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● *Original Contribution*

CONTRAST-ENHANCED ULTRASOUND QUANTIFIES THE PERFUSION WITHIN TIBIAL NON-UNIONS AND PREDICTS THE OUTCOME OF REVISION SURGERY

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Abstract—Vascularity is one of the factors determining successful bone regeneration. This prospective study focused on quantifying the microperfusion of tibial non-unions with contrast-enhanced ultrasound (CEUS) 12 wk after revision surgery and comparing it with the osseous consolidation at a maximum of 24 mo assessed with standard radiography and computed tomography. Of 36 patients with tibial non-unions, 28 (77.8%) manifested consolidation, and 8 patients required further revision surgery. CEUS revealed significantly higher perfusion in consolidated versus persistent non-unions for all quantification parameters (e.g., wash-in perfusion index p = 0.036). Receiver operating characteristic analysis revealed a sensitivity of 82.1% and specificity of 75.0% with a wash-in perfusion index cutoff at 19.9 a.u. for diagnosing persisting non-unions. More than 1 y ahead of the final radiologic diagnostic examination, CEUS could predict eventual consolidation based on the osseous perfusion as soon as 12 wk postoperatively. This information can be crucial for the decision-making process for re-revision at an early stage.
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Key Words: **Contrast-enhanced ultrasound, Non-union, Bone regeneration, Revision surgery.**

INTRODUCTION

Approximately 10% of long-bone fractures become non-unions; this rate increases to 30% in high-risk patients (Tzioupis and Giannoudis 2007). The radiologic definition of a non-union is the absence of consolidation on radiography or computed tomography (CT) 12 to 26 wk after initial treatment (Bhandari et al. 2012). Non-unions consolidate more slowly than fractures, with treatment processes lasting longer than 1 y depending on the size of the defect (Fischer et al. 2017; Moghaddam et al. 2015). Patients usually describe constant pain in the affected limb, which aggravates under load, impairing the quality of life (Brinker et al. 2013).

Therefore, adequate revision surgery is paramount for a successful outcome. The diamond concept (Giannoudis et al. 2007) was developed for this reason and comprises the pillars of bone regeneration that need to be considered when treating non-unions, including their vascularity (Keramaris et al. 2008).

In this study, the non-union perfusion was measured with dynamic contrast-enhanced ultrasound (CEUS) using the contrast agent SonoVue (Bracco Imaging, Milan, Italy). There have been studies concerning peri-operative perfusion diagnostics of non-unions using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (Fischer et al. 2017). However, CEUS (Albrecht et al. 2004) has become an easily accessible alternative to DCE-MRI for non-hepatic applications as well (Piscaglia et al. 2012) and has successfully been used for non-union perfusion and infection analysis in conjunction with DCE-MRI (Fischer et al. 2016) before non-union revision surgery. CEUS has certain advantages compared with DCE-MRI: lower rate of complications from the ultrasound contrast agent (Jung et al. 2012; Piscaglia et al. 2006; ter Haar 2009), no requirement for laboratory testing before examination, no renal or hepatic toxicity and the possibility of bedside examination. Several studies have reported that the performance of CEUS in diagnosing malignant liver lesions is comparable to that of other contrast-enhanced examination modalities at a reduced cost (Westwood et al. 2013).

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Our intent in performing the post-operative perfusion analysis with CEUS was to decipher the process of bone regeneration in non-unions and explore further the uses of this cost-effective method. The CEUS results were compared with the definitive clinical and imaging outcome of the non-union. Differences between patients with osseous consolidation and persistent non-union were analyzed.

METHODS

This prospective study was conducted in accordance with the Declaration of Helsinki in the present form and was approved by the local ethics committee (S-033/2014). Thirty-eight patients with tibial non-unions were consecutively recruited before revision surgery between 2014 and 2016 at our tertiary care center. All participants agreed with the study protocol and gave their written informed consent before any study-relevant intervention. Inclusion criteria were a minimum age of 18 y, presence of a tibial fracture non-union, scheduled revision surgery and formal agreement with the study. Patients with a history of recent myocardial infarction (according to U.S. Food and Drug Administration guidelines), severe respiratory disease (as the contrast agent is eliminated via the lungs) or known allergic reaction to the ultrasound contrast agent SonoVue were excluded.

Twelve weeks after the last revision surgery, study patients underwent a CEUS examination in addition to the standard examinations, which included X-rays in two perpendicular planes and CT scans of the non-union, as well as a clinical examination by a board-certified trauma consultant (C.F./G.S.). The reason for the CEUS examination at the 12-wk follow-up was the intention of this study to capture the vascularization of soft callus formation, which begins after the initial inflammatory phase and slows down before the hard callus formation or remodeling phase (Tall 2018).

Non-union surgery

Depending on the initial condition of the non-union, two surgical methods were chosen. Without clinical or ultrasonographic signs of infection, debridement, implant replacement and bone grafting were performed in a single step (n = 10). In cases of suspected infection (*e.g.,* after initial open fracture, history of multiple previous operations, purulent secretion or strong non-union perfusion in pre-operative CEUS (Fischer et al. 2016)), a multistep Masquelet procedure with debridement, implant removal and insertion of a Refobacin Palacos spacer (Heraeus, Wehrheim, Germany) was performed (n = 26). This procedure was repeated at 1-wk intervals until bacteria were no longer microbiologically confirmed and there was no longer any clinical aspect of infection intra-operatively, so that re-osteosynthesis and bone grafting could be realized. Autologous bone graft *via* the reamer–irrigator–aspirator (RIA) technique (Kobbe et al. 2008) or from the iliac crest was used depending on the size of the defect. Locking compression plates and intramedullary nails were the two methods of choice for revision osteosynthesis.

Radiologic evaluation

A board of three consultants (one radiologist and two trauma surgeons), who were blinded to all other data, evaluated the X-rays and CT scans at regular follow-up examinations for consolidation up to a maximum of 24 mo after the last revision surgery (Fig. 1). The CT criteria of non-union consolidation were used according to previous

Fig. 1. Radiologic evaluation of a healing tibial non-union. The three stages showcased are before the last revision surgery (a), 12 wk postoperatively (b) and 52 wk postoperatively (c). The contrast-enhanced ultrasound examinations predicting the consolidation of a non-union were also carried out 12 wk postoperatively.