ΔThe Temporal and Spatial Development of Vascularity in a Healing Displaced Fracture

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Background/Purpose: Underlying vascular disease is an important pathophysiology shared among many comorbid conditions associated with poor fracture healing, such as diabetes, obesity, and age. Determining the temporal and spatial patterns of revascularization following fracture is essential for devising therapeutic strategies to augment this critical reparative process. Seminal studies conducted in the last century have investigated the pattern of vascularity in bone following fracture. The consensus model developed from these studies is of angiogenesis emanating from both the intact intramedullary and periosteal vasculature. Since the plethora of experimental fracture angiography in the early to mid-20th century there has been a paucity of reports describing the pattern of revascularization of a healing fracture. Consequently the classic model of revascularization of a displaced fracture has remained largely unchanged. Overcoming the limitations of animal fracture models performed in the above-described classical studies, we demonstrate for the first time the complete temporal and spatial pattern of revascularization in a displaced/stabilized fracture. These studies were designed specifically to (1) validate the classic model of fracture revascularization of a displaced/stabilized fracture, (2) assess the association between intramedullary and periosteal angiogenesis, and (3) elucidate the expression of vascular endothelial growth factor (VEGF)/VEGF-R (VEGF receptor) in relation to the classic model.

Methods: Midshaft femoral osteotomies (n = 52) were fixed with an intramedullary nail. Fracture healing was followed with radiographs, micro-CT, angiography, and histology at 7-42 days post fracture

Results: Representative data of vascularity during fracture repair are presented in Figure 1. Fractures with significant injury to the intramedullary vasculature revascularize initially through the development of a transperiosteal vascular network as a result of increased flow diverted centrifugally resulting from interruption of downstream medullary vascularity. In support of this observation, many enhanced vascular anastomoses developed between the medullary vasculature and the areas of periosteal vascular engorgement. Following the initial phases of fracture revascularization, there exists centrally an avascular cartilaginous matrix predominated by VEGF-A/VEGFR-1 negative cells surrounded by a richly vascular new bone matrix predominated by endothelial cells and osteoblasts expressing high levels of VEGF-A/VEGFR-1 peripherally. Histological data revealed hypertrophic VEGF-A producing chondrocytes in all areas of transition from avascular/soft tissue to vascular hard tissue callus. The chondrocytes continued to hypertrophy and release VEGF-A in a manner that directs the polarized bone formation together; the periosteal vasculature and bone

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eventually unite. Following vascular union our results reveal that bone remodeling follows vascular remodeling in which intramedullary vascularity is re-established.

Conclusion: From these data, in conjunction with classic studies of fracture angiogenesis, we propose a novel model defining the process of bone revascularization. It is our hope that this new model of fracture revascularization of displaced/stabilized fractures will provide insight into the cause of impaired fracture healing, and potential means to restore bone healing.

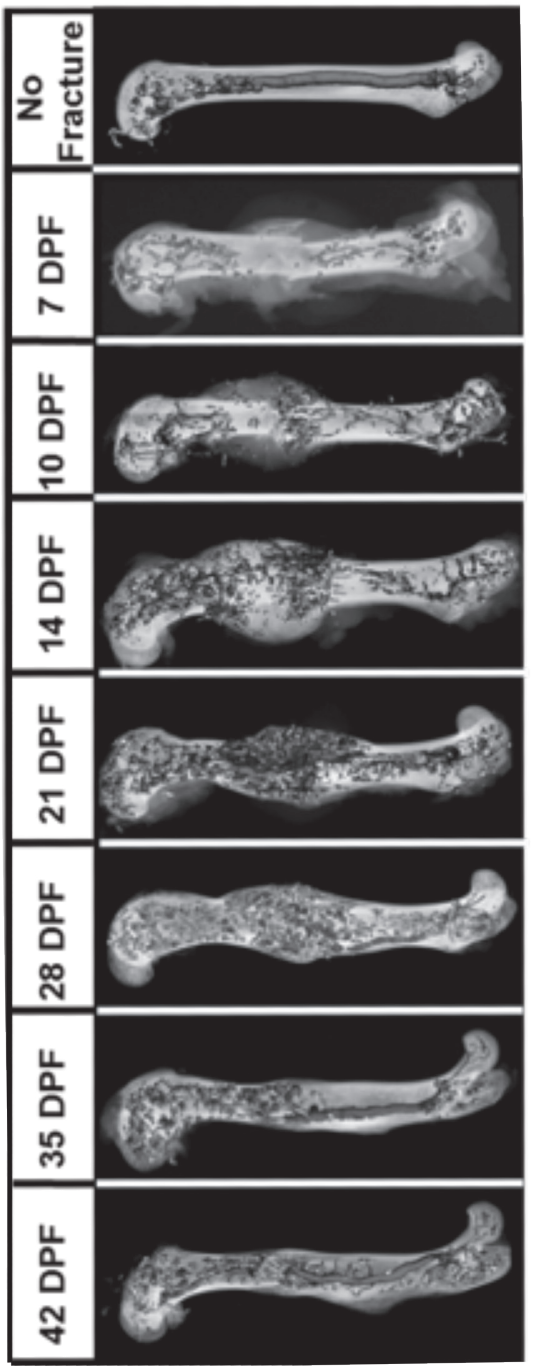

Figure 1.
Angiograph of femur facture from 0 to 42 days post fracture (DPF). Color denotes vessel size

See pages 99 - 147 for financial disclosure information.