EVIDENCE FOR DOSE-DEPENDENT REPERFUSION INJURY IN BONE AFTER LIMB ISCHEMIA: A RABBIT Tibial BONE CHAMBER INTRAVITAL MICROSCOPY STUDY

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INTRODUCTION: Traumatic ischemic osteonecrosis (T-ION) is a complication found most frequently in the hip following subcapital fracture or dislocation. Untreated, it will usually advance to osteoarthritis after the subchondral cortical plate collapses, leading to a need for total hip arthroplasty. In its early stages it is undetectable. All cases of ION are highly correlated with ischemia and models developed for T-ION directly create ischemia. In the present model traumatic ischemia was created by compressing the thigh, and the cortical plate was modeled by tibial cortex. The hypothesis tested was that reperfusion injury (RI) during the 24 hours following occluder release and net resorption of bone during the creeping substitution of bone recovery would exhibit dose-dependent effects.

METHODS: Critical limb ischemia was produced in 18 NZW rabbits by occluding limb vessels at mid-thigh with a pneumatic cuff for 2, 4 and 6 hours (2h, 4h, 6h). Six rabbits were used for each ischemia dose. Controls were 6 unoccluded rabbits (0h). Immediate sequelae and subsequent recovery were observed in vivo through an implanted tibial window, the optical bone chamber (BCI), using brightfield and epi-fluorescence intravital microscopy.

RESULTS: Figure 1, 2) vessel caliber history, shown in Fig. 2, and 3) net bone resorption history, shown in Fig. 3. Mean differences in vessel dose-responses to 4 and 6 hours ischemia were not significant, as shown in the table. But net bone resorption was strictly dose-dependent. Reperfusion injury was confirmed by decrease in perfusion, increase in vessel permeability and caliber (see Fig. 2), and leukocyte adherence during the first 14 hours post-ischemia.

CONCLUSIONS: The data do not support a simple dose-dependency of RI extent on ischemia duration. Rather, a threshold at or above 2h is associated with the appearance of RI, the extent of which plateaus near 4h. It appeared that RI produced a secondary ischemia, which amplified the artificially created primary ischemia and may have been followed by successive episodes of ischemia, which followed the infarction pattern of ischemic coronary vessels. The conclusion of dose-dependent post-ischemia increased angiogenesis is supported by the drop in vessel caliber coupled with increased perfusion for the 6h and 4h doses. When this conclusion is coupled with dose-dependency of net resorption one is led to the further conclusion that resorption is linked to a high incidence of small caliber vessels such as venular capillaries from which circulating pre-osteoclasts can easily extravasate. Bundles of such vessels were observed in Haversian canals of old (presumably at least partially necrotic) bone which exhibited large resorption pits.

DISCUSSION: The present model does not duplicate clinical conditions commonly associated with T-ION. Its ischemia results from compression, which introduces crush injury and compartment syndrome, which nonetheless can cause clinical ION. Trabecular, not cortical bone is the major osseous component of clinical ION. However, the subchondral cortical plate which forms a protective shell between articulating surface and trabecular bone is an important mechanical component of the hip. Its role in the etiology of and healing response to T-ION has not been adequately studied. In a circulatory disease such as ION an understanding of the behavior of vessels during each phase is critical for detecting causal links which determine its etiology. In particular, understanding the interplay between resorption, apposition and microradiation during creeping substitution is a key to being able develop both diagnostic approaches and treatments.


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