Dr. James P. Rathmell: Hello. I’m Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women’s Hospital. I’m one of the Executive Editors for Anesthesiology and you’re listening to an Anesthesiology podcast that we’ve designed for physicians and scientists interested in the research that appears in the journal.

Today we’re going to talk with the lead author of an original research article and an accompanying editorial view that appear in the September 2019 issue.

With us today is Dr. Albert Dahan. Dr. Dahan is Professor of Anesthesiology, in particular the pathophysiology and physiology of respiratory regulation at Leiden University Medical Center in Leiden, The Netherlands. Dr. Dahan is the first author on an article that appears in the September 2019 issue of the journal and it’s titled “Influence of Reversal of Partial Neuromuscular Block on the Ventilatory Response to Hypoxia: A Randomized Controlled Trial in Healthy Volunteers.” Dr. Dahan, thank you for joining me.

Dr. Albert Dahan: Thank you very much. A very warm welcome from Leiden in The Netherlands.

Dr. James P. Rathmell: Also with us today is Dr. Jaideep Pandit. Dr. Pandit is a Consultant Anaesthetist at the Oxford University Hospitals and Supernumerary Fellow in Physiologic Sciences at St. John’s College in Oxford, the United Kingdom. Dr. Pandit wrote an editorial view that accompanies Dr. Dahan’s research article in the September 2019 issue and it’s titled “Reversing Neuromuscular Block: Not Just the Diaphragm, but the Body Muscle Function Too.” Dr. Pandit, thank you for joining me.

Dr. Jaideep J. Pandit: Thank you very much. Thank you for having me.

Dr. James P. Rathmell: Dr. Dahan, what a terrific study and congratulations on publication of your work. The ventilatory response to hypoxia is a critical reflex, we know that as anesthesiologists. And we’ve known for some time that this reflex is impaired by neuromuscular blocking drugs. But we’ve never determined the degree to which this reflex is restored after reversal of neuromuscular blockade.

You designed this study to determine if and to what degree the ventilatory response to hypoxia is restored after reversal of neuromuscular blockade. Can you tell listeners briefly how this reflex works and what your original hypothesis was when you began the study?

Dr. Albert Dahan: Certainly. Well, we’re talking about what we call the peripheral chemoreflex loop. It’s a chemoreflex that responds to hypoxia and hypercapnia. So, if we become hypoxic — and there are many reasons why people may become hypoxic. We all know that in the perioperative care, people may become hypoxic due to hypoventilation, people with obstructive sleep apnea might become hypoxic. Or if you travel to heights, you might become hypoxic, and the chemoreflex then becomes activated. The carotid body’s position to the bifurcation of the common carotid artery are activated by hypoxia and the response is hyperventilation. So, this is a crucial, lifesaving reflex that allows us to function and keep breathing and hyperventilating in hypoxic conditions so that our uptake of oxygen increases.

So, we designed this study with the hypothesis that there are notable receptors in the carotid bodies that if activated causes the depression of the hypoxic ventilatory response. You already knew this in studies that we’ve done before, but also Dr. Pandit did it previously—that’s inhalational anesthetic, depressed — this life-saving hypoxic ventilatory response and we also know from work done in Scandinavia by Lars Eriksson that neuromuscular blockers depress this hypoxic ventilatory response.

And we were extremely interested if we could replicate those data from Scandinavia and, most importantly to us, we wanted to know whether — if we would restore the function of the muscles at the thumb using EMG monitoring, if we could ‘reversal the degree of the hypoxic ventilatory response induced by these neuromuscular relaxants.

And the hypothesis was, in fact, that indeed we would be able to cause complete reversal in all subjects after reversal at the thumb. So, that was the idea of the study.

Dr. James P. Rathmell: You conducted a study in healthy human volunteers. Please talk us through how you went about doing this study.

Dr. Albert Dahan: Yes. This was not a simple study I have to say. It was a complex study because we have to induce a certain level of relaxation in volunteers. So, after some debate and some review of the literature, we looked at others that have done similar studies; we looked at the data from Scandinavia.

So, we wrote protocol, discussed it with the Ethics Committee, the IRB in our hospital, and we started doing the study. We used healthy volunteers and we informed them quite extensively. We even had a small film showing them what it meant when you would be relaxed while awake.

And then we did the study. We induced a level of hypoxia initially prior to the induction of the low-level relaxation and we also measured the hypercapnic ventilatory response during hyperoxia. This allows us to measure muscle function, per se, not because the hypoxic response is mediated through the carotid bodies with these receptors, as to common receptors, but hypercapnic ventilatory response is mediated through central sensors in the brain and they’re not influenced by these receptors, but only under conditions of hyperoxia.

Anyway, we induced a low level of neuromuscular relaxation and we did it very carefully. We initially modeled all these — the doses that we needed, we did a whole simulation study prior to the actual study and during the low level of relaxation, about the top ratio of around 70%, we performed the study again. Again, hypoxia and hypercapnia; in that area we did a randomized administration of these tests.

And then the actual study was performed in a randomized and double-blind fashion; whether either infused placebo, neostigmine or sugammadex. And sugammadex is an old relaxant in our hospital; it’s a very different mode of reversal relaxation.

And we kept measuring the EMG at the thumb. So, we kept measuring the level of relaxation and as soon as the level was around 100% plus or minus 5%, we reid initially the hypoxic response and later we reid the hypercapnic response because we really wanted to know what the hypoxic response would be upon reversal of the neuromuscular block at the thumb. So, that’s how we did the study. It was not an easy study; we saw some subjects that obstructed and because we used quite a sophisticated method to induce hypercapnia and hypoxia, these subjects — well, we couldn’t use the data upon obstruction. So, we really had to position the subject in such a way that the probability of obstruction was as small as possible.

So, they were complex studies but in the end we achieved good datasets in around 33 subjects.

Dr. James P. Rathmell: So, just to go over that: 33 human volunteers and you compared reversal of neuromuscular blockade with sugammadex or neostigmine with spontaneous reversal in a blinded fashion.

Dr. Albert Dahan: Correct.

Dr. James P. Rathmell: And then you measured this chemoreflex once the train-of-four was back to 1.0 or what we loosely call full reversal was achieved — what we would call full reversal clinically in the operating. So, what did you find?

Dr. Albert Dahan: Well, this is correct. This is how we did the study. What we found was that contrary to our hypothesis is some subjects, the hypoxic response was still blunted. And this was very surprising to us because we had complete reversal of the neuromuscular block at the thumb measured by EMG.

But the hypoxic response was still depressed and some subject depression was even 40% to 50% still. So, indicating that although you have full reversal at the thumb, like you said, full reversal that you want following anesthesia, but still ventilatory control remains impaired in a subset of subjects.

And what’s very surprising to me, that it didn’t really make a difference whether or not you had reversal of placebo, neostigmine or sugammadex; although, there was a small difference. The subject of a reversal of sugammadex did a little bit better than the ones that received neostigmine that, again, did better than the ones with placebo. But all over, we didn’t find a statistical difference. But there was a trend towards the difference; but all over on average, the response might still be depressing subset of subjects.
Dr. James P. Rathmell: So, that’s pretty astounding. Despite full reversal of neuromuscular blockade at the thumb, the way that we measure it every day in the operating room using different classes of drugs for the reversal, the hypoxia chemoreflex isn’t fully restored.

Were there any limitations to your study?

Dr. Albert Dahan: Well, certainly. We used volunteers and realize we deal with patients, elderly patients especially. There are other drugs involved, you realize; either intravenous anesthetics, like we use propofol. In other hospitals they use inhalational volatiles like sevoflurane and desflurane that also have an effect.

In many cases there are still opioid on board that depress the chemoreflex. So, this means that under our conditions, we looked at best conditions possible, best case scenarios, in fact, while we realize this – the conditions might be even worse.

So, although we found in a small subset of subjects that the response was still depressed, we realized in many more patients the response will be depressed and part of that depression is related to the relaxants.

Another issue in our study was that we used awake subjects and we measured EMG at the thumb; and it’s not an easy measurement, especially when you’re awake, it’s a little bit painful. So, there might be some excitation due to the pain; the subjects might have moved a little bit, their thumb. So, we’re not 100% sure whether or not the measurement wasn’t over- or underestimated, so that makes the measurement a little bit unsure.

But on average we believe that we have good measurements and that we’re looking at best case scenarios.

Dr. James P. Rathmell: From your viewpoint, what’s the take-home message for practicing anesthesiologists who use these agents every day?

Dr. Albert Dahan: Yes, good question. First of all, I think when you use neuromuscular relaxant, neuromuscular blockers, you also need to measure the level of relaxation, if possible, at the thumb. We nowadays use different monitors that use it on the arm but doesn’t make a difference. You need to measure the level of relaxation.

It becomes especially important at the end of the case when you give a reversal agent, measure the response. Don’t blindly assume that after you’ve given neostigmine or sugammadex that the response is sufficiently back at the 100% (sounds like: top) ratio.

And even if you have a reversal towards 100% reversal, the hypoxic response might still be depressed, especially if you have residual relaxants on board, especially if you have opioids on board. You need to realize that. That means that in the PACU post-anesthesia care you have to monitor your patients and for an appreciable amount of time. That’s really important.

So, measure your patients with respect to relaxants and monitor your patients with respect to the ventilatory system. That’s really really important.

Dr. James P. Rathmell: Good advice. Dr. Pandit, I want to turn to your editorial view. It’s titled “Reversing Neuromuscular Blockade: Not Just the Diaphragm, But Carotid Body Function Too.” You do a good job of putting the article into perspective.

Please tell us about some of the important studies that came before Dr. Dahan’s new work that helped form our understanding of the effects of neuromuscular-blocking drugs on the acute ventilatory response to hypoxia.

Dr. Jaideep J. Pandit: Well, thank you. Thank you for those words. I think the original groundbreaking studies were, in fact, done by Lars Eriksson and his group and he was a coauthor of this editorial. And he did that initial work back in the 1990’s where they administered sub-paralyzing concentration of neuromuscular blockade to two volunteers and first noted that this hypoxic ventilatory response was depressed.

And the line of work they went on after that was really more animal work to elucidate exactly where in the pathway, the chemoreflex pathway that Dr. Dahan previous described, where these drugs might be acting. And because their animal studies they were able to replicate those results first in whole animals and then study the isolated carotid body to – and record from the afferent nerve, the carotid sinus nerve, to find that the drugs were inhibiting the process at that sort of carotid body level.

Now, we know that’s not the carotid body cells itself that drug are acting on to be inhibitory, but on the synapse. There’s the cell that responds to hypoxia and when there’s hypoxia, the cell secretes acetylcholine that crosses the synapse and then excites the afferent nerve terminals.

And so, it’s acting on the nicotinic receptors of these afferent nerve terminals and that’s where the neuromuscular blockade is acting. So, broadly similar to the neuromuscular junction, but at the hypoxic chemoreflex.

Dr. James P. Rathmell: How does Dr. Dahan’s new work expand our understanding of these effects?

Dr. Jaideep J. Pandit: Well, in several ways, I think. I think the first thing is to reacknowledge the really challenging nature of the methodology that Dr. Dahan’s group has used. This is not sort of, you could say, easy work and the care and dedication in which they did this study is really quite remarkable.

And I think there are three key results. The first is that the resting-minute ventilation was not affected. This is a specific response of the neuromuscular blockade on the hypoxic ventilator response and that’s a significant sort of reemphasis.

The second is clearly that reversal of blockade is beneficial, but not completely so. So, it’s what I would call a sort of sine qua non, that we must have full reversal; if we don’t have full reversal we for sure know that the carotid body chemoreflex is depressed as well. But even if we do have full reversal detectable, we mustn’t assume that the carotid body reflex is recovered as well. We must be vigilant about that.

On the third really interesting finding is that potential for differences between the different types of reversal, sugammadex being possibly more effective than neostigmine.

So, I think those are the three main extensions that Dr. Dahan’s group has contributed.

Dr. James P. Rathmell: Yes, I want to emphasize that having a normal resting minute ventilation doesn’t necessarily mean that the patient will respond with hyperventilation to hypoxemia.

Dr. Jaideep J. Pandit: Correct.

Dr. James P. Rathmell: You hinted at this, but I want you to delve a little deeper. Can you explain briefly what the role of the acetylcholine receptor is at the neuromuscular junction, which I think anesthesiologists all know pretty well, but also at the carotid body and a very, very different function in how the effect of neuromuscular blocking agents differ at the two sites?

Dr. Jaideep J. Pandit: Yes, so as I hinted at, in both sites, the neuromuscular junction and the carotid body, the acetylcholine is being used to translate a signal in the carotid body; this is the signal of hypoxia to excite the cell.

And although they’re acting on nicotinic receptors – we call them nicotinic receptors, the subtypes of the two nicotinic receptors are different between the neuromuscular junction and the carotid body.

And, in essence, we already know, for example, that even with detectable recovery of neuromuscular blockade, 75% of the receptors at the neuromuscular junction could still be occupied.

In the carotid body, the response is much more dose-dependent. And we sort of know already that this has been from Eriksson’s work in the animal studies and this explains why you can have a situation where the detectable neuromuscular blockade has recovered, say, at the thumb, but, of course, the carotid is still being inhibited in that dose-dependent manner.

Dr. James P. Rathmell: So, as an anesthetist, what is the clinical implications of the new findings to you?

Dr. Jaideep J. Pandit: Well, definitely that we should monitor the neuromuscular junction to ensure that there is reversal. We need to reverse the patient. In the UK, we know from previous studies that there has been an unfortunate habit of assuming reversal without either monitoring or using reversal agents. And in that process of reversal, we must be vigilant at not just monitoring neuromuscular function, but also respiratory function.

And then finally is attention to type of reversal being used. If we’ve recently had to paralyze the patient to administer neuromuscular blockade, this is going to tip the balance towards using something like sugammadex to achieve a fuller reversal than with neostigmine. If we’re limited by repeated dosing of neostigmine, again, we must think about sugammadex.

So, those are the main clinical implications that I take away of this study.

Dr. James P. Rathmell: I just want to reemphasize that just as you did in your editorial, it underscores the need for monitoring for complete return
of neuromuscular function to limit this risk and we also need to recognize that there are a subset of patients in whom despite objective reversal of neuromuscular block, there may be remaining impact of neuromuscular blockade on ventilatory regulation.

Dr. Dahan, what comes next for you and your research group?

Dr. Albert Dahan: Yes, we are planning to continue our research on this topic. I’m really very interested in the dynamics of the response, the timing of the response, because the next study will be to investigate at what timepoint carotid body function, the hypoxic ventilatory response has been restored to normal.

So, that will be the first study. And then we’ll do a next study in which we will look at the interaction between anesthetics and neuromuscular relaxants on the carotid body. And again, also, we’ll be looking at the reversal paradigm here.

So, we will continue this line of research. But like I said, it’s not easy to do these experiments. So, we are still working on the protocol because we want to do these studies as safely as possible. So, these are not the easy studies, but we will get there.

Dr. James P. Rathmell: Terrific. I hope today’s discussion will lead many of you listening to read this new article and the editorial view that appear in the September issue of Anesthesiology. You can learn more about the acute ventilatory response to hypoxia and the effects of neuromuscular blocking agents.

Dr. Jon Wanderer from Vanderbilt and I also created an infographic that appears in the same issue that’s titled “Full Strength, but Impaired Response: Neuromuscular Blockade and the Carotid Body” where we aim to better explain the major finding of this study and some of the ideas put forth in Dr. Pandit’s editorial view.

Drs. Dahan and Pandit, thank you very much for joining me today and for the terrific explanations.

Dr. Jaideep J. Pandit: Thank you very much.

Dr. Albert Dahan: Thank you very much.

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