Early origins of cardiovascular disease: The heart of the matter

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Cardiovascular disease currently affects over 3 million Australians. Reduced growth in fetal life together with accelerated growth in childhood results in an increased risk of hypertension and ~50% greater risk of coronary heart disease in adult life. It is unclear why changes in growth patterns in early life lead to a vulnerability to cardiovascular disease. Left ventricular hypertrophy is the strongest predictor of progressive heart disease and poor cardiovascular outcomes in adult life. Pathological ventricular hypertrophy begins as an adaptive response to increase cardiac pump function. However, if this response is prolonged it can lead to dilated cardiomyopathy, heart failure and sudden death. We propose that the mechanisms that support the growth of the heart when substrate supply is restricted during fetal life are the same as those which are recruited to induce pathological hypertrophy in later life. This may explain the vulnerability of the heart to the development of cardiovascular disease as the heart ages and is required to undergo hypertrophy in response to ischemic heart disease or hypertension in order to maintain cardiac output. Insulin-like growth factor 1 (IGF1) has been implicated in the initiation of ventricular hypertrophy. In a range of experimental models, IGF1 acts *via* the IGF1 receptor (IGF1R) both *in vivo* and *in vitro* to increase the size of cardiomyocytes. Recently it has been shown *in vitro* that when the IGF1R signalling pathway is blocked, addition of IGF2 results in an increase in the size of cardiomyocytes. This suggests that IGF2 may act to stimulate heart cell growth through the IGF2 receptor (IGF2R), which is interesting as the IGF2R has traditionally been viewed as a receptor which acts to clear IGF2, rather than as a receptor which is part of a ligand mediated growth pathway.

The adaptation of the fetal heart to a period of reduced substrate supply and decreased body growth has critical consequences for heart health in later life because at birth, the human heart contains most of the cardiomyocytes it will have for life. The growth of the heart in early development initially occurs through the division and hence proliferation of mononucleated cardiomyocytes which then undergo differentiation to form binucleated cardiomyocytes. These cells are unable to divide and heart growth then predominantly occurs through an increase in the size of the binucleated cardiomyocytes (hypertrophy). In a sheep model of intrauterine growth restriction (IUGR), induced by restriction of placental growth, we have investigated the proliferation and growth of cardiomyocytes and the pattern of differentiation of mononucleated to binucleated cardiomyocytes in the fetal heart. We have found that heart mass was maintained relative to fetal body mass, but that there was a relative increase in the size of binucleated cardiomyocytes in the heart of the IUGR sheep fetus. In addition, the low birth weight lamb has increased relative left ventricular weight at 21d of age. We propose that in response to a poor substrate supply in the fetus, the IGF1R signalling pathway plays a protective role in the heart through its anti-apoptotic and angiogenic actions. We also suggest that once up-regulated, the IGF2R signalling pathway mediates cardiomyocyte hypertrophy. This is a novel and significant hypothesis as it places the IGF2R, rather than the IGF1R, signalling pathway as a key mechanism underlying the changes in heart cell growth *in utero* which may contribute to a later vulnerability of the heart to pathological hypertrophy.