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Status 5 Years after Bilateral Hand Transplantation

S. Schneeberger[a,*], M. Ninkovic[a], H. Piza-Katzer[b], M. Gabl[c], H. Hussl[b], M. Rieger[d], W. Loescher[e], B. Zelger[f], G. Brandacher[a], M. Ninkovic[g], H. Bonatti[a], C. Boesmueller[a], W. Mark[a] and R. Margreiter[a]

[a]*Department of General and Transplant Surgery,* [b]*Department of Plastic and Reconstructive Surgery,* [c]*Department of Traumatology,* [d]*Department of Radiology,* [e]*Department of Neurology,* [f]*Department of Pathology, Innsbruck Medical University, Anichstrasse 35, Innsbruck, Austria*
[g]*Department of Reconstructive and Hand Surgery, Burn Centre, Bogenhausen Hospital, Munich, Germany*
**Corresponding author: S. Schneeberger, stefan.schneeberger@uibk.ac.at*

Graft survival and function early after hand transplantation is good. It remains unknown, however, whether long-term survival is limited by chronic rejection. We here describe the clinical course and the status 5 years after bilateral hand transplantation with emphasis on immunosuppression (IS), function, morphology and graft vascular changes.

Clinical observation, evaluation of hand function, skin biopsies, X-ray, ultrasound, angiography, CT angiography, electrophysiologic studies including compound motor and sensory action potentials (CMAP, CSAP) and somatosensory evoked potentials were performed and results recorded at regular intervals.

Following reduction of IS one mild (grade II) rejection episode occurred at 4 years. Subsequently, skin histology remained normal and without signs of chronic rejection. Hand function continuously improved during the first 3 years and remained stable with minor improvement thereafter. CMAP and CSAP progressively increased during the observation period. Latencies of the cortical responses were prolonged but amplitudes were within normal range. Investigation of hand vessels revealed no signs of occlusion but showed revascularization of a primarily occluded right radialis artery.

Motor and sensory function improved profoundly between years 1 and 5 after hand transplantation. No signs whatsoever of chronic rejection have been observed.

Key words: Hand, transplantation, CTA, composite tissue, rejection, outcome

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Introduction

Initial fears that hands would be rejected early after transplantation have waned in light of reports on the first clinical cases (1–6). Immunosuppressive protocols similar to those used in solid- organ transplantation were widely effective in preventing rejection as reflected by a 1-year graft survival of 100%. Regain of protective and discriminative sensation together with recovery of extrinsic and—in some cases—intrinsic muscle activity enabled patients to perform many activities of daily life (6). Despite these promising early results, no hand transplants have been performed since 2003 (www.handregistry.com). The unclear long-term outcome, a limited number of "good candidates" and the high costs may be responsible for this development.

In cardiac, kidney and intestinal transplantations, myointimal proliferation with luminal occlusion of graft vessels is the most relevant criterion for chronic allograft vasculopathy/nephropathy (7–9). The potential existence, relevance and speed of progression as well as morphological correlates of such changes in hand transplantation, however, are unknown. As perivascular infiltrates are the main feature of acute rejection and acute rejection is the most relevant risk factor for chronic allograft vasculopathy/nephropathy, it can be hypothesized that graft vessels are the major target for changes over time, even in hand transplantation. This article deals with the anticipated changes, namely myointimal proliferation in graft vessels and tissue fibrosis as chronic rejection (CR).

In solid-organ transplantation early signs of chronic allograft vasculopathy/chronic allograft nephropathy can be observed at 1 year after transplantation (7,8). At 5 years, changes affects 44% and 100% of cardiac and renal grafts, respectively (8,9). As chronic rejection could be a major hurdle to wider clinical application of hand transplantation, it is of utmost importance to closely follow those patients living with a hand transplant and to make data on hand function and morphology including changes over time available to the scientific community.

This article provides data on the dynamics of motor function and sensitivity, the IS regimen, rejection and skin histology at 5 years after double hand transplantation.

Ultrasound studies, angiography and CT angiography were analyzed with particular regard to potential signs of chronic rejection.

Patient and Methods

A detailed description of patient and donor selection, the surgical procedure and the clinical course during the first postoperative year was published earlier (1,2). In brief, a 48-year-old policeman was given a bilateral hand transplant after traumatic amputation at the wrist level. He experienced one acute rejection episode and an additional 'incipient' rejection at 55 and 188 days, respectively. The overall range of motion (ROM) at 1 year was 60.1%, and initial function was sufficient to perform activities of daily life including writing, operating a cell phone, eating and drinking, attending to his personal hygiene and dressing himself.

Immunosuppression

The patient had received antithymocyte globulin for induction therapy and tacrolimus, mycophenolate mofetil (MMF) and prednisone as maintenance immunosuppression (1). Rejection was treated with bolused steroids and transient increase of the tacrolimus dosage. After 30 months, IS was changed according to a previously designed protocol: rapamycin was started and aimed for trough levels of 4–8 ng/mL. Simultaneously, tacrolimus was reduced to trough levels of 3–4 ng/mL. Six months later, steroids were withdrawn in a stepwise fashion. Over the following 3 months, tacrolimus was slowly tapered and then discontinued, leaving the patient on rapamycin and MMF.

Skin biopsies

Skin biopsies were performed bilaterally at weekly intervals during the first month, monthly until month 6 after transplantation and once a year thereafter. Additional biopsies were performed whenever clinically indicated. Biopsies were read and graded according to a previously established scoring system for skin rejection after hand transplantation (10).

Rehabilitation program and evaluation of hand function

A specific rehabilitation program based on EPM (early protective joint motion) combined with Perfetti cognitive exercise training, electrotherapy and occupational therapy was designed (17). Intensive physiotherapy for 6 hours daily was reduced after 12 months to 4 hours per week.

Motor function was investigated by range of motion (ROM), electromyography, Kapandji test, pinch and grip observation and hand dynamometer test performed monthly for the first year, at intervals of 2 months during the second year and every 3 months thereafter. Hand sensitivity and tactile gnosis were assessed with Tinel's sign, the Semmes-Weinstein monofilament test, Weber static two-point discrimination and the Dellon moving two-point discrimination test.

Electrophysiological studies were performed using a Nicolet Viking IV device (Nicolet Biomedical, Madison, WI). CMAP were recorded using disposable surface electrodes for the abductor pollicis brevis and abductor digiti minimi muscles after stimulating the median and ulnar nerve just proximal to the site of coadaption. CSAP were recorded for the index and fifth fingers using band electrodes.

Somatosensory evoked potentials were studied 3 years after transplantation. The left and right index and fifth fingers were electrically stimulated and recordings were made over Erb's point, C5 and the somatosensory cortex using a Nicolet Viking IV device (Nicolet Biomedical, Madison, WI).

Electrophysiological studies, somatosensory evoked potentials as well as clinical evaluation of hand function were performed every 3 months.

Imaging modalities

Graft vessels, nerves, muscles and tendons were investigated by ultrasonography at monthly intervals during the first 6 months and every third month thereafter. The hands and forearms underwent the first angiogram 1 year after transplantation and every 9 months thereafter. CT angiography with three-dimensional reconstruction of graft vessels was undertaken once a year.

Helical CT were performed with two different multi-detector row CT scanners (LightSpeed QX/i; LightSpeed 16; General Electric Medical Systems, Milwaukee, WI) with 0.8- and 0.5-second gantry rotation, respectively. CT angiographic reconstructions were calculated from 1.25 mm (0.625 mm) thick slices at pitch 6 (1.35) and reconstruction intervals of 0.6 mm (0.4 mm).

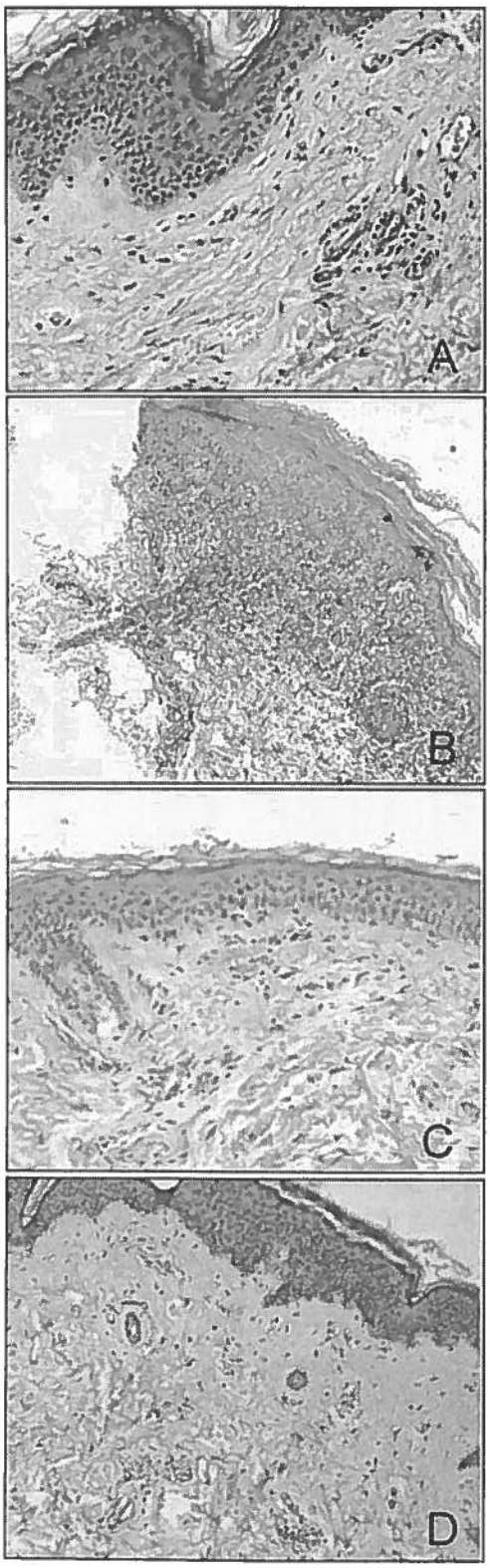
A non-ionic contrast medium (140 mL) was administered intravenously at a rate of 5 mL/sec. Scan delay was determined using Smart Prep software (General Electric Medical Systems, Milwaukee, WI). The CT data sets were transferred to a three-dimensional rendering workstation for volume rendering reconstructions (Advantage Windows 4.0; General Electric Medical Systems, Milwaukee, WI).

Results

Immunosuppression and related side effects

One year after transplantation, IS consisted of tacrolimus (trough level 10 ng/mL), steroids (5 mg) and MMF (2 g/day). Incipient calcineurin inhibitor (CI)-induced nephrotoxicity reflected by an increase in urea (59.3 mg/dL [base line: 30.9 mg/dL]) and creatinine (1.45 mg/dL [base line: 0.84 mg/dL]) was observed 24 months after transplantation. When rapamycin was started at 30 months and tacrolimus simultaneously reduced to maintain trough levels between 3–4 ng/mL, urea and creatinine levels returned to normal. Rapamycin-associated disturbances in lipid metabolism were treated with fenofibrat at a dose of 200 mg/day. Increased serum glucose (134 mg/dL) and HbA1c levels (8.3%) prompted oral anti-diabetic therapy with pioglitazon-hydrochloride (30 mg/day), which was sufficient to normalize glucose metabolism.

No signs of acute rejection were encountered and hand function remained stable after steroids and later also tacrolimus were withdrawn at 39 months. However, upon occurrence of maculopapulous lesions characteristic for acute rejection at month 48, tacrolimus was restarted and targeted for trough levels of 3–4 ng/mL. Skin biopsies showed diffuse lymphocytic and eosinophilic interstitial infiltrates reaching adnexal structures together with interphase dermatitis (rejection grade II, Figure 1B). Treatment with tacrolimus resulted in restitution of normal skin histology (Figure 1C); the drug was continued for 8 months and withdrawn thereafter. Since then, neither acute rejection nor side effects other than those described above have been observed.



After hair regrowth on the transplanted hands, hairs from proximal and distal sites of the graft were analyzed for the presence of recipient cells using the SGM+ system kit. Despite a very uniform pattern of hair (re)growth on recipient and donor skin of the forearm, regrowth was found to be of donor origin (data not shown).

Morphology

Apart from a solitary rejection episode described above (Figure 1B), no alterations in skin morphology were seen. Texture, composition and proportions of the skin remained unaltered at 5 years after transplantation (Figure 1D). Importantly, histology revealed neither vascular luminal occlusions, myointimal proliferation in small skin vessels nor necrosis or fibrosis as indirect signs of insufficient blood supply.

Function

At 1 year, active wrist ROM (ext/flex) was 70° on each side and has remained stable since then (65° at 5 years, Figure 2). For ulnar and radial deviation ROM for the right hand was 30°, 35° and 27° at 1, 3 and 5 years, respectively. Active deviation ROM on the left side showed the best result, namely 40° at 3 years. A fracture of the radial bone of the graft suffered in an accident in which the patient's forearm was hit at a sports event at month 56 caused the left forearm to be immobilized with a splint for 4 months. In response, active ROM decreased to 15° at 5 years.

Active finger ROM continued to improve for both hands after the first postoperative year (Table 1). After the third year overall finger ROM remained stable, while a minor decrease in the left small finger ROM was again attributed to the transient immobilization. The splint was removed as bone healing was completed.

Intrinsic muscle activity was first observed at 4 months and improved during the subsequent 3 years. Reinnervation was confirmed by electromyography. Thumb opposition improved during the first 3 years (Figure 3).

At 1 year, the patient had a grip strength of 14.0 kg in his right and 8.5 kg in his left hand. Subsequently, overall strength remained stable with some minor improvement. In contrast, kip, key and three-fingered pinch constantly improved during the 5-year observation period (Figure 3). At 5 years, tip pinch is 1 kg for the right and 0.8 kg for the

Figure 1: Skin histology. Normal skin histology at 1 year after transplantation (A). After reduction of IS a grade II rejection episode occurred with dense lymphocytic infiltrate and an interphase reaction in epidermis and adnexal structures (B). Following treatment with tacrolimus lesions disappeared completely (C). At 5 years after transplantation normal skin texture, composition and proportions were observed; neither myointimal hyperplasia nor a perivascular lymphocytic infiltrate was found (D).

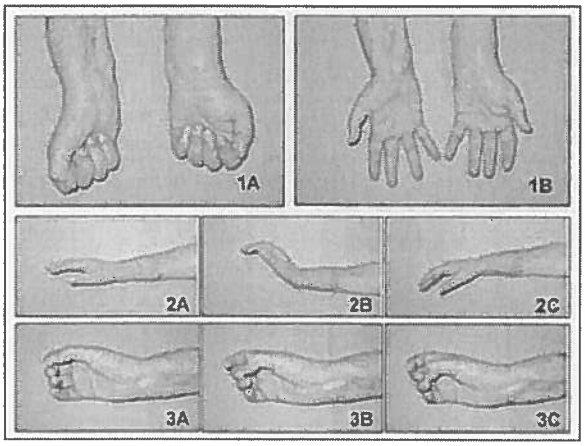


Figure 2: Hand function at 5 years after transplantation. Depicted are finger flexion (1A) and extension (1B), extension (2B) and flexion (2C) of the wrist as well as key pinch (3A–C).

left side. Key pinch is 1.8 kg and 2.7 kg for the right and the left hand, respectively; chuck pinch is 1.3 kg for the right and 1 kg for the left side.

Nerve regeneration was first observed at 2 weeks after transplantation, progressing 1.5 mm per day on average. At 1 year, Tinel's tingling sign was detectable in all fingertips of both hands. Sensitivity to pain and thermal discrimination were present in both hands at 1 year. The moving two-point discrimination test showed sensory function to improve in most fingers during the first 3 years. Thereafter, it remained stable with some minor improvement (Figure 3).

Nerve conduction studies demonstrated motor and sensory reinnervation to various degrees in both hands (Figure 4). Six months after transplantation electromyographic signs of reinnervation were observed only in the left abductor digiti minimi muscle (ADM). One year after transplantation reinnervation was also seen in the right ADM and the abductor pollicis brevis (APB) in both hands. Reinnervation progressed and long-duration polyphasic potentials were recorded after 3 years. Loss of motor units was seen in all muscles studied, but was more pronounced in the APB of both hands.

Cortical responses were recorded after stimulation of the left and right index and fifth fingers, while no potentials were recorded over Erb's point or C5. Latencies of the cortical responses were prolonged, but amplitudes were within normal range (for details, see 11).

Imagery

At 1 year after transplantation, ultrasound, CT angiography and angiography demonstrated normal blood flow through the radial and ulnar arteries in the left hand and forearm. The right radial artery was occluded at the level of the retinaculum flexorum along a distance of approximately

Table 1: Active finger movement at 1 and 5 years after bilateral hand transplantation. Range of motion further increased in most fingers after the first postoperative year

At 1 Year							
Right	MCP	ROM	PIP	ROM	IP/DIP	ROM	TROM
Thumb	0–5–20	15			0–5–70	65	80
Index	30–0–60	90	0–30–100	70	0–0–40	40	200
Long	20–0–80	100	0–40–80	40	0–20–70	50	190
Ring	0–0–70	70	0–20–80	60	0–5–50	45	175
Small	20–0–80	100	0–30–90	60	0–0–40	40	200
Left	MCP	ROM	PIP	ROM	IP/DIP	ROM	TROM
Thumb	0–20–35	15			0–20–40	20	35
Index	0–0–70	70	0–30–80	50	0–5–35	30	150
Long	0–0–70	70	0–20–85	65	0–0–35	35	170
Ring	0–0–55	55	0–10–70	60	10–0–50	60	175
Small	10–0–70	80	0–0–65	65	10–0–40	50	195
At 5 Years							
Right	MCP	ROM	PIP	ROM	IP/DIP	ROM	TROM
Thumb	0–0–20	20			0–0–70	70	90
Index	20–0–60	80	0–5–105	100	0–0–65	65	225
Long	0–0–70	70	0–5–90	85	0–0–70	70	225
Ring	0–0–75	75	0–0–85	85	0–0–40	40	200
Small	5–0–75	80	0–5–95	90	0–0–35	35	200
Left	MCP	ROM	PIP	ROM	IP/DIP	ROM	TROM
Thumb	0–20–45	25			0–0–20	20	45
Index	0–0–65	65	0–5–80	75	0–0–30	30	170
Long	5–0–70	75	0–5–80	75	0–0–45	35	190
Ring	0–0–65	65	0–0–80	80	0–0–25	60	170
Small	0–0–65	65	0–0–70	70	0–0–40	50	175

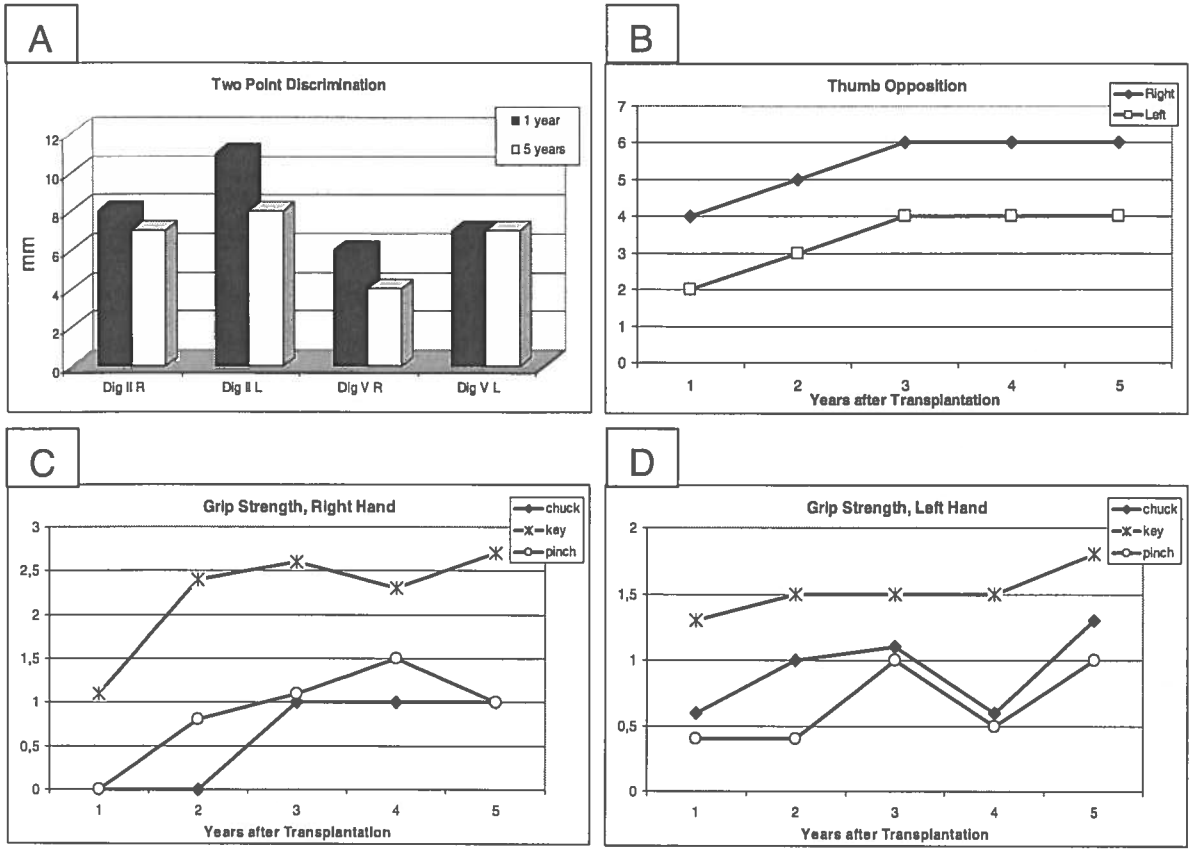


Figure 3: Moving two-point discrimination (A), thumb opposition (B) and grip strength (C, D) between 1 and 5 years after hand transplantation. Thumb opposition was measured according to Kapandji criteria, grip strength is given in kilograms. After the first postoperative year, sensitivity as measured by two-point discrimination as well as thumb opposition and grip strength improved particularly during the first 3 years and remained stable with some minor improvement thereafter.

2 cm and the distal part perfused retrograde via the arcus palmaris profundus (Figure 5, indicated by arrows). The left superficial palmar arch was occluded. On both sides a kinking of radial and ulnar arteries was caused by excess length of the grafted vessels.

No radiomorphologic changes were observed during the first 3 years, as reflected by stable proportions and consistent perfusion of all tissue components. Surprisingly, at 4 years post-transplantation the left radial artery was seen to be recanalized and the deep palmaric arch was perfused orthograde (Figure 5; 5 years after transplantation).

Discussion

To prevent rejection of a composite tissue allograft, prophylactic immunosuppression used for organ transplants seems to be sufficient in most cases (1–6). However, the incidence and characteristics of chronic rejection after hand transplantation are currently unknown. Therefore, a protocol for accurate monitoring of graft vessels combined with a specific IS protocol was designed. Since rapamycin seems to have the potential to prevent or slow down progression of CR in cardiac and kidney transplantation, this drug was chosen for long-term IS (12,13). In order to avoid CI-related complications such as nephrotoxicity, rapamycin was initiated at a time when no further nerve regeneration was expected. Although the combination of MMF and rapamycin has been reported to cause leukocytopenia in some cases, the regimen was well tolerated and permitted nephrotoxic calcineurin inhibitors to be discontinued. In addition to its effect on CR, rapamycin was chosen for its anti-tumor properties (14–16). One moderate rejection episode was observed, but the IS administered was sufficient to prevent repetitive or severe rejection. Transient tacrolimus administration was effective for treatment of acute rejection in this case.

The regimen was chosen for long-term IS in awareness of an increased risk for acute rejection. However, as the hand (and the abdominal wall) is the only allograft constantly

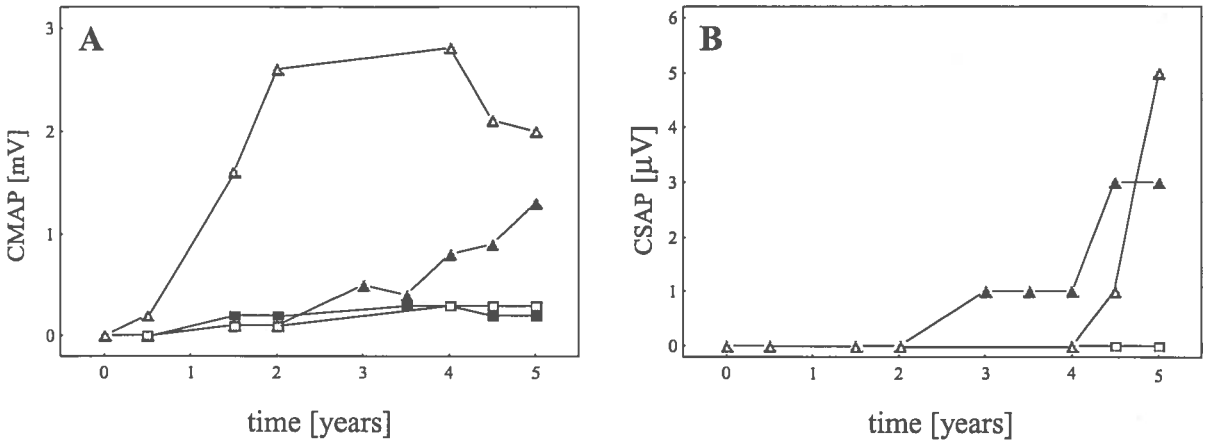


Figure 4: Amplitudes of compound (A) motor and (B) sensory action potentials (CMAP, CSAP) are shown from 8 weeks after transplantation (time 0) to the last assessment at 5 years. Filled symbols (■, ▲), right hand; open symbols (□, △), left hand; squares (■,□), median nerve stimulation; triangles (▲, △), ulnar nerve stimulation. A progressive increase in compound motor and sensory evoked potentials was seen after ulnar nerve stimulation, whereas only small compound motor evoked potentials were recorded after median nerve stimulation. Normal values for median and ulnar CMAP are 5 and 4 mV, respectively, and for median and ulnar CSAP 10 and 8 µV, respectively.

available for visual inspection and the skin is the major or only compartment affected by acute rejection, we felt that lowering IS in order to find the minimum level required to prevent rejection was justified. In addition, in view of the fact that hand transplantation is not a life-saving intervention, minimizing the risks for tumor and infection is of particular importance.

In protocol biopsies of kidney transplants and in coronary angiography of heart transplants, first signs of chronic allograft vasculopathy/nephropathy were observed early in a large percentage of cases (8,9). In the case presented here, morphological analysis of skin biopsies and investigation of graft vessels failed to demonstrate any signs of CR. Instead, the left radial artery recanalized at 4 years after transplantation. Such a phenomenon has not been previously described in organ transplantation. It can only be speculated that a constant stimulatory effect caused by improved and increasingly applied motor activity was the underlying mechanism.

The texture and composition of the skin remained unaltered during the observation period. No dermal fibrosis or atrophy as indirect signs of insufficient blood supply was found. The uniformity of regrown hair on the transplant and on the recipient forearm hair was surprising and further improved donor and recipient cosmetic match. However, anticipated peripheral chimerism in the roots of hairs from the graft was not observed.

For rehabilitation, EPM, a program similar to that applied for hand replantation was utilized. Specific therapeutic goals such as pain and edema control, prevention of soft tissue adhesions and joint stiffness as well as tendon glide maintenance and motor and sensibility reeducation were achieved. To promote cortical reintegration, the specific exercise program designed by Perfetti was applied (17).

At 2, 2.5, 3 and 4 years following transplantation, intensified therapy was performed for 3 weeks each. After these sessions, motor function improved in specifically trained compartments. This observation confirms the beneficial effect of physiotherapy at later times following transplantation.

Overall, ROM improved during the first 2 years post-transplantation and has remained stable since then. Recovery of intrinsic muscle activity was far advanced at 3 years, further improved after intensified rehabilitation and was best at 3.5 years after transplantation. A slight transient impairment in the left hand at 5 years was attributed to splint stabilization after a radial bone fracture together with reduced intensity of physiotherapy. Peripheral sensory reinnervation and reorganization of the somatosensory cortex were confirmed by EVP. Sensitivity improved during the first 2 years and remained stable with minor improvement thereafter.

It is striking that motor as well as sensory action potentials increased at 4 and 5 years after transplantation. This refutes earlier expectations that nerve regeneration would occur only during the first postoperative year. Recovery of motor function and sensitivity preceded the late improvement in action potentials, and it is difficult to judge whether increasing action potentials indicate additional peripheral nerve regeneration or reorganization of the somatosensory cortex. Nevertheless, the overall regenerative potential of the sensomotor complex was clearly better than expected.

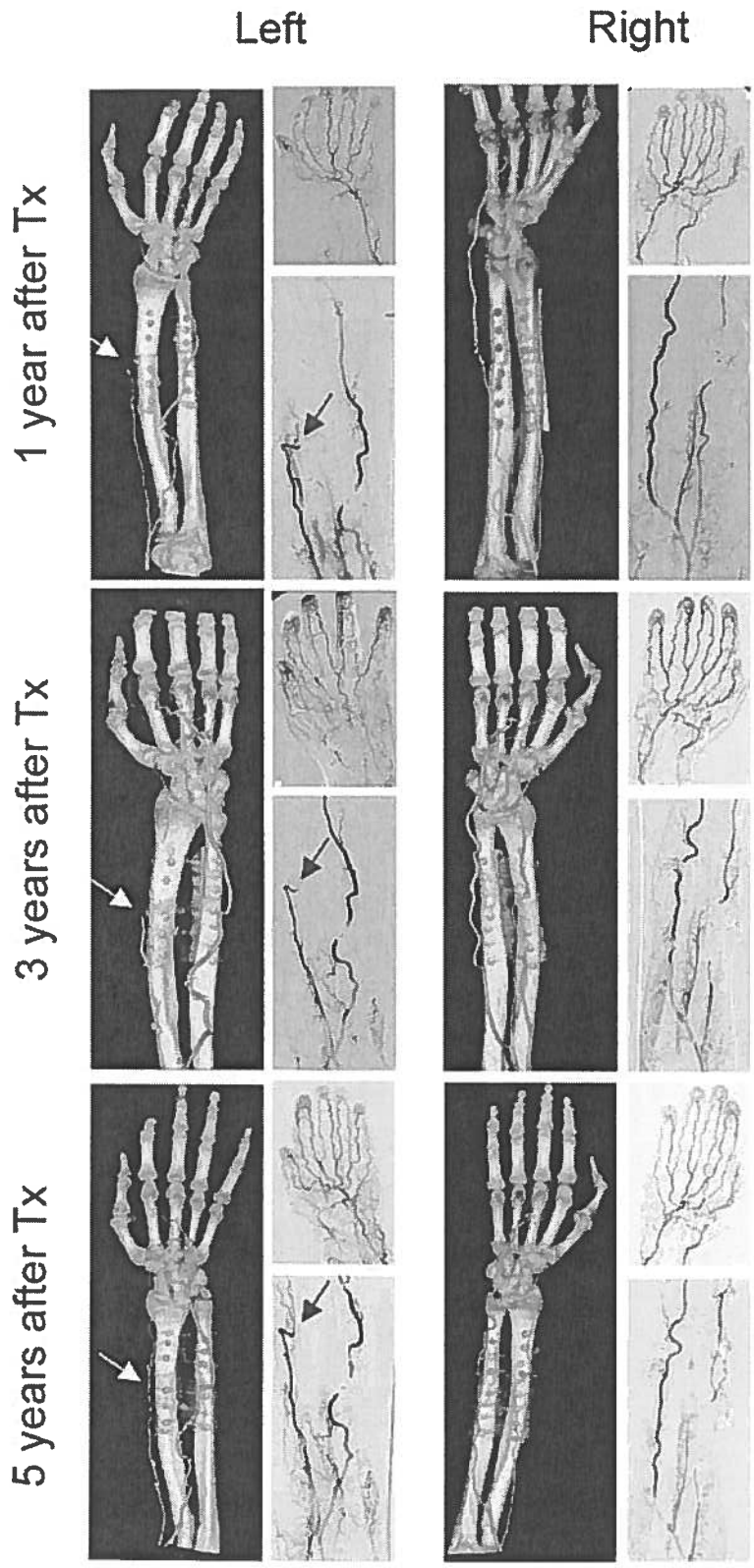


Figure 5: CT angiography and angiography at 1, 3 and 5 years after hand transplantation. The left radial artery was occluded early after transplantation (arrow). At 5 years after transplantation the vessel was found to be recanalized and orthograde blood flow was observed. Neither in larger nor in small vessels were signs of luminal narrowing or occlusion found at any time.

After the initial excitement over the first hand transplantations, little information on these patients' follow-up was made available during the past 3 years. This is surprising as the most important question, namely whether survival and function are long term, remains to be answered. Hence, we here present the first complete 5-year follow-up after hand transplantation. Briefly, no signs of chronic rejection or loss of function were observed. Instead, the patient is very pleased with the sensomotor and cosmetic outcome, he considers his daily life 'completely normal' and remains highly active in his job as a police officer. His new hands enabled him to undertake transcontinental motorcycle trips in Europe and South America. The clear long-term improvement in the patient's quality of life prompted us to continue our double hand transplant program in selected patients. Although conclusive statements can certainly not be made on the basis of a single patient, we provide first evidence that long-term graft survival and function in composite tissue allografts seems realistic. Our findings, however, need to be confirmed in a larger series of patients.

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References

1. Margreiter R, Brandacher G, Ninkovic M, Steurer W, Kreczy A, Schneeberger S. A double-hand transplant can be worth the effort! Transplantation 2002; 74: 85–90.
2. Piza-Katzer H, Ninkovic M, Pechlaner S, Gabl M, Ninkovic M, Hussl H. Double hand transplantation: Functional outcome after 18 months. J Hand Surg (Br) 2002; 27: 385–390.
3. Dubernard JM, Owen E, Herzberg G et al. Human hand allograft: Report on first 6 months. Lancet 1999; 353: 1315–1320.
4. Jones JW, Gruber SA, Barker JH, Breidenbach WC. Successful hand transplantation. One-year follow-up. Louisville Hand Transplant Team. N Engl J Med 2000; 343: 468–473.
5. Dubernard JM, Petruzzo P, Lanzetta M et al. Functional results of the first human double-hand transplantation. Ann Surg 2003; 238: 128–136.
6. Lanzetta M, Petruzzo P, Margreiter R et al. The international registry on hand and composite tissue transplantation. Transplantation 2005; 79: 1210–1214.
7. Costanzo MR, Naftel DC, Pritzker MR et al. Heart transplant coronary artery disease detected by coronary angiography: A multiinstitutional study of preoperative donor and recipient risk factors. Cardiac transplant research database. J Heart Lung Transplant 1998; 17: 744–753.
8. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med 2003; 349: 2326–2333.
9. Sharples LD, Jackson CH, Parameshwar J, Wallwork J, Large SR. Diagnostic accuracy of coronary angiography and risk factors for post-heart-transplant cardiac allograft vasculopathy. Transplantation 2003; 76: 679–682.
10. Schneeberger S, Kreczy A, Brandacher G, Steurer W, Margreiter R. Steroid- and ATG-resistant rejection after double forearm transplantation responds to campath-1H. Am J Transplant 2004; 4: 1372–1374.
11. Brenneis C, Löscher WN, Egger KE et al. Cortical motor activation patterns following hand transplantation and replantation. J Hand Surg 2005; 30b: 530–533.
12. Eisen HJ, Tuzcu EM, Dorent R et al. RAD B253 Study Group. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med 2003; 349: 847–858.
13. Ruiz JC, Campistol JM, Grinyo JM et al. Early cyclosporine a withdrawal in kidney-transplant recipients receiving sirolimus prevents progression of chronic pathologic allograft lesions. Transplantation 2004; 78: 1312–1318.
14. Guba M, von Breitenbuch P, Steinbauer M et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: Involvement of vascular endothelial growth factor. Nat Med 2002; 8: 128–135.
15. Majumder PK, Febbo PG, Bikoff R et al. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med 2004; 10: 594–601.
16. Stallone G, Schena A, Infante B et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005; 352: 1317–1323.
17. Perfetti C. Der hemiplegische Patient (Kognitiv therapeutische Übungen). Pflaum Verlag Munich, 1997.