# *Episode 1 –Hemodialysis: the thrice-weekly challenge*
## *Guest: David Keane, PhD*

**Peter Kotanko**
Welcome to the Renal Research Institutes frontiers in kidney medicine and biology, where we share knowledge and advances in kidney research with the world. In this episode, we talk with Dr. David Keane to discuss if hemodialysis is a thrice weekly challenge. Here we take an in depth look at the time of onset of intradialytic hypotension, and its association with clinical parameters and mortality.

It's a great pleasure today to welcome Dr. David Keane from Leeds hospital for a discussion of the thrice weekly stress of hemodialysis. David, he is a medical physicist at the Leeds Hospital. And he has published extensively in the field of hemodialysis, especially body composition. So my first question is really, David, what brings a physicist into dialysis?

**David Keane**
I did a physics degree initially, and we did some medical physics as a part of my degree. And I guess, coming out of my degree, I wanted to go down a medical physics route. Now, it's not that uncommon, really, there's quite a lot of people working in medical physics in hospitals, what is uncommon is working in renal medicine. So the story there really was that during my sort of rotations around my training. And I did the sort of areas that most people go into radiation protection, radiotherapy, MRI, these type of areas. I actually really enjoyed a rotation, which was physiological measurement. And it was during that rotation I did a little bit of work with Dr. Lizzie Lindley, who, of course, you know, and, and I really enjoyed the interaction with the dialysis team and the dialysis patients. And so I really wanted to continue working in the area. Now, as I say, there's not many physicists working, particularly in the in the health service and not in academia. So this training program really was for people embedded within the NHS, the health service in UK. So that's really what got me into research, because, actually, for me to keep on my contract and keep working here, I had to really bring research monies in so that's really effectively what got me into research and got me into renal at the same time.

**Peter Kotanko**
yeah, that David, quite interesting take, can you tell us a little bit about your recent research?

**David Keane**
I've got particular interest in measures of body composition, particularly bioimpedance in dialysis. And I guess a lot of the work I did initially when I came in, and my PhD was around, really around how we use bioimpedance for fluid management in hemodialysis routinely, in the nitty gritty of clinical practice. Because if you if you look at most of the devices, how they are set up to work, and I guess the populations they've been validated, and they're really not that representative of, of the typical patients you'd see in a dialysis unit. So, for example, you know, a lot of the bioimpedance devices are set up to measure from hand to foot. And, you know, if we, if you come around dialysis units, it's not that uncommon to see patients who have amputation. So a lot of my work was around validating, and understanding how to use the bioimpedance

measurements in typical dialysis populations. So both from the aspect of measurement, how we can get good quality measurements across the sort of population we're dealing with, but also interpretation, because again, the equations and the devices are validated, generally in quite healthy, usually Caucasian populations. And so we did a lot of work about making a lot of measurements to try and understand how we can best interpret the data in all the different sort of populations and patients that we've got on the dialysis unit. So I guess that was what I did initially. And I've then followed that up, and I'm doing similar sort of work with absolute blood volume measurements at the minute. So again, there's been techniques described for making, routinely making absolute blood volume measurements. And these have been validated in quite controlled situations. But again, I'm doing a lot of work making a lot of measurements in our dialysis patients and trying to understand how well this technique can be used routinely day to day.

4:31 And aside from that, I've done quite I've had a really nice sort of relationship with school of psychology, University of Leeds, and we've just published a paper actually, in the last few days around the patient perspective of fluid management. So we've had a PhD student working on this, and I think this is a really important area that is often neglected. And the minute whereby we've really shown that patients genuinely do have the final decision on how much fluid we take off them on dialysis and you know, that they're ultimately deciding this. And no matter how good our clinical assessment and our devices and everything is, it's kind of pointless if we don't really engage and understand better how patients feed into this decision process. So that's another ongoing strand. And then I guess Aside from that, I've been involved because I've done so many, I've made so many *bioimpedance* measurements, I've been working with quite a few trials in the UK, now using bioimpedance. So the, the *BISTRO* trial is a really exciting one, which should be coming out later this year, which is looking at how we can use bioimpedance to preserve residual kidney function with a trial looking at bioimpedance and AKI and looking at bioimpedance in a sub study of the EMPA-kidney trial as well. So that's  trial work. And I guess finally would be what took me over to the Renal Research Institute. So I was I was really grateful for the opportunity to come over with your team. And I learned an awful lot about statistical analysis and analyzing big data and epidemiology. So that was a really, really valuable experience for me and something I'd like to build on definitely, in the future. I guess that kind of covers most of the things I've been interested in.

**Peter Kotanko**
Well, David, I have to see the breadth of your research activity. I mean, this is really, really remarkable. And I believe something you wouldn't have dreamt about when you entered the field. I mean, you published recently, quite remarkable paper in kidney international about *intradialytic*, hypotension. Can you say a few words? Why is intradialytic hypotension? important? Why is it important to research, this complication at all?

**David Keane**
I think the simple answer is that, you know, the data shows that it is really closely associated with outcomes. So, you know, we know it's really associated with mortality, in kidney patients on dialysis, and it's also really associated with patient experience. So any, any patient undergoing dialysis will probably have had a symptomatic episode of intradialytic hypotension. And they will

tell you how uncomfortable and how awful some things, I mean, I think the rest of us can't really understand how, how awful *cramping is* for example, for patients who have symptomatic episodes. So I think that's the simple thing. It associates with hard clinical outcomes and patient experience. But there's a whole load of other factors as well. So, you know, we know that patients who have episodes of intradialytic hypotension are more likely to finish their sessions earlier. So it may impact on the amount of dialysis, we're able to give them routinely. I think it brings on some of the work I've done with the psychology team. Have shown, it brings on psychological impact on the patient. So if they have episodes that are really awful for them that they experience, this can often prevent them from having, you know, a similar amount of fluid removed on subsequent sessions. So even though clinically, that the situation might be different, they have some form of effectively, psychological scarring that they refuse to engage with clinicians on maybe taking off the amount of fluid that they need. So we might not be given enough of dialysis clearance and we might not be taken off enough fluid as well. So there's a whole bunch of things, I think, kick on from that. So undoubtedly, it's a really important area and something that I don't think, as a community, we've really made huge indents in over the last couple of decades, like we have done in so many other areas of dialysis.

**Peter Kotanko**
Would you mind just explain to us a bit how you even define intradialytic hypotension? Is there a uniform definition, or Are there many different definitions? Just, if you could, could explain this to us a little bit?

**David Keane**
The simple answer is we don't have a unified definition. There's been a really nice piece of work from Jenny Flythe, has done around looking at associations with heart outcomes. And that clearly suggests that a systolic blood pressure that falls below 90 millimeters of mercury, is the definition that was most strongly associated with mortality. And that's fine, actually, you know, there are a whole number of other definitions used by guideline groups by researchers in clinical practice, and actually the definition used probably will be different in different situations. So if you went and spoke to a dialysis nurse on the floor, they're probably more interested in the episodes that become symptomatic. So we are going to be checking blood pressures during dialysis. But this is not continuous measurement. So you may be getting lots of patients who have a symptomatic episodes during dialysis that isn't picked up. But they're obviously going to be much more focused on episodes that results in some of these quite distressing symptoms for patients. So we have the definitions that are based on the absolute value of systolic blood pressure, like I mentioned, we have definitions that are based on patient symptoms, we also have definitions that are based on the fall in systolic blood pressure. So depending on how much the blood pressure drops from pre dialysis levels, and we also have composite definitions that will include some or all of these different parameters. And as I say, , this does cause problems, because it's hard to then, you know, do really good literature reviews and analyses comparing different studies, different interventions, as I say, may well just be simply, you know, actually part of the problem. And this is a complex problem, and it may need some complex definitions and complex management.

**Peter Kotanko**
Yeah, I think that's very true. There is a clear patient perspective, there is a provider perspective, there is research that tries to unify definitions, just for, for the sake of better analyses or more comparable analysis. Yeah. So, David, can you just tell us what were the key findings of your of your study that you published? I mean, what novel aspects did you discover and what were the potential consequences of those novel findings?

**David Keane**
So I think the main thing really, which is, it's relatively simple, on one level was just to describe when these episodes occur, because I think we, we had a look in the literature and there really is very, very little data about when hypotensive episodes occur. And actually, all we, all we could find is some general sentiments and feelings that that intradialytic hypotension tends to occur towards the end of dialysis. And this does have logical rationale. So we know that the prime driver of intradialytic hypotension is the removal of fluid during dialysis. And this is cumulative. So, the further into a dialysis session we go, the more fluid removal and , the more likely you would think a hypotensive episode is to occur. But actually, what we found in the paper is that this isn't really the case. And you rightly highlighted the definitions, and the differences in the definitions and we looked at four definitions in our study. So we looked at the one we described that is most strongly associated with mortality, which is a nadir systolic blood pressure below 90 millimeters of Mercury, we looked at a fall a drop of 30 millimeters of mercury, we looked at a composite of the nadir plus the fall in, in systolic blood pressure. And we looked at using - this was all routinely collected data - And we looked at using the administration of fluid boluses, which is recorded in the, in the treatment data as a surrogate for sort of a symptomatic episode. And we did see differences as you would rightly expect between the distributions of episodes of intradialytic hypotension. Actually, in all the definitions, there was notable incidence in the first half right up to the first hour even. So I think that the main thing as simple as it is, is probably dismissing this idea that most episodes occur in the final third or towards the end, which is all that's presented in the literature of the minute. And the findings, we then we then looked at how these relate to other clinical and demographic parameters. We did have some intradialytic measurements, so we measured relative blood volume andt oxygen saturation, we have intradialytic cumulative ultrafiltration volumes. And so we looked at whether some of these measures are predictive of the onset of intradialytic hypotension. And I think interesting in this sense, was that if we look at something like relative blood volume that has been around for a long, long time, and there's been a struggle in many ways to demonstrate really good outcomes in clinical trials with relative blood volume. And perhaps what we're able to show in our data is that the ability for relative blood volume to predict hypotensive episodes is actually different depending how far into a session we go. So the implications here may be that we become a bit smarter in how we use interventions. And, you know, the, the idea of individualizing treatment is, is often talked about but is, is never more true than in the current day and age because all our patients are different. And we need to, I guess, understand what is leading to the episodes of intradialytic hypotension in different people and tailor our interventions accordingly. We also looked at sort of clinical and treatment data to see what associate what associates with patients who tend to have intradialytic hypotension earlier on in the session. And we also demonstrated quite clearly that patients who have hypotensive episodes early in the session,

have much poorer outlook in terms of mortality, and all cause and cardiovascular mortality, and quite strong associations we shown as well.

**Peter Kotanko**
you were, in essence, the first one to describe this, that hypotension so low blood pressure can happen in the in the first half of the treatment, not just as the sentiment was towards the second half in the second half of the treatment. That's quite a remarkable finding. You earlier mentioned oxygen, can you can you say a few words about that?

**David Keane**
we are able to measure with the relative blood volume device that we have with that we were using them in the study is also able to measure intradialytic oxygen saturation. So this is a continuous measurement throughout treatment. And within dialysis, we typically have two main forms of vascular access. So we can access the blood through arteriovenous fistulae or grafts and where we're getting arterial blood, which we pass through the dialyzer circuit. And this is the point where we'll be measuring the oxygen saturation. So I mean, most of our patients are using arterial access. So this will give us intradialytic, arterial oxygen saturation. But we also have a sizable number of patients on who are dialyzing via central venous catheters. So in these patients, the oxygen saturation that we're measuring is central venous oxygen saturation. So in different patients, we're able to look at different things. So in our study, we were able to map out arterial oxygen saturation in a subgroup. And in the other subgroup, we mapped out central venous, central venous oxygen saturation. And what we really looked at in the study was looking at all the patients who at any given time point in the study, were just about to have an intradialytic hypotensive episode, and all the patients who are going to be hemodynamically stable for the, for the following 30 minutes. And we could really clearly show with central venous oxygen saturation, there was a significant difference in patients who were about to have an intradialytic hypotensive episode, compared to those who were stable. With the arterial oxygen saturation, there was no difference between the groups. And, and this, this does make sense, there is good rationale here. So obviously, with the arterial saturation, we're really looking at the ability of the body to oxygenate the blood, the blood and obviously lung function. Whereas with the central venous oxygen saturation, we're really looking at a sort of composite of the oxygen demand from the tissues, and we're looking at with the central venous access, we're looking at the upper body blood supply, really, so the, the balance between oxygen demand and the ability for the for the heart to respond to the demand and, and supply more blood. So, so really giving us different things. And it's, it's probably the, the impaired cardiac output, perhaps that some patients have that we can link directly to the sort of pathophysiology of intradialytic, hypotensive onset that we demonstrated.

**Peter Kotanko**
Yeah, I think this will be really interesting to look into in in future studies. And to see if, what's the predictive value of using this, this kind of metric. David, I wanted to get your thoughts around, I guess, what's the elephant in the room that we usually deliver dialysis three times a week which is, very different of course from the continuous delivery of dialysis with peritoneal dialysis patients or let alone the function of the, of the natural kidney. So, do you expect that say with more frequent dialysis, the number of, of these episodes of low blood pressure intradialytic

hypotensive episodes would change? What are your thoughts around this, the frequency of dialysis?

**David Keane**
So, intuitively, you would think that, you know, the, we know it intradialytic hypotensive episodes are strongly linked to the ultra-filtration rates. So, this is the amount of fluid we take off per unit time. So, the more time we have dialysis we give the lower the ultra-filtration rates will be so, it makes complete sense that if we get more frequent dialysis that the ultrafiltration rate will be lower. And the frequency of intradialytic hypotensive episodes will naturally be lower. I guess the swing to that is that, you know, we will be providing more dialysis sessions. So, perhaps the frequency as, I think, as was shown in the, in the frequent hemodialysis network trials, you might have less chance of having a hypotensive episode in any one given session. But overall, because you're delivering more sessions, you may have a cumulative increase in the number of sessions. Do we know which is more harmful? I'm not sure we do right now. I think this question of three, three times a week is much bigger than that. And, you know, we think about delivering more dialysis, but actually, we need to focus on the other side as well. And this we, we are obviously fixated on starting all our patients on three times a week. And I know there is a lot more interest in looking at incremental dialysis now. And you referred to PD and it's something they do really well in PD, but we really don't do very well in hemodialysis. And, incremental dialysis has been shown to preserve residual renal function. And we know that if you can preserve residual renal function, you are going to reduce the intradialytic fluid gains, and you will reduce how much fluid we need to take off patients. So I think, again, I talked before about individualization of care, and I think we need to really, we definitely need to move away from the three times weekly fixed schedule that we have. Exactly where we go, we probably don't know the exact answer, but I think we need to be brave and think, you know, we should be offering incremental dialysis for, for our patients. I know in our unit we are we're not quite there, we would probably do, you know, decremental dialysis, so we start everyone on three times a week, but there's lots of patients we would reduce their frequency, we do routinely monitor residual kidney function. We do urine collections. You know, there is this myth that they're very cumbersome and inaccurate but I think from our experience, that's not true. We do have bioimpedance now so we can monitor fluid status better and I think I mentioned the *BISTRO* trial earlier. So we will potentially have some outcomes there. But you know, by shifting some people on to lower frequency analysis, it will also open up this this problem with scheduling you know, people often talk about the issue with fitting patients in and some patients will need more dialysis, you know, maybe not everyone some patients may benefit from three sessions a week with longer time, some patients may benefit from shorter sessions more than three times a week. And, you know, I think we just need to move away from the fixed three sessions a week, of four hours with a long break which we also know, has associated complications. I'm not saying it's an easy solution but I think, I'm not saying we know exactly what the solution is but I think we need to be a bit braver and a bit more flexible in, you know, tailoring our prescriptions to what the patient's needs are.

**Peter Kotanko**
Yeah. Yeah, and I think your research clearly indicates that we need to move towards personalized medicine, patients aren't equal. And then each patient has his or her specific

biology, and we need to respect this. We also need to respect patient's wishes and desires. So and I think your research really contributes to this substantially. Now, let me just come back to, to a finding of your research that I think is really remarkable that there is a subgroup of patients who experience, hypotension, early on in dialysis so it seems to me that this cannot be due to volume removal because at the very beginning of the dialysis there is hardly any volume removed. I'm wondering if, for example, the contact of blood, with, with the dialyzer with the bloodlines so in other words was the extracorporreal circuit, if this could trigger mechanisms that may result in intradialytic hypotension, early on in the treatment.

**David Keane**
Yeah, I think absolutely we, we think about you know, 20-30 years ago where adverse reactions were really common, and you know we, we, people were really used to seeing them, and dealing with them. I think we think because we've got better biocompatibility and we've moved away from *acetate dialysis* I think we, we assume that we are, if we're away from, you know, lots of having lots of adverse reactions. I think you're absolutely right, you know the, I think one of the, I remember very distinctly before embarking on this study we had a patient here in Leeds who every single session for a long time, within five minutes of connecting him up to the machine, he would crash really badly. And we, you know, this has nothing to do with food removal, we we've measured, we measured bioimpedance we measured relative blood volume changes. And, you know, this clearly was something different going on. And this was a very dramatic, you know example of this, but there'll be lots of other things happening, happening within that sort of early period of time.

And I think that this is one of the things I think that the findings we had here is opening up really stressing the need for us to look at the different subgroups that make up intradialytic hypotension, being clever about what is causing it, What the pathophysiology is. And, and I think this is really going to help us, you know, deliver the trials and interventions that we need, and then obviously the patient care will follow from that because we struggle to get. We struggle to get the research and the research outcomes that we need to justify the interventions. And part of this, to my mind is thinking that your intradialytic hypotension is one has one common causal pathway, which, you know, traditionally we think is, we take too much food off, or we take it off too quickly, or a combination of them two, but we know it's more common with that and then that we're starting to see different interventions coming in now and so we have, you know, temperature management of the patient, which will clearly be linked to hemodynamic stability, we have, we've played with sodium levels in the dialysate and profiling sodium levels for a long time. And like so many things in dialysis there's, you know, you know there's pros and cons for going in either direction, but generally when we do these studies we are trying to treat a group of patients, just a general group of patients from our dialysis units and I think we just need to be a little bit smarter in designing specific trials to deal with specific interventions for specific patient subgroups.

**Peter Kotanko**
Yes, I really think, David that your research helped us to broaden our view of intradialytic hypotension, it's not just volume. There are clearly many, many other mechanisms involved and what I really like about it, that you address a problem in your research that you thought we knew

everything about, right? We thought, well, it's clear, it's volume removal, but there may be many other things, other physiological systems involved. Be it activation of the immune system, be it, be it the autonomous nervous system and others, and I think your research really helped to broaden that perspective.

Well, David, we are coming towards the end of our, of a really wonderful conversation and I just wanted to ask you, could you summarize in, I don't know, three, four or five sentences, what are the main insights from your research, were, and what do you think are the next important steps?

**David Keane**
I think you summarize the, the main finding yourself there really well but this, this, we have broadened what we think intradialytic hypotension is and I think, I hope it will dispel a myth that maybe existed in the literature but I'm I know probably doesn't exist in clinical practice - I think if we went and talked to our nurses they would probably say that we you know we do get problems throughout treatment - and that is that hypotensive episodes occur towards the end of dialysis. So I think you know this. I think the thing about this paper is, it's actually a really straightforward thing we've done by this just describing when the episodes occur, but I think, as you say that the consequences of this realization, consciously rather than perhaps sitting in our subconscious maybe for many of us opens a lot more doors and I think that's, that's what it does, I think it will, maybe prompt us, as I say to be a bit smarter about our interventions, and, and opens a whole number of avenues now. I think intradialytic hypotension is something that's been studied quite a lot. We have lots of big databases for blood pressure measurements so we can do lots of epidemiological studies, and perhaps as you say we thought we knew everything we needed to know but we can take this on a lot more now. And I think one area where I think we did a little bit in our study but really I would like to really expand on is trying to understand who these patients are, who have intradialytic hypotension early on is an individual who has episodes early on, likely to always have episodes early on or. Is it quite a mix, and look at the sort of the phenotype of the patient who's having these types of episodes, you know, one of the things we found was lots of indices that were linked to nutritional status with were associated with patients who have early, early onset intradialytic hypotension. So when we talk about smart trials, perhaps, you know that using a sodium profile in these patients who may not have big intradialytic food gains may not be so detrimental and may help their hemodynamic stability. So, yeah, I think, to try and become concise before I speak too much, it is about opening doors and opening avenues and asking more questions, getting us to ask more questions to hopefully deliver the knowledge and the research outcomes to empower us to deliver better care, which, as I've mentioned a few times I think just needs to be more tailored to a person's individual needs,

**Peter Kotanko**
David, I have to say it was such a pleasure talking to you and, and they said what I really loved about your research because it was challenging, clearly hold beliefs, and, and as you. Beautifully said it opened up doors that eventually I'm really convinced will result in better care for patients. So, great pleasure talking to you. I wish you well. Stay safe, and I'm looking forward to our next conversation.

**David Keane**
Absolutely. Thanks so much.

**Peter Kotanko**
Thank you for joining the Renal Research Institute for this episode of frontiers in kidney medicine and biology. We invite you to engage with us on our social media channels, and look forward to seeing you again soon for the next episode of frontiers in kidney medicine and biology.