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Myocardial perfusion and function dichotomy in growth restricted preterm infants

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Original Article

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Abstract

Compared to preterm appropriate for gestational age (AGA) fetuses, fetuses with fetal growth restriction (FGR) have earlier visualisation of coronary artery blood flow (CABF) but impaired cardiac function. This dichotomy remains uncharacterised during postnatal life. This study compared CABF and cardiac function in preterm FGR infants, against AGA infants during the postnatal period. FGR was defined as birthweight < 10th centile for gestation and sex with absent/reversed antenatal umbilical artery Doppler. Diastolic CABF was measured in the left anterior descending coronary artery. Twenty-eight FGR infants were compared with 26 AGA infants (gestation and birthweight, 29.7 ± 1.3 vs 29.9 ± 1 weeks, $P = 0.6$ and 918 ± 174 vs 1398 ± 263g, $P < 0.001$, respectively). Echocardiography was performed in the second week of life. FGR infants had higher CABF (velocity time integral, 2.4 ± 0.9 vs 1.6 ± 0.8 cm, $P = 0.002$). Diastolic function was impaired (↑ trans-mitral E/A ratio in FGR infants; 0.84 ± 0.05 vs 0.79 ± 0.03, $P = 0.0002$) while the systolic function was also affected (mean velocity of circumferential fibre shortening [mVCFc], 1.9 ± 0.3 vs 2.7 ± 0.5 circ/s, $P < 0.001$). Indexing CABF to cardiac function noted significant differences between the groups (CABF: E/A [FGR vs AGA], 2.9 ± 1.1 vs 2.1 ± 1, $P = 0.01$ and CABF: mVCFc [FGR vs AGA], 1.3 ± 0.5 vs 0.6 ± 0.3, $P < 0.001$). Diastolic blood pressure (BP) was significantly higher, and CABF to diastolic BP ratio trended higher in FGR infants (30 ± 2 vs 25 ± 3 mmHg, $P < 0.001$ and 0.08 ± 0.03 vs 0.06 ± 0.03, $P = 0.059$, respectively). Greater CABF in FGR infants did not translate into better cardiac function. This dichotomy may be a persistent response to fetal hypoxaemia (fetal programming) and/or reflection of altered cardiac architecture.

Introduction

Fetal growth restriction (FGR) affects a significant proportion of pregnancies delivered prematurely. Various datasets estimate FGR to range from 18 to 30% amongst infants delivered at <32 weeks gestational age (GA).[1-3] FGR predominantly results from placental insufficiency, characterised by failure of the placenta to supply adequate oxygen and nutrients to the developing fetus. Fetal programming, as seen in FGR fetuses, is a process whereby permanent alterations in physiology and metabolism result from insult or stimuli during early critical periods of development. The resulting chronic fetal hypoxaemia influences organ growth, and preferential blood flow to vital organs such as the brain, adrenals and heart.[4-6] The redistribution of blood to the brain is assessed by increased end-diastolic flow in the middle cerebral artery, and is termed the 'brain-sparing effect'.[7] However, this 'preferential' fetal brain perfusion does not translate into improved short or long-term neurodevelopmental function.[8,9]

Improved ultrasound technology now permits visualisation of small calibre vessels. The flow pattern in coronary arteries is typically biphasic, with a dominant diastolic and minor systolic component. The latter is not easily detectable, hence assessments typically pertain to the dominant diastolic phase. Diastolic arterial flow is characterised as area under the curve (velocity time integral, cm) and velocities. Non-invasive measurement of coronary artery blood flow (CABF) using transthoracic echocardiography (Echo) closely reflects invasive measurements using Doppler guidewire.[10,11] Spectral Doppler and colour flow measurements detect clinically important changes in CABF patterns.[12] CABF assessments in left anterior descending (LAD) artery in healthy term newborns and various neonatal clinical situations using transthoracic Echo have been previously published.[10,13-16] CABF is visualised much earlier in FGR fetuses, may reflect selective adaptation of vascular resistance in myocardial vascular beds and is proposed as a 'heart sparing effect' induced by chronic, and acute on chronic hypoxaemia.[17,18] Data on lamb fetuses using radio-labelled microspheres for myocardial blood flow quantification noted a 2.5 fold increased flow under hypoxaemic conditions, correlating inversely to partial pressure of oxygen.[19] Putatively, visualisable CABF suggests augmentation of coronary flow to attempt compensation and maintain myocardial oxygen balance.[17,18] Unfortunately in spite of the above adaptation, and similar to the brain, the end-organ functionality of fetal heart in FGR is not

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improved. Preterm FGR fetuses are known to have globular hearts with reduced function.[20] Elevated cord blood levels of cardiac troponin in FGR deliveries indicate that increased fetal CABF may not prevent cardiac function deterioration.[21]

Postnatal data on preterm infants are limited, but confirmed similar and continued alterations (increased sphericity, diastolic dysfunction [higher trans-mitral E/A ratio and end-systolic wall stress {ESWS}] and systolic dysfunction [lower mean velocity of circumferential fibre shortening {mVCFc}]).[22-24] Serial Echo assessments in the first two weeks of life in preterm infants ranging from 23 to 32 weeks showed that while left ventricular (LV) output increased in appropriate for gestational age (AGA) infants over a period of time, this did not materialise in FGR infants. By 14 d of life, LV output was significantly lower in FGR infants.[22] Arguably, a preferential blood supply to the myocardium as part of *in-utero* adaptation in FGR, may not translate into better cardiac function in the postnatal period. Based on fetal data, we hypothesise that CABF will be increased but cardiac function impaired in preterm FGR infants, compared to AGA infants, when evaluated in the initial weeks of postnatal life. The aim of this study was to evaluate CABF and indices of cardiac function in preterm FGR infants, against AGA infants using transthoracic Echo.

Methods

Archived images from the database of our previously published studies were accessed to ascertain presence of CABF Doppler and colour flow recordings.[23,24] Both studies as well as the current appraisal of pre-recorded data were approved by Monash Health Ethics Review Committee. Infants <28 weeks GA were excluded as they are more likely to have a patent ductus arteriosus (PDA) which influences Echo measurements. Assessments were performed in the second week of life and infants with a PDA on the initial scan were reassessed at the end of the second week; continued patency resulted in exclusion of the infant. FGR was defined as birthweight <10th centile for GA and sex with absent/reversed antenatal umbilical artery Doppler recordings.[1,25] Our cohort born between 28 and 32 weeks GA reflects the majority of moderate to severe FGR cases.[2] We excluded infants with possible asphyxia, congenital malformations or chromosomal abnormalities and born to diabetic mothers. Demographic and clinical information was recorded for the study cohort. Non-invasive blood pressure (BP) measurements were obtained using an appropriate-sized cuff on the right arm with the infant in a quiet state and positioned supine (using model IntelliVue MX800; Philips, Boeblingen, Germany). The average of 2 readings were recorded. Details about Echo assessments have been reported by us and other investigators earlier.[23,24] These were performed using the Vivid E95 Advantage Cardiovascular Ultrasound System (GE Medical Systems, Milwaukee, Wis., USA) using a 12 Hz probe, with the infant in supine position. Offline analysis was performed using *EchoPAC*™ (Horten, Norway) software. All Doppler measurements were calculated from an average of three consecutive cardiac cycles, the angle of insonation being kept to <15°.

CABF evaluation: The LAD coronary artery was interrogated as this is the main vessel supplying blood to the LV. Previous studies in term and preterm infants have evaluated coronary flow in this vessel using Doppler methods.[12-16] The vessel was identified using colour Doppler flow analysis, set to a low Nyquist limit (15–30 cm/sec) (Fig 1). The internal LAD vessel dimensions were measured at end diastole with callipers applied to the endothelial border at origin. The pulse wave Doppler sample gate was placed over the LAD distal to the bifurcation. As the majority of CABF occurs during diastole, diastolic arterial flow was measured (Fig 1). The inclusion criteria to include the infants from the archived studies was the presence of CABF Doppler recordings.

Statistics

Amongst the total cohort of 80 infants (40 FGR and 40 AGA) in the two previous studies,[23,24] CABF recordings were documented in 28 FGR and 26 AGA infants. This selected cohort of 54 infants formed the subjects of the current study. Hence, the subsequent analyses refer to 54 infants. Indices were summarised as mean ± standard deviation. Continuous variables (such as GA, birthweight, BP, ventilation requirements) were compared using Student's *t* test and categorical variables (such as sex, antenatal steroids, surfactant) were compared using χ^2 or Fisher's exact tests. Analyses were performed using Stata software BE/17. Two-tailed significance was set at $p < 0.05$.

Results

The GA at birth and postnatal age at assessment in the two groups were comparable. Demographic and clinical characteristics are depicted in Table 1. None of the infants were mechanically ventilated, all were on nasal continuous positive airway pressure at assessment. Respiratory support requirements (distending airway pressure and fractional inspired oxygen) were comparable between the two groups. Specific treatment for PDA closure was not administered; all infants had spontaneous closure. No infant was on inotropic support before or at the time of assessment. The systolic BP (mm Hg) in FGR infants was 51 ± 3 compared to 46 ± 3 in AGA infants ($p < 0.001$). Non-invasive BP and rate pressure product (RPP = heart rate × systolic BP) were significantly higher in FGR infants (Table 1). The RPP in FGR and AGA infants was 7576 ± 535 vs 6833 ± 493, respectively, $p < 0.001$.

Table 2 depicts parameters evaluating cardiac structure and function. The LV in FGR infants was dilated and hypertrophied (↑end-diastolic diameter, posterior wall thickness and mass). The LV end-diastolic diameter in FGR vs AGA infants was 14.6 ± 9.6 vs 13.6 ± 7.3 mm, respectively, $p = 0.0001$. The LV mass was also greater in FGR infants, 6.4 ± 0.8 vs 5.3 ± 3g, respectively, $p < 0.001$. LV function was noted to be impaired (↑trans-mitral E/A, greater wall stress [47 ± 6 in FGR vs 33 ± 3 g/cm^2 in AGA, $p < 0.001$] and ↓ velocity of fibre shortening [1.9 ± 0.3 in FGR vs 2.7 ± 0.5 circ/s in AGA, $p < 0.001$]). Table 3 depicts CABF in FGR and AGA infants. While LAD artery calibre was comparable, CABF was significantly higher in FGR infants (LAD velocity time integral, 2.4 ± 0.9 vs 1.6 ± 0.8 cm, $p = 0.002$). As CABF is closely interlinked with cardiac function and diastolic BP, CABF was indexed to systolic function (LV output and circumferential fibre shortening), diastolic function (trans-mitral E/A velocities), diastolic BP and RPP. Indexed CABF was significantly higher in FGR infants (Table 3). In essence, in this group of moderately FGR preterm infants, our data noted cardiac hypertrophy and dilatation with impaired myocardial function in the presence of higher coronary flow.

Discussion

This Echo study noted elevated CABF in the FGR cohort ('heart sparing effect'). However, this was not accompanied by better heart function. The above dichotomy may be a persistent response to

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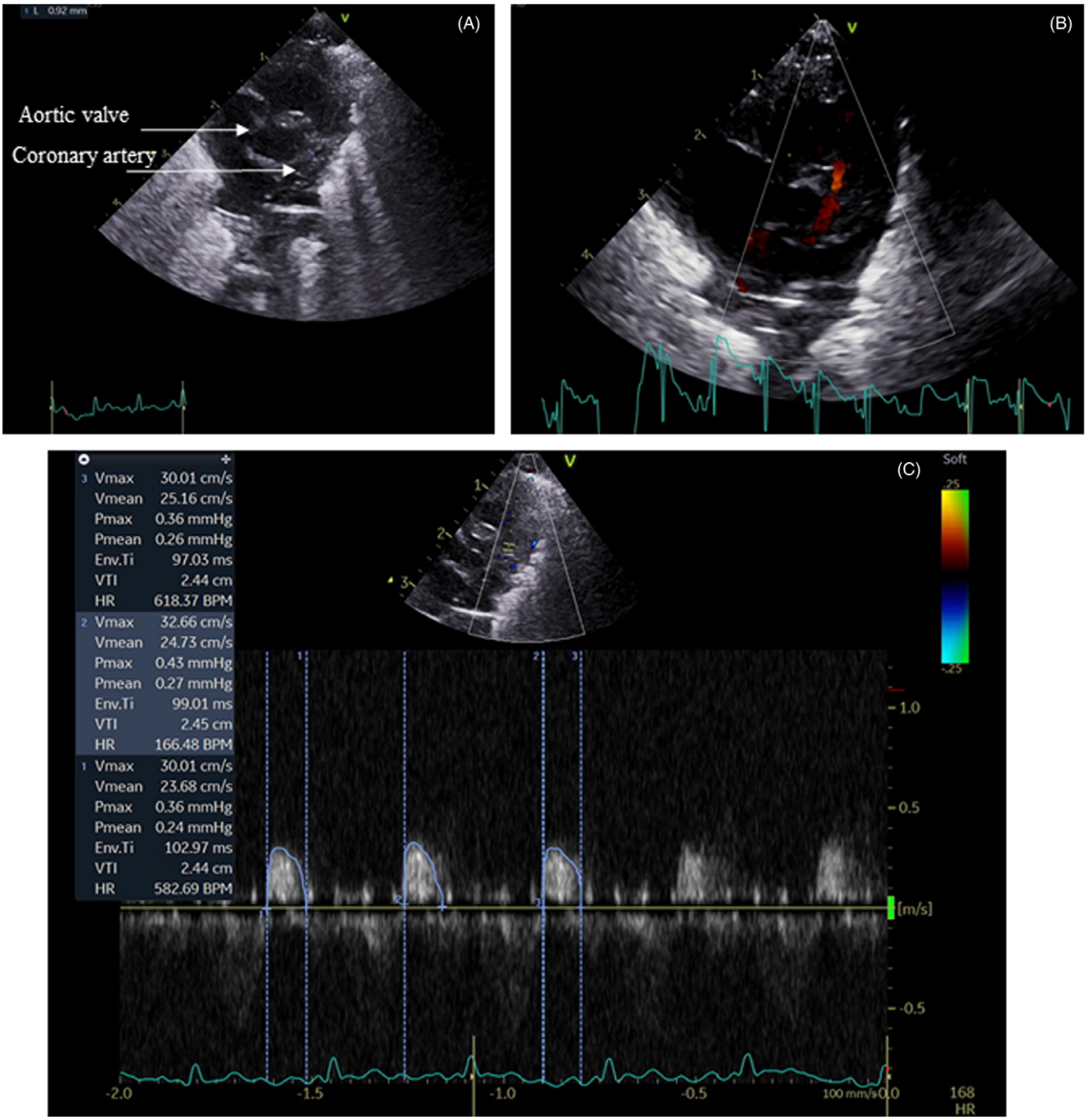


Fig. 1. Coronary artery imaging. Panel A: Short axis view showing coronary artery origin. Panel B: Colour Doppler. Panel C: Pulse wave Doppler showing predominant diastolic trace.

fetal hypoxaemia (fetal programming) and circulatory adaptation (oxygen sensitivity of the coronary vasculature) or reflection of altered cardiac architecture and function. Alongside reduced cardiomyocyte binucleation and maturation, these findings could have lifelong implications for cardiovascular function. Vasodilation of coronary arteries in an attempt to spare the heart putatively signifies use of 'last flow reserves'.[26,27] This is corroborated by data from animal studies where greater compliance of coronary vessels has been noted in FGR lambs.[28]

Autoregulation and mechanistic linkages

The adaptation of the transitional circulation in acute and chronic hypoxaemia has been recently summarized by our group.[29] Myocardial oxygen requirements are met by regulation of CABF, which is determined by coronary perfusion pressure and vascular resistance.[17,18,29,32] Acute hypoxaemia in fetal lambs led to a redistribution of cardiac output (↑ in CABF 2–3 fold). Chronic hypoxaemia resulted in a 5–6 fold increase, possibly reflecting adaptation, remodelling and reactivity of the coronary

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Table 1. Demographic and clinical variables

Variable	FGR	AGA	*P*
Gestational age (weeks)	29.7 ± 1.3	29.9 ± 1	0.59
Postnatal age at assessment (d)	9.9 ± 1.7	10.3 ± 1.7	0.5
Birthweight (g)	918 ± 174	1398 ± 263	<0.0001
Apgar score at 5 min (median, range)	8 (7, 9)	8 (7, 9)	0.14
Antenatal steroids, *n* (%)	23 (82)	23 (88)	0.6
Surfactant replacement therapy, *n* (%)	21 (75)	16 (61)	0.4
Mode of delivery, *n* (%) (vaginal)	20 (71)	20 (77)	0.8
Male sex, *n* (%)	19 (68)	14 (54)	0.4
Mean airway pressure (cm of H_2O)	7 ± 0.8	7 ± 1	0.5
Fractional inspired oxygen	0.26 ± 0.02	0.26 ± 0.02	0.8
Systolic BP (mmHg)	51 ± 3	46 ± 3	<0.001
Diastolic BP (mmHg)	30 ± 2	25 ± 3	<0.001
Mean arterial BP (mmHg)	37 ± 2	33 ± 2	<0.001
Heart rate (beats/min)	147 ± 5	146 ± 3	0.3
Rate pressure product	7576 ± 535	6833 ± 493	<0.001

FGR, fetal growth restriction; AGA, appropriate for gestational age; BP, blood pressure; rate pressure product = heart rate × systolic blood pressure

Table 2. Comparison of echocardiographic variables of cardiac function

Variable	FGR	AGA	*P* value
LVEDD (mm)	14.6 ± 9.6	13.6 ± 7.3	0.0001
LVPWd (mm)	2.7 ± 0.25	2.5 ± 0.2	0.003
Fractional shortening (%)	33.6 ± 2.6	34.6 ± 3	0.17
Trans-mitral E/A	0.84 ± 0.05	0.79 ± 0.03	0.0002
End-systolic wall stress (g/cm^2)	47 ± 6	33 ± 3	<0.001
LVO (ml/kg/min)	262 ± 50	285 ± 65	0.15
mVCFc (circ/s)	1.9 ± 0.3	2.7 ± 0.5	<0.001
LV mass (g)	6.4 ± 0.8	5.3 ± 3	<0.001

FGR, fetal growth restriction; AGA, appropriate for gestational age; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVPWd, left ventricular posterior wall in diastole; LVO, left ventricular output; mVCFc, mean velocity of circumferential fibre shortening.

vascular tree.[31,33] Prostaglandins (PG) are thought to play an important role in CABF regulation.[34] Intra-coronary instillation of PG in animal models led to a dose-dependent reduction in coronary vascular resistance and increase in CABF.[35-37] Ewes affected by chronic placental restriction demonstrate higher levels of PG endoperoxide synthase (inversely associated with fetal partial pressure of oxygen) as well as greater numbers of PG receptors.[38]

CABF and interactions with cardiac milieu

Table 4 outlines available ultrasound data on human neonates during the initial postnatal days[12-16]; assessments in FGR infants have not been performed previously. Lower CABF was associated with lower cardiac output in healthy neonates and those with acute hypoxaemia,[15,16] while LV hypertrophy in aortic stenosis

Table 3. Comparison of coronary indices

Variable	FGR	AGA	*P* value
LAD mm	0.96 ± 0.02	0.92 ± 0.01	0.36
LAD VTI cm	2.4 ± 0.9	1.6 ± 0.8	0.002
LAD velocity cm/s	30 ± 10	23 ± 9	0.02
LAD VTI/LVO	0.01 ± 0.004	0.006 ± 0.003	0.002
LAD VTI/mVCFc	1.3 ± 0.5	0.6 ± 0.3	<0.001
LAD VTI/E/A	2.9 ± 1	2.1 ± 1	0.01
LAD VTI/DBP	0.08 ± 0.03	0.06 ± 0.03	0.059
LAD VTI/RPP	0.0003 ± 0.0001	0.0002 ± 0.0001	0.017

FGR, fetal growth restriction; AGA, appropriate for gestational age; LVO, left ventricular output; mVCFc, mean velocity of circumferential fibre shortening; LAD, left anterior descending; VTI, velocity time integral; DBP, diastolic blood pressure; RPP, rate pressure product.

or hypertrophic cardiomyopathy, and ventricular septal defects are accompanied by higher CABF,[39-41] putatively as adaptation to higher myocardial oxygen demand and increased LV mass. However, our study demonstrated that this relationship (termed aorto-myocardial coupling) is not maintained in FGR infants, plausibly due to chronic intrauterine hypoxaemia induced myocardial architectural changes such as decreased cardiac sarcomeric proteins, compensatory increase in glycogen and collagen deposition, and reduction in the number of binucleated cardiomyocytes and decreased matrix metalloproteinase-2 activity.[42-45] While low partial pressure of oxygen is mainly responsible for changes in fetal CABF, high systemic afterload (higher end-diastolic intraventricular pressure [↑ trans-mitral E/A and ↑ ESWS]) further increases myocardial oxygen requirements. Myocardial dysfunction with a subsequent fall in cardiac output[17,30,46] could jeopardise CABF itself as a terminal event. Our findings of increased CABF in hypertrophied FGR myocardium should be seen in this context.

A number of previous studies have highlighted early visualisation and increased CABF in hypoxaemic FGR fetuses (25 weeks vs 31 weeks in AGA),[18,26,47-50] indicating a global increase in myocardial blood flow throughout the cardiac cycle. Visualization of CABF in FGR fetuses was associated with circulatory redistribution, acidemia, poorer perinatal outcomes and impaired myocardial function.[46,51] Myocardial hypertrophy/dysfunction may be primary (internal myocardial changes) or a combined effect due to systemic vascular stiffness. The ESWS was higher in the FGR cohort in our study. Higher ESWS is also noted in patients with aortic stenosis (↑ LV mass and hypertrophied myocardium), where it correlated with markers of LV remodelling.[52] Preservation of ESWS (lower ESWS) is considered important, as it has been demonstrated to be the most important determinant of LV oxygen consumption in pressure overload; elevated ESWS increases the risk of myocardial ischaemia.[53,54] Unlike other parameters such as stroke volume and ejection fraction, wall stress is an index of LV performance that is considered afterload independent, since it accounts for both wall thickness and pressure generation. The alteration of ventricular wall stress is associated with morphological and functional changes in the myocardium. Higher CABF in FGR cohort of our study may reflect increased oxygen consumption due to such pressure overload, and may be a driving force behind higher CABF.

Figure 2 summarises interactions of various haemodynamic forces in the hypoxaemic milieu. *In-utero* hypoxaemia influences

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Table 4. Previous studies in human neonates documenting coronary indices

Patient profile	LAD characteristics	Clinical construct - study conclusions	Reference
12 healthy neonates vs 9 neonates with VSD. Age range (d)[#] 6–8 vs 5–10. Birthweight (g)[#] 3116 ± 167 vs 2996 ± 126.	Diameter (mm)[#] −1.1 ± 0.1 vs 1.2 ± 0.3^ Diastolic PFV (cm/s)[#] −15 ± 4 vs 28 ± 6* Diastolic VTI (cm)[#] −2.3 ± 0.6 vs 5.9 ± 1.5* Rate pressure product[#] −9198 ± 124 vs 9240 ± 145^	↑Coronary flow in infants with VSD may be a compensatory mechanism for the ↑in oxygen demand of the hypertrophied LV myocardium.	Harada, 2001
Term infant, birthweight 2600g. Assessments after balloon valvuloplasty for severe aortic stenosis	Flow velocity ↑ from 22 to 45 cm/s. VTI ↑ from 3.1 to 6.4 cm	Improvement in CABF, suggesting Improved imbalance between CABF and metabolic demand for oxygen.	Harada, 2003
55 healthy neonates, aged 12 h–30 d, 10 (18%) born <38 weeks, birthweight range 1700–4800 g	Diameter (mm) −1.18 ± 0.13 Diastolic PFV (cm/s) −25.5 ± 8.3 Diastolic VTI (cm) −4.5 ± 1.3 Rate pressure product −9724 ± 2042	Left coronary flow parameters were linearly related to age, LV mass, and LV systolic and diastolic function.	Oskarsoon, 2004
18 preterm infants, echocardiographic assessments (pre-indomethacin, immediately after the 1-h infusion, and 1-h post-indomethacin. Gestation range[$] (weeks) (25.8 [24.2,28.1]) Birthweight[$] (g) (827 [704,1002]) Age at assessment[$] (d) (7 [4,17])	Diastolic PFV (cm/s) −30 ± 10 vs 22 ± 8 vs 26 ± 8 ($P = 0.4$) Diastolic VTI (cm) −3.19 ± 1.2 vs 2.01 ± 0.9 vs 2.4 ± 0.9 ($P = 0.004$) Rate-pressure product** −7200 (6600–7860) vs 7400 (6550–7930) vs 7580 (7140–8140)[%]	In mechanically ventilated infants with haemodynamically significant patent ductus arteriosus, intravenous indomethacin was followed by a significant decline in coronary arterial diastolic blood flow.	Sehgal, 2012
20 healthy controls vs 14 term infants with severe perinatal asphyxia receiving therapeutic hypothermia Gestation age**[@] (weeks) 39 (37–41) vs 39 (37–42)[%] Birthweight** (g) 3180 (3012–3521) vs 3550 2380–3992)[%]	Diastolic PFV (cm/s)**[@] −32 (29–34) vs 17 (13–24)* Diastolic VTI (cm)**[@] −4.9 (4–5.6) vs 2.1 (1.3–2.9)*	Coronary flow had a significant positive correlation with LV output. Close association between cardiac output, coronary flow and troponin.	Sehgal, 2012

PFV, peak flow velocity; VTI, velocity time integral; LV, left ventricular; VSD, ventricular septal defect.
*$P < 0.01$.
^Not significant, [#]Normal vs VSD, [$]median (IQR-interquartile), **median (range), [@]normal vs infants with severe asphyxia, [%]Not significant.

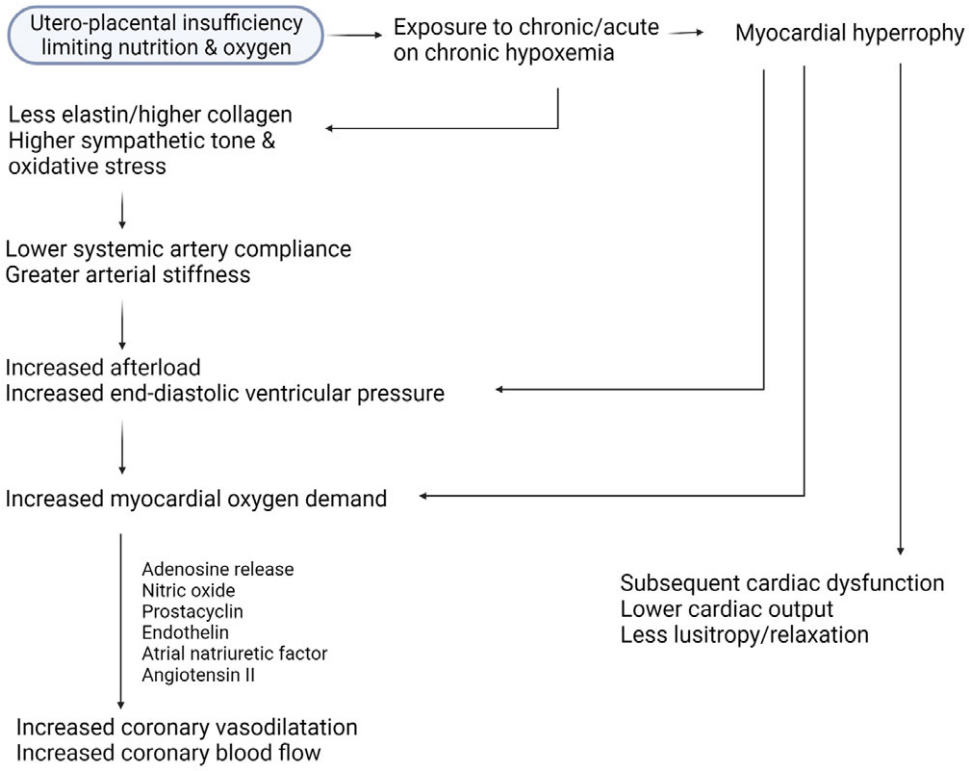


Fig. 2. Interaction of various haemodynamic forces in the hypoxaemic milieu.

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changes in vascular architecture and hence, flow dynamics. Majority of elastin deposition in the arteries occurs in the third trimester; infants born premature miss out on that surge. Compounded by the deposition of collagen and other cyto-architectural changes, the elevation in systemic afterload has back-pressure effect on the structure and function of the LV myocardium. Intrinsic myocardial changes may happen concurrently, and contribute to impaired cardiac function.

The RPP was higher in FGR infants. The RPP correlates with measured LV myocardial oxygen consumption as indicated by experiments in lambs exposed to infusion of phenylephrine and sodium nitroprusside.[55] The non-invasive index of RPP also had the best correlation with exercise-induced myocardial oxygen consumption ($r = 0.88$) in healthy human volunteers as measured via aortic catheters.[56] While prognostic data in infants is unavailable, a study on >7000 adults with heart failure-preserved ejection fraction noted that an increase in RPP from baseline to discharge was associated with increased 30-d mortality/heart failure.[57] Possibly, a higher RPP in FGR infants is a surrogate for higher myocardial oxygen consumption, and may drive the need for higher CABF. In essence, the increase in CABF in FGR cohorts may be a persistent end-organ adaptation. The presence of increased CABF (heart sparing) but lower cardiac function parallels the finding of increased cerebral blood flow (brain sparing) but lower neuro-development function. This may be related to alterations in cardiac architecture itself.

Clinical relevance of dichotomy between CABF and cardiac function

Aorto-myocardial coupling seems disrupted in FGR infants, as explained above. In patients with known diastolic dysfunction secondary to LV hypertrophy, the failure of myocardial relaxation and drop in coronary vascular resistance in the face of increasing demand (e.g. obesity) may plausibly heighten the risk of cardiovascular disease (CVD), as CABF augmentation may not increase as per need, as it is already amplified having used up its 'coronary flow reserve'.[58,59] Abnormal relaxation (higher LV end-diastolic pressure [↑trans-mitral E/A ratio and ESWS]) indicates pathological cardiac remodelling, diastolic dysfunction and possibly may increase sensitivity to ischaemic injury during adult life in FGR offspring.[60] Epidemiological studies by Barker and colleagues have demonstrated higher CVD related mortality due to circulatory causes amongst adults who had lower birthweight.[61,62] Combined with intrinsic cardiac changes, the above flow dynamics in FGR infants may putatively increase the risk of CVD in adulthood, when faced with additional workload such as strenuous exercise, obesity or hypertension. Indexed CABF data in our cohort should be seen in this context. 'Catch-up growth' (*in-utero* undernutrition followed by rapid childhood growth) may be deleterious in this context as it might require further augmentation of CABF.[63] This is supported by data that mean 24-h ambulatory BP is higher in adolescents born low birthweight in combination with later obesity, in comparison to normal birthweight, with or without obesity.[64] Higher BP (and the consequent RPP) would augment myocardial oxygen demand. Other relevant mechanistic links between FGR, hypertension and risk of adult onset CVD such as accelerated vascular ageing and programming of the renin-angiotensin system, may work in tandem with our present postulations.[65]

Potential drugs and diet recommendations for improving cardiovascular outlook in FGR infants

An important next step would be to explore interventions to stop or reverse the cardiovascular effects secondary to FGR. The interventions may be during fetal life or postnatally.

Drugs: Phosphodiesterase-5 breaks down cyclic guanosine monophosphate; sildenafil decreases the activity of Phosphodiesterase-5, thereby increasing the levels of cyclic guanosine monophosphate, thereby improving vascular relaxation. Decreased release of endothelial nitric oxide synthase and thus, less nitric oxide (vasodilator) is seen in pregnancies complicated by pre-eclampsia or FGR, which explains the rationale to use sildenafil as a therapeutic option.[66] However, a recent randomised controlled trial investigating the effect of sildenafil compared with placebo in pregnancies with severe FGR showed no differences on the main outcome of prolongation of pregnancy. A non-significant 2.3% increase in BW was noted.[67] Trapani et al. investigated 100 women with pre-eclampsia, randomised to sildenafil or placebo. Lower mean BP and improved utero-placental resistance were noted but no improvement in neonatal outcomes.[68] Further refinement in dosage and time of intervention may be required.

Diet: In one study on 81 FGR-born children were compared with 121 AGA-born children at age 4–5 years.[69] Breastfeeding and postnatal nutrition improved cardiovascular remodelling (heart sphericity) and lowered carotid wall thickness induced by FGR. In children and adolescents who were born FGR, dietary intake of omega-3 poly-unsaturated fatty acids was inversely associated with BP and also resulted in decreased arterial wall thickness. In this study of >3000 children aged 8–15 years, pulse pressure was significantly higher in children born FGR compared with normal BW children. Importantly, children with the highest tertile of omega-3 poly-unsaturated fatty acids intake had significantly lower BPs.70 Dietary consumption of omega-3 fatty acids led to lower BP in childhood and adolescence and lower aortic wall thickness.[71,72] In a large cohort of racially and ethnically diverse, low-income women, the effect of Mediterranean-style diet as protective for pre-eclampsia was evaluated. Data were obtained via interview and food frequency questionnaire within 24–72 h postpartum, respectively. After multivariable adjustment, greatest adherence with Mediterranean-style diet was associated with lower pre-eclampsia odds.[73]

Challenges and limitations of the technique

Although advancement in ultrasound technology has improved image resolution, Echo evaluation of CABF may be limited by spatial resolution. As the calibre of the LAD coronary artery in this cohort of infants is small, accurate measurement of CABF is particularly dependent on the accuracy of vessel diameter measurement. We used a 12 Hz probe; the availability of further higher frequency probes may enhance accuracy by improving spatial resolution. The flow pattern in coronary arteries is typically biphasic flow, with a dominant diastolic and minor systolic component. As the latter is not easily detectable; assessments are limited to the dominant diastolic phase. We kept the angle of insonation to <15°. If this is not achieved, modern machines allow use of angle correction to avoid under-reading of the flow curve. CABF Doppler were not available for the whole cohort; this may be contributed by both incomplete data collection and lack of visualisation of vessels. Presently, there is insufficient data on CABF in relation to GA during postnatal period. We did not follow the cohort for subsequent analyses at term corrected GA, which would

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have given sequential information about postnatal adaptation. Whether CABF in FGR infants return to normal AGA levels, and the possible timeline when this would happen, is unknown.

Conclusions and future directions

In this study we demonstrated a dichotomy between CABF and cardiac function in preterm FGR infants in the initial postnatal weeks. CABF was higher but cardiac function was lower in FGR, compared to equally preterm AGA infants. This is similar to the uncoupling noted in studies on FGR fetuses. The *in-utero* increased CABF is a cardiac adaptation to the hypoxaemic fetal state secondary to utero-placental insufficiency. Postnatally, it may reflect altered state of metabolism, fetal programming, higher PG levels in FGR, effects of altered myocardial architecture leading to greater oxygen consumption/requirements, but likely a combination of all the above. While coronary imaging and CABF assessment may be technically challenging, necessitating enhanced learning and imaging skills, it does provide important physiological data in high-risk cohorts such as FGR. Earlier visualisation of coronary flow alongside myocardial dysfunction and perinatal outcome data indicates possibility of earlier stratification (e.g. vs pregnancies where LV function is reduced but normal CABF). Whether assessments of CABF in FGR-born adults provide predictive ability for CVD in middle-older ages, needs prospective study. Our findings add the role of CABF to this biological plausibility, making stress-induced CABF assessments attractive monitoring and prognostic tools in select populations.

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Conflicts of interest. No conflicts.

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