# The Impact of a Minimally Invasive Approach on Oral Wound Healing

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**Abstract**

Wound healing is a spontaneous occurring process in a state of hemostasis. Surgical interventions rely on the stages and processes naturally orchestrated by the host and influenced by the operator in the surgical theater.

Biological pathways to mucosal wound repair and regeneration are staged and defined as a preamble to the impact of the microsurgical technique on healing processes of oral wounds, emphasizing the relevancy of incision tracing and flap design.

Micromechanical aspects of the blood clot during wound healing of oral mucosal tissues are defined under the symbiotic interaction of microsurgically controlled instrument handling and its impact on tissue mechanotransduction is elucidated and discussed.

**Keywords**

Wound healing · Angiogenesis · Microsurgery · Mechanotransduction

## 1 Introduction

Writing a book chapter about oral wound healing and how it is affected by a microsurgical approach is a challenging task for various reasons. Firstly, our understanding of wound healing has vastly increased in the last decades, a fact which was accompanied by an explosion in the number of publications, ranging from basic science to clinical studies. A recent literature search in PubMed with the terms "wound healing" resulted in almost 200,000 publications, with an upward tendency of more than 10,000 new articles annually. Such a dramatic rise in new knowledge makes it very difficult to select the relevant information and to process and condense it into meaningful concepts.

Secondly, wounds in the oral cavity are common manifestations, intentionally caused by surgical procedures or unintentionally, when, for example, pulp tissues are injured during tooth preparation. Depending on the intraoral area and the type and composition of the tissues, the healing characteristics of the different sites may vary substantially. Conversely, oral wound healing processes such as mucosal healing, regeneration of periodontal structures, healing of bone and extraction sockets, and healing around oral implants have also many basic features in common. To investigate the effects of a microsurgical approach on the healing processes and postsurgical results, we have to distinctly determine the intraoral area and define the

tissues of interest and whether we focus on biological outcomes (cellular and molecular), clinical results, and/or the patient-reported outcome measures.

Thirdly, for the presentation of scientific findings and a critical discussion of the results in a book chapter, it is necessary to be precise in the wording because the reader does not have a direct chance to check the meaning and may come from a totally different background where the same term has another connotation. Therefore, definitions of terms matter, because concepts, and thus definitions, are shaped by the perceptions of the readers, and these perceptions might differ as a result of language, education (especially the education of a health professional), and the cultural differences [1]. As a consequence, we have to define the periodontal key terms used in the present chapter and contextualize them with each other.

Commonly, the definition of *periodontal microsurgery* refers to a refinement in surgical technique by which normal vision is enhanced through magnification [2]. Such attempts of definition emphasize the importance of the technical equipment, including surgical microscopes and loupes, the utilization of ergonomic microinstruments, and the inclusion of fine suture materials. In a broader sense, however, microsurgery implies an extension of surgical principles by which gentle handling of tissues is of paramount importance. This relates to the invasiveness of the surgical procedure which comprises the experience, expertise, and motor skills of the surgeon and depends on how tissues react on the application of physical forces. According to the National Institute of Health (NIH Cancer Institute), *minimally invasive surgery* is defined as "*…surgeries that encompass surgical techniques that limit the size of incisions needed and so lessen wound healing time, associated pain, morbidity and risk of infection*." Minimally invasive surgical procedures have been enabled by the advance of various medical technologies (microsurgery, laparoscopic surgery, robotic surgery, augmented-reality surgery) and are summarized in the scientific literature under the abbreviation MIS (minimally invasive surgery).

In periodontal and periimplant surgeries, a technique or procedure should be regarded as *minimally invasive* when its effectiveness is combined with the attempt to minimize the extent of surgical trauma (e.g., accelerating early wound healing), minimizing the need for additional surgical sessions and in some specific tasks as well as reducing chair time needed for each session, eliminating or minimizing the need for reconstructive devices such as membranes or graft materials through maximizing the inherent healing potential of the treated lesion, limiting intraoperative morbidity, with lower incidence and severity of intra-surgery complications and adverse events, limiting postoperative morbidity, with lower incidence and severity of postsurgery complications and adverse events, including higher patient acceptance, tolerance, and satisfaction, and maintaining or improving pre-existing esthetics (e.g., limited to no scarring and/or gingival recession). In the following, we will use the term *minimal invasiveness* when at least one of the above-mentioned criteria is fulfilled and, by mutual agreement, we take it for granted that a microsurgically modified procedure aims at reducing the invasiveness.

Since a comprehensive description of the different clinical wound healing processes in the oral cavity would go beyond the scope of the present chapter, we will

focus on the impact of minimal invasiveness on the healing of mucosal flaps and grafts, the regeneration of periodontal structures, and the interface between mucosal flaps and root surfaces.

The present chapter about wound healing of oral tissues after microsurgical interventions is organized into four sections. The first one reviews the fundamentals of current knowledge in mucosal wound healing and offers the surgeon a practical guide as the outcome ultimately depends on uncomplicated procession through normal wound healing.

The second section gives an overview of the available literature data regarding the results of periodontal and periimplant plastic and reconstructive microsurgeries and depicts how the minimally invasive modification may impact on the clinical outcome. As wound healing is one of the most complex biological processes and in order to understand how a microsurgical approach can trigger the wound healing phases, it is important to additionally evaluate the potential interfaces in the daunting array of mechanical and biochemical factors on a cellular and molecular level.

Section 3 sheds light on the clinical aspects of microsurgery and tries to identify how applied mechanical forces can be used as effective control levers to positively influence the molecular interplay during wound healing and, thereby, improve the clinical outcomes.

In the last section, a summary of the key relevant aspects of periodontal microsurgery, and how they are interconnected with the complex process of wound healing, is provided. It serves as a guidance for the clinicians how to learn the correct surgical techniques, emphasizing the most critical details, and on what they have to focus in order to achieve the well described beneficial clinical effects of a microsurgically modified intervention.

## 2 An Overview of the Biological Pathways to Mucosal Wound Repair and Regeneration

Understanding mucosal wound healing today involves much more than simply stating that there are three phases. Although a simplification, the classic division of wound healing into inflammatory, proliferative, and remodeling phases is still useful in understanding both routine and pathologic wound healing. Given the complexity of the mucosal wound repair process, it is remarkable how uneventful intraoral wounds heal and that, in general, they rarely become uncontrolled.

The oral mucosa is composed of a dense network of collagen fibers [3], the extracellular matrix (ECM), which provides the mucosal tone and is connected to a high number of embedded cells [4]. In health, together they maintain a tensional homeostasis which is crucial to keep the cells alive. After injury when tissue boundaries are disintegrated, the mechano-protective architecture of the ECM is disturbed and, in addition to these mechanical changes, bleeding occurs and cells come exposed to an overwhelming cocktail of cytokines initiate and orchestrate the process of wound healing.

Similar to other organ systems, the mucosal response to injury occurs in the same three overlapping but distinct wound repair stages which will be described in the following subsections.

## 2.1 Inflammation Phase (First Stage of Mucosal Wound Healing)

In all kind of wounds, the precondition for the initiation of the inflammatory phase is the control and stop of bleeding, known as coagulation, which however is just one part of the complex hemostatic process (for overview see [5]). During clotting, thrombin converts fibrinogen, an abundant plasma protein, into fibrin [6]. When fibrin molecules align to protofibrils and grow sufficiently long, they aggregate laterally to form fibers. These fibers, together with entrapped red blood cells and platelets, form the thrombus, or the blood clot. For clinicians it is important to know that blood clots are not uniform, homogenous structures but differ substantially based on individual patients. They are characterized by a great diversity of structural, biological, physical, and chemical properties, depending on the conditions of formation [7]. The resistance of the clot to mechanical and fibrinolytic dissolution, for example, plays an important role for early wound stability, a fact that might have an impact on the healing process when macroscopic physical forces are applied on mucosal flaps.

Immediate vasoconstriction upon wounding and the fibrin clot formation are the first sequences of healing and, thus, paving the way for appropriate inflammation. Besides its mechanical function, the blood clot and surrounding tissue release pro-inflammatory cytokines and growth factors. Once bleeding is controlled, inflammatory cells migrate into the wound (chemotaxis) and promote the inflammatory phase [8].

The first inflammatory cells infiltrating the wound are neutrophils. Their main function is considered to be prevention of infection by clearance of bacteria, foreign body materials, and damaged cells in the wound by phagocytosis [9]. Actual studies emphasize the importance of a balanced neutrophil recruitment to limit their tissue-destructive potential [10]. In the absence of microbial contamination, neutrophils may be even detrimental to tissue repair [11].

In the early wounds, likewise, the macrophages release cytokines which promote the inflammatory response. In the later stages, the same cells undergo a phenotypic transition to clear apoptotic cells (including neutrophils) and to ingest wound debris. Their critical role in non-specific defense and their recruitment of other immune cells such as lymphocytes (specific defense) underline the importance and multiple functions of this cell type in the inflammatory stage. Additionally, by the stimulation of keratinocytes, fibroblasts and the angiogenic potential [12], macrophages promote the transition to the proliferative phase of healing [8]. Figure 1 provides an overview of the timely occurrence and quantity of the different cells, interacting with each other in the wound healing process.

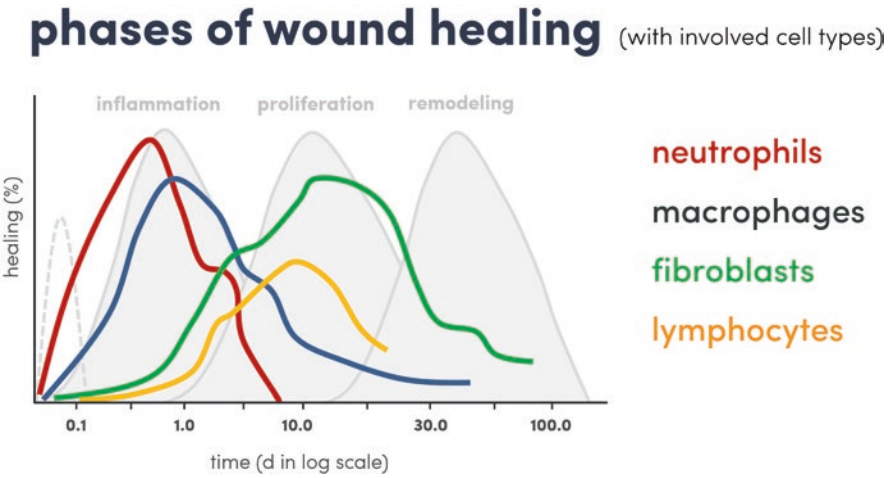


**Fig. 1** Presentation of the main wound healing cell types (temporal occurrence and quantity) in relation to the classical wound healing stages. Despite many similarities in the healing characteristics of skin and oral mucosal wounds, it should be noted that mucosal wounds heal faster and with lower complication rates. Most of what we know about wound healing has been investigated in skin models. The present graphic representation is adapted to the healing process of the oral mucosa. Temporal occurrence and quantity of individual cells might differ depending on wound size and modality of healing (primary or secondary intention)

## 2.2 Proliferation Phase (Second Stage of Mucosal Wound Healing)

The proliferative phase is overlapping the previous one and characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction. While in the early wound healing stages the blood clot served as a temporary shield protecting the denuded wound tissues and as a reservoir of cytokines, the provisional matrix of the clot now builds the scaffold through which cells can migrate during the repair process.

### 2.2.1 Epithelialization

For proper wound healing, the process of re-epithelialization has to be initiated rapidly after injury in order to form a protective barrier against fluid losses and further bacterial invasion and to re-establish mucosal integrity (for overview see [4]). The first migratory cells derive from the suprabasal layer of the residual epithelial structures in the wound margins. These epithelial cells have to dissolve their hemidesmosomal connections, to detach from the basement membrane and to proliferate, which takes time and lasts about 24 h, corresponding with the observed lag phase between injury and cell migration [13]. During migration, most of the basement membrane components underneath the keratinocytes are missing and the cells move forward on the exposed connective tissue matrix underneath the fibrin clot [14]. In small gingival wounds (2–3 mm between wound margins), however, the

high phagocytic activity of the keratinocytes allows them to directly penetrate through tissue debris and the clot without interacting with the connective tissue matrix. With a forward movement of about 1 mm per day, the keratinocytes continue migration until they are stopped moving by mechanical cues. They change their gene expression and become basal stationary keratinocytes. There is evidence that keratinocytes themselves are capable of making extracellular matrix that they can use to support or modulate their own migration if the provisional matrix is not permissive to migration [15]. Once changed into a stationary phenotype, the keratinocytes contribute to the regeneration of the basement membrane even if a significant portion of the basement membrane components is synthesized by the wound fibroblasts [16]. There is no doubt that the interaction between the wound keratinocytes and the underlying fibroblasts, described as cross-talk, influences and regulates the healing process of re-epithelialization [17]. The complete reorganization of the basement membrane is complete at 4 weeks. It is well recognized that epithelial cells have a crucial function in the healing process of the injured oral mucosa. Even in healthy periodontal tissues, keratinocytes are not just passive bystanders, but rather are metabolically active and capable of reacting to external stimuli by synthesizing a number of cytokines, adhesion molecules, growth factors, and enzymes.

### 2.2.2 Angiogenesis

Macroscopically, the granulation tissue of the healing mucosal wound gets its granular, pink appearance by the numerous capillaries that invade the newly formed connective tissue matrix. Many studies from the second half of the last century document the course of new vessel formation after injury of the oral mucosa and periodontal tissues on a light microscopic base [18–22]. The advent of molecular biology in the last decades enabled a deeper insight into the mechanism of vasculogenesis (de novo formation of capillaries deriving from the hematopoietic system), arteriogenesis (formation of a collateral circulation by arterial assembly), and angiogenesis (sprouting of new capillaries from already existing blood vessels), the latter being the predominant modality of revascularization in mucosal wound healing.

The uneventful and quick re-establishment of the vasculature of the injured mucosal area is of importance as nutrients and oxygen supply to the newly formed tissues are mainly provided by a functional blood perfusion [23]. The complex process of capillary sprouting, originating from vessels of the wound bed and neighboring tissues, is precisely regulated and strongly modulated by mechanical and chemical factors, with the vascular endothelial growth factor (VEGF) family as the main regulator (for overview see [24]).

There are some controversies in the literature about the angiogenic regulation and the promotion of wound healing. While some authors state that blocking angiogenesis does not have a significant influence on wound healing [25, 26], others document that the inhibition of angiogenesis significantly delays wound repair [27, 28].

The contradictory results can be explained on the one hand by the fact that most of the studies evaluated angiogenesis by counting the number of blood vessels and

not the functionality of the vessels. In fact, many blood vessels formed during wound repair are not perfused [29], thus, the decrease in blood vessels density by the selective elimination of non-perfused blood vessels may not have a significant effect on wound healing.

On the other hand, angiogenesis correlates with the inflammatory process as inflammatory cells release proangiogenic factors [30]. In skin wounds, angiogenesis produces an up to ten times more dense network of capillaries than exists in unwounded tissue. In the consecutive healing stages, the density of capillaries returns to that of normal by selective apoptosis of many of the recently formed blood vessels [31].

Comparing skin and mucosal wounds, the intraoral wound, similar to the fetal one, seems to be a privilege site of healing with reduced scar formation and less inflammation [32, 33]. During the initial wound healing stage in skin, stimulated macrophages and keratinocytes produce high levels of proangiogenic factors such as VEGF which are much less pronounced in the oral mucosa. As a consequence, oral mucosal wounds seem to circumvent the development of excess vasculature, proceeding directly to a well-formed vascular network. Therefore, both decreased inflammation and well regulated, refined angiogenesis are features of optimal healing after injury of the intraoral mucosa. It has to be noted that the density of vascular capillaries and blood flow in healthy oral mucosa is significantly higher compared to healthy skin [34].

### 2.2.3 Granulation Tissue Formation

Collagen, produced by fibroblasts, is the main structural protein in the extracellular matrix and the repaired mucosal wound. In healthy tissues, fibroblasts reside in a quiescent state and have a slow proliferation rate and metabolic activity. Upon wounding they become activated and attracted from the wound margins by chemotactic cues and start to initially synthesize and deposit a primitive, unorganized, and structurally weak ECM. The major fibrillar collagen produced early in the granulation tissue is type III. Later on, type I collagen production speeds up, accounting for at least 75% of the whole collagen content in the granulation tissue after the first postoperative week [35, 36]. The first secretion of new extracellular matrix proteins in the granulation tissue seems to occur approximately two to four days after wounding. In this stage of wound healing, the primary role of the fibroblasts is to rapidly produce new connective tissue in the ECM to re-establish tissue strength and function [37].

In the second half of the proliferation stage, around the seventh postoperative day, when granulation tissue is well established, some of the fibroblasts differentiate into myofibroblasts [38], cells with contractile elements that bring collagen fibrils together and reorganizes them, thus promoting wound closure and increasing the mechanical strength of the wound [39]. Based on more actual data, myofibroblasts seem to originate not only from fibroblasts but other cells such as mesenchymal stem cells, endothelial cells, pericytes, and epithelial cells [40].

Exposure of fibroblast to serum that is present in the blood clot in the wound initiates not only a rapid general stimulus for cell proliferation but also a more specific gene expression that controls function of other cells involved in inflammation, angiogenesis, and re-epithelialization.

Therefore, it is likely that fibroblasts and their subsets or fibroblast-like cells originating from various sources play a more important role in the physiology of wound repair than has been previously realized (for overview see [37]).

## 2.3 Remodeling Phase (Third Stage of Mucosal Wound Healing)

Tissue maturation and remodeling of mucosal wounds begin at approximately seven to ten days after injury and can last up to several months. But the start of tissue remodeling is individual and depends on the size of the wound. In surgical wounds caused by a small releasing incision and healing by primary intention, only very little granulation tissue is formed so that wound contraction can already occur at day three post-wounding, followed by an early balance between ECM production and degradation. In larger excisional wounds such as those left in the hard palate after harvesting a free masticatory mucosal graft, more granulation tissue is accumulated and it may take more than two weeks until remodeling commences [38]. In the remodeling phase, the number of cells secreting the ECM is reduced and their secretion downregulated. Additionally, the components of the ECM are reorganized and the stability of the ECM is increased by appropriate cross-linking of the collagen. Optimal mucosal wound healing leads to an early qualitatively and quantitatively normal connective tissue with re-establishment of a quiescent fibroblast phenotype responsible for tissue maintenance and homeostasis.

Wound healing is a complex biological process and the ideal outcome strongly depends on timing, duration, and the well-coordinated interactions of inflammatory and tissue resident cells, structural molecules, and mechanical forces generated in the wound environment (Fig. 2). The notion among clinicians that wounds in oral mucosa heal fast and with low complication rates has been supported by systematic studies [32, 33, 41]. Nevertheless, with few exceptions, wounds of the oral mucosa rather heal in tissue repair than regeneration, including complete restoration of the tissues in form and function. When the application of a microsurgical technique has been shown to improve the clinical results of traditional periodontal surgical interventions, it might be reasonable to assume that a change in the incision design and/or the modification of the exerted forces on the tissues (interface instrument–tissue) interfere with the biological processes of wound healing. Therefore, in the following sections, we try to identify the surgically accessible and controllable lever arms and to discover how one can intentionally interfere with the wound healing process in order to achieve the aforementioned improved surgical results.

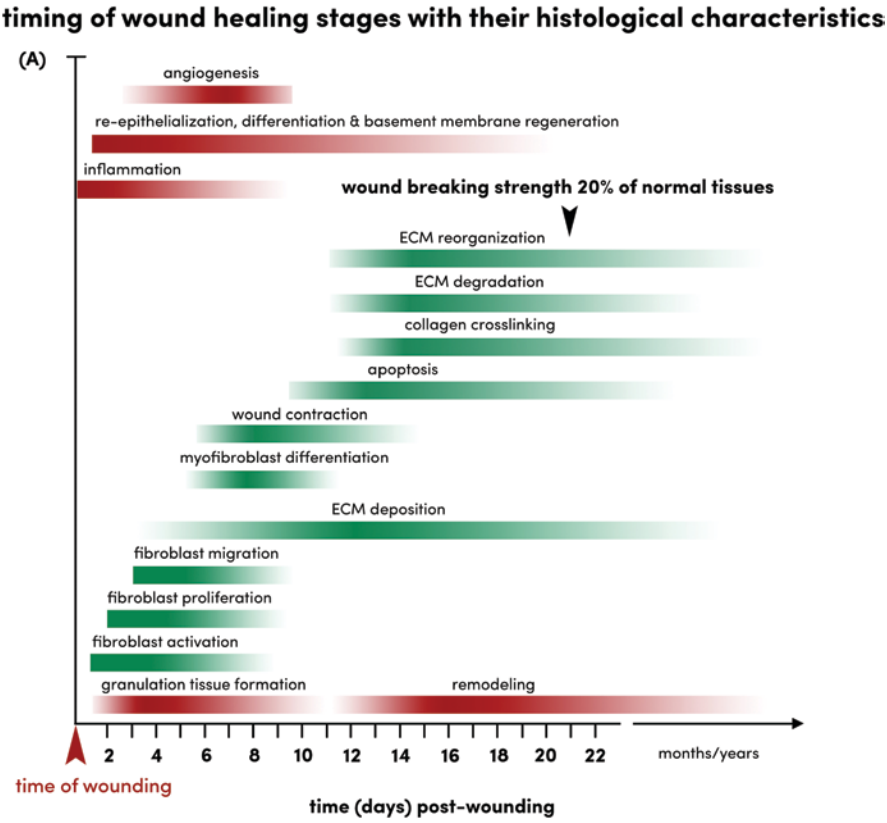


**Fig. 2** Schematic presentation of timing of the wound healing stages and the corresponding histological characteristics (**A**) after full-thickness excisional skin wounds in pig. Red color indicates the chronological sequences of the different wound healing stages. Green color depicts the histological events in relation to the wound healing stages (figure adapted from Häkkinen et al. 2012)

## 3 Impact of the Microsurgical Technique on the Healing Process of Oral Mucosal Wounds: Clinical Results and Potential Triggers for Enhanced Healing

### 3.1 Scientific Evidence of Improved Outcomes After Periodontal Plastic Microsurgeries: Some Critical Comments about the Clinical Relevance of the Results

A considerable amount of data, published in the last decade, document the beneficial impact of a microsurgical approach on the clinical postoperative results after periodontal plastic surgical interventions. Additionally, the patient-reported outcome measures also favor microsurgery with improved esthetics, patient's satisfaction, and reduced pain (for review see [42]). Some of the

articles, investigating the application of a microsurgical technique in periodontal surgery, rank high in the evidence pyramid and underline the sound documentation of the procedures. There is no doubt that clinical practice guidelines based on the principles of evidence-based medicine (EBM) build the basement for teaching and implementing available knowledge about microsurgery into clinical workflows.

Nevertheless, since the introduction of EBM in the mid-nineties, we have learned that, despite the considerable benefits of EBM, there have also been unintended consequences and the evidence-based "quality mark" has been misappropriated and distorted by vested interests [43–46].

On one side, the energetic intellectual EBM community, committed to making clinical practice more scientific and thereby achieving safer, more consistent clinical results, underestimated the time, effort, and skills needed on part of the clinicians, to access the right information among the massive volumes of research. Furthermore, many practitioners did not learn how to interpret and use scientific evidence in their daily practice and how to amalgamate it with their clinical experience and expertise as a basis for good clinical decisions in each individual patient. Without knowledge dissemination and implementation, evidence derived from systematic reviews only improves the dentist's knowledge but does not change their clinical performance by establishing a relevant improvement of their technical skills and/ or clinical decision-making competences [47].

Conversely, and apart from the fact, that surgeons not always apply to the existing evidence when making their treatment plans, for a large number of clinical problems, there is simply not enough practice-related evidence available. The fact that in periodontal microsurgery the influencing factors are numerous and interconnected with each other, underlines the difficulty to find the relevant, practice-related evidence.

Along with the different levels of technical skills, there is an entire array of non-technical skills such as teamwork with the chairside assistant, the quality of intraoperative decision-making, and the ability of self-reflection, which influence the quality of the microsurgical results and which are described in the specialist literature as *center-*, or more precise, *provider-effect* [48, 49]. It is therefore not surprising that a Cochrane review including endodontic surgery, a closely related specialty to periodontal microsurgery, ended up with the conclusion that "there is no evidence to support or refute a difference in clinical outcomes when either a microscope, endoscope or surgical loupes are adopted during endodontic surgery" [50]. The authors justified the findings with the low number and average quality of the included articles as well the high number of factors that might have an impact on the success of the surgical therapy.

As it is the goal of the present book to provide interested clinicians with an overview of the current state of knowledge in periodontal microsurgery and thus help them to improve performance and reduce errors, it becomes obvious that these goals cannot be achieved by summarizing the actual evidence-based literature about microsurgery. There would be too many important questions remaining unanswered by just choosing this approach. In the following section we will direct attention to

the surgical technical variables such as applied physical forces and incision design, their interconnectedness with each other, and how they may interfere with the wound healing process.

## 3.2 The Interconnectedness of the Microsurgical Technique with the Healing Process of Mucosal Wounds

The biological concept of regenerative periodontal surgery has been developed in the last decades of the twentieth century (for overview see Chap. 9). The results from multiple animal studies strongly suggested that the exclusion of epithelial and gingival connective tissue cells from the healing area by the use of a barrier membrane may allow (guide) periodontal ligament cells to repopulate the detached root surface (for overview see [51]). This observation provided the basis for the clinical application of the principle termed "guided tissue regeneration" (GTR) which, in those times, was perceived as a paradigm shift. The prospects of achieving a healing result that includes a reconstruction of lost or injured tissues in such a way that the architecture *and* function of the involved tissues are completely restored led to an eruption of enthusiasm in the worldwide community of periodontists, which soon after was followed by a great deal of frustration. The reason was that the promising results of GTR described in the early animal studies [52] and first clinical case reports on human teeth [53] could not be duplicated with just approximately sufficient prognosis in the clinical settings. There were simply too many interconnected factors, systemic-, site- and surgeon-related ones, that influenced the outcome and thus increased the technical complexity of GTR interventions. It took almost another decade to unravel the critical influencing factors and make GTR a reliable treatment option with predictable prognoses (for overview see [54]). Among other aspects, the maintenance of wound integrity turned out to be a major problem as bacterial contamination of the exposed non-resorbable membranes often led to infections [55]. The systematic assessment of the relevant surgical factors associated with variability of clinical attachment gain provided evidence that minimal-invasive and low traumatic soft tissue manipulation have the potential to substantially decrease the risks for wound dehiscences and, thus, having a great impact on the wound healing processes.

### 3.2.1 Influence of Modified (Minimal-Invasive) Incision Designs on Wound Stability and Wound Integrity

Clinical reports from the nineties emphasized the importance of flap and incision designs in order to maintain primary soft tissue closure after regenerative periodontal surgeries in the course of time [56, 57]. In this context, the preservation of the interdental gingiva and the papillary structures gained more and more importance and gave rise to redesigning the surgical approaches following the guidelines of minimal invasiveness. In the first decade of the current century, the modified (MPPF) and simplified (SPPF) papilla preservation flap [58, 59], the single flap approach (SFA) [60], and the papilla amplification flap (PAF) [61] were generally regarded as

the golden standards of flap design when it came to guided regenerative therapies. Despite the many published clinical trials, documenting the beneficial effects of the above-mentioned flap designs on the results after GTR treatments (for overview see [54]), one has to critically comment that a statistically significant influence of such minimally invasive approaches on clinical attachment gain could not be confirmed by a high ranking Cochrane systematic review [62]. Again, the findings from the meta-regression analyses regarding a potential influence of the surgical procedure on the outcome were explained by the many influencing variables and the troubling extent of clinical heterogeneity, which not only existed between studies but also within multicenter trials.

Nevertheless, the efficacy of GTR therapies was scientifically proven and in compliant, non-smoking patients with good oral hygiene and presenting with a narrow, angular defect with an infrabony component of three and at least six millimeters of probing pocket depth, probing attachment level gains of four to five millimeters after one year of healing were more the rule than the exception [63]. In those times, the materials used for space provision and cell occlusion were either non- or bioresorbable barrier membranes and the flaps were raised according to the above described designs extended at least one tooth unit mesially and distally to the defect area of the affected tooth. Buccal releasing incisions were chosen on the surgeon's discretion when either flap mobilization was impaired or visual access to the defect site was restricted.

At the turn of the century, enamel matrix derivatives (EMD) extended the spectrum of regenerative therapies [64], but despite the lower risks for postoperative mucosal dehiscences, probing attachment level gains in sites with similar defect morphologies were substantially lower in the ones treated with enamel matrix derivatives compared to those treated with GTR [65]. The predominant flap designs used for regenerative periodontal surgeries with EMD were congruent with the above described and extensively documented ones for GTR therapies.

Within the scope of a lively stream of publications on regenerative periodontal procedures, all of a sudden, the outcome of surgical therapies combined with EMD dramatically increased to a level that could not anymore be explained by the learning curve and increased skills of the individual clinicians. The unexpected improvement of clinical attachment gain after regenerative surgeries with EMD can be attributed to the continuous modifications of flap design. By using barrier membranes which itself are characterized by a certain thickness of the material and which are indicated to provide space, flaps had to be mobilized and advanced in order to achieve primary wound closure. In contrast, EMD is applied in a gelform and, thus, adds much less to the volume of the defect site when a three-wall, self-containing bony defect has to be covered with the local mucosal flap. Attentive surgeons soon became aware of this fact and started to modify the already existing papilla preservation flaps, following the concepts of MIS [66, 67]. Modifications directed at the reduction of the number and the extension of incisions at the expense of impaired visual accessibility of the defect site. To overcome the disadvantage, high-power magnification devices such as loupes or surgical microscopes were recommended and became indispensable components of the surgical equipment.

The development of flap designs in the field of regenerative surgery nicely documents how the waiver of releasing incisions and the reduction of tissue elevation to a minimum required for visual and instrumental access to the root surfaces positively affect the patient morbidity, improve the prognosis for wound integrity and stability and, thus, the regenerative result of the surgical intervention. Surprisingly, split-mouth design studies of regenerative treatments of three-wall infrabony defects even proved that the minimal invasiveness of the approaches and gentle handling of the soft tissues, in some specific clinical circumstances, have a more pronounced impact on the healing capacity of the tissues than the use of any biomaterial [68].

The above summarized scientific data paired with personal experience perfectly illustrate the effectiveness and external validity of minimal-invasive flap designs applied in regenerative therapies. Additionally, they indirectly confirm the clinically observed positive impact of MIS on the wound healing process. A paradigm shift from a conventional to a less invasive approach, using magnification aids, newly designed instruments, and fine suture materials can be observed in many different indications of periodontal plastic surgery (e.g., tunnel techniques for recession coverage which, at least partly, replaced the conventional coronally advanced flaps with releasing incisions or in implant surgeries, the flapless approaches for implant placement). So far, it is still unclear to what extent the magnification influences the wound integrity and the subsequent clinical results after healing. One might speculate that in periodontal plastic surgeries at sites with unproblematic visual access and limited to buccal or oral surfaces, high-power loupes might be sufficient to duplicate the good results from randomized trials. When it comes to modern, minimally invasive regenerative surgeries (modified minimally invasive surgical technique, m-MIST) where root surfaces have to be accessed via a small keyhole [68], it is evident, even without scientific evidence, that surgical access and light transmission to the root surface and bottom of the bony defect is impossible without a coaxial light direction and, thus, the aid of a surgical microscope.

Periodontal plastic surgeries are characterized by a high biocomplexity as hard, acellular, non-vascularized, and non-shedding surfaces of teeth or implants with their components might be included in the wound area and constitute parts of the wound boundaries. Therefore, it is difficult to isolate single factors such as the number and the extension of the incisions and directly relate them to wound stability and the final clinical outcome. A reduction of the incision design to maintain mucosal blood perfusion might also present a higher risk for residual flap tension with all the negative consequences.

The fact that already minor incisions have a substantial negative impact on the vascularity of the gingiva has been shown in a study on humans [19]. By injecting a fluorescent dye, it could be observed how lengths of mucoperiosteal flaps directly correlate with the reduction of blood perfusion in the flaps. Even more negative impact on the vascularity of the mucosal tissues than flap design could be registered for advanced flaps, stabilized, and sutured under residual tension.

A conventional flap and incision design for periodontal surgery (control site) was compared with a minimally invasive approach (test site) by histological assessment in an animal experiment [69]. The sites treated with different levels of invasiveness

were followed up with particular focus on the distribution of type III collagen, which plays a crucial role in the early wound healing phases and provides a scaffold required for angiogenesis and the migration of various types of cells. The histological and immunohistochemical analyses revealed a higher type III collagen content in the experimental sites compared with the conventionally treated ones, reaching statistical significance on day 3 and 5. The results from this study, comparing the early wound healing processes after conventional and minimally invasive flaps by histological analyses, clearly documented that a reduction of the surgical tissue trauma positively interferes with the wound healing process by markedly less neutrophils in the infiltration area and a timely acceleration of the healing phases, resulting in earlier tissue maturation.

From a clinician's perspective, there is no doubt that the application of MIS techniques in periodontal plastic surgery results in increased wound stability, faster tissue maturation, less scar formation, reduced patient morbidity, better esthetic appearance, and overall improvement of the healing outcome. However, it should be noted that most of these findings evolve from studies based on clinical measurements or subjective observations of the surgeons. Scientific evidence based on direct comparisons of healing processes after the application of different incision designs on the level of inflammatory cellular composition, blood microcirculation, or wound fluid cytokine levels is still scarce and needs further elucidation.

### 3.2.2 Healing of Periodontal Wounds Created by Traditional, but Microsurgically Modified Flap Designs

While in the previous section we shed light on the impact of applied MIS techniques (fewer incisions and restricted soft tissue elevations) on the clinical results and documented their overall beneficial effects, it is the goal of the subsequent one, to evaluate if, and if yes, how the application of a microsurgically modified technique influences the healing process and clinical outcome of traditional flaps. The modification consists of the use of high-power magnification (surgical microscope), microsurgical instruments, and fine suture materials while the flap design and extension of the incisions remain unchanged and correspond to those of traditional approaches.

Referring to the scientific literature of regenerative periodontal therapies, wound integrity seems to be a crucial aspect for undisturbed healing and is considered as a requirement for clinical success. As reported above, mucosal dehiscences with denudation of non-shedding surfaces such as roots, implant components, or inserted biomaterials are prone to bacterial colonization and, thus, once exposed to the oral cavity, promoting infections [55]. It has been documented that such adverse events are highly prevalent [62] and still remain a problem that is difficult to circumvent in many clinical situations [70]. The difficulty lies in the primary closure of the interdental soft tissues and its maintenance over the first postoperative weeks, especially if accesses are restricted by tooth proximities or locations in the posterior area of the dental arch. With traditional incision designs (access flaps), dissecting the interdental gingiva in the mid-col area, it is almost impossible to closely adapt the mucosal flaps with reliable prognosis for primary intention healing. The prevalence of

dehiscences, reported in published studies, decreased when papilla preservation techniques have been introduced [58, 59, 71, 72]. Nevertheless, mucosal dehiscences remained predominant complications after GTR therapies, even in the hands of skillful, experienced surgeons.

In a patient cohort study, investigating the probing attachment level gains after GTR therapies, the application of a simplified papilla preservation flap (SPPF) provided a complete primary wound closure in all treated sites at the end of the surgical procedure [59]. Six weeks postoperatively, clinical examinations have shown that only 67% of the originally completely closed wounds could be maintained intact, indicating the fragility of the interdental tissues in response to surgical manipulation and the difficulties to avoid partial necrosis of the col. area.

In patients with more favorable papillary morphologies, ideally treated with modified papilla preservation flaps (MPPF), primary interdental wound closures could be achieved in 93% of all treated sites and 73% remained completely closed for the entire observation period of six weeks [58].

When the same, previously mentioned clinicians modified their clinical approach and accessed the interdental area by using a surgical microscope and corresponding instruments, all treated sites could be completely closed after the intervention and mucosal closures were maintained in 92.3% of all treated defects for the entire follow-up period [73].

These results clearly documented that the use of a surgical microscope, provided that the surgeons are familiar with the characteristics of the microsurgical technique, allowed a much more accurate and less traumatic manipulation of the interdental tissues compared to conventional approaches performed without magnification aids. It is reasonable to assume that primary wound closures stabilized the underlying blood clot, sealed the environment from bacterial invasion and, thus, had a substantial impact on the healing processes and final clinical outcome.

The impact of a microsurgical modification on mucosal healing and clinical outcome was evaluated for another periodontal plastic indication, namely the coverage of gingival recessions [74]. In split-mouth design, bilateral symmetric mucosal dehiscences were randomly treated with either a double pedicled flap or the corresponding flap design but microsurgically modified. The influence on healing was assessed by angiographic techniques, measuring the mucosal blood perfusion on a previously defined, squared area in the center of the covered recession. The vascularity of the treated sites was recorded immediately after the surgery and three and seven days postoperatively (Fig. 3). Clinical parameters were evaluated before and several times, up to 12 months, after the interventions.

The results have shown that the use of a surgical microscope, corresponding instruments and 9–0 sutures had a substantial impact on the mucosal blood perfusion of the treated sites, reaching statistical significance on the third and seventh postoperative day. Interestingly, the sites with a very good vascularity in the early wound healing stages were the ones presenting with the highest percentage of root coverage at the end of the one year follow-up period. The positive impact of a microsurgical approach on the clinical outcome after the surgical coverage of mucosal dehiscences has been documented in several other studies (for review see [42]).

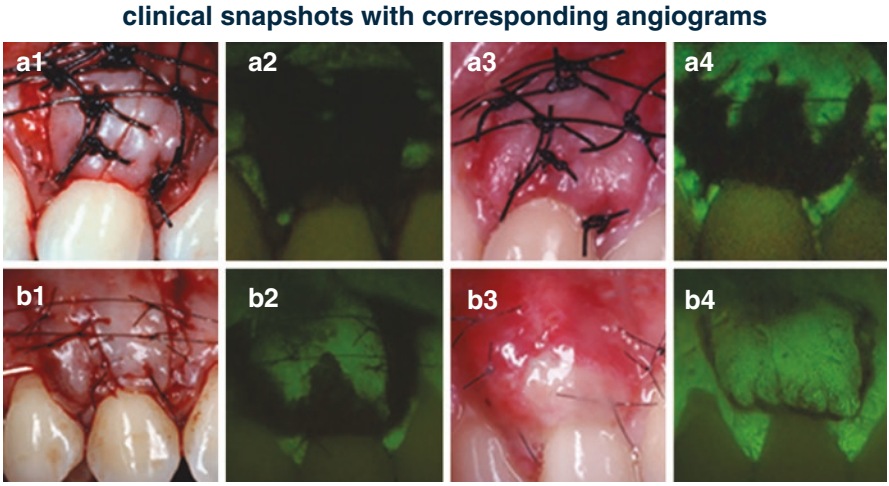


**Fig. 3** Micro- (b1-4) and macrosurgically (a1-4) treated mucosal recessions with corresponding angiograms. a1/b1 depict the surgical sites immediately after the interventions; a2/b2 angiograms representing the blood perfusion of the treated sites immediately after the interventions (green = perfused); a3/b3 surgical sites, 7 days postoperatively; a4/b4 corresponding angiograms at day 7 postsurgery

Despite the documented promising results of microsurgically modified interventions, it is still unclear how visual enhancement can influence the instrument–tissue interface and how the applied physical forces can trigger the wound healing processes. In the following section, we try to shed light on the questions raised above and, based on findings from basic research, to substantiate the hypothesis that the magnitude of mechanical forces applied on mucosal tissues directly affects the wound healing process on a cellular and molecular level.

## 4 How to Translate Findings from Basic Research into Clinical Success?

### 4.1 Incision Design and Wound Healing from a Histological and Physiological Perspective

To plausibly explain the mechanisms how a microsurgical modification of a traditional flap approach can positively interfere with the wound healing processes, we first have to focus on the single aspects of the microsurgical technique and equipment. The surgical microscope, widely considered as the core component of the microsurgical technique, can just have an indirect impact as there is no direct interface between the visual acuity and the tissue trauma. The magnified vision and bright illumination of the surgical site might enhance the detection of tissue microstructures and, after appropriate clinical training, help the surgeon to improve

bimanual control and fine motor skills. One can only speculate how an utmost careful manipulation of the oral mucosa during flap preparation has the potential to minimize the reduction of the presurgically existing blood perfusion and the amount of cellular debris caused by tissue damage and, thus, paves the way for an uneventful healing. In fact, animal studies have shown that the size of the surgical site characterized by an extension of the incision design positively correlates with the size of the infiltration area of neutrophils [69], which partly explains the faster wound healing after MIS interventions. These findings were supported by another animal study on skin wounds [75], documenting that all inflammatory mediators, tested in serum of the operated animals, and immune reactions induced by skin surgical trauma are closely correlated to the length of the skin incisions. The presented results from clinical studies on patients and animals are concordant with the common sense that a minimally invasive surgical approach, with limited incisions and accesses via keyholes, positively affects the wound healing process, resulting in better final outcome and reduced patient morbidity. Nonetheless, it does not explain if the use of a surgical microscope, combined with corresponding instruments and fine suture materials, has a beneficial effect on the outcome likewise, when flap preparation, mobilization, and fixation are technically executed in the same manner, macro- and microsurgically.

When similar surgical approaches were directly compared from which one was microsurgically modified, such immediate postsurgical trauma reduction could not be confirmed, at least for the vascular blood supply in the treated areas [74]. This, in turn, and as the initial impairments of blood supply after macro- and microsurgical operations were relatively similar, might be an indicator that the true microsurgical control lever that triggers wound healing must be searched elsewhere.

In most periodontal surgical procedures, after flap preparation and flap elevation, the mucosal tissues must be mobilized, advanced, stabilized, and fixed in a new position. In the last stage of the surgery, when flaps have to be firmly stabilized and closed, a passive adaptation of the flap margins seems to be an indispensable prerequisite for uneventful healing and the maintenance of wound integrity during the entire postoperative period. Tensionless or *passive wound closure* became a tenet in periodontal and implant surgery since long ago and its importance is emphasized in numerous clinical studies, articles, and book chapters. This is somewhat surprising as a digital search in the Medline database, entering key terms related to passive wound closure, provided only very few studies including clinical measurements of flap tension after periodontal and implant surgeries [76–78]. Current findings document that the available scientific evidence of the concept of *passive wound closure* is relatively scarce and its validity in periodontal surgery may at least be questioned. Additionally, it must be noted that almost none of the authors stressing the tenet of *passive wound closure* ever defined the term and explicitly described their ideas about it.

Studies on patients have shown that residual flap tensions tend to impair blood supply [19] and increase the risk for wound dehiscences, especially when forces beyond 0.1 N are applied [77]. It is important to note that the experienced periodontal surgeon who treated the sixty patients in the just mentioned study did not

perceive any differences in residual flap tension and prepared all the flaps in good faith of complete passivity (personal comment of the author). Interestingly, in the group of low residual tensions, between 0.01 N and 0.05 N, none of the 25 patients exhibited a mucosal dehiscence—a finding which was independent of flap thickness.

The fact that uneventful healing with maintenance of wound integrity is compatible with residual flap tensions was confirmed in another clinical study on patients treated with bone grafts [78]. The authors defined a wound closure with a residual flap tension of up to 0.05 N as completely passive and did not observe any adverse healing outcome in the group of patients with low-tension flap closures. Data from animal studies confirmed the above-mentioned findings and, surprisingly, even proved that some soft tissue wounds closed under tension showed significantly higher tensile strength between one and three weeks postoperatively [79, 80] compared to wounds which were passively closed.

These observations raise an important question, namely how much tension, applied to the wound margins, is compatible with an uneventful mucosal healing? Or more provocative: Is there a range of applied minimal tension that has a beneficial effect on the wound healing process compared to a completely passively closed wound?

## 4.2 Micromechanical Properties of the Extracellular Matrix of the Oral Mucosa and the Blood Clot after Wounding

### 4.2.1 Micromechanical Aspects of Oral Mucosal Tissues

In health, the fibroblasts as the predominant cell type of the oral mucosa are connected to the dense network of collagen fibers, the main structural element of the extracellular matrix (ECM) [3, 81]. Under physiological conditions, the ECM maintains a tensional homeostasis which is crucial to keep the embedded cells alive. That means, in concrete terms, residing fibroblasts experience, and vitally need, specific mechanical signals within a distinct range of magnitude, caused by gravity [82], tension [83], compression [84], shear stress [85], and osmosis [86].

After injury when tissue boundaries are disintegrated, the mechano-protective architecture of the ECM is disturbed and, in addition to the mechanical changes, cells become exposed to an overwhelming cocktail of cytokines [87]. Little was known about how cells convert mechanical signals into a chemical response, named mechanotransduction, and how these signals are integrated with other signals, until a group of researchers, almost two decades ago, presented reliable models. These models were based on experimental findings which documented that cells are hard-wired to respond immediately to mechanical stresses transmitted over cell surface receptors that physically couple the cytoskeleton to the extracellular matrix or to other cells [88, 89]. We now have evidence from numerous studies that mechanical stimuli are transduced into a biochemical response through force-dependent changes in scaffold geometry (for overview see [81, 90]). The molecular signaling pathways of applied mechanical forces are described for the biological processes in the ECM [91], the cell membrane [90] as the interface between the ECM and the cell, for the

intracellular mechanical force transmission via the cytoskeleton [41] and even the interface between the cytoplasm and the nucleus of the cell [92].

While the research community, interested in wound healing and for a long time, was focused on identifying the molecular components that trigger wound healing processes, it is now clear that there is more to the equation: the whole is truly greater than the sum of its parts. Today, we know on a solid base of evidence-based research, that mechanical forces, rather than chemicals cues, act as biological regulators and have a substantial impact on embryogenesis [93], the function of organs [94], the growth of skin and muscles [95], but also the etiology of many debilitating diseases [96] and last but not least on wound healing of the oral mucosa [81]. Additionally, the cells of the oral mucosa and the periodontal ligament, such as fibroblasts and keratinocytes, have been shown to be highly mechanosensitive [97] which underlines the potential role of applied mechanical forces in the wound healing process when flaps are manipulated and sutured under tension of different magnitudes.

An excellent way to illustrate the applied principle of mechanotransduction in a therapeutical concept is the orthodontic movement of teeth. As most dentists might have observed in everyday clinical practice, by just applying a small mechanical force on a macroscale within a range of few grams, after an initial lag phase of about one month the teeth start to move, indicating that the mechanical impulse has been transmitted into biochemical signals and activating the genetic machinery of the ligament cells, changing their phenotype and starting with a new behavior [98].

### 4.2.2 Micromechanical Aspects of the Blood Clot during Healing

Referring to the beginning of the present chapter and the illustration of the different wound healing stages (Fig. 2), we have seen that blood clot formation to prevent local hemorrhage and to build a provisional matrix for wound healing is one of the first processes to take place after wounding [36]. Blood clots can best be described as branched three-dimensional networks of taut fibrin fibers with entrapped blood cells. But the heterogeneity of fibrin as a main component of the fibrin fiber results in blood clots which are characterized by different viscoelastic properties such as rigidity and elasticity. Immediately after clot formation, stability means the resistance of the clot to mechanical stress which is essential to withstand arterial pressure and to stabilize the early wound [99]. After surgical wound closure, the viscoelastic properties of the blood clot might determine how it responds to treatment. A stiff or brittle clot might have a greater tendency to disrupt from a root surface or other wound beds, while those that are more viscous or plastic might deform and maintain their mechanical function [100]. Although not much is known about the relationship between mechanical properties of fibrin and its impact on clinical wound stability, it has been documented on periodontal wounds in an animal experiment that the tissue characteristics of the wound bed have a substantial effect on blood clot stability and adherence. Interfaces between a non-shedding avascular surface, such a dentin, and the blood clot were more prone to disruption when forces were applied in the early wound healing phases than those consisting of mucosal connective tissues and blood clots [101].

In the subsequent wound healing phases, blood clot stability refers more to the fibrinolytic properties of fibrin and the balanced equilibrium between clotting and the lytic susceptibility of the clot [99] than purely mechanical aspects. To reinforce the wound and initiate wound contraction, fibroblasts have to migrate into the provisional matrix and deposit collagen which requires a local dissolution of the blood clot. Research findings from a study on human blood clots revealed that mechanically stretched fibrin fibers in the blood clot (e.g., by increased wound tensions) are more resistant to proteolytic dissolution, which again documents the biological mechanisms of mechanotransduction and the interconnectedness of applied mechanical forces with undisturbed wound healing [102]. In this regard it has to be noted that the above-mentioned findings must be viewed from a qualitative perspective than being judged on the basis of absolute numbers and the magnitude of the actually exerted mechanical forces.

The biocomplexity of wound healing is mirrored in the fact that uneventful healing depends on finely balanced mechanical forces in the microenvironment of the wound. While excessive mechanical stress in the granulation tissue and early connective tissue matrix leads to a delay in healing and increases the risks for adverse outcome, an insufficient amount of mechanical force can have a similar effect, well documented by the phenotypic changes of fibroblasts. Few days after injury, fibroblasts in the wound area undergo a phenotypic change into myofibroblasts, cells that are significant for wound contraction and characterized by de novo development of in vivo stress fibers and contractile forces [83]. The transition of fibroblasts into proto- and fully differentiated myofibroblasts requires, along with a cocktail of cytokines (TGF-ß, fibronectin), mechanical tension. Without an appropriate mechanical wound environment, fibroblasts do not undergo the phenotypic changes, or comparably, when fully differentiated myofibroblasts are cultivated in collagen gels, kept under tension, and tensions are suddenly released, the cells will undergo apoptosis (for review see [103]).

A last example of mechanotransduction and its importance in the wound healing process is the morphogenesis of new capillaries. Since the 1990s, a sound basis of scientific evidence documents and explains the mechanisms of angiogenesis [104] and how surgically injured tissues are newly revascularized [105]. After migration of endothelial cells into the wound area, it is the mechanical configuration of the fibrin clot that mainly determines the capillary morphogenesis driven by local thinning of the ECM which results in local cell distortions. These well-coordinated changes in cell and cytoskeletal form with consequent changes in the cellular biochemistry result in cell growth and motility that drive morphogenesis and lumen formation of the new capillary [89, 93] (Fig. 4).

Findings from the above-mentioned basic research document how mechanically exerted forces, on a microscale, may influence the wound healing sequences and provide new insights into the complexity of the biological processes of mucosal healing. Additionally, the findings are confirmed by clinical observations on a macroscale, which corroborate the hypothesis that, firstly, applied mechanical forces on flap margins which exceed a certain magnitude

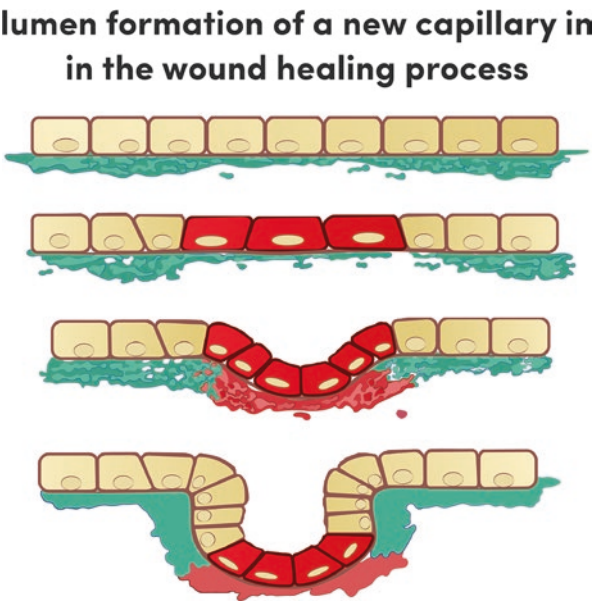


**Fig. 4** Schematic representation how local changes in the extracellular matrix (ECM) may guide morphogenesis of a new capillary. Local accelerated turnover of the ECM results in local cell distortions with consequent coordinated changes in cell and cytoskeletal form. The latter produce changes in cellular biochemistry that result in cell proliferation and motility. Cell growth and migration are constrained to the small group of cells (red) that is underlined by the thinned region of the basement membrane (green). Outward budding results when red cells extend and grow because neighboring cells along the same basement membrane do not experience the stress and hence remain quiescent (white cells). (Graphic adapted from Ingber 2003)

can have a deleterious effect on soft tissue healing and, secondly, that residual flap tensions within a very low range of force are fully compatible with an uneventful healing.

## 4.3 Microsurgically Controlled Instrument Handling and its Impact on Tissue Mechanotransduction

The remaining question now still is how a microsurgical modification of a traditional flap approach can have the potential to positively interfere with the wound healing process in a way that blood perfusions of the microsurgically treated sites, just few days postoperatively, are significantly better compared to those treated by a conventional approach without a surgical microscope [74].

Keeping in mind that mechanical forces applied on wound margins play a pivotal role in the course of healing, and remembering the technical core components of the microsurgical technique (surgical microscope, fine suture materials, and micro instruments), one can safely assume that the lever arm for recorded improved

outcome after microsurgical interventions has to be looked for in the quality of the suture materials.

In the previously mentioned randomized clinical trial, comparing macro- and microsurgical techniques in the coverage of mucosal recessions, suture diameters of either 9-0 (micro) or 4-0 (macro) were used which obviously are characterized by different mechanical properties such as rigidity and breaking strength of the threads.

An in vitro study on mucosal samples harvested from pig jaws, fixed in an apparatus with suture materials of different diameters (3-0, 5-0, 7-0) and continuously loaded with increasing forces has shown that, in fact, tissue trauma could be reduced just by choosing finer suture diameters. While 3-0 sutures mainly led to tissue breakage at an average of 13.4 N, the corresponding 7-0 ones only resulted in breakage of the thread at a mean applied force of 3.7 N [106]. As thinner sutures lead to thread breakage rather than tissue breakage, fine suture materials can be considered as the weakest link in the transmission of macroscopically applied forces and, thus, limiting the application of excessive forces. For better illustration, a 4-0 suture with a diameter of 0.2 mm and a resulting breaking strength of 1540 g (straight pull) is faced with a 9-0 suture of 0.04 mm diameter and a corresponding breaking strength of 60 g.

Focusing on mechanotransduction from applying a surgical force to the ECM to the genome and asking if all the pieces are now in place, we can state that in the last decade, basic research has proven that oral mucosal tissues are susceptible to externally applied physical forces [81] and that such forces, by the communication of mechanical cues between the ECM and the cells, can directly influence gene expression [87]. The fact that a surgically applied force on flap margins is transferred to the cytoskeleton of the involved cells, which, in turn, change their phenotype and function [107], might be used as an ideal biomechanical model to explain the beneficial impact of the microsurgical technique on wound healing. That the magnitude of applied tensional forces on flap margins trigger wound healing can also be observed clinically by inspecting the dimension of the scar when wound healing is completed. Both, skin and mucosal wounds, closed and healed in the presence of tension, end up in significantly more scarring and fibrosis [87, 108], the latter being slightly less prone to fibrosis because of the different biochemical environment [32].

The above-mentioned scientific findings paired with the clinical observations of improved healing pattern after microsurgical interventions suggest that a mechanomodulatory approach might be a promising way to address the multiple pathways involved in the healing response, at least in the oral mucosal wound healing setting. A better understanding of the microenvironmental cues within mucosal wounds and how they influence the behavior of cells and tissues in the healing process would help to identify therapeutic targets for mechanomodulatory approaches in periodontal surgery. The microsurgical modification of traditional surgical interventions might have the potential to be identified as such novel mechanosensitive approach and, thus, open the door for innovative surgical orientations. Until the regulatory mechanisms of applied surgical forces in periodontal surgery are better understood and surgeons trained in fine motor touch perception, the traditional tenet of passive wound closure is still justified.

## 5 Closing Remarks

Mucosal wound healing is a complex process, which is dependent on many cell types and mediators interacting in a highly sophisticated temporal sequence. Usually, wounds in the oral mucosa heal fast and with low complication rates.

For many years, efforts to modulate wound healing focused on the biochemical mechanisms, while more recent research has revealed a central role for mechanical forces in triggering these pathways. Mechanotransduction, which refers to the mechanisms by which mechanical forces are converted to biochemical stimuli, has been closely linked to inflammation, angiogenesis, wound contraction, collagen synthesis, and scar formation.

In the periodontal surgical setting, minimally invasive surgical procedures have shown to minimize the extent of surgical trauma, limit patient's morbidity and improve the esthetic results. Most of these beneficial effects can be explained by miniaturized flap designs and its consequent impact on blood clot stability and wound integrity.

When traditional surgical techniques have been compared with microsurgically modified ones, faster wound healing and better revascularization of the injured tissues could be observed. The underlying biological mechanisms that explain the substantial positive impact of a microsurgical modification on wound healing still are a subject of speculation. Nevertheless, the model of mechanotransduction might explain, at least partly, how microsurgery affects the microenvironmental cues that trigger cell behavior and, as a consequence, the wound healing process.

## 6 Key Points

1. **Mucosal wound healing**
   Mucosal wound healing after periodontal surgical interventions occurs through a complex cascade of carefully orchestrated biochemical and cellular events in overlapping phases, namely hemostasis, inflammation, proliferation, and ultimately remodeling.
2. **Minimally invasive surgical (MIS) techniques in periodontal therapy**
   From a clinical perspective, microsurgical modifications of periodontal surgical interventions minimize the trauma, limit intra- and postoperative patient morbidity, and improve the surgical outcome regarding esthetics and the quality of healing (regeneration rather than repair).
3. **Effects of MIS on the biological processes of wound healing**
   Microsurgically executed periodontal interventions limit the size of incisions needed and alter the magnitude of applied forces on the oral soft tissues (bioengineering interface between instrument and mucosal tissues), two surgical key factors which have a mechanomodulatory influence on the wound environment.
4. **Mechanotransduction**
   Mechanotransduction is defined as a biological process which refers to the mechanisms by which mechanical forces, applied on a macroscale, are converted to biochemical stimuli which substantially influence the behavior of the cells participating in wound healing.

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