Episode 9 – Hemodialysis: the far side of the moon

Guest: Nicholas Selby, BMedSci, BMBS, MRCP, DM

Peter Kotanko
Welcome to the Renal Research Institute's Frontiers in Kidney Medicine and Biology, where we share knowledge and advances in kidney research with the world. In today's episode we discuss hemodialysis. It is a life sustaining treatment for kidney patients. And yet over time, it also can have a negative impact on the human body. My guest today is Dr. Nicholas Selby. He is Professor of Nephrology at the University of Nottingham, and Honorary Consultant Nephrologist at the Royal Derby Hospital in England. Dr. Selby is a leading clinical expert on both the hemodynamic and the cardiovascular consequences of dialysis.

Nick, you're very much welcome to this series of kidney medicine and biology.

Nicholas Selby
Thank you very much for having me, Peter. It's my pleasure.

Peter Kotanko
Nick, you've performed a lot of research into the into the various effects haemodialysis exerts on the human body and the patient's body. I was always wondering, I mean, you know, hemodialysis is a life sustaining treatment. So there is a clear benefit to hemodialysis. Now, on the other hand, we learned over the past years that hemodialysis can actually exert negative influence negative impact on the on the patient's body. So what have you learned actually over the years? What was surprising? What was less surprising? Can you just say a few words about this? How dialysis possibly impacts the patient's physiology in a negative way?

Nicholas Selby
I mean, the starting point is just to acknowledge that's the development and widespread availability now of dialysis is one of the marvels of modern medicine.That's changed in the second half of the 20th century, at such a rapid pace to great benefit of many patients. But I think the question about how dialysis can have negative effects on the human body is probably the place to start to answer that question is by looking at how dialysis works, and how different it is from your normal kidney function. So all of the time, whether you're awake or whether you're asleep, your kidneys are working 24/7 to filter the blood, meet you and get rid of the waste products of metabolism, and do a myriad of other functions to but the way that that patients receive haemodialysis is not at all like that. It's delivered in intermittent sessions for four hours, three times a week. So the patient's body's not continuously being helped in the way that the kidneys are. But there's the peaks and troughs that happen in between each each dialysis session

followed by this intense dialysis treatment. And so what that means then is that things can happen during the dialysis process. Because everything's happening really fast, you're having to clean the blood in a highly efficient way, and also removing excess fluid from the body that jobs that the kidney would normally do. And what what you see during this intense four-hour treatment time, is that this can have great effects on, on different parts of the body. But what our program of research and many others has been focused on over the last few years is how this then affects the blood flow to different parts of the body. And there's good evidence now to suggest that Dallas's causes reductions in the delivery of blood to critical vascular beds. And by doing so, and on a repeated basis, three times a week, every time a patient comes for dialysis, that's that can have negative effects. So it's life saving, but it's not a perfect treatment. And it can have adverse effects on the human body.

Peter Kotanko
I'm very happy that you put this question to their framework. physiology of North normal physiology and, and pointing out that and kidney healthy subjects, this clean thing is going on on a continuous basis. And so you're saying it's really this intermittent character there, the fact that solutes and fluid are removed within a very short timeframe, say, within 12 hours a week, which is around 70% of the week, instead of 100% of the big this is really the root cause of these negative effects. Right?

Nicholas Selby
Absolutely. And I think later on in the conversation, we may, we'll circle back to that very point. But that just to give you a sort of an example, we know that that transplantation is often the gold standard treatment in many patients. And by having a kidney transplant you go back to to having that that 24/7 kidney function that you clearly don't have when you're on dialysis.

Peter Kotanko
So think other actually certain organs that are particularly affected by this repetitive loading and unloading? And if so, what organs would that be? And what would be the clinical consequences of, of this? It used perfusion of those organs.

Nicholas Selby
Yes, there are and I think there are differences between organs, but also differences in how much we know about the different organs. And the place to start is the heart. We've known for for several decades now that patients on dialysis have significantly worse outcomes in terms of their cardiac health, and they're more susceptible to heart failure, and more susceptible to, to death from from cardiac causes. And that's got many causes. And you're right, there's a direct effect from volume loading, and then unloading and that that sort of repetitive nature, which isn't good for cardiac function. But if we focus in on the effects of perfusion, then really, it was the heart that this this process

was discovered, discovered in first. And what we know is that blood flow to the myocardium, so that the heart muscle falls during dialysis. And in tandem with that, we also see changes in how the heart functions. And so there's a reduction in cardiac function during the four hour dialysis treatment. And research has also shown that when that happens on a repetitive basis, so every time the patient does dialysis, over a longer period of time, say after 12 months, patients who are being affected by that process, end up with fixed long term reductions in kind of function. And then that becomes a very serious situation, because that is this scenario where patients are more vulnerable, and at higher risk of having a worse outcome. So the heart was where it's discovered, and the heart is where it's been been been studied the most. That being said, I think there's good evidence now to show that the same process happens in other parts of the body. Probably the next most important and maybe most important in terms of symptoms. And what it means to patients is that the same process also happens in the brain. So blood flow to the brain changes. We we can see using very detailed MRI scans of the brain that certain areas of the brain and dialysis patients become affected by ischemic change. And what I mean by that is changes due to reduced reduced blood flow. And those areas of the brain are often those that are important for higher executive functioning. So those very tasks that we need to carry out our daily lives are being targeted by this process. So straightaway, you can see that that's that's really important for patients, and also contributing to cognitive decline. And then other areas of the body I think we also think a very important our residual kidney function. And that might sound a bit strange because the patient's got kidney failure. So why do we worry about their kidney function anymore? But the answer to that is this, those patients who have even got a little bit of kidney function left and still making a little bit of urine themselves, that's really helpful to to their health. And if you lose that more quickly, because of this same process happening in the kidneys, that is also and negative and negative consequence. And then possibly some evidence around that same process happening in the gut. And maybe the skin, which is relevant for patients with diabetes with with foot ulcers, for example.

Peter Kotanko
So it seems that there's a wide range of organs of vital organs really affected by those, by by this reduction in perfusion of blood, per se, is there actually is other certain patients who are particularly vulnerable to the effect of hemodialysis on the on the hemodynamics?

Nicholas Selby
I think that's a great question. And I think we know some things about the answer to that. But maybe I think there's also more to learn. I think there are some patient related factors that might increase the risk. And then there are some factors that relate to how dialysis is delivered and how patients are getting on on with with with their dialysis and in terms of making it work work for them. So, so patients clearly that are more at risk of

those that have vascular disease, diabetes, that type of thing. But then on top of that, the elements that are related to dialysis are those that tend to make it more of a stressor on the body. So bigger changes in blood pressure, taking larger amounts of fluid during each each dialysis session, a two key factors that we know that are related. But that doesn't explain it all. And some patients still exhibit these changes, even even without those factors. And we're not always 100% sure that we're confident in predicting which patients this is happening to so. So I think we know part of the answer to that. But But I think there's still more more to be discovered.

Peter Kotanko
You were focusing so far, we were discussing so far, the hemodynamic impact, the impact on blood pressure. There is the risk some patients who are particularly prone to add dramatic reduction of blood pressure during dialysis in what's called interdialytic hypotension. I do we see the changes you just described in brain and heart and gut and skin and function? Are these all predominantly observed in patients who actually experience interdyalitic hypotension? Or are those seen in offering patients who do not have infertility, hypertension?

Nicholas Selby
And it's a great question, Peter, and logically think that the patients that you've described are the ones that this process is happening in, and I think they're clearly the most vulnerable? And the answer is that it happens more often and to a greater severity in those types of patients. And I think the symptoms that those patients experienced both when their blood pressure drops, but also in how long it takes them to recover after dialysis, it links in there the most severely affected that that's that's for sure. But you also see changes in organ perfusion happening in patients who don't exhibit such such dramatic changes during dialysis. And then really intriguing data shows that some of these changes can be detected quite early on during dialysis. So it's not just a change in in blood pressure, per se. It's more complex than that. And that's, that's why I think we haven't totally characterized which patients that this happens in, we know which patients are at greater risk, but it's still happening undetected in other patients that we can't currently identify at the bedside.

Peter Kotanko
It's interesting that you you talked about those changes that happen early on in the treat in the mean, with dialysis, blood touches non physiological surfaces, the dialyzer, the cloud lines, at do you think that this interaction of blood with those non physiological surfaces can can play a role, particularly in these early changes?

Nicholas Selby
I think it's, again, a great question. And I think that that hope that's a hypothesis to be tested. So you could certainly construct an argument by which that that contact of the

blood with with the artificial surfaces triggers either clotting or inflammatory processes, and we know very well from other disease areas, for example, sepsis, where you see activation of those pathways, you see changes in blood flow at the micro vascular level. So some areas where blood flow increases other areas where it disappears. So you get a mismatch and a disorder of blood flow at the microcephaly, circulatory level. And that's disconnected from what's happening with blood pressure. So so it's, it's, it's a hypothesis, I think that needs to be tested, because you could certainly make a scientific argument of why that's plausible.

Peter Kotanko
And then those things can leak in. There are also many other things that happen when dialysis is starting during the alysus. I'm thinking for example, that certain solutes say you have, for example, where there's a high concentration and the patient are removed rapidly from from most of the body, but not from other parts of the body, like the brain. In the brain, there is a delay of urine removed from the body. So from the origin. So I'm wondering how you to what extent you think this could play a role say, in in impairing cognitive functions in patients? Because with yoga, sticking long in the brain, this could cause brain swelling, for example, do you think that this may have an effect on impacting, say, cognitive functioning patients?

Nicholas Selby
I do. And I think there is some, not a lot of evidence, but some evidence over the years that sort of support that. And we've recently completed a research study at that would also support that premise. So So we saw changes in brain volumes, for example, that were unrelated for changes in blood flow and perfusion. And linking that to a sort of an accelerated aging process in the brains of patients with with with dialysis, could be a new way of looking at hemodynamic stress on that, on that really critical organ, which is clearly so important for for symptoms, and well, yeah, for, obviously, for everything, but for activities of daily living in in particular. So yeah, I do I do do accept that.

Peter Kotanko
So this is a this very interesting, and we did some research where we measure your levels in the cerebral spinal fluid, before and after the LSM, you see different dynamics there and patient where it would go in parallel with the blood human levels, but in others, it will stay almost constant. And then and then there are differences in psychological tests of those groups, actually. So it's a it's a very, it's a very, very, very limited experience. But I was really wondering, if this, these osmotic shifts that may be induced by by you have stained for a long period of time high and in dialysis patients could actually contribute to, to damage and I'm so interested on more about the study you did on brain volume,

Nicholas Selby
Absolutely. And device is the rapidity of change isn't set and the way that we deliver dialysis, it's it's everything is done at maximum efficiency. So that initial change in in the concentration of different different solutes in the blood is very rapid.

Peter Kotanko
And I mean, it's not just here, if I'm thinking like, like potassium that's removed rapidly during dialysis patients arrive with usually with elevated potassium levels, and then it's reduced rapidly and which may affect conductivity in Martin and others fifth year, do you think that this could play a role with respect to long term changes is when acute effect but people have to to to be concerned about the arrhythmia?

Nicholas Selby
I think for potassium, I think it probably probably more of more acute effects. And that sort of links into the sort of a readme is that you see during dialysis and that link to sudden death, which which is more frequent around the fall of that long gap when you have a two day gap between dialysis sessions rather than just just a one day gap. So I think I and I'm struggling to see how changes in potassium, I'd have those sort of long term effects as clearly as some of the other mechanisms.

Peter Kotanko
Are there other electrolytes that come to your mind such as, for example, sodium, that the sodium that is removed from the patient have possibly been loaded to the patient during dialysis. Do you think that this is part of this? Of this call? complex of an intervention that would affect patient's physiology.

Nicholas Selby
Yeah, absolutely. And we know sodium is important and, and really, our understanding of sodium is changed a lot. So over the last few years with some really inspirational research that that's been been done particularly by the entities, but also others using new ways of imaging sodium, so. So I guess traditionally, we thought about sodium as the sort of predominant extracellular cateye. And so it affects is this, it's linked to how much fluid and water is in your body. And that sort of links into what we're saying about changes during dialysis. And I think the relevance of sodium is separate from your ear or potassium, it's something that we might be able to change and modulate more easily with with dialysis. And that's why that's why it's why it's so interesting that some of the the really interesting research around sodium has shown that there's actually storage of sodium in places in the body that we didn't appreciate previously, and it's stored in the skin and in the muscle. Separate from water, which which is, which is really fascinating. And there's no questions about what that 30 was doing. How how it can be changed and manipulated. But it's relevant because it links to blood pressure and possibly

cardiovascular health. So linking that to how we handle sodium during dialysis, I think is a very, very pertinent area that we need to see more researching.

Peter Kotanko
Yeah, clearly a new area. And we just have to learn so much about this now, but this, this brings me a little bit to what can we do actually to to reduce the impact of haemodialysis on the patient's physiology? So I believe it was really one of the first papers I read with us the first author about the use of cooled LSA to perform the meta analysis and this, this paper of yours and together. It was just it was to get with other other data on this. I mean, it was just such an eye opener. Could you say a few words about what can be done to to mitigate those effects of haemodialysis?

Nicholas Selby
Yeah, definitely. And I think probably sort of answer that that question in terms of sort of two to two blocks really that the first is what do we know about interventions that have actually been shown to lessen that effect of reduced perfusion to organs? So actually studying the effect of dialysis on organs and looking at the benefit of an intervention? And then there's a sort of a second question about what evidence do we know about Making Dialysis more more tolerable? And there's some links there across those two sort of different parts of the question. And some, some maybe that's a little bit more common sense. But the intent of the intervention is that we we've we've got evidence that improves improves the tolerability of dialysis and reduces that change in blood flow. So very complex process intervention called biofeedback, dialysis, where the machine senses changes in blood volume, and then automatically react to that to try and reduce hypotension. And some of the early work that I did under the supervision of Chris McIntyre was was showed that that that approach had a benefit, but it's hard to take that into the clinic, it's a bit too a bit too cumbersome. And then cool data feeds, which we've known the benefits in terms of its effect on blood pressure since 1980s. We then became interested in that because it's much easier to apply and it's effective at reducing blood pressure. And we were able to demonstrate that it reduced the changes in cardiac function during dialysis. So it lessened the effect there. We showed that it is able to have less of effects in terms of reductions in blood flow to cardiac muscle. And then an important study done by a colleague called James Burton but also under Chris's supervision, showed that the long term effects of cardiac function are equally important on patient health. So a randomized trial then followed, demonstrated that cooling the data sites actually protected cardiac function in the site in the long term and the same process in the brain. So cooling the dialysis affects the short term process. And it also provides long term organ protection. So, so that's, that's what that's what we know. The second question is about how can dialysis be made more tolerable in general. And so in addition to what we've we've said, there are other ways of trying to reduce drops in blood pressure. But but the approach that might be effective, but not always welcomed by patients is to increase the time that dialysis is delivered over. So it's, it's more gentle

and not not not not as rigorous, or to dialyze more frequently. So instead of doing three times a week, he might dialyze, six times a week. And actually, we've got quite a big home dialysis program at our center, and that it not just has those benefits patients, he can see that their symptoms are much better. And he can imagine how dilating overnight for 10 or 12 hours six times a week is very, very different from short, intermittent dialysis three times a week. And finally, peritoneal dialysis. So a different modality of dialysis. We know that that doesn't cause the same hemodynamic effects and end organ damage in a way that intermittent haemodialysis does so. So I think I think there's a range of things that can be do can be done and individualizing. That is quite important.

Peter Kotanko
Yeah, I think you bring up this important point about home dialysis and, and how well patients are actually doing when they dialyze say six times we get home. I mean, this will take some time to evolve, but we see penances that the numbers are increasing. And wondering, what are your thoughts about just getting rid of this long interpretability intervals as patients are valid, say, Monday, Wednesday, Friday, and then the next is dialysis is a Monday? What if this interval would be reduced, say, to two days, so it would be a dialysis every other days in those patients were in center? And they know that there may be tons of logistic problems? But what do you think in principle about that?

Nicholas Selby
Intuitively makes sense, doesn't it? We know that long gap did have those they do emulation, it's associated with caffeine levels on patient tone and electrologist. associated with higher rates of sudden cardiac death. It makes it makes sense. But whether they need logistic barriers in western mountain I think is a big challenge. I don't know. I don't know how you see that question, Peter. It's, it sounds simple. Doesn't have to dialyze, but it's not. People have a routine and changing that favorite?

Peter Kotanko
personalized medicine, I think is really gaining a lot of ground. So how would you stratify patients for a specific treatment? So would you use traditional, say, clinical acumen? Would this be supplemented by certain studies of the patient's physiology by biomarkers? How can you give us some, some insights how actually to advance the personalization of the patient's treatment? Sure,

Nicholas Selby
I think we, we do it a little bit. And it is mostly based on clinical acumen, if we're going to be honest at the moment. So if somebody is approaching dialysis, they're choosing which modality that they're sort of planning for. If somebody's got very bad cardiac function or low blood pressure, are they going, you know, they're going to be at risk of

having hypotension with intermittent hemodialysis. Those considerations need to be brought in to the shared decision making. And that might be a factor that swings the choice towards peritoneal dialysis, for example. So I think we're doing that type of type of medicine already. Going back to what we said before, it's actually difficult to fully provide personalized medicine in this area at the moment because we're not good enough at detecting which patients are sustaining the process. And most of the the tools that we've used to identify patients, they've used research grades, imaging techniques, quite specialized at the moment, not immediately around. relevant to clinical practice. So we have to bridge that gap and take some of those methods and bring them a little bit closer to the bedside. You mentioned biomarkers, which is sort of blood tests. And, again, they're not the perfect solution. So they give information at a population level. But when you're actually trying to evaluate an individual patient, they're not not good enough to tell us what what to do yet. So maybe we need to sort of get a little bit more creative. I know you've done some fantastic work around monitoring oxygen levels in venous blood, for example, which which might be a way of gaining some insights into the hemodynamic response to dialysis, we are focusing at the moment on approaches to non invasively monitor blood pressure continuously. And if you get that really close resolution of blood pressure, yes, that might be a way that then you can apply machine learning or even predictive algorithms to say, okay, blood pressure is about to drop, let's do something now before that happens. And we don't do that at the moment, we've got a blood pressure cuff that goes off every 30 or 60 minutes, sometimes less. And I think getting a tighter grip on blood pressure monitoring might might be a way a way through.

Peter Kotanko
We are almost coming to the end of this really interesting conversation, like maybe two or three sentences, what would you want the viewer, the listener to really take away what would be important points you would want to, to convene to communicate to our audience? It's sort of summary.

Nicholas Selby
So I think I think the first thing is we sort of focus a lot on the adverse consequences of dialysis. But let's get back to where we started. And actually, dialysis is an amazing treatment. And my sort of first take home message is actually by concentrating on dialysis and attention to detail and delivering it as well as we possibly can, is is is likely to to have benefit to patients. And that's a move away from a sort of a conveyor belt approach, which, which we've sometimes seen in the past. And then I guess the sort of the second point is actually thinking about personalized medicine, what we need to do is be able to not just understand physiology, which we started to do a little bit in the research setting. But we actually need to be able to measure that in in clinical practice. And until we can sort of get a handle on that, then we can't really sort of improve the way that we prescribe and deliver dialysis at the moment. So understanding and

measuring physiology will allow us to sort of move forward in terms of treatment improvements.

Peter Kotanko
This was a such an insightful conversation. And I think it laid also out in what direction we need to go in the in the years to come. So Nick, Dr. Selby, thank you so much for spending half an hour or so with us and with the audience. And I'm of course looking forward to outcomes of your research in the in this really important area. Thank you.

Nicholas Selby
And thank you for having me. It's been a great pleasure talking to you. Thank you.

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 for the next episode on Frontiers in Kidney Medicine and Biology.

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