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## **Altered Coronary Arterial Reactivity Following Pharmacological Perinatal Interventions**

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## Altered Coronary Arterial Reactivity Following Pharmacological Perinatal Interventions

R. P. Steeds<sup>1</sup>, A. Morice<sup>2</sup>, K. Channer<sup>1</sup>, C. Emery<sup>3</sup>

The Barker hypothesis proposes that the risk of ischaemic heart disease may be increased in later life by perinatal events that programme permanent alterations to the body's structure and metabolism. Perinatal modification of arterial compliance and function could initiate and amplify this risk of disease in later life. The aim of this study was to determine whether short-term nitric oxide synthase (NOS) inhibition and transient hypoxia in the perinatal period could initiate changes in vasomotility demonstrable in later life.

Dams were given N<sup>g</sup>-nitro-L-arginine methyl ester (n = 5) in drinking water or were kept in a normobaric hypoxic chamber (FiO<sub>2</sub> 10 %) for one week pre- and one week post-partum. Male offspring were sacrificed at 10 weeks and results compared with the male offspring of control dams (n = 7). Coronary artery reactivity, to both constrictors and dilators, was studied using the wire myograph and isolated blood perfused heart preparations.

Perinatal inhibition of NOS increased the contractile response of coronary arteries in adulthood in both isolated vessels and in perfused heart preparations without a change in dilator responses to ACh and hypoxia. These differences were not associated with changes in arterial compliance and body weight. Perinatal hypoxia enhanced the vasodilatation to hypoxia in adulthood in perfused heart preparations with a reduction in vasodilatation to ACh. These differences were associated with a reduction in body growth, a shift in the pressure-flow relationship indicative of vascular remodeling and evidence of right ventricular hypertrophy.

It is concluded that short-term perinatal insults may alter coronary arterial reactivity in adulthood independent of an effect of birth weight. Perinatal modification of arterial function may be one mode by which risk of disease in later life may be initiated or amplified. *J Clin Basic Cardiol* 2002; 5: 109–114.

**Key words:** coronary artery reactivity, programming, perinatal, birth weight

Extensive epidemiological evidence indicates that individuals who have a low weight at birth or who show signs of disproportionate foetal growth have an increased risk of high blood pressure, stroke and coronary artery disease in later life [1]. The association between small size at birth and cardiovascular disease is specific, since death rates from non-cardiovascular disease (with the exception of chronic obstructive airways disease) are independent of birth weight. The association is also graded, since the standardised mortality ratio for coronary artery disease falls with increasing birth weight. These data led to the hypothesis that differences in the uterine environment of the foetus could permanently change the body's structure, physiology and metabolism to increase susceptibility to disease in later life. Two concepts are relevant to this hypothesis. Firstly, that there are "critical periods" of development in later foetal life at which the tissues and organs of the body are particularly susceptible to influence. Secondly, that an insult coinciding with such a critical period could "programme" changes in the foetus which would enhance the development of disease in adulthood [1].

It has been proposed that perinatal modification of arterial compliance and function may initiate and amplify the risk of disease in later life [2]. Altered arterial reactivity *per se* appears to be an early marker of disease, since the normal dilator response to acetylcholine is lost in subjects with normal coronary angiograms who have been exposed to classical risk factors for ischaemic heart disease [3]. However, it has not been shown previously whether specific perinatal insults may alter arterial reactivity in adulthood. The aim of this study was to determine whether the reactivity of coronary arteries could be altered in adulthood by pharmacological interventions in the perinatal period.

### Methods

#### Experimental Animals

Pregnant rats were maintained on a standard chow and tap water diet in a common environment before and after the interventions and allowed to litter down as normal. Pups were nurtured by the mother and weaned at 24–26 days and maintained on standard rat chow and water *ad libitum*. Young adult male progeny (10 weeks old) only were included in the study. Female offspring were excluded to avoid the potential confounding effects of their hormonal cycle on arterial reactivity. Age-matched males from untreated dams (n = 7) were used as controls (PNC).

#### Perinatal Interventions

Two interventions were studied:

##### *Perinatal L-NAME (PNLN)*

In the first group, 300 mg/ml N<sup>g</sup>-nitro-L-arginine methyl ester (L-NAME) was added to the drinking water provided *ad libitum* to five dams for one week pre- and one week post-partum (approximate total dose consumed was 197 mg; approximate dose per day 14 mg). As endothelial NOS mRNA is increased in the later stages of gestation and falls only after birth to the low level seen in adults, this dosing schedule was selected to cover the period of peak endothelial NOS activity [4].

##### *Perinatal Hypoxia (PNCH)*

In the second group, four pregnant Wistar dams were exposed to hypoxia (10 % oxygen) in a normobaric chamber for one week pre- and one week post-partum. This intervention leads to changes in the pulmonary vascular bed in adulthood that may lead to the development of pulmonary hypertension

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[5]. Acute hypoxia induces vasodilatation in systemic arteries, whereas chronic hypoxia may remodel the coronary arterial vasculature [6]. Although it is known to alter the reactivity of pulmonary resistance arteries in adulthood, the effect of transient perinatal hypoxia on the reactivity of the coronary circulation has not been studied [7].

#### Experiment 1: Myograph Preparations

Pups were sacrificed by overdose of anaesthetic with intraperitoneal pentobarbitone sodium (15 mg/100 g body weight). Coronary arteries (2 per rat) were dissected free and loaded onto a wire myograph using established methods [8]. Myograph baths (Cambustion, Cambridge, UK) were filled with 5 mls physiological saline solution (PSS) super-fused with 95 % O<sub>2</sub>/5 % CO<sub>2</sub>, maintained at 37 °C. pH was stable at 7.4 throughout. Coronary arteries were pre-tensioned to an equivalent pressure of 100 mmHg using the Laplace equation and studied at 100 % internal diameter. Tension was recorded as mN/mm. Following loading of the vessels, dynamic diameter-tension curves were obtained by radial stretch of the vessel. The reciprocal slope of the linear portion of the curve was taken as a measure of dynamic vessel compliance. Vessels were then allowed to equilibrate for 45 minutes after normalisation and pre-tensioning. Arteries were maximally contracted with potassium chloride (KCl, 100 mmol/L) until a stable response was obtained. Following these preliminary contractions, cumulative concentration-response curves were obtained for prostaglandin F<sub>2a</sub> (PGF<sub>2a</sub> 1–100 mmol/L – receptor-dependent vasoconstriction). Once the maximal response had been recorded, cumulative doses of acetylcholine were added (ACh 1–1000 mmol/L – receptor-mediated NO release). The vessels were washed with PSS and allowed to relax to their original baseline tension. Cumulative concentration-response curves were obtained for KCl (1–100 mmol/L – direct smooth muscle contraction following membrane depolarisation). The vessels were then washed with PSS and allowed to relax to their original baseline tension. The contractile response to L-NAME was then studied as an indirect assessment of basal NO release using a dose found in our laboratory to be sufficient to inhibit maximal ACh-induced vasodilatation (100 mmol/L). L-NAME was added at the end of the experiment due to the inability to reverse its effect by washing.

#### Experiment 2: Isolated Heart Perfusion Preparations (Modified Langendorff)

Pups were anaesthetized by intraperitoneal pentobarbitone sodium (6 mg/100 g body weight), heparinised intravenously (sodium heparin 100 units/100g body weight) and then exsanguinated via the inferior vena cava. The chest was opened and the aorta cannulated retrogradely close to the heart. The beating heart was then removed and suspended over a heated reservoir containing autologous blood and blood from a donor rat (20 ml). This blood was oxygenated by passage through an isolated, ventilated (air + 5 % CO<sub>2</sub>) rat lung perfused in parallel [9]. The coronary arteries were perfused from the reservoir via retrograde constant flow perfusion of the aorta (5 ml/min) achieving a Pca in the normal range. Blood exited through the open atria into the reservoir for recirculation to the lungs and heart. Coronary artery pressure was recorded from the perfusion circuit, close to the heart, via a transducer (Sensnor, UK) connected to an amplifier (Electromed) and pen recorder (Bryans Medical, UK). The circuit consisted of silastic, non-toxic tubing and a small piece of rubber for injection of drugs. The heart continued to beat throughout the experiment at approximately 200 beats/min.

Having established a stable baseline at 5 ml/min, the coronary artery pressure (Pca) and coronary artery flow (Q) rela-

tionship (P/Q) was determined. Over a range of Q studied (1–5 ml/min), the P/Q was linear with a positive intercept on the Pca axis. Flow was reduced in stages of 1 ml/min. The values of Pca were plotted against Q and the slope of the line calculated as a measure of coronary vascular resistance (CVR). Coronary artery reactivity was studied in this preparation using single bolus doses of ACh 1–100 mmol/L. Coronary artery reactivity to acute hypoxia was assessed by perfusing the vessels with hypoxic blood from the parallel isolated lung that was ventilated with 2 % oxygen and 5 % carbon dioxide until the resultant fall in Pca was stable. This ventilation lowers the blood pO<sub>2</sub> to 4.0 – 4.5 KPa. Pca returned to baseline levels on resumption of normoxic perfusion. Finally, the coronary arteries were perfused with L-NAME 10 mmol/L (equivalent doses in the isolated heart preparations are lower than those used in the myograph).

#### Heart Ventricular Weights

At the end of the experimental period the hearts were dissected for the measurement of right and left ventricular + septum weights. These are expressed as absolute/g body weight and as a ratio, RV/LV + septum.

#### Statistical Analysis

The concentration of an agonist causing half-maximal contraction (EC<sub>50</sub>), the maximum contraction and maximum dilatation (expressed as a percent of the maximum active contraction to PGF<sub>2a</sub>) were calculated for each myograph experiment. To calculate EC<sub>50</sub>, concentration-effect curves were drawn for each vessel, a sigmoid function attached and the concentration producing 50 % of the maximal response was estimated. EC<sub>50</sub> was expressed as negative log molar value. The coronary artery pressure (Pca), P/Q slope (CVR), and intercept were calculated for each isolated heart preparation. Means for each experimental group were then compared with the relevant control. Data are given as mean ± standard error of the mean. Statistical analysis was carried out by independent t-tests and ANOVA as appropriate. Means were considered significantly different at  $p < 0.05$ .

## Results

#### Body Weight and Vessel Characteristics

There was a reduction in the adult body weight of PNCH rats compared to controls and an increase in RV/100 g body weight but no change in LV/100 g body weight in the PNCH rats. There was no difference in the adult body weight of PNLN rats compared to controls. There was no variation in right ventricular nor left ventricular ratios in the PNLN rats (Tab. 1). There were no differences in the size of the coronary arteries studied in the myograph experiments between the intervention groups and controls (mean 335 ± 9 mm,  $p > 0.05$ ) and no difference in dynamic coronary artery compliance between groups assessed using the length-tension protocol (mean 23 ± 2 mm/mN,  $p > 0.05$ ).

**Table 1.** Body weight and vessel characteristics

	Rats (n)	Body weight (g)	LV/100 g	RV/100 g
Control	15	307 ± 8	0.255 ± 0.017	0.052 ± 0.001
Perinatal L-NAME	13	327 ± 10	0.231 ± 0.005	0.058 ± 0.002
Perinatal hypoxia	12	242 ± 15*	0.217 ± 0.003	0.073 ± 0.005*

\* $p < 0.05$

### Offspring of Rats Treated With Perinatal L-NAME (PNLN)

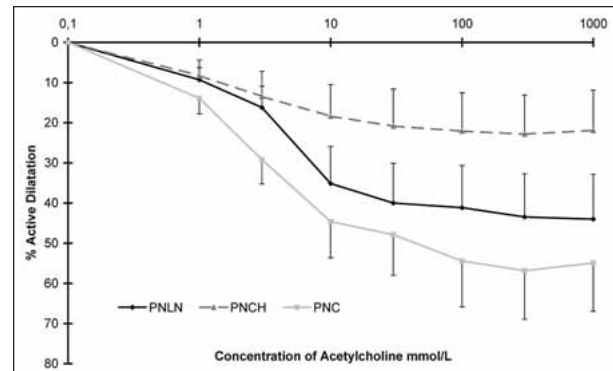
#### Myograph Preparations

There was an increase in maximum contraction in the isolated coronary arteries to PGF<sub>2</sub>a ( $E_{\max}$  PNLN  $2.2 \pm 0.53$  vs PNC  $0.97 \pm 0.2$  mN/mm,  $p < 0.05$ ) and KCl ( $E_{\max}$  PNLN  $1.69 \pm 0.26$  vs PNC  $0.67 \pm 0.2$  mN/mm,  $p < 0.05$ ), but without a change in potency (Figs. 1, 2). Calculation of the  $-\log EC_{50}$  for the responses to KCl was complicated by a dilator response to lower doses in some of the preparations (in 8/12 PNLN  $E_{\max} - 29.62 \pm 12.34$  % vs in 6/10 PNC  $E_{\max} - 28.55 \pm 11.65$  %). However, there was no difference in the frequency ( $p > 0.1$ ) or magnitude ( $p > 0.1$ ) of the dilator response between groups. There was no difference in the dilator response to ACh (Fig. 3). There was an increase in contraction to L-NAME (PNLN  $2.28 \pm 0.55$  vs PNC  $0.29 \pm 0.26$  mN/mm,  $p < 0.01$ ) (Fig. 4A).

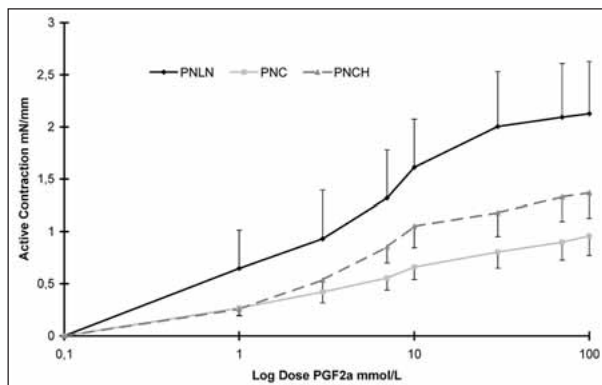
#### Isolated Heart Perfusion Preparations

There was no change in the pressure-flow relationship between PNLN and controls (Fig. 5). There was no difference in the dilator response, fall in Pca, to ACh 1 mmol/L (DPca PNLN  $-7.5 \pm 0.8$  vs PNC  $-8.0 \pm 0.9$  %). With higher doses

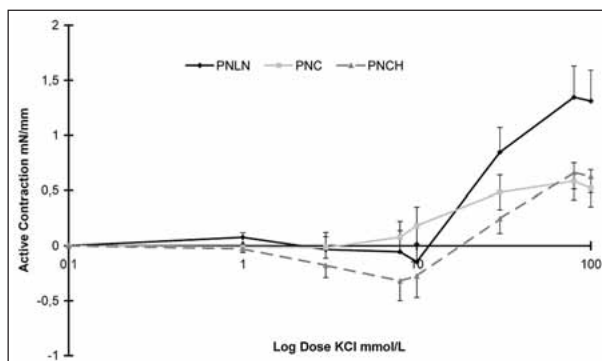
an initial constriction, rise in Pca, was observed followed by a fall in Pca in 6/6 PNLN and 3/5 PNC. There was no significant difference in magnitude between groups. There was an increase in the constrictor response to 10 mmol/L L-NAME (DPca PNLN  $37.8 \pm 6.2$  vs PNC  $21.8 \pm 0.6$  mmHg,  $p < 0.05$ ) (Fig. 4B). There was no difference in the dilator response to



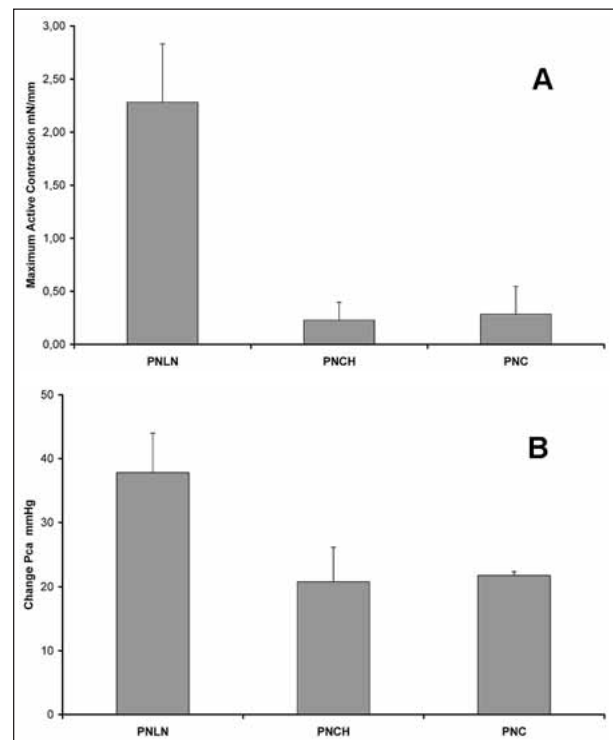
**Figure 3.** Isolated coronary artery reactivity to acetylcholine effect of increasing concentrations of acetylcholine (ACh) on tension in isolated rat coronary arteries mounted on a wire myograph and pre-constricted with PGF<sub>2</sub>a. ACh caused a fall in tension (dilatation), which is calculated as a %-fall of the maximum rise in tension with PGF<sub>2</sub>a. Results are expressed as mean change in tension (mN/mm)  $\pm$  SEM. PNLN: adult male rats exposed to perinatal L-NAME ( $n = 13$  vessels); PNCH: adult male rats exposed to perinatal hypoxia ( $n = 12$  vessels); PNC: control adult male rats ( $n = 15$  vessels)



**Figure 1.** Isolated coronary artery reactivity to prostaglandin F<sub>2</sub>a effect of increasing concentrations of prostaglandin F<sub>2</sub>a (PGF<sub>2</sub>a) on tension in isolated rat coronary arteries mounted on a wire myograph. Results are expressed as mean change in tension (mN/mm)  $\pm$  SEM. PNLN: adult male rats exposed to perinatal L-NAME ( $n = 13$  vessels); PNCH: adult male rats exposed to perinatal hypoxia ( $n = 12$  vessels); PNC: control adult male rats ( $n = 15$  vessels)



**Figure 2.** Isolated coronary artery reactivity to potassium chloride effect of increasing concentrations of potassium chloride (KCl) on tension in isolated rat coronary arteries mounted on a wire myograph. Results are expressed as mean change in tension (mN/mm)  $\pm$  SEM. PNLN: adult male rats exposed to perinatal L-NAME ( $n = 13$  vessels); PNCH: adult male rats exposed to perinatal hypoxia ( $n = 12$  vessels); PNC: control adult male rats ( $n = 15$  vessels)



**Figure 4.** Coronary artery reactivity to L-NAME in (A) isolated coronary arteries, (B) isolated perfused heart preparation. A. Mean  $\pm$  SEM rise in tension with 100 mmol/L LNAME in isolated coronary arteries mounted on a wire myograph. PNLN ( $n = 13$  vessels); PNCH ( $n = 12$  vessels); PNC ( $n = 15$  vessels) B. Rise in coronary artery pressure with 10 mmol/L LNAME in isolated blood perfused hearts. PNLN ( $n = 4$  rats); PNCH ( $n = 4$  rats); PNC ( $n = 6$  rats). Results are expressed as mean change in tension (mN/mm)/mmHg  $\pm$  SEM

acute hypoxia (DPca PNLN  $-12.0 \pm 2.3$  vs PNC  $-7.1 \pm 5.6$  %,  $p < 0.05$ ).

### Offspring of Rats Treated With Perinatal Hypoxia (PNCH)

#### Myograph Preparations

There was no difference in coronary artery reactivity to PGF<sub>2a</sub> (Fig. 1). There was an increase in maximum contraction to KCl ( $E_{\max}$  PNCH  $1.21 \pm 0.15$  vs PNC  $0.67 \pm 0.2$  mN/mm,  $p < 0.05$ ) but without a difference in potency. Again, calculation was affected by an initial dilatation to lower doses of KCl (in 8/11 PNCH  $-44.63 \pm 11.64$  % vs in 6/10 PNC  $-28.55 \pm 11.65$  %) but with no difference in magnitude ( $p > 0.1$ ) or frequency ( $p > 0.1$ ) (Fig. 2). There was a reduction in maximal dilatation to ACh (PNCH  $-24.9 \pm 10$  % vs PNC  $65.8 \pm 12$  %,  $p < 0.05$ ) but without a change in potency (Fig. 3). There was no difference in coronary artery response to L-NAME (Fig. 4A).

#### Isolated Heart Perfusion Preparations

There was a parallel upward shift in the pressure flow line in PNCH rats with a significant increase in the intercept but no difference in slope (Intercept PNCH  $41.9 \pm 6.3$  vs PNC  $24.5 \pm 8.5$  mmHg,  $p < 0.05$ ) (Fig. 5). There was a reduction in dilatation to 1 mmol/L ACh (PNCH  $-3.5 \pm 1.2$  % vs PNC  $7.5 \pm 0.8$  %,  $p < 0.05$ ). There was no difference in response to L-NAME (DPca PNCH  $20.8 \pm 5.3$  vs PNC  $21.8 \pm 5.3$  mmHg) (Fig. 4B). There was an enhanced dilatation to acute hypoxia (PNCH  $-14.5 \pm 2.3$  % vs PNC  $-7.1 \pm 2.0$  %,  $p < 0.05$ ).

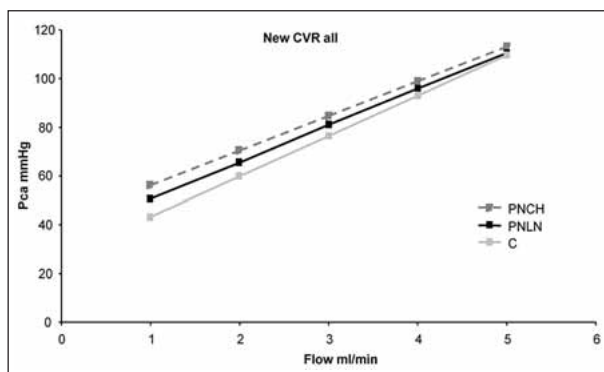
## Discussion

Short-term exposure to perinatal NOS inhibition and perinatal hypoxia induced changes in coronary arterial reactivity that persisted to adulthood. Perinatal inhibition of NOS increased the contractile response of coronary arteries in adulthood in both isolated vessels and in perfused heart preparations without a change in dilator responses to ACh and hypoxia. However, there was a greater incidence of coronary vasoconstriction, followed by dilatation, with ACh in the treated group. These differences arose in the absence of changes in arterial compliance, body weight and without left ventricular hypertrophy. Perinatal hypoxia enhanced the vasodilatation to hypoxia in adulthood in both isolated vessels and in perfused heart preparations with a reduction in vasodilatation to ACh. These differences arose in association

with a reduction in body growth and evidence of right ventricular hypertrophy. It has been demonstrated using two different models that short-term perinatal insults may alter coronary arterial reactivity in adulthood independent of an effect of birth weight. Therefore, in principle, perinatal modification of arterial function may be one mode by which risk of disease in later life may be initiated or amplified.

Endothelial nitric oxide synthase activity (NOS), which releases NO from L-arginine, is increased prior to birth and then falls to the low levels seen in adulthood. NO is an important endogenous vasodilator involved in the maintenance of vascular tone. NO decreases vessel permeability and reduces arterial tone. It is also a principal factor in the anti-atherosclerotic properties of the endothelium. NO interferes with key events in the development of atherosclerosis, such as leucocyte adhesion and rolling, platelet-vessel-wall interactions, and smooth muscle cell proliferation and migration [10]. Classical risk factors for coronary artery disease, such as hypercholesterolaemia and smoking, have been associated with impaired NO activity and reversal of normal responses to NO-dependent vasodilators [11]. Therefore, NO inhibition with L-NAME was selected as one of the interventions that could affect vascular reactivity in a manner mimicking pathological changes in coronary artery disease.

Ischaemic heart disease is characterised by dysfunction of the vascular endothelium, with loss of nitric oxide bioavailability playing a central role in its pathogenesis [12]. This dysfunction is identified clinically by the paradoxical vasoconstriction that occurs following intracoronary injection of acetylcholine in patients with ischaemic heart disease both in coronary arteries directly affected by atherosclerosis and in adjacent arteries with no detectable plaque on angiography [11, 13]. Paradoxical vasoconstriction also occurs in the angiographically-normal coronary arteries of individuals without a history of ischaemic heart disease, but who have been exposed to classical risk factors such as hypertension, smoking [14], hypercholesterolaemia [15], and diabetes mellitus [3]. Serological markers of endothelial dysfunction such as von Willebrand factor and tissue plasminogen activator increase in conjunction with changes in arterial motility and are elevated in the presence of classical risk factors for ischaemic heart disease [16]. The Barker hypothesis is based on epidemiological evidence that low birth weight may be associated with an increased risk of ischaemic heart disease in adulthood. It is thought that changes in arterial function may link the causative factors behind low birth weight with the increase in adult risk and there is some evidence to support this theory. Leeson (1997) and Goodfellow (1998) both found a correlation between low birth weight and impaired endothelial function in adulthood as assessed by a reduction in flow-mediated dilatation using ultrasonic measurement of the brachial artery in the fore-arm (a measure of stimulated NO release) [17, 18]. Low birth weight has been associated with increased arterial stiffness and with increased serum levels of von Willebrand factor [2, 19, 20]. In the twin-twin transfusion syndrome, the donor twin (usually of lower birth weight) has a relative increase in pulse wave distensibility and lowered arterial distensibility which cannot be explained by genetic influence [21]. The data from the study by Cheung suggested that cardiovascular adaptation of the donor fetus to hypovolaemia changed the physical properties of the arteries to a degree sufficient to prejudice long-term cardiovascular health, although arterial distensibility was only studied in infancy. The data from our study indicate that perinatal insults can alter the vasoactive properties of the coronary arteries in a manner persisting to adulthood without affecting arterial compliance or birth weight.



**Figure 5.** Pressure flow lines from isolated perfused heart preparations. The mean pressure-flow relationship in isolated blood perfused hearts. PNLN: adult male rats exposed to perinatal L-NAME ( $n = 7$  rats); PNCH: adult male rats exposed to perinatal hypoxia ( $n = 5$  rats); PNC: control adult male rats ( $n = 5$  rats)



In the isolated coronary arteries of PNLN rats, maximum contraction was increased in response to the receptor-dependent agonist PGF<sub>2</sub>a and to the receptor-independent agonist KCl. L-NAME is an orally-active inhibitor of NOS [22], and since a reduction in NO results in greater vasoconstriction to receptor-dependent and receptor-independent contractile agonists [23], could the increase in  $E_{\max}$  be due to a reduction in basal or stimulated NO release in the offspring? This would seem unlikely. Firstly, the duration of action of L-NAME is too short for a two week period of consumption in the perinatal period to interfere directly with the capacity of the coronary arteries of the adult offspring to release nitric oxide. Secondly, if there was a reduction in basal NO release in the offspring, one would expect a reduction in contraction to an acute dose of L-NAME, since this induces an arterial response by inhibition of NOS and has no intrinsic contractile properties. In fact, constriction to an acute dose of L-NAME was increased in offspring of PNLN rats in both models studied. Thirdly, if there were a reduction in stimulated NO release in the offspring, one would expect reduced dilatation to ACh. In fact, the dilator response to ACh was not altered in offspring of PNLN rats in either model studied. The mechanism by which perinatal L-NAME altered coronary arterial reactivity in adulthood is not clear from our study, although it does not appear to arise from a change in either the basal or stimulated release of NO. No histological data from the coronary arteries of the offspring in adulthood or from the placenta of the treated dams were collected. Therefore, it is not possible to comment on whether structural vascular remodeling in utero, intended to be adaptive, resulted in the persistent functional abnormalities noted.

Pups exposed to normobaric hypoxic conditions for one week pre- and one week post-partum were smaller than the controls and developed right ventricular hypertrophy, an effect which has been documented previously [5]. The results of our study extend these findings with the discovery of a change in coronary vasoreactivity, including an increase in maximal contraction to KCl, reduction in dilatation to ACh, and increase in intercept of the pressure flow line in the isolated perfused heart. In our experiment, these changes were found after exposure to hypoxic conditions limited to only two weeks in the perinatal period and despite a subsequent return to normoxic conditions. Acute hypoxia acts as a vasodilator in a variety of isolated systemic vessels, whilst chronic hypoxia mediates changes predominantly in the pulmonary circulation [24]. In isolated pulmonary vessels, chronic hypoxia causes an increase in response to constrictor agents, which is thought to be due to arteriolar muscularisation and narrowing [9, 25]. In chronic hypoxia, a reduction in dilatation following acetylcholine is considered an indicator of endothelial dysfunction [25]. The changes in the coronary arteries mimic those expected in pulmonary arteries exposed to chronic hypoxia and may be due to similar structural change. Right ventricular hypertrophy is associated with right coronary artery remodeling, with an increase in total cross-sectional area of the vessel wall, which may reflect arteriolar muscularisation [6]. In the isolated hearts, the increase in the pressure-flow line intercept on the pressure axis is suggestive of a remodeling in the coronary vessels, ie increased muscle in the vascular wall is associated with elevated "critical closing pressure". However, there was no alteration in arterial compliance in our experiment and no consistent increase in response across all the vasoconstrictor agonists used, as would be expected with arteriolar muscularisation. It is possible that the duration of the hypoxia was too limited to induce arterial modification sufficient to affect the response in adulthood to all the vasoactive agents tested in this study and that the sys-

temic circulation of the foetus was partially protected by maternal placental oxygen delivery or other compensatory mechanisms. Indeed, in experimental work on sheep, exposure of the pregnant ewe to chronic hypoxia for three weeks led to a persistent 30 % reduction in foetal PaO<sub>2</sub> and haemoglobin saturation. Although O<sub>2</sub> content was initially reduced, this returned to near normal levels within a few days, associated with a rise in foetal haematocrit [26].

Some of the isolated coronary arteries from rats in all groups relaxed in response to low concentrations of KCl but subsequently contracted to higher concentrations. There was no significant difference in the degree or timing of the dilatation in either of the intervention groups compared to controls. Potassium influences contractile response by a direct effect on depolarisation of the smooth muscle membrane with passage of extracellular calcium through the sarcolemma [27]. However, it may induce a vasodilator response in low concentrations by an effect on inward rectifier (K<sup>+</sup>) channels [28]. Potassium also has an indirect effect by varying the release of norepinephrine from nerve endings within the vessel wall (reduced extracellular potassium increases norepinephrine release from the vessel wall) [29]. The overall effect of potassium on vascular response is dependent on the experimental conditions and tissues used but the findings of a weak vasodilator effect at low concentrations in rat coronary arteries is in agreement with previous published work [30].

In summary, we have shown that consumption of the nitric oxide inhibitor, L-NAME, for one week pre- and one week post-partum by pregnant dams increased the contractility of the coronary arteries of the offspring in adulthood, without impairing dilatation to acetylcholine. These differences arose in the absence of a change in rat body weight. Exposure to chronic normobaric hypoxia of pregnant dams over the same time period increased contractile response to potassium chloride and reduced dilatation to acetylcholine in adult offspring. These differences were associated with a reduction in rat body weight in adulthood. What could be the pathophysiological relevance of such observations? The clinical correlate of perinatal inhibition of NOS with L-NAME would be maternal cigarette smoking, which also impairs NOS activity and has a clear role in the pathogenesis of atherosclerosis. Perinatal hypoxia carries its own risk in relation to developmental delay but any association with adverse risk in adulthood could be transmitted by arterial structural change.

## References

1. Barker DJP. Mothers, babies and health in later life. Churchill Livingstone, Edinburgh, 1998.
2. Martyn CN, Barker DJP, Jespersen S, Greenwald S, Osmond C, Berry C. Growth in utero, adult blood pressure, and arterial compliance. *Br Heart J* 1995; 73: 116-21.
3. Quyyumi AA, Dakak N, Andrews NP, Husain S, Arora S, Gilligan DM, Panza JA, Cannon RO. Nitric oxide activity in the human coronary circulation: impact of risk factors for coronary atherosclerosis. *J Clin Invest* 1995; 95: 1747-55.
4. North AJ, Star RA, Brannon TS, Ujiie K, Wells LB, Lowenstein CJ, Snyder SH, Shaul PW. NOS type I and type III gene expression are developmentally regulated in the lung. *Am J Physiol* 1994; 266: L635-41.
5. Herget J, Hampl V. Pulmonary vasculature of adult rats is influenced by perinatal experience of hypoxia. *Pulmonary blood vessels in lung disease. Progress in Respiratory Research* 1990; 26: 70-6.
6. Kassab GS, Imoto K, White FC, Rider CA, Fung YC, Bloor CM. Coronary arterial tree remodeling in right ventricular hypertrophy. *Am J Physiol* 1993; 265: H366-75.
7. Harrison GL, Moore LG. Systemic vascular reactivity during high altitude pregnancy. *J Appl Physiol* 1990; 69: 201-6.
8. Steeds RP, Thompson J, Channer KS, Morice AH. Response of normoxic pulmonary arteries of the rat in the resting and contracted state to NO synthase blockade. *Br J Pharmacol* 1997; 122: 99-102.
9. Emery CJ, Bee D, Barer GR. Mechanical properties and reactivity of vessels in isolated perfused lungs of chronically hypoxic rats. *Clin Sci* 1981; 61: 569-80.
10. Wever R, Luscher TF, Cosentino F, Rabelink TJ. Atherosclerosis and the two faces of endothelial nitric oxide synthase. *Circulation* 1998; 97: 108-12.

11. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986; 315: 1046–51.
12. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; 362: 801.
13. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Reduced coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. *N Engl J Med* 1994; 331: 222–7.
14. Celermajer DS, Sorensen KE, Georgakopoulos D, Bull C, Thomas O, Robinson J, Deanfield JE. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation* 1993; 88: 2149–55.
15. Vita JA, Treasure CB, Nabel EG, McLenachan JM, Fish D, Yeung AC, Vekshtein VI, Selwyn AP, Ganz P. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. *Circulation* 1980; 81: 491–7.
16. Blann AD, Lip GY. The endothelium in atherothrombotic disease: assessment of function, mechanisms and clinical implications. *Blood Coag & Fibrinolysis* 1998; 9: 297–306.
17. Leeson CPM, Whincup PH, Cook DG, Donald AE, Papacosta O, Lucs A, Deanfield JE. Flow-mediated dilation in 9- to 11-year old children: the influence of intrauterine and childhood factors. *Circulation* 1997; 96: 2233–8.
18. Goodfellow J, Bellamy MF, Gorman ST, Brownlee M, Ramsey M, Lewis MJ, Davies DP, Henderson AH. Endothelial function is impaired in fit young adults of low birth weight. *Cardiovasc Res* 1998; 40: 600–6.
19. Martin H, Gennser G, Norman M. Impaired endothelial function and increased carotid stiffness in 9 year old children with low birth weight. *Circulation* 2000; 102: 2739–44.
20. McAllister AS, Atkinson A, Johnston G, McCance D. Relationship of endothelial function to birth weight in humans. *Diabetes Care* 1999; 22: 2061–6.
21. Cheung YF, Taylor MJO, Fisk NM, Redington AN, Gardiner HM. Fetal origins of reduced arterial distensibility in the donor twin in twin-twin transfusion syndrome. *Lancet* 1995; 345: 1157–8.
22. Gardiner SM, Compton AM, Bennett T, Palmer RMJ, Moncada S. Regional haemodynamic changes during oral ingestion of N<sup>g</sup>-monomethyl-L-arginine or N<sup>g</sup>-nitro-L-arginine methyl ester in conscious Brattleboro rats. *Br J Pharmacol* 1990; 101: 10–2.
23. Gruetter CA, Ryan ET, Lemke SM, Bailly DA, Fox MK, Schoepp DD. Endothelium-dependent modulation of angiotensin II-induced contraction in blood vessels. *Eur J Pharmacol* 1988; 146: 85–95.
24. Gellai M, Norton JM, Detar R. Evidence for direct control of coronary vascular tone by oxygen. *Circulation Res* 1973; 32: 279–89.
25. Carville C, Raffestin B, Eddahibi S, Blouquit Y, Adnot S. Loss of endothelium-dependent relaxation in proximal pulmonary arteries from rats exposed to chronic hypoxia: effects of in vivo and in vitro supplementation with L-arginine. *J Cardiovasc Pharmacol* 1993; 22: 889–96.
26. Kitanaka T, Alonso JG, Gilbert RD, Siu BL, Clemons GK, Longo RD. Fetal responses to long-term hypoxaemia in sheep. *Am J Physiol* 1989; 256 (Regulatory Integrative Comp Physiol 25): R1348–54.
27. Knot HJ, Zimmerman PA, Nelson MT. Extracellular K(+) induced hyperpolarisations and dilatations of rat coronary and cerebral arteries involve inward rectifier K(+) channels. *J Physiol* 1996; 492: 419–30.
28. Whall CW, Havlik RJ, Halpern W, Bohr DF. Potassium depolarisation of adrenergic varicosities in resistance arteries from SHR and WKY rats. *Blood Vessels* 1983; 20: 23–33.
29. Sjogren A, Edvinsson L. Vasomotor changes in isolated coronary arteries from diabetic rats. *Acta Physiol Scand* 1988; 134: 429–36.
30. Amann K, Gharehbaghi H, Stephen S, Mall G. Hypertrophy and hyperplasia of smooth muscle cells of small intramyocardial arteries in spontaneously hypertensive rats. *Hypertension* 1995; 25: 24–31.

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