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EDITORIAL COMMENT

A New Risk Factor for Early Heart Failure

Preterm Birth*

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

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The striking new finding was that a disproportionate number of individuals born preterm developed HF, even when there was no history of structural cardiac problems (2). The impact of pregnancy history was so pronounced that being born extremely preterm (<28 weeks' gestation) increased risk 17-fold, whereas those born very preterm (28 to 31 weeks' gestation) had a 4-fold increased risk. These findings were independent of other potential confounders (e.g., growth restriction), providing the first evidence of a link between the degree of prematurity and risk of incident HF by young adulthood.

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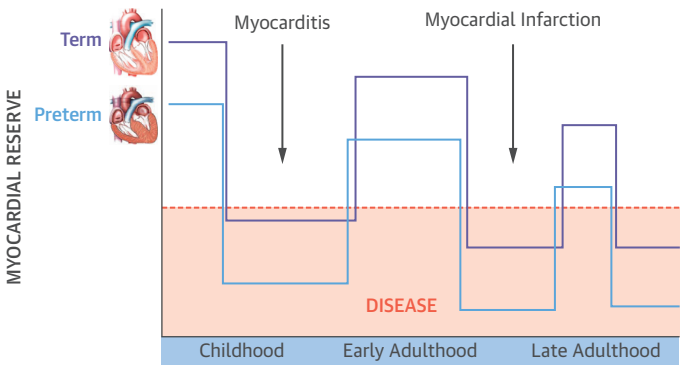
WHY PRETERM BIRTH MIGHT PREDISPOSE TO EARLY HF

Why are those born preterm more likely to develop new-onset HF 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. (2) had an a priori hypothesis that preterm birth would increase risk based on a body of evidence which has shown that premature delivery is directly linked with altered myocardial development. Several years ago, it was noted that preterm-born sheep have a 5- to 7-fold greater cardiomyocyte hypertrophy during postnatal development than term control animals (3). On histologic examination, their hearts exhibited increased interstitial myocardial fibrosis and abnormal cardiomyocyte maturation. Bertagnolli et al. (4) reported similar results in a rat model of an extrauterine preterm environment, with a sustained increase in left ventricular hypertrophy during the postnatal period.

Clinical studies in humans support these observations. Kozák-Bárány et al. (5) found that left ventricular mass increased 56% in preterm infants during the first postnatal month compared with 35% in those born at term. We performed serial echocardiograms during fetal and postnatal development in a study involving nearly 400 infants; we showed 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 3 months of life is 2-fold greater, relative to the change in body size, than

FIGURE 1 Potential HF Progression Throughout Life in Preterm- and Term-Born Individuals



Human and animal experimental studies show a reduced myocardial reserve in preterm-born individuals compared with 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 experience 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 (HF).

occurs in those born at term. Young adults born preterm exhibit 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 (6–8). 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 HF RISK?

Although strong evidence exists for an altered cardiac phenotype in those born preterm, it seems unlikely these differences could be the sole "cause" of the acute episodes of HF in the report by Carr et al. (2). Up to two-thirds of children and young adults with acute HF recover their cardiac function after the episode (1), and the majority of young people with HF in the registry were actually born at term (2). Both observations suggest that a pathogen, agent, or familial predisposition, independent of preterm birth, remains the most likely "trigger" of episodes of acute HF 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, which showed that the myocardial developmental patterns linked with preterm birth progress more rapidly to HF when challenged with a low-dose angiotensin II infusion, mimicking exposure to hypertension (9). It is possible that other biological variations linked with preterm birth, such as altered immune, respiratory, or vascular development, may also contribute; this theory requires further investigation (10–12). An immediate question that arises is: could this same reduced resilience be relevant to adult-onset HF? 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 HF in adult life (Figure 1)?

FUTURE DIRECTIONS

Substantial evidence indicates that 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 (7,8). Carr et al. (2) have provided the first evidence that preterm birth also substantially increases the risk of clinical HF, demonstrated in the rare situation of HF presenting during childhood and adolescence. Would it have been possible to intervene to improve myocardial development and protect against this future risk of cardiovascular disease? Experimental studies have indicated that some interventions, including postnatal pharmacological approaches, can improve myocardial development during the critical postnatal window (9). In humans, we have shown that postnatal nutrition may also be relevant because exclusive human milk feeding during early postnatal development relates to improved cardiac size and function in young adulthood compared with those fed formula (14).

For those who are already entering adulthood, it will be important to understand whether current treatment strategies for HF 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 distinct from typical patterns of cardiac remodeling (7). Whether current pharmacological and lifestyle interventions (e.g., nutrition, exercise) used to manage risk factors in young people beneficially modify 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 HF may be of public health importance, while also providing insights into how novel myocardial phenotypes influence HF development in the wider population.

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