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The Role of Blood Lactate (Jan Bakker)

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Can you explain the significance of lactate monitoring in critically ill patients and what it means in practice for the intensivist?

From the very first description in 1843 increased lactate has been associated with dying patients or patients that go on to develop morbidity like organ failure. The initial level, the trend, the time it takes to decrease to normal levels have all been associated with mortality and morbidity as long as intensive care medicine has existed. When Max Harry Weil did his first studies in the 1960s he found that between 4 and 5 was associated with 50% mortality. When we looked a few years ago, we found this level was associated with 45% mortality. Over the last 40-50 years nothing has changed in the relationship between lactate level and mortality.

For intensivists, the question is firstly, if I have this problem of high or non-decreasing lactate, what should I do? Secondly, if I could change it will my patient benefit? There have been few studies addressing this topic. The Pölönen study showed that there was less morbidity when they chased lactate levels to remain normal or be normal as soon as possible (Pölönen 2000). Our multicentre study accepted that increased lactate is not a good sign, especially in the early phase (8 hours) of ICU admission (Jansen et al. 2010). In this phase there is more likely a haemodynamic cause of increased lactate, so low perfusion, low tissue saturation/ perfusion, whatever you want to call it, there is a time window where optimisation of the circulation should lead to a decrease in lactate. We tested how to get adequate tissue oxygenation. I think it's the only study ever that incorporated oxygen demand and oxygen delivery into a resuscitation protocol. We said if you want to optimise tissue oxygenation and do something about the need for oxygen and the amount of oxygen going to the tissues, do this very aggressively for maximum 8 hours and then the goal should be to decrease lactate rapidly. What's a significant amount of lactate decrease? About 10% an hour. We measured every two hours. You've done all your stuff and everything seems ok, but your lactate is not coming down, then what? That's a question that's never been addressed in critical care. That could be microcirculatory dysfunction, maldistribution of blood flow in the tissue, so mandatory in the protocol was the use of a vasodilator. With this array of interventions, we showed a risk reduction in mortality by 20%, but to our surprise, there was no effect on lactate at all. In the control group they didn't know lactate for 8 hours, just the first level in order to randomise the patient. In the protocol group every two hours they got a signal, but the actual decrease in lactate was exactly the same. Without knowing the lactate level, it decreased to a similar amount in the control group, despite the fact that the absolute mortality was almost 20% higher [it was absolute 10% difference and relative 20% difference] in this group. The only explanation we could find was that if the lactate was in the very high levels (5-10), if you compare the groups there was about a 30% absolute difference in mortality.

We speculated that especially in this group of patients with very high lactate levels if you don't know the lactate when the patient comes in, then you have no clue what you're doing, because you don't get the signal that you are doing the right stuff, e.g. stop giving fluids or dobutamine. In the lacta te group you have the signal that this is going the right way – it was 10 now it's 6, then it's 4, and the patient is improving. This signal was completely lacking in the control group, so we think that this contributed to the difference in mortality. In the post-hoc analysis, we found that the real decrease in lactate occurred in the first two hours of resuscitation not in the first eight hours. Also not studied yet is what the lactate that is not decreasing tells you.

In most patients, lactate is a marker of disease and adequacy of resuscitation, where we have doubt what the specific place is of the circulatory optimisation in lactate. We think there is absolutely a signal that your circulation is inadequate, but it's probably in the very first hours. We just submitted a study with Glenn Hernandez from Chile, where we looked at the bi-phasic change in lactate. I think there is a bi-phasal change, so that very early it drops dramatically, and then it trends down a little. We have an indication in the study we just finished that this indeed is present, but the interval of measurements was very large, so it's a bit difficult, so the first significant rapid drop is circulation, and the next is metabolism. This is optimisation of the balance between oxygen demand and oxygen delivery and the rest is marker of disease.

Lactate is not an easy parameter, it's a mixed bag of signals. I always say to my residents, "Lactate means trouble." You have to go to the bedside and find out what the message is.

Do you think we have enough data from RCTs to answer the question you have posed on the routine use of lactate as a resuscitation endpoint?

I don't think there is convincing evidence that decreasing lactate levels should be a target of therapy in ICU patients. When lactate is decreasing, that is a good signal, but when lactate is not decreasing, whether you should then optimise or more aggressively treat the circulation I don't think there is enough evidence. Especially we lack evidence for when should we stop 'chasing the circulation' and look at lactate as a marker of metabolism, a marker of something wrong with the patient, but which won't be fixed by giving fluids or dobutamine or whatever. A recent dramatic case we had was a patient with severe septic shock, due to melioidosis, he was on ECMO (extracorporeal membrane oxygenation), and he had a lactate of 12 for three days. His circulation was optimal, as far as we could optimise his c irculation, but due to the severe disease and the diffuse intervascular coagulation, his hypermetabolism, he had very high lactate levels, but it came down after three days. He made an uneventful recovery and went home, without any macro organ failure. He was on renal replacement therapy and he was off when he left the ICU. In that particular case it was a marker of disease at very high levels but couldn't have been fixed by circulatory management.

You have suggested that we need to define the correct context for use of fluids for brain injury, sepsis, haemorrhage etc. Could you expand on this?

There is an incredible amount of evidence that HES products have negative effects on a large proportion of ICU patients, in, for instance, renal function. We use a lot of HES products in our brain injury patients to lower intra-cranial pressure. In our study on a marker of kidney injury (de Geus et al. 2011) in almost 800 critically ill patients. there were around 30 patients with isolated brain injury, but none developed renal failure, despite our use of HES products.

Asking why we should use something where we have not shown that the patient will benefit is very valid. But crystalloids in brain oedema are risky. In the context in which you use these HES products, for example colloids are frequently used in surgery and they all improve outcome, maybe the signal is too weak in this population. If you have a huge outcome difference, then some harm is not bad. The context question is good, because basically we do not understand why HES products 'kill' your kidney. I could stop using it, but then let's research the adequate context, or the mechanism of harm in order to understand why we should not use HES products. It's important to know the possible side effects and before we introduce something new to do adequate studies on what's the mechanism of action and what's the safety issue. That's a day-to-day problem in the current ICU, because we have no definitive clues about the endpoint of resuscitation. Fluid unresponsiveness is a strange endpoint of resuscitation, because we are all fluid responsive. Fluid unresponsiveness by definition means the patient is fluid overload. What amount of stroke volume variation is safe, we don't know, we only know when you are not fluid responsive any more you are very unlikely to be hypovolemic. We don't know when it's going to harm you. What's a clinical problem that's going to be solved with fluids is one. If you have a clinical problem that's going to be solved, should you drive for fluid unresponsiveness? We don't know.

Our study in *Critical Care Medicine* on sepsis vs tamponade, lowering cardiac output to the same amount in both models, then resuscitating the animals clearlyshowed you needed more fluids and a higher cardiac output to resuscitate the septic microcirculation. However, in a study we just submitted with Glenn Hernandez we showed that the microcirculation may not be an adequate endpoint of survival. Non-survivors to a large extent have abnormal microcirculation so I wonder about the endpoint. To what point should we resuscitate with fluids? In order to risk assess fluid responsiveness, what is hypovolaemia, I have no clue what hypovolaemia is. There's much more to gain, because that's what we do daily on our pa tients.

An important problem during the night in many ICUs: many patients are treated with fluid because their blood pressure drops when they sleep (I hope mine does when I sleep!), so probably that is normal physiology that doesn't require fluids. When do we need an increase in cardiac output brought about by fluids? We don't really know, we have no clear answers.

What do you see as challenges for critical care in the Netherlands?

The challenge will be to develop our specialty into a primary specialty like anesthesiology, internal medicine etc., and not be a subspecialty of anaesthesiology. That will be extremely hard, because everyone is fighting to keep their territory. Especially for anaesthesiology, it's a good variation of their daily routine to mix between OR and ICU. There are various reasons other then money to keep intensive care in the 'wrong' specialty. I don't think it will happen in the next 10 years in the Netherlands, although I would like it to.

Also, it's very difficult to translate research results from other countries into practice. We are very restrictive in the

patients we admit, and there has to be a clear benefit for ICU admission. It's very different in the U.S. and the South of Europe and difficult to translate results. I would favour physiologic, mechanistic studies because tha t data is the same as in the Netherlands. Now we focus on fixing the patient more in a surgical type of way - you have a tumour, we get it out, you're fixed, you have hypotension, we give you volume and drugs, now it's fixed. When you turn it around to ask why the patient has hypotension, what is adequate blood pressure, go from there, then recovery is the result and not the goal. That's a completely new area of r esearch.

You've written about the ethics of using data from patients who die before consent was given. Can you comment about this?

We convinced our ethics committee that if you're running a resuscitation study, you cannot allow patients or relatives to think for 24 hours whether to participate. They agreed we could start the study, then ask permission and, when the patient survives, ask again. We found that if the patient dies in the middle of the night, and the family left, it's difficult and maybe even unethical to contact them. We asked the committee about the data we had without consent, and the committee said we couldn't use it, as it's unethical. We explained that this would introduce bias, as the

sickest patients die in the early hours of admission. If we remove the sickest patients from our study, we could end up in a negative study, when it should be positive. So we went to the national ethics committee, which took another approach. There is a file of data that you gathered ethically, as you had permission from the ethics committee. The data no longer belong to the patient, because he's dead. There is no law in the Netherlands to say these data automatically transfer to the relatives. The data is from the hospital. As long as you anonymise the data, you can do what you want with the data from that patient. Problem solved.

What research are you working on currently?

I am still pursuing lactate, looking at where it's coming from, why is there lactate, why is it not coming down, what is the role of the liver, and the liver perfusion in lactate.

In ethics I'm interested in end-of-life care, futile/ disproportionate care, these difficult terms that are used interchangeably. The differences between the U.S. and Netherlands systems are clear. My U.S. colleagues are not allowed to do much without family consent. They have to keep patients alive when there is no chance of reasonable recovery. I'm interested in the financial and economic aspects. It's very difficult to study, to compare these two different moral/ ethical systems. My sense is that it costs an enormous amount of money. We argue about what an added Quality Adjusted Life Year (QALY) costs, but we never discuss what futility may cost. In the Netherlands the intensivist cannot be forced to continue care, if he thinks it's inappropriate. By law you have to stop treatment that doesn't make any sense. We are liable if we go on with treatment and the family changes their mind. That's to do with communication, informing (we do not ask for permission in the Netherlands!) the family to stop life support and continue to comfort care and explain what will happen. I would love to study something like that, but it's tricky.

This interview will be in our Winter issue, which has a cover story on severe pulmonary infections. What do you see as the challenges of these?

In the Netherlands we have a debate with authorities and insurance companies over the use of extracorporeal membrane oxygenation (ECMO). It's extremely easy to use ECMO to solve the problem of oxygenation or hypercarbia or a combination. There are very scarce data that this is really good or should be a regular intervention in patients with pulmonary failure. If you are young, have H1N1 it works fine, because you know it's a transient disease and if there's not a lot of lung destruction then it's ok, but what about immune system diseases such as Lupus, Wegener's disease, necrotising diseases that destroy the lung, should they be on ECMO, if so, how long to try? We found that after 1-2 weeks, we doubted whether we should go on. Other centres go on for longer, a month to six weeks, then decide it hasn't worked. Should you go from ECMO to the waiting list for lung transplantation? We do it for patients with heart disease. Should we put in new lungs in a 26 year old with necrotising pneumoccal disease? The authorities are not interested to regulate, and would rather wait for guidelines from the national society. The insurance companies don't want to pay, saying there is no evidence. It's an expensive treatment, the incremental costs are significant. We found because you keep these lung patients alive much longer than before, they develop complications like fungi, candida infections in the lung that are very expensive to treat. It's a big question mark. Easy to do, so effective when you start, but you don't have a good endpoint, we don't have a good start point, so that's an open area of a new device looking for clear indications.

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