

Effect of mechanical stability on fracture healing – an update

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Summary¹ The effects of mechanical stability and mechanical stimulation have been studied extensively in vivo using a variety of animal models and stimulators. Early results indicated that stimulation does not significantly contribute to fracture healing. Lately, however, more rigid external stimulators that withstand increased callus formation have identified a contribution of mechanical stimulation in the initial period of fracture healing. However, these studies also show that the same amount of movement inhibits union during the last phase of fracture healing. On the cellular level, most investigations have used 2-dimensional cell culture systems to study the response of different cell phenotypes to mechanical stimulation, shear stress, and hydrostatic pressure. Cell proliferation and differentiation are clearly altered by these stimuli, however, the response depends on the cell type, the magnitude of the strain, and the co-factors applied. Lately, 3-dimensional cell cultures in mechano-bioreactors have been used to investigate the response of bone marrow stromal cells. These results indicate that the predominant stimulus for proliferation is perfusion. Mechanical stimulation affects cell differentiation and depends on the strain magnitude and the cell phenotype. As a consequence, today's implants should be applied in a fashion that supports maximum perfusion at the fracture site. In the early period, the osteosynthesis should facilitate micromotion of the fragments if secondary fracture healing is desired. At the same time, joint congruency, and axial and rotational positions have to be maintained. In the final period of healing, motion within the calcifying callus should be limited, which is naturally achieved by the increasing stiffness of the callus ossification.

Introduction

The interfragmentary strain concept of Perren [40] has been used to describe primary and secondary fracture healing. The theory suggests that the strain that causes healthy bone to fail is the upper limit that can be tolerated for the regenerating tissue. Today, stimulation of fracture healing has been investigated extensively both in vivo and in vitro. These experiments have refined strain types and limits and have

identified cofactors that are necessary to successfully stimulate callus formation. This review article shall discuss the current state of the field and draw conclusions for successful fracture stabilization.

In vivo experiments

Numerous animal models have been used to test the effects of mechanical stimulation on fracture healing [4, 11, 16, 19, 34, 39, 46, 47]. According to the size of the animals and loads applied, different types of fixators [4, 19, 34, 39, 47] were applied. Predominantly, external fixators were used to stabilize a

¹ Abstracts in German, French, Italian, Spanish, Japanese, and Russian are printed at the end of this supplement.

3 mm osteotomy of the tibial shaft in sheep [4, 16]. A motor gear unit [4, 11], a telescoping system [39], or a rigid hydraulic actuator [19] were attached and cyclic loads applied. The strain was altered between 7% [4] and 50% [19]. Strain frequency was modified between 0.5 Hz [16] and 10 Hz [4].

Earlier experiments suggested that tissue quality is not enhanced by mechanical stimulation [4, 11], although there is increased callus formation in the mechanically stimulated groups [11]. Fracture healing is hampered by increased fracture gap.

A potential shortcoming of the setup used in this study is the limited maximum force that was applied by the system [19]. Thus, with increasing callus formation, the displacement of the fragments could not be maintained [39]. The same holds true for other investigations that have compared static and dynamic (compression and distraction) systems in the rat model [34]. There was no difference in callus formation between both stimulated groups.

A more recent study applied a servohydraulic actuator to enforce a given displacement up to 22.5 Nm [19]. In this study, bridging in the cycled groups was observed exclusively at the medullary side. There was significantly more callus on the compressed side than the distracted. Groups that were strained with 1000 cycles demonstrated 50% more callus than specimens loaded ten times per day. This study only observed one time point after six weeks.

Goodship et al [16] compared the application of early versus late stimulation. In the latter group, sheep received 400 mm/second of applied

micromovement after six weeks. Stimulation was enforced up to a total force of 200 N. Healing progress and callus formation were controlled for another six weeks. This study demonstrated a difference between early and late application of motion within the fracture gap. Early micromovement fosters increased bone mineral density and stiffness. There is a positive effect of the magnitude of strain (up to 400 mm/second) on these parameters. Contrarily, the late onset of stretching diminishes bone mineral density and impedes the progress of walking stiffness.

In conclusion, there is a clear contradiction between the results of the studies mentioned regarding the contribution of strain to fracture healing. If a lack of maximum displacement with increasing callus is assumed [4, 11], the results are uniform and can be summarized as follows (Table 1):

In early fracture healing, mechanical stimulation enhances callus formation. However, there is no common opinion as to whether compression or distraction is the more effective stimulus [19, 34]. Higher strain magnitudes up to 50% of the fracture gap are more efficient than lower strain. For the first weeks following fracture, the optimum magnitude of displacement has yet to be identified. The amount of callus does not correspond with stiffness [11].

High strain magnitudes applied after six weeks inhibit callus bridging and fracture stiffness. Since all of the animal studies have used defined osteotomies, the strain limits and gap width for oblique and spiral fractures may be underestimated.

Authors	Animal model	System applied	Load controlled	Distance controlled	Fracture gap (mm)	Strain applied (mm)	Frequency applied (Hz)	Results
Augat et al [2]	Sheep	Combined distraction and compression	No	Yes	3	0.2 and 0.8	1, 5, 10	No effective enhancement of bone healing
Matsushita and Kurokawa [7]	Rat	Isolated compression and distraction	No	Yes				Both compression and distraction stimulate callus formation
Hente et al [8]	Sheep	Combined distraction and compression	Yes (22.5Nm)	Yes	2	1 (distraction and compression)	1.25; 10 and 1000 cycles per day	Bridging exclusively on the medullary side, non union on the cortical sides
Park et al [9]	New Zealand white rabbits	Telescoping external fixator	Yes (body weight as tolerated)	No	Transverse and oblique fractures	0.6 (transverse); 1.5 (oblique)	Not controlled	Oblique fractures with shear motion create most callus and stiffness
Goodship et al [6]	Pig	Combined distraction and compression	200N	No	3	1mm at 2, 4, 400mm sec ⁻¹	0.5	High strain rates increased callus formation early and inhibited the progress of healing when applied after 8 weeks

Table 1: In vivo experimental setups and results

In vitro experiments

Undifferentiated [1, 35, 22] and differentiated cells [27, 45, 48] have been used to study the response to mechanical strain in vitro, usually using 2-dimensional tissue culture systems. Flexible silicone dishes [22, 38, 44] are used that can be connected to step engines that promote predominantly longitudinal strain (Fig. 1). 3- or 4-point bending machines were used to investigate changes in cell metabolism. However, the distribution of strain is less uniform in these systems [35]. Fluid shear stress [2], hydrostatic [1], and hydrodynamic loading [5] were applied to the cell cultures. In the 3-dimensional system, similar stress applications were investigated [3, 5, 35, 20]. Strain levels of between 1% (1,000 μ strain) and 10% (10,000 μ strain) were applied. Lately, mechano-bioreactors have been developed that support both simultaneous perfusion and mechanical stimulation [20]. Table 2 provides an overview of relevant studies that have investigated different strain patterns on undifferentiated and differentiated cells.

The response to the individual stress pattern depends on the initial cell phenotype, which is of eminent importance because in callus formation, differentiated and undifferentiated cells can typically be found simultaneously [10].

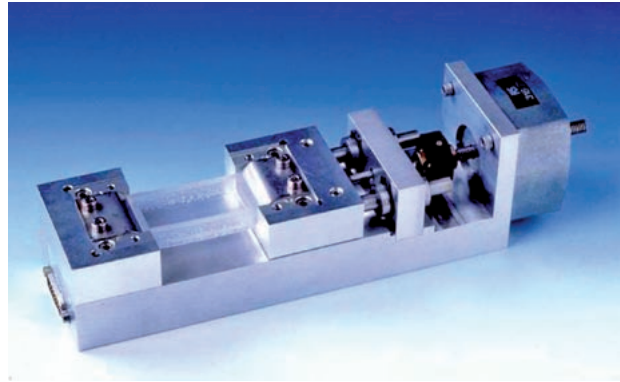


Figure 1: 2-dimensional mechanical stretching machine that has been used to investigate the effects of cyclic, mostly uniaxial stretching on fibroblasts [6, 17, 43, 48] and BMSCs [22]

Fibroblasts [48] have a time-dependent proliferative response to predominantly uniaxial stretching of 5% at 1Hz. After 6 and 24 hours, increased proliferation was observed following a period of 15 and 60 minutes of stretching. Cell alignment and orientation change as a response to the magnitude of applied stretching [38]. In this system, fibroblasts tolerate a lower strain limit than osteoblasts. Fibroblasts accumulate heat shock protein (HSP-72) within the nucleus after 15 and 60 minutes of cyclic stretching [23].

Reference	2-D/ 3-D	Cell origin	Stimulation	Results
Zeichen et al [13]	2-D	Human fibroblasts	5% at 1 Hz	Biphasic increase in proliferation after 15 and 60 minutes of cyclic stretching
Jin et al [25]	2-D	Bovine chondrocytes	1–3% sinusoidal shear stress; 0.01–1 Hz	50% increase in protein, 25% increase in proteoglycane
Kaspar et al [27]	2-D	Human osteoblasts	1% (=1000 μ strain)	Increased cell number, collagen I propeptide (CICP), decreased alkaline phosphatase (ALP), osteocalcine (OC)
Allen et al [19]	2-D	Bone cells	Fluid flow	Increased Ca ⁺⁺ deposition
Jagodzinski et al [12]	2-D	Bone marrow stromal cells (BMSC)	2 and 8% with and without 2.55 μ M dexamethasone	Upregulation Runx-2, collagen I and III, ALP, predominantly in groups stimulated with 8% stretching
Mauney et al [10]	3-D	BMSC; Clonetics®	4-point bending approximately –3% 0, 10, 100 nM dexamethasone	8 and 14 days: Proliferation, ALP and OC enhanced in groups with 10 nM dexamethasone
Angele et al [11]	3-D (pellet)	BMSC	Hydrodynamic	DNA equal, glycosaminoglycan and collagen contents higher after continuous stimulation
Bancroft et al [20]	3-D	BMSC	Hydrodynamic 0, 0.3, 1, 3 ml/min	Increased dose dependent Ca ⁺⁺ deposition, ALP and osteopontine (OP) higher after low perfusion
Jagodzinski et al [21]	3-D	BMSC	Perfusion 10ml/min, Compression 10% 10 nM dexamethasone	Perfusion significantly increases proliferation, tenascin-C expression enhanced by compression

Table 2: In vitro experiments using mechanical stimulation or perfusion and corresponding cell types

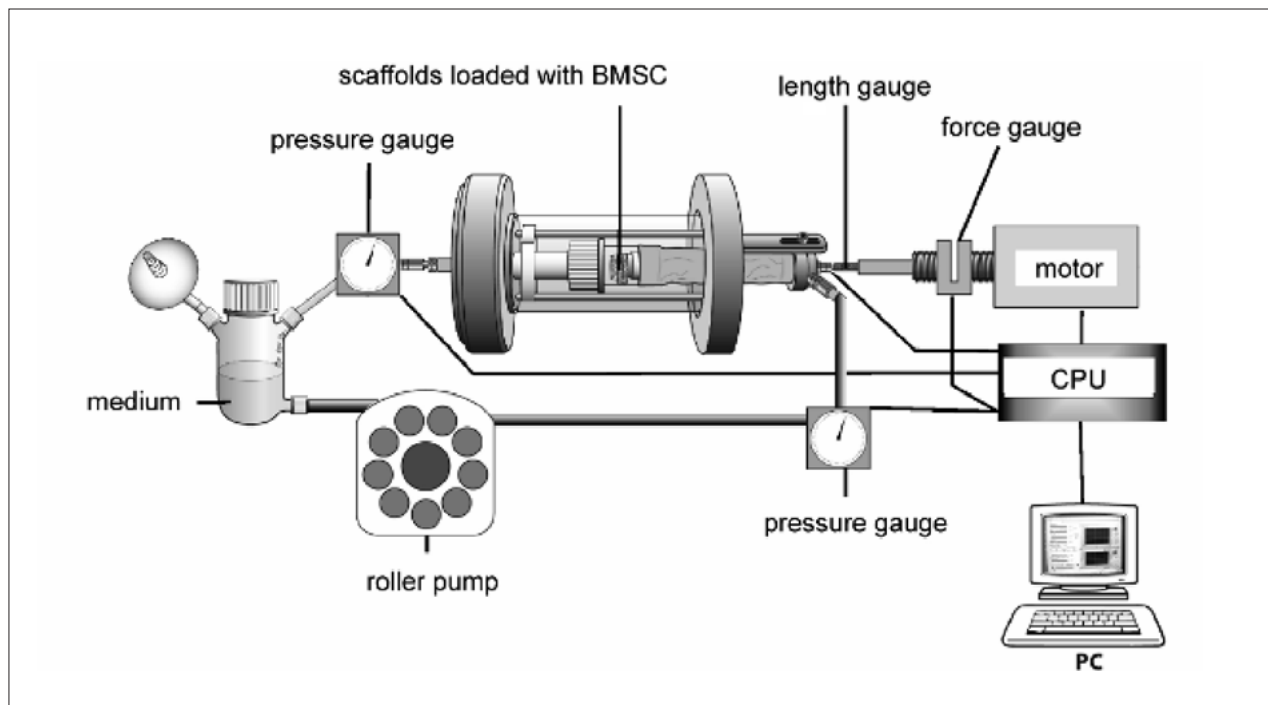


Figure 2: Perfusion-mechano-bioreactor used for the stimulation of 3-dimensional scaffolds seeded with BMSCs [21]. Hydrodynamic perfusion and/ or mechanical stimulation can be used to investigate cell proliferation and differentiation. Material testing can be performed during the experiment.

Chondrocytes [24] respond to shear loading at frequencies of 0.01–1 Hz with 1–3% strain magnitude with 50% increased synthesis of protein and a 25% increase in proteoglycan production. On the gene expression level, Maeda and colleagues elucidated a change in cartilage-specific (insulin like growth factor I (IGF-1), type II collagen, and aggrecan) mRNA

expression as a response to centrifugal stress of 2.7 MPa. The expression of IGF-1 for the stress groups was found to be significantly greater compared with the control group between days 3–5 of incubation, as was the mRNA expression of the type II collagen gene from days 7–14. No difference was found for the aggrecan content. This study and others [37]

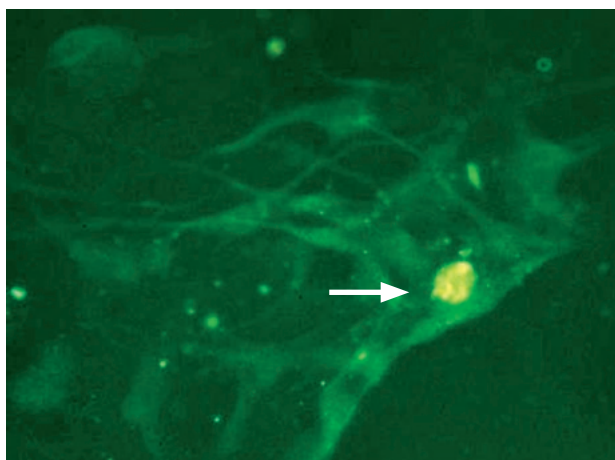


Figure 3: Fibroblasts seeded on silicone dishes respond to mechanical stretching of 10% for 15 minutes with a nuclear accumulation of heat shock protein (HSP-72; arrow) 4 hours after the termination of stretching [23]. Immunohistochemistry, magnification 400x

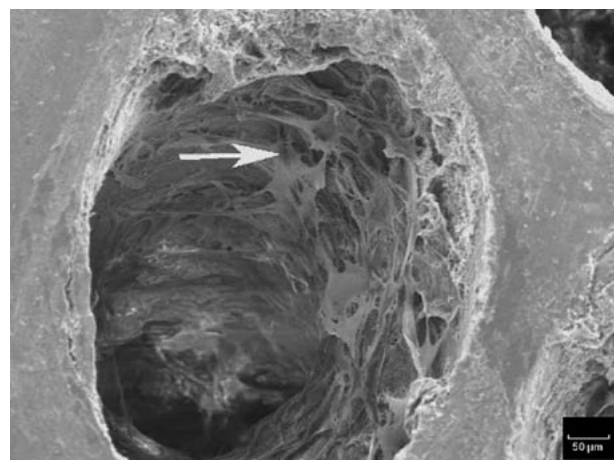


Figure 4: BMSCs (arrow) become adherent to the wall of a pore of a partially demineralised porous scaffold (Tutobone®, Tutogen Medical GmbH, Neukirchen a. Br., Germany) forming 3-dimensional clusters [21]. These constructs can be readily stimulated in a perfusion-mechano-bioreactor (Fig. 2). Raster electron microscopy, magnification 1500x

show that cellular stress in healthy chondrocytes is a prerequisite to stimulate collagen II expression.

Experiments with osteoblasts derived from cortical bone [25] indicate that there is an increase in proliferation and carboxyterminal collagen type I propeptide release as a response to predominantly uniaxial movement of 1% at 1Hz. At the same time, alkaline phosphatase (ALP) [20] and osteocalcin (OC) levels were significantly reduced. Cell orientation changes as a response to longitudinal stretching [38]. For strain rates up to 6%, osteoblasts align in the direction of the mechanical loading axis.

Bone marrow stromal cells (BMSC) can be differentiated into chondrogenic [1], fibroblast [3], and osteogenic phenotypes [21, 35] using mechanical stimulation. Differentiation depends on strain magnitude [20, 22] and growth factors, such as fibroblast growth factor (FGF-2) [3] or dexamethasone [10]. Indeed, Mauney and coworkers identified mechanical strain of approximately 3% supporting osteogenic differentiation if 100nM dexamethasone was added to the culture medium. No osteogenic response was found when no or 10nM dexamethasone were applied.

In conclusion, differentiated cells can be stimulated to proliferate and synthesize the cell-specific matrix components (fibroblasts [48], chondrocytes [33]). Osteocytes respond in a different manner by dedifferentiation and proliferation [24]. There is a cell-type-specific upper strain limit [38]. BMSCs can be differentiated into all cell phenotypes typically found in callus [1, 3, 10, 22] and this differentiation process can be supported by culture conditions and growth factors.

Is the interfragmentary strain theory relevant today?

The interfragmentary strain hypothesis predicts that fracture healing will occur only if the interfragmentary motion divided by the fracture gap width is less than the fracture strain of bone (2%) [10, 40]. Several studies that monitored fracture gap and movement of the fragments demonstrate that much higher initial movement is tolerated [9, 26, 36].

Moreover, according to the interfragmentary strain hypothesis, the likelihood of union will increase for a given interfragmentary movement if the fracture gap increases. There is now clear evidence that the opposite is true [9, 15] and that the strain patterns within an osteotomy or fracture gap are heterogeneous [12].

There is, however, a correlation between the size of the fracture gap and the time to union [9,

36]. A stimulation of 0.2 mm is necessary to support the production of callus. Higher amplitudes of up to 1 mm are tolerated; however, the fracture gap in a transverse osteotomy should not exceed 2 mm [10].

Consequences for up-to-date fracture fixation

Fracture fixation of the long bones has changed dramatically from the concepts of Böhler [7] with treatments ranging from a majority of conservative treatments and external fixation to open reduction and plate osteosynthesis. Today, intramedullary nailing and minimal invasive percutaneous plate fixation (MIPPO) are competing techniques that both enable restoration of axes, length, and rotation with limited impact on the fracture's perfusion levels (Fig. 5) [13, 14, 31, 41].

In a series of 99 open tibial shaft fractures [28], it was demonstrated that lag screws applied to further stabilize the fracture in combination with

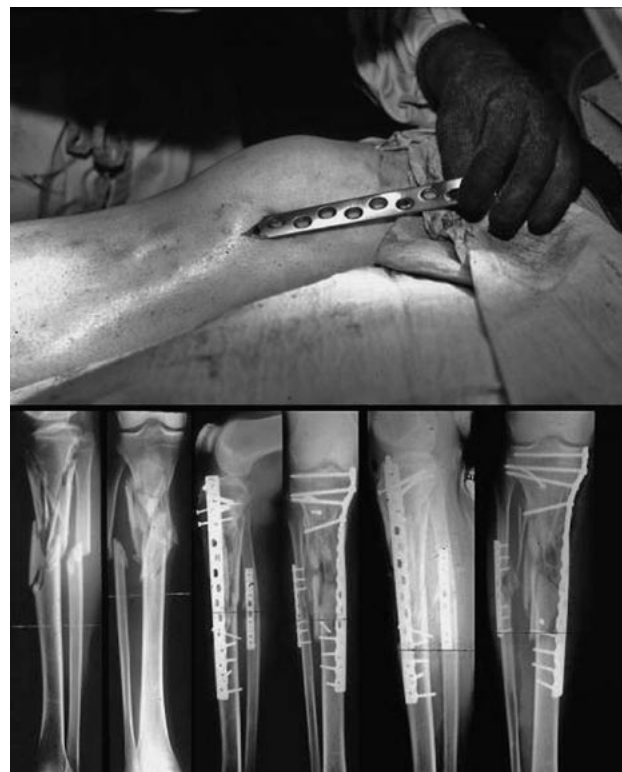


Figure 5: Minimally invasive plate osteosynthesis (MIPO) using a limited contact direct compression plate (LCD-CP) in an AO 42 C3.3 fracture [31]: care is taken to restore axis, rotation and length. The fracture site is left untouched to provide maximum blood supply and controlled micromotion of the fracture gaps.

external fixation, significantly reduce fracture consolidation (Fig. 6). In contrast, there are good union rates for shaft fractures that are stabilized with external fixators alone [9]. Time to union increases with increasing fracture gap size and is less in younger patients with less complex fractures and lesser degrees of soft tissue damage. In a series of 41 open tibial fractures, tibial nailing was superior to external fixation for time to full weightbearing, number of reoperations, isolated bone grafting, walking range, and average Karlstrom and Olerud scores [42].

In appreciation of the results that have been outlined in this article, today's fracture fixation should follow these principles:

1. Accurate joint surface reconstruction using open or arthroscopically guided osteosynthesis [30]. Lag screws are beneficial to achieve primary fracture healing in closed fractures [32].

2. In fractures of the long bones, accurate reduction of axes and rotation are desirable [29].



Figure 6: In a series of 99 open fractures [28], 55 were treated with external fixators and additional lag screw fixation, and 44 with external fixator alone. There were significantly more refractures in the group treated with lag screws. From left to right: AO 42 B2.1 fracture, OIIIA according to Gustillo and Anderson [18]: the fracture was treated with external fixator and four lag screws. After 35 weeks, refracture occurred and the fracture had to be stabilized with intramedullary reaming and an AO nail.

Whenever possible, blood supply of the fracture site should not be compromised [14, 31, 42].

3. If secondary fracture healing is the goal, movement of the fragments along the axes is beneficial for the formation of soft callus [19]. However, the fracture gap and the amplitude of movement should be kept small (amplitude: 0.2–1 mm; fracture gap < 2 mm) [10]. Higher strain amplitudes may be tolerated for different fracture patterns (spiral fracture, multiple fragments). Later, the formation of hard callus is compromised by vigorous mechanical stimulation [16]. Therefore, motion should be limited in the final phase of fracture consolidation. Ideally, this increase in fracture site stiffness is a biological response in terms of formation of hard callus.

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