

Coverage of Exposed Bones and Joints in Critically Ill Patients: Lower Extremity Salvage with Topical Negative Pressure Therapy

Raymund E. Horch, Adrian Dragu, Werner Lang, Paul Banwell, Mareike Leffler, Andreas Grimm, Alexander D. Bach, Michael Uder, and Ulrich Kneser

Background: Soft tissue defects of the limb with exposure of tendons and bones in critically ill patients usually lead to extremity amputation. A potential treatment with topical negative pressure may allow split-thickness skin grafting to the bone, which leads to limb salvage.

Materials and Methods: We report on 21 multimorbid patients, 46 to 80 years of age, with severe lower limb soft tissue loss and infection with exposed bone following débridement with critical limb ischemia. Attempts to salvage the extremities were undertaken with repeated surgical débridement followed by vacuum-assisted closure therapy and subsequent split-thickness skin grafting procedures.

Results: Infection control and limb salvage were achieved in all cases with multiple débridements, topical negative pressure therapy, and skin grafts. In all patients, the exposure of tendons and bones was reversible by this strategy without a free flap transfer.

Discussion: The patients described in this study were severely compromised by systemic and vascular disorders, so extremity amputation had been considered owing to the overall condition and the exposure of tendons and bones. Since it was possible to salvage the affected limbs with this straightforward and simple procedure, this type of treatment should be considered as a last attempt to prevent amputation.

Antécédents: Chez les patients gravement malades, l'atteinte du tissu mou au niveau des membres accompagnée d'une exposition des tendons et des os mène normalement à l'amputation. Un traitement possible par pression négative pourrait permettre une greffe dermo-épidermique sur l'os et sauver ainsi le membre.

Matériel et méthodes: Rappporter les cas de 21 patients âgés entre 46 et 80 ans qui souffrent de maladies multiples et qui présentent une perte importante du tissu mou au niveau des membres inférieurs avec infections et exposition des os à la suite d'un parage et d'ischémie grave dans le membre atteint. Des tentatives pour sauver les membres atteints ont été entreprises avec des parages répétés suivis d'une thérapie de cicatrisation par pression négative et finalement de greffes dermo-épidermiques.

Résultats: Grâce au parage, à la thérapie par pression négative, et à la greffe de peau, il a été possible de maîtriser les infections et de sauver les membres chez tous les patients. L'exposition des tendons et des os a été réversible au moyen de cette stratégie sans nécessiter le transfert d'un lambeau libre.

Discussion: La santé des patients qui ont fait l'objet de cette étude était largement compromise en raison de troubles systémiques et vasculaires. L'amputation des extrémités était envisagée vu leur condition générale et l'exposition des tendons et des os. Étant donné qu'il a été possible de sauver les membres affectés grâce à une procédure simple et directe, il faudra toujours envisager cette procédure en dernier recours afin de prévenir l'amputation.

From the Department of Plastic and Hand Surgery, Department of General, Visceral and Thoracic Surgery, and Institute of Radiology, Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, Germany; and Department of Plastic and Reconstructive Surgery, Nuffield Hospital Brighton and Queen Victoria Hospital, East Grinstead, UK.

R. E. Horch has held lectures on vacuum therapy and has received funding to attend international congresses where he presented surgical results of vacuum-treated patients.

Address reprint requests: Raymund E. Horch, MD, Department of Plastic and Hand Surgery, Friedrich-Alexander Universität Erlangen-Nürnberg, Krankenhausstrasse 12, D-91054 Erlangen, Germany; e-mail: raymund.horch@uk-erlangen.de.

DOI 10.2310/7750.2008.07073

COMPLEX WOUNDS with exposed bones secondary to débridement of severe soft tissue infections and ulcerations in peripheral vascular disorders in the lower limb still represent a major challenge to any reconstructive surgeon. Local tissue advancement techniques for reconstruction of soft tissue defects are often limited owing to poor vascularization and considerable damage to surrounding tissues. Vascular bypass surgery in combination with microsurgical free tissue transfer is applicable only in selected patients since extensive soft tissue defects and multimorbidity may constitute contraindications to such complex reconstructive procedures. Split-thickness skin

grafting onto the exposed bone does not provide reliable coverage of these defects. Therefore, a limb amputation may often become necessary to save the patient's life when local infection proceeds or the general condition of the patient deteriorates.

The introduction of topical negative pressure (TNP) therapy or vacuum-assisted closure (VAC) devices has changed some approaches to wound management.¹⁻¹⁶ It is based on the insertion of a polyvinyl or polyurethane foam sponge into a wound cavity that is sealed airtight with an adhesive foil. A computer-assisted and -controlled suction device is connected to this dressing and provides negative pressure to the wound. Treatment of wounds with subatmospheric pressure dressings leads to a fourfold increase in local blood flow, stimulation of granulation tissue formation, and removal of interstitial edema. Healing of chronic wounds^{13,17-19} may be enhanced owing to these changes within the wound. It has also been shown experimentally that tissue bacterial counts were significantly reduced ($p \leq .05$) after 4 days of negative pressure therapy.^{1,17,20-23}

In this article, we present 21 patients suffering from critical limb ischemia and extended soft tissue loss of the lower extremity, infection, and exposed bone. Owing to multimorbidity, free tissue transfer in combination with vascular bypass surgery was not an option. In these patients, VAC therapy was applied as a last resort and made soft tissue coverage with subsequent split-thickness skin grafting possible. Despite exposure of bones and joints in the lower limb, salvage was achieved in each of these severe cases. Therefore, this approach appears to be a very valuable treatment option for critically ill patients with impending loss of the lower extremity.

Materials and Methods

Critically ill patients with multiple underlying diseases for which conservative measures had failed to cure extensive infected ulcers of the lower leg with exposed bones and joints were included in the study. Revascularization procedures had been ruled out by interdisciplinary consent of interventional radiologists and vascular surgeons. As a last attempt to salvage the extremity, serial débridement with TNP therapy was performed. Under continuous TNP treatment, granulation tissue subsequently grew over the exposed bones and tendons. Eventually, skin grafts were applied for definitive closure of the wounds.

Technically, a radical surgical débridement was performed and the whole débrided extremity with exposed

bone was wrapped in a polyurethane sponge. The polyurethane sponge was sealed airtight with a surgical plastic film tape and then connected to a computer-controlled suction device with a continuous negative pressure of -75 mm Hg (V.A.C., KCI, Wiesbaden, Germany) (Figure 1). The dressing was changed every third to fifth day, and surgical débridement was repeated if necessary. The surrounding skin was protected with a hydrocolloid dressing before the sealing film was applied. In some cases, the sponges were attached with a few surgical staples to the wound margins to ensure proper application during the dressing procedure.

When exposed bone areas and remaining tendon structures were adequately covered with granulation tissue, a 0.2 to 0.3 mm split-thickness skin graft was harvested from the upper leg, the thigh, or the back of the patients. Skin grafts were meshed with a ratio of 1.5 to 1 or 3 to 1, secured with staples, and then fixed with a vacuum dressing using the polyurethane foam and a negative pressure of -125 mm Hg (V.A.C.) as described above.

Results

We included 21 patients with exposed bone, joints, and tendons in the lower extremities who were treated between January 2003 and January 2007. The age of this highly selected collective of critically ill patients ranged from 46 to 80 years (mean age 69.8 years). These patients suffered from peripheral arterial occlusive disease with or without concomitant renal insufficiency ($n = 17$), diabetes ($n = 10$),



Figure 1. The vacuum-assisted closure (V.A.C.) dressing, including the black polyurethane foam, plastic film, and the track pad for connection to the microprocessor-controlled pump.

acute pancreatitis ($n = 2$), and autoimmune disease with immunosuppressive medication ($n = 2$), as well as septic conditions owing to local infection or pneumonia. All patients presented with necrotic tendons and/or affected and exposed tibia or fibula bones. All patients had undergone conservative treatment with repeated chemical débridements, biologic débridement ($n = 1$), and antibiotic therapy over various periods. All ulcerations and partially gangrenous lesions had been refractory to such conventional therapy so far. These critically ill patients had been ruled out as candidates for vascular surgery or interventional vascular dilatation, and extremity amputation had been considered (Table 1).

As early as 6 to 14 days following initiation of TNP therapy, granulation tissue started to grow, and over time (between 12 and 35 days following initiation of treatment), the exposed bones and tendons were completely covered.

Dressing changes were initially performed under general anesthesia or spinal anesthesia every third to fifth day, and wounds were débrided if needed. Later, dressing changes were performed following injection of 1% lidocaine (40 cc) solution into the polyurethane sponge without general anesthesia. This procedure was well tolerated by all patients.

TNP treatment was discontinued in three patients owing to local infection. However, after repeated débridements, changes in antibiotic regimen, and open wound treatment, TNP treatment was successfully completed, and healthy granulation tissue could be induced even in these patients. Eventually, all wounds were adequately conditioned and skin grafts could be performed. Some patients needed skin grafting up to three times owing to insufficient initial take. No extremity amputation was necessary during this phase of treatment. However, one of the patients developed gangrene in his forefoot and lower leg 7 months

Table 1. Patient's Details

	<i>Patient</i>	<i>Age (yr)</i>	<i>Concomitant Disease</i>	<i>Exposed Bone</i>
1	N.T.-G., female	80	PAD, cachexy, RI, lymph edema,	Tibia, fibula
2	R. D., female	79	PAD, cachexy, RI	Tibia, fibula
3	M.R., female	78	PAD, cachexy, RI, aortic aneurysm, heart failure	Tibia
4	I.L., female	77	Diabetes, PAD, sepsis	Metatarsal, cuboid
5	M.J., male	76	Sepsis, PAD	Tibia
6	I.M., female	76	Diabetes, PAD, liver cirrhosis, myocardial infarction	Ankle, forefoot
7	G.S., male	75	Sepsis, liver cirrhosis, diabetes, renal failure, PAD, venous insufficiency	Tibia
8	I.M., female	75	Diabetes, PAD	Ankle
9	K.L., male	73	Resuscitation, heart failure, resuscitation, diabetes, PAD, melanoma	Calcaneus
10	E. S., female	72	LE, autoimmune disease, renal transplantation,	Fibula, lateral malleolus
11	I. T., female	72	Diabetes, PAD, cachexy	Tibia
12	D.H., female	72	Diabetes, RI, dialysis,	Metatarsals
13	E B., male	71	Diabetes, PAD	Fibula, lateral malleolar joint
14	H.L., male	70	Diabetes, PAD, pneumonia	Calcaneus
15	H.F., male	69	Pancreatitis, PAD, liver cirrhosis, colon carcinoma, diabetes	Tibia, lateral malleolar joints
16	J.S., male	66	PAD, cerebral insufficiency	Achilles tendon, calcaneus
17	E.G., male	65	PAD, cerebral insufficiency	Medial ankle joint, calcaneus
18	D.D., male	63	Diabetes, PAD, cerebral insufficiency, heart insufficiency	Metatarsals
19	W.K., male	58	PAD, sepsis, pneumonia	Calcaneus, Achilles tendon
20	W.F., male	52	PAD, cerebral and heart insufficiency	Calcaneus Achilles tendon
21	H.W., male	46	LE, PAD, sepsis, pancreatitis	Tibia, lateral malleolar joint

LE = lupus erythematosus; PAD = peripheral arterial disease; RI = renal insufficiency.

after successful initial salvage and underwent lower leg amputation owing to overwhelming sepsis secondarily.

Case Report

A multimorbid 79-year-old female patient (with cardiomyopathy, heart insufficiency, chronic renal insufficiency, renal anemia, thyroid malfunction, and extreme weight loss with cachexy) presented with a circular ulceration of her left lower leg caused by a blunt trauma 15 months previously. Despite several conservative and surgical treatment attempts, a severe local infection of the lower leg with consecutive septicemia developed, and the patient was finally referred for an above-the-knee amputation given a past medical history of chronic occlusive arterial disease and that revascularization procedures had been ruled out by interventional radiologists and vascular surgeons. On admission, nearly all tendons and the gastrocnemius muscles, tibia, and fibula bones were exposed in a superinfected gangrenous wound bed (Figure 2).

The patient categorically refused an amputation of her leg and was prepared to succumb to the infection. In an attempt to treat the infectious process, we therefore performed a radical surgical débridement with resection of necrotic tendon fascia, muscle, and periosteum. A TNP dressing with -75 mm Hg continuous negative pressure was applied as a salvage procedure. After 6 days, during the first dressing change, a film of granulation tissue was found unexpectedly. Repeated vacuum dressing changes and minor débridements for 21 days led to a granulating wound bed that had covered the once exposed bones so that a meshed split-thickness skin graft was transplanted from the back of the patient (Figure 3). The mesh grafts (1.5:1 und 3:1 ratio) were secured to the wound bed with a VAC device. After 4 days, when this vacuum dressing was removed for the first time, we observed a 90% skin graft



Figure 2. Preoperative situation with necrotic tendons, fascia, and muscle after 15 months of conservative treatment in arterial occlusive disease and infection of the forefoot and lower leg.



Figure 3. Formation of granulation tissue on the exposed tibia and fibula bone after a 21-day period of repeated continuous vacuum therapy.

take rate (Figure 4A). Local débridement and vacuum treatment for 7 days led to further wound closure. Another minor débridement was performed, and skin grafting was repeated. After a total vacuum treatment time of 7 weeks with débridements and skin grafts and 1 more week of fat gauze dressing, the wound was almost completely closed, and the patient was discharged without any signs of infection and with stable wound coverage (Figure 4B). The entire procedure also enabled full mobilization of the patient, who had previously been bedridden for 9 months. A follow-up examination after 3½ years showed stable coverage of the formerly exposed bones and tendons (Figure 5).



Figure 4. A, Four days after split-thickness skin grafting and vacuum fixation onto the granulation tissue (95% take rate). B, Almost complete reepithelialization at 8 weeks after débridement, three skin grafting procedures, and continuous vacuum treatment.



Figure 5. Three and a half years after reconstruction, the skin is completely healed, stable, and without evidence of recurrent ulcerations. There is still some remaining lymphedema of the forefoot owing to former circular ulceration, with loss of lymph drainage vessels.

Discussion

Despite recent advances in clinical practice, many wounds involving vital structures such as tendons, nerves, bones, or major blood vessels are characterized by delayed healing and remain difficult to manage. On the lower extremity, these wounds may result from traumatic injury, diabetes, peripheral vascular disease, and complications following surgery, rheumatoid arthritis, congestive heart failure, arterial or venous ulcers, lymphedema, and many other conditions that compromise circulation. More than 2 million of the estimated 14 million Americans living with diabetes will develop foot ulcers at some time. The causes of such diabetic foot ulcers are known to be multifactorial. Impaired circulation, loss of sensation, and impaired immune response are major contributing factors. Local problems such as calluses, deformed nails, inadequate hygiene, and poorly fitting footwear also play an important role in these individuals. In the United States, more than 67,000 patients with diabetic foot ulcers require surgical amputation each year, necessitating long and costly rehabilitation. For many, mobility and independence are severely affected, permanently impairing their quality of life.

If radical surgical débridement has resulted in exposure of structures such as bones, tendons, nerves, or joints, plastic surgical techniques may be required to close the wound or to salvage the affected extremity. Therapeutic options include skin grafting procedures, local flaps, or transplantation of healthy vascularized tissue from a distant site (free flaps) using microsurgical techniques. There is no doubt that surgically transferred flaps provide optimal soft tissue coverage. Therefore, in recent years, microsurgical flap coverage of exposed bones, joints, or

tendons in the lower extremity has become the most popular method of reconstruction. If the patient has sufficient perfusion of the posterior tibial artery, the procedure can be straightforward and should have a failure rate of less than 5%. If no appropriate vessels are available, a combined approach of simultaneous revascularization and free flap surgery is a possible solution.²⁴ However, microsurgically transferred free flaps are long procedures that require unaffected recipient vessels in the lower leg and may cause some morbidity at the donor site.

On the other hand, vacuum therapy or TNP therapy has been established in a variety of problem wounds in the lower and upper extremities.^{1-4,6,8-11,14,16,25-37} The recently introduced technique of TNP therapy applies a negative pressure at the surface of the wound and has been developed to overcome some well-known difficulties in complicated wounds. Especially in situations of exposed vital structures, where direct split-thickness skin grafts are not an option (such as bone, tendons, nerves, vessels, and joints), this modality was shown to be very efficient.^{12,38,39} The effect of TNP on dermal perfusion was thought to be the principal mechanism of action of this therapy. However, although several studies have shown significant increases in blood flow in both clinical and experimental models, this may well be secondary to mechanical, deformational changes on the matrix and the vasculature residing within this.

Our clinical examples of chronic lower extremity wounds with exposed bones and tendons that had previously been refractory to therapy show that TNP application may well be used to heal soft tissue wounds completely or to prepare such complex wounds for a minor surgical intervention with greater chances for a successful outcome. In the future, the combination of tissue-engineered tools with TNP may also add new perspectives to this therapeutical challenge.⁴⁰⁻⁴⁴ In all cases described herein, the affected extremities were primarily salvaged and imminent amputation was avoided, although all of these patients had considerable concomitant systemic or arterial occlusive diseases.

Major amputations of the lower extremity significantly influence quality of life and sometimes life expectancy as well. There are no valid studies available that directly compare quality of life following amputation of the lower leg versus surgically reconstructed extremities. It is also extremely difficult to extract valid data from patients whose legs were salvaged using different techniques (TNP, vascular surgery, flap surgery, skin grafting). We learned from our patients that the salvaged extremity, although not completely functional, allowed for some mobility, and

these patients unanimously rated the quality of life at least “fair.” Therefore, we postulate that salvage of extremities using TNP techniques improves quality of life. There is also a lack of studies that directly compare total costs for treatment of patients with amputation of the lower extremity versus reconstruction using TNP dressings. However, it is well known that major amputations cause high costs during initial treatment and rehabilitation. Transtibial amputations owing to “nondiabetic” diseases, for example, accounted for more than \$74,000 (US) within the first year in 1996.⁴⁵ Unfortunately, direct and indirect costs significantly vary between different health care systems. Therefore, an efficient comparative cost analysis requires not only a large and standardized collective of patients but also valid and profound information on the local health care system. Although these data are not available, so far we assume that salvage of extremities even in critically ill patients is at least cost-efficient in comparison with major amputations.

There is no doubt, of course, that one should aim for revascularization or therapeutic angiographic intervention whenever possible to optimize blood flow in the lower extremity. However, when this is not feasible, as in our patient population, even in poorly perfused lower extremities with no healthy recipient vessels for free flap transfer, surgical débridement followed by vacuum therapy with the V.A.C. device can apparently induce granulation tissue. The latter eventually covers the exposed bone under the influence of TNP. Once granulation tissue has grown over the bone, a simple split-thickness skin graft can be transplanted and secured with the help of a VAC. A similar effect has been reported by DeFranzo and colleagues, who observed that even several exposed osteosynthetic hardware plates had been covered successfully by VAC mobilization of skin without muscle or by granulation tissue and skin grafts generated as a result of the treatment.³⁸ Contrary to our study, their patients were not critically ill. These authors mentioned, however, that poorly fitting plates or loose screws in unhealthy bone cannot be reliably covered by VAC therapy and that free flap cover instead of sponge placement is still required in many wounds of the lower extremity. From their findings, it had been concluded that large superficial exposed plates and large areas of exposed and damaged bone, with extensive muscle and skin loss, are not proper candidates for this therapy. On the other hand, our experiences and the previously published observations seem to justify the treatment of at least smaller areas of exposed bone besides the larger soft tissue defects in selected patients when other options are not feasible.³⁹

Because this new treatment modality seems to contradict our classic observations that exposed bones always need a well-vascularized soft tissue flap to heal at all and to salvage the afflicted extremity, one might speculate that a possible change of paradigms and treatment algorithms⁴⁶—at least in such desperate cases as reported here—could enrich the therapeutic armamentarium to deal with this problem entity of these unfortunate elderly patients.

Acknowledgment

The authors want to thank Prof. Werner Hohenberger for his support, in recognition of his anniversary.

References

1. Loos B, Kopp J, Hohenberger W, Horch RE. Post-malignancy irradiation ulcers with exposed alloplastic materials can be salvaged with topical negative pressure therapy (TNP). *Eur J Surg Oncol* 2007;33:920–5.
2. Strecker T, Feyrer R, Horch RE, et al. Simultaneous heart valve replacement and reconstruction of the radiation-damaged chest wall with a delayed vertical rectus abdominis myocutaneous flap. *J Thorac Cardiovasc Surg* 2006;132:980–1.
3. Seyhan H, Kopp J, Polykandriotis E, Horch RE. [Vacuum-assisted closure as temporary coverage in the “problem zone hand”]. *Zentralbl Chir* 2006;131 Suppl 1:S33–5.
4. Schipper J, Ridder GJ, Maier W, et al. Laryngotracheal reconstruction using prefabricated and preconditioned composite radial forearm free flaps: a report of two cases. *Auris Nasus Larynx* 2007; 34:253–8.
5. Schipper J, Leffler M, Maier W, et al. [Reconstruction of tumor induced defects in head and neck surgery with individualized prefabricated three dimensional flaps with the use of continuous vacuum therapy]. *Zentralbl Chir* 2006;131 Suppl 1:S141–5.
6. Polykandriotis E, Kneser U, Kopp J, Horch RE. [Modified gloving technique for vacuum therapy in the hand]. *Zentralbl Chir* 2006; 131 Suppl 1:S36–9.
7. Morykwas MJ, Simpson J, Pungner K, et al. Vacuum-assisted closure: state of basic research and physiologic foundation. *Plast Reconstr Surg* 2006;117:121S–6S.
8. Loos B, Kopp J, Kneser U, et al. [The importance of vacuum therapy in the treatment of sternal osteomyelitis from the plastic surgeons point of view]. *Zentralbl Chir* 2006;131 Suppl 1:S124–8.
9. Kopp J, Bach AD, Kneser U, et al. [Use of vacuum therapy in a huge arterialized venous flap to reconstruct a complete avulsion of a thumb]. *Zentralbl Chir* 2006;131 Suppl 1:S3–6.
10. Kopp J, Bach AD, Kneser U, Horch RE. [Application of V.A.C.-therapy during plastic surgical treatment of a bifocal Marjolin ulcer]. *Zentralbl Chir* 2006;131 Suppl 1:S29–32.
11. Kneser U, Leffler M, Bach AD, et al. [Vacuum assisted closure (V.A.C.) therapy is an essential tool for treatment of complex defect injuries of the upper extremity]. *Zentralbl Chir* 2006;131 Suppl 1:S7–12.

12. Dedmond BT, Kortesis B, Pungner K, et al. Subatmospheric pressure dressings in the temporary treatment of soft tissue injuries associated with type III open tibial shaft fractures in children. *J Pediatr Orthop* 2006;26:728–32.
13. Banwell P, Teot L. Topical negative pressure (TNP): the evolution of a novel wound therapy. *J Tissue Viability* 2006;16:16–24.
14. Molnar JA, Simpson JL, Voignier DM, et al. Management of an acute thermal injury with subatmospheric pressure. *J Burns Wounds* 2005;4:e5.
15. Kopp J, Strand V, Bach AD, et al. Vacuum application increases therapeutic safety and allows intensified local radiation treatment of malignant soft-tissue tumors. *Strahlenther Onkol* 2005;181:124–30.
16. Horch RE, Gerngross H, Lang W, et al. [Indications and safety aspects of vacuum-assisted wound closure]. *MMW Fortschr Med* 2005;147 Suppl 1:1–5.
17. Argenta LC, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg* 1997;38:563–76; discussion 577.
18. Grimm A, Dimmler A, Stange S, et al. Oxygenation in irradiated tissue is altered by topical negative pressure therapy. *Strahlenther Onkol* 2007;182:15–9.
19. Walgenbach KJ, Voigt M, Andree C, et al. Management of hypovascularized wounds not responding to conventional therapy by means of free muscle transplantation. *Vasa* 2001;30:206–11.
20. Argenta LC, Morykwas MJ, Marks MW, et al. Vacuum-assisted closure: state of clinic art. *Plast Reconstr Surg* 2006;117:127S–42S.
21. Morykwas MJ, Falser BJ, Pearce DJ, Argenta LC. Effects of varying levels of subatmospheric pressure on the rate of granulation tissue formation in experimental wounds in swine. *Ann Plast Surg* 2001;47:547–51.
22. Morykwas MJ, Hills H, Argenta LC. The safety of intravenous fluorescein administration. *Ann Plast Surg* 1991;26:551–3.
23. Walgenbach KJ, Riabikhin AW, Andree C, et al. Induction of angiogenesis following vacuum sealing. *J Wound Healing* 2000;5:9–10.
24. Horch RE, Horbach T, Lang W. The nutrient omentum free flap as a new tool in vascular surgery: revascularization and extremity salvage with minimally-invasively harvested microsurgical omentum maius flap connected to multiple sequential autologous bypasses in severe arterial ulcers of the lower leg. *J Vasc Surg* 2007;45:80–4.
25. Carson SN, Overall K, Lee-Jahshan S, Travis E. Vacuum-assisted closure used for healing chronic wounds and skin grafts in the lower extremities. *Ostomy Wound Manage* 2004;50:52–8.
26. Dedmond BT, Kortesis B, Pungner K, et al. The use of negative-pressure wound therapy (NPWT) in the temporary treatment of soft-tissue injuries associated with high-energy open tibial shaft fractures. *J Orthop Trauma* 2007;21:11–7.
27. DeFranzo AJ, Marks MW, Argenta LC, Genecov DG. Vacuum-assisted closure for the treatment of degloving injuries. *Plast Reconstr Surg* 1999;104:2145–8.
28. Horch RE. [Basics foundation and results of the vacuum therapy in the reconstructive surgery]. *Zentralbl Chir* 2004;129 Suppl 1:S2–5.
29. Jones SM, Banwell PE, Shakespeare PG. Advances in wound healing: topical negative pressure therapy. *Postgrad Med J* 2005;81:353–7.
30. Karl T, Modic PK, Voss EU. Indications and results of VAC-therapy treatment in vascular surgery—state of the art in the treatment of chronic wounds. *Zentralbl Chir* 2004;129:74–9.
31. Kneser U, Bach AD, Polykandriotis E, et al. Delayed reverse sural flap for staged reconstruction of the foot and lower leg. *Plast Reconstr Surg* 2005;116:1910–7.
32. Kopp J, Bach A, Loos B, et al. [Use of vacuum therapy during defect coverage of the upper extremity with microsurgically grafted arterialized venous flaps]. *Zentralbl Chir* 2004;129 Suppl 1:S82–4.
33. Leffler M, Kneser U, Bach AD, et al. [Vacuum-assisted closure (V.A.C.) of disastrous wound conditions in Madelung disease]. *Zentralbl Chir* 2006;131 Suppl 1:S15–8.
34. Marathe US, Sniezek JC. Use of the vacuum-assisted closure device in enhancing closure of a massive skull defect. *Laryngoscope* 2004;114:961–4.
35. Schipper J, Klenzner T, Arapakis I, et al. [The transverse rectus abdominis muscle (TRAM) flap. A “second defensive line” in microvascular reconstructions of defects in the head and neck area]. *HNO* 2006;54:20–4.
36. von Gossler CM, Horch RE. Rapid aggressive soft-tissue necrosis after beetle bite can be treated by radical necrectomy and vacuum suction-assisted closure. *J Cutan Med Surg* 2000;4:219–22.
37. Webb LX, Laver D, DeFranzo A. Negative pressure wound therapy in the management of orthopedic wounds. *Ostomy Wound Manage* 2004;50:26–7.
38. DeFranzo AJ, Argenta LC, Marks MW, et al. The use of vacuum-assisted closure therapy for the treatment of lower-extremity wounds with exposed bone. *Plast Reconstr Surg* 2001;108:1184–91.
39. Nugent N, Lannon D, O'Donnell M. Vacuum-assisted closure—a management option for the burns patient with exposed bone. *Burns* 2005;31:390–3.
40. Polykandriotis E, Horch RE, Arkudas A, et al. Intrinsic versus extrinsic vascularization in tissue engineering. *Adv Exp Med Biol* 2006;585:311–26.
41. Kopp J, Seyhan H, Muller B, et al. N-Acetyl-L-cysteine abrogates fibrogenic properties of fibroblasts isolated from Dupuytren's disease by blunting TGF-beta signalling. *J Cell Mol Med* 2006;10:157–65.
42. Kneser U, Schaefer DJ, Polykandriotis E, Horch RE. Tissue engineering of bone: the reconstructive surgeon's point of view. *J Cell Mol Med* 2006;10:7–19.
43. Kneser U, Polykandriotis E, Ohnolz J, et al. Engineering of vascularized transplantable bone tissues: induction of axial vascularization in an osteoconductive matrix using an arteriovenous loop. *Tissue Eng* 2006;12:1721–31.
44. Horch RE. Future perspectives in tissue engineering. *J Cell Mol Med* 2006;10:4–6.
45. Dillingham TR, Pezzin LE, Shore AD. Reamputation, mortality, and health care costs among persons with dysvascular lower-limb amputations. *Arch Phys Med Rehabil* 2005;86:480–6.
46. Horch RE. [Changing paradigms in reconstructive surgery by vacuum therapy?]. *Zentralbl Chir* 2006;131 Suppl 1:S44–9.