The Effect of Long-term Administration of Prostaglandin E₁ on Morphological Changes in Ductus Arteriosus

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Abstract

The morphological and histopathological effects of PGE₁ infusion for ductus arteriosus were clarified through novel modality XPCT and immunohistochemical analyses, EP4, and LOX expression. Recognition of microstructural changes of ductal tissue induced by extended administration of PGE₁ is profound to establish the safety usage of PGE₁ for HLHS patients with staged Norwood repair.

Keywords

Ductus arteriosus · Prostaglandin E₁ · Hypoplastic left heart syndrome · X-ray phase contrast tomography

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44.1 Introduction

Prostaglandin E₁ (PGE₁) is essential to maintain the ductus arteriosus (DA) in ductal-dependent congenital heart diseases. Recently, relatively long-term administration of PGE₁ has become common, especially in patients with hypoplastic left heart syndrome (HLHS). Staged Norwood approach which consists of PGE₁ infusion, bilateral pulmonary artery banding and Norwood procedure provided excellent survival benefit. However, microstructural changes in DA after long-term PGE₁ administration remain unknown. Therefore, we sought to investigate the features of DA after long-term PGE₁ infusion using synchrotron-based X-ray phase contrast tomography (XPCT), a novel modality to inspect biological soft tissue and pathological scrutiny including DA-specific immunostaining.

44.2 Methods

Seventeen DA tissues from HLHS patients were obtained during the Norwood procedure. The median duration of PGE₁ was 48 days (range 3–123). Radiographic microstructural analysis of DA was performed using XPCT at SPring-8 (Hyogo, Japan). Histological changes focused on elastic fiber and smooth muscle formation were evaluated by Elastica van Gieson staining. Expressions of prostaglandin E₂ receptor (EP4) and LOX, a cross-linking enzyme that forms insoluble mature elastic fibers, were evaluated by immunohistochemical analyses.

44.3 Results

The XPCT study showed sclerotic changes in ductal media. There was a significant correlation between the duration of PGE₁ infusion and the mass density of ductal media ($R: 0.723, p = 0.001$). The histological study showed that the duration of PGE₁ infusion was positively correlated with the elastic fiber formation ($R: 0.795, P = 0.002$) and negatively correlated with smooth muscle formation in a disorganized manner ($R: -0.83, P < 0.001$). EP4 was disappeared in DAs that were administered PGE₁ over 20 days. LOX expression was observed in all DAs, especially LOX strongly emerged in specimens where elastic fiber formation was immature.

44.4 Conclusion

Long-term administration of PGE₁ induced disorganized elastogenesis and density growth of the ductal media. In addition, downregulation of EP4 and LOX expression might emphasize this hypothesis. These results suggested that the dosage of PGE₁ could be decreased after a definite period of administration.

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