most important indicators of the effect of anesthetics.[4] Rather than the electrosubcorticogram, the signal from the subthalamic electrode is the cortical electroencephalogram, recorded from or near the subthalamic nucleus. It is mainly the same cortically generated signal, the electroencephalogram, but recorded from the other side of the cortex.

The article by Velly *et al.* therefore may not present the differences in electrical activity of deep structures and the cerebral cortex, as the authors claim. Both signals are mainly electrical activity of the cerebral cortex. This shows the importance of understanding the physiology and electrical fields of the electroencephalogram during anesthesia.

Ville Jäntti, M.D., Ph.D.,* Esa Heikkinen, M.D., Ph.D., Seppo Alahuhta, M.D., Ph.D., Raija Remes, R.N., Kalervo Suominen, Phil.Lic. *Tampere University Hospital, Tampere, Finland.
ville.jantti@uta.fi

References

1. Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM: Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. ANESTHESIOLOGY 2007; 107: 202–12

2. Sonkajärvi E, Puumala P, Erola T, Baer GA, Karvonen E, Suominen K, Jäntti V: Burst suppression during propofol anaesthesia recorded from scalp and subthalamic electrodes: Report of three cases. Acta Anaesthesiol Scand 2008; 52: 274–9

3. Huotari AM, Koskinen M, Suominen K, Alahuhta S, Remes R, Hartikainen KM, Jäntti V: Evoked EEG patterns during burst suppression with propofol. Br J Anaesth 2004; 92:18–24

4. Jäntti V, Sloan T: EEG and anesthetic effects, Intraoperative Monitoring of Neural Function. Edited by Nuwer MR. Elsevier BV, 2008, chap. 4, pp. 77–93. Handbook of Clinical Neurophysiology, vol. 8

(Accepted for publication January 3, 2008.)

Anesthesiology 2008; 108:964–5

In Reply:—We thank Dr. Jäntti *et al.* for their interest in our study on the differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia.[1] The location of the signal recorded through deep-brain electrodes is clearly a concern for all stereoelectroencephalography measurements. In epilepsy surgery, neurophysiologists and neurosurgeons rely on deep-brain recordings to precisely delimit the brain region to remove surgically. If such a gross contamination due to volume conduction were to occur, the clinical results would certainly be poor. We agree that one problematic issue in combined scalp cortical (electroencephalographic) and subcortical (electrosubcorticographic) electrogenesis recording is that of volume conduction from cortical to subcortical regions or the opposite. But first, we observed different data from each site showing that we observed synaptic activity from different regions of the brain (as shown in fig. 2 in the article). Second, we used a bipolar recording for the scalp and the deep-brain electrode. Wennberg *et al.*[2] demonstrated that scalp potential recording in the subthalamic nucleus with monopolar montage totally disappears with a bipolar montage.

We do not believe that the illustration provided by Dr. Jäntti *et al.* supports their claim that we recorded only cortical activity both on the scalp electrodes and from the deep-brain electrode. First, the authors suggested that plot 4 of the deep-brain electrode was "close to the vertex," which is not correct. As shown in figure 1 in the article, this plot is far from the cortex and close to the thalamus. Second, it shows a burst constituted of one slow wave superimposed with rapid activities of various frequencies. These rapid activities are more complex than classic spindles. In addition, the illustration shows, at the beginning of the burst, high-frequency activity in the cortex but not on the depth electrode. The interpretation made to explain this discrepancy is purely speculative. In fact, it demonstrates that cortical and subcortical electrogenesis were different.

We were also surprised to read, in their letter and in the published material from which the patient data came,[3] that spindle generation occurred in the cortex, contrary to a large body of data showing the crucial role of the thalamus.[4] This is not new, because Morrison and Bassett[5] showed in 1945 that spindles survived in the thalamus after bilateral decortication. We also published in another article that spindles appeared in the thalamus during physiologic sleep before they appeared in the temporal cortex in epileptic patients undergoing stereoelectroencephalography.[6] In this study, the same surgically implanted electrode was used to record, using bipolar montage, both cortical and thalamic activity. This clearly shows that we recorded deep-brain electrophysiology and not only the electroencephalogram through the implanted electrode.

We found the topographic interpretation of Dr. Jäntti *et al.* confusing. In their article, they state that the phase reversal of the initial component of the burst in figure 2 of this study (Cz–D1/D1–C7, where D1 is the depth electrode) is an argument for a thalamic origin. That is correct according to the classic rule of electroencephalographic bipolar interpretation,[7] but they do not use the same rule for the latter component of the electroencephalographic data (δ activity and "spindle" in fig. 1), and they conclude that there is a cortical origin of this component. We believe this interpretation is incorrect and question their comments regarding topography in our data.

Dr. Jäntti *et al.* also suggest that cortical and subcortical activities are similar at a deep anesthetic state in our study (fig. 2 of the article), demonstrating that we recorded the same signal in both settings. As we write in the article, the activities are similar during deep anesthesia (T4). What were important in our study were the differences in electrophysiology between the electroencephalogram and the electrosubcorticogram we observed during induction of anesthesia, which were obvious from our figures and data, demonstrating that we recorded different activities. We discarded periods with a burst suppression pattern, which in our opinion cannot be interpreted, because electrophysiology tends to be uniform throughout the brain at a very deep anesthetic state (ultimately identical when the electroencephalogram is flat).

Finally, the scalp derivation we used did not minimize slow wave activity. It did not maximize the amplitude of slow waves, but it did not change the dynamics of slow wave appearance. This is clear in our article (figs. 2 and 4) showing the early appearance of δ waves.

We agree with Dr. Jäntti *et al.* that a thorough understanding of basic electrophysiology is mandatory to interpret the electroencephalogram during anesthesia.[8] We disagree, however, with their interpretation and believe that routine electrophysiologic recordings with depth electrodes, work in our laboratory,[9] and evidence from the literature support the validity of our data.

Marc F. Rey, M.D., Ph.D., Lionel J. Velly, M.D.,* Nicolas J. Bruder, M.D. *Centre Hospitalier Universitaire Timone, Université de la Méditerranée, Marseille, France. lionel.velly@ap-hm.fr

References

1. Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM: Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. ANESTHESIOLOGY 2007; 107:202–12

2. Wennberg R, Pohlmann-Eden B, Chen R, Lozano A: Combined scalp-thalamic EEG recording in sleep and epilepsy. Clin Neurophysiol 2002; 113:1867–9

3. Sonkajärvi E, Puumala P, Erola T, Baer GA, Karvonen E, Suominen K, Jäntti V: Burst suppression during propofol anaesthesia recorded from scalp and subthalamic electrodes: Report of three cases. Acta Anaesthesiol Scand 2008; 52:247–9

4. Fuentealba P, Steriade M: The reticular nucleus revisited: Intrinsic and network properties of a thalamic pacemaker. Prog Neurobiol 2005; 75:125–41

5. Morison RS, Bassett DL: Electrical activity of the thalamus and basal ganglia in decorticated cats. J Neurophysiol 1945; 8:309–14

6. Rey M, Bastuji H, Garcia-Larrea L, Guillemant P, Mauguière F, Magnin M: Human thalamic and cortical activities assessed by dimension of activation and spectral edge frequency during sleep wake cycles. Sleep 2007; 30:907–12

7. Niedermeyer E: The EEG signal: Polarity and field determination, Electroencephalography: Basic Principles, Clinical Applications and Related Fields, 2nd edition. Edited by Niedermeyer E, Lopes da Silva F. Baltimore, Urban and Schwarzenberg, 1987, pp 79–83
8. Bruder N, Velly L, Rey M: A low voltage EEG signal may give low bispectral index values (letter). Anesth Analg 2004; 98:873
9. McGonigal A, Bartolomei F, Régis J, Guye M, Gavaret M, Trébuchon-Da Fonseca A, Dufour H, Figarella-Branger D, Girard N, Péragut JC, Chauvel P: Stereoelectroencephalography in presurgical assessment of MRI-negative epilepsy. Brain 2007; 130:3169–83

(Accepted for publication January 3, 2008.)

Anesthesiology 2008; 108:965

Anticholinesterase Drugs and the Transplanted Heart

To the Editor:—I perused with interest the report by Dr. Sawasdiwipachai *et al.*[1] detailing bradycardia followed by cardiac arrest in an infant cardiac transplant recipient after intravenous administration of neostigmine–glycopyrrolate. The authors speculate that rejection of the conducting system may have contributed to this response that is considered to be unusual because of the low likelihood of parasympathetic reinnervation. Asystole preceded by bradycardia after neostigmine–glycopyrrolate administration has been described in three adult transplant patients,[2,3] and neostigmine has been shown to produce an atropine-sensitive dose-dependent bradycardia in recent (<6 months) and remote (>6 months) adult cardiac transplants.[4] Contrary to the authors' assertion, rejection in these patients was neither confirmed nor refuted. The observation that remote cardiac transplants may demonstrate greater bradycardic responses to neostigmine compared with recent transplants may be explained by weak, variable parasympathetic reinnervation and/or by a denervation supersensitivity to the cholinergic agonist effect of neostimine.[4] The influence of rejection on these responses is an intriguing confounding variable that remains to be determined. Regardless of the underlying mechanisms mediating the bradycardia in cardiac transplant patients after anticholinesterase administration, it is clear that caution should be exercised when reversing neuromuscular block even when a muscarinic antagonist is coadministered with the anticholinesterase. To avoid a potentially catastrophic response to neostigmine, the authors suggest avoidance of neuromuscular block if possible, or use of short-acting drugs if paralysis is required. They speculate that this problem may be circumvented by the use of new reversal agents such as sugammadex. Another possibility not considered is reversal of neuromuscular block with edrophonium (and of course a muscarinic antagonist!). While edrophonium, too, produces bradycardia in cardiac transplant recipients, the decrease in heart rate is smaller in magnitude and much more consistent compared with neostigmine.[5]

Steven B. Backman, M.D.C.M., Ph.D., F.R.C.P.C., Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada. steven.backman@muhc.mcgill.ca

References

1. Sawasdiwipachai P, Laussen P, McGowan FX, Smoot L, Casta A: Cardiac arrest after neuromuscular blockade reversal in a heart transplant infant. ANESTHESIOLOGY 2007; 107:663–5
2. Bjerke RJ, Mantione MP: Asystole after intravenous neostigmine in a heart transplant recipient. Can J Anesth 2001; 48:305–7
3. Beebe DS, Shumway SJ, Maddock R: Sinus arrest after intravenous neostigmine in two heart transplant recipients. Anesth Analg 1994; 78:779–82
4. Backman SB, Fox GS, Stein RD, Ralley FE: Neostigmine decreases heart rate in heart transplant patients. Can J Anaesth 1996; 43:373–8
5. Backman SB, Stein RD, Fox GS, Polosa C: Heart rate changes in cardiac transplant patients and in the denervated cat heart after edrophonium. Can J Anaesth 1997; 44:247–54

(Accepted for publication January 30, 2008.)

Anesthesiology 2008; 108:965

In Reply:—We appreciate Dr. Backman's thoughtful comments about our article,[1] including discussion of data from his studies in humans and denervated feline hearts, which suggest that edrophonium may be more predictable and (consistent with its pharmacology) cause less bradycardia than neostigmine in transplant recipients. He is also correct in noting that denervation hypersensitivity (as well as variable parasympathetic reinnervation) may underlie the bradycardiac effects of neostigmine in some of these patients, although the data that specifically support this mechanism in transplant recipients are in our minds relatively modest and indirect.[2,3] We did want to use our case to heighten awareness of the phenomenon of acute humoral rejection. Although humoral mechanisms have been recognized for some time as an important and pathologically distinct form of rejection, potentially useful diagnostic methods and distinct therapies are a more recent development. We also thought this case would be useful to stimulate speculation about the potential interaction of humoral rejection and its consequences with drugs used during an anesthetic; this includes not only anticholinergics and anticholinesterases, but also agents that alter myocardial contractility.

Prasert Sawasdiwipachai, M.D., Peter C. Laussen, M.B.B.S., Leslie Smoot, M.D., Francis X. McGowan, Jr., M.D., Alfonso Casta, M.D.* *Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts. alfonso.casta@childrens.harvard.edu

References

1. Sawasdiwipachai P, Laussen PC, McGowan FX, Smoot L, Casta A: Cardiac arrest after neuromuscular blockade reversal in a heart transplant infant. ANESTHESIOLOGY 2007; 107:663–5
2. Backman SB, Stein RD, Fox GS, Polosa C: Heart rate changes in cardiac transplant patients and in the denervated cat heart after edrophonium. Can J Anaesth 1997; 44:247–54
3. Backman SB, Stein RD, Blank DW, Collier B, Polosa C: Different properties of the bradycardia produced by neostigmine and edrophonium in the cat. Can J Anaesth 1996; 43:731–40

(Accepted for publication January 30, 2008.)