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Commentary: Preventive treatment of right-sided heart failure before adulthood?

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Some cardiac dysfunction develops early before leading to cardiac failure. Increased ventricular pressure load leads to right-sided heart failure and determines outcome in many congenital heart diseases, including pulmonary hypertension and hypoplastic left heart syndrome.^{1,2} Treatment options are scant since the chronic nature of pressure overload induces often irreversible remodeling of the heart.

Bossers and colleagues³ present an experimental model to study the interaction of neuregulin-1 during the development of right-sided heart failure in rat pups. Neuregulin-1 is an endothelial cell-derived growth factor that is essential to functional and structural development of the heart, including cardiomyocyte antiadrenergic and antiapoptotic effects.⁴ Pulmonary artery banding was done in a controlled fashion, which resulted in a reproducible range of cardiac dysfunction. Neuregulin-1 was administered intraperitoneally, the rats were humanely killed after due follow-up, and echocardiography, histology, immunohistochemistry, and gene expression results were analyzed. The aim was to assess the adaptation to pulmonary artery pressure load in the postnatal phase and to investigate the effects of neuregulin-1 on developing right-sided heart failure.

As compared with controls, pressure load of the right ventricle increased in the banded pups, resulting in reduced cardiac index and increased cardiac stroke volume, all of which led to clinical signs of right-sided dysfunction, increased fibrosis, and changes in cardiomyocyte cell-cycle activity. Markers of cardiac and oxidative stress increased during pressure load. Temporary cardiomyocyte

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CENTRAL MESSAGE

When would it be safe to treat right-sided heart failure with neuregulin-1, which interacts with cardiomyocyte cell-activation?

cell-cycle, metabolism, and immunity-related genes reflected the development of right-sided heart failure. Neuregulin-1 treatment of banded pups adapted cardiomyocytes to enhanced cell-cycle activation, delayed fibrosis, and improved cardiac function.

The project was logically written and clear. An excellent video clip was provided to show the elegant technique of the pulmonary artery banding in a standardized fashion. The model described cardiac remodeling from rat childhood until early stages of right-sided heart failure. The authors concluded that neuregulin-1 may provide a means to delay the onset of right-sided heart failure after pulmonary pressure load.

In contrast, neuregulins participate in the regulation of cell survival and proliferation also in cancer cells and neural cells.⁵ Neuregulin-1 may include dualistic development of fibrosis including both adaptive and maladaptive responses to heart failure and cardiomyocyte cell-cycle activation without progression to actual mitosis during cardiac remodeling. The authors interpret the described gene expressions at different time points as part of metabolism, maturation, cell-cell activation, and immunity, but are the molecules reflecting the state of cardiac remodeling or the effect of neuregulin-1 itself?

Previously, progression of experimental heart failure induced by aortic stenosis was associated with both the activation and inactivation of neuregulin-1-related molecular interactions in a time-dependent fashion.⁶ Similarly, Bossers and colleagues³ hint that there is an effective treatment time window to postpone the onset of right-sided heart failure. Since the consequences of right ventricular pressure

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load are difficult to treat once right-sided heart failure has occurred, it may be worth aiming medical treatment already at the very early phase of childhood. Plausible neurotoxicity of early neuregulin-1 administration would also be interesting to study before heart failure.⁷

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