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 November 2019 issue.

With us today is Dr. Åse Lodenius. Dr. Lodenius is a Senior Consultant affiliated with the Department of Pharmacology and Physiology at Karolinska Institutet in Stockholm, Sweden. Dr. Lodenius is the first author on an article that appears in the November 2019 issue of the journal and it’s titled “Upper Airway Collapsibility During Dexmedetomidine and Propofol Sedation in Healthy Volunteers: A Nonblinded Randomized Crossover Study.” Dr. Lodenius, thank you for joining us.

Dr. Åse Lodenius: Thank you for inviting me to participate in the podcast. It’s a pleasure to attend.

Dr. James P. Rathmell: Also with us today is Dr. Denham Ward. Dr. Ward is Professor Emeritus of Anesthesiology and Past Chair of the Department of Anesthesiology at the University of Rochester in Rochester, New York. Dr. Ward wrote an editorial view that accompanies Dr. Lodenius’s research article in the November 2019 issue and it’s titled “‘Upper Airway Collapsibility During Dexmedetomidine and Propofol Sedation in Healthy Volunteers: A Nonblinded Randomized Crossover Study.’” Dr. Ward, thank you for joining us.

Dr. Denham S. Ward: Thank you, Jim. I’m looking forward to an interesting discussion.

Dr. James P. Rathmell: Dr. Lodenius, congratulations on the publication of your work. I want to start by giving listeners some background. Dexmedetomidine is a sedative that is promoted as having minimal impact on ventilatory drive or upper airway muscle activity. But a recent series of articles have demonstrated impaired ventilatory drive and induction of apnea in volunteers sedated with dexmedetomidine.

In the study we’re discussing today—your study—you measured upper airway collapsibility during sedation with dexmedetomidine and you compared that to upper airway collapsibility during sedation with propofol. What was your hypothesis when you started this study?

Dr. Åse Lodenius: Well, the hypothesis that we wanted to examine was whether dexmedetomidine would have less effect on upper airway collapsibility than propofol sedation.

Dr. James P. Rathmell: You conducted this study in 12 healthy human volunteers. Can you talk us through how the study was done?

Dr. Åse Lodenius: Yes. We included adult individuals of ASA Class I to II and a body mass index of less than 37 and these individuals were examined on two separate days, sedated with dexmedetomidine on one day and propofol on the other.

They were equipped with standard perioperative monitoring but also an electroencephalogram and Bispectral Index score monitoring. Respiratory effort was measured with thoracic and abdominal inductance plethysmograph and a pressure transducer catheter passed via the nostril to the esophagus. A nasal mask was applied and the mouth was sealed with tape. Fresh gas was delivered in the nasal mask with a custom-built pressure source, a modified CPAP machine, if you will, that can deliver both positive and negative pressure. A maintenance nasal pressure was given to allow for inspiratory flow with-out flow limitation. Intravenous sedation was then initiated with a bolus of the drug given during ten minutes and this was followed by a maintenance infusion aiming for light sedation.

We checked the sedation level with clinically used sedation scales and recorded this continuously. After 20 minutes of maintenance infusion allowing for steady state to occur, pharyngeal critical pressure was measured and immediately after the first set of measurements, the maintenance infusion was increased to induce deep sedation. Airway measurements were then repeated during deep sedation.

Thereafter, the protocol was ended with the first drug and this was repeated on a second day with the other drug.

Dr. James P. Rathmell: So, I’m trying to imagine being a volunteer in this study. You studied 12 human volunteers and you watched—you looked at upper airway collapsibility at infusion rates that produced low and moderate levels of sedation with dexmedetomidine and propofol. Talk us through in lay terms exactly how this upper airway collapsibility was measured and what that measurement means.

Dr. Åse Lodenius: Well, pharyngeal critical pressure is measured by conducting a series of pressure drops in the nasal mask to induce flow-limited breathing. And then flow and pressure during flow-limited breaths are plotted in a graph and the pharyngeal critical pressure—the Perit as it is called—is derived from linear regression of this relationship between flow and pressure at which the flow is 0 but if the airway is totally occluded is the pharyngeal critical pressure.

Now, the higher the pharyngeal critical pressure is, the more prone the upper airway is to collapse. So, if the Perit, for instance, is above 0, the upper airway will collapse to atmospheric pressure and we know that the Perit during sleep differs between normal individuals, snorers and individuals with obstructive sleep apnea with increased values for the latter.

Dr. James P. Rathmell: So, a measure of the tendency of the upper airway to collapse during sedation.

So, one of the missing elements in many of the prior studies of dexmedetomidine was some measure of the depth of sedation to correlate with the degree of airway collapsibility or apnea, what have you. How did you determine the depth of sedation during this study? And I think you used more than one method.

Dr. Åse Lodenius: We did. We measured it with two different sedation scales that are clinically used: one for—mainly for healthy volunteers participating in studies and the other one is widely used in the intensive care units. And we also measured BIS, Bispectral Index score. And adding to that, we used an encephalogram to make sure that there were no arousals during these flow-limited breaths. So, there was several ways of measuring the sedation level.

Dr. James P. Rathmell: So, what did you find?

Dr. Åse Lodenius: Our findings were that we could not show a difference in pharyngeal critical pressure when comparing sedation with these two drugs. The level of sedation during deep sedation did differ somewhat according to the sedation scales and BIS even though we could not make out a difference in the pharyngeal critical pressure.

And we also found that three of the participants had periods of central apnea with both drugs starting during the bolus infusion.

Dr. James P. Rathmell: So, a wide range of different findings in this small group. Now, I’m going to steal a few questions from Dr. Ward; he sent me some suggestions via email over the weekend. You were able to use a wider range of subject demographics and characteristics like sex, age, body mass index, Mallampati Score, than is usually seen in a laboratory study.

But with this heterogeneous small group, only nine patients were analyzed; subgroup analysis was impossible. In future studies, is there a subgroup that you would want to focus on?
Dr. Åse Lodenius: It would have been of interest to analyze by sub-
group since we know that the PeriP differs during sleep between these
different type of subject: normal subjects, snorers, people with obstructive
sleep apnea. So, that would have been really interesting to see how they
differed.
And if you’re already prone to airway obstruction, you might be more
vulnerable to airway obstruction during sedation. And also pathology of
the airway puts you more at risk and these people were excluded from
the study.
But as you say, there was a very small number and a variability within the
subjects in the study. So, it would have been nice to have a larger number of
cohorts to study. That would be ideal for the future.
Dr. James P. Rathmell: One of your subjects didn’t get sedated
and another had too much obstruction to be able to make any of the
measurements that you made. To find those extremes in such a small
study seems pretty interesting. How should that be followed up in future
studies?
Dr. Åse Lodenius: Well, the person that could not keep an airway open
just from lying down would not be ideal to include in the study as was
found when trying to conduct the protocol with this person. The indi-
vidual that never got sedated enough is very difficult to foresee.
So, I guess with a larger number included you can sort of adjust for some
people dropping out that you cannot foresee that they will not be able
to follow through with the protocol. But maybe it’s not ideal to include
individuals with a very high collapsibility of the airway just from lying in
a supine position.
Maybe changing the body position would be one way of doing it, but
traditionally these examinations are done with the individuals lying
supine and in a very controlled manner.
Dr. James P. Rathmell: Now, this was a very small number of subjects
and you used a physiologic measurement. Can you talk a little bit about
generalizing this to clinical practice? How well do you think the results
actually generalize?
Dr. Åse Lodenius: From a clinical point of view I think since we have
made observations of both upper airway obstruction and centrally evoked
apnea, for patient safety reasons the assumption must be that the results
generalize to clinical practice, and also from a former study that we have
made when we observed upper airway obstruction during dexmedeto-
midine sedations.
I think the fact that we allowed for individuals with a varying collaps-
ibility of the upper airway to take part in the study makes interpretation
more difficult, but we also have used propofol—which is a drug that is
well-known to cause upper airway obstruction—as a comparator and
found no difference with the two drugs.
And the correlation in Pcrit between dexmedetomidine and propofol
was actually a strong one. So, that sort of strengthens the fact that it might
be generalizable to a clinical situation as such.
Dr. James P. Rathmell: So, some pretty strong hints at generalizability.
Dr. Ward, I want to turn to your editorial view. For listeners, again, the
editorial is titled “Dexmedetomidine and the Upper Airway: Not as
Simple as We Hoped.” You do a terrific job of putting this article in
perspective. Your editorial begins by telling readers that sedative agents
depress ventilation through a variety of actions. Can you talk us through
the various ways that sedative hypnotics can depress ventilation?
Dr. Denham S. Ward: Sure, Jim. Classically the sedative hypnotics or
the analgesics are tested through their effects on the chemoreflexes and
and a previous paper by Dr. Lodenius addressed that with dexmedetomidine
also; that is, the hypoxia through the carotid body causes an increase in
ventilation and hypercapnia through both the carotid body and the cen-
tral chemoreceptors increase ventilation. And the sedative hypnotics will
decrease that response to hypoxia and hypercapnia.
But the upper airway muscles are also sensitive to sedation and hypo-
notics and it may not be in the same proportion as their effect on the
chemoreflexes.
And thirdly, many years ago Ray Fink pointed out to us that there’s
another effect known as the wakefulness drive that normally during
resting breathing neither hypoxia or hypercapnia is causing our resting
ventilation, but there’s another drive that’s neurological in origin. And, of
course, the sedative hypnotics are going to remove that wakefulness drive
and that’s going to cause a decrease in ventilation and most likely an
increased propensity to upper airway collapse.
Dr. James P. Rathmell: How does Dr. Lodenius’s new work expand
our understanding of the effects of dexmedetomidine and propofol?
Dr. Denham S. Ward: Well, I think as she just nicely pointed out, the
fact that even though it’s a small study and obviously heavily instru-
mented volunteers with their mouths taped shut, which would be quite
different than the clinical situation, because they do have the propofol
comparator there in the same subjects with their crossover design, they
can really show it can have similar effects.
And coupled with their previous work, they seem to have the same kinds
of effects on all three and ways in which ventilation can be affected:
chemoreflexes, the upper airway and the wakefulness drive.
I also thought it was very interesting, again, small numbers, but in their
discussion she points out that the subjects who had kind of the same
effects with both propofol and dexmedetomidine—that is, the subjects
that had the most airway obstruction—had the most airway obstruction
with both drugs.
Perhaps some of this is because of a loss of consciousness in the wakeful-
ness drive rather than a specific drug receptor brain effect because these
two drugs have very different mechanisms of action.
Dr. James P. Rathmell: You were surprised by the wide variation of
outcomes that were seen in this small study. Can you say more about
what you found surprising?
Dr. Denham S. Ward: Well, I think the fact that they include such a
wide range of subject characteristics which is, I think, a wonderful thing
to do even though it obviously makes the study harder to do than a very
homogeneous set of subjects.
Particularly the subject not getting sedated, I think, points out one of the
limitations of their study as far as its clinical applicability and that they
use fixed doses rather than the clinical way that we would titrate that we
would use in practice.
If a titration had been used, it would be interesting to see that if subjects
that require more of the drug to reach the same level of sedation have
more of an effect on the respiratory effect because the drug concentra-
tion levels are going to be higher.
And I also found out, perhaps not as surprising, the fact that some
subjects really have a hard time laying down and breathing in a supine
position.
Dr. James P. Rathmell: You wrote to me over the weekend and
you said this: from a scientific point of view, I’m interested in better
understanding a specific drug effect versus the effect that’s due to loss of
consciousness.
Can you explain a little bit more about what you mean? You already
hinted at this, but why are you interested in differentiating these two
effects? Why is that important?
Dr. Denham S. Ward: Well, that really goes back to, as I said, both the
work back in the 60’s that Ray Fink did and also my mentor J. Bellville
did looking at a drug effect in either natural sleep or sedation, a decreased
level of the consciousness.
These two are drugs that, I think, are great examples. They’re very differ-
ent receptor profiles and where they act in the brain, yet they have very
similar respiratory effects. Are those respiratory effects caused by the drug or are they caused by the loss of consciousness, per se?

This is really different that for the opioids which we know have a very specific opioid receptor depression of ventilation and one in which we would love to find a strong analgesic that doesn’t have this respiratory depression.

But the loss of consciousness plus the opioid causes a much more depression in ventilation. So, just this loss of consciousness, the loss of the higher levels of the brain modulating the respiratory centers in the brain stem, can have a pronounced effect.

So, maybe we need to find the right drug that gives sedation without respiratory effects, but maybe we won’t be able to because the final common pathway, of course, is the desired efficacy of loss of consciousness.

Dr. James P. Rathmell: So, loss of consciousness itself has profound effects on ventilation.

Dr. Denham S. Ward: Yes. And it may be different than natural sleep. Loss of consciousness through any kind of drug effect may have a different effect than when somebody falls asleep and may have some of the same effects. Some of the studies we’ve been doing in our laboratory have looked at kind of the slow way of sleep that can occur in EEG manifestation during sedation.

Dr. James P. Rathmell: So, what are the clinical implications of these new findings?

Dr. Denham S. Ward: As Dr. Lodenius had pointed out, the clinical implications are when you’re using a drug or drugs that causes decrease in consciousness, then that patient – and there may be variation in how much, but that patient is going to be at risk for upper airway obstruction.

Not to be too simplistic, but vigilance is important. There’s no way that you can just assume because I’m using dexmedetomidine that it’s not going to be the same propensity to upper airway obstruction.

Dr. James P. Rathmell: Dr. Lodenius, your work really brings into question the notion that dexmedetomidine produces less respiratory depression at similar levels of sedation when compared to propofol. What’s next for you and your research group?

Dr. Åse Lodenius: Well, we have nothing for the moment planned regarding dexmedetomidine. The research area I’m in now is more (sounds like: defined) high-flow nasal oxygenation during apnea, so it has sort of shifted towards that way. So nothing at the moment regarding dexmedetomidine.

But I’m really anxious. I’m hoping to see some new studies in the future regarding the subject.

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 November 2019 issue of ANESTHESIOLOGY. You can learn more about the effects of dexmedetomidine and propofol on the upper airway.

Dr. Jon Wanderer from Vanderbilt and I also created an infographic that appears in the same issue and it’s titled “Safe Sedation Re-examined: Comparing the Respiratory Effects of Dexmedetomidine and Propofol” where we aim to explain the major findings of this study and compare it to our understanding from previously published study.

Drs. Lodenius and Ward, thank you for joining me today and for the terrific explanations.

Dr. Åse Lodenius: Thank you.

Dr. Denham S. Ward: Thank you, Jim, and thanks to you and Jon for making that nice infographic. I think that’s a real valuable addition.

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