Dr. BobbieJean Sweitzer: Hello, I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and an Associate Editor for Anesthesiology and you are listening to an Anesthesiology podcast designed for physicians and scientists interested in the research that appears in our journal.

Today we are speaking with the author of a publication that appears in the September 2018 issue of the journal. With us is Dr. Charles H. Brown IV. Dr. Brown is the lead author of an article titled “Cognitive Decline after Delirium in Patients Undergoing Cardiac Surgery.”

He is an Associate Professor and Director of Clinical Research in the Cardiac Division in the Department of Anesthesiology and Critical Care Medicine at Johns Hopkins University School of Medicine in Baltimore, Maryland. Welcome, Dr. Brown.

Dr. Charles H. Brown IV: Thank you for having me.

Dr. BobbieJean Sweitzer: So, can you tell us a bit more about the pertinent comorbidities that the patients had? And why did you pick this group?

Dr. Charles H. Brown IV: Sure. So, the group of patients that we examined were generally patients undergoing cardiac surgeries and, in particular, generally coronary artery bypass, valve and/or root surgery that did require cardiopulmonary bypass and were at higher risk for neurologic complications.

We did exclude people who were not English-speaking, had contraindications to MRI and renal failure. But generally we try to enroll a higher-risk cohort of on-pump, bread-and-butter cardiac surgery patients. And the reason we really focused on cardiac surgery was because of the relatively high incidence of postoperative delirium in this population; the incidents vary, but up to 50%. And then in addition to changes in cognition that potentially occur after cardiac surgery and have been investigated over the past two decades in the anesthesia community.

And so, we were really focused on how delirium, in particular after cardiac surgery, was associated with cognitive changes in the month to year after the procedure.

Dr. BobbieJean Sweitzer: So, can you tell us a bit more about the pertinent comorbidities that the patients had? And I think you mentioned a couple of exclusion criteria, but if you could maybe highlight the situations you excluded.

Dr. Charles H. Brown IV: Yes. So, the patient population really was fairly typical for our cardiac surgery population. So, the mean age was 70, approximately 75% were male and approximately 80% Caucasian. The education level was high, so greater than a mean of 15 to 16 years of education and then the comorbidities were what you would expect in a cardiac surgery population: so, greater than 90% had high blood pressure baseline, 13% had a prior stroke, 45% had diabetes. So, typical in cardiac surgery population.

As I said, we try to enroll patients who are undergoing typical cardiac surgery, so coronary bypass, valve, some aortic surgery. And then a lot of the exclusion criteria were germane to how we were conducting the study. So, as part of the study, we obtained MRIs in the postoperative period and so patients with contraindications to MRI, some certain types of pacemakers, et cetera, we excluded. We also excluded for that reason patients in renal failure. And then patients who were non-English speaking; we really felt that we would not be able to rigorously assess delirium and cognitive change and so we excluded those patients. And in the Johns Hopkins’ sort of catchment area, the non-English speaking population is relatively sparse.

Dr. Charles H. Brown IV: So, our anesthetic management has been fairly standard up until probably one to two years ago and generally that has been an opioid and/or benzodiazepine induction, maintenance with isoflurane and then propofol for postoperative sedation.

Generally this anesthetic regimen was fairly stable, although I will say that the use of benzodiazepines declined over the course of the study due to increasing awareness of associations with delirium and cognitive change after cardiac surgery.

Dr. BobbieJean Sweitzer: It’s interesting because I think a fair number of these patients did get midazolam for both indication as well as postoperatively for those requiring more than 24 hours of mechanical ventilation. And as you mentioned, the increasing awareness of that association. What impact do you think this may have had on your findings?

Dr. Charles H. Brown IV: I think you raise a good point. We allowed for the use of benzodiazepines in the postoperative period for patients undergoing long-term mechanical ventilation and this was really the minority of patients. Most patients were maintained on propofol until extubation within the first 24 hours.

We have noticed over the years a general decline in the use of midazolam during the OR procedure and, as you pointed out, midazolam has been associated with postoperative delirium and delirium in the ICU.

In this study, there was some variability and we allowed for that variability among practitioners. But when we looked at different levels of midazolam usage, we did not find that it impacted the association of delirium and cognitive decline that we looked at primarily in the study.

Dr. BobbieJean Sweitzer: So, let’s dive a bit deeper into the design of your study. I think you describe this as a “prospective observational study, nested in an ongoing trial.” Can you help me understand what this means?

Dr. Charles H. Brown IV: Yes. So, we have been conducting a trial in which blood pressure during cardiopulmonary bypass was titrated based on monitoring of brain blood flow. As part of the trial, we have conducted rigorous delirium assessments in the first several days after surgery and...
conducted neurocognitive testing with the baseline a month and a year after surgery.

And so, the primary question of the trial was not the focus of this paper. This paper was a nested question that allowed us to ask a very particular question about the association of delirium in cognitive change nested in an ongoing study that allowed us to have very good delirium and cognitive assessments.

Dr. BobbieJean Sweitzer: So, kind of a study within a study.

Dr. Charles H. Brown IV: A study within a study.

Dr. BobbieJean Sweitzer: So, what was that primary trial or study designed to answer?

Dr. Charles H. Brown IV: So, the primary study was designed to address the question of whether titrating blood pressure during cardiopulmonary bypass based on monitoring of real-time cerebral autoregulation could reduce the instance of a composite outcome of cognitive injury, stroke and lesions on MRI.

Dr. BobbieJean Sweitzer: An important question to answer. What do we already know about postoperative delirium in cardiac surgery patients?

Dr. Charles H. Brown IV: So, we know that postoperative delirium is common and the incidence varies, but using one of the best validated tests, the Confusion Assessment Method, our group and others have published incidents of up to 50% of patients. We also know what are the predominant risk factors for delirium and they would really be age, baseline cognitive impairment, lower education, cerebral vascular disease like stroke, as well as a complicated postoperative course. And then we also know that delirium appears to be associated with longer-term changes both in cognition and potentially function, but those studies have had weaknesses and need to be repeated in different settings. And then finally I would say that there has been a lot of work on how to prevent delirium and the strongest evidence appears to be nonpharmacologic approaches that are easy to talk about but can be hard to implement, such as enhanced mobility in the postoperative period, careful use of medications, careful attention to hydration, cognitive engagement—giving patients back hearing aids and glasses. These nonpharmacologic approaches have proven effective across many different patient populations.

Dr. BobbieJean Sweitzer: So, I recall that in your methods you even described details about the cardiopulmonary bypass circuit, the oxygenator and the filter. Why is this important?

Dr. Charles H. Brown IV: We described details about our protocol so that practitioners and other institutions can interpret the generalizability of our results. And so, if we have a finding in patients who undergo cardiac surgery that are always on cardiopulmonary bypass but another institution only does off-pump surgery, well, our findings may be applicable to their population, but it may not depending on some of the underlying ideology or pathophysiology. And so, we tried to describe a lot of the protocols and the sort of care parameters that these patients received so that readers in other institutions can evaluate how our results might be generalizable in their population.

Dr. BobbieJean Sweitzer: So, when were patients assessed and who did the evaluations?

Dr. Charles H. Brown IV: So, we assessed patients on three of the first four postoperative days in person and supplemented with a chart review for times that we could not assess and some of that was due to logistical and staff availability on weekends.

We used the Confusion Assessment Method and that was developed by Sharon Inouye. And I'm lucky at Hopkins to have a delirium expert and collaborator, Dr. Karen Neufeld. We have developed a delirium assessment program over the years that we believe is rigorous and is sensitive and uses a lot of the methodology from Dr. Inouye's group.

And so, we assess patients using the Confusion Assessment Method with a structured cognitive exam that every patient gets, including the Mini-Mental Status Exam. We also ask unstructured questions in conversation with patients and questions that are open-ended such as, did patients experience any strange visions or strange senses or did they feel fearful, did they trust the staff? Questions that allowed patients to respond and for us to gauge their responses.

We followed that by questions to nurses and any patient family that was around to judge how the patient had acted over a 24-hour period. And that allowed us to glean information about periods where we actually weren't assessing the patient in person; it allowed us to understand what happened at night or earlier in the morning.

And so, that combination of structured questions and unstructured questions gave us insight into how to score and rate delirium using the Confusion Assessment Method.

Dr. BobbieJean Sweitzer: So, that was interesting approach. It seems like you were more likely to find, perhaps, patients that would otherwise have been overlooked because you sort of raised the awareness over various people, even if you weren't there or the patient was not delirious at the time you were evaluating them, you would have gotten reports from their caretakers.

Dr. Charles H. Brown IV: Yes. I would say that in general our methods are sensitive in that we pick up delirium episodes amongst patients who might not be recognized clinically as delirious and that might be because of timing or it might be because we have asked and answered structured questions that we know what the patient's score was at baseline.

And so, importantly, we were able to gauge change and it's important as you look across the literature because different studies will report different instances of delirium and some of those discrepancies relate to the type of battery or testing that was used. But others relate to how different criteria are interpreted.

And so, we have done a lot of work over the years to ensure consistency among raters and consistency in our approach with Dr. Inouye's group who really has been a leader in delirium research. We know that we are sensitive and probably pick up more delirium than might be recognized clinically, but we see that there are relationships with postoperative outcomes. So, we think that that is important.

Dr. BobbieJean Sweitzer: So, I may regret asking you this, but – and – because I'm a little bit jetlagged from a long trip from overseas, but can you maybe do a little bit of an exam on me? Ask me a few of the questions that you would have asked a patient?

Dr. Charles H. Brown IV: Sure. Well, we would ask some structured questions, as I alluded to, and one structured question would be, please tell us the months of the year backwards and I'm going to time you.

Dr. BobbieJean Sweitzer: December, November, October, September, August, July, June, May, April, March, February and January.

Dr. Charles H. Brown IV: Great. So, in this case you got all correct in a good time. We would have that information from your baseline, so we would know how long it took you and how many you got correct and you would be surprised how many patients cannot do that correctly in the postoperative period and how time actually correlates with recovery. So, we will often see a doubling of time on postoperative day one and then...
a gradual resolution to normal over the next couple days. That would be one example of a structured question that we would ask.

Another structured question would be digit span. So, I would ask you to repeat the numbers that you hear after I say them, but repeat them backwards: 5, 2, 9, 7.

Dr. BobbieJean Sweitzer: 7, 9, 2 5.

Dr. Charles H. Brown IV: Correct. And we ask five of those digit-span questions. So, those are the structured questions that we would ask.

We also ask patients unstructured questions about how their postoperative period has been, how their thinking has been, have they noticed anything unusual. And then we talk to family, other medical staff and we ask questions about if they have noticed patients appearing disoriented or confused or having memory problems or appearing agitated, trying to get out of bed. Or conversely, too slow to answer questions and too slow to move around. It gives us a full picture.

Dr. BobbieJean Sweitzer: How much time would you spend with a patient asking them these kinds of questions?

Dr. Charles H. Brown IV: I think around half an hour between asking formal questions to patients, examining the chart, talking to family, talking to nurses and walking to the floor and back. Half an hour would be an average estimate, even though with the patient it's him or herself might only be seven or eight minutes.

There are shorter batteries that have been developed and we are using some of them now but the CAM has really been one of the most widely used tests both in our group and in other groups and so I really consider it very important and sort of gold-standard test.

Dr. BobbieJean Sweitzer: Can you assess intubated patients for delirium? And if so, how?

Dr. Charles H. Brown IV: We do. We use the CAM-ICU— which is a test developed by Wes Ely—to assess domains of the CAM in patients who can't talk because they're intubated. And so, a particular question that we might ask to a patient is the question: Does one pound weigh more than two pounds? And I want you to squeeze my finger if yes. Are there fish in the sea? Squeeze my finger if yes.

And so, we can start to ask simple questions that test thinking and attention, we can gauge level of consciousness and we can obtain the information necessary for a delirium assessment even in patients who are intubated.

Now, you'll notice that the test does require some level of interaction. And so, patients that are too sedated we cannot assess with a CAM-ICU.

Dr. BobbieJean Sweitzer: So, I think you used another assessment scale, the Richmond Agitation-Sedation Scale, also known as a RASS, to assess coma. I'm a bit familiar with this tool being used in PACUs, for example, by nurses to assess sedation levels. Can you tell us a little bit about this scale?

Dr. Charles H. Brown IV: Sure. So, this scale, as you alluded to, measures agitation and sedation and we use it as a first step to judge whether the CAM-ICU can be used as a tool in an intubated patient in front of us.

So, if the RASS score is too low and patients are not responsive to even physical stimulation or even unarousable, then we would say, "The RASS is too low. We cannot assess these patients." And this happened in a minority, but we thought it was important to make sure we included in the analysis in some way. They weren't formally delirious because we hadn't assessed them, but they had some underlying brain dysfunction either due to brain injury or to sedation.

And so, we included them later as a sensitivity analysis of people whose RASS was too deep. But generally we used it as a way to decide if the CAM-ICU was appropriate to use as a delirium assessment tool.

Dr. BobbieJean Sweitzer: I think you also did a battery of neuropsychological tests. Can you tell us about these?

Dr. Charles H. Brown IV: Sure. So, we have a history, at least in Johns Hopkins, of looking at cognitive change after cardiac surgery and are fortunate to work with neuropsychologists who have thought about this over the years. And clearly a number of other groups have done a lot of seminal work in this as well and have come up with recommendations for what a battery should look like.

And we tried to really craft a battery that fit both with our experience and with sort of general consensus. And so, there are many of tests that we used and different tests we thought would help gauge different domains of cognition, either by themselves or together, and we would really provide a more full picture than one test. For instance, a screening test, like the Mini-Mental Status Exam.

We gave this neuropsychologic test to patients at baseline and then within four to six weeks and a year after surgery, and that allowed us to look at change over time from baseline.

Dr. BobbieJean Sweitzer: So, you speak about baseline. Did you actually measure baseline cognitive function in these patients before their surgery?

Dr. Charles H. Brown IV: We did. And we tried to get baseline data within approximately two weeks of surgery and it was really important for this question because baseline cognition is a strong risk factor for delirium.

So, we knew upfront that patients who got delirious probably had lower cognitive scores at baseline. We were interested to see how they changed in relation to the non-delirious group.

Dr. BobbieJean Sweitzer: But you didn't exclude anybody or people didn't have to have normal cognitive function at baseline to be included in your study?

Dr. Charles H. Brown IV: Correct. And as context, our mean Mini-Mental score is approximately 28 from the cardiac surgery patients that we've assessed over the years. So, I think that gives you a sense that the mean is cognitively preserved and this would be in contrast to a hip fracture population where the mean might be more like 23 or 24.

Dr. BobbieJean Sweitzer: So, for the listeners who are not familiar with a Mini-Mental Status Exam, can you give us perspective on that scaling?

Dr. Charles H. Brown IV: Sure. So, the Mini-Mental Status Exam, I think, is a widely used multi-domain test that can be administered generally in under ten minutes on a scale from 0 to 30. People use it in large part because it is so prevalent and across cognitive testing it's very transferrable. People understand what goes into it and how the scoring is. But there can be limitations of, let's say, for instance, ceiling effect where someone can complete the Mini-Mental Status Exam correctly, suffer a decrement in cognition, but still complete it correctly because they have enough reserve.

Dr. BobbieJean Sweitzer: So, when do you expect to see delirium in patients after major cardiac surgery?

Dr. Charles H. Brown IV: The highest instant that we found is on postoperative day two. We generally think that about 90% delirium will have manifest by postoperative day four; that's why we, in our studies, have generally looked at this early postoperative period.
Dr. BobbieJean Sweitzer: So, can you summarize what you found with this?

Dr. Charles H. Brown IV: We had data available from 142 patients and we found an incidence of delirium in 53.5% of patients. So, in line with what we and others have reported.

We further found that patients with delirium, as expected, had lower cognitive scores at baseline compared to the non-delirious group. Cognitive scores were also lower at the one-month and one-year follow up. And then importantly, a question of interest, we found that cognition declined greater in patients with delirium from baseline to one month compared to patients without delirium from baseline to one month. So, there was a significant difference with greater cognitive decline in the delirious patients.

By one year this gap had narrowed, so there was still greater decline in the delirious patients, but this was no longer significant.

Dr. BobbieJean Sweitzer: I think you assess some specific skills, not just sort of global cognitive skills or delirium. In fact, you talked about looking at psychomotor skills. Why is this important and exactly what were you assessing here?

Dr. Charles H. Brown IV: Yes, so we looked at several different domains of cognition that had thought to be important after cardiac surgery.

And so, one particular domain was processing speed and we found that in this domain, delirious patients declined greater from both baseline to one month and baseline to one year compared to non-delirious patients.

So, processing speed is cognitive ability that reflects the time it might take someone to do a mental task and so people with difficulty in that may have difficulty in reading, math, listening, conversations, some of these activities that we know are important for function in all of us, in particular older adults and in particular the postoperative period of recovery.

Dr. BobbieJean Sweitzer: Can you explain and provide an example of the visuoconstruction which was another assessment that you looked at?

Dr. Charles H. Brown IV: Sure. We looked at visuoconstruction and this we think of as the domain that really involves the ability to manipulate information in space. And so, the way we assessed it is using a complex figure and how you're able to copy that complex figure.

In this domain we saw greater decline in the delirium group from baseline to one month, but there was no difference from baseline to one year compared to the no delirium group. And visuoconstruction can be important in activities involving spatial information such as driving, even, which we know is important for older adults.

Now, I will say we assessed seven domains and two of them had results suggesting that the delirious group did worse, but the other domains did not have statistically significant differences in the delirium versus non-delirium group. Generally there is more decline across all domains from baseline to one month in the delirium group, but it wasn’t always significant.

And so, this is a secondary outcome that we presented to generate hypotheses and might need further explanation but wasn’t the primary outcome of the study.

Dr. BobbieJean Sweitzer: So, in your paper I think you refer to delirium as possibly being a “stress test for the brain.” Can you explain what you mean by this?

Dr. Charles H. Brown IV: The fundamental question is whether delirium is simply a marker for someone who will have cognitive decline anyway or if there’s somehow a causative role for delirium.

And so, if delirium is simply a marker—and I use the analogy of a stress test—a stress test doesn’t cause you to have coronary dysfunction later, but it is a marker of someone who’s at higher risk.

Similarly, delirium may simply be a sign of a vulnerable brain who will have ongoing cognitive decline. That’s an important distinction because that would allow people to assess risk in the postoperative period and provide a projected course. But it would also suggest that modifying delirium might not affect longer-term cognitive outcomes.

However, if the converse is true, if there is a causal role for delirium, then it implies that efforts to prevent delirium may be effective in preventing longer-term cognitive change. And I really see a potential or a causal role in one of two ways: one, patients who have delirium may have things that happen after the delirium: they get antipsychotics, they have more bedrest, sleep disturbances. The other explanation might be that there is an underlying insult, such as cerebral ischemia, that predisposes someone to delirium and longer-term cognitive change.

Understanding what that common insult might be is critical because then the intervention is to prevent the common insult, preventing, thus, the delirium and the longer-term cognitive change.

So, all of that's a long answer to say understanding whether delirium is causal or not is critical to understand how to use this information to really preserve brain health after surgery.

Dr. BobbieJean Sweitzer: So, some very important questions. So, is there any good news you can share with our audience about delirium and our cognitive decline? What's the future hold? Where are we making progress?

Dr. Charles H. Brown IV: The good news is that delirium is much more recognized and because of that has become a target for improvement efforts both in research and in quality improvement. And anecdotally from our experience, both in the perioperative and in the ICU, that the instance of delirium has been declining and I think some of it is due to increased recognition, increased recognition of the importance of delirium, medication management, nonpharmacologic approaches. And so, the good news is that the incidence appears to be declining, although it is still quite prevalent.

The other thing I would say is that most patients do well from a cognitive perspective in the long term after surgery and cardiac surgery. There appears to be decrements in the weeks to months, but by a year to two years later the cognitive trajectory recovers in many patients.

There is some data in a noncardiac surgery population that there may be cognitive decline among delirious patients in the long term, so two, three and four years later. That deserves more investigation and we, in fact, would love to follow this study up with longer-term cognitive assessments in this study population at four, five, six years, even later because it’s a unique population that we have rigorous delirium and perioperative cognitive assessments and would really shed some insight into the long-term associations of delirium and cognitive change.

Dr. BobbieJean Sweitzer: Well, good luck with that.

Dr. Charles H. Brown IV: Thank you very much.

Dr. BobbieJean Sweitzer: I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more.

Thank you, Dr. Brown, for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

Dr. Charles H. Brown IV: Thank you very much for having me on this program.

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