Dr. BobbieJean Sweitzer: Hello. I am 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 two authors of publications that appear in the March 2020 issue of the journal. With us is Dr. Michael R. Mathis. Dr. Mathis is the lead author of an article titled “Preoperative Risk and the Association between Hypotension and Postoperative Acute Kidney Injury.” Dr. Mathis is Assistant Professor, Department of Anesthesiology at the University of Michigan Medical School in Ann Arbor, Michigan. Welcome, Dr. Mathis.

Dr. Michael R. Mathis: Thank you. It’s a pleasure to have the invitation.

Dr. BobbieJean Sweitzer: And joining Dr. Mathis is Dr. Louise Y. Sun who wrote an accompanying editorial “Preoperative Risk, Blood Pressure, and Acute Kidney Injury.” Dr. Sun is Assistant Professor of Anesthesiology and Epidemiology and a Clinician Scientist in the Division of Cardiac Anesthesiology at the University of Ottawa Heart Institute and the School of Epidemiology and Public Health at the University of Ottawa in Ottawa, Ontario, Canada. And she’s also at the Cardiovascular Research Program and the Institute for Clinical Evaluative Sciences in Toronto, Ontario, Canada. Welcome, Dr. Sun.

Dr. Louise Y. Sun: Thanks for having me.

Dr. BobbieJean Sweitzer: Let’s start with you, Dr. Mathis. How common is acute kidney injury in patients having noncardiac surgery?

Dr. Michael R. Mathis: Sure, that’s a great question. The short answer is that it’s fairly common; about 6% to 10% of noncardiac surgical patients will have acute kidney injury. A more nuanced answer is that it probably depends on the exact definition of acute kidney injury and the exact noncardiac surgical population.

There’s a number of studies that have been done over the past decade; there’s a study by the Cleveland Clinic team that found that the rate was around 6% to 7% of acute kidney injury. Dr. Sun herself has a study using the noncardiac surgical population at the University of Health Network in Toronto and they found an acute injury rate of 6%.

And then the POISE-2 study, another landmark study, looking at noncardiac surgical patients, older patients having more comorbidities and the rate of acute kidney injury in that population was 13%. In our study we found that among noncardiac surgical patients across the US academic centers and private hospitals, the rate was around 9%.

Dr. BobbieJean Sweitzer: And I think in taking into context of the millions of surgeries that are performed every year, that’s not an insignificant number of patients.

Dr. Michael R. Mathis: Absolutely, yes. It has a potential for huge health-care impacts, both patients and healthcare costs.

Dr. BobbieJean Sweitzer: So, can you tell us maybe what we already know about acute kidney injury perioperatively and the outcomes of patients experiencing AKI?

Dr. Michael R. Mathis: Beyond how common it is, we know, as I mentioned, it has a major health impact. It’s associated with a six-fold increased risk of mortality, it increases hospital length of stay, the cost mortality and we know that even small perturbations in renal function, small increases in creatinine or mild AKI can be associated with long-term renal dysfunction.

There’s another study recently published in Anesthesiology from the Cleveland Clinic that examined mild AKI and it showed that patients having mild AKI had about two-and-a-half times the odds of having long-term renal dysfunction versus those without AKI. So, it certainly has some major negative health impacts.

The other important thing to note is that most pharmacologic attempts to prevent AKI have been unsuccessful. There’s been a number of different studies looking at medical therapies such as N-acetyl cysteine, statins, prophylactic use of low-dose dopamine and virtually all pharmacologic attempts to prevent AKI have been unsuccessful.

And so because of the many failed attempts to prevent or reduce the impact of AKI, this remains a very intense area of research.

Dr. BobbieJean Sweitzer: Yes, thanks for pointing that out. I think both of those points are really worth emphasizing that we’ve identified a problem but we’ve failed to find a solution yet. And then that other part about, I think, in the past many people were led to believe that if you recovered your renal function or your creatinine went back to normal or back to baseline, then everything was okay.

But now I think we appreciate more that it’s like sort of having a myocardial infarction; you’ve damaged tissue, you’ve lost some function there that later can have an impact.

Dr. Michael R. Mathis: Yes, that’s absolutely correct. Yes. Even subclinical AKI we’re finding has long-lasting health impacts and if there are things that we can do to mitigate the risk of AKI, we should be focusing on what we can do to mitigate that risk.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, you kindly pointed out several different studies that have appeared recently around this subject. So, maybe can you tell us what specific question or questions you decided to try to address with your study?

Dr. Michael R. Mathis: Sure. So, we did want to build upon previous literature, we wanted to take into context the multiple different studies; some from the Cleveland Clinic, another study from Dr. Sun herself. Really a lot of the studies over the past decade have tried to focus on a convenient single kind of magic number that is “This is the blood pressure that we should try to maintain; below this blood pressure range clinically significant hypotension occurs.”

That’s been very useful and informative, but it goes against a little bit of the clinical intuition that anesthesiologists have that it’s basically that not all patients are equal and there’s an intuitive kind of notion that healthier patients may be more tolerant of hypotension compared to sicker patients.

And so that’s really what our study set out to ask: we wanted to, I guess, first develop an improved preoperative prediction model for acute kidney injury across the multicenter population. But secondly, and more importantly, we wanted to examine whether the association between hypotension and acute kidney injury varies by preoperative risk and that is to say, are sicker patients more sensitive to hypotension than healthier patients?

Dr. BobbieJean Sweitzer: Which I think is very much in line with medicine currently looking at personalized medicine.

Dr. Michael R. Mathis: Yes.

Dr. BobbieJean Sweitzer: So, Dr. Sun, let’s ask a question here. Your feelings about do we know what the optimal blood pressure is needed to maintain end organ perfusion under general anesthesia of maybe any organ, but specifically the kidney since that’s what we’re talking about today?

Dr. Louise Y. Sun: And you know, Dr. Sweitzer, I think that’s a very good question because I think the classic answer that I usually give to a question like these is it depends. And the reason I say that is I think the optimal blood pressure is dependent on a lot of things: it would depend on the definition of hypotension that we use, whether it’s absolute threshold versus relative, it would depend on the type of procedure, it would depend on baseline patient risk like Dr. Mathis was just discussing.

Dr. BobbieJean Sweitzer: Well, we hope to explore that a little bit more, then, in this discussion, I guess, to try to get to what it depends on.
Dr. Louise Y. Sun: Definitely.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, was this a randomized prospective trial or what did you use to answer these questions?

Dr. Michael R. Mathis: Yes, that's an important point because we -- so, this was simply a retrospective study and although the associations that you can glean from the study can provide some insight into the clinical care processes that may lead to acute kidney injury and specifically ranges of hypotension, if you're a clinician reading this article you should be careful not to interpret these findings as causal and that blood pressure thresholds identified by this study will require prospective validation to reach a level of evidence that's strong enough to guide clinical care.

Dr. BobbieJean Sweitzer: Good points. So, can you tell us a little bit more about this study, for example, like what populations of patients, the number of patients you had, the types of surgeries or anesthetics they received?

Dr. Michael R. Mathis: So, this was a dataset that was a part of the Multicenter Perioperative Outcomes Group which is a group of academic and private hospitals across the United States, multiple centers.

Within the Multicenter Perioperative Outcomes Group database, we selected eight institutions with the data that was curated and complete enough to do this analysis and those spanned academic hospitals including the University of Michigan, the University of Virginia, the University of Pennsylvania, Oregon Health & Science University and Yale and then some community hospitals across the State of Michigan as well.

It was a noncardiac surgery dataset; we analyzed roughly 138,000 patients and split these patients into derivation and validation datasets that improve methodologic rigor.

Some of the most common noncardiac surgeries in this population included upper and lower abdominal procedures, about 30% of these cases were abdominal surgeries. There were some noncardiac thoracic surgeries, about 10% of the cases in this dataset were noncardiac thoracic; another 10% were spine and spinal cord procedures.

They were primarily general anesthetics, close to 90% of these cases were general anesthetics, but certainly there were sedation cases and neuraxial anesthetics and about 13% of these cases were emergency cases.

The cohort had a median age of 58 years; there was a fairly even split across gender and then usual comorbidities that you might expect in a noncardiac surgical population: almost half the patients had hypertension, many of the patients had a history of cardiac arrhythmia, chronic pulmonary disease and diabetes.

Dr. BobbieJean Sweitzer: So, Dr. Sun, let's build a little bit more on that “it depends” question. So, can we agree on what we call hypotension, how it's defined? And tell us a little bit more about what you thought of Dr. Mathis's study parameters.

Dr. Louise Y. Sun: Sure. I think the definition of hypotension is a much debated topic as well because about a decade ago Dr. Bijker's group did a systematic review of existing literature that described hypotension and what they found was that there are many different definitions for hypotension; however, a few common definitions included first of all definition in terms of systolic blood pressure.

So, systolic pressure of less than 80 or 90 mmHg and when you’re talking in terms of mean arterial pressure or MAP you’re talking about MAP less than 55, 60 and 65 as a common definition. So, those are the absolute thresholds that people very often refer to.

So, when you talk about relative decreases in blood pressure, they found that relative decreases in MAP of above 20% or 25% is on the baseline value as being pretty commonly defined hypotension thresholds.

And so, I would say Dr. Mathis's study parameters were fairly consistent with these commonly defined thresholds in that they defined severe range intraoperative hypotension as not being less than 50 mmHg and the defined milder hypotension ranges as MAP between 55 to 59 mmHg.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, were there specific patients or surgeries that you excluded?

Dr. Michael R. Mathis: So, we started with an initial cohort of about 500,000 patients within the eight centers that we studied; some of the simpler exclusions were cardiac cases. We excluded outpatient surgeries mostly for the reason that most outpatients do not get a follow-up creatinine level within seven days of surgery as is needed to determine if they had acute kidney injury.

We excluded urologic and renal surgeries which imposed a direct kidney injury. So, we thought the mechanism of kidney injury per urologic and renal surgeries would be different from other noncardiac surgeries and those were excluded.

We excluded other surgeries with unique intraoperative physiologies such as a liver transplant, lung transplant and, of course, cardiac surgeries. And we also excluded patients with preoperative renal failure defined as an estimated glomerular filtration rate of less than 15.

We excluded short anesthetics, and so anesthetics with a duration less than 45 minutes or surgery less than 30 minutes and we excluded other minor nonoperative cases such as electroconvulsive therapy or pain procedures or labor and deliveries.

And then finally we excluded -- there's a small number of cases that had missing data and these were missing preoperative or postoperative creatinine values as would be needed to determine if a patient had acute kidney injury.

So, from initial cohort of about 500,000 patients, we weaned it down to 138,000 or so patients.

Dr. BobbieJean Sweitzer: And how did you define AKI or acute kidney injury?

Dr. Michael R. Mathis: Great question. So, we defined acute kidney injury using the creatinine component of the kidney disease improving global outcomes or KDIGO definition defined as a creatinine increase of 0.3 mg/dl or greater within 48 hours or at 50% increase from baseline in seven days after surgery. And that's consistent with KDIGO Stage 1 kidney injury or mild kidney injury and, of course, we included any other more severe range of kidney injury.

A limitation to this study is that we did not have complete data available on postoperative urine output or renal replacement therapy, so those components of the KDIGO definition were not used. It was simply the creatinine value that was used.

The KDIGO definition differs slightly from the Acute Kidney Injury Network's definition or AKIN definition and also this differs from the RIFLE criteria, another method of measuring acute kidney injury. But we decided that based on the dataset that we had and in consultation with nephrologists that were a part of this investigation that the KDIGO definition was most appropriate.

Dr. BobbieJean Sweitzer: All those acronyms to keep straight.

Dr. Michael R. Mathis: Sure.

Dr. BobbieJean Sweitzer: So, there have been other studies looking at adverse events occurring in patients with various low blood pressures for varying amounts of time You and Dr. Sun, I think, have both highlighted and even done some of this work and I believe even acute kidney injury was included in many of those outcomes of those studies. So, can you highlight again for us what makes your study unique?

Dr. Michael R. Mathis: So, beyond just being a multicenter study, so validating some of the past single-center studies that have been done over the past decade and using both preoperative and intraoperative data, it's really the nuance of this study it examining how the association between hypotension and acute kidney injury varies by patient, underlying patient risk.
And the idea here is trying to reflect how practicing anesthesiologists generally will care for a patient: we’ll make a preoperative assessment, we’ll weigh competing risks for a particular patient to guide our treatment goals. And so, that’s how this study was carried out; we have a preoperative risk score that’s developed for each patient based on information that’s available at the time of surgery.

And then we stratify the patients into low, medium, high and highest risk and then we look at within each strata what is the association between hypotension and acute kidney injury, testing the hypothesis that sicker patients will tend to not tolerate hypotension as well as healthier patients.

Dr. BobbieJean Sweitzer: So, I want to ask you a little bit more about that, those risk stratifiers. But I want to ask Dr. Sun a question first. As we noted, there have been other studies examining hypotension on adverse outcomes. Can you maybe again get back to that “it depends” question about blood pressure and give us a little bit more information? Is there a consistent blood pressure threshold that at least these other studies have identified as perhaps being important or critical?

Dr. Louise Y. Sun: Right. So, there have been a number of studies to look at critical hypotension thresholds in association with bad outcomes and I think AKI is actually one of the more frequently studied outcome that’s been examined in these studies. So, when we’re talking about the context of noncardiac surgery, we can safely say that 65 mmHg seems to be associated with poor outcomes.

So, there have been a number of seminal papers, in other words, larger single-center studies published prior to Dr. Mathis’s study, and I will say one of the first ones published on the subject of AKI after noncardiac surgery was led by Dr. Wakh’s group and this group concluded that there’s no safe duration of MAP below 55 mmHg during noncardiac surgery.

So, a few years later, a study led by our group, which also looked at AKI after noncardiac surgery, concluded something similar in that MAP less than 60 mmHg was associated with AKI in a dose-dependent fashion.

So, after our study—soon after, actually—a paper was published by Dr. Salmasi and colleagues and this was a paper that reported a MAP less than 65 mmHg as absolute threshold or relative threshold of more than 20% decrease from baseline was associated with AKI.

And so, although studies identifying a slightly different threshold, but it seems to be fairly consistent across the board that less than 55 mmHg there’s really no safe duration for this threshold. And generally speaking, MAP less than 65 mmHg is associated with poor outcomes.

And so, when you’re talking about other outcomes such as mortality, you also find varying thresholds. But most of the thresholds can be summarized around those ranges.

Dr. BobbieJean Sweitzer: Thank you. So, for those that are interested, we actually interviewed Dr. Salmasi for a similar podcast a couple years back right after his paper came out. So, look for that in our archives.

Dr. Louise Y. Sun: Great.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, I feel like we’ve sort of kept our audiences on their edge of their chairs here, so let’s have you tell us what you’ve found in this study.

Dr. Michael R. Mathis: Sure. Yes, so there’s a number of different findings. I’ll summarize four key points and the first is that we confirmed that acute kidney injury is, in fact, very common; around 9% in our study and that’s consistent with all of the studies that Dr. Sun alluded to.

Second, we found that intraoperative hypotension for greater than 10 minutes—that was the definition we used in our study, intraoperative hypotension for greater than 10 minutes is exceedingly common. We found that patients had absolute hypotension for greater than 10 minutes in up to 44% of patients. Up to 44% of the cases included in the study had a cumulative duration of hypotension of any severity; so hypotension less than 65 or more severe ranges of hypotension; 44% of patients had hypotension for greater than 10 cumulative minutes.

We also found that relative hypotension, which we defined as greater than 20% decrease below preoperative baseline or greater, occurred also very commonly in up to 68% of the patients in this study. So, hypotension is a very, very common occurrence.

The third thing we found, we were able to reconfirm that there are a number of preoperative risk factors that predict acute kidney injury, most of which have been already determined in prior studies. So, our study corroborated prior literature about which specific risk factors may predict acute kidney injury.

But then finally, and most importantly, we found that the associations between absolute hypotension and acute kidney injury did, in fact, vary by baseline risk. And what I mean by that is that patients with lowest preoperative risk, the patients that were in the lowest risk quartile, were robust to hypotension; they could endure any range of hypotension, mild or severe, and incurred no additional risk of acute kidney injury. We found that patients with medium risk that were in the second quartile of preoperative risk could tolerate mild hypotension.

Again, as Dr. Sun alluded to, this was defined as a mean arterial pressure of 55 to 59 mmHg. They could tolerate mild hypotension without any associated increased risk of acute kidney injury, but they did not tolerate a severe range hypotension or mean arterial pressures less than 55 mmHg.

And then, finally, patients with high and highest risks in the third and fourth quartiles using our preoperative risk score, they did not even tolerate mild ranges of hypotension and, again, defined as between 55 to 59 mmHg.

The big picture is that our study does corroborate what a practicing anesthesiologist may consider clinically intuitive: that healthy patients are robust to even severe ranges of hypotension and sicker patients—patients with higher risk of acute kidney injury and that have a higher preoperative risk—are sensitive to even mild ranges of hypotension.

And then, interestingly, the last thing I’ll point out is that relative hypotension, again, defined as a decrease from preoperative baseline, didn’t demonstrate any reliable association with acute kidney injury in our study. We found associations in our derivation cohort that were not able to be replicated in the validation cohort. So, the signal was really there for absolute hypotension but not for relative hypotension.

Dr. BobbieJean Sweitzer: Which may make it a bit easier for us because then we don’t have to know what the blood pressures were or try to figure out what baseline because I think that’s part of the problem. We often just have the preop the morning or maybe one or two of their blood pressures, so we’re not necessarily knowledgeable about what the patient’s true baseline blood pressure may be.

Dr. Michael R. Mathis: Sure, that’s exactly right. And I think at the point of discussion I think is, what is baseline? Is it the blood pressure the morning of surgery or is it a range of blood pressures obtained in preop clinic or some average value over the past year? You can debate that. But at least in our study we found that if you’re an anesthesiologist that does not want to do any algebra, you can just focus on the absolute number and not do any calculation of relative hypotension.

Dr. BobbieJean Sweitzer: I like that approach as well. So, I must throw in a comment here. You too are both probably way too young to have read these because I think the cardiologists actually don’t say this so often anymore, but they used to write in their clearance notes warning us to avoid hypovolaemia and hypotension and many anesthesiologists found that quite insulting: “Well, you don’t have to tell us to avoid hypovolaemia and hypotension.”

But, I – maybe they need to bring that back because obviously you pointed out that patients have a lot of hypotension and I believe Dr. Salmasi’s study showed something similar and others as well have shown that.

Dr. Sun, I think your manuscript showed that, that we have a lot of hypotension during our cases.

Dr. Louise Y. Sun: Yes, definitely.
Dr. Michael R. Mathis: Practice patterns vary from hospital to hospital, but to some extent I think anesthesiologists may become a bit desensitized to the cardiovascular depressing effects of general anesthesia and, yes, hypotension is very common.

Dr. Louise Y. Sun: Yes. And just to go along with Dr. Mathis’s comment, I think one of the factors that leads to underestimation of hypotension for us practicing anesthesiologists is that I think our minds may keep shifting between MAP and the systolic blood pressure and it seems that psychologically we may be adapting to the lowest allowable pressure that seems convenient to us.

And what I mean by this is personally I go for a MAP of 65 and because I practice solely in cardiac anesthesia I often even target a MAP of 70 in the very high-risk patients that are deemed to be at high risk of either dying, having a stroke or having renal injury postoperatively.

But sometimes what happens is that there are periods where we are forced to tolerate a lower blood pressure and so we will shift to tolerating a systolic blood pressure. So, that’s all good for people with normal arterial vasculature, but for people with advanced hypertension, for instance, they would have to go through a concept that we would refer to as ventricular arterial coupling in which the ventricle is stiff and thick due to chronic hypertension and secondary to that effect, the vasculature becomes very stiff.

So, your pulse pressure actually increases, so those people typically have very high systolic blood pressure but a very low diastolic blood pressure. So, their MAPs by default will be much, much lower than what we would expect for a given systolic pressure. So, if we’re targeting to get systolic pressure 90 or 100, that may be vastly inadequate for these patients. So, I think that may in part contribute to our clinical underestimation of hypotension.

Dr. BobbieJean Sweitzer: It’s a really good point and I think we as human beings also we see the glass is half full more than we see it as half empty.

Dr. Louise Y. Sun: That’s right.

Dr. BobbieJean Sweitzer: We look for the best number up there, not the worst number.

Dr. Michael R. Mathis: That’s absolutely true. Yes, if there’s a low blood pressure, just cycle the cuff one more time.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, what were the factors that identified the patients at risk for acute kidney injury or are those—can you help us understand? You’ve mentioned there’s low-risk, intermediate-risk and the high-risk patients.

Dr. Michael R. Mathis: Sure. Yes, so the low-risk, medium-risk and high-risk patients are just based on a point score—I won’t get into details here, but you can see in our paper there’s a scoring system—but among the factors that were most influential of your preoperative risk score, the most important factors were: any existing renal insufficiency, so we excluded patients with renal failure, but certainly if you had a baseline renal dysfunction, if you have a glomerular filtration rate that was low, that would certainly impact your risk of postoperative acute kidney injury and that was probably the strongest predictor.

Other important predictors were anemia, ASA status, if you had an ASA status of 3, 4 or 5, that was a strong predictor of acute kidney injury. And then the expected anesthesia duration. So, longer cases and particularly cases that goes over four hours, you had an increased risk of acute kidney injury.

And then the surgery type. So, if the surgery was a major abdominal surgery or a thoracic surgery or other higher-risk surgeries, that influenced the risk of acute kidney injury as well.

Dr. BobbieJean Sweitzer: What level of hemoglobin? Do you remember what the cutoff was?

Dr. Michael R. Mathis: Sure, yes. So, we just used preexisting definition, the World Health Organization’s definition of anemia and we stratified by normal, mild and moderate to severe. And so for normal we defined as a hemoglobin for female is greater than 12 and for male is greater than 13, mild anemia was hemoglobin of 10 to 12 in females and 10 to 13 in males and then moderate to severe anemia we defined as a hemoglobin less than 10. And this is the World Health Organization’s definition of anemia.

Dr. BobbieJean Sweitzer: So, even mild degrees of anemia impacted outcomes?

Dr. Michael R. Mathis: Correct. Yes, so any—yes, often we’ll see a hemoglobin of 10 or 11 and not flinch, but that did significantly impact the patient’s risk of acute kidney injury. So, even mild anemia did have an impact on your AKI risk.

Dr. BobbieJean Sweitzer: Yes. I’m–it’s tricky in also that ASA status, I know it sort of comes under fire sometimes as being subjective and so this depends on the situation and the person who’s assigning that score.

But once again, I think ASA status has shown that it can be a predictor and it can help us identify patients. I think it’s like we know the sick ones when we see them even though it’s hard to define sometimes.

Dr. Michael R. Mathis: Yes. Exactly. It’s just a gestalt that the anesthesiologist will have. Interestingly, this is a multivariable analysis, so this ASA status is independent of any comorbidity that we also measured. So, it’s components of ASA status beyond the comorbidities and demographic data that are also included as covariants. But that’s that gut feeling by the anesthesiologist and their classification by ASA physical status is a very important predictor of acute kidney injury.

Dr. BobbieJean Sweitzer: Dr. Sun, what are the modifiable risk factors for AKI?

Dr. Louise Y. Sun: So, there surprisingly are not very many modifiable risk factors for AKI. So, I would say that in the noncardiac surgery literature, hypotension may be one of the only ones.

In the very limited cardiac surgery literature, which our group had contributed to with a recent paper on stroke in association with AKI after surgery requiring cardiopulmonary bypass and a paper that’s to be sounds like: in press describing blood pressure thresholds in association with renal replacement therapy after cardiac surgery, what we found consistently was new onset postoperative atrial fibrillation was a strong predictor of complications including AKI. So, that in itself may be modifiable in some ways.

Dr. BobbieJean Sweitzer: We look forward to that. I had the opportunity of also doing a podcast with Dr. Longros who had published an article recently in Anesthesiology on the perioperative and postoperative atrial fibrillation and outcomes. So, that’s starting to surface as something that I think we need to be aware of and look out for.

Dr. Louise Y. Sun: Definitely.

Dr. BobbieJean Sweitzer: So, Dr. Mathis, can you recap again for us so that it’s very clear, I guess, in everyone’s minds here as those practicing anesthesiologists, you have to go out tomorrow and provide anesthesia, what were the blood pressure levels associated with risk in your patients?

Dr. Michael R. Mathis: Sure. Yes, I do think it bears a repeating and reemphasizing. Patients with low preoperative risk when you are in the lowest quartile of preoperative risk based on our risk score, those patients can tolerate hypotension of any severity. So, anything from a mean arterial pressure of less than 65 to a mean arterial pressure less than 50. Hypotension of any severity in a low-risk patient confers no additional risk of acute kidney injury.

Contrast that with patients that were at medium risk based on their preoperative characteristics, these patients can tolerate mild hypotension defined as a mean arterial pressure of 55 to 59 but not severe hypotension defined as a mean arterial pressure less than 50.

Contrast that again with patients that are at high and highest risk in the highest two quartiles, these patients did not even tolerate mild
hypotension. So, in these patients, a mean arterial pressure of 55 to 59 conferred additional risk of acute kidney injury not explainable by their preoperative risk factors.

And then interestingly, again, relative hypotension, at least in our study, defined as a decrease from preoperative baseline did not demonstrate any reliable association with acute kidney injury in any of the preoperative risk quartiles.

Dr. BobbieJean Sweitzer: Thank you. That was a nice summary and it begged me to ask Dr. Sun to put that in perspective for us because, with all due respect, your study looked at acute kidney injury.

So, Dr. Sun, you mentioned about your practicing in cardiac anesthesia and this was a noncardiac study that Dr. Mathis did and then we should talk about other risks like stroke risk or MI risk.

So, is there – do you believe in absolute minimum blood pressure for all patients for all kinds of risks and outcomes or do you believe that we probably need to personalize targets and have this relative hypotension depending on either patients’ usual blood pressures or the outcomes that we’re interested in or comorbidities such as what Dr. Mathis looked at in categorizing patients with different risk factors?

Dr. Louise Y. Sun: I would have my foot in two boats. {Laughter} So, to start I would say that as you probably already know that the question of whether we should be targeting for absolute versus relative blood pressure thresholds has been the subject for a lot of debate recently in our anesthesia world.

There’s quite a bit of literature coming out showing consistently absolute hypotension thresholds to be associated with poor outcomes after cardiac and noncardiac surgery, whereas the evidence is somewhat inconsistent and inconclusive when relative thresholds are being studied.

And as Dr. Mathis mentioned before, the big part of this is due to the fact that our definition of baseline pressure is poorly defined, especially across the retrospective cohort. So, I personally target an absolute threshold when I’m treating patients.

But when we’re talking about personalizing blood pressure therapy, what I have in mind is not absolute versus relative thresholds; what I have in mind is really tailoring to the patient and procedure risk. So, that comes back to the theme of Dr. Mathis’s study and I think it highlights the importance of risk stratification prior to the operation in our approach to personalizing blood pressure management.

Dr. BobbieJean Sweitzer: So, someone who lives and breathes in the preoperative world, that’s music to my ears. {Laughter} So, we’ve talked a lot about blood pressure numbers, but can you perhaps, Dr. Mathis, expand on whether your study looked at this? What’s the duration of low pressures that matters? Is it a minute under a certain amount? Is it five minutes? Can I recycle that blood pressure and wait for the next one or should I treat right away?

Dr. Michael R. Mathis: So, our study defined a clinically meaningful hypotension as greater than 10 minutes, cumulative minutes of hypotension during the surgery and we chose that simply based on previous studies have used this definition and to make our study comparable to previous literature, we’ve settled on that definition.

That isn’t to say that shorter durations of hypotension are safe; it’s just that we chose a definition of greater than 10 minutes as clinically relevant. Other studies that Dr. Sun mentioned, Salmasi’s study found that even one minute of hypotension is associated with some increased risk of acute kidney injury.

So, the verdict is out still on what becomes clinically relevant. But if you’re looking for a statistical association between the duration of hypotension in acute kidney injury, even short durations have some signal, some association with poor postoperative outcomes.

So, what I would say is that low blood pressure and short durations are not innocuous and to get to your point, too, about the fact that this study is just focusing on acute kidney injury but not stroke, not mild cardio ischemia, not other outcomes, that’s another point to just remember is that even though in healthy patients we found no association between hypotension and acute kidney injury, that’s not say that there weren’t other risks that we did not measure such as risk of mild cardio ischemia, stroke, postoperative cognitive dysfunction. Those things may have had some increased risk that went unmeasured by this study.

Dr. BobbieJean Sweitzer: Yes, thank you for pointing that out because, as you said, I think at the beginning we wanted to take it into context and for what your study was able to show, but it didn’t look at everything.

So, Dr. Sun, renal perfusion is not just pressure dependent. Can you explain to us what else is important?

Dr. Louise Y. Sun: Absolutely. I think in the anesthesia world we often talk about the relationship between pressure and flow; I would say that flow is equally as important as the blood pressure management during any case. So, it really does us no good to have a very high blood pressure but very little flow because we know that many of the critical organs are dependent on adequate cardiac output as well as adequate mean arterial pressure.

So, I think the reason that we do not completely understand this pressure and flow relationship to date is that this relationship is incredibly difficult to model physiologically in animals or in humans and it’s also incredibly difficult to model mathematically using retrospective data only because it’s a very multidimensional type of relationship that may not be adequately looked after by traditional modeling techniques.

Dr. Michael R. Mathis: I think it’s a great point, Dr. Sun, on top of the fact that acute kidney injury may not hinge only on mean arterial pressure, and renal blood flow is actually really what we’re after. The relationships there are difficult to measure, but also there’s this issue of what’s pragmatic. We have millions of patients having a surgery and we’re not going to be putting some flow transducer in the renal artery; we’re going to be measuring their blood pressure.

And so, to the extent that mean arterial pressure is a surrogate for renal perfusion, that’s the pragmatic approach but certainly not the full picture. And so, there’s this issue of what is measurable, but not only that, what is a pragmatic way to monitor – safely monitor millions of patients having surgery each year.

Dr. Louise Y. Sun: Definitely.

Dr. BobbieJean Sweitzer: So, we’re running short on time. This is an interesting conversation and I’d love to continue it, but I think I have time for one more question. So, Dr. Mathis, I know this is a bit beyond probably your study, but do you have any insights, perhaps, from your study or the literature you know as to best way to prevent or treat hypotension to lower the risks specifically of acute kidney injury?

Dr. Michael R. Mathis: Based on this study, because it’s an observational study, we don’t really have any further insight about what treatments for hypotension will best mitigate the risk of acute kidney injury. But this study does set up targets for potential future prospective studies and when we realistically think about what are the available options for treating hypotension, there’s really four options that an anesthesiologist has commonly available.

We can give fluids, we can treat with vasopressors, we can lower the anesthetic depths and then we could also give an inotrope or a chronotrope and these are not usually things like epinephrine infusions. I’m talking more commonly we’re giving ephedrine or glycopyrrolate and those medications could potentially treat hypertension.

And so a prospective study would need to incorporate these treatments into some goal-directed therapy that includes hypotension as a parameter guided by retrospective studies such as this one and the one that Dr. Sun conducted. You can use these targets as a parameter for your goal-directed therapy and you could also include other parameters possibly getting at volume status and anesthetic depth you could be measuring pulse pressure variation or mean alveolar concentration.
But that’s really where the future is is conducting a prospective study, looking at those commonly available tools for treating hypotension and using targets that are developed that have been observed in these retrospective studies associating hypotension with acute kidney injury.

**Dr. Louise Y. Sun:** Right. And if I may add to Dr. Mathis’s excellent comments, I would think that the state-of-the-art intraoperative monitoring doesn’t need to be very high tech. I think there are a lot of traditional parameters that we could be using in our everyday practice that are very good surrogates for systemic perfusion.

So, you know that the cardiac output is stroke volume times heart rate. So, something like the pulse rate, the contour of the sat tracing can tell us about volume status and it can tell us about (sounds like: beat-to-beat) variability and something like the end tidal carbon dioxide tracing and the number that it gives and any sudden changes in that number can be a good surrogate of changes in perfusion status as well.

So, I think all of those things could be incorporated into everyday clinical practice to assess systemic perfusion on top of mean arterial pressure and these could, perhaps, be explored in prospective trials as well.

**Dr. BobbieJean Sweitzer:** Those are all really great practical advice for our listeners. I do hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Drs. Mathis and Sun, 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. Michael R. Mathis:** Thank you.

**Dr. Louise Y. Sun:** Thank you so much.

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