Effect of mechanical stability on fracture healing — an update

Michael Jagodzinski, Christian Krettek
Hannover Medical School, Hannover, Germany

KEYWORDS:
bone marrow stimulation; mechanical stress; strain; stability fracture

Summary
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...
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 medullar 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.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Animal model</th>
<th>System applied</th>
<th>Load controlled</th>
<th>Distance controlled</th>
<th>Fracture gap (mm)</th>
<th>Strain applied (mm)</th>
<th>Frequency applied (Hz)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augat et al [2]</td>
<td>Sheep</td>
<td>Combined distraction and compression</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>0.2 and 0.8</td>
<td>1, 5, 10</td>
<td>No effective enhancement of bone healing</td>
</tr>
<tr>
<td>Matsu-shita and Kurokawa [7]</td>
<td>Rat</td>
<td>Isolated compression and distraction</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Both compression and distraction stimulate callus formation</td>
</tr>
<tr>
<td>Hente et al [8]</td>
<td>Sheep</td>
<td>Combined distraction and compression</td>
<td>Yes (22.5Nm)</td>
<td>Yes</td>
<td>2</td>
<td>1 (distraction and compression)</td>
<td>1.25; 1000 cycles per day</td>
<td>Bridging exclusively on the medullar side, non union on the cortical sides</td>
</tr>
<tr>
<td>Park et al [9]</td>
<td>New Zealand white rabbits</td>
<td>Telescoping external fixator</td>
<td>Yes (body weight as tolerated)</td>
<td>No</td>
<td>Transverse and oblique fractures</td>
<td>0.6 (transverse); 1.5 (oblique)</td>
<td>Not controlled</td>
<td>Oblique fractures with shear motion create most callus and stiffness</td>
</tr>
<tr>
<td>Goodship et al [6]</td>
<td>Pig</td>
<td>Combined distraction and compression</td>
<td>200N</td>
<td>No</td>
<td>3</td>
<td>1mm at 2.4, 400mm sec⁻¹</td>
<td>0.5</td>
<td>High strain rates increased callus formation early and inhibited the progress of healing when applied after 8 weeks</td>
</tr>
</tbody>
</table>

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 µstrain) and 10% (10,000 µstrain) 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].

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

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

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].
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-I 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]...
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]. 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 (MIPO) 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]. 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.

Bibliography


Correspondence Address:
Michael Jagodzinski
Hannover Medical School,
OE 6230, Carl-Neuberg-Str. 1,
30625 Hannover, Germany.
Tel: ++49 511 532 2050
Fax: ++49 511 532 5877
Email: Jagodzinski.michael@mh-hannover.de

This paper has been written entirely by the authors, and has received no external funding. The authors have no significant financial interest or other relationship.