Ultrasound stimulation of mandibular bone defect healing
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Chapter 1

General introduction
Chapter 1

Introduction
As long as humans exist, their bones have been at risk for fracturing by either injury or disease. As a consequence, various strategies have been developed to ensure an undisturbed healing of the bone after a fracture has occurred. In Hippocrates’ time, the principle of closed reduction and fixation of fractures was already known and applied, and in the last century the principle of open (operative) reduction and internal fixation became well-established. Nevertheless, bone healing does not always occur after the initial treatment of the fracture. To stimulate bone repair in these cases, different surgical and nonsurgical strategies have been explored. A widely used surgical strategy is the secondary surgical intervention in which bone grafts are used to stimulate the healing process. Non-surgical ways to stimulate fracture healing, by using for example electric and electromagnetic fields, can be found in early and recent literature. One relatively unknown way to influence bone healing is the use of ultrasound. Ultrasound therapy is based on the application of (micro)mechanical vibrations to the bone and bone cells. This treatment, using high frequency pressure waves, dates back more than 60 years and might eventually be used to stimulate maxillofacial bone healing.

Historical development
In France, at the beginning of World War I, the first ultrasound devices were constructed for military purposes to produce a high frequency sound wave for echo-location of submarines and measuring the depth of the sea. It was found that fish died when exposed to a strong ultrasound field, and this lead to the investigation of other biological effects. Therapeutic applications of ultrasound were initiated by Pohlman in 1938. In his opinion, the “root of disease lies in a stasis of metabolism” and ultrasound could eliminate this stasis by sending intense mechanical pulses through the bodily tissues. He constructed an ultrasound device that heated tissue locally (Figure 1). Empirically, ultrasound had been found beneficial in the treatment of various soft tissue disorders such as neuralgia’s and myalgia’s and this started a widespread use of ultrasound therapy to treat almost any physical disorder. Because ultrasound treatment of soft tissues occasionally involved the irradiation of bony structures, there was need to study the influence of ultrasound on bone. Since bone has a higher density than muscle or fat, ultrasound energy is more easily absorbed in bone and this would lead to bone overheating and possible damage.
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Indeed, it was found in animal experiments that ultrasound could lead to bone sclerosis, growth retardation, cyst formation and spontaneous fractures.\textsuperscript{11,12} Although the research on ultrasound and bone initially focused on bone damage,\textsuperscript{11-14} Maintz (1950)\textsuperscript{15} decided to focus on bone healing. In rabbits he attempted to stimulate fracture healing with ultrasound, but the ultrasound intensity was too high and resulted in bone damage. Later it became clear that ultrasound could in fact stimulate bone healing in certain cases when lowering the ultrasound intensity and by spreading the ultrasound energy over the tissue by moving the transducer across the skin during treatment.

After a few human case series in which ultrasound appeared to promote the healing of fractures in cases with a disturbed healing pattern,\textsuperscript{16-18} Hippe and Uhlman (1953)\textsuperscript{19} presented one of the first large series of 181 slow uniting fractures that were treated with ultrasound. In 154 cases (85\%), healing was obtained by using 800 kHz ultrasound with an intensity of 1 - 1.5 Watts per square centimetre (W cm\textsuperscript{-2}) for five minutes every other day, in total for 10 - 12 times. Treatment was applied under water or using a viscous gel. The ultrasound was administered through a moving transducer. An example was presented of a 41-year-old crane driver who suffered from a pseudarthrosis of his left humerus (Figure 2a). After 16 ultrasound treatments, the fracture was clinically stable. At this time, the radiograph showed bridging of the fracture gap (Figure 2b) and complete union remained in the following years (Figure 2c).
Despite the high success rate, ultrasound therapy did not show any effect in 4 cases. One of these cases involved a 51-year-old lady with a non-union of the femoral shaft. After 19 ultrasound treatments, no callus formation could be observed. A further attempt of open reduction and internal fixation using steel wires was unsuccessful, so the leg eventually had to be amputated.

Another large study has been conducted by Knoch (1965). More than 250 patients with fractures were treated with ultrasound. One series involved 31 slow uniting fractures at different locations (malleolar, patellar, clavicular, humeral, olecranon, radial and navicular fractures). 800 kHz ultrasound of 0.3 - 0.8 W cm\(^{-2}\) intensity was used for 5 - 8 minutes every other day. After 10 - 20 sessions, all fractures had united clinically. In another series, 100 fresh radial fractures were treated with ultrasound, and another 100 fresh radial fractures were not. The disability time, defined as the period from fracture until the patient resumed working again, was measured. Using ultrasound, a 41% reduction in disability time was observed. In another series of 28 fresh navicular fractures, a 60% reduction in disability time was noted. Despite these promising results, these studies on ultrasound and bone healing remained isolated in the literature and in the seventies there seemed to be little interest in this area.

Renewed interest in ultrasound treatment of bone

In South-America, research on ultrasound and bone healing was initiated by Duarte. After his thesis about ‘ultrasound stimulation of callus’, Xavier and Duarte reported the successful application of low intensity pulsed ultrasound (30 mW cm\(^{-2}\)) in the treatment of 27 non-unions. In 70% of the cases, complete healing was obtained by daily 20 minutes ultrasound exposure of the

Figure 2. A case of pseudarthrosis of the left humerus (a) successfully resolved with ultrasound therapy (b, c).
non-union site. This low intensity pulsed ultrasound field was later used in the development of the Sonic Accelerated Fracture Healing System (SAFHS, Smith & Nephew, Exogen, TN, USA) (Figure 3).

**Figure 3.** The Sonic Accelerated Fracture Healing System (SAFHS Model 2000®).

This is a battery-operated device, which emits a high frequency, pulsed, low intensity, ultrasound field. This ultrasound therapy is applied onto the skin overlying the fracture through a window made in the immobilisation plaster. In 1986 and 1987, two double blind randomised clinical trials were started with SAFHS ultrasound to treat fresh radial\(^23\) and tibial fractures.\(^{24}\) It was found that the time to union could be reduced up to 38%. The 20 minutes daily ultrasound treatment was also studied in large series of non-unions.\(^{25}\) A non-union was defined as a fracture that did not show clinical or radiographic signs of healing for more than 256 days (9 months). The average fracture age in this group was 692 days. Overall, healing was obtained in 83% of 1546 cases of non-union. After an average of 136 days of ultrasound treatment, these fractures were healed. In further studies, the positive effect of ultrasound on bone healing was found in different species such as the rat,\(^{26}\) rabbit,\(^{27}\) dog,\(^{28,29}\) and homo sapiens,\(^{23,24}\) and in different circumstances such as fresh fractures,\(^{23,24,30}\) delayed unions, non-unions,\(^{25,30,32}\) osteotomies,\(^{32}\) osteodistructions,\(^{33,35}\) and in cases of osteoradionecrosis.\(^{36}\) It has been reported that the pressure wave serves as a surrogate for physiological stresses in bone, which normally would stimulate bone formation.\(^{37}\) On a more basic level, the therapeutic effect of ultrasound may be related to piezo-electric\(^{38-41}\) and cell membrane effects,\(^{42-44}\) or to effects on the angiogenesis.\(^{45-48}\)

In 1994, the SAFHS device was approved by the American Food and Drug Administration (FDA) for 'the acceleration of the time to a healed fracture for
fresh, closed, posteriorly displaced, distal radius (Colles’) fractures and fresh, closed or grade I open tibial diaphysis fractures in skeletally mature individuals when these fractures are orthopedically managed by closed reduction and cast immobilization’,49 and later also for ‘non-unions excluding skull and vertebra’.50 In the Netherlands, the SAFHS device has been approved by the Dutch Medical Council (Ziekenfondsraad) only for the treatment of fractures without a tendency to heal.51 This approval was based on an estimated cost reduction in the management of these fractures of about Fl 10.000,- (Euro 4550,-) per patient when treated with ultrasound instead of surgical intervention. The treatment costs are, therefore, reimbursed by the Dutch health care providers.51

Therapeutic ultrasound in the maxillofacial region: focus on soft tissue disorders
In dentistry and maxillofacial surgery, ultrasound has largely been applied to treat various soft tissue and temporomandibular joint disorders. In the early years (1938 - 1949) ultrasound therapy of sinusitis, parotitis, trismus and trigeminal neuralgia had been advocated,52 but little notice was given to it within the maxillofacial surgery profession outside Germany. In fact, Erickson’s report published in an international journal (1964) to promote the use of ultrasound as a useful adjunct in temporomandibular joint therapy received little attention.53 Apart from one report in the seventies,54 it was not until the nineteen eighties that further research on maxillofacial therapeutic ultrasound was conducted. This research mainly concerned the reduction of postoperative edema55-57 and the treatment of musculoskeletal disorders such as temporomandibular joint pain and myofascial pain in the head and neck region.58-60 A definite effect of ultrasound could not be established. Ultrasound for the treatment of healing disturbances in the maxillofacial skeleton remained a curiosity. The few available reports concern the treatment of mandibular fractures in rabbits61 and humans,18 and the treatment of osteoradionecrosis of the mandible in humans.36 So, despite the reported positive effects of ultrasound on bone healing of the long bones, it may be concluded that little attention has been given to the possible effects of ultrasound on bone healing of the maxillofacial skeleton. If bone healing of the facial skeleton can be stimulated with ultrasound, several fields in maxillofacial surgery might benefit from this non-invasive therapy such as traumatology (accelerated fracture healing), oncology (treatment/prevention of osteoradionecrosis), implant surgery (accelerated implant osseointegration), and reconstructive surgery (bone defect healing, accelerated callus maturation after osteodistraction). However, this potential has not been investigated. Of the facial bones, the mandible is most frequently subject to fracture, osteoradionecrosis and in need of reconstructive pre-prosthetic surgery.
Especially the treatment of bone defects pose considerable challenges to the maxillofacial surgeon. It is therefore that the experiments presented in this thesis focus on the healing of bone defects of the mandible.

**Aim of thesis**
The aim of this study was to decide whether mandibular bone defect healing can be stimulated with low intensity pulsed ultrasound. This was done by:
1. Investigating the potential of ultrasound to stimulate maxillofacial bone healing in a literature review (Chapter 2),
2. Evaluating microradiography for the identification of bone/no-bone boundaries of rat mandibular defects (Chapter 3),
3. Using this technique to measure areas of bone growth into defects when exposed to low intensity pulsed ultrasound;
   - in plain mandibular defects in rats (Chapter 4.1),
   - in rat mandibular defects covered with expanded polytetrafluoroethylene (e-PTFE) membranes (Chapter 4.2),
   - and in rat mandibular defects covered with collagen membranes (Chapter 4.3),
4. Assessing if ultrasound can stimulate early bone formation in a distraction gap in the severely resorbed edentulous mandible in humans (Chapter 5).

**References**
Chapter 1