Processed Electroencephalogram and Depth of Anesthesia

Window to Nowhere or into the Brain?

TRY to imagine this: a dozen operating rooms filled with patients having surgery while a lone anesthesiologist, gazing at live data and video feeds on a tablet computer or wall of computer monitors, manages their general anesthetic from a distant location. Far fetched? If you think so, consider that earlier this year an IBM computer dubbed “Watson” beat the best human contestants on the television game show Jeopardy, your iPhone can now talk back, and in some hospitals, the sickest patients are managed remotely by critical care physicians who may not be in the same time zone, let alone same building.1 Of course, there are many hurdles to clear (e.g., airway management and line placement) before this futuristic scenario could become reality for intraoperative anesthesia. Arguably one of the main ones is that only a trained observer using clinical judgment can determine the adequacy of unconsciousness and make appropriate adjustments in drug dosing to assure adequate surgical anesthesia. The article by Liu et al.2 in this issue of the Journal provocatively challenges that assumption and moves us a step closer to the future.

Liu et al.2 tested the hypothesis that two machines—an infusion pump running software that calculates effect-site concentrations and a processed electroencephalographic device that analyzes a parameter called entropy—could outperform skilled manual control of drug titration by an experienced clinician during surgery using total intravenous anesthesia with propofol and remifentanil. In this context, entropy is essentially a measure of the disorder in the electroencephalogram signal; the electroencephalogram of an awake person will have high entropy, whereas an isoelectric electroencephalogram will have no entropy. What makes this randomized controlled trial interesting is that it took advantage of the fact that electroencephalogram entropy analysis generates measures of both hypnosis (i.e., state entropy [SE]) and analgesia (i.e., response entropy) and programmed the infusion controller to adjust the corresponding agent (propofol for hypnosis, remifentanil for analgesia) appropriately. Note that this was not a test of electroencephalogram-guided drug delivery per se; both the infusion controller and clinicians had access to the same electroencephalogram data. Rather it was about who or what did a better job using the information. And use the information they did. During the maintenance phase, the dual-loop controller made nearly triple the number of dosing modifications per hour than did the clinicians (21 vs. 8 for propofol and 28 vs. 10 for remifentanil). Performance was rated on how well the machines and skilled clinicians did at keeping patients within predetermined electroencephalogram parameters (e.g., SE 40–60, defined as adequate anesthesia; de-

“... the contest [on titrated administration of propofol and remifentanil] between man and machine was a tie. That itself is thought-provoking and potentially important.”

Illustration: J. P. Rathmell.

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viation from target; intraindividual variability; and SE under-
shoot and overshoot), as well as by clinical measures such as drug
consumption, hemodynamics, movement, time to tracheal ex-
tubation, and recall of intraoperative events. The machines
bested the clinicians on some electroencephalogram measures of
performance (e.g., Global Score [a combined measure of frac-
tion of time the SE and response entropy were within the target
range, performance error, and intraindividual variability]; frac-
tion of time at “adequate anesthesia” as defined by SE 40–60;
duration at excessive anesthesia as defined by an SE less than 40),
but there were no differences between the groups on clinical
endpoints.2 In essence, the machines did well what they were
told (programmed) to do as far as managing electroencephalo-
gram targets and matched the performance of skilled clinicians
on clinical outcomes. Thus, the contest between man and ma-
chine was a tie. That itself is thought-provoking and potentially
important.

The electroencephalogram has been the Holy Grail of
anesthetic depth monitoring for more than half a century but
has fallen on hard times lately, largely because the focus of the
dialog changed from electroencephalogram as a monitor of
“depth” to one of intraoperative awareness. As reviewed and
commented upon recently3–6 consciousness and intraopera-
tive awareness are neurobiologically exceedingly complex
phenomena. This makes these states difficult to capture or
evaluate with electroencephalography, no matter the param-
eter or sophistication of the processing algorithm. Recent
studies examining the efficacy of the electroencephalogram
bispectral index for minimizing the risk of intraoperative
awareness confirm as much. Thus, although some contro-
versy remains,7 two recent large prospective, randomized tri-
als of high-risk patients found no benefit of bispectral index
monitoring compared with the traditional practice of mon-
toring end-tidal anesthetic gas concentration.8,9 However,
generic monitoring of anesthetic depth is something else en-
tirely. The very term “depth” as it applies to consciousness
and anesthesia is a nebulous nineteenth century descriptor
that lacks scientific exactness. It is crude but yet clinically
useful, just the sort of thing that a processed electroenceph-
alogram probably can handle. After all, although limited in
its ability to provide information about complex, integrated
forebrain functions such as memory, the electroencephalo-
gram is good at identifying whether a brain is active or inac-
tive. As such, it may provide a window into brain activity or
“depth” during general anesthesia that may be clinically use-
ful. And that is the key point of the study by Liu et al.2
Machine-driven, electroencephalogram-guided drug deliv-
ery, even to somewhat arbitrary endpoints of depth such as
SE, response entropy, and time to burst suppression, pro-
duced an anesthetic that clinically was indistinguishable
from that provided by an experienced human. After a series
of recent defeats, score a win for processed electroencephalo-
gram as a tool for titrating anesthetic depth.

But can a processed electroencephalogram and a drug
pump do our job? Not likely, at least not yet. This was a small
study (30 and 31 patients per group), the electroencephalo-
gram target defined as adequate anesthesia (SE 40–60) is
debatable and seemingly not adjusted for age, and the study
was grossly underpowered to detect differences in the risk of
intraoperative awareness. Validation in a larger and more
diverse cohort is clearly necessary. Indeed, because of wide
interindividual variation in the bispectral index or spectral
entropy during administration of commonly used anesthetic
agents, others have questioned the ability of these indices to
differentiate reliably consciousness from unconsciousness.10
What’s more, as the author’s acknowledge, the measure used
to guide administration of the analgesic remifentanil (i.e.,
response entropy) reflects activity of the frontalis muscle,
which is not well validated as an index of nociception, pain,
or sensibility. In fact, more complicated neural events and
responses, including activation of cortical circuits, occurs in
vegetative patients and is not necessarily a sign of self-aware-
ness.11 Another important limitation is that the study used
only two of the many medications commonly used clinically
for general anesthesia. Most such medications, but especially
ketamine, nitrous oxide, and dexmedetomidine, have elec-
troencephalogram signatures different from those of propof-
ol and remifentanil, and partly because of persistent disorder
in the signal, it has proven difficult to find reliable electro-
encephalogram indices of unresponsiveness when these
agents are used.12,13 Therefore, it is premature and perilous
to conclude from the data of Liu et al.2 that the electroen-
ccephalogram is a generally or broadly useful tool for guiding
anesthetic “depth.” In addition, because no group was man-
aged blind to the electroencephalogram, Liu et al.2 have not
demonstrated that electroencephalogram data add value be-
yond that provided by simply having an experienced clini-
cian manage the anesthetic.

Still, as one of us suggested elsewhere,6 having a window
into the brain during general anesthesia makes sense. It is also
long overdue; 165 yr after the first public demonstration of
er@a anesthesia, we still rely on the patient to tell us whether
our medications are having the desired effect on the central
nervous system (e.g., “can you open your eyes?”), and then we
get only yes-no, on-off information. The brain is more nu-
anced than that, and in 2012, we ought to be able to do
better. The work of Liu et al.2 suggests that the processed
electroencephalogram can be such a window if the condi-
tions are tightly controlled and the expectations are low.
That is, if we ask the electroencephalogram to evaluate
“depth,” not awareness, it can with little or no human inter-
vention and a well-programmed infusor-controller do a fine
job of guiding delivery of some drugs to produce acceptable
clinical anesthesia and sedation. Whether or not it is justified
and safe, it is easy to see such systems taking root in endos-
copy suites and critical care units, where sedative or anes-
thetic medications are administered by nonanesthesia spec-
ialists for brief, relatively unstimulating procedures or for
long periods under relatively stable conditions. Whether the
quality of surgical anesthesia benefits from electroencephalo-
gram guidance of "depth" is another matter and one not addressed by Liu et al.\textsuperscript{2} The current processed electroencephalogram monitors are no panacea for anesthetic depth monitoring and likely will never be able to handle all eventualities, patients, and drug combinations. But considering how primitive the tools and how low the bar on "depth" assessment now, the foggy window into the brain the processed electroencephalogram provides might be enough to light the path forward.

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\section*{References}

\begin{enumerate}
\item Lilly CM, Cody S, Zhao H, Landry K, Baker SP, McIlwaine J, Chandler MW. Irwin RS. University of Massachusetts Memorial Critical Care Operations Group: Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. \textit{JAMA} 2011; 305:2175–83
\item Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesis. \textit{Science} 2008; 322:876–80
\item Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: From neurobiology to clinical practice. \textit{Anesthesiology} 2011; 114:1218–35
\item Crosby G. General anesthesia-minding the mind during surgery. \textit{N Engl J Med} 2011; 365:660–1
\item Ropper AH. Cogito ergo sum by MRI. \textit{N Engl J Med} 2010; 362:648–9
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