Journal of Cranio-Maxillo-Facial Surgery 44 (2016) 148–154

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Free flap transplantation using an extracorporeal perfusion device: First three cases☆

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ARTICLE INFO

Article history:
Paper received 13 October 2015
Accepted 10 November 2015
Available online 1 December 2015

Keywords:
Microvascular free flap
Reconstructive surgery
Vessel-depleted neck
Extracorporeal perfusion

ABSTRACT

Background: Free flap transplantation may not be feasible in patients with inadequate or absent recipient vessels. We report successful mandibular composite reconstructions without anastomosis in three consecutive patients with vessel-depleted neck. Based on clinical reports describing early neovascularisation, temporary extracorporeal perfusion of flaps was maintained until the flaps had become independent from the extracorporeal blood supply.

Methods: A blood transfusion bag filled with the patients' arterialised blood was connected to the flap artery and set under rhythmic compression to ensure continuous blood supply to the flap. The returning venous blood was collected but not reinfused. Extracorporeal circulation was sustained for 10–13 days until flaps had become independent from the external blood supply. Flap viability was assessed every 2 h using combined laser Doppler flowmetry and remission spectroscopy.

Results: Successful bony reconstructions were achieved in all three consecutive patients substantiated by MRI-, CT-scan or bone scintigraphy. Neovascularisation occurred within the soft tissues of all flaps with the exception of one skin paddle, which later developed necrosis. Systemic transfusion of 12–25 units of packed red cells was necessary to compensate for the blood loss.

Conclusions: With this technique, transplantation of composite free flaps becomes feasible even in the absence of recipient vessels, opening up new treatment options to a broad range of complex surgical problems. Blood reinfusion should be pursued in the future to avoid excessive blood transfusions. The trial is registered with ClinicalTrials.gov, number NCT02449525.

1. Introduction

For reconstruction of the mandible in irradiated patients, vascularised bone flaps are essential to achieve long term complication-free healing and recovery (Deutsch et al., 1999; Ang et al., 2003; Buchbinder and St Hilaire, 2006; Hirsch et al., 2008; Cannady et al., 2011). However, in some cases this is far more difficult or all but impossible. For instance, if suitable neck vessels have already been removed in former operations like neck dissections or salvage surgery with inadvertent vascular injury or ligation of potential recipient vessels. In such situations, recipient vessels of the thoracoacromial or cephalic system can provide an alternative source of blood supply. However, vein grafts or vascular loops are necessary to provide a pedicle long enough for tensionless anastomosis (Urken et al., 2006; Ethunandan et al., 2007; Aycock et al., 2008; Quilichini et al., 2012; Roche et al., 2012; Karle et al., 2013), significantly increasing the risk for flap loss (Bozikov and Arnez, 2006). For these patients, we described a temporary perfusion of composite fibular flaps by anastomosing the flaps to the radial vessels ("carrier flap") with long-term fixation of the arm in an elevated position (Wolff et al., 2003, 2009). Repetitive occlusion of the vascular bridge was performed to induce gradually increasing ischemic periods. By doing so, flap autonomisation occurred as

☆ Presented at the 5th World Congress of the International Academy of Oral Oncology: 8–11 July 2015, São Paulo, Brazil.

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http://dx.doi.org/10.1016/j.jcms.2015.11.007

early as day 16 and 18, respectively (Wolff et al., 2003, 2009). Other clinical reports have described a complete survival of free flaps after an inadvertent early disruption of the blood supply between days 7 and 17 (Chen et al., 2002; Wise et al., 2011), but not in irradiated defects (Salgado et al., 2002). On the basis of published reports as well as the cumulative anecdotal experience of many surgeons, it was concluded that most flaps might safely be divided between 10 days and 3 weeks (Kayser, 1999). With this in mind, we developed an extracorporeal perfusion device to provide temporary blood supply to the flap until neovascularisation had taken place.

2. Materials and methods

2.1. Ethical statement

All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the institutional ethics committee of the Technische Universität München, Klinikum rechts der Isar. Patient consent was written. The study was registered at ClinicalTrials.gov, number (NCT02449525). The authors confirm that all ongoing and related trials for this intervention are registered.

2.2. Development of an extracorporeal perfusion device

According to in vivo measurements that have revealed flow rates between 6 ml/min in radial forearm and 16 ml/min in latissimus dorsi flaps (Lorenzetti et al., 2001, 2010, 2012), the device here was developed to enable pulsatile flow with adjustable pressure and pulse rates for small ejection fractions. All blood conducting parts of the system were approved for medical use.

The main components of the device were (1) a ventricle-like clack driven by a programmable electric motor and (2) a blood transfusion bag, which was set under rhythmic compression by the clack, generating adjustable systolic pressures between 20 and 180 mmHg (Fig. 1). Diastolic pressure was generated by an inflatable blood pressure cuff positioned behind the transfusion bag. The pulse rate could be adjusted between 5 and 100 beats per minute (bpm) and programmed to include pauses after a chosen number of ejections. Perfusion of the flap was ensured by pumping arterialised patients' blood into the flap's artery and collecting the venous return. Before clinical use, the system was tested in fresh and embalmed cadavers and proofed for causing no haemolysis in donated human blood (Wolff et al., 2014).

2.3. Setup and clinical use of the extracorporeal perfusion device

A transfusion bag was filled with 150 ml of heparinised blood (Heparin-Sodium 25.000 I.E./ml, ratiopharm GmbH, Ulm, Germany, 500 I.E. per bag), taken from a central arterial catheter and connected to the flap artery via a 60 cm long extension line (type: Heidelberger, B. Braun Melsungen AG, Melsungen, Germany) and a 2 mm arteriotomy cannula (Art. No. 31002, Medtronic Inc., Minneapolis, MN, USA). A 3 mm cannula was inserted in each of the two flap veins to collect the returning blood in a second bag. Blood temperature was raised to 38 °C by wrapping the extension line around a cylinder warmed by a water circulation based heat exchanger (Hilotherm Clinic, Hilotherm® GmbH, Argenbühl-Eisenharz, Germany). Perfusion was started at 30 bpm and a pressure of 120/80 mmHg and was reduced to 100/60 mmHg after 4–6 h. Haemoglobin level (Hb), capillary blood flow, velocity and oxygen saturation (SO_2) were monitored every 2 h using combined laser Doppler flowmetry and remission spectroscopy (O2C, Oxygen to See, Lea Medizintechnik, Giessen, Germany).

Returning venous blood was collected and analysed for pO_2, pH, lactic acid and glucose, but not re-infused. Heparin was given intravenously to keep the partial thromboplastin time (PTT) at 60%. Over the following days, flaps were continuously monitored for

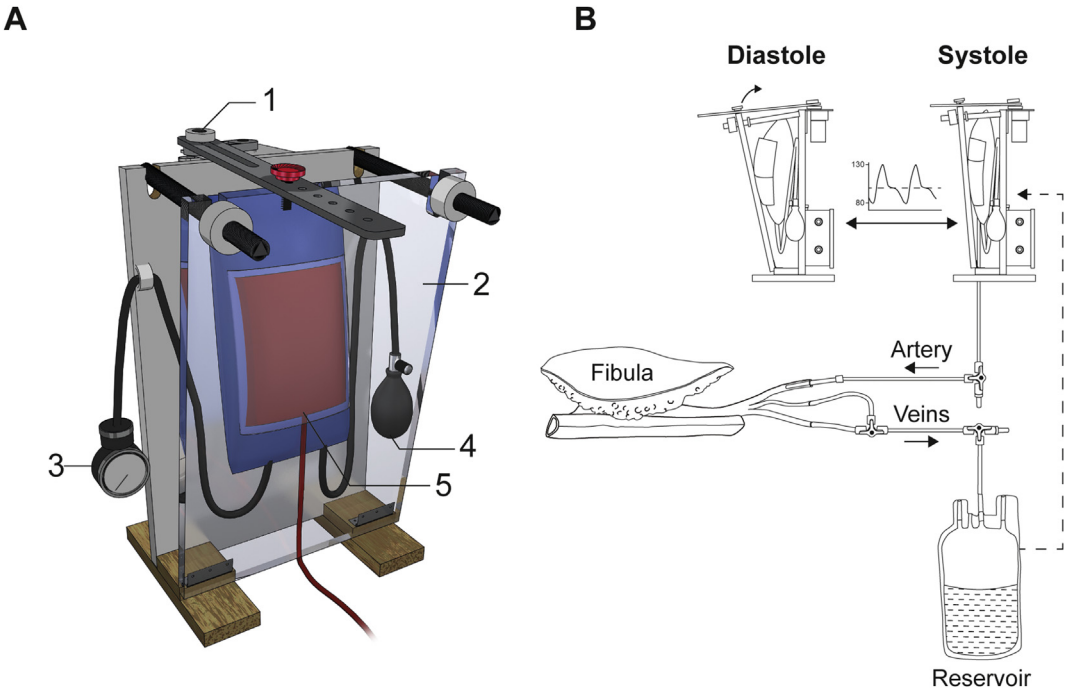

Fig. 1. Experimental setup. (A) 3D-rendering of the pulsatile pump system used in this study. Diastolic pressure is generated by inflating a conventional blood pressure cuff (4) mounted behind a blood bag filled with autologous heparinised blood (5). During systole, a glass plate (2) is pulled back by a mechanical lever arm (1), squeezing the blood bag against the inflated blood pressure cuff. A pressure indicator (3) connected to the blood pressure cuff displays all pressure changes. (B) Schematic drawing of the experimental setup. Although technically feasible (broken arrow), no blood was reinfused in the described patient cases for fear of infection.

normal blood circulation by gross examination (colour, capillary refill, venous return) and combined laser Doppler flowmetry and remission spectroscopy.

Every hour, blood was drawn from the arterial blood bag for blood gas analysis. Depending on the remaining blood volume and the results from the blood gas analysis, the arterial blood bag was refilled every few hours. The patients' blood was controlled daily, and packed red blood cells were given if haemoglobin had dropped below 8 g/dl. Patients were initially sedated for 24 h. Subsequently, sedation was gradually reduced and patients were instructed to avoid any sudden movements. Throughout the whole procedure, patients were observed at an intensive care unit. All patients had tracheostomies for the time of extracorporeal perfusion.

2.4. Flap conditioning and autonomisation

After 4–6 h, blood pressure was reduced to 100/60 mmHg at a frequency of 25 bpm. Venous blood flow varied over time and between patients around an average flow rate of 3 ml/min. After 24 h, perfusion was further reduced to 20 bpm and a blood pressure of 80/40 mmHg, resulting in a flow rate of 1 ml/min. The warm ischemia tolerance of muscle of up to 4 h allowed for intermittent interruption of perfusion, starting with 10 min/h at day three. Intervals were increasingly extended to up to 4 × 30 min/day during the next 5 days and 4 × 60 min until day 10.

Apart from clinical appearance, flap viability was assessed every 2 h using the combined laser Doppler flowmetry and remission spectroscopy (O2C). Moreover, blood gas analysis of arterial and venous blood drawn from the extracorporeal tubing system with assessment of pH, haemoglobin levels, partial oxygen and carbon dioxide pressures and calculation of arterio-venous oxygen saturation was regularly performed. The darker colour of the venous blood and the arterio-venous oxygen extraction, which was measured from the venous return were taken as a proof of continuous flap metabolism and viability (Fig. 4A). In the attempt to further accelerate neovascularisation, the settings of the perfusion system were regularly adjusted to gain low-normal O2C values while avoiding critical values (Fig. 2). According to previous studies (Holzle et al., 2010), permanent flow values of <15 AU (arbitrary units) and SO_2 of <10% were identified to be critical for the arterial blood supply to the flap. A rapid increase in Hb concentration of >30% was taken as a sign of venous congestion.

The primary endpoint of the study was the maintained flap viability after temporarily stopping external blood supply for >4 h starting at day 10, assessed by combined laser Doppler flowmetry and remission spectroscopy (Fig. 2) and intravenous Indocyanine-Green (ICG, ICG-PULSION®, Pulsion Medical Systems SE, Feldkirchen, Germany) fluorescence angiography (Fig. 5B). The catheters connected to the flap vessels were removed 2–4 days after finishing extracorporeal perfusion. As secondary endpoints, stabile bony dimensions and maintained bone perfusion was defined at three and six months postoperatively, assessed by magnetic resonance imaging, 99Tc-scintigraphy, or PET-CT.

3. Results

3.1. Patient 1

In this first patient, a 66-year-old male with a history of osteoradionecrosis after radiotherapy for squamous cell carcinoma, the external perfusion device was used to salvage a fibular flap after unsuccessful anastomoses due to severe arteriosclerotic damage to the neck vessels. The patient had already lost a fibular flap 11 months previously and tested positive for MRSA. Nutrition supply was achieved via gastrostomy. Since no sufficient flow was obtained from the external carotid arteries intraoperatively, the second fibula, which had already been raised for reconstruction, was connected to the perfusion device, and the anterior mandible was reconstructed by splitting the 7.3 cm long bone into two segments. The skin paddle, including parts of the soleus muscle, served for extraoral coverage (Fig. 3A). After four complication free days, at day 5, a hematoma had formed under the flap compromising the perfusion of the skin paddle. Although the hematoma was evacuated immediately after becoming evident, O2C measurements indicated critical capillary flow (<10 AU) and increased haemoglobin concentration (>90 AU) in the skin island at day 6.

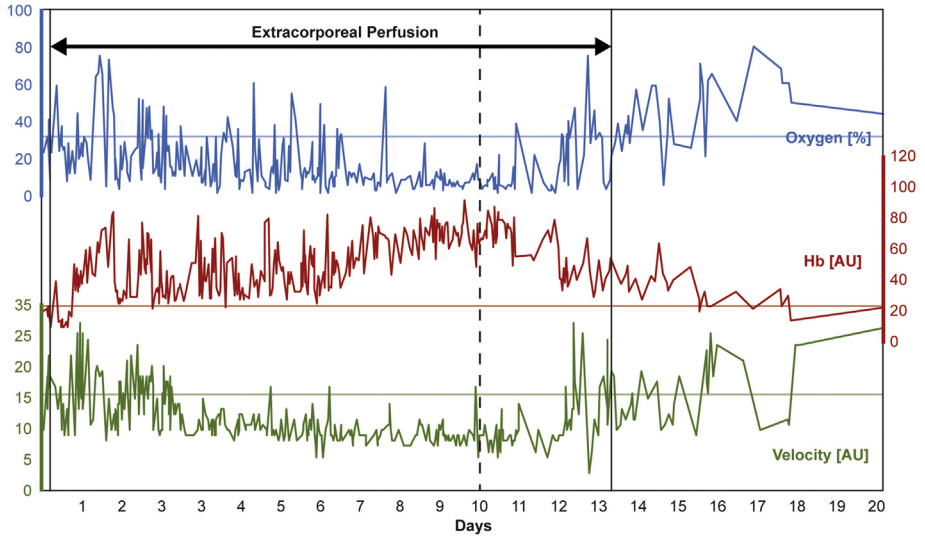

Fig. 2. Temporal progression of microcirculation parameters (patient 3). Combined laser Doppler flowmetry and remission spectroscopy (O2C) was used to closely monitor changes in the microcirculation system during (days 0–13) and after (days 13–20) extracorporeal perfusion of a fibular flap. The coloured straight lines indicate base level values for oxygen saturation [%] (blue), haemoglobin (Hb) levels [arbitrary units, AU] (red) and blood flow velocity [AU] (green). In the attempt to accelerate neovascularisation while ensuring flap viability, the pulsatile perfusion system was adjusted regularly to keep O2C values low but well above critical levels. First signs of a developing independency of the skin island from the perfusion system became evident at around day 10 (see broken line), with increasing oxygen and flow and decreasing Hb levels despite slowly tapering extracorporeal perfusion. At day 20 (=6 days after extracorporeal perfusion stop) O2C values where equal to or above base line values, proving the viability of the skin paddle.

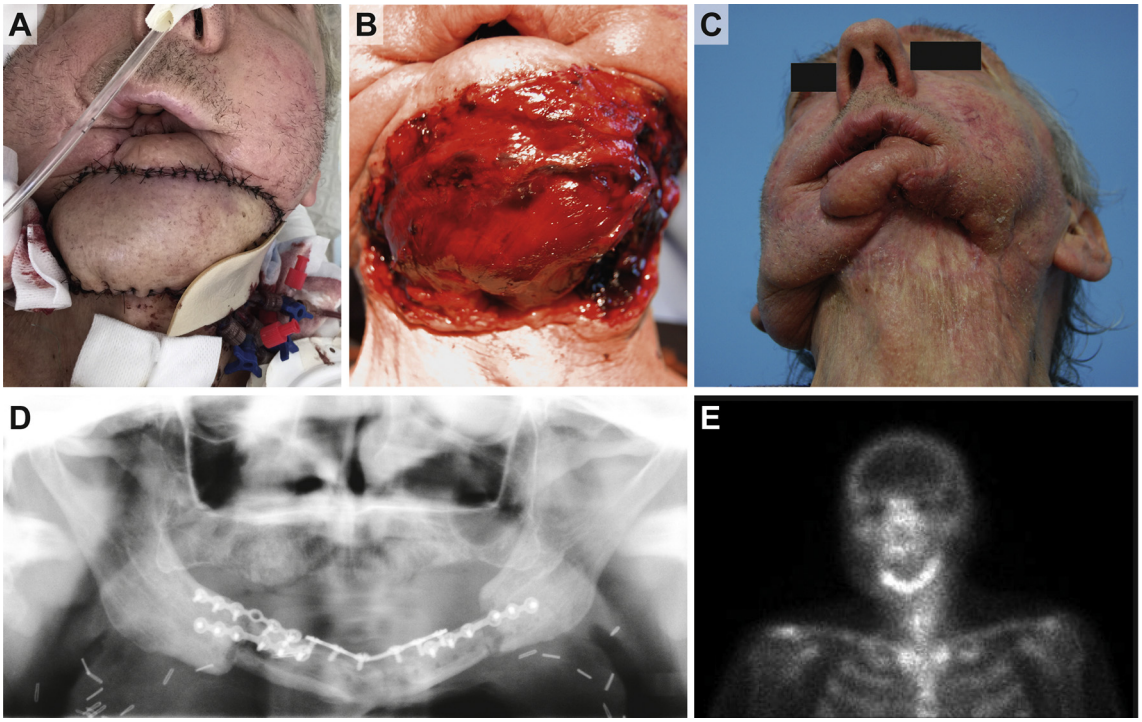

Fig. 3. Patient 1. Clinical and radiographic aspects. (A) Large skin paddle of a fibular flap at day 3 of extracorporeal perfusion. (B) After extracorporeal perfusion stop at day 10 and resection of the necrotic skin at day 12, the underlying muscle tissue was viable and well perfused. (C) Final outcome 6 months postsurgery with the fibular flap still in position with no signs of fistula or infection. (D) The panoramic radiograph taken 6 months after flap transfer shows regular bony structures with clear signs of bone healing. (E) SPECT image (late phase) with storage of the radionuclides indicating intact bone metabolism 6 months after fibula flap transfer using extracorporeal perfusion.

Nevertheless, continuous flow through the flap with oxygen extraction from the circulating blood and visible capillary refill at the flap margins were maintained, and there were no signs of local or systemic infection or wound dehiscence. Microbiological analysis from the venous blood revealed no bacterial contamination. Venous return started to decrease continuously at day 9. At day 10, the device was switched off, and intravenous injection of ICG led to mild fluorescence of skin with few capillaries crossing the flap margins. At day 12, the necrotic skin was removed, and the viable muscle component of the flap covering the bone was exposed (Fig. 3B). At day 16, the muscle component of the flap was covered with a skin graft, and further healing was uneventful. The patient was treated 11 days at the ICU and another 23 days on the ward. During the procedure, he was given 15 units of packed red blood cells. The patient started a soft diet. Panoramic X-ray and Tc99-scintigraphy at six months showed stable configuration of the fibula and viable bone metabolism (Fig. 3D and E).

3.2. Patient 2

In this 66-year-old female patient with a long history of repetitive squamous cell carcinomas, multiple surgeries and irradiation, another recurrence had quickly developed at the right cheek, infiltrating the mandible. A fibular flap was planned, but CT angiography showed a vessel-depleted neck. For lack of alternative surgical options, the extracorporeal perfusion device was used for temporary perfusion. The resection defect included the right lateral segment of the mandible and extended from the subcutis to the pharyngeal wall, which was partly removed during resection. The bone defect was bridged with a 6.5 cm fibula flap, the muscle component was used for dead space filling. A small muscle cuff was sutured to the skin and served as a monitor. During extracorporeal perfusion, the muscle showed bleeding after pricking, and circulation was maintained for 10 days with good return of dark blue venous blood as a sign for oxygen consumption by a viable flap (Fig. 4A). Blood samples taken from the flap's vessels at regular intervals proved an arterio-venous oxygen extraction throughout the whole procedure (mean values; arterial: $pO_2 = 114.9$ mmHg, $pCO_2 = 32.8$ mmHg; venous: $pO_2 = 67.7$ mmHg, $pCO_2 = 38.2$ mmHg). Since no skin flap was necessary for extraoral coverage, O2C measurements could not be performed in this case. The course of wound healing was uneventful. The patient was fully awake from day two and spent 11 days at the ICU and another 6 days at the hospital ward and received a total of 12 units of packed red blood cells. After 25 days, magnetic resonance imaging showed normal perfusion of the fibula with healthy fatty marrow (Fig. 3B). After 6 months, panoramic X-ray and CT-scans revealed osseous consolidation of the bone flap without signs of resorption (Fig. 3C and D).

3.3. Patient 3

This 43-year-old female patient had a history of two failed flaps (radial forearm and fibular flap) after resection of a squamous cell carcinoma of the left buccal mucosa and subsequent hemimandibulectomy because of osteoradionecrosis. Blowout of the external carotid artery had occurred during the first flap revision, and clotting analysis showed evidence for factor V Leiden mutation. A wide defect of the left submandibular neck skin had previously been closed with a deltopectoral flap. Severe deviation of the residual mandible had developed, and mouth opening was limited to less than 5 mm due to scarring. CT angiography revealed a vessel-depleted neck. Based on CT data, an individualised fibular flap was planned with perfusion via the extracorporeal system. After undermining the thin deltopectoral flap, the pre-shaped fibula flap was subcutaneously positioned to reconstruct the lateral segment

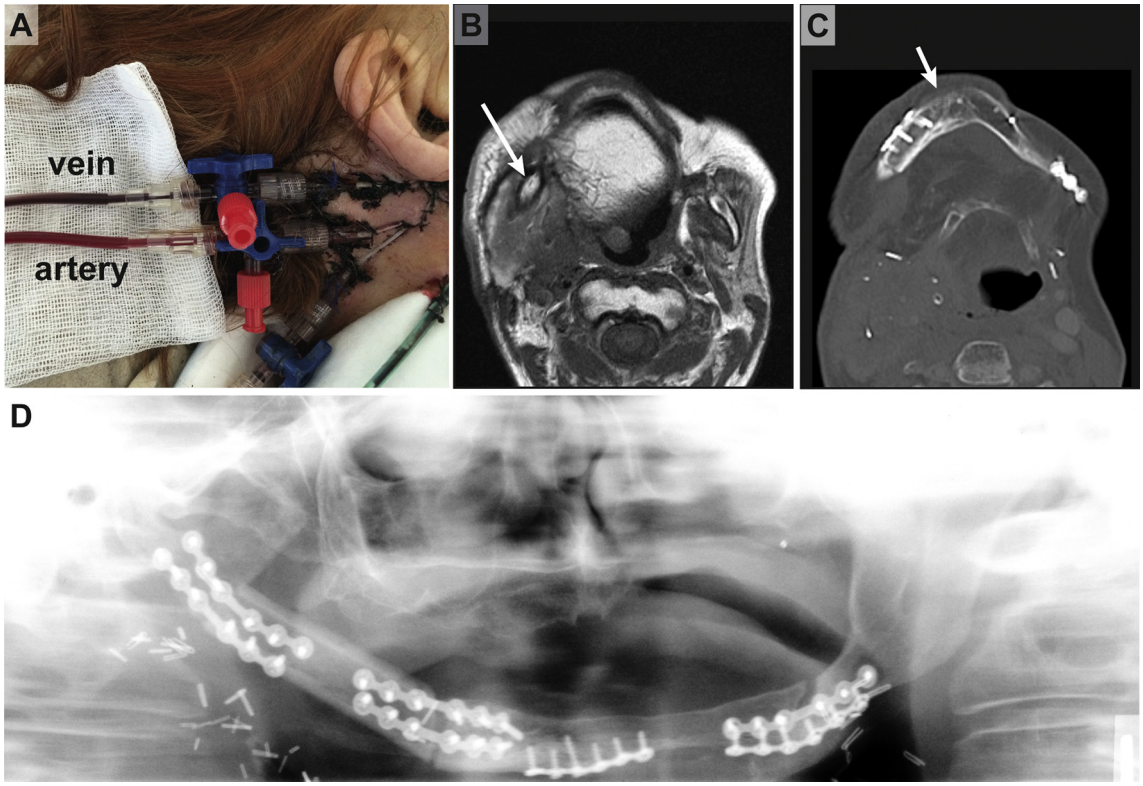

Fig. 4. Patient 2. Clinical and radiographic aspects. (A) Although no skin was raised in this patient, flap viability could be monitored by a significant difference between arterial and venous oxygen saturation, indicating an intact flap metabolism. The colour difference of the blood in the efferent (vein) and afferent (artery) extension lines caused by the different oxygenation was even visible to the naked eye. (B) MRI-scan performed at day 25 shows regular bony structures with healthy fatty marrow (arrow) and regular perfusion signals. (C) CT-scan 6 months postsurgery with clear signs of bone healing in the anterior segment (arrow). (D) The panoramic radiograph taken 6 months after flap transfer shows regular bony structures with clear signs of bone healing.

and part of the ascending branch on the left side. A 4 × 6 cm septocutaneous skin paddle of the fibula flap was used for extraoral coverage. Extracorporeal perfusion was maintained for 13 days without complications. The skin paddle showed a normal appearance with good capillary refill at all times. First signs of an independency of the flap's skin island from the perfusion device were seen at day 10, indicated by normal perfusion values, continued venous return and visible capillary refill after temporarily switching off the device (Fig. 2). Venous return from the flap started to decrease slowly at day 11 and was still observed after switching off the device. Systemic injection of ICG at day 13 was followed by intense staining of the skin island and the flap veins further proving flap autonomisation (Fig. 5B). At day 22, 99Tc-scintigraphy described normal metabolism of the fibula. While the skin island of the fibular flap remained viable, a perforation started to develop on the contralateral neck and large parts of the deltopectoral flap become necrotic due to local pressure of the distal fibula segment to the thin deltopectoral skin (Fig. 5B). We decided to shorten and reposition the distal fibular segment at day 27. During this intervention, bleeding was obtained from the viable flap. The deltopectoral skin defect was covered using a local skin flap from the posterior neck. The patient was treated for 14 days at the ICU and another 32 days at the ward and received a total of 25 units of packed red blood cells. At discharge, she was able to take a soft diet.

4. Discussion

Microsurgery has revolutionised modern reconstructive surgery. However, even today, all complex reconstructions are likely to fail in the absence of adequate recipient vessels. In this study, we describe a fundamentally new surgical approach that facilitates complex soft- and hard tissue reconstructions even in patients with vessel-depleted neck, increasing their quality of life and ability to eat. To our knowledge, this is the first description of a successful transfer of composite free flaps in humans *without* anastomoses. Successful transplantation was facilitated by maintaining an extracorporeal autologous blood circulation until neovascularisation had occurred in the defect area and the transferred flaps had become independent from their extracorporeal blood supply.

An important reason why free flap transplantation using extracorporeal perfusion has not been tried so far on humans might be the assumption that flap viability is dependent on a continuous blood flow through the pedicle for many months or even permanently (Machens et al., 1998; Moolenburgh et al., 2005; Heitland et al., 2009; Kadota et al., 2011). On the other hand, clinical reports describe complete flap survival despite early disruption of the pedicle (Chen et al., 2002; Salgado et al., 2002; Wolff et al., 2003, 2009; Wise et al., 2011); this has also been shown in experimental work (Civelek et al., 2009; Mucke et al., 2011). In all three patients, 10–13 days of extracorporeal perfusion were sufficient for bone and muscle tissue, but not for the large skin paddle in patient 1. Here, the skin covered the flap's muscle component, and autonomisation could only occur from the flap margins. In patient 3, the skin paddle was largely positioned to the original soft tissues of the neck, which allowed for ingrowth of new capillaries from the flap's undersurface. We believe, that the skin flap should be placed directly on the recipient tissue, and that neovascularisation mainly occurs from below. With regard to bone autonomisation, it seems intuitive that interconnecting vessels start to cross the spongiform interface

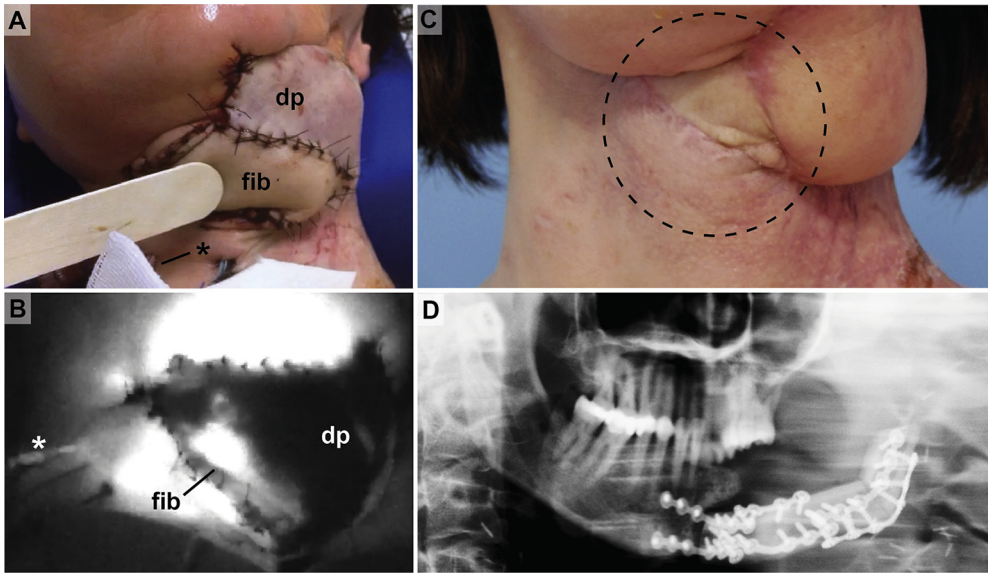

Fig. 5. Patient 3. Clinical and radiographic aspects. (A) Clinical image at day 2 of extracorporeal perfusion of a fibular flap used to reconstruct the lower jaw and neck. Apart from its healthy colour tone, the skin island of the fibular flap (fib) showed a clear flush, indicating the viability of the flap. (dp) Deltopectoral flap. (*) Supplying catheters. (B) Rapid neovascularisation starting at day 10: after administration of Indocyanine-Green (ICG) via femoral catheter at day 10, fluorescence angiography showed first signs of perfusion of the fibular skin island (fib). A strong ICG signal could also be observed in the draining veins (*). Since ICG was administered systemically, these observations prove the flap's developing independency from the perfusion system. (C) Final outcome 6 weeks after surgery with integration of the fibula skin island (broken circle). (D) Follow-up panoramic radiograph 3 months postsurgery with bone segments in correct position and stabile dimensions.

between flap and mandible early. Autonomisation of the muscle might be facilitated by its gradual atrophy following denervation.

Despite successful reconstruction and evidence for maintained bone metabolism in all three patients, a strict perfusion protocol cannot be provided because of the different flap sizes and soft tissue components. In our patients, we have shown that a perfusion of about 3 ml/min during the first day and an average flow rate of about 1 ml/min are sufficient to maintain flap viability. We believe that this reduction of blood supply stimulates ingrowth of new capillaries into the flap; moreover it helps to reduce blood loss during the procedure. Due to the slow but continuous blood loss, blood bags have to be refilled almost every hour and blood transfusions are inevitable. The necessity for blood transfusions and the considerable amount of time and personnel effort are the most significant disadvantages of our technique to date. For fear of infection, and since we wanted to have a continuous direct control of blood volume, pH, oxygen extraction and bacterial growth of the flap's venous return, we decided not to reinfuse the blood (Fig. 1B). According to the results obtained so far, direct reinfusion seems to be possible in a future setting, which might overcome the abovementioned disadvantages.

The idea of temporary extracorporeal perfusion of human tissue is not new, however, in this study, the extracorporeal perfusion of the tissue was not performed *ex vivo* as a bridge to later transplantation (Greaney et al., 2010), but *in vivo* as a bridge until neovascularisation of the flap had occurred in the defect area and the transplanted tissue had become independent from its extracorporeal blood supply. This novel method offers treatment options to a broad range of surgical problems – even if all other therapy options fail. Considering the numerous possibilities for soft tissue reconstruction in the vessel-depleted neck using local skin or pedicled myocutaneous flaps from the chest or dorsum (Feng et al., 2006; Kekatpure et al., 2012), we see the indication of extracorporeal perfusion mainly in extended defects of the mandible with a poor recipient site. Extracorporeal perfusion might also be considered at the lower limb in case of severe vascular disease or other complex defects that require complex hard- and soft tissue reconstructions at poor recipient sites.

It needs to be emphasised, however, that we used this technique as an individual treatment attempt in extreme cases of vessel-depleted-neck. Although the overall clinical course was uneventful in all three patients, the considerable blood loss requiring repetitive blood substitution with all accompanied risks (infections, coagulation disorders) and the considerable investment of time and labour are major drawbacks of this technique in its current form. Moreover, there seems to be a higher risk of partial skin necrosis in comparison with standard treatment. In its current form, the described technique can therefore only be advocated as a last resort in severe cases when all standard treatment options fail. Modifications to the technique, like direct recirculation of the venous blood and modifications of the perfusate are likely to improve outcome and reduce risks in the future. Experimentally, application of vascular endothelial growth factor or the use of blood substitute solutions have already been tested with promising results (Chang et al., 2009; Angelos et al., 2011).

5. Conclusions

Successful mandible reconstruction in three consecutive patients with irradiated, vessel-depleted neck using an extracorporeal perfusion device provides proof that complex tissue transplantations can be achieved even *without* microvascular anastomosis by temporarily maintaining an extracorporeal blood flow to the transplanted tissue. Neovascularisation of bone and ingrowth of new vessels to soft tissues occur within 10–13 days, if direct contact to the recipient site is provided. With this technique, complex reconstructions become possible even in the absence of recipient vessels.

Contributors

KDW and AMF conceived and designed the trial. KDW, TM, LMR, MH and AMF developed the extracorporeal perfusion system. TM, AB, LMR, JS and AMF contributed to the acquisition and review of the data. KDW recruited the patients and wrote the original draft of

the manuscript. AMF analysed the data, revised the manuscript and created all figures and illustrations. All authors contributed to the interpretation of data and the drafting of the report. They revised it critically for important intellectual content and approved the version to be published.

Funding

Preliminary laboratory animal studies were supported by the Deutsche Forschungsgemeinschaft (WO 507/4-1). In this study, no external funding source had any involvement in study design; in the collection; analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Conflicts of interest

None.

Acknowledgements

The authors would like express their gratitude to all the aspiring medical students and the ICU team who spent days and nights helping to sustain the extracorporeal perfusion.

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