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The Role of Hemodynamics for AKI and Maintaining Hemodynamic Stability in KRT Patients

Announcer:
Welcome to this episode of KDIGO Conversations in Nephrology. This episode, titled The Role of Hemodynamics for AKI and Maintaining Hemodynamic Stability in KRT Patients, is provided by KDIGO and supported by an independent educational grant from Baxter. Here's your host, Dr. Marlies Ostermann.

Dr. Ostermann:
Hello, and welcome to another episode of KDIGO Conversations in Nephrology. My name is Marlies Ostermann and I'm a consultant in critical care and nephrology at Guy's and St Thomas' Hospital in London. And joining me today to discuss the role of hemodynamics in acute kidney injury and the importance of maintaining hemodynamic stability during kidney replacement therapy is Professor Rinaldo Bellomo. Professor Bellomo is Professor of Intensive Care Medicine at the University of Melbourne in Australia, and he is one of the fathers of modern critical care nephrology. He's led many landmark studies in this field, and contributed to many guidelines and recommendations, including the management of hemodynamics in acute kidney injury. Professor Bellomo, welcome to this program.

Dr. Bellomo:
Thank you very much for the kind introduction, Marlies. It's nice to talk to you.

Dr. Ostermann:
So let's begin our discussion with a very general question. Why is hemodynamic stabilization important to protect kidney function?

Dr. Bellomo:
The main reason is that the kidney is a uniquely sensitive organ to hemodynamic changes, both in terms of blood pressure and in terms of cardiac output. It is a sensor for hemodynamic changes and it responds to it by modifying the hemodynamics within the kidney by modifying the loss of salt and water and its retention, and by releasing a key enzyme – renin, which regulates, in part, the concentration of angiotensin 2, which is a major vasopressor response to hypotension. And it's not a surprise, therefore, that it is uniquely sensitive to changes in hemodynamics themselves. When the blood pressure is low, there is significant renal vasoconstriction, in order to maintain intravascular volume, not to lose urine, to retain sodium. And so, for the kidney, the preservation of mean arterial pressure is a key protective function, from a physiological point of view.

The kidney is also sensitive to back pressure because of course trying look at mean arterial pressure in of itself, in the absence of consideration of what the intraorgan pressure, or the back pressure against which the mean arterial pressure is pushing blood into the kidney misses an important physiological point, and that is why multiple observational studies have linked a high central venous pressure as a surrogate of venous pressure and tissue pressure within the kidney. So, that difference between mean arterial pressure and central venous pressure is what we call the mean profusion pressure – the MPP – for the kidney, and it is also a fundamental hemodynamic element which you, yourself have written about, Marlies.

Dr. Ostermann:
Thank you. It's a very important summary of the physiology. But in patients on kidney replacement therapy, is it still important to maintain hemodynamic stability? And if so, what are the key factors?

Dr. Bellomo:
So one of the interesting things about the physiology of the kidneys that have failed and are now supported by kidney replacement therapy is that there is limited information about what a failed renal system, or failed kidneys actually do in response to hemodynamics.

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We're all familiar with the concept of autoregulation, and that is that within a particular blood pressure range in human beings – probably somewhere between 65, 70 millimeters of mercury, or mean arterial pressure to probably about 120 millimeters of mercury or blood pressure renal blood flow is autoregulated and kept stable. And that is, indeed, true in rats. However, after you've induced acute kidney injury, the injured kidneys do not have that autoregulation property, and their renal blood flow decreases linearly with blood pressure changes, so that if anything, from the experimental data that we have, the kidneys that have been injured and are in a state of shutdown are likely to be particularly sensitive to hypotension, in terms of decreased renal blood flow.

So, you could make an argument that on the basis of experimental data available, there is even more compelling reason for wanting to maintain adequate mean arterial pressure, adequate mean profusion pressure, and adequate cardiac output and adequate intravascular filling in these patients.

Dr. Ostermann:
Thank you very much for summarizing the results of experimental studies. But this leads me to clinical practice. When looking after patients with acute kidney injury or patients on kidney replacement therapy, what are the hemodynamic targets to prevent progression of acute kidney injury?

Dr. Bellomo:
So I – the data based on clinical trials is pretty limited in terms of what we should do to protect the kidneys. The principles that I've just outlined obviously apply, but in terms of trial medicine, we've really not had any randomized controlled trials to compare different hemodynamic targets in the setting of AKI, in terms of renal recovery and renal protection. So we know the kidneys are very sensitive to hemodynamic insults in general. And so, one would have to say that the hemodynamic targets would be very much focused on preventing hypotension, preventing decreases in mean profusion pressure, preventing intravascular volume depletion and preventing decreases in cardiac output. Now, what are the limits of that prevention, and what is the mean arterial pressure at which we would be uncomfortable? No one really, truly knows because the mean arterial pressure that we use is really a composite of different elements. You can have a mean arterial pressure of a particular level, sustained by a large degree of vasoconstriction, in the setting of a cardiac output that is insufficient, or you can have a mean arterial pressure that's relatively low, or maybe the same level, in the setting of a very high cardiac output due to vasodilatation. And it is likely that those two different states have got different repercussions on the kidney.

Nonetheless, within the limitations, there's such thinking that really, kind of worries me quite a lot. The mean arterial pressure that we've been operated – operating with has been around 65 millimeters of mercury for patients admitted to intensive care particularly those with vasodilatory shock. We don't really have very good detailed data on people outside of the vasodilatory shock. There's some data, in general, from the '65 trial that all the patients might even tolerate a mean arterial pressure of 60. Again, from the point of view of the kidney, I would think all of that would have to be contextualized to the cardiac output, which in the studies that I was – has not been done. And finally, we have the study of SEPSISPAM, published in New England, where patients were randomized to a high mean arterial pressure in the setting of vasodilatory septic shock targeting a mean arterial pressure of 85 millimeters of mercury versus 65, showing that in those patients with a history of hypertension, delivering a higher blood pressure target was associated with a decrease in the incidence of acute kidney injury. So, again, there is another element to the contextualization of the hemodynamic targets – not only the blood pressure, not only the central venous pressure or what that does to the mean profusion pressure, not only the cardiac output and its adequacy in the setting of any given mean arterial pressure and a mean profusion pressure, but also the patient's background in terms of whether the kidney and indeed, the physiology of the patient, is used to a higher input pressure and what that does to the ability of the kidney to adjust. And you can see then, that you have this kind of equation, that has in it mean arterial pressure, cardiac output central venous pressure, mean profusion pressure and underlying history of hypertension. And that increases the complexity of what needs to be done in the assessment and care of patients quite a lot.

Dr. Ostermann:
Thank you. For those just tuning in, you're listening to KDIGO Conversations in Nephrology. Our topic today is the role of hemodynamics for management of acute kidney injury and the role of maintaining hemodynamic stability in patients receiving kidney replacement therapy. I am Marlies Ostermann, and I am delighted to speak with Dr. Rinaldo Bellomo.

Dr. Bellomo, you've already touched on it in the previous answers, but I'd like to talk and get back to patients on kidney replacement therapy – so patients with advanced kidney injury. In this scenario, is it still important to optimize hemodynamics, or do you think it's too late?

Dr. Bellomo:
Look, my response is absolutely, it's still very important, and I find this a frustrating environment, particularly in patients that are receiving artificial renal support. We've just started a recent program here to look at patients with acute kidney injury that go to the ward without full resolution of their acute kidney injury, and remain on intermittent hemodialysis, and what we started setting up and

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investigating is just what happens to hemodynamics in patients with recovering AKI that are still dependent on renal replacement therapy, in terms of hemodynamics. And so, we've set up a multimodal system of monitoring. We're – we have simultaneous blood volume assessment by measuring changes in hematocrit, in order to derive a surrogate of intravascular volume state, as well as applying the technology of the ClearSight. ClearSight is a device that can be wrapped around your second phalanx, in your hand – in the finger, and uses multiple fast compressions to derive an area under the curve of the blood pressure tracing, and gives you not only a pretty accurate blood pressure every heartbeat, as though you might have an arterial line – and it has been validated against arterial lines – but it also gives you a pretty accurate estimate of cardiac output. And so, you can have continuous blood pressure monitoring, continuous blood volume monitoring, and continuous cardiac output monitoring in patients having intermittent hemodialysis in the renal ward, who are recovering from acute kidney injury that was treated in the ICU.

And, you know, what we've seen so far is pretty scary. And the last one we did last week – we had a patient whose blood pressure remained stable. You know, 140/70, during the 4 hours of dialysis but who was having quite a significant amount of fluid removed, and we saw the intravascular blood volume decrease by 8% over a period of about 90 minutes, and we saw the cardiac index go from 3 liters per meter squared per minute, to 1.6 liters per meter squared per minute. And clearly and logically, the patient was maintaining blood pressure only by means of severe vasoconstriction, and dodgily generated in the setting of a decreased cardiac output. And so, it's very likely that we are inducing hemodynamic instability that is not detectable by blood pressure measurements, and that has significant – must have significant injurious consequences on the recovering kidney. So, is it important? Hell, yeah, it is. Are we doing it right? No. Could we do it better? Absolutely. Should we do it better? Absolutely. Do we need to do more work in this area? Absolutely.

Dr. Ostermann:
So if we could do it better – and we should do it better – are there any specific drugs to achieve better stability during kidney replacement therapy?

Dr. Bellomo:
Yeah, no, this is an interesting question. You know, the drugs that we use, first of all, are vasopressor drugs to deal with the low blood pressure and really, the 2 major ones that are available in the market really are norepinephrine or noradrenaline, and Vasopressin. Now there is a new kid on the block, which is angiotensin 2, and I'll talk about that in a minute. So let me focus for a moment on norepinephrine – that's a dominant treatment for vasodilator shock. It's been compared to alpha dose dopamine in a large, randomized, controlled trial and found to be superior in terms of clinical outcomes and the avoidance of atrial fibrillation, and in terms of effectiveness of reaching blood pressure targets, and it is therefore the dominant vasopressor drug.

It has also been studied in combination with vasopressin, and the – I guess the major trial there is the VASST trial, where vasopressin was added to norepinephrine once you got to a certain level of norepinephrine dose, and its administration did not overall modify renal or clinical outcomes in patients. However, in a group of patients that had acute kidney injury Stage 1 at the time of randomization in a subgroup analysis, those randomized to have early introduction of vasopressin combined with no epinephrine their renal – and indeed, even the patient outcomes – were superior. So it is possible that vasopressin is more nephroprotective than norepinephrine alone so a vasopressin/no epinephrine combination may be wiser in patients that have evidence of renal impairment in the setting of vasodilatory septic shock.

The new kid on the block is angiotensin 2. Angiotensin 2 was FDA-approved in 2017, following the ATHOS trial, which showed that it was able to increase blood pressure in a sustained way in patients with catecholamine resistant or refractory vasodilatory shock. In that setting in the group of patients that were on renal replacement therapy at the time, subgroup analysis revealed a clear independent association between allocation to angiotensin 2 and faster recovery from – or greater recovery from renal replacement therapy at 1 week compared to placebo, and also potentially greater and more successful survival rates in such patients. There is a whole lot of rationale for believing that angiotensin 2 will be beneficial in the setting of vasodilatory sepsis, in particular its effect on the efferent arteriole in order to maintain glomerular pressure is likely to protect GFR in this setting. But clearly, we need more data.

Dr. Ostermann:
Thank you. This is clearly an evolving area. We're coming to the end of this conversation, and I'd just like to ask you 2 more questions. First one is what best practice recommendations can you tell us, to increase the chances of achieving the hemodynamic targets?

Dr. Bellomo:
Well, I think from my point of view, the most significant recommendation is, you know, senior, thoughtful, clinical input – you know, people that are in the setting of acute kidney injury are typically very unwell whether they are receiving renal replacement therapy or not. If they are on vasopressor drugs, they are very unwell, and, you know, you really need clinical input to continuously monitor whether the blood pressure is adequate, whether the fluid resuscitation is optimal, whether the mean profusion pressure is adequate, whether the cardiac output is maintained, whether intravascular volume status assessed by a variety of means which include evasive measurements,

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as well ultrasonographic measurements or relevant variables is appropriate whether the patient is in a state of fluid responsiveness. All of those issues have to be addressed on a regular basis – you know, every – every hour, every 2 hours, very thoughtfully, very carefully, in order to optimize the hemodynamic state of – of the patient.

And all of those considerations must play very much into mind of the treating clinician, and – and in some patients, they demand that there should be continuous cardiac output monitoring, in order to ensure – and possibly even intravascular volume monitoring by measurement of the hematocrit – in order to ensure that intravascular volume is maintained – and that cardiac output is maintained. So, careful, thoughtful, multi-modal assessment of the patient is vital in order to increase the chances of achieving the hemodynamic target, and to achieve recovery.

Dr. Ostermann:
And as one of the leading researchers worldwide in this area, I'd like to ask you, what are the urgent questions for future research?

Dr. Bellomo:
Well, you know, there are – there's a whole list. I think some of them will be addressed soon. I think the first is to identify high-risk populations. We have not really done any good work around randomizing patients to a specific mean profusion pressure, rather than a mean arterial pressure and adjusting that mean profusion pressure to the patient's premorbid mean profusion pressure. And really, you know, we've talked about bundles of care in patients with acute kidney injury, and creating a multimodal set of characteristics in the care of these patients. I think it's an important process that we should be working towards to optimize the care of these patients. We talked about the choice of vasopressors, and the use of angiotensin 2. There will be work in that space, for sure, in the next couple of years.

And we are funded to do a study, where we randomize patients to usual care or – or to a net ultrafiltration strategy that avoids large fluid removal over a short period of time during continuous renal replacement therapy. The study's called NEPTUNE, and we should be starting that next year. So, there are lots of questions in this space. There's no shortage of issues to be addressed.

Dr. Ostermann:
Thank you very much. Before we close, Dr. Bellomo, are there any final messages or key takeaways you'd like to leave with our listeners?

Dr. Bellomo:
Yeah, I think my major message and kind of key point is there is no substitute for thoughtful, engaged, kind of careful, multimodal assessment of patients, on a frequent basis, with an understanding of renal physiology and trial evidence. Having informed clinicians at the bedside, that know all of the things that we've talked about, in my mind is crucial to anything that can be done to help the patient.

Dr. Ostermann:
That's a great way to round up our discussion today. I want to thank my guest, Professor Rinaldo Bellomo, for joining me. Professor Bellomo, it was great having you on the program.

Dr. Bellomo:
It's always a pleasure to talk to you, Marlies. Thank you.

Dr. Ostermann:
I am Marlies Ostermann, and to access this and other episodes in our series, visit KDIGO on Spotify, or kdigo.org/podcast. Thank you for listening.

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