

## MINI-SYMPOSIUM

# Fetal roots of cardiac disease

K L Thornburg, S Louey

*Heart* 2005;91:867–868. doi: 10.1136/hrt.2004.047407

In western countries, cardiovascular disease is the leading killer of men and women. In the past decade, it has become increasingly clear that women are just as vulnerable to heart disease as men. In 2004, the number of women with some form of the disease will exceed the number of such men in the USA ([www.americanheart.org](http://www.americanheart.org)). While new medical treatments are prolonging the lives of people with cardiovascular disease, an increasing number of men and women are living with cardiovascular limitations or outright heart failure. The total estimated cost of cardiovascular disease in the USA will exceed \$300 billion in 2004. In the coming decades, the disease burden that is directly attributable to cardiovascular disease is expected to increase dramatically in developing countries.

### RISK FACTORS

The American Heart Association (AHA) has identified risk factors that were derived from statistical associations with the incidence of coronary disease ([www.americanheart.org](http://www.americanheart.org)). Some factors not under the control of an individual include age, hereditary factors, and diabetes mellitus. Other risk factors are influenced by lifestyle choices and include smoking tobacco, sedentary lifestyle, hypertension, and blood lipid profile. These risk factors have been enormously valuable in emphasising prevention as a way to reduce the morbidity and mortality of coronary atherosclerosis. Nevertheless, many cases of heart disease remain unexplained. Every cardiologist sees cases of coronary artery disease in patients with none of the AHA risk factors, and it is well known that many individuals who have multiple risk factors never get disease. Thus, it is not known why some individuals are much more vulnerable for cardiovascular diseases than others. While this uncertainty is usually attributed to differences in genetic background, recent population studies shed new light on other causes of disease vulnerability.

In 1989, Barker and colleagues used birth and death records to show the relation between birth weight and mortality caused by ischaemic heart disease in 10 000 men and 6000 women born between 1911 and 1930 in Hertfordshire.<sup>1</sup> Their studies demonstrated a profound decrease in cardiovascular mortality with increasing birth weight over the range of 5–9 lbs (2.3–4 kg). This relation has been confirmed in western and developing countries around the world. It is now clear, after 15 intervening years of research, that the environment in which an individual develops has a very powerful influence on the long term health of the cardiovascular system with a poor developmental environment imparting a substantial risk for disease. This finding goes full circle; many of the recognised risk factors for cardiovascular disease are now known to have their origins in early development.

### PROGRAMMING

The process by which developmental stress leads to disease is known as “programming”. Programming is an early change in gene expression pattern that leads to metabolic, anatomic,

and hormonal changes that impart disease vulnerability. Each organ has a “critical window” during which it is particularly sensitive to environmental insults. For example, the kidney is most vulnerable to intrauterine stress during the period of nephrogenesis. Intrauterine stressors that are known to lead to the programming include undernutrition, hypoxia, and excess glucocorticoid values.

There are three areas of programming in the cardiovascular arena that have received special attention: endothelial impairment, haemodynamic load, and hypoxia. There is evidence from human studies and from animal models that impaired endothelial function is associated with low birth weight. For example, Martin and colleagues<sup>2</sup> tested endothelial function in nine small for gestational age infants (birth weight 2.5 kg) at 1 week of age. Acetylcholine was administered through the skin by iontophoresis and blood flow increases were measured by laser Doppler methods and compared to babies of normal weight. The small babies showed a 2.4-fold increase in flow above baseline compared to a 6.5-fold increase for 10 babies of normal weight. These data suggest that low birth weight babies show signs of endothelial dysfunction related to impaired nitric oxide (NO) release.

### ENDOTHELIAL FUNCTION

Several studies have been designed to determine whether adults that were undergrown as fetuses have persistently impaired endothelial function. Using forearm plethysmography techniques, Leeson *et al*<sup>3</sup> and Goodfellow *et al*<sup>4</sup> both found deficits in endothelial function using similar techniques in young adults. McAllister *et al*<sup>5</sup> found evidence of endothelial injury in adults that were undergrown at birth based upon increased plasma von Willebrand factor, but did not find a deficit in the vasodilatory acetylcholine response. Hermann *et al*<sup>6</sup> found a reduced insulin stimulated glucose uptake in the forearms of 20 year olds that were born small. Studies in adult rats have also shown endothelial dysfunction associated with either maternal protein restriction<sup>7</sup> or reduced uterine blood flow during prenatal life.<sup>8</sup>

In summary, these studies suggest that global endothelial function is compromised in humans and animals that were stressed during fetal life or under grown at birth. It is well known that compromised endothelial function may lead to increased risk for coronary disease.<sup>9–10</sup> However, it has not yet been shown that fetal undergrowth or nutritional deprivation lead to coronary endothelial dysfunction as a precursor to adult onset coronary disease.

During embryonic and fetal life, many different conditions including a small placenta can lead to diastolic or systolic pressure loading of the heart. The immature myocardium is able to respond to changes in loading condition. Applying a moderate (Pinson *et al*<sup>11</sup>) or severe (Barbera *et al*<sup>12</sup>) pressure load to the right ventricle (RV) of the sheep fetus leads to right ventricular thickening and improves right ventricular function considerably. For example, an acute 20 mm Hg increase in pulmonary arterial (PA) pressure will reduce the stroke volume of the normal fetal right ventricle by about

50%. However, after 7–10 days of increased mean PA pressure by 10 mm Hg pressure, the stroke volume will be reduced by only ~10% with the same 20 mm Hg increase. Is there a long term cost associated with such accommodation?

Ordinarily, the ventricular myocardium grows by hyperplastic growth (cell replication with relatively constant cardiomyocyte volume) from the time that the embryonic heart is formed until the myocardium reaches a stage of maturity where cardiomyocytes exit the cell cycle (so called "terminal differentiation"). In sheep, rats, and mice this phase is accompanied by the formation of a second nucleus in each cell (binucleation). We now know that mononucleated cells are able to proliferate but are not able to enlarge to any great degree.<sup>13, 14</sup> On the other hand, binucleated cardiomyocytes are not able to divide but can enlarge. Thus, as the population of cells within the myocardium becomes binucleated, the generative potential of the myocardium decreases. Loading leads to a dramatic increase in the portion of cardiomyocytes carrying two nuclei indicating a net reduction in the portion of cardiomyocytes that can divide. These findings raise the question of whether the total number of cardiomyocytes will be reduced for life.

### NUMBER OF CARDIOMYOCYTES

The issue of cardiomyocyte number is of importance because it influences the final architecture of the coronary tree. In the immature myocardium there are many capillaries per cardiomyocyte, but with maturation this ratio decreases; in the mature myocardium, there is a one-to-one capillary to myocyte ratio.<sup>15</sup> If the number of cardiomyocytes is greatly reduced, the size of the myocytes will be enhanced to accommodate the size of heart that is needed to carry the pump function of the adult individual. However, fewer large cells mean fewer capillaries and thus a myocardium that is potentially more vulnerable to ischaemic damage than normal.

Do these experiments apply to the human fetus? There is reason to believe that they do. It is well known that in severe cases of intrauterine growth restriction, placental vascular resistance is increased with gestational age rather than decreased as in normal development. Thus, babies born under intrauterine stress may develop under the influence of an increased systolic and/or diastolic pressure load.

Li *et al*<sup>16</sup> reported that adult rats that were hypoxaemic in utero have hearts that are more vulnerable to hypoxic insults and have fewer cardiomyocytes than controls. These data suggest that prenatal hypoxic stress potentially alters the growth and maturation of cardiomyocytes and makes the myocardium of the offspring more vulnerable to myocardial dysfunction and infarction.

In summary, current data suggest that prenatal programming sets the level of vulnerability for ischaemic heart disease before birth via pressure load conditions and hypoxia, and that these lead to abnormal myocyte maturation and ultimately global impairment of endothelial function.

### Authors' affiliations

**K L Thornburg, S Louey**, Heart Research Center, Oregon Health & Science University, Portland, Oregon, USA

Correspondence to: Professor Kent L Thornburg, Heart Research Center, L464, Oregon Health & Science University, 3181 Sam Jackson Park Road, Portland, Oregon 97239, USA; thornbur@ohsu.edu

### REFERENCES

- 1 **Barker DJ**, Winter PD, Osmond C, *et al*. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989;ii:577–80.
- 2 **Martin H**, Gazelius B, Norman M. Impaired acetylcholine-induced vascular relaxation in low birth weight infants: implications for adult hypertension? *Pediatr Res* 2000;47:457–62.
- 3 **Leeson CP**, Kattenhorn M, Morely R, *et al*. Impact of low birth weight and cardiovascular risk factors on endothelial function in early adult life. *Circulation* 2001;103:1264–8.
- 4 **Goodfellow J**, Bellamy MF, Gorman ST, *et al*. Endothelial function is impaired in young adults of low birth weight. *Cardiovasc Res* 1998;40:600–6.
- 5 **McAllister AS**, Atkinson AB, Johnston GD, *et al*. Relationship of endothelial function to birth weight in humans. *Diabetes Care* 1999;22:2061–6.
- 6 **Hermann TS**, Rask-Madsen C, Ihlemann N, *et al*. Normal insulin-stimulated endothelial function and impaired insulin-stimulated muscle glucose uptake in young adults with low birth weight. *J Clin Endocrinol Metab* 2003;88:1252–7.
- 7 **Brawley L**, Itoh S, Torrens C, *et al*. Dietary protein restriction in pregnancy induces hypertension and vascular defects in rat male offspring. *Pediatr Res* 2003;54:83–90.
- 8 **Payne JA**, Alexander BT, Khalil RA. Reduced endothelial vascular relaxation in growth-restricted offspring of pregnant rats with reduced uterine perfusion. *Hypertension* 2003;42:768–74.
- 9 **Playford DA**, Watts GF. Special article: non-invasive measurement of endothelial function. *Clin Exp Pharmacol Physiol* 1998;25:640–3.
- 10 **Takase B**, Uehata A, Akima T. Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. *Am J Cardiol* 1998;82:1535–9.
- 11 **Pinson CW**, Morton MJ, Thornburg KL. Mild pressure loading alters right ventricular function in fetal sheep. *Circ Res* 1991;68:947–57.
- 12 **Barbera A**, Giraud GD, Reller MD, *et al*. Right ventricular systolic pressure load alters myocyte maturation in fetal sheep. *Circ Res* 1991;68:947–57.
- 13 **Sundgren NC**, Giraud GD, Schultz JM, *et al*. Extracellular signal-regulated kinase and phosphoinositid-3 kinase mediate IGF-1 induced proliferation of fetal sheep cardiomyocytes. *Am J Physiol Regul Integr Comp Physiol* 2003;285:R1481–9, Epub 2003 Aug 28.
- 14 **Sundgren NC**, Giraud GD, Stork PJ, *et al*. Angiotensin II stimulates hyperplasia but not hypertrophy in immature ovine cardiomyocytes. *J Physiol* 2003;548:881–91.
- 15 **Rakusan K**. Cardiac growth, maturation, and aging. In: Zak R, ed. *Growth of the heart in health and disease*. Raven Press, 1984:131–64.
- 16 **Li G**, Xiao Y, Estrella JL, *et al*. Effect of fetal hypoxia on heart susceptibility to ischaemia and reperfusion injury in the adult rat. *J Soc Gynecol Invest* 2003;10:265–74.

### Call for papers

#### 11th European Forum on Quality Improvement in Health Care

26–28 April 2006, Prague, Czech Republic

Deadline 30 September 2005.

For further information and to submit online go to: [www.quality.bmjpub.com](http://www.quality.bmjpub.com)