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Microcirculation injury is involved in anthracycline-induced cardiac toxicity

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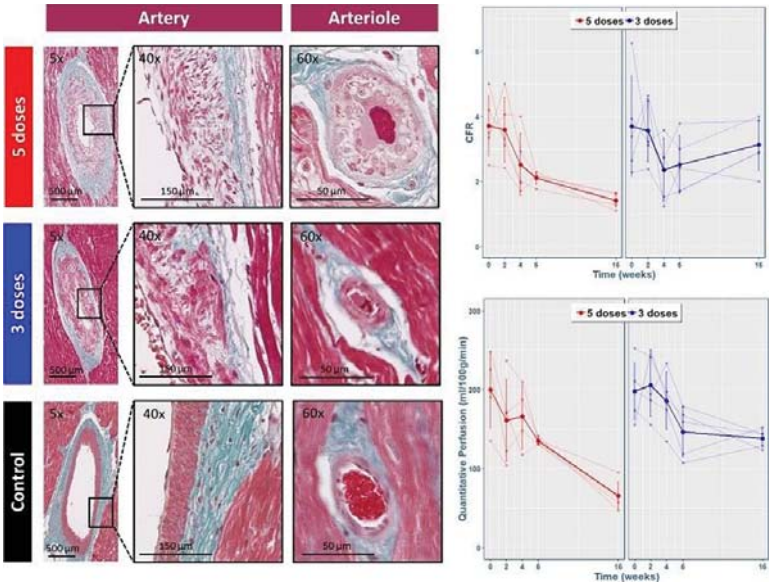
Background/Introduction: Cardiotoxicity (CT) is a major concern for cancer patients receiving anthracyclines. While the effect of anthracyclines on cardiomyocytes is well established, its impact on myocardial microcirculation has not been characterized.

Purpose: To evaluate the effect of low and high cumulative doses of doxorubicin (doxo) on anatomical and functional vasculature status evaluated by serial invasive Coronary Flow Reserve (CFR) and Cardiac Magnetic Resonance (CMR)-based quantitative perfusion in a large animal model.

Methods: Large-white male pigs (n=15, 30 kg) were distributed in 2 doxo regimes: Group 1) high cumulative dose (5 biweekly intracoronary (i.c) injections of 0.45 mg/kg of doxo) followed-up until week 16 (a time when severe left ventricular systolic dysfunction is present) and then sacrificed (N=5); Group 2) low cumulative dose of doxo (3 biweekly i.c. doses) followed-up until week 16 and then sacrificed (N=5)). Group 3) pigs sacrificed at 6 weeks (2 weeks after third doxo dose), N=5. Invasive catheter-based CFR was evaluated after i.c papaverine (0.5 mg/kg) while CMR quantitative rest perfusion maps were obtained after intravenous injection of gadolinium. CFR and CMR were performed before doxo, and at 0, 2, 4, 6 and 16 weeks thereafter. Cardiac vessels were evaluated ex vivo with trichrome staining. Statistical analysis was performed using one-way ANOVA with multiple pairwise comparisons (vs. baseline) and Bonferroni corrected p-value.

Results: CFR and CMR-quantitative myocardial perfusion were non-significantly reduced after 3 doxo doses despite myocardial vasculature was overtly injured on histology at this timepoint. Animals receiving 5 doxo doses suffered a progressive deterioration of CFR and CMR-perfusion until week 16 (1.41±0.23 vs 3.71±0.94 at baseline [p=0.014] and 65.4±18.2 ml/100g/min vs 154.9±56.3 ml/100g/min at baseline [p=0.046], respectively). At 16 weeks histology revealed extensive microvascular damage with media layer involvement and perivascular fibrosis. Pigs receiving 3 doxo doses showed less pronounced CFR reduction on long-term follow-up (3.13±0.82 vs 3.69±1.57 at baseline [p>0.05] but overt CMR-perfusion reduction (138.3±11.9 vs 197.8±37.1 at baseline [p=0.045]). On histology, damage of vasculature including arterioles was evidenced to a lesser extent than in the high cumulative doxo dose group with mild microvascular disruption and smooth muscle vacuolization.

Conclusions: Doxorubicin results in a progressive damage of the myocardial microcirculation. Even low cumulative doxo doses (resulting in no overt left ventricular dysfunction) results in vascular damage. The microcirculation status may serve as an early marker of doxorubicin cardiotoxicity.



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