Episode 3 – From dialysis to Mount Everest and back
Guest: Jeroen Kooman, 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. Jeroen Kooman, Professor of Chronic Kidney Failure at the University of Maastricht about his recent paper regarding a comparison between the oxygen handling of Sherpas and dialysis patients. We will talk in depth about the oxygen cascade in hemodialysis patients in native high altitude dwellers and lessons learned from extreme physiology that might benefit patients with end-stage kidney disease.

It's a great pleasure to welcome Professor Jeroen Kooman. He graduated from medical school in Maastricht in 1990. And in 1992, Professor Kooman completed his PhD on the role of the venous system in hemodynamics. During dialysis, he was then trained in internal medicine and nephrology. Professor Kooman spent time at the Karolinska Institute in Stockholm, Sweden, as a as a guest scientist, and in 2012, he was appointed a Professor of Chronic Renal Failure. Professor Kooman was also head of the department of nephrology at the Maastricht University Hospital. And since 2020, he is Director at the University Maastricht University Institute of Education. So it's a great pleasure having you with us here.

Jeroen Kooman
Thank you very much, Peter. I'm happy to be here.

Peter Kotanko
Jeroen, you're really one of those scientists and clinicians who have such a broad scope of interests you're interested in, not just the into medicine or nephrology. You you're interested in connecting dots that seem so far away from each other. And you recently published a really interesting paper about oxygen and hypoxia in sherpas and compare them to patients with chronic renal failure. I think it was your trip to the Himalayas that actually made you think about this topic. Now, you're home. Can you tell us a little bit more about this?

Jeroen Kooman
Yeah, sure. And actually It was a course organized by World Extreme Medicine, they organize courses and they learn, you actually have to perform medicine in extreme environments. And I took this course which was called mountain medicine. And actually you make a trip to the Himalayas and you hike yourself until 5600 meters. So you also experience the effects of the altitude itself. And what you also saw you read, of course, also a lot about the specific region is that people live or have they haven't lived there for generations, like Sherpas, and they can really perform very well actually. And under extreme physical demands, they can really perform very well. Like climbing Mount Everest, aiding climbers there. And yeah. Actually, I was really admiring what they did, but of course, I also learned from studies which you did, of course, at RRI where we, where you look at dialysis patients in relation to hypoxemia. And dialysis patients

with hypoxemia, they actually they do not do really very well, but they have an increased mortality. So I was actually struck by this difference in handling reduced oxygen levels. So this is one group of people who actually really tolerate recused oxygen levels very well and could have could performed a lot of work and an exercise there, whereas the other group of people will for which we also take care, perform badly under episodes of hypoxemia. And that was actually the idea because this difference, having experienced the effects of hypoxemia myself or as I saw myself, actually let me know how to make this connection.

Peter Kotanko
So Jeroen, this is really interesting that you started with a course on high altitude medicine and then came up with the idea to connect those two scenarios. So what were really the main insights you got from this research?

Jeroen Kooman
What you actually see is that Sherpas have adapted to low ambient oxygen levels over generations and their surprising adaptations. For instance, they have increased number of capillaries . So they can really extract oxygen in their tissue very well. For instance dialysis patients do have a reduced number of capillaries and so are at the opposite. And what you actually see if you look at Sherpas, is that they adapted and-at different levels in the body to low ambient oxygen levels. Whereas, if you look at dialysis patients, they have actually kind of problems all at different levels of the oxygen cascade, which can reinforce each other. So whether one group of people actually shows adaptation, dialysis patients show abnormalities as different levels of oxygen and cascade. And as you know, the oxygen cascade actually goes from ambient oxygen to the lungs, actually, to the tissue themselves. You can see there is a lot of difference over down. And I hope that actually we could learn a little bit from these adaptations, which had to evolve in Sherpa over many generations to adapt that it could improve the care for the for our patients, maybe in the future, that would lead to some new insights. But admittedly, this obviously will take a long time.

Peter Kotanko
Yeah, I was just wondering, really, can you learn something by comparing Sherpas with dialysis patients that really could be applied in the care for dialysis patients. Now, when I talk about the career, I really mean, both diagnostically and therapeutically, but also in terms of basic science, for example, or, or other intervention that would kind of convert dialysis patients who had so many of those are within the conditions of hypoxia and hypoxemia, you think, will eventually convert them into a Sherpa-like oxygen metabolism?

Jeroen Kooman
Yeah, that would be great. Actually, the two main differences at the end of the oxygen cascade, which could be of relevance. And if you look at Sherpa actually, if they, as already mentioned, have an increased number of capillaries, whereas dialysis patients have a reduced number of capillaries, that's one. And on the other hand, actually, the oxygen metabolism and handling by the mitochondria is more efficient and much less oxidative stress, whereas dialysis patients have increased oxidative stress and their oxygen handling at the mitochondrial level is not very efficient. Now, first looking into the capillaries, it's of course, very difficult to increase your

number of capillaries, although under hypoxemia, increased number and levels of HIF can increase VEGF levels and this way also increase the number of capillaries. Whereas in dialysis patients, the number of capillaries could be reduced because of reduced VEGF levels. And for instance, data from institutes have shown that high salt diets can reduce VEGF levels. So maybe reducing dietary salt intake might positively affect the capillary structure, but it's still hypothetical and to the best of my knowledge, this has not been studied yet. And of course, we could also think about, let's say the effect of nitric oxide donors in patients on dialysis, but the effect on capillary structure also has not been studied yet,, as far as I know.

Perhaps there is a little bit more evidence if we look at the mitochondria. For instance, NFR 2 agonist, or NRF2 containing foods, like polyphenols might reduce oxidative stress which could also be of relevance for dialysis patients by reducing oxidative stress. So maybe there could be some potential interventions which obviously need to be studied in a clinical setting.

Peter Kotanko
I really love research that looks into “experiments” of nature and, and try to understand what can we learn from this. I think this is also very, really fascinating from an evolutionary standpoint. You know, Jeroen, are there actually any genetic differences between say, Sherpas and non-Sherpas that could make them more resistant against the effects of hypoxia and hypoxemia.

Jeroen Kooman
What was interesting is very recent paper actually showing polymorphisms of VEGF Sherpa, that's one. And the other one is a little bit unexpected. And that's the fact that in contrast to people from Anders, and actually Sherpa do not have polyglobulia (increased number of erythrocytes). So increasing hematocrit levels under ambient hypoxia is not necessarily beneficial; they have a polymorphism in the EPAS-1 one gene. And actually, this reduces HIF2 alpha, which plays a role in in erythropoiesis. So actually, this can be a beneficial adaptation at extreme altitude, when in contrast to Andean people, a chronic mountain sickness, is nearly absent in Sherpa. So actually, this is somewhat unexpected in a way that the HIF2, which plays a role in erythropoiesis, is actually inhibited by one of these polymorphisms. It's a very ancient gene, which is this E plus one gene, which actually also was discovered in a very old human race, the Denisovans. But it's a different story, actually. But it's very interesting.

Peter Kotanko
Yeah, so actually, it's interesting, because they knew, so we in state, I mean, we're identified, not too far away, I mean, few 1000 miles from, from the, from the area where Sherpas live nowadays. So it's always interesting to speculate.

Jeroen Kooman
It's interesting, although we do not know if there's any connection there. It's just coincidence. Yeah.

Peter Kotanko
Of course. Now, just to drive that point home, because I think this might be of great interest to, to our, to the audience, unlike those people living at high altitude that usually develop polyglobulia So high hematocrit levels, that's something that Sherpas don't.

Jeroen Kooman
No.

Peter Kotanko
And, and the current hypothesis is that this is because of genetic differences. And, yeah, and, indeed it might be beneficial to some extent, because the blood viscosity doesn't increase as much as it might increase in I other populations that dwell at high altitude.

Jeroen Kooman
Correct. That's indeed, that's indeed true. And because your normal response on this, let's say chronic levels of ambient hypoxia would be an increase in and hematocrit. As already mentioned, if we look at the Andean population, but also people who came later to the Andes, and worked for instance, in mines there, they developed severe chronic mountain sickness, which is absent, as already said in, in Sherpa. So probably, there's this beneficial adaptation.

Peter Kotanko
I'm just wondering, do you know, has anyone measured EPO levels in Sherpas? And in related this to, to red blood cell level?

Jeroen Kooman
It's a good question, I don't know. I'm not aware whether EPO levels themselves have been have been measured. They might, but I'm not sure. Part of it can also be a little bit difficult sometimes, because part of these experiments are actually done on location.

Peter Kotanko
In recent months and years, there was some research on what's called remote ischemic preconditioning. So could you just say a few words about this, explain to the audience what it is, and if there might actually be a relationship to the hypoxia hypoxemia, I should say, maybe experienced by Sherpas?

Jeroen Kooman
It's(if?) you have remotes preconditioning actually, in which you have, let's say, for instance, you induce hypoxia. Let's say for instance in the arm and, and in this way actually hope to increase your tolerance for organ damage at different organs, that's one, but you also have another which comes a little bit closer. It's hypoxic preconditioning, where actually, let's say, ambient, low ambient oxygen levels are induced, artificially, obviously, during relatively short periods of time. And this does not, of course, not come into the neighborhood of, let's say, the multi generation adaptation of Sherpa. But it's an interesting model. And it comes back to what we call hormesis, it's actually that mild stress episodes of stress might increase your tolerance for more severe stress at the stage, especially this hypoxemic, hypoxic preconditioning has been used and lot of

preclinical trials. Animal trials showed beneficial effects on reducing brain injury,. That's been somewhat less evidence in a clinical and in a clinical setting in a way. Theoretically, is seems to be a good model.

I think there is one point of caution, if you would induce this in an already susceptible population, where with multiple abnormalities, due to the oxygen cascade, you should also be of course, be a little bit careful with inducing severe hypoxia, I think, even for relatively short periods of time. So it would be of relevance whether a pharmaceutical approach, like PHD inhibitors which are used for the treatment of, could also have potentially some effects apart from anemia, but I'm not an expert on that. Evidence is still relatively limited, although it has been hypothesized that these could also be used for instance, to prevent neural damage, etc. But as far as I know, there are not many clinical data out there yet.

Peter Kotanko
So if you would, have funds of your own, what kind of research would you want to conduct by further advancing this field of comparing, you know, people living in such extreme environments such as Sherpa, with say CKD patients? What would be your, the primary hypothesis you would like to test? And, and what would you expect?

Jeroen Kooman
What would be interesting, I think, is to focus on two aspects. And I think that's firstly the mitochondrial efficiency. And secondly, \be the capillary rarefaction, in dialysis patients capillary, and increased capillary density in Sherpa. And that I would really be interested to see whether interventions could increase handling of our energy handling at the cellular level, in dialysis patients, which I think is a big problem. An increased oxidative stress has been known for a long period of time, can reduce inflammation, can reduce oxygen handling leads to toxicity at a cellular level. I think, that's also a big problem. And to dive more deeply into these two aspects, capillary rarefaction and mitochondrial efficiency, I think with different methods, nutraceutical maybe, or even, let's say, with mild, hypoxic preconditioning, could be of interest. So this would be I think, effective the topics, which would be more relevant from a comparative physiology point of view.

Peter Kotanko
Yeah, and who knows, maybe a member in the audience is Oh, yeah, cool project. And, and let's see if we can work together. Who knows, you know, Jeroen. I'm just wondering, because research requires frequently animal models, cell models. Are you aware of actually animals living in high altitude. Oh, yeah. They may have developed mechanisms that are somewhat that are somewhat developed, that can somehow be compared to the mechanics is that were developed in Sherpas?

Jeroen Kooman
One of this is an unexpected animal. They live in hypoxic environments, not at altitude, it's the naked mole rat, which is already I think, quite a well-established anti-aging model actually had its which also seems to be very resistant to oxidative stress. -From animals living of altitude, let's say, we have references to certain geese who fly very high; I'm not aware that they are

actually used to as a kind of a hypoxic model. Probably, it may be very difficult to expose high altitude living geese due to these kind of, of experiments. But there have been; I'm not completely aware of the details. But there have been tests on these animals actually looking at their handling of oxygen. They can actually fly over the Himalaya. So they must be extremely tolerant of low oxygen levels.

Jeroen Kooman
In the Everest a lot of transport is done by yaks work and also, who are very tolerant to ambient hypoxia. And yeah, they carry huge loads, and they really help trekkers and climbers a lot there. And also not so much aware of wherever tests have been done on these on these animals. I'm sure there must be but I cannot recall them yet.

Peter Kotanko
Might be interesting to look into this because this could be another test done that's worthwhile to connect back to the human condition. When they think about the questions related to allometry. Throughout the sayr , the mammalian kingdom, there might be many interesting, many interesting aspects, aspects to that. You are a man of such broad interests. Can you tell us a little bit what your current research is and what areas you think should be researched more intensely, in the chronic kidney disease field?

Jeroen Kooman
Thank you very much. It's a lot of some of the research which I'm doing now is actually looking to the most optimal methods to detect sarcopenia in patients on dialysis, looking at different techniques and methodologies because sarcopenia also a big problem, of course. As you know, I'm also interested in the phenotype of premature and accelerated aging and inpatients on dialysis. And muscle wasting is one of the very important component. Next to this, it's very interesting, is also that we are also working together are looking at, as I was sometimes like to call it, it's more of a kind of a mechanistic epidemiology to look at it together at large data sets for which we actually can learn about more basic mechanisms, actually looking at, yeah, who can have impact on survival or well-being of patients on dialysis. And, also there connecting different risk factors like fluid overload, inflammation, muscle wasting, etc. So these are actually the main points of research at present. But I think it would be interesting to extend this also maybe a little bit more, let's say, as already said, mechanistic studies into intuitive the mechanisms of capillary rarefaction and patients on dialysis. And maybe that would be a topic for the next future.

Peter Kotanko
Yes, especially I think the whole question about sarcopenia is something that that will be a new frontier, I believe, in kidney research, because they're the metabolic activity of muscle. Of course, the importance of muscle for mobility, which has in turn effects on the hemodynamics. And I think cannot be overstated. Are there other any advances in this research that you would want to highlight?

Jeroen Kooman
Yeah, it's that there's a lot of research, of course, being done at the basic level, but I'm actually interested in a kind of a follow-up project: to connect with other organ specialists like rheumatologists, pulmonologists and cardiologists, because I think that's the muscle wasting, and we see that patients with chronic diseases can have a lot of common denominators actually. Now, I'm looking at dialysis patients, my colleague, a rheumatologist, that's just looking at patients with rheumatoid arthritis. But I think to look at the connections there to the similarities between patients, I think, and if we could identify which, I'm sure there are final common pathways of much muscle wasting, that would I think, give the field a big impetus. So I think that's one of my next projects, actually, you just go to do kind of a literature search on what's all mechanistically known on all these different patient populations.

Peter Kotanko
I think, the research you in part together with RRI and others did on the events before death, I think also highlights that there is maybe the same processes, in other chronic conditions similar to what you and others described, for example, this weight loss before people die. In the end, what is increasing the inflammation, this has been identified in patient with chronic heart failure, this has been identified in patients with chronic infections like HIV AIDS and others. So I think there is a lot of merit to really to venture out of this out of the box, and look what's going on in other fields. And see what can be learned from this. The fact that we are in sort of our own boxes, I think, it's what we owe in this enlightenment era. And, because separating things into small boxes has been so extremely successful in the history of science, it's time really to look outside now of our own field and see what can we learn from it? We agree on that, in principle.

Jeroen Kooman
Yeah, absolutely. And now, we of course, have the possibility of deep phenotyping. And I think it would be very interesting to look, also, if we have, let's say, common phenotypes, which I'm sure there are between patients with chronic, different chronic organ diseases. But also you might have, let's say, the patients with, let's say, severe sarcopenia, you know, there are also dialysis patients with severe sarcopenia, you have dialysis patients who do not have any sarcopenia, they're all new fluid overload, no inflammation, and they're assumed to do they seem to do very well, whereas another group of patients actually, more or less unexpectedly, can do very badly. And actually to look at let's say more systems biology approach, connecting patients actually with different organ diseases who do very well, and do, in a way to see if you can, actually by grouping things together and doing a few deep phenotyping approach to look more at mechanisms, actually, which could tell us a little bit more why patients are doing well or not well at all, and what could be potentially intervenable factors. I think that would be very interesting, in a way.

Peter Kotanko
Yeah. And in one of those series talks, we had a conversation with Dr. Richard Weller, I mean, if you know him, he is his dermatologist, and actually moved into the field of you know, hemodynamics, because he identified mechanisms how UV light interacts with a new system in the skin, UV light actually results in lowering blood pressures. I think this is another prime

example of how the action between various fields really advance science, really advance our knowledge. Absolutely. That's fascinating to hear. Yeah.

Peter Kotanko
Now, I, I couldn't end this talk before, I mean, without raising this really fascinating research, or thinking you did about the evolution of the kidney. And where you really connected areas as divergent paleontology with kidney medicine. Could you just say a few words about that? And you know how fascinated I was about your really wildly thinking outside of the box.

Jeroen Kooman
I don't have a large expertise in any of these fields. I don't have a large expertise in evolution, or even in geology or paleoclimatology. It's more than that: I was interested in it… that's how I tried to connect these points. It's actually fascinating to see, but it was already, you know, already described in great detail by Homer Smith. He wrote a very beautiful book, ***From Fish to Philosopher*** and actually, I was inspired by this book. And also to connect them a little bit with new insights on geology and continental changes, leading to changes in environment induced by changes in environments actually, which were induced by the by plate tectonics. And actually, if you look at this, also from a more popular scientific books, that different environments actually really stimulated evolution. Also, environments also stimulates adaptations and I think it's really fascinating to see how these fields can be connected. But basically, I was just actually stimulated and fascinated by this wonderful book of Homer Smith, actually, which is still, I think, it was written around 1957. But it's still very, very worthwhile to read it, to still read, it hasn't lost any of its novelty in its value.

Peter Kotanko
Yeah, so what I learned from this is really that, first we shouldn't let ourselves be bound by certain disciplines, and the other thing is that curiosity, which is the main. the key driver, of all of our research interests, that this is really, we should we should just live curiosity and let no stone unturned.

Jeroen Kooman
It makes life a lot more fun. Actually, I must say, and also this kind of hobby project, of course, is also interesting to do.

Peter Kotanko
So Jeroen with maybe a minute or so left or two minutes, if you want to, what do you want the audience to take home?

Jeroen Kooman
I think that we can really, I think, learn by looking at differences between people and trying to look at mechanisms of these differences, and just let's say Sherpa and dialysis patients, we're just an example. But I think it, let's say looking into physiology in more extreme environments can really help us learn a lot I think, also, which might benefit base maybe patient care in the future. It was also fascinating for me, just to experience it and to also to dive into the literature there and really mentioned that, just to then curiosity is, gives me a lot of fun in life, I think.

Peter Kotanko
Thank you for being our guest today, at this front working in the medicine and biology. And I'm looking forward to meeting in person at some point in time.

Jeroen Kooman
Absolutely, Peter. Thank you very much for the invitation. It was also, as always, great talking to you again. And 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 soon for the next episode of Frontiers in Kidney Medicine and Biology.

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