Enhanced expression of iNOS is associated with aortic valve stenosis in patients with bicuspid aortic valve

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Background: A congenital bicuspid aortic valve (BAV) is one of the most common congenital cardiac abnormalities, with a prevalence estimated between 0.5% and 2%. Aortic valve stenosis (AS) is the most common complication in patients with BAV. The mechanisms responsible for the rapid progression of AS in patients with BAV relative to those with a tricuspid aortic valve (TAV) are unknown. A previous study showed that the pathogenesis of AS in patients with BAV is associated with a more aggressive inflammatory process, with increased macrophage infiltration and neo-vascularization when compared with that seen in patients with TAV. A considerable number of human diseases have an inflammatory component, and a key mediator of immune activation and inflammation is inducible nitric oxide synthase (iNOS). Overexpressed iNOS has been implicated in the pathogenesis of numerous conditions, including coronary plaque destabilization. To elucidate the role of iNOS in the aortic valve of patients with AS, we carried out an immunohistochemical study of the presence of iNOS in aortic valve specimens from patients with AS with either TAV or BAV.

Methods: Frozen aortic valve samples were obtained surgically from patients with AS with TAV (n=34) or BAV (n=34), and stained with antibodies against macrophages, microvessels, iNOS and 4-hydroxy-2-nonenal (4-HNE), an index of lipid peroxidation. The immunoreactivity of macrophages, microvessels, iNOS and 4-HNE was quantified using computer-aided polarimetry. Double immunostaining was also performed to identify cell types that stained positive for iNOS.

Results: Quantitative analysis demonstrated that macrophage-, iNOS-, and 4-HNE-positive areas, as well as the number of microvessels, were significantly higher in patients with BAV than with TAV (macrophages, P<0.001; microvessels, P<0.05; 4-HNE, P<0.05; iNOS, P<0.001). The iNOS-positive area was positively correlated with the 4-HNE-positive area (R=0.43, P<0.0001). Double immunostaining for both iNOS and macrophages identified iNOS-positive cells as macrophages.

Conclusions: These findings suggest that accumulation of iNOS in macrophages may increase oxidative stress and contribute to the rapid progression of AS in patients with BAV.