INTERVIEW:
THE FIRST BILATERAL HAND TRANSPLANT IN THE NETHERLANDS

Anna-Lena Boller[1] and Minke Holwerda[2]

[1]Master's Student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, the Netherlands
[2]Master's Student Biomedical Sciences, Radboud university medical center, Nijmegen, the Netherlands

Insight

When the first attempt at hand transplantation was performed in 1964 in Ecuador, the recipient experienced acute and irreversible rejection of the donor hand within two weeks [1]. Hand transplantation has come a long way since then, with the development of enhanced immunosuppressive treatment and advances in microsurgery. While hand transplantation is an amazing feat, it remains a complex procedure, limited by difficulties surrounding limb preservation and accompanied by ethical, financial, and psychological complications [1, 2]. If you lost your hands, would you jump at the chance to get a hand transplant?

Worldwide, over 130 hand-arm transplantations have been performed. However, none of these hand-arm transplantations had taken place in the Netherlands [3]; until recently, that is. After years of intense preparation, the first bilateral hand-arm transplantation was successfully performed in the Radboudumc in July of 2019, led by Prof. Dr. Hovius and Prof. Dr. Ulrich. Maartje Bijl was the first patient to undergo hand transplantation in the Netherlands. In order to discover the ins and outs of this complicated procedure, RAMS sits down with Anne Sophie Kruit, a plastic surgeon in training who was closely involved in this surgery. Anne Sophie also recently successfully obtained her PhD in extracorporeal perfusion and limb preservation.

Limb preservation: current state and research

A crucial part of any transplantation is to ensure the transplant is not damaged. When tissue is no longer attached to the body, damage occurs due to ischemia. This is a lack of oxygen and nutrients, which are usually supplied by blood flow. Considering that ischemia can develop quickly after tissue removal, the current standard is to store the tissue on ice, increasing the time until ischemia occurs. 'The common practice for a limb is to flush it with preservation fluid to prevent clotting inside the vascular system, to cool it, and then store it in bags on melting ice,' Anne Sophie explains. This can be done up to approximately six hours before the tissue is damaged irreversibly [2, 4]. 'Clinically, this type of damage will give fibrosis, which means that the muscle contraction will be less powerful or the nerve will function a bit less.'

In comparison, a kidney can be stored on ice for up to 24 hours before the tissue starts to deteriorate [5]. This difference results from limbs containing a lot of muscle and nerves, which are both tissues that are highly susceptible to ischemia and cell death [2, 4]. Transplanting a hand or arm is also exceedingly more difficult than transplanting an organ, as you have to connect nerves, tendons and bones instead of 'just' blood vessels. 'You are battling against time to keep the surgery as short as possible before replanting [the limb], and you hope the muscle is still vital.'

Due to the more complicated nature of hand-arm transplantations, research is necessary to find ways to improve the procedures surrounding limb preservation. One of those researchers is Anne Sophie: 'Most of the time I start explaining [my research] by referring to a heart-lung machine, which most people know from organ donation and cardiac surgery. My main goal was to change this machine to also be able to use it for limbs. There has been some research in the field, but a lot of it lacks methodology or has contradicting outcomes, and the quality of all these studies was quite low.'

'You have to see the heart-lung machine as the replacement of the body', Anne Sophie explains, 'You can attach the arm to it, and there is a fluid running through the machine. This can be blood, which is the most body-like, or you can use a cold over-the-counter available fluid, and this is what we have done to keep it simple. A pump, similar to the heart, has to pump [the fluid] back and forth through the tissue. There is also a heater-cooler machine, so you can set the temperature either at body temperature or cool [the limb], and there is an oxygenator. So there is a fluid, which is cooled, and there is oxygen and nutrients in it.' Anne Sophie and colleagues then compared this updated heart-lung machine to the current practice. 'Cold storage is able to preserve tissues from four to six hours, and then it starts to degrade. With the machine, we were now able to at least store it [tissues] for 18 hours. We ended up with my final model, which was to amputate a pig's forelimb, put it on the machine for 18 hours, and then replant it back to the pig. We did that, compared it to four hours on ice and replanted it back. The outcomes were actually quite equal, so that was encouraging.'

Finding the right setting for this machine was not as easy as Anne Sophie makes it sound.

'The tricky part was to find the right balance and the right setting. The second thing, which was really important, was to find an outcome that can reliably measure the amount of muscle damage. This is a holy grail in this research, to find one measure and one cut-off value which tells you if the muscle is dead or alive, and that is something we are still searching for'.

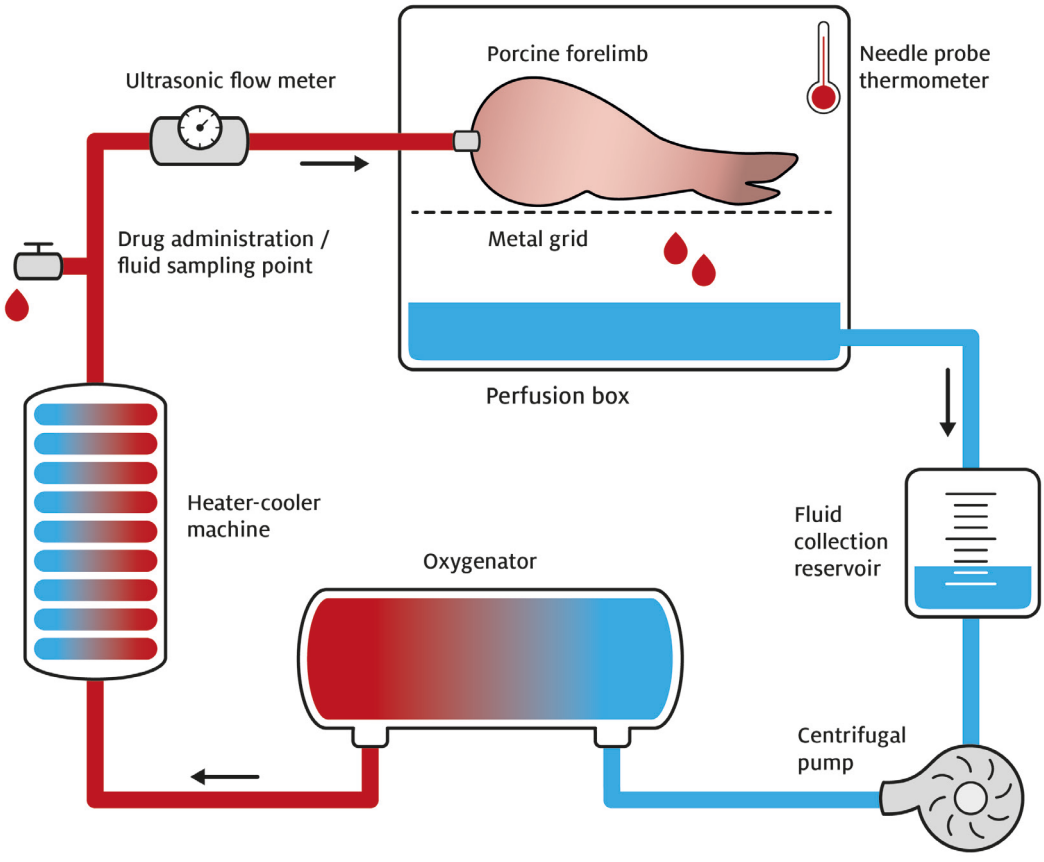

Figure 1: *A systematic illustration of the extracorporeal perfusion set-up, as optimized by Anne Sophie and her colleagues.*

First double hand transplantation

One example that illustrates the importance of this research is the first double hand transplantation recently performed in the Netherlands on Maartje Bijl. She lost both arms and legs due to sepsis. This surgery was performed according to the current standards but could benefit greatly from Anne Sophie's research: 'With the research I did, we proved that 18 hours of extracorporeal perfusion is feasible, and my successor is researching 24 hours. So, this would mean a prolonged time period for patient stabilisation and surgery'.

The preparation for the surgery took nearly three years, including ethical and legislative approval, writing protocols, and practising in the anatomy lab. However, one of the most important and equally tricky parts was finding a donor. 'First of all, it has to match with the patient. You cannot just put a really large manly hand on a petite woman's wrist, so it had to match.' Besides the hands needing to match cosmetically, the Human Leukocyte Antigen (HLA) type also had to match. HLA molecules are expressed on most cells, and they help the immune system distinguish between the body's own 'self' cells and non-'self' cells [6]. 'This was the tricky part because our patient had some antigens against HLA-specific-types because she had had blood transfusions previously. There was a 5% chance of getting a match.'

Next to finding an appropriate donor, the patient needed to be prepared, although Anne-Sophie wonders if you can really prepare a person for such a life-changing procedure. This specific preparation for the patient included psychological testing as well as a moral and ethical debate where all the complications and possible side effects were addressed. This is not without its reasons. 'Because donation is a procedure that involves immune medication, which has large side-effects when you use them for a lifetime – for instance, the risk of developing diabetes and increased risk of skin malignancies. Furthermore, the patient had to be mentally very strong. You have to accept there is a chance that you end up with nothing if the procedure fails or if you get a rejection. She [Maartje] was that kind of person.'

After two mismatches, a match was found, and the 24-hour surgery could begin. 'It felt surreal', Anne Sophie says, 'it was an adrenaline rush just to start.' Anne Sophie was involved in the flushing of the transplant and was one of the two people who overviewed the surgery and made sure everything happened at the right time in the right order. 'All the plastic surgeons and trainees were involved in this procedure, and we had one surgical room, and the OR next to it was a dormitory. I felt tiny because I was just one wheel in the entire machine. On the other hand, it was an extremely unique experience because we already had two times of no match, and I was in the state where I thought, 'well, probably this time it won't be a match again, but then it suddenly was a right match'. We were waiting for that moment, and then we really had to do everything that we had prepared so long for.'

The double hand transplantation gave Maartje Bijl a lot of freedom and independence back. Small tasks as preparing a sandwich, but also things most people would probably not think about. 'Now she can go on an electric stair. She never dared to go on it because you can imagine that with prosthetic legs and no hands to hold the sidebar, it is very dangerous. Now she dares to go on it because she

can at least hold herself.' Having visible transplanted arms could sound uncomfortable to some people, but the patient adapted very fast and well to her transplants. From day one, she said, 'they're mine, they feel like my own, they really match me well' and from day one, 'she was able to move them because the tendons were connected to her own.' The quality of her life has been improved drastically by the transplants giving her the freedom to perform everyday tasks on her own [7].

As with every intervention, this surgery came with a risk of dangerous complications; especially rejections are a risk. However, the patient is doing very well so far. 'She is really well-set with her immune medication regime, so the chances for her are good that nothing of that [rejection] will happen.' Also, there is still room for improvement in controlling the transplants and tasks she can do independently. After full nerve regeneration, further improvements are expected, for instance sensation in her fingers, but also finding ways and tricks on how to solve daily problems.

For the future, Anne Sophie hopes to improve the processes surrounding limb preservation even more. For example, she would like to miniaturise the machine: 'I really envision that it is a pocket-sized machine that you can put in an ambulance and take to the donor hospital or have it at the emergency department and use it in the case of a limb amputation.' Next to the materialistic part, she dreams about improving international collaborations with research groups with different fields of expertise to 'bundle knowledge'. While talking about the future of limb preservation, Anne-Sophie also gave some insight into how she envisions her own future: 'I want to keep being involved in this research. I am still involved and helping my colleagues and doing what I can. […] of course, in the future, I would like to be the surgeon that actually uses the thing that I helped to develop. That would be perfect.'

Anne Sophie Kruit

Acknowledgements

RAMS would like to thank Anne Sophie Kruit, MD-PhD, Radboudumc, Nijmegen, the Netherlands, for the interview and for providing the authors of this article with feedback, as well as Mèlanie Reijnaers, BSc., for reviewing the article.

References

1. Errico, M., *et al.* History and ethics of hand transplants. *JRSM Short Rep* **3**, 74 (2012).
2. Ozer, K. Advances in Limb Preservation: From Replantation to Transplantation. *J Hand Surg Am* **45**, 626-637.e625 (2020).
3. Hovius, S.E.R., *et al.* [The first bilateral hand transplantation in the Netherlands: results after 1 year]. *Ned Tijdschr Geneeskd* **165**(2021).
4. Blaisdell, F.W. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: a review. *Cardiovasc Surg* **10**, 620-630 (2002).
5. Lee, C.Y. & Mangino, M.J. Preservation methods for kidney and liver. *Organogenesis* **5**, 105-112 (2009).
6. Sheldon, S. & Poulton, K. HLA typing and its influence on organ transplantation. *Methods Mol Biol* **333**, 157-174 (2006).
7. Herrington, E.R. & Parker, L.S. Narrative methods for assessing "quality of life" in hand transplantation: five case studies with bioethical commentary. *Med Health Care Philos* **22**, 407-425 (2019).