A NEW RISK FACTOR FOR EARLY HEART FAILURE: PRETERM BIRTH

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Preterm birth as a new risk factor for heart failure

New onset heart failure in children and adolescents, in the absence of congenital cardiac disease, is very rare, estimated at <1:100,000. However, when it occurs, it is devastating, with some reports suggesting up to one third of patients either die or require heart transplantation (1). In this issue of the *Journal*, Carr *et al.* report incidence of heart failure in a Swedish national cohort registry of over 2.6 million young people, with and without structural cardiac disease, born between 1987-2012 (2). Rates of early heart failure during this period appear to be similar in Scandinavia as previously reported for other countries, with a typical bimodal age distribution characterised by peaks before age 5 years and in very early adulthood.

The striking new finding was that a disproportionate number of individuals born preterm developed heart failure, even when there was no history of structural cardiac problems. The impact of pregnancy history was so pronounced that being born extremely preterm (<28 weeks gestation) increased risk 17-fold, while those born very preterm (28-31 weeks gestation) had a 4-fold increased risk. These findings were independent of other potential confounders, such as growth restriction, providing the first evidence of a link between the degree of prematurity and risk of incident heart failure by young adulthood.

Why preterm birth might predispose to early heart failure

Why should those born preterm be more likely to develop new onset heart failure during the first decades of life? During this period, idiopathic dilated cardiomyopathy or myocarditis are considered the most likely causes, with a smaller number of individuals identified as having a family history or arrhythmia (1). Mechanistic links between these diagnoses and a preterm delivery, which could have occurred 15 to 20 years before the event, might not immediately be apparent. However, Carr *et al* had an *a priori* hypothesis that preterm birth would increase

risk based on a body of evidence that has shown premature delivery is directly linked with altered myocardial development. Several years ago it was noted that preterm-born sheep have a five- to seven-fold greater cardiomyocyte hypertrophy during postnatal development than term controls. On histology, their hearts showed increased interstitial myocardial fibrosis and abnormal cardiomyocyte maturation (3). Bertagnolli *et al.* demonstrated similar results in a rat model of an extrauterine preterm environment with sustained increases in left ventricular hypertrophy during the postnatal period (4).

Clinical studies in humans support these observations. Kozák-Bárány *et al.* found left ventricular mass increased 56% in preterm infants during the first postnatal month compared with 35% in those born at term (5). We performed serial echocardiograms during fetal and postnatal development in a study involving nearly 400 infants and demonstrated that this hypertrophic response occurs exclusively postnatally and is disproportionate to the normal body size catch up seen in those born preterm (6). The left ventricular mass increase during the first three months of life is two-fold greater, relative to the change in body size, than occurs in those born at term. Young adults born preterm show similar patterns of increased left ventricular mass related inversely to gestational age and independent of variation in blood pressure in later life (7). Interestingly, the geometric shape of the heart is distinct in both infancy and adult life and can be captured with cardiac statistical atlases built from echocardiography and cardiovascular magnetic resonance images. Cardiac function also differs with reduced left and right ventricular systolic and diastolic measures (6). Strikingly, 6% of those studied in adulthood had right ventricular systolic function below the clinically accepted lower limit of normal (8).

Why might altered myocardial development increase heart failure risk?

Although there is now strong evidence for an altered cardiac phenotype in those born preterm, it seems unlikely these differences could be the sole 'cause' of the acute episodes of heart failure in the report by Carr *et al.* Up to two thirds of children and young adults with acute heart failure recover their cardiac function after the episode (1) and the majority of young people with heart failure in the registry were actually born at term (2). Both observations suggest a pathogen, agent or familial predisposition, independent of preterm birth, remains the most likely 'trigger' of episodes of acute heart failure during this early period of life. The altered myocardial development in those born preterm could then make them less 'resilient' and result in a more precipitous decline in cardiac function [Figure 1].

This hypothesis is consistent with experimental models that show the myocardial developmental patterns linked with preterm birth progress more rapidly to heart failure when challenged with a low dose angiotensin II infusion, which mimics exposure to hypertension (9). It is possible other biological variation linked with preterm birth, such as altered immune, respiratory or vascular development, may also contribute and this will require further investigation (10-12). An immediate question that arises is: could this same reduced 'resilience' be relevant to adult-onset heart failure? In the last 20 to 30 years perinatal survival of those born preterm has increased significantly due to advances in medical care. This generation of preterm survivors is now entering adulthood (13). When exposed to adult cardiovascular risk, hypertension or myocardial injury will they also be more likely to develop heart failure in adult life? [Figure 1]

Future directions

Substantial evidence indicates preterm birth results in altered postnatal myocardial development (6) and that these patterns of change in myocardial structure and function are still evident in adult life (7). Carr *et al* have provided the first evidence that preterm birth also substantially increases risk of clinical heart failure; demonstrated in the rare situation of heart failure presenting during childhood and adolescence (2). Would it have been possible to intervene to improve myocardial development and protect against this future risk of cardiovascular disease? Experimental studies have indicated some interventions, including postnatal pharmacological approaches, can improve myocardial development during the critical postnatal window (9). In humans, we have shown postnatal nutrition may also be relevant as exclusive human milk feeding during early postnatal development relates to improved cardiac size and function in young adulthood compared to those fed formula (14).

For those who are already entering adulthood, it will be important to understand whether current treatment strategies for heart failure adequately address the type of myocardial dysfunction exhibited by preterm offspring. The pattern of myocardial changes, including the degree of fibrosis, cardiomyocyte hypertrophy and the geometry in cardiac atlases, appears to be quite distinct from typical patterns of cardiac remodelling (7). Whether current pharmacological and lifestyle interventions, such as nutrition and exercise, used to manage risk factors in young people, beneficially modifies cardiac morphology and function needs to be explored (15). Given that nearly 10% of births worldwide are now preterm, understanding links between early myocardial development and future risk of heart failure may be of public health importance, while also providing insights into how novel myocardial phenotypes influence heart failure development in the wider population.

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FIGURE LEGENDS

Figure 1 – Potential heart failure progression throughout life in preterm- and term-born individuals. Human and animal experimental studies demonstrate a reduced myocardial reserve in preterm-born individuals compared to their term-born counterparts, with increased cardiac mass and reductions in systolic and diastolic function first emerging in early postnatal development. This underlying reduction in myocardial reserve may explain why preterm-born individuals suffer greater consequences from acute perturbations such as myocarditis in childhood. If so, then myocardial damage in later stages of life, caused by myocardial infarction or prolonged exposure to hypertension, might also be expected to lead to greater susceptibility to heart failure.