

## REVIEW

# Is the first bilateral hand transplantation feasible in the Netherlands?

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**Keywords** - hand-arm transplantation, hand-arm donation, vascularised composite allograft

## Abstract

Worldwide, more than 100 hand-arm transplantations have been performed since 1998. However, in the Netherlands an upper limb transplant has not yet been performed. Following the presentation of a feasible recipient candidate in 2015, a platform has been created in the Radboud University Medical Centre in Nijmegen, the Netherlands, to be ready for the first upper limb transplantation. The patient in question lost both her legs below the knee and both hands due to severe sepsis in 2014 and is highly motivated and psychologically strong, making her an ideal candidate for a bilateral forearm transplant. The aim of this paper is to describe the history of limb transplantation and the ethical and medical aspects of initiating a vascularised composite allotransplant program. Recipient screening and donor selection are highlighted, the surgical procedure is portrayed and postoperative protocols including immunosuppressive therapy and rehabilitation are presented.

## Introduction

In the Netherlands, a hand or forearm transplantation has not been performed before. Following the presentation of a suitable recipient, a platform has been created in the Radboud University Medical Centre in Nijmegen, the Netherlands, to be ready for the first upper limb transplantation. The patient is a 44-year-old former hairdresser who suffered severe sepsis with acute kidney failure and diffuse intravascular coagulation in 2014. Both hands and legs were amputated due to necrosis: her left hand at the radiocarpal level, the right and dominant hand at the metacarpal level and both legs below the knee. She recovered remarkably well with full restoration of kidney function. She is mobile with her leg prostheses but only wears a left arm prosthesis if necessary for demanding activities. She finds the arm prosthesis heavy and often restricting. The patient is not a good candidate for sophisticated robotic hands as there is no space for the computerised hardware. The aim of this article is to create awareness of the possibility of hand and

forearm transplantation and to investigate the requirements for such an endeavour.

## History

The first attempt at human hand transplantation was performed in Ecuador in 1964 by a team led by Robert Gilbert. However, due to limited immunotherapy options at that time a strong rejection reaction led to removal of the graft two weeks after transplantation.<sup>[1]</sup> After the discovery of cyclosporine in the 1980s and later the development of tacrolimus (FK-506) and mycophenolate mofetil, research on limb transplantation commenced on rats and monkeys.<sup>[2-6]</sup> Following good results for organ transplantation in humans on these new immunosuppressive regimes, the first successful hand transplantation was performed in Lyons, France, in 1998. The patient was 48 years old and lost his right forearm in a circular saw accident in prison.<sup>[7]</sup> This case was quickly followed by a second in January 1999, performed by the Louisville team in the United States. This 37-year-old patient lost his left hand in a fireworks accident.<sup>[8]</sup> These two cases perfectly illustrate the importance of cautious patient selection and the need for life-long immunotherapy. The first patient lost his graft to rejection at 27 months after transplantation and was noncompliant to immunosuppression, while the second patient has always been compliant and to date the graft is still working.<sup>[9-11]</sup> The first bilateral hand transplantation was performed in Lyons in 2000. This complex procedure required a 50-member surgical team with surgeons from around the world.<sup>[12,13]</sup> The first bilateral arm transplantation in a paediatric patient was performed in Philadelphia in 2015. The eight-year-old Zion was already on immunosuppressive drugs due to a prior kidney transplantation.<sup>[14]</sup>

## Current situation

The most current update of the worldwide experience with hand-arm transplantation was provided by Shores, Brandacher and Lee in February 2015.<sup>[10]</sup> A total of 107 hand-arm transplants

were performed on 72 patients at the time of their writing. At least three additional double and one single upper limb transplantation were performed thereafter.<sup>[15]</sup>

A large proportion of the upper limb transplants were performed in Europe, with a total of 33 patients receiving 54 upper limb transplants (21 bilateral transplants). Procedures were performed in France, Germany, the United Kingdom, Austria, Belgium, Italy, Poland, Spain and Turkey. A total of 31 upper limb transplantations in 22 patients were performed in the United States (9 bilateral transplants). Other countries that have performed hand transplantations are Australia, Malaysia, Mexico, Iran and China, accounting for another 22 transplants in 17 patients (5 bilateral transplants). When excluding patients who received multiple vascularised composite allografts during transplantation (i.e. combined face and hand transplant), good results remain. Only one Mexican patient died due to sepsis, resulting in a very low mortality rate. However, the resulting mortality rate of 99% is based on case reports and anecdotes and might underestimate the actual rate due to publication bias. To date, a 5- or 10-year mortality rate remains unpublished. Graft survival in Europa and the United States is estimated to be 94.1%, with a total of five grafts that had to be removed in the non-acute phase after transplantation. Based on the available information, four of these losses can possibly be assigned to noncompliance of the patients to their immunosuppressive therapy. It has been estimated that a compliant patient with an upper limb transplant has a long-term graft survival of 88-90% per limb after initial surgical success.<sup>[10,16]</sup> This illustrates the importance of careful patient selection to achieve good results after hand transplantation.

### Recipient selection and ethical aspects

Only a select group of patients are suitable candidates for upper limb transplantation. Apart from general requirements of the patient's overall health and age (<65 years), there are procedure-specific criteria that need to be considered. Hand transplantation should generally not be performed in under-aged patients due to the side effects of immunosuppressants and the assumed incompetency at that age to make such an important and life changing decision. The level of amputation is most favourable between the elbow and wrist, but might be more proximal. A both personal and also widely advocated requisite is the bilateral loss of hands.<sup>[17]</sup> The need for lifelong immunotherapy and initial higher level of functioning and psychological well-being of unilateral compared with bilateral amputees are the most important arguments. For less functional gain, unilateral transplant patients will have to endure the same side effects. A patient with reasonable functionality with prosthetic hands can still be a potential candidate for a hand transplantation, as hand transplants have proven to be superior to prosthesis regarding functionality (especially sensation), aesthetic appearance as well as their unique quality to complete the body image of the patient again.<sup>[10]</sup>

Based on previous experience, the psychological state of the recipient is a very important factor in patient screening.<sup>[18]</sup> Apart from being motivated and compliant, the patient must understand the risks of the procedure and of lifelong immune suppression therapy and be able to weigh these risks against the expected functional improvement. It is important that the patient is fully aware of these risks, including the increased risk of solid cancers, lymphoproliferative diseases and lethal infections as the most devastating side effects of immunosuppressive therapy. As vascularised composite allograft (VCA) transplantation procedures are non-life saving, the decision to transplant has to be weighed more carefully compared with organ transplantation.<sup>[19-21,22]</sup> To help guide this decision, it is therefore recommended to initiate a moral debate with all involved parties and the patient under the guidance of an independent medical ethicist. Such a moral debate both tests and prepares the patient for the upcoming life-changing procedure.

### Legal aspects

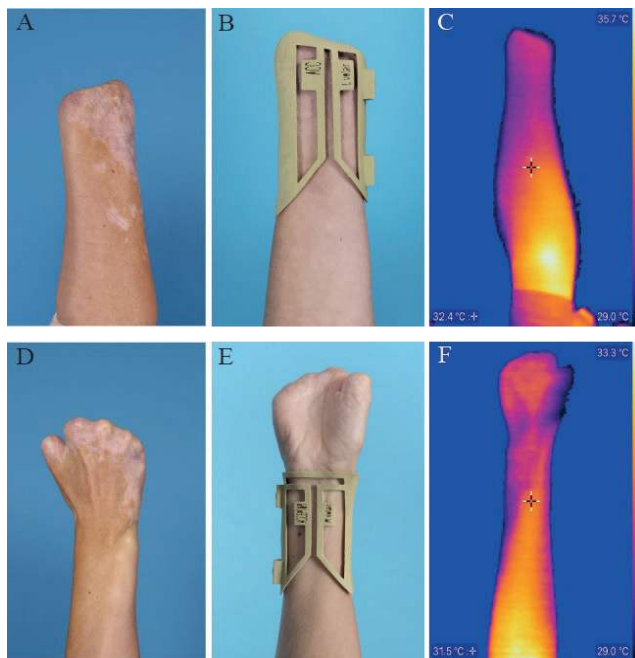
The Central Committee on Research Involving Human Subjects of our hospital reviewed the intended procedure under the scope of legislation under the Medical Research involving Human Subjects Act (the WMO) and concluded that this procedure concerns patient care and not research since it has already been performed over 100 times worldwide.

Concerning the donor, the process workflow of the donor hand-arm program was set up together with a highly motivated team of transplantation coordinators. A selection of Dutch ICUs with regular donor procedures is participating in the donor screening. Since registration for hand-arm donation is not possible in the Dutch donor registry, the Dutch Transplant Foundation (NTS), Ministry of Health, Welfare and Sport (VWS) and Eurotransplant were contacted to explore the legal framework of this procedure. They concluded that the hand is considered as an organ based on the Organ Donation Act (WOD). Initially, the decision was taken that only families of patients with positive registration in the donor register without exclusion of any organ or tissue could consent for hand-arm donation. However, since december 2018 an addendum to this rule was made, allowing to also include patients as possible hand-arm donors if they were not registered in the donor register or if they appointed their family to make the final decision for them. If the potential donor is eligible by law, the family will be asked to decide after a comprehensive explanation of the process by a dedicated transplant coordinator together with a designated intensivist. In this process, the visible loss of both arms and attachment of life-like prostheses require special attention. One of the lead surgeons will be available for additional family counselling. The consent should be unanimous between all important family members and granted in writing. Additionally, the family should be informed extensively about the media attention that this procedure will generate and the likelihood that the family will see the recipient in the media, including seeing the hands of their deceased family member.

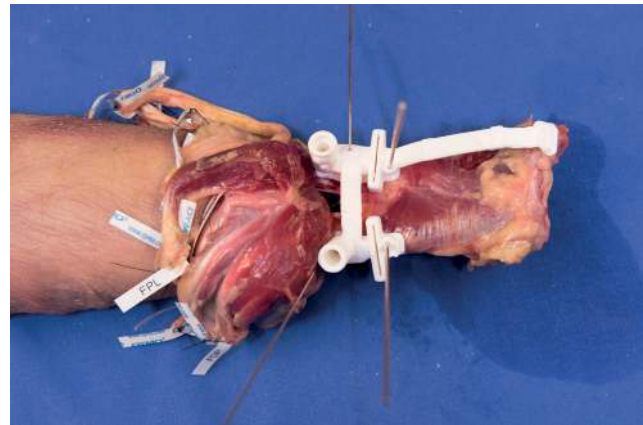
**Medical aspects**

*Preoperative planning and recipient assessment*

An upper limb transplant can be considered as specialised individual medical care, with a need for extensive preoperative assessment and planning.<sup>[23]</sup> A team of rehabilitation doctors and hand therapists assessed our patient’s functionality and composed a list of desirable goals after transplantation (i.e. holding a bottle; dressing herself; cutting and eating with hands). Photographs of the forearms were taken, with additional thermal camera images (FlirOne thermal camera) to objectify the temperature difference that was noted across the patient’s arms (*figure 1*). The nutritional and cardiopulmonary status of the patient were checked. Multiple blood tests were performed for evaluation of the patient’s metabolic (e.g. liver and renal function), haematological (e.g. ABO and HLA profile, blood count, coagulation) and infectious profile (e.g. viral infections). Extensive evaluation of the arms followed to obtain more information and to plan the level of transplantation. The osseous state (X-ray, CT with 3D reconstruction of bones), location and quality of arteries and veins (CT-angiography, MR-angiography) and quality of the muscles and nerves in the forearm (MRI, nerve ultrasound and EMG) were mapped (*table 1*). A personalised cutting guide was manufactured based on the 3D reconstruction of the bones to facilitate the osteosynthesis process during transplantation (*figure 2*).



**Figure 1.** Photographs of the recipient’s arms A) dorsal left arm, D) dorsal right arm, B/E) palmar view with 3D printed incision guide applied to the wrist, C/F) thermal camera images; note the decrease in temperature towards the distal arm



**Figure 2.** Practising the arm transplantation procedure in a cadaveric patient. All tendons, nerves and vessels are tagged. A custom-made cutting guide is applied with K-wires to the distal radius and ulna to define the osteotomy plane and position of fixation screws

**Table 1.** Components of the extensive preoperative planning and screening of a bilateral hand transplant recipient

Recipient Screening tests	
Physical examination incl. hands	
Nutritional status	
Cardiopulmonary	ECG, chest radiography, pulmonary function tests
Haematological	Complete blood cell count, platelet count, coagulation, ABO blood type, rhesus factor, HLA typing, reactive antibodies
Metabolic	Serum electrolytes, liver function, creatinine clearance and urinalysis
Infectious disease	CMV, EBV, VZV, HIV, hep B, hep C, toxoplasmosis, Syphilis, ParvoB19, Strongyloides
Imaging	Normal photographs X-ray hands and forearms CT/MR-angiography, including 3D bone reconstructions Nerve ultrasound, EMG conduction studies Ultrasound of peripheral arteries and veins (neck and groin area, for intraoperative catheters)
Psychosocial screening and functional assessment	Hospital Anxiety Depression Scale (HADS), RAND (SF-36), Disability of the Arm Shoulder and Hand (DASH)

*Donor and graft selection*

Apart from legal donor prerequisites, there are also medical and procedural conditions to consider during the donor selection process. To minimise ischaemia time (time between the harvest of the donor arms and their revascularisation on the recipient’s vessels) which is related to graft failure, hand-arm donation can only occur in a brain death donor within an approximately two-hour travel distance from the acceptor hospital. The hands need to be in overall good condition and match the recipient. A close match of the donor hands to the recipient is not only important for the aesthetical result, but also for functional recovery. Therefore, for every recipient an individual list of criteria needs to be defined to obtain such a match (e.g. hand size, skin colour, age). The most important contraindications

for donor arms are: donor too old, hand size difference >15%, systemic diseases affecting the hand or the postoperative healing process and large vessel thrombosis (table 2).<sup>[23,24]</sup> The donor is first assessed by ICU physicians.<sup>[25]</sup> To structure and uniform this process, detailed protocols describing the steps have been developed. When contraindications are ruled out, blood will be withdrawn for HLA matching. A cautious HLA matching procedure is warranted, since skin is highly immunogenic tissue and forms a major component of the hand-arm transplants. The risk of rejection is therefore higher compared with solid organ transplants, although most rejection episodes are reversible.<sup>[10]</sup> In case of a match in HLA profiles of donor and recipient, all catheters need to be removed from the donor's arms and perfusion to the extremities should be protected to preserve the arms in optimal condition for the graft procurement procedure.

**Table 2.** Contraindications in upper limb donor assessment – adapted to our case

Donor criteria
<b>Absolute contraindications</b>
Non-heart beating donor Donor age <20 or >60 years No match to recipient Not fitting following criteria: Female patient Hand size 6-7.5 Fair skin colour Blood type A or O
<b>Hand condition</b> Skin conditions (e.g. scleroderma), arthritis, polyneuropathies, severely injured (trauma or cannula), prior large hand surgery
<b>Systemic conditions</b> Chronic infections (HIV, hepatitis), sepsis, neurodegenerative conditions (e.g. ALS, MS), malignancy <5yr with osseous metastasis, clotting disorders, autoimmune diseases
<b>Relative contraindications</b>
Long ICU admission (affecting condition of arms) Malignancy >5yr Old hand fractures (X-ray for evaluation)

### Surgical procedure

During the past 18 months, the surgical team has practised extensively on cadaveric limbs on graft procurement, hand-arm dissection, osteosynthesis and replantation of the limbs. When initiating the actual procedure, the team will be divided into a donor and recipient team, both consisting of a minimum of four members. The donor team travels to the donor hospital to procure the arms of the heart-beating donor and attach the prosthetic arms (figure 3). At a backside table, 4°C University of Wisconsin fluid is flushed through the brachial artery of the donor arms at a pressure of 30-60 mmHg to remove blood and preserve the tissue. The ischaemic period is initiated and the arms are brought to the recipient hospital as fast as possible, wrapped in sterile bags and cooled on melting ice. Meanwhile, after final preparations, the other team has already started operating on the recipient in the Radboud University Medical Centre. The two teams merge in the operating room and

start working simultaneously on donor and recipient arms. During this procedure, communication between all teams is of utmost importance and is secured by a coordinator who is not performing surgery and checking progress. All structures will be tagged with labels during the procedure, easing later identification (figure 2). After complete dissection of donor and recipient arms, osteosynthesis with plates and screws follows, assisted by the 3D manufactured cutting guides. Subsequently, the vascular anastomoses are made and blood is reintroduced into the arms. The total ischaemia time is preferably less than 6-8 hours to decrease ischaemic cell damage and obtain good functional outcomes of the graft. Further reconnection of tendons, additional vessels and nerves will be made, cautiously taking the right balance between flexors and extensors into account. Nerves will be connected as distally as possible to promote early ingrowth into the donor arms. If necessary, tendon transfers can directly be performed to optimise functional outcome. The physiotherapy team provides the first postoperative splints and the recipient will be transferred to the ICU for recovery.



**Figure 3.** Prosthesis for the donor patient, overview (left) and close-up of the hands (right)

### Postoperative care

During the first days after surgery, monitoring of the vascularisation of the grafts is important. Any pressure to the grafts needs to be prevented, as protective sensation is missing. Prophylactic drugs (antibiotics and antiviral agents) are administered to prevent infection, and extensive blood tests and urinalysis are performed regularly to check the patient's wellbeing. In case of any signs of acute rejection, skin biopsies need to be taken and immediately assessed.

### Immunosuppression therapy

After revascularisation of the transplanted graft, the immune response immediately starts. Innate immune cells present donor antigens to lymphocytes and activate them with two signals. T-helper cells (CD4+) are the key cells in this activation process and are involved in cytotoxic-T-cell (CD8+) activation in the cellular response and in initiating B-cell activation in the humoral immune response.<sup>[26]</sup> The closer the HLA profiles of donor and acceptor match, the lower the rejection risk will be. Our patient developed anti-HLA antibodies, especially in Class II. These antibodies must be considered during the matching procedure and decrease the chance of an HLA match. The

predicted chance of a match based on blood-type is 88% for her blood group A. This chance is reduced to 8.8-20% when additionally taking her HLA profile into account, depending on the level of desired cautiousness.

Without immunosuppressive therapy, a graft will be destroyed within two weeks. As skin is a higher antigenic tissue compared with most solid organs, an adequate suppression of the immune system is very important in VCA.<sup>[9,27]</sup> Immunosuppression therapy consists of high-dosed induction therapy followed by oral maintenance therapy. Induction therapy starts at the day of surgery and consists of intravenous recombinant antithymocyte globulin (rATG), highly dosed corticosteroids, a calcineurin inhibitor and a selective T-cell immunosuppressant. The goal is to deplete the T-cell population during the first two weeks through rATG and to additionally inhibit lymphocyte activation and proliferation by the other drugs. Administration of rATG can usually be discontinued after three days. The other drugs will be decreased stepwise over a period of months but should not be stopped. A large study by Ekberg et al. set ground for the commonly used triple therapy maintenance regime in VCA consisting of a calcineurin inhibitor (tacrolimus), corticosteroids and a selective T-cell inhibitor (most commonly mycophenolate mofetil).<sup>[28]</sup> This is further endorsed by the Kidney Disease Improving Global Outcome (KDIGO) guidelines, recommending the same regime as preferred choice maintenance therapy in kidney transplantation.<sup>[29]</sup> Calcineurin inhibitors inhibit T-cell activation, mycophenolate mofetil inhibits lymphocyte proliferation and prednisone adds a more general immunosuppression to these agents. An advantage of tacrolimus is its positive effect on nerve regeneration.<sup>[30]</sup>

The key to adequate immunotherapy, however, is to find the right balance between under-suppression (rejection) and over-suppression (opportunistic infections, malignancies and metabolic side effects) of the immune system. In case of under-suppression, T-cells are not sufficiently blocked and rejection occurs through a cellular rejection (CD8+ cells), humoral rejection (donor-specific antibodies) or a combined response.<sup>[31,32]</sup> The graft will show signs of acute rejection, clinically recognisable by a maculopapular erythematous rash which may be diffuse, focal or patchy over the donor skin. Biopsies of the involved skin need to be taken and scored using the Banff classification (*table 3*).<sup>[33]</sup> Immunotherapy will have to be adjusted depending on the severity of the rejection to prevent damage to the graft. Optionally, topical therapy can be added (i.e. corticosteroid cream). One of the lessons learned from previous experience in VCA is to be cautious when minimising immunotherapy, as this often causes under-suppression and leads to acute rejection. In case of severe side effects, a switch to another drug is therefore preferred above stopping an agent.

**Table 3.** The Banff VCA working classification system<sup>[33]</sup>

Grade	Inflammatory infiltrate	Involvement of epithelium
0 (no rejection)	None/rare	None
I (mild rejection)	Mild perivascular	None
II (moderate rejection)	Moderate-severe perivascular	Mild (limited to spongiosis or lymphocytic exocytosis)
III (severe rejection)	Dense	Apoptosis, dyskeratosis, and/or keratinolysis
IV (acute necrotising rejection)	Frank necrosis of the epidermis or other skin structures	

#### *Rehabilitation – hand therapy*

Rehabilitation protocols should always be personalised and adjusted to the patient's individual goals and hand dominance. Generally, the postoperative rehabilitation protocol is divided into three phases.<sup>[34,35]</sup> The first three to four weeks are devoted to protective splinting in a resting position and oedema prevention, but also include a passive range of motion exercises to prevent adhesion and promote movement. Active motion exercises are introduced in the intermediate phase (1-2 months), starting with tenodesis exercises and slowly increasing tensile strength to the tissues. Electrostimulation is also initiated during this phase. From two months on, the patient can fully train the hands to increase function and strength as well as practise routine activities.<sup>[36]</sup> Neurocognitive rehabilitation according to Perfetti can be introduced early in the protocol, promoting the recovery of sensory, motor and cognitive function of the grafts.<sup>[37]</sup>

#### *Routine screening*

After discharge from the hospital, the patient will be routinely checked and continue hand therapy on a very frequent outpatient basis. The check-ups follow an elaborate schedule and involve: physical examination, blood and urinalysis, X-rays, drug level monitoring, virus screening and assessment of hand function. Yearly controls additionally consist of analysis of skin biopsies and screening for donor specific antibodies as well as evaluation of the skin for malignancies. Furthermore, the patient will be enrolled into preventative screening programs for breast, cervix and colon cancer as offered by the Dutch government and is advised to take yearly influenza vaccines.

#### **Long-term complications**

The most important long-term complications after upper limb transplantation are the consequences of lifelong immunosuppression therapy and the risk of chronic rejection of the graft. With the longest survival of an upper limb transplant graft being currently 19 years, much of the knowledge on long-term complications is derived from solid organ transplantation. Although upper limb transplant patients are generally healthier than solid organ recipients, it appears that the long-term effects of immunotherapy are similar.<sup>[26,38]</sup> Side effects include leukopenia/anaemia, nephrotoxicity, neurotoxicity, diarrhoea,

cutaneous and metabolic effects (e.g. skin atrophy, Cushing, diabetes, osteopenia).<sup>[16]</sup> More severe complications include malignancies or potentially lethal infections.

Chronic rejection occurs as a long-term reaction of the recipient to the graft and is related to under-suppression of the immune response. The rejection response can be cell-mediated with fibrosis and inflammation or antibody-mediated with vasculopathy and eventually small-vessel thrombosis.<sup>[32]</sup> Chronic rejection usually starts with a decrease in function due to stiffness and eventually leads to ischaemia and loss of parts of the graft or the entire graft. Early therapy consists of increasing or changing immunotherapy regimes.<sup>[39]</sup> The vasculopathy is difficult to monitor with regular ultrasound or CT-angiography since it first presents in small vessels. New trials are currently being performed, investigating new methods for the detection of vasculopathy in the digital arteries, such as flow MRI.

### Outcomes

Most forearm transplantation recipients function at a level similar to that with prostheses after a year and continue to improve thereafter.<sup>[34]</sup> A 2010 report from the International Registry on Hand and Composite Tissue Transplantation described the outcomes of 31 patients with a follow-up >1 year. Around 85% of patients had an acute rejection episode within the first year of transplantation, of which nearly half experienced  $\geq 2$  episodes. The events were often preceded by a change in immunotherapy, either as a team decision (side effects) or when a patient was not compliant to the therapy. Importantly, all episodes were reversible if quickly reported by the patient and treated.<sup>[40]</sup> All patients developed protective sensation, 84% developed discriminative sensibility. The majority of patients could perform most activities of daily living (i.e. writing, eating or shaving) and were able to work again.<sup>[10]</sup> Functional MRI demonstrated that the hand representation in the motor cortex regained a normal pattern in the years after transplantation, illustrating plasticity of the brain, even in adult patients.

### Future aspects

Following the presentation of a feasible recipient candidate for bilateral arm transplantation, a platform for VCA transplantation has now been created in the Radboud University Medical Centre in Nijmegen. This patient is the first and only patient on the Dutch waiting list at the moment. However, the program will not be limited to this patient. More feasible recipients will be screened and treated in the future following this program. Furthermore, a research line has been connected to the transplantation program, testing methods for prolonged ex-vivo preservation of VCAs.<sup>[41]</sup> Pilot experiments with long-term hypothermic oxygenated extracorporeal perfusion have shown promising results.<sup>[42,43]</sup> In the future, ex-vivo perfusion might be clinically applied to increase graft preservation, with a prolonged maximum safe ischaemic period leading to improved graft outcomes.

### Conflicts of interest

All authors declare no conflicts of interest. No funding or financial support was received.

### Acknowledgements

The authors kindly thank the patient for giving permission for the use of her photographs in this article. We also thank Stephan van Raay for his contribution as medical photographer.

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## Luchtwegmanagement op IC

Maandag 17 juni - dinsdag 18 juni 2019  
Dinsdag 26 november - woensdag 27 november 2019

Hotel Houten / OSG  
Houten

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