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## **Hypoxia in Static and Dynamic 3D Culture Systems for Tissue Engineering of Bone**

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### **Abstract:**

Tissue engineering of sizeable cell-scaffold constructs is limited by gradients in tissue quality from the periphery toward the center. Because homogenous delivery of oxygen to three-dimensional (3D) cell cultures remains an unsolved challenge, we hypothesized that uneven oxygen supply may impede uniform cellular growth on scaffolds. In this study we challenged static and dynamic 3D culture systems designed for bone tissue engineering applications with a well-growing subclone of MC3T3-E1 preosteoblasts and continuously measured the oxygen concentrations in the center of cell-seeded scaffolds and in the surrounding medium. After as little as 5 days in static culture, central oxygen concentrations dropped to 0%. Subsequently, cells died in central regions of the scaffold but not in its periphery, where oxygen levels were ~4%. The use of perfusion bioreactors successfully prevented cell death, yet central oxygen concentrations did not rise above 4%. We conclude that 3D culture *in vitro* is associated with relevant oxygen gradients, which can be the cause of inhomogeneous tissue quality. Perfusion bioreactors prevent cell death but they do not entirely eliminate 3D culture-associated oxygen gradients. Therefore, we advise continuous oxygen monitoring of 3D culture systems to ensure tissue quality throughout engineered constructs.