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Manuscript - The Impact of Ischemia on Limb Replantation

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Abbreviations
FDS – Flexor Digitorum Superficialis
IPC - Ischemic Preconditioning
IRI – Ischemia Reperfusion Injury

Abstract

Traumatic amputations of the extremity are relatively common catastrophic injuries that adversely affect a patient's physical function and wellbeing. This article reviews the current management of amputated limbs and discusses the role of ischemia and the reperfusion processes in its future management. The decision to replant an extremity depends on numerous factors which include, but are not limited to, the time from injury, mechanism of injury, site of injury, patient factors and technical know-how of replantation surgery. Despite the significant progress in most of these aspects over the last decades, the management of the amputate has not significantly advanced. The outcomes of replantation are related to the amount of tissue injury incurred by the amputate and the time without blood supply. To further the optimisation of the amputated extremity and improve the success of replantation, the future of this field relies in the research into both pharmacological post-conditioning and ex vivo perfusion to overcome Ischemic Reperfusion Injury, particularly in proximal injuries.

1. Introduction

Traumatic amputations of the extremity are catastrophic injuries that adversely affect a patient's physical function and wellbeing.[1] In the USA, the risk of amputation injuries is 7.5/100,000 person years rendering it an infrequent but devastating injury.[2] These cases are highly complex surgical emergencies that after careful consideration may undergo replantation - the reattachment of all soft tissues and bone. This is performed using microvascular techniques in a process referred to as revascularisation. Of note, surgical replantation involves prolonged rehabilitation that is also costly to the patient with subsequent time away from work.

The first reportedly successful hand replantation was reported by Malt & McKhann in 1962.[3] This was shortly followed by the first successful thumb replantation carried out by Komatsu & Tamai in 1965.[4] This was regarded as a significant surgical milestone providing evidence that microsurgical replantation is technically feasible which resulted in a temporary exponential growth in the volume of attempted replantations. Despite the stable incidence in amputation injuries over the last two decades, there has been a steady decline in the numbers of attempted replantations.[5] This decreasing trend is attributed to rising health care costs, low reimbursement rates for digit replantation, evolving clinical decision making and the requirement for hand surgeons that possess microsurgical skills.[6-8] Specialised regional microsurgical centers with rehabilitative facilities have been developed in response to managing these complex injuries. Hospitals that frequently manage such patients have better outcomes, with an overall replantation success rate of 70% for the thumb and digits.[9] Nevertheless, the incidence of secondary procedures following replantation reported in the literature is approximately 50% but this can range between 15-80%.[10-19]

1.1. The clinical challenge

The technical know-how of replantation surgery has become more refined since it was first performed over five decades ago. Furthermore, the clinical decision-making has improved in identifying which replantations will provide acceptable functional outcomes.[20] However, one key aspect that has not changed and requires addressing is the management of the amputated part. Once amputated, tissues inherently lose their blood supply resulting in reduced oxygenation to tissues. This causes loss of ATP and dysfunction of ion-dependant membrane channels which result in cell swelling and death.[21] Further ischemic compromise yields an acidic environment with a build-up of lactate and loss in cell calcium. Consequently, the outcomes of replantation are related to the amount of tissue injury incurred and the time without blood supply. For this reason, it is a time dependent emergency. Paradoxically, the restoration of blood flow (reperfusion) incites a further injury to tissues via free radicals. The magnitude of ischemia dictates this response. This article aims to review the current management of amputated limbs to combat these deleterious processes.

2. Pre-Hospital Management of the Amputated Limb

Patients with amputation injuries present directly to their local Emergency Department (Figure 1). An immediate traumatic life support assessment should be performed with referral (and prompt transfer) to a center with microsurgical expertise in extremity replantation.

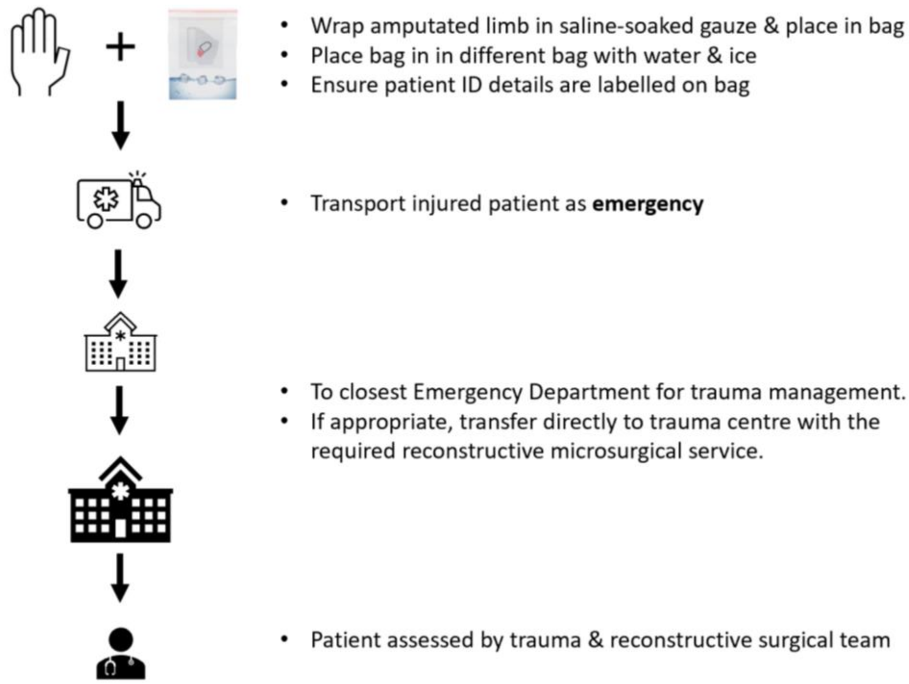

Figure 1. Illustration of the key steps in the journey of a patient with an amputated limb.

The pre-hospital basic management of the amputated limb has not changed since the 1960's. Current practice recommends wrapping the amputated extremity in sterile soaked gauze in a sealed plastic bag. This bag is then kept at 4°C after submerging it in iced water.[22,23] The amputate should not be placed directly on ice as this may cause damage secondary to frostbite.[24] The purpose of these steps is to extend the time before irreversible damage is sustained secondary to anoxia, and this is particularly relevant when the amputate comprises large volumes of muscle, which tolerate ischemia poorly. This is typically the case with proximal limb amputations.[25] Muscle tissue has high metabolic demand and rapidly deteriorates in ischemic conditions, which leads to irreversible myonecrosis.[26]

3. Surgical replantation

The decision to replant a limb depends on multiple factors (Table 1), expertise and surgical maturity.[27,28]

Chung et al. advocate that, considering the improved patient-reported outcomes and long-term functional benefits, when technically feasible, replantation should be attempted in digital amputations involving [29]:

- Three or more digits
- Single finger amputation (excluding thumb) distal to the insertion of the Flexor Digitorum Superficialis insertion (Distal to proximal interphalangeal joint)
- The thumb

Table 1. Relative indications and contra-indications for limb replantation. Abbreviations: Flexor Digitorum Superficialis (FDS).

Relative Indications	**Relative contra-indications**
Thumb amputation	Life threatening injury/ systemically unwell
Single digit amputation distal to FDS insertion	Location of finger injury proximal to FDS
Multiple Digit amputation	Mechanism of injury: Crush / Avulsion
Mid-palmar/hand/ proximal upper limb amputation	Multi-level injury
Pediatric amputation	Significantly prolonged ischemia time
	Patient factors: age, diabetes, smoking, motivation

When replanting an amputated part, the surgeon should ensure that function is maximised and that the predictive outcome is better than that of a prosthesis. The thumb provides 40-50% of hand function and has an essential role in opposition. One should recognise that a thumb with limited movement is more functional than other reconstructive procedures or prosthetics.[30] Multi-digit amputations result in significant functional issues thus in these patients the thumb and middle fingers are prioritised to allow for a pincer grip. An important landmark regarding the level of amputation is the Flexor Digitorum Superficialis (FDS) insertion. There is ongoing debate in the literature regarding replantation of a single digit relative to this level. Evidence suggests that a replanted finger with amputation distal to FDS insertion is associated with limited function and has an overall negative effect on dexterity, especially with a poorly-functioning proximal interphalangeal joint.[31] However, this is often attempted as the function of the replanted finger is enhanced by the additional length even if there is a stiff or fused DIPJ.[32] Consequently, surgical practice varies internationally and by surgeon. In addition, some units across the globe perform microvascular replantations of distal fingertips.[33]

4. Ischemia & Reperfusion Injury

Ischemia is an important predictor of successful replantation.[34] The ischemic process leads to elevated glycolysis, lactic acid production and subsequent intracellular pH reduction.[35] Prolonged ischemia results in a variety of cellular metabolic changes (Figure 2). Ischemia leads to depletion of ATP in individual cells, altering the ionic pump functions and favouring entry of calcium, sodium, and water into it.[21] This process also promotes the expression of pro-inflammatory gene products in the endothelium, whilst repressing protective gene products; thus inducing a cellular state that increases tissue vulnerability to further injury on reperfusion.[36] If the duration of ischemia lengthens beyond a critical point of tolerance, extensive liquefactive necrosis will result.[37,38]

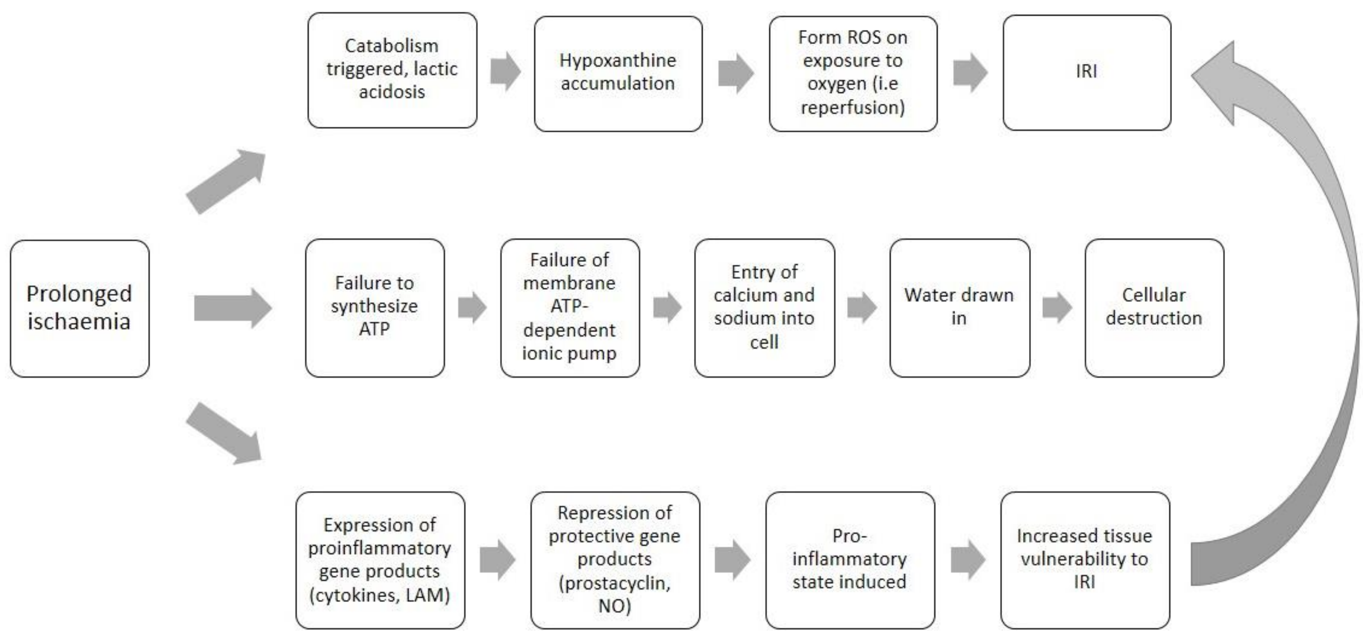

Figure 2. Flowchart illustrating the cellular effects of ischemia. Abbreviations: ATP- Adenosine Triphosphate; IRI- Ischemic Reperfusion Injury; LAM- Lipoarabinomannans; NO- Nitric Oxide; ROS-Reactive Oxygen Species.

Irreversible ischemia reportedly occurs in muscle tissue after 4 hours of warm and 6-8 hours of cold ischemia time.[39] In digital amputations, due to the lack of muscle tissue, replantation is not generally recommended when maximal warm and cold ischemic times exceed 12 hours and 24 hours, respectively.[40] Alternatively, for proximal amputated limbs with high muscle mass, six hours of warm and twelve hours of cold ischemia is maximally advocated. However, the literature suggests that cold ischemia should not influence the decision-making process because this does not compromise amputate survival and functional recovery.[41] For instance, reports include successful replantation of digits at 94 hours of cold ischemia time and hands at 54 hours of cold ischemia time with satisfactory results.[37,38] However, in proximal limb amputations, if this is not promptly replanted, there is an increased risk of life-threatening complications including rhabdomyolysis, myonecrosis and life-threatening IRI, on top of the already detrimental effect of fibrosis and scarring.[42]

Many situations impede replantation within these recommended times but still warrant an attempt, particularly in paediatric patients or occupations that require high manual dexterity. Factors delaying time to replantation include multiple trauma, other life-saving surgery that takes priority, and multiple amputated part replantation.

IRI is a phenomenon that results from the abrupt reperfusion of the ischemic vascular bed that provokes a degree of tissue injury.[43] Its pathogenesis has been studied and described as early as 1965 by Anon et al. who experimented with replantation of totally amputated canine extremities.[44] Acute ischemia reperfusion of a severed limb leads to deleterious local as well as systemic effects by stimulating cytokine activation (specifically TNF- α and IL-6) and simultaneous multiple organ dysfunction. The abrupt reperfusion generates a burst of reactive oxygen species from the vascular endothelial cells in the post-ischemic amputate causing an inflammatory-like response to occur at the onset of reperfusion.[45] Although literature is inconclusive regarding the source of the cytokine production, local production in the reperfused limb seems to be the most likely source, leading to a massive influx of polymorphonuclear leukocytes.[46] The continuous rise in plasma concentration of IL-6 throughout the period of reperfusion, observed by Yassin and his colleagues suggests that reperfusion injury, rather than ischemia, is the stimulus for the cytokine production.[46] This results in endothelial dysfunction,[47] decreased endogenous nitric oxide generation,[48] increased superoxide anion generation,[49] and release of pro-inflammatory cytokines into the interstitial and vascular space.[50] The vascular endothelium has been found to play an important regulatory role. Examples include the control of haemodynamic processes, vascular remodelling, immunity, metabolic functions, and anti- and pro-thrombotic processes.[48,50] The term "arterial insufficiency" has been used to describe the inadequate and lack of uniform perfusion at microcirculatory level as a result of endothelial dysfunction.[51]

IRI may involve not only the ischemic limb being replanted but also induce systemic damage to distant organs, potentially leading to multi-system organ failure. Although a similar risk in cytokine increase is observed postoperatively following major surgery, endotoxemia in the absence of bacterial translocation remains a feature uniquely attributed to the cellular mediators produced locally in the reperfused tissue.[21] Animal experimental studies have shown that the lung is particularly vulnerable to remote ischemia compared to the hepatic and renal systems. Several theories have been postulated, concluding that this may be due to the sequestered pulmonary leukocytes which are activated by the humoral mediators generated in the reperfused tissue. This causes damage by plugging pulmonary capillaries and disrupting their vascular endothelium.[53-55] It is also possible that resident mast cells and macrophages amplify this injury in the lung by producing potent neutrophil chemo-attractants like leukotriene B4, in addition to histamine, serotonin, and platelet activating factor.[55] Other organs frequently involved include the cardiac, renal and gastrointestinal systems.

Clinically, IRI can manifest diversely, ranging from benign transient arrhythmias to fatal multiorgan dysfunction syndrome.[56] The response to IRI varies greatly among individuals, with increased vulnerability in the high risk group.[35] Risk factors for IRI are categorised into fixed and modifiable risk factors. Fixed risk factors include advanced age, male gender, hereditary factors and significant muscle mass. Modifiable risk factors include tobacco smoking, hyperlipidaemia, hypertension, obesity and diabetes mellitus.[21]

There have been many controlled, experimental models which have demonstrated therapeutic strategies – alone or in combination – in the prevention of IRI. This includes ischemic preconditioning, antioxidant therapy, calcium antagonists and leukotriene B4 antagonists to name a few.[57–59] However, these have tended to yield equivocal results in the clinical setting, or have not been approved for human trials. Therefore, as it stands, timely reperfusion of the ischemic limb remains the cornerstone of clinical practice.

Ischemic preconditioning (IPC) refers to adaptive mechanisms that are triggered by brief episodes of ischemia and reperfusion. This protects tissues from the sustained post reperfusion-ischemic injuries that may occur.[60] IPC, however, is not pertinent to unexpected amputated extremities. In such situations, manoeuvres such as intermittent reperfusion or post-conditioning are more relevant.[61,62] Both intermittent reperfusion and ischemic post-conditioning refer to the same concept whereby alternating episodes of reperfusion are employed after a prolonged episode of ischemia, as seen in amputated extremities. Intermittent reperfusion has been shown to attenuate the IRI as seen in IPC although not to the same extent.[61] Subsequently, the term post-conditioning, first reported by Zhao et al.,[62] has been documented as an effective protective strategy in different disciplines and animal models.[65-67]

The future of this field relies upon optimisation of the amputated extremity by addressing the ischemic and reperfusion process particularly in proximal limb amputations. In order to improve ischemia time, temporary catheter shunting can be used in major limb replantation.[66] Studies evaluating ex vivo perfusion with anticoagulated blood and medications including allopurinol and streptokinase have demonstrated prolonged warm ischemia time although these are not common in pre- or intra-operative surgical practice.[67,68] Additionally, the perfusion of the amputate using a modified solution before allowing normal blood to flow has also been explored with promising results.[69] Yet, a randomised multi-center trial has shown no difference among those patients with acute ischemic limbs treated with routine thrombo-embolectomy and normal blood reperfusion and those treated with thrombo-embolectomy and controlled reperfusion (autologous blood mixed with crystalloid solution, with supplemented allopurinol).[70]

5. Conclusion

There is no doubt that for successful replantation surgery to take place an organised network able to promptly manage, refer and transfer patients with these devastating injuries to a high volume center with available microsurgical expertise is essential. Nonetheless, minimal scientific progress in this field has been witnessed to meaningfully improve the care provided to the patients falling victim to such injuries. The principal limiting step is to improve the handling of the amputated part. Research into pharmacological post-conditioning is a possible strategy when combined with ex vivo perfusion to overcome IRI preventing oxygen free radical injury to skeletal muscle, particularly in proximal injuries. Regardless of its promising research, its therapeutic benefits await to be seen.

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7. References

1. Cumberworth J, Kieffer WKM, Harry LE, Rogers BA. Perioperative management of traumatic limb amputations due to civilian trauma: Current practice and future directions. J Perioper Pract. 2015 Dec 1;25(12):262–6.

2. Reid DBC, Shah KN, Eltorai AEM, Got CC, Daniels AH. Epidemiology of Finger Amputations in the United States From 1997 to 2016. J Hand Surg Glob Online. 2019 Apr 1;1(2):45–51.

3. Malt RA, Mckhann CF. Replantation of Severed Arms. JAMA J Am Med Assoc. 1964 Sep 7;189(10):716–22.

4. Komatsu S, Tamai S. Successful replantation of a completely cut-off thumb. Plast Reconstr Surg. 1968;42(4):374–7.

5. Reavey PL, Stranix JT, Muresan H, Soares M, Thanik V. Disappearing digits: Analysis of national trends in amputation and replantation in the United States. Plast Reconstr Surg. 2018 Jun 1;141(6):857e-867e.

6. Chung KC, Kowalski CP, Walters MR. Finger replantation in the United States: Rates and resource use from the 1996 Healthcare Cost and Utilization Project. J Hand Surg Am. 2000 Nov 1;25(6):1038–42.

7. Hustedt JW, Bohl DD, Champagne L. The detrimental effect of decentralization in digital replantation in the United States: 15 years of evidence from the national inpatient sample. J Hand Surg Am [Internet]. 2016 May 1 [cited 2020 Mar 25];41(5):593–601. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27021636

8. Maroukis BL, Chung KC, Maceachern M, Mahmoudi E. Hand trauma care in the United States: A literature review. Vol. 137, Plastic and Reconstructive Surgery. Lippincott Williams and Wilkins; 2016. p. 100e-111e.

9. Brown M, Lu Y, Chung KC, Mahmoudi E. Annual Hospital Volume and Success of Digital Replantation. Plast Reconstr Surg. 2017 Mar 1;139(3):672–80.

10. Buncke H, Whitney T. Secondary reconstruction after replantation. In: Buncke H, editor. Microsurgery: Transplantation– Replantation. Philadelphia/London: Lea & Febiger Inc; 1991. p. 651–83.

11. Morrison W, O’Brien Bm, Macleod A. Digital replantation and revascularization. A long-term review of 100 cases. Hand. 1978;10:125–34.

12. Tamai S. Twenty years’ experience of limb replantation—Review of 293 upper extremity replants. J Hand Surg Am. 1982;7(6):549–56.

13. Wu Y, Chen L, Scott PG, Tredget EE. Mesenchymal Stem Cells Enhance Wound Healing Through Differentiation and Angiogenesis.

Stem Cells [Internet]. 2007 Oct [cited 2018 Apr 5];25(10):2648–59. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17615264

14. Frey M, Mandl H, Holle J. Secondary operations after replantations. Chir Plast. 1980;5(4):235–41.

15. Pitzler D, Buck-Gramcko D. Secondary operations after replantation. Ann Chir Gynaecol [Internet]. 1982 [cited 2020 Mar 26];71(1):19–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7092123

16. Jupiter JB, Pess GM, Bour CJ. Results of flexor tendon tenolysis after replantation in the hand. J Hand Surg Am [Internet]. 1989 Jan [cited 2020 Mar 26];14(1):35–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2723366

17. Scott FA, Howar JW, Boswick JA. Recovery of function following replantation and revascularization of amputated hand parts. J Trauma - Inj Infect Crit Care. 1981;21(3):204–14.

18. Tark KC, Kim YW, Lee YH, Lew JD. Replantation and revascularization of hands: Clinical analysis and functional results of 261 cases. J Hand Surg Am. 1989 Jan 1;14(1):17–27.

19. Tamai S. Digit replantation. Analysis of 163 replantations in an 11 year period. Clin Plast Surg [Internet]. 1978 Apr [cited 2020 Mar 26];5(2):195–209. Available from: http://www.ncbi.nlm.nih.gov/pubmed/679604

20. Chim H, Maricevich MA, Carlsen BT, Moran SL, Salgado CJ, Wei FC, et al. Challenges in replantation of complex amputations. Semin Plast Surg. 2013 Nov 20;27(4):182–9.

21. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell Biology of Ischemia/Reperfusion Injury. In: International Review of Cell and Molecular Biology. Elsevier Inc.; 2012. p. 229–317.

22. Atkins SE, Winterton RIS, Kay SP. MINI-SYMPOSIUM: HAND TRAUMA (v) Upper limb amputations: Where, when and how to replant. [cited 2020 Mar 25]; Available from: www.elsevier.com/locate/cuor

23. Sorensen K, Allison K. An overview of limb replantation. Trauma [Internet]. 2009 Oct 17 [cited 2020 Mar 25];11(4):209–20. Available from: http://journals.sagepub.com/doi/10.1177/1460408609349889

24. Graham T., Sapega A, Heppenstall B, Sokolow D, Graham T, Maris J, et al. Bioenergetics of Preservation of Limbs before Replantation. J Bone Jt Surg. 1988;70(10):1500–13.

25. Gold AH, Lee GW. Upper extremity replantation: current concepts and patient selection. J Trauma [Internet]. 1981 Jul [cited 2020 Mar 25];21(7):551–7. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/7253053

26. Webb JB. Replantation in trauma. Trauma [Internet]. 2005 Jan 24 [cited 2020 Jun 6];7(1):1–9. Available from: http://journals.sagepub.com/doi/10.1191/1460408605ta325oa

27. Amillo S, Leyes M, Fernández J, Torres R. [Current indications for reimplantation of the upper extremity]. Rev Med Univ Navarra [Internet]. [cited 2020 Mar 26];40(4):34–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9499833

28. Zhong-Wei C, Meyer VE, Kleinert HE, Beasley RW. Present indications and contraindications for replantation as reflected by long-term functional results. Orthop Clin North Am [Internet]. 1981 Oct [cited 2020 Mar 26];12(4):849–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7322515

29. Chung KC, Yoon AP, Malay S, Shauver MJ, Wang L, Kaur S. Patient-Reported and Functional Outcomes after Revision Amputation and Replantation of Digit Amputations: The FRANCHISE Multicenter International Retrospective Cohort Study. JAMA Surg [Internet]. 2019 Jul 1 [cited 2020 Mar 24];154(7):637–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30994871

30. Janezic TF, Arnez ZM, Solinc M, Zaletel-Kragelj L. One hundred sixty-seven thumb replantations and revascularisations: Early microvascular results. Microsurgery. 1996 Jan 1;17(5):259–63.

31. Waikakul S, Sakkarnkosol S, Vanadurongwan V, Un-Nanuntana A. Results of 1018 digital replantations in 552 patients. Injury. 2000;31(1):33–40.

32. Koman; JURNG. The results of replantation after amputation of a single finger. J Bone Jt Surg. 1985;67(4):611–9.

33. Venkatramani H, Sabapathy S. Fingertip replantation: Technical considerations and outcome analysis of 24 consecutive fingertip replantations. Vol. 44, Indian Journal of Plastic Surgery. Thieme Medical Publishers; 2011. p. 237–45.

34. Brunelli G. Experimental studies of the effects of ischemia on devascularized limbs. Textbook of Microsurgery. Milan; 1988. 89–99 p.

35. Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. J Pathol. 2000 Feb;190(3):255–66.

36. Zhang C. The role of inflammatory cytokines in endothelial dysfunction [Internet]. Vol. 103, Basic Research in Cardiology. NIH Public Access; 2008 [cited 2020 Jul 6]. p. 398–406. Available from: /pmc/articles/PMC2705866/?report=abstract

37. Wei FC, Chang YL, Chen HC, Chuang

CC. Three successful digital replantations in a patient after 84, 86, and 94 hours of cold ischemia time. Plast Reconstr Surg [Internet]. 1988 Aug [cited 2020 Mar 25];82(2):346–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3399566

38. VanderWilde RS, Wood MB, Zeng-gui S. Hand replantation after 54 hours of cold ischemia: A case report. J Hand Surg Am. 1992;17(2):217–20.

39. Lin CH, Aydyn N, Lin Y Te, Hsu CT, Lin CH, Yeh JT. Hand and finger replantation after protracted ischemia (more than 24 hours). Ann Plast Surg. 2010 Mar;64(3):286–90.

40. Wilhelmi BJ, Lee WPA, Pagenstert GI, Pagensteert GI, May JW. Replantation in the mutilated hand. Hand Clin [Internet]. 2003 Feb [cited 2020 Mar 25];19(1):89–120. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12683449

41. Prucz RB, Friedrich JB. Upper extremity replantation: Current concepts. Plast Reconstr Surg. 2014 Feb;133(2):333–42.

42. Battiston B, Tos P, Clemente A, Pontini I. Actualities in big segments replantation surgery. J Plast Reconstr Aesthetic Surg. 2007 Jul 1;60(7):849–55.

43. Quiñones-Baldrich WJ, Chervu A, Hernandez JJ, Colburn M, Moore WS. Skeletal muscle function after ischemia: “no reflow” versus reperfusion injury. J Surg Res [Internet]. 1991 Jul [cited 2020 Mar 25];51(1):5–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2067359

44. Eiken O, Nabseth DC, Mayer RF, Deterling RA. Limb Replantation: II. The Pathophysiological Effects. Arch Surg [Internet]. 1964 Jan 1 [cited 2020 Jul 6];88(1):54–65. Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/561743

45. Korthuis RJ, Granger DN, Townsley MI, Taylor AE. The role of oxygen-derived free radicals in ischemia-induced increases in canine skeletal muscle vascular permeability. Circ Res [Internet]. 1985 Oct [cited 2020 Mar 25];57(4):599–609. Available from: http://www.ncbi.nlm.nih.gov/pubmed/4042285

46. Yassin MMI, Harkin DW, Barros D’Sa AAB, Halliday MI, Rowlands BJ. Lower limb ischemia-reperfusion injury triggers a systemic inflammatory response and multiple organ dysfunction. In: World Journal of Surgery [Internet]. World J Surg; 2002 [cited 2020 Jul 6]. p. 115–21. Available from: https://pubmed.ncbi.nlm.nih.gov/11898044/

47. VanBenthuysen KM, McMurtry IF, Horwitz LD. Reperfusion after acute coronary occlusion in dogs impairs endothelium-dependent relaxation to

acetylcholine and augments contractile reactivity in vitro. J Clin Invest [Internet]. 1987 Jan [cited 2020 Mar 25];79(1):265–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3793926

48. Davies MG, Hagen PO. The vascular endothelium: A new horizon [Internet]. Vol. 218, Annals of Surgery. Lippincott Williams and Wilkins; 1993 [cited 2020 Mar 25]. p. 593–609. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8239773

49. Münzel T, Afanas'ev IB, Kleschyov AL, Harrison DG. Detection of superoxide in vascular tissue. Vol. 22, Arteriosclerosis, Thrombosis, and Vascular Biology. 2002. p. 1761–8.

50. Frangogiannis NG, Youker KA, Rossen RD, Gwechenberger M, Lindsey MH, Mendoza LH, et al. Cytokines and the microcirculation in ischemia and reperfusion. In: Journal of Molecular and Cellular Cardiology. Academic Press; 1998. p. 2567–76.

51. Buncke H, Jackson R, Buncke G. The surgical and rehabilitative aspects of replanation and revascularization of the hand. 4th editio. Hunter J, Mackin E, Callahan A, editors. Mosby; 1995. 1075–1083 p.

52. Fantini GA, Conte MS. Pulmonary failure following lower torso ischemia: Clinical evidence for a remote effect of reperfusion injury. Am Surg [Internet]. 1995 Apr 1 [cited 2020 Jul 6];61(4):316–9. Available from: https://europepmc.org/article/med/7893094

53. Gadaleta D, Fantini GA, Silane MF, Davis JM. Leukotriene Generation and Pulmonary Dysfunction following Aortic Cross Clamp in Humans. Ann N Y Acad Sci [Internet]. 1994 [cited 2020 Jul 6];723(1):470–2. Available from: https://pubmed.ncbi.nlm.nih.gov/8030915/

54. Goldman G, Welbourn R, Klausner JM, Kobzik L, Valeri CR, Shepro D, et al. Mast cells and leukotrienes mediate neutrophil sequestration and lung edema after remote ischemia in rodents. Surgery [Internet]. 1992 Sep 1 [cited 2020 Jul 6];112(3):578–86. Available from: http://www.surgjournal.com/article/003960609290263Y/fulltext

55. Welbourn R, Goldman G, Kobzik L, Paterson IS, Valeri CR, Shepro D, et al. Role of neutrophil adherence receptors (CD 18) in lung permeability following lower torso ischemia. Circ Res [Internet]. 1992 [cited 2020 Jul 6];71(1):82–6. Available from: https://pubmed.ncbi.nlm.nih.gov/1351425/

56. Neary P, Redmond HP. Ischaemia-Reperfusion Injury and the Systemic Inflammatory Response Syndrome. In: Grace PA, Mathie RT, editors. Ischaemia-Reperfusion Injury [Internet]. Oxford: Blackwell Science; 1999 [cited 2020 Jul 6]. p. 123–36.

Available from: https://www.scirp.org/(S(351jmbntvnsjt1aadkposzje))/reference/ReferencesPapers.aspx?ReferenceID=2066230

57. Maxwell SRJ, Lip GYH. Reperfusion injury: A review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol [Internet]. 1997 Jan 31 [cited 2020 Jul 6];58(2):95–117. Available from: https://pubmed.ncbi.nlm.nih.gov/9049675/

58. Dhalla NS, Elmoselhi AB, Hata T, Makino N. Status of myocardial antioxidants in ischemia-reperfusion injury [Internet]. Vol. 47, Cardiovascular Research. Oxford Academic; 2000 [cited 2020 Jul 6]. p. 446–56. Available from: https://academic.oup.com/cardiovascres/article-lookup/doi/10.1016/S0008-6363(00)00078-X

59. Panés J, Perry M, Granger DN. Leukocyte-endothelial cell adhesion: Avenues for therapeutic intervention [Internet]. Vol. 126, British Journal of Pharmacology. Wiley-Blackwell; 1999 [cited 2020 Jul 6]. p. 537–50. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1565837/

60. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation. 1986;74(5):1124–36.

61. Wang WZ, Anderson G, Firrell JC, Tsai TM. Ischemic preconditioning versus intermittent reperfusion to improve blood flow to a vascular isolated skeletal muscle flap of rats. In: Journal of Trauma - Injury, Infection and Critical Care [Internet]. Lippincott Williams and Wilkins; 1998 [cited 2020 Mar 26]. p. 953–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9820708

62. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: Comparison with ischemic preconditioning. Am J Physiol - Hear Circ Physiol. 2003 Aug 1;285(2 54-2).

63. Loukogeorgakis SP, Panagiotidou AT, Yellon DM, Deanfield JE, MacAllister RJ. Postconditioning protects against endothelial ischemia-reperfusion injury in the human forearm. Circulation. 2006 Feb;113(7):1015–9.

64. McAllister SE, Ashrafpour H, Cahoon N, Huang N, Moses MA, Neligan PC, et al. Postconditioning for salvage of ischemic skeletal muscle from reperfusion injury: Efficacy and mechanism. Am J Physiol - Regul Integr Comp Physiol [Internet]. 2008 Aug [cited 2020 Mar 26];295(2):R681-9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18509099

65. Moon JG, Lim HC, Gye MR, Oh JS, Park JW. Postconditioning attenuates

ischemia-reperfusion injury in rat skin flap. Microsurgery [Internet]. 2008 Jan 1 [cited 2020 Mar 26];28(7):531–7. Available from: http://doi.wiley.com/10.1002/micr.20530

66. Cavadas PC, Landín L, Ibáñez J. Temporary catheter perfusion and artery-last sequence of repair in macroreplantations. J Plast Reconstr Aesthetic Surg [Internet]. 2009 Oct [cited 2020 Mar 25];62(10):1321–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18650139

67. Cunha MS, da Silva JCF, Nakamoto HA, Ferreira MC. Study of warm ischemia followed by reperfusion on a lower limb model in rats: effect of allopurinol and streptokinase. Clinics (Sao Paulo). 2005;60(3):213–20.

68. Li X, Cooley BC, Gould JS. Ex vivo perfusion with anticoagulated blood decreases ischemia/reperfusion injury. J Hand Surg Am [Internet]. 1993 Jul [cited 2020 Mar 25];18(4):629–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8349970

69. Beyersdorf F, Matheis G, Krüger S, Hanselmann A, Freisleben HG, Zimmer G, et al. Avoiding reperfusion injury after limb revascularization: Experimental observations and recommendations for clinical application. J Vasc Surg. 1989 Jun 1;9(6):757–66.

70. Heilmann C, Schmoor C, Siepe M, Schlensak C, Hoh A, Fraedrich G, et al. Controlled reperfusion versus conventional treatment of the acutely ischemic limb: results of a randomized, open-label, multicenter trial. Circ Cardiovasc Interv [Internet]. 2013 Aug [cited 2020 Mar 26];6(4):417–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23881815

