# INTEGRATION OF HYPERBARIC OXIGEN, VACUUM ASSISTED CLOSURE THERAPY AND MICROSURGICAL RECONSTRUCTION IN THE TREATMENT OF COMPLEX AND CONTAMINATED UPPER LIMB INJURIES

M. RICCIO, P.P. PANGRAZI, A. CAMPODONICO, A. MARCHESINI, A. BERTANI

Hand Surgery and Microsurgery Unit, Department of Plastic and Reconstructive Surgery, Ancona University School of Medicine, Ancona Teaching Hospital, Italy

## SUMMARY

**Purpose:** The treatment of severe wounds of the extremities characterized by large post traumatic tissue loss represents a clinical problem difficult to resolve. **Materials and method:** The authors present their experience based on a combined treatment by medical support methods like Hyperbaric Oxygen (HBO) and Vacuum Assisted Closure Therapy (VAC) and microsurgical reconstruction of the limbs, within a precise therapeutical protocol. **Result:** The use of this protocol in the appropriate times and ways has allowed to successfully treat severe post-traumatic sequelae of the upper limb. **Conclusion:** Avoiding delayed healing typical of these pathologies, both on the donor site of the flap and on the repaired area, or an unsuitable microsurgical reconstruction for the limbs, allowing a satisfactory morpho-functional restoration and a reduction of the hospitalization period. **Riv Chir Mano 2006; 3: 271-279** 

#### **KEY WORDS**

Free flaps, limb injury, post-traumatic wounds, HBO therapy, VAC therapy

## Introduction

In the treatment of severe lesions of the upper limbs due to crush injuries microsurgical repair methods can be supported by therapies that lead to a quick ad complete resolution of the clinical situation.

There is no doubt that the free tissue transfer by the use microsurgical techniques is now routine for the salvage of traumatized extremities while the transplant of well-vascularized tissue on the site of lesion, after the excision "en bloc" with the ulcer, of all the distrophic tissue around it which prevents healing (1-3).

As a matter of fact this method represents the best treatment in acute and severe traumas of the

upper limbs where large exposition of vascular and nervous structures and bone fractures are involved.

In these cases, but with wounds uncontaminated by exogenous material, exists the indication of large debridment of devitalized areas around the lesion and coverage by free flap within 72 hours from trauma (4, 5).

On the contrary, in severe traumas of the upper limbs contaminated by mineral oils, ground and vegetable cleis or material from the asphalt sometime coming from road traumas it is compulsory to clean the site of trauma before the microsurgical coverage avoiding the risk of serious infection or septic pseudoartrosis that could undermined the success of the reconstruction procedure.

Corrispondence: Dr. Michele Riccio, Clinica di Chirurgia Plastica e Ricostruttiva, Università Politecnica delle Marche - Azienda Ospedaliero Universitaria "Ospedali Riuniti di Ancona", Via Conca 71 - 60020 Torrette di Ancona - Tel. 0039 071 5963484 - 0039 071 5963485 - Fax. 0039 071 5963481 - E-mail: michriccio@libero.it

In these cases it seems to be opportune to differ the reconstructive time employing during this period all the medical support at the disposal of the therapy (HBO, VAC therapy, specific antibiotic therapy) and any further repeated debridment to clean the site of the lesion (5-8).

However, it sometimes happens that the "Zone of Injury", caused by the inflammatory response of the soft tissue around the ulcer, isn't so evident making difficult the radical treatment that should include debridement of all devitalized, distrophic and contaminated tissue around the ulcer (5, 9).

So the radical exeresis could involves excessive demolition which is difficult to repair, especially in the limbs, even with microsurgery procedures because the real extension of the zone of injury is larger than the visible one.

As a matter of fact, whenever the transfer of the free flap does not allow to entirely replace the distrophic tissue around the ulcer, either because of its size or because the presence of areas of devitalized tissue around and below the ulcer makes it difficult to mark the boundaries macroscopically, some inevitable sequelae are foreseable like local infections, wound diastasis, fistolae, and, at a later stage, omologous ulcerative lesions in the anatomical areas adjacent to those which have been repaired, which usually require multiple surgical procedures (10).

In our experience we have observed that in severe and wide lesions of the upper limbs, microsurgery procedures can be successfully combined, after debridement, with Hyperbaric Oxygen Therapy (HBO), Vacuum Assisted Closure Therapy (VAC) and selective antibiotic therapy whose effect is to limit the extension of the area to be repaired, improve the trophism of the chronically inflammed tissue around the ulcer and create the conditions most suitable for the implant of the free flaps.

#### **MATERIALS AND METHODS**

## Patient Database

From 2001 to 2005, 5 patients were treated, suffering from severe large lesions of the skin and the soft tissue of the limbs, with exposure of bone and joint structures in consequence of serious crush injury.

Whatever the origin the treatment consisted of a combination, at different pre-fixed stages, of debridement surgical procedures, medical support methods and definitive surgery by microsurgical free-tissue transfer.

The patients were selected for the combined Medical Support Methods and Microsurgery protocol according to the following criteria:

- severe crush injury of the limbs with large tissue loss;
- 2. massive necrosis areas 2-3 days after injury;
- 3. deep post-traumatic ulcers with exposure of joint, bone and tendon structures;
- 4. wide and deep wounds, contamined by exogeneous material, with severe bacterial infections;
- 5. large distrophic tissue around the ulcer tending to become necrotic and ulcerous;
- 6. no chance of spontaneous repairing;
- 7. repeated unsuccessful attempts to repair the ulcer with traditional surgical procedures;
- 8 possibility to maintain or recover ambulation with the repairing treatment.

The group treated includes 5 patients who presented ulcers due to crush injury in all cases with tissue loss and exposure of bones and tendons.

All of them were considered for a three-phase protocol: debridement, Medical Support Methods and microsurgical procedures.

#### **MEDICAL SUPPORT METHODS**

#### HBO Treatment

In all the cases in which HBO was chosen, a minimum of 10 sessions at 2.5 ATA was necessary; in each of them, once the treatment pressure level was reached with air, 100% oxygen was administered through a hermetic mask for 30 and 20 minutes with an interval of 5 minutes' air breathing and then returning to normal atmospheric pressure at the speed of 1 meter per minute oxygen breathing. (11, 12) In this protocol HBO treatment was always preceded by a radical debridement of the ulcer and the distrophic tissue around it and came before the definitive repairing procedure usually consisting of the transplant of a free flap.

## Vacum Assisted Closure (VAC) Therapy

Vacuum assisted closure terapy is designed to promote the formation of granulation tissue for faster healing in the wound beds of patients with acute and chronic wounds and we have used this device both in devitelized and infected tissue.

VAC device consists of a non-collapsible, opencell, polyurethane sponge with embedded vacuum tubing, a vacuum pump, and transparent adhesive dressing and the wound management technique exposes the wound bed to negative pressure by way of a closed system.

Theoretically, the method acts by removal of excess tissue fluid from the extravascular space, which lowers capillary after-load and thereby promotes the microcirculation and the proliferation of exuberant granulation tissue during the early stages of inflammation (13, 14).

#### Microsurgical Procedures

In all the patients in whom the definitive repairing of the ulcer was obtained through microsurgical procedures, the transfer of the free flap was preceded by a routine vascular scan of the limbs involved in the pathology.

Limb perfusion was always assessed clinically, while the site of the potential microvascular anastomosis needs a meticulous evaluation with Doppler mapping that can give reliable information without the need for routine angiography of the recipient site (15).

Particularly the "Directional Doppler-flow" allows to check the quality of the blood flow, while eco-doppler visualizes the atherosclerotic areas responsible for hemodynamic problems.

Such an accurate study allows the choice of the best recipient site for anastomoses, drastically reducing the risk of failure. In our opinion an arteriogram should be considered if the zone of injury is wide and in the region of potential anastomoses (5).

The timing of microsurgical tissue transplantation was delayed of 10-15 days in accordance with our "Combined Protocol Therapy".

4 free flaps were transplanted for the treatment of the ulcers, of which 2 fasciocutaneous flaps and 2 muscular flaps and 1 island flap.

We used:

1 radial fasciocutaneous flaps from contralateral forearm;

1 Latissimus Dorsi muscular flap combined with Serratus Anterior muscular;

1 Serratus Anterior muscular flaps;

1 Becker's ulna flap;

1 Antero-lateral Tight perforator flap

## **CASE REPORT**

C.D., 8, was treated for a severe avulsion and crush injury of the left arm and forearm following a car accident.

This lesion caused also the fracture-dislocation of the elbow which the rupture of biceps tendon, the interruption of the brachial artery, and the loss of median nerve for 10 cm (Fig. 1, 2)



Figure 1. Severe avulsion and crush injury of the left arm and forearm with fracture-dislocation of the elbow, the rupture of biceps tendon and the interruption of the brachial artery.



Figure 2. Severe avulsion and crush injury of the left arm and forearm with fracture-dislocation of the elbow, the rupture of biceps tendon and the interruption of the brachial artery.

Angiography showed the interruption of the brachial artery but the clinical evaluation and the Doppler assessment showed a good radial pulse at the wrist and an optime peripheral flow.

So we did't repaire the continuity of the brachial artery toward the artery of the forearm for the growing of an effective collateral circulation for the forearm and the hand.

After the immediate first debridement she was subjected to 25 HBO sessions and further debridments for the extreme contamination by ground and vegetable cleis and for a progressive enlargement of the necrotic area (Fig. 3).

The repairing was undertaken through the transplant of an Antero Lateral Tight perforator flap after 27 days when no signs of infection were found. The arterial anastomoses was performed



Figure 3. After immediate debridement and an exeresis of contaminated teguments the patient was subjected to 25 HBO sessions.



Figure 4. Repairing and reconstruction of the elbow joint using a graft of fascia lata and the median nerve by means of a graft of 10 cm of autologous bilateral sural nerve.

end-to-end between brachial artery and the pedicle artery of the ALT perforator flap, as well as the venous anastomoses was performed between the comitantes veins (Fig. 5).

In the same operative section the repairing of the elbow fracture was performed as well as the artroplasty of the elbow joint using a graft of Fascia Lata and the reconstruction of the median nerve using a bilateral graft of sural nerve (Fig. 4).

The resurfacing of the forearm was completed by Engineered Tissue by colture of autologus fibroblasts and keratinocites in order to limit the extension of scar debit (16) (Fig. 6).



Figure 5. Harvesting the Antero Lateral Tight flap transferred by microsurgical anastomoses on the brachial artery.



Figure 6. Post-operative result. Engineered Tissue used for skin resurfation around the free-flap in order to reduce the scar debit.

Six months' follow-up shows no sign of tissue distrophy and the covering tissue appears trophic and well vascularized.

The functional ability of the upper limb is improving (Fig. 7-10). The patient is waiting the last operative procedure to gain the active flexion of the



Figure 7. Active extension but passive flexion of the elbow.



Figure 8. Active extension but passive flexion of the elbow.



Figure 9. Active flexion and extension of the fingers.



Figure 10. Active flexion and extension of the fingers.

elbow by the transposition of functional Latissimus Dorsi myocutaneous flap (17, 18).

#### RESULTS

All the patients treated with medical support methods and microsurgery have well tolerated the therapy without developing any problem in any of its phases.

Particularly, no form of immediate intolerance to HBO has been registered, nor have sistemic sequelae appeared during the follow-up period.

The combined protocol (medical support methods and microsurgery) has allowed the complete and quick resolution of the clinical problem in the case of large lesions difficult to treat by traditional non-microsurgical procedures, creating the anatomic conditions most suitable for the flap transplant and therefore reducing the incidence of sequelae.

HBO, accelerating the healing process, makes it possible to transplant the flaps on recipient well vascularized trophic beds and favours the taking of the free skin grafts on the donor sites.

In particular, in our experience any time we used HBO treatment in accordance with the combined protocol after the debridement and before the definitive wound management by free-tissue transfer, no complication has occurred at the recipient site and a considerable reduction of the chronic phlogosis around the lesion has been observed. A well vascularized tissue bed received the free-flap.

## DISCUSSION

The treatment of the mangled extremities still presents a reconstruction challenge difficult to resolve and sometimes an emotional problem, whose sequelae demanded, in a recent past, the frequent amputation of the limb when an insufficient blood inflow determined the progressive deterioration of the ulcers (10).

The massive extremities injury following crush high energy traumas characterized by massive necrosis of wide soft tissue areas and infections with large exposure of bone fractures and joint structures was a main indication for the limb amputation (19).

There is no doubt that in all these cases microsurgery procedures allowing the transfer of viable autologous tissue and, where necessary, restablishing continuity between the main vessels, enable the en bloc reconstruction of the morpho-functional unit without size limits and an aesthetic and functional recovery of the limb (9, 20), sometimes aclowing surgeons to salvage extremities in patients who would formerly have required amputation (1-3).

Also in less wide lesions microsurgery procedures are preferred to traditional ones because of a smaller number of sequelae and deficits at a local level. The most important factors influencing the microsurgical reconstruction of the limbs are:

- the selection of free-flap;
- the timing for the microsurgical reconstruction of the extremities.

Primarly, the choice of the flap depends to the recipient site requirements or the type of tissue deficency (isolate or composite replacement) and its volume.

The lengh of vascular pedicle should allow anastomoses in a "safe zone" far from the "zone of injury", where the inflammatory response of the soft tissue around the wound increases the vascular friability and the perivascular scar tissue, causing an higher rate of microvascular thromboses expecially localized in the veins (21).

But a greater factor, in prognostic sense, is the timing for the microsurgical reconstruction of the limbs that emphasizes the importance of radical debridment and early tissue coverage within the first 72 hours in the treatment of high energy traumas (4).

But frequently the massive soft tissue necrosis and the contaminated surrounding tissue require several debridments to obtain a good prognosis in terms of decreased risk of in fection and flap survival (22).

In these severe traumatic ulcers of the limbs, the key factor considered in the timing of the microsurgical reconstruction is the "risk of infection" in presence of exposed "vital structures".

So on the base of the ideal "reconstructive ladder" the surgeon should decide to perform the "primary coverage" by a free flap only when the bacterial status of the wound allowes the microsurgical reconstruction without risk of infection, within 7-15 days after the initial debridment using that period to prepare the recipient-site by medical support such as HBO or VAC therapy (5).

Besides, also the use of free muscular flaps, although it is theoretically the best repairing procedure for infected and ischemic wounds (23, 24), also with chronic osteomielitis because provides coverage for the debrided bone and soft tissue, obliterate dead space, as well as improve vascularity and enhance leukocyte function (24-26), frequently are complicated with high number of local sequelae, as the difficult taking of skin grafts on the transplanted muscle.

The consequence of all this is often an unsatisfactory recovery of the limb function. From this point of view medical support methods tretment has considerably improved prognosis in the above cases.

The effect of HBO therapy seems to be particularly dramatic in reducing the phyisiopathologic problems responsible for cutaneous distrophic diseases which rarely heal spontaneously.

The healing process of a wound is oxygen-dependent, as shown by the fact that all the wounds that do not heal are hypoxic and more prone to infections (27-29).

Wound healing takes place thanks to macrofagi, fibroblasts and collagen synthesis.

Hypoxia slows down the synthesis and metabolism of collagen proteins through the inhibition of proline and lisine hidroxilation.

In this condition the collagen produced appears to be less stable and less resistant to tension, the lack of idroxiproline and hidroxilisine being an obstacle to the formation of intermolecular crosslinks (30).

Moreover, although the healing process is triggered by hypoxia, the migration and intervention of the macrofagi and fibroblasts is inhibited by  $pO_2$ values less than 10 mmHg at wound level.

In this microenvironment the production of new angiogenesis factors by the macrofagi is inhibited, in consequence of scarce granulation tissue (31, 32).

This effect can be reversed reaching optimal levels of neoangiogenesis and growth factors by the macrofagi at a  $pO_2$  of 15-20 mmHg (33).

Another serious problem is the bacterial infection of these ulcers which can not only interrupt the healing process but also cause a worsening of the distrophy and the widening of the ulcer.

With HBO treatment an adequate partial pressure of  $O_2$  on the distrophic ulcer is reached, allowing the oxidative killing responsible for the respiratory bust by polimorphonucleates, as well as an indirect bactericidal action through the macrofagi. All these events are oxygen-dependent. HBO treatment at 2.8 ATA increases 10-13 fold the quantity of oxygen transported per blood unit versus a condition of normal atmospheric pressure and this because the oxygen can be physically diluted in the plasma and more easily carried to the sites of tissue distrophy and ischemy around the ulcer or to the sites with blood flow obstructions (11). In this physiopathological condition HBO at 2.5 ATA interrupts the strong relationship between ischemia and edema on the distrophic tissue around the lesion, which in turn aggravate tissue distrophy owing to the progressive increase of intercapillary distance (34).

The mechanism through which HBO works is based on a 20% reduction of the blood flow in the limb which is however balanced by an increase in the content of oxygen per blood unit. This means a progressive improvement of the microcirculation through the decrease of the pressure in the capillary interstice (35, 36).

This effect proves particularly useful in correcting the iperflow sindrome following the anomalous opening of arterio-venous shunts of a neuropatic origin, as happens in patients with diabetes (37, 38).

In conclusion, HBO main action manifests itself in the injured tissue maintaining viability in the hypoxic phase, preventing infections and enhancing healing and the recovery of the function through a greater diffusion of  $pO_2$  in the stasis areas of the microcirculation.

As regards the necrotic tissues, HBO, through the activation of specific and aspecific cellular cleaning mechanisms, which are more effective at tissue levels of 30 mmHg of  $pO_2$ , hastens the demarcation of the necrotic area and prevents infection from passing to ischemic tissues.

In our experience the HBO has been the most widely used medical support method while our experience with VAC therapy is much less which was only employed as complementary method or whenever it was not possible to use HBO due to patient's problems linked to chamber compression.

We used VAC device only in two cases of crush injury of the upper limb. Suction (75-125 mmHg)

was continous for the first 48 hours, then intermittent (2 min on, 5 min off) (13).

This initial wound management technique has exposed the contaminated wound bed and its deep bone structures to negative pressure by way of closed system.

This system permits the removal of edema fluid from the extravascular space, thus eliminating an extrinsic cause of microcirculatory stasis and improving blood supply during this phase of inflammation (14).

After the formation of granulation tissue and when systemic signs of infection and quantitative cultures indicated the resolution of local infection, microsurgical procedure for wound colsure were performed.

# CONCLUSIONS

As far as our experience is concerned, it seems that the combination of medical support methods treatment and microsurgery procedures represents the right solution for the difficult treatment of large serious wounds of the extremities due to acute injury in which the risk of infection is high either for contamination of exogenous materials or for the amount of non-viable tissue around it.

Therefore in these cases and in the cases which have come under our observation with an ulceration already post-traumatic it is necessary to delay the treatment from 7 to 14 days to permit the cleaning of the "zone of injury".

That's when we propose a protocol in 3 phases:

- 1. radical surgical debridment, multiple if necessary;
- 2.10 seats of HBO or alternatively VAC therapy;
- 3. microsurgical reconstruction with well vascularized tissue.

From this point of view the combination of medical support methods before the definitive microsurgery tretament of severe and infected wounds allows to hit the following targets:

1. Limitation of the exeresis area of the distrophic tissue around the ulcer through HBO therapy, after the debridement, which makes the ischemic border line tissue viable again, interrupting the progressive development of necrosis on the boundaries of the debridement. On a clinical plan, this allows a precise macroscopic demarcation of non-viable tissues.

- 2. Enhancement of wound detertion and reparative granulation tissue formation of the recipient bed of severe and infected wound through HBO or VAC therapy
- 3. Radical exeresis of non-viable tissues, which are now well demarcated, and functional and aesthetic reintegration, no matter the size, of the tissue loss through microsurgical transplant of a free flap.
- 4. Elimination of local sequelae both on the recipient and the donor site of the flap, through adequate HBO therapy.

The use of HBO and VAC therapy combined with a delayed microsurgical reconstruction, in a precise protocol, for the treatment of severe wounds of the limbs, allows to save injuried limbs improving the functional outcome.

# References

- 1. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma 1984; 24: 742-6.
- Lange RN, Bach AW, Hansen ST jr, et al. Open tibial fractures with associated vascular injuries: prognosis for limb salvage. J Trauma 1985; 25: 203-8.
- 3. Howe HR jr, Poole GV jr, Hansen KJ, et al. Salvage of lower extremities following combined orthopaedic and vascular trauma: a predictive salvage index. Am Surg 1987; 53: 205-8.
- Lai CS, Lin SD, Yang CC, Chou CK, et al. Limb-salvage of infected diabetic foot ulcers with microsurgical free-muscle transfer. Ann Plast Surg 1991; 26: 212-20.
- 5. Godina M. Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg 1986; 78: 285-92.
- Heller LS, Scott Levin. Lower extremity microsurgical recostruction. Plast Reconstr Surg 2001; 108: 1029-41.
- Strauss MB. Crush injury and other acute traumatic peripheral ischemias. In Kindwall EP (Ed): Hyperbaric Medicine Practice - Best Publishing Company; 1995: 525-49.

- Hoffman RD, Adams BD. The role of antibiotics in the management of elective and post-traumatic hand surgery. Hand Clin 1998; 14: 657-66.
- 9. Barbieri RA, Freeland AE. Osteomyelitis of the hand. Hand Clin 1998; 14: 589-603.
- Oishi SN, Levin LS, Pederson WC. Microsurgical management of extremity wounds in diabetics with peripheral vascular disease. Plast Reconstr Surg 1993; 92: 485-92.
- Hammarlung C. The physiologic effects of hyperbaric oxigen. In Kindwall EP (Ed): Hyperbaric Medicine Practice -Best Publishing Company; 1995: 17-32.
- Brummelkamp WH, Boerema I, Hoogendijk L. Treatment of clostridial infections with hyperbaric oxygen drenching. A report on 26 cases. Lancet 1963; 1: 235-8.
- 13. Deva AK, Buckland GH, Fisher E et al: Topical negative pressure in wound management. Med J Aust 2000; 173: 128-31.
- Webb LX. New techniques in woundmanagement: vacuum-assisted wound closure. J Am Acad Orthop Surg 2002; 10: 303-11.
- Lutz BS, Ng SH, Cabailo R, et al. Value of routine angiography before traumatic lower-limb recostruction with microvascular free tissue transplantation. J Trauma 1998; 44: 682-6.
- Sefton MV, Woodhouse KA. Tissue engineering. J Cutan Med Surg 1998; 3: S1-18-23.
- 17. Hovnanian AP. Latissimus dorsi transplantation for loss of flexion or extension at the elbow: a preliminary report on technic. Ann Surg 1956; 143: 493-9.
- Zancolli E, Mitre H. Latissimus dorsi transfer to restore elbow flexion. An appraisal of eight cases. J Bone Joint Surg Am 1973; 55: 1265-75.
- Gregory RT ,Gould RJ , Peclet M, et al. The mangled extremity syndrome (M.E.S.): A severity grading system for multisystem injury of the extremity. J Trauma 1985; 25: 1147-50.
- Reicle FA, Rankin KP, Tyson RR, et al. Long-term results of femoroinfrapopliteal bypass in diabetic patients with severe ischemia of the lower extremity. Am J Surg 1979; 137: 653-6.
- Arnez ZM. Immediate recostruction of the lower extremity: an up-date. Cl Plast Surg 1991; 18: 449-57.
- 22. Yaremchuck MJ, Brumback RJ, Manson PN, et al. Acute and definitive management of traumatic osteocutaneous defects of the lower extremity. Plast Reconstr Surg 1987; 80: 1-14.
- Chang N, Mathes SJ. Comparison of the effect of bacterial inoculation in musculocutaneous and random pattern flaps. Plast Reconstr Surg 1982; 70: 1-10.

- 24. Mathes SJ, Feng LJ, Hunt TK. Coverage of the infected wound. Ann Surg 1983; 198: 420-9.
- Mathes SJ, Alpert BS, Chang N. Use of the muscle flap in chronic osteomyelitis: experimental and clinical correlation. Plast Reconstr Surg 1982; 69 (5): 815-29.
- Eshima I, Mathes SJ, Paty P. Comparison of the intracellular bacterial killing activity of leukocytes in muscolocutaneous and random-pattern flaps. Plast Reconstr Surg 1990; 86: 541-57.
- 27. Niinikoski J. Cellular ad nutritional interaction in healing wounds. Med Biol 1980; 58: 303-9.
- 28. Karanfilian RG. The value of laser doppler velocimetry and transcutaneous oxygen tension determination in predicting healing in ischemic forefoot ulceration ad amputations in diabetic ad non-diabetic patients. J Vasc Surg 1986; 4: 511-23.
- Hunt TK. The physiology of wound healing. Ann Emerg Med 1988; 17: 1265-73.
- Chvapil M, Huryc J, Erlichova E. The influence of various tension upon proline hydroxilation and the metabolism of collagenous proteins in skin slices. Z Physiol Chem 1968; 349: 211-7.
- Hunt TK, Niinikoski J, Zderfeld BH, Silver IA. Oxygen in wound healing enhancement: cellular effects of oxygen. Hyperbaric Oxygen Terapy. Davis JC, Hunt TK (Eds) U.M.S. Bethesda Md. 1977: 112.
- Hunt TK, Pai MP. The effect of varyng ambient oxygen tension on wound metabolism ad collagene synthesis. Surg Gynecol Obstetr 1973; 135: 561-71.
- 33. Dvorak HF, Kaplan AP, Clark RAF. Potential function of the clotting system in wound repair. In Clark RAF, Henson PM, Eds: The molecular and cellular biology of wound repair. New York: Plenum Press 1988: 57-85.
- Peirce ECII: Pathophysology, apparatus, and methods including the special techniques of hypothermia and hyperbaric oxygen. In: Extracorporeal circulation for open-heart surgery. Charles c. Thomas, Springfield, IL 1969: 84-8.
- Bird AD, Telfer HB. Effect of hyperbaric oxygen on limb circulation. Lancet 1965; 13: 355-6.
- Schraibman IG, Ledingham I McA: Hyperbaric oxygen and local vasodilation in pheripheral vascular disease. Br J Surg 1969; 56: 295-9
- Boulton AJ, Scarpello JHB, Ward JD: Venous oxygenation in the diabetic neuropathic foot: evidence of arteriovenous shunting? Diabetologia 1982; 22: 6-8.
- Edmonds ME, Roberts VC, Watkins PJ: Blood flow in the diabetic-neuropatic foot. Diabetologia 1982; 22: 9-15.