connected consciousness detected by the isolated forearm technique, none of whom had explicit recall
- Connected consciousness was more common in younger patients and those less deeply anesthetized as detected by depth of anesthesia monitors.

connected to the environment).[4,6] Hence, the IFT collects data on *clinically relevant* connected consciousness,[7] as subjects need to be aware of their sensory environment to hear the command. The IFT does not discriminate between disconnected consciousness (*e.g.*, dreaming) or unconsciousness, both of which may be considered acceptable states under anesthesia because they are not associated with awareness of surgery. One limitation of the IFT is that patients with connected consciousness may still not respond to the command despite hearing it (for example, due to impaired motivation or anesthetic actions on motor responses).[4] As such, the IFT represents a conservative estimate of connected consciousness.

Our review of previous studies of the IFT after a clinically relevant noxious stimulus, such as tracheal intubation or skin incision, identified that approximately 37% of patients report connected consciousness of the stimulus under general anesthesia (based on 13 studies).[4] If this estimate is correct, it would imply a number needed to treat of 1,587 for anesthesia, representing a very different therapeutic effectiveness compared to calculations based on explicit recall. However, many of the studies included in our review were small, single-center studies, with variable—and sometimes contrived or controlled—dosing of anesthetics reflecting only one hospital or provider or experimental protocol. To overcome these limitations, we conducted an international, multicenter, pragmatic study to establish the incidence of IFT responsiveness after tracheal intubation in routine practice (hence, the anesthetic technique was left to the discretion of the anesthesiologist). This is the first multi-institution collaboration investigating the use of the IFT and is the largest single study on the topic.[4] Our study benefits from greater internal validity than many previous studies with the methodologic advantage of having an adjudicator, who is independent of the clinical team, judge the IFT response. External validity is conferred by a cohort design recruiting from six international centers. We collected data on the incidence of IFT responsiveness before and after intubation and on variables that may be associated with the likelihood of responsiveness including patient and anesthetic factors.

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Materials and Methods

Ethics board approval was obtained locally at each site, and the study was registered at clinicaltrials.gov before commencement (NCT02248623). All patients provided written informed consent to participate in the study after a careful discussion of risks and benefits. All adult patients (older than 18 yr) undergoing general anesthesia with endotracheal intubation were considered eligible if they could follow the commands for the IFT test. Exclusion criteria included a contraindication to the IFT, such as the inability to have tourniquet on arm for the IFT (*e.g.,* lymphedema or operative site). Patients were recruited from August 2014 to August 2015 from six centers: University of Wisconsin (Madison, Wisconsin), Waikato Hospital (Hamilton, New Zealand), University Hospital RWTH Aachen (Aachen, Germany), University of Michigan (Ann Arbor, Michigan), University Medical Centre Groningen (Groningen, The Netherlands), and CHR Citadelle Hospital of Liège (Liège, Belgium).

Primary and Secondary Endpoints

The primary endpoint of this study was to observe the incidence of IFT responsiveness after intubation in a routine clinical setting. All clinical decisions, such as drugs, approach to intubation, and so forth, were left to the discretion of the attending anesthesiologist. The attending anesthesiologist was not blinded to the IFT results. A blood pressure cuff was placed on the forearm (preferably the dominant arm) and inflated to 50 mmHg above systolic blood pressure during injection of induction agents but before administration of neuromuscular blockers. The cuff remained inflated for the duration of the IFT (typically less than 5 min) and was deflated after the final command.

IFT responses were recorded by an observer, who was not the attending anesthesiologist and, where possible, verified by a second witness. A positive cognitive IFT response was defined as a contraction of the hand in response to a verbal command. The first command was "[NAME], squeeze my hand." If there was a positive response, a second command was given "[NAME], squeeze my hand twice if you have pain." Given the pragmatic nature of this study, attempts were not made to control ambient noise in the operating room.

These questions were asked immediately before laryngoscopy and after securing the endotracheal tube (typically within 1 min of intubation). For the IFT to be considered movement to command, the hand had to be still immediately before the command. In situations where the hand was spontaneously moving, and hence response to command was difficult to confirm, the IFT was considered negative giving us a conservatively biased estimate of the incidence of connected consciousness. Lack of paralysis of the hand was confirmed using a train-of-four monitor with four twitches present in all cases.

Secondary endpoints included the following:

1. Establish the incidence of IFT responsiveness with pain after laryngoscopy (prespecified outcome).

2. Establish the incidence of IFT responsiveness before laryngoscopy defined as after induction of anesthesia but before laryngoscopy (prespecified outcome).
3. Establish the combined incidence of IFT responsiveness before and after laryngoscopy (*post hoc* outcome).
4. Establish the incidence of postoperative explicit recall of events in IFT responders *versus* nonresponders identified using the modified Brice questionnaire[8] within 24 h of the operation (prespecified outcome).
5. Identify any alterations in patient satisfaction, measured by the Bauer satisfaction scale,[9] associated with IFT responsiveness compared to nonresponders (prespecified outcome).
6. Identify risk factors for IFT responsiveness after intubation (prespecified outcome).

Variables Collected

Collected variables included surgical site, age, sex, body mass index, race, American Society of Anesthesiologists physical classification score, significant comorbidities, Mallampatti score, observer-predicted difficult intubation (yes/no), drug exposure before intubation, observer-rated difficult intubation (yes/no), number of attempts at intubation, estimated duration of intubation, depth of anesthesia monitor use (yes/no) and numerical values, hemodynamics before and after intubation, response to the IFT before and after intubation, and whether witnessed by a second observer. For the depth of anesthesia monitoring data, we combined data from the Bispectral Index (BIS) and Neurosense monitors as both are on a scale of 0 to 100 with a clinical range of 40 to 60; hence, clinicians will use the information in the same way for either monitor. Postoperatively, within 24 h of emergence, participants were asked the modified Brice and Bauer questionnaires.[8,9] Data were entered locally into a REDCap database managed at the University of Wisconsin.

The primary outcome was the incidence of IFT responsiveness after intubation, and hence, we were unable to conduct a power calculation for the study. The study sample size was estimated based on previous data suggesting an event rate of up to 40% after intubation[10] and review of IFT responses after noxious stimuli during anesthesia.[4] Based on an upper limit estimate of a 40% response rate, recruitment of 260 patients would provide approximately 100 events. If achieved, this would allow multivariable modeling of up to 10 risk factors for postintubation IFT responsiveness. In this instance, the risk factors we considered were age, gender, preoperative midazolam, preoperative β-blocker, propofol dose, opioid dose, volatile anesthetic before intubation, duration of laryngoscopy, number of attempts at laryngoscopy, and depth of anesthesia monitor value at IFT response. We planned to competitively enroll at eight centers with a minimum recruitment rate of 25 patients per center but two centers had to withdraw before patient recruitment. Consequently, we enrolled at six centers.

Statistical Analysis

Continuous data are presented with mean ± SD, and categorical data are presented as frequencies and percentages. Univariate comparisons of continuous variables were made with Student's *t* test assuming equal variances, and comparisons between categorical variables were made with Pearson chi-square or Fisher exact test. As age may act as a confounder for both incidence of IFT response and selection of induction medications, we conducted logistic regression with bivariate models including age and drug variable. All *P* values were set at 0.05 with two-tailed hypothesis testing. All analyses were performed using SAS software (SAS 9.3; SAS Institute, USA).

Results

Of the 260 patients enrolled (fig. 1), 4.6% (12) were IFT responsive after intubation (table 1). Eighteen patients moved spontaneously after postlaryngoscopy prohibiting the IFT and therefore were designated as nonresponders because spontaneous movement compromises IFT assessment. We assumed that these movements were probably some manifestation of spinal reflex response but cannot exclude that at least some of these subjects were also conscious. Seven subjects were lost to postoperative follow-up (fig. 1). Of the 12 responders after intubation, five reported pain through a second hand squeeze (42% of IFT responders; 1.9% of total cohort). There were no reports of explicit awareness of intraoperative events by either responders (n = 12) or nonresponders (n = 241) when asked within 24 h of the operation.

Variation in IFT Response Rate by Study Center

We conducted *post hoc* sensitivity tests for the incidence of IFT responsiveness. The incidence of IFT responsiveness after intubation did not vary significantly by center (range, 0 to 12%; *P* = 0.27 by chi-square test). We excluded the lowest (0/25) and highest (3/25) responding centers; the remaining centers' response rates were 2% (1/50), 4% (1/25), 4% (4/100), and 9% (3/35), respectively. The mean response

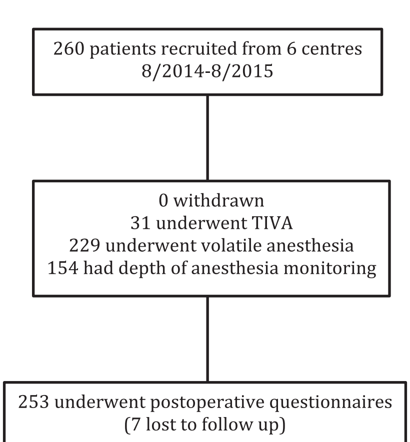

Fig. 1. Strobe diagram for a prospective cohort study. TIVA = total intravenous anesthesia.

Table 1. Responder Characteristics

	Age, yr	Sex	BMI	ASA	MS	Fentanyl Equivalent, µg/kg	Propofol, mg/kg	Other Medications	Pre-IFT+	Intubation Attempts	Post-IFT Pain	Post-IFT Signs of Distress	DOA Pre-IFT	DOA Intubation	DOA Post IFT	Comorbidities
1.	34	Female	19	2	2	3.7	2.6	Lidocaine, midazolam	No	1	Yes	Yes	N/A	N/A	N/A	Breast cancer, bipolar disorder type I, depression, PTSD, Marijuana dependence, tobacco dependence, chronic back pain
2.	23	Male	21	2	1	0.7	2.7	Lidocaine, midazolam	No	1	No	No	40	40	39	Duodenitis, GERD, depression, infectious mononucleosis, shift work sleep disorder
3.	39	Female	23	1	1	1.7	3.3	Lidocaine, midazolam	Yes	1	No	No	N/A	N/A	N/A	Hearing loss
4.	32	Female	28	3	2	3.4	2.0	Lidocaine, midazolam	No	1	No	No	N/A	40	21	Cerebral aneurysm, anxiety, migraine
5.	31	Female	27	2	2	0.4	2.5		No	2	No	Yes	45	40	32	Uterus myomatosus
6.	74	Male	26	3	2	0.5	1.8	Norepinephrine	No	2	No	No	77	34	30	Coronary heart disease, condition after myocardial infarction, asthma, diabetes mellitus type II
7.	19	Female	25	2	3	1.1	2.9		No	2	No	Yes	28	45	67	None
8.	68	Male	33	3	3	N/A*	N/A*	Lidocaine	No	1	Yes	No	43	47	68	Total hip replacement, COPD, proteinuria and kidney insufficiency
9.	40	Female	37	2	2	0.9	1.8	Ketamine	No	1	Yes	Yes	72	71	79	Asthma, OSA, esophagitis, obesity
10.	27	Female	21	3	2	2.1	2.5		No	1	No	Yes	37	N/A	46	VATER syndrome, end-stage renal failure, anxiety, depression
11.	38	Male	36	2	2	0.9	1.7	Ketamine	No	2	Yes	Yes	50	70	77	Obesity, obstructive sleep apnea
12.	40	Male	26	1	1	1.6	2.0	Ketamine	No	1	Yes	No	81	72	90	None

*Data not available (N/A) due to total intravenous anesthesia.

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; DOA = depth of anesthesia monitor; GERD = gastroesophageal reflux disease; IFT = isolated forearm technique; MS = mallampati score; OSA = obstructive sleep apnea; pre-IFT = prelaryngoscopy IFT; post-IFT = postlaryngoscopy IFT; PTSD = posttraumatic stress disorder; VATER = verterbrae, anus, trachea, esophagus, renal.

Table 2. Univariate Associations of Baseline Characteristics of Nonresponders and Responders

	Nonresponder (n = 248)	Responder (n = 12)	*P* Value
Age, yr	51 ± 16	39 ± 17	0.01
Gender, n (%)	Male, 131 (52.8)	Male, 5 (41.7)	0.56
	Female, 117 (47.2)	Female 7 (58.3)	
Race,* n (%)			0.50
Caucasian	221 (92.3)	10 (83.3)	
African American	4 (1.6)	1 (8.3)	
Native American	0	0	
Asian	1 (0.4)	0	
Pacific Islander	11 (4.4)	1 (8.3)	
Other	3 (1.2)	1 (8.3)	
BMI	26.7 ± 5.7	28.6 ± 6.4	0.26
ASA score, n (%)			0.78
1	48 (19.4)	2 (16.7)	
2	143 (57.7)	6 (50)	
3	53 (21.4)	4 (33)	
4	4 (1.6)	0	
5	0	0	
Mallampatti†			0.82
1	80 (32.3)	3 (25.0)	
2	131 (73.0)	7 (58.3)	
3	25 (10.1)	2 (16.7)	
4	5 (2.0)	0	
DOA placed (yes)	144 (58.1)	10 (83.3)	0.13

*Mixed races possible. †Two hundred fifty-three reports available.
ASA = American Society of Anesthesiologists; BMI = body mass index; DOA = depth of anesthesia monitor.

rate in this sensitivity analysis was 4.3%. We also conducted a sensitivity analysis in participants who responded after a protocol deviation of being asked the first question more than twice. On this basis, two IFT responders were excluded, leaving a mean response rate of 3.9%. Hence, our sensitivity analyses suggest that the response rate is approximately 4%, which is similar to the rate at the largest single site (4/100).

IFT Responsiveness before Intubation

Five (1.9%) patients were IFT responsive before intubation, but only one patient was responsive before and after intubation. Of these five patients who responded before laryngoscopy, BIS values were only available in one patient. In this patient, the BIS was 46 at the time of prelaryngoscopy IFT responsiveness, followed by 66 at intubation, and 38 at the time of the postintubation IFT. This individual did not respond to the IFT questions after intubation. As a secondary *post hoc* outcome, we calculated the total IFT response rate, including both the preoperative and postoperative IFT response rate, as 6.2%.

Characteristics of the IFT Responders and Nonresponders Postlaryngoscopy

The characteristics of the responders and nonresponders are reported in tables 2 to 4. The age range for the whole cohort was 18 to 88 (51 ± 16) yr old. On average, the responders were younger than nonresponders but otherwise were not different in terms of baseline characteristics including American Society of Anesthesiologists score and body mass index (table 2; fig. 2). There were no differences between anesthesiologist rating of the difficulty of intubation, number of intubations, or estimated duration of intubations between the responders and nonresponders (table 3).

Medications

Total intravenous anesthesia (TIVA) was used in 31 cases (12.7%) with the majority achieved by a bolus of propofol, followed immediately with a continuous infusion. Only one patient (a nonresponder) received an α-2 adrenergic agonist as part of induction. There was no difference in exposure to TIVA or volatile anesthesia, fentanyl equivalents, midazolam, ketamine, propofol, or β-blockers between responders and nonresponders (table 4). As age may influence the administration of different medications, and also the risk of IFT responsiveness, we then performed logistic regression to adjust for the effect and interaction of age on the putative effect of relevant drug variables. After adjustment for age, in patients not receiving TIVA, exposure to volatile anesthetic before intubation was associated with a reduced odds of responding (odds ratio, 0.2 [0.1 to 0.8]; *P* = 0.02). However, induction doses of propofol (1.4 mg/kg [0.6 to 3.5]; *P* = 0.47) and ketamine (3.75 [0.9 to 15.7]; *P* = 0.07) were not associated with altered odds of responsiveness after adjustment for age. Of the responders, there was no difference in fentanyl equivalents between those subjects who reported pain *versus* no pain (*P* = 0.81). Interestingly, all three responders who were administered ketamine (25 mg) as part of their induction reported pain despite coadministration of opioids.

Monitoring

No adverse events related to the IFT were reported. In 154 patients, a depth of anesthesia monitor was placed (Neurosense, n = 25; BIS, n = 129); use of depth of anesthesia monitoring did not differ between the groups (table 2). Depth of anesthesia monitoring values showed a wide range in both groups; however, mean values were higher for responders before (54 ± 20 *vs.* 42 ± 14; *P* = 0.02) and after (57 ± 25 *vs.* 43 ± 16; *P* = 0.02) intubation (fig. 2; table 3). The effect was not pronounced enough for receiver operator characteristic (ROC) calculations to demonstrate the ability to predict IFT responsiveness after laryngoscopy for either preintubation (ROC area = 0.69 [0.49 to 0.89]; *P* = 0.08) or postintubation (ROC area = 0.66 [0.42 to 0.89]; *P* = 0.11) values.

Responders had a higher incidence of observer-rated signs of sympathetic activation (signs of lacrimation, tachycardia, or hypertension) after intubation (50% *vs.* 2.4%; *P* = 0.03). Three of the five responders who reported pain demonstrated observer-rated signs of sympathetic activation (table 1). However, there were no differences in prelaryngoscopy or

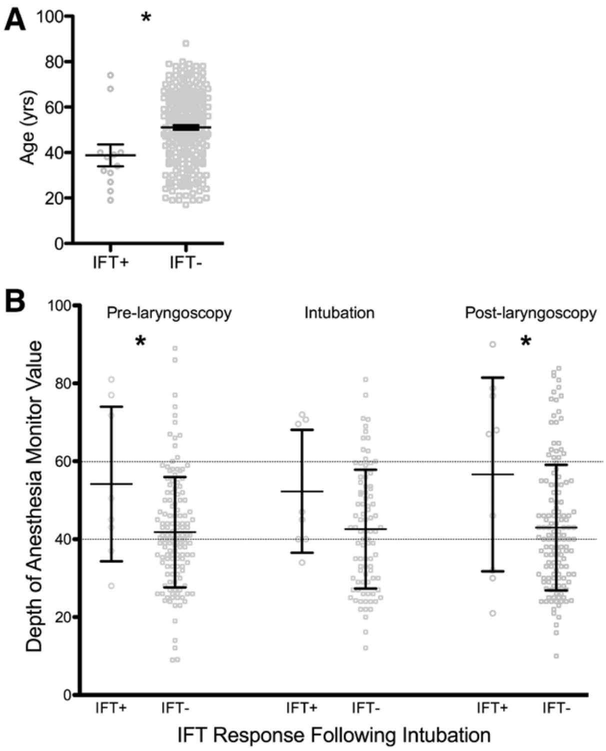

Fig. 2. Age and depth of anesthesia monitoring values differ between responders and nonresponders on the isolated forearm technique (IFT) after intubation. (*A*) Age in responders is lower than that in nonresponders, and (*B*) depth of anesthesia monitoring values, before and after intubation, are higher in IFT responders than in nonresponders after intubation. *Dashed lines* represent the proposed clinical range of 40 to 60. *$P < 0.05$ on Student's *t* test. Data shown are individual data points (*gray*) with superimposed mean ± SD (*black*).

postlaryngoscopy heart rate between responders and nonresponders. There was also no difference in blood pressure between the groups before and after laryngoscopy.

Postemergence Questionnaire

Given the low event rate of IFT responsiveness, we urge caution with the following findings due to the potential for confounding and our lack of statistical power to adjust for multiple comparisons. These data must be only considered hypothesis generating. In addition to conducting the modified Brice questionnaire for explicit recall (available in 253 patients only), we also conducted the Bauer patient satisfaction survey to understand if IFT responsiveness was associated with reduced postoperative satisfaction.[9] One IFT responder (8.3%) reported dreams (which were reported as disturbing), while 24 out of 241 nonresponders (10.3%) reported dreams ($P = 1.00$) with one patient reporting disturbing dreams. There were no univariate differences in patient-reported drowsiness ($P = 1.00$), pain at the surgical site ($P = 0.14$) or injection site ($P = 0.64$), thirst ($P = 0.59$), hoarseness ($P = 0.88$), sore throat ($P = 0.29$), nausea or vomiting ($P = 0.45$), or feeling cold ($P = 0.60$). We previously hypothesized that overlapping mechanisms of connectedness may link IFT responsiveness and postoperative delirium.[3] However, there was no difference in patient reporting of feeling confused or disoriented (responders 33%, nonresponders 14%; $P = 0.20$). IFT responders appeared more likely to report shivering ($P = 0.04$; n = 253) at the univariate level: severe shivering (responder 17% *vs.* nonresponder 2%), moderate shivering (responder 0% *vs.* nonresponder 10%), and no shivering (responder 83% *vs.* nonresponder 88%). Univariate differences in patient satisfaction were not observed regarding the information they received preoperatively ($P = 1.00$), their wake up ($P = 0.63$), their nausea ($P = 0.10$), or their general impression of the anesthesia department ($P = 0.79$). However, IFT responders reported being less satisfied with their pain after surgery ($P = 0.02$ by Fisher exact test; n = 252): very satisfied (responder 42% *vs.* nonresponder 57%), satisfied (responder 33% *vs.* nonresponder 38%), dissatisfied (responder 16% *vs.* nonresponder 4%), and very dissatisfied (responder 8% *vs.* nonresponder 0.4%).

Discussion

In this prospective, multicenter, pragmatic, international cohort study, we established that the incidence of IFT responsiveness after intubation was 4.6%. An estimate of 4% was supported by sensitivity analyses. Five patients (1.9% of the whole cohort) reported pain at the time of postintubation IFT. Although our previous review suggested that only 14% of IFT responders report pain,[4] 42% reported pain in this study. This may reflect the intensity of the nociceptive stimulation of laryngoscopy.[11] Our data argue for the clinical importance of the IFT, as few patients would regard intraoperative pain as acceptable. Consistent with previous data,[4] and the known clinical effectiveness of anesthetic drugs to suppress memory at concentrations well below hypnotic doses,[12] IFT responsiveness was not associated with postoperative explicit recall of the event. Our data suggest that the incidence of intraoperative connected consciousness (with responsiveness) after intubation may be 25 times higher than the incidence of explicit recall of events.

Interpretation of the IFT Response

As we have previously discussed, a positive IFT response represents the standard in consciousness research—behavioral report.[6] Interpretation of a negative response is more complicated because behavioral confirmation of unconsciousness is impossible. Our parsimonious explanation is that these subjects are either disconnected from their environment or unconscious. However, it is possible that these subjects are conscious and either choose not to respond or are unable to respond. Further discrimination between these states is not possible with current methodologies in the field. It is possible that administration of a volatile anesthetic may affect any/all of these endpoints through affecting motor responsiveness, motivation, or consciousness itself.[4]

Table 3. Univariate Associations of Nonresponders and Responders with Intubation and Monitoring Related Factors

	Nonresponder (n = 248)	Responder (n = 12)	*P* Value
Time from induction to intubation, min	4.5 ± 2.6	5.4 ± 2.5	0.27
Observer rated difficult intubation, yes/no, %	17 (6.9)	1 (8.3)	0.59
Number of attempts at intubation (IQR)	1 (1–2)	1 (1–1)	0.13
Estimated duration of intubation, s	30 ± 15	42 ± 43	0.34
Prelaryngoscopy IFT response, yes (%)	4 (1.6)	1 (9.1)	0.21
DOA value prelaryngoscopy*	42 ± 14	54 ± 20	0.02
DOA value at intubation†	43 ± 15	52 ± 16	0.09
DOA postintubation‡	43 ± 16	57 ± 25	0.02
Signs of distress (IQR)	6 (2.4)	6 (50)	0.03
Heart rate prelaryngoscopy, beats/min	72 ± 13	73 ± 13	0.96
Heart rate postintubation, beats/min	86 ± 18	95 ± 17	0.08
Systolic blood pressure prelaryngoscopy, mmHg	122 ± 29	120 ± 27	0.85
Systolic blood pressure postintubation, mmHg	130 ± 33	135 ± 27	0.60
Diastolic blood pressure prelaryngoscopy, mmHg	73 ± 21	69 ± 22	0.53
Diastolic blood pressure postintubation, mmHg	77 ± 19	87 ± 24	0.08

*Data available from 8 responders and 137 nonresponders. †Data available from 8 responders and 89 nonresponders. ‡Data available from 9 responders and 137 nonresponders.

DOA = depth of anesthesia monitor; IFT = isolated forearm technique; IQR = interquartile Range.

Table 4. Univariate Associations of Nonresponders and Responders with Medications

	Nonresponder (n = 248)	Responder (n = 12)	*P* Value
Preoperative β-blocker, (%)	54 (21.8)	0	0.07
Midazolam, yes (%)	125 (50.4)	4 (33)	0.38
Fentanyl equivalents dose, μg/kg*	1.4 ± 1.1	1.5 ± 1.1	0.79
Propofol dose, mg/kg	2.0 ± 0.7	2.3 ± 0.5	0.11
Ketamine, yes (%)	25 (10.1)	3 (25)	0.13
Volatile anesthetic preintubation, (%)†	158/218 (72.4)	5/11 (45.5)	0.08

*Excluding patients on remifentanil infusions (n = 234: 223 nonresponders and 11 responders). †For patients not exposed to total intravenous anesthesia (n = 229: 218 nonresponders and 11 responders).

We concentrated on providing a methodologically robust incidence of connected consciousness after intubation; however, several factors make our estimate conservative. We excluded patients with spontaneous movement as it made interpretation of the IFT difficult. Without an unambiguous behavioral response to command, the conscious state of subjects moving spontaneously is unclear. We also cannot exclude that further episodes of intraoperative awareness occurred after intubation (during surgery). Nonetheless, while our estimate should be considered conservative, it is methodologically robust as we used observers who were independent from the clinical team caring for the patient to judge the IFT responses.

We studied intubation because it is a clinically relevant stimulus, and the IFT tourniquet can easily be applied for less than 20 min. Longer durations of IFT testing are complicated by the need to reperfuse the hand to prevent ischemic paralysis. Importantly, our study was inclusive, to allow a broad population of the patients undergoing general anesthesia, and we did not seek to control the anesthesia to allow insights about routine clinical practice in six centers. This pragmatic design increases the external validity of our study though we cannot exclude a Hawthorne effect, whereby observation decreased the actual incidence of responsiveness.

Comparison to Previous Studies

The incidence rate in our study is lower than the rate we predicted based on our systematic review. Some studies identified in our review[4] and published after it[13] conducted the IFT *during* intubation, which we avoided in this study due to the high incidence of spontaneous movement at that time. Furthermore, it is not always clear from previous studies how spontaneous movement affected methodology. However, when we focus on studies that concentrated on postintubation IFT testing, a few notable, but small, studies deserve mention. St Pierre *et al.*,[14] testing three different doses of etomidate, found that 5 of 30 patients (17%; aged 29 to 80 yr old), responded to the IFT in 120 s after intubation. Similarly, a study of ketamine and succinylcholine anesthesia (1.5 mg/kg) showed that 0 of 13 patients responded in the 10 min after induction for cesarean section.[15] Using the LMA-Fastrach insertion technique and remifentanil-propofol anesthesia titrated to a BIS of 40 to 65, an IFT response rate of 7/51 (13.5%; aged 22 to 75 yr old) was observed.[16] In another small study, Schneider *et al.*[10] found that 8 of 20 (40%) patients responded to the IFT after intubation with propofol-alfentanil anesthesia titrated to a preintubation BIS of 50. A key difference with our study was that the preintubation BIS values were typically lower than 50. Our estimate of IFT responsiveness after intubation in real-world practice, falls within the range of response rates (0 to 40%) of these heterogeneous previous studies. Nonetheless, the wide range in the previous studies emphasizes the need for the current investigation.

Risk Factors for IFT Responsiveness

Our data do not suggest a clear way of identifying those at risk despite responders being younger than nonresponders on average. The wide range of ages, drug doses, and depth of anesthesia monitoring values associated with IFT responsiveness (table 1; fig. 2) indicate these variables are poorly predictive. However, given that age will bias the selection of anesthesia medications, we also performed logistic regression to adjust for this variable. After adjustment for age in those patients undergoing inhalational anesthesia, nonexposure to volatile anesthetic before laryngoscopy was associated with significantly increased odds of responsiveness. This implies that early administration of a volatile anesthetic drug, while waiting for the muscle relaxant to take effect, may reduce the odds of responding to the IFT questions after intubation. Another interpretation is that a single bolus of intravenous anesthetic may be insufficient to ensure anesthesia through to intubation. Consistent with this, in patients who had depth of anesthesia monitoring placed, prelaryngoscopy monitoring values tended to be higher in responders *versus* nonresponders. However, the wide interpatient variance suggests caution in relying on the monitors: values below 40 occurred in both responders and nonresponders, as has been observed previously.[13,17,18] Our receiver operator curve data appear consistent with previous studies showing that BIS[13,18] and Narcotrend[17] values are poorly predictive of IFT responsiveness. Furthermore, recent estimates for the BIS value with 100% sensitivity to prevent IFT responsiveness to intubation are disproven[13]: three subjects responded with BIS values below the previously identified threshold of 37.[13] Hence, while using population-level summary statistics can discriminate the groups in some instances (such as age or depth of anesthesia monitoring values), this was not possible at the individual level. A much larger study will be required to identify the individual risk factors that have useful prognostic value.

Overall, our data indicate that in patients who ultimately receive volatile anesthetics for maintenance of general anesthesia, commencing the vapor before intubation may reduce IFT responsiveness (connected consciousness) after intubation. Biologically, this appears plausible if a single bolus of intravenous anesthetic is used to induce anesthesia. This suggests that continual administration of an anesthetic to the time of laryngoscopy may be a prudent strategy to reduce connected consciousness. However, we recognize that in some situations, such as rapid sequence induction, this strategy may be inappropriate.

Postoperative Impact of Connected Consciousness

We consider intraoperative-connected consciousness, particularly with pain, an important clinical problem. However, the longer term effects of this state, especially given the lack of recall of the events, is unclear. Postoperative questionnaires were conducted to begin to probe some possible associations but we urge caution against overinterpreting our postoperative secondary endpoints; these should be considered hypothesis generating only. Responders appeared to be more likely to be dissatisfied in their pain management and had an increased incidence of shivering postoperatively. If this is a real effect, it remains unclear whether patients who are more likely to be dissatisfied with these outcomes are prone to intraoperative connected consciousness or whether patients who experience intraoperative connected consciousness are more likely to report adverse outcomes. Furthermore, we do not have data on important confounders related to the propensity of each endpoint, such as temperature.

Caveats

We report a large prospective, multicenter cohort study that establishes the incidence of IFT responsiveness after intubation in present clinical practice, but there are limitations to our study. First, while it is reassuring that the incidence of IFT responsiveness after intubation is approximately 10-fold lower than previous data suggested, this left us underpowered for multivariable analysis of the data. Hence, our secondary analyses should largely be considered hypothesis generating. Future studies should investigate how to reduce the incidence of, and identify electroencephalograph biomarkers of, connected consciousness during anesthesia. Nonetheless, we were able to establish a simple message: younger patients who are not exposed to continuing anesthesia (*e.g.*, volatile anesthesia) after an induction bolus appear more likely to respond on the IFT. Finally, while we had no episodes of explicit recall in the study, the cohort was small and our questioning was performed within 24 h of the operation to keep the study pragmatic; this is not the optimal time point for capturing these events (which is typically better done at 3 to 7 days or later).

Conclusions

In this international, multicenter, prospective cohort study, IFT responsiveness occurred in 4.6% of subjects with 1.9% of subjects reporting pain. At the population level, age and depth of anesthesia monitoring values distinguished responders and nonresponders. Our data also support the continued administration of anesthesia before intubation to reduce the odds of connected consciousness.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Sanders: robert.sanders@wisc.edu. Raw data available from Dr. Sanders: robert.sanders@wisc.edu

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