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Relationship of prelabor fetal cardiac function with intrapartum fetal compromise and neonatal status at term

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KEYWORDS: adverse neonatal outcome; cardiac function; cerebroplacental ratio; Cesarean section; fetal compromise; fetal hypoxia

ABSTRACT

Objectives *To investigate prospectively the relationship of fetal cardiac function and Doppler ultrasound parameters with intrapartum fetal compromise (IFC) in appropriately grown term fetuses. Secondary aims were to correlate prenatal cardiac function with neonatal acid–base status, intrapartum fetal heart rate (FHR) abnormalities and adverse neonatal outcomes.*

Methods *This was a blinded, prospective, observational, cohort study of 270 women with an uncomplicated singleton pregnancy who underwent fortnightly ultrasound assessment from 36 weeks' gestation until delivery at the Mater Mother's Hospital, Brisbane, Australia. Fetal cardiac output and blood flow parameters were assessed and correlated with intrapartum and neonatal outcomes. The primary outcome was need for operative (either Cesarean or instrumental vaginal) delivery for IFC. Secondary outcome measures were acidosis at birth, 5-min Apgar score* ≤ 7*, suspicious or pathological FHR abnormalities and admission to the neonatal intensive care unit.*

Results *Two hundred and seventy women were included in the analysis, of whom 51 (18.9%) had an emergency operative delivery for IFC. Fetuses that had emergency delivery for IFC showed lower mean left ventricular cardiac output (LVCO) (*560 ± 44 *mL/min* vs 617 ± 73 *mL/min;* $P < 0.001$*), lower mean LVCO/right ventricular cardiac output (RVCO) ratio (*0.55 ± 0.07 vs 0.64 ± 0.11*;* $P < 0.001$*), lower mean cerebroplacental ratio (CPR) (*1.62 ± 0.3 vs 1.90 ± 0.5*;* $P < 0.001$*) and higher mean RVCO (*1026 ± 105 *mL/min* vs 978 ± 110 *mL/min;* $P = 0.003$*) compared with those that did not develop IFC. Additionally, LVCO and CPR were lower in fetuses with adverse neonatal outcome.*

Conclusion *Term fetuses with estimated fetal weight* $> 10^{th}$ *centile that develop IFC have evidence of lower LVCO and higher RVCO, which are in turn associated with poorer condition of the newborn. Fetal CPR is positively correlated with LVCO.* *Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Low cerebroplacental ratio (CPR) at term is an independent predictor of intrapartum fetal compromise (IFC)[1,2], poor acid–base status at birth[3,4], increased risk of admission to the neonatal intensive care unit (NICU)[5] and increased risk of stillbirth[6], and is now believed to reflect failure of a fetus to reach its genetic growth potential at term[7]. Labor can be an asphyxial process, as myometrial contractions reduce blood flow in the uterine arteries, thus decreasing oxygen availability to the fetoplacental unit[8], and can result in IFC in vulnerable fetuses. Fetal cardiac output is altered in response to hypoxia to facilitate cerebral redistribution[9,10], evidenced by a low CPR. In addition, there is evidence that some growth-restricted fetuses demonstrate features of *in-utero* cardiac dysfunction[11–13].

The aim of this study was to evaluate prospectively fetal cardiac function and CPR measured within 2 weeks of birth, and to correlate these with intrapartum and neonatal outcomes in a cohort of women with a normally grown fetus and otherwise uncomplicated pregnancy.

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METHODS

This was a blinded, prospective, cross-sectional cohort study carried out at the Mater Mothers' Hospital, Brisbane, Australia, between March 2015 and August 2016. Inclusion criteria were women with an uncomplicated, singleton pregnancy without fetal anomaly who were planning a vaginal birth. Exclusion criteria included known fetal growth restriction or small-for-gestational-age fetus, multiple pregnancy, previous Cesarean section (CS), pre-eclampsia and maternal age < 18 or > 50 years. Women were approached to participate in the study at the time of a routine appointment at the antenatal clinic. Ethical and governance approvals were granted by the Mater Human Research Ethics Committee and Research Governance Office, respectively (Ref no: HREC/13/MHS/173).

Gestational age was calculated based on first-trimester ultrasound scan. All participants underwent ultrasound scans fortnightly, from 36 weeks' gestation (± 1 week) until delivery. Ultrasound examinations were performed using an Acuson S2000 (Siemens Medical Systems, Erlangen, Germany) ultrasound system with a 3–8-MHz curvilinear transducer. Fetal biometry, umbilical artery pulsatility index and middle cerebral artery pulsatility index were measured in triplicate and mean values were calculated. CPR and estimated fetal weight (EFW) were calculated at each attendance. Doppler measurements were acquired during periods of fetal quiescence, with the angle of insonation maintained at < 15° and wall filter set at 70 Hz.

The aortic outflow tract was evaluated on a long axis of the left ventricle with the aorta in continuity with the interventricular septum. The pulmonary artery was evaluated in either a short- or long-axis view of the right ventricle. The Doppler sample gate (gate size set at 2–3 mm) was placed at the level of the appropriate valve to obtain the relevant waveform, with the angle of insonation maintained as close to 0° as possible and, when an angle of 0° could not be achieved owing to fetal position, the angle correction function was used and the angle was maintained at ≤ 15° (Figure 1). The inner diameters of both outflow tracts were also measured in triplicate at this level and the average measurements recorded. Velocity waveforms of three representative heart cycles were traced manually to obtain the time-velocity integral (TVI) and fetal heart rate (FHR). All cardiac measurements were obtained during fetal quiescence, when the FHR was within the normal range (120–160 bpm), as it is known that fetal breathing movements and tachycardia can increase the velocity in the outflow tracts. All examinations were performed by one operator (A.A.A.). In a subcohort of 30 women, diameter and flow measurements of the

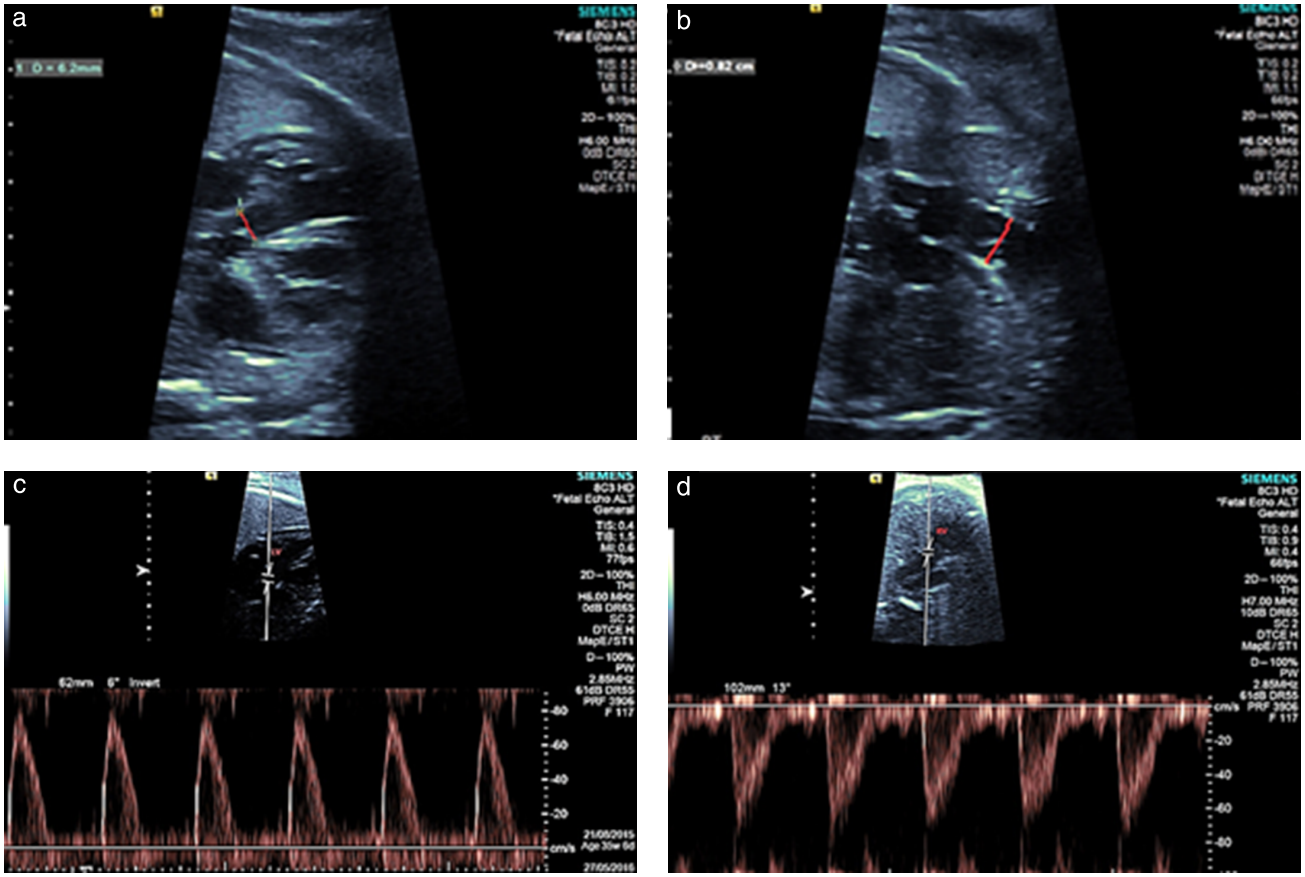

Figure 1 Assessment of fetal cardiac output. Ultrasound images show measurement of aortic (a) and pulmonary artery (b) valve diameter (red lines) and of aortic (c) and pulmonary artery (d) pulsed Doppler waveforms, with sample gate placed just distal to valve of both great vessels.

aorta and pulmonary artery were repeated by the same operator to establish intraobserver variability of these parameters.

The reported Doppler and cardiac measurements are those obtained at the last assessment prior to delivery. The left ventricular stroke volume (LVSV) and right ventricular stroke volume (RVSV) were calculated according to the formula SV (mL) = $\pi \times r^2 \times$ TVI, where r is the valve radius of the right or left ventricle and is calculated as valve diameter/2. Cardiac output (CO) was calculated using the formula: CO (mL/min) = SV × FHR. Combined CO (CCO) was defined as the sum of left ventricular cardiac output (LVCO) and right ventricular cardiac output (RVCO). Corrected LVCO, RVCO and CCO were assessed by dividing these measurements by the EFW. The ratio LVCO/RVCO was calculated by dividing the corrected LVCO by the corrected RVCO (mL/min/kg).

Both women and obstetric caregivers were blinded to the ultrasound results. The only exceptions for disclosure of ultrasound findings were malpresentation, severe oligohydramnios (deepest pool < 1 cm) or absent or reversed flow in the umbilical artery, as these findings would influence immediate obstetric management. Labor and delivery were managed according to local protocols and guidelines.

Primary outcome was need for operative (either CS or instrumental vaginal) delivery for IFC. The diagnosis of IFC was made by either abnormal fetal scalp pH (pH < 7.2) or serum lactate level (> 4 mmol/L), or pathological FHR pattern or both. The diagnosis of abnormal intrapartum FHR pattern was made using criteria detailed in the Royal Australian and New Zealand College of Obstetricians and Gynaecologists FHR guidelines[14]. These classifications are very similar to those advocated by the American College of Obstetricians and Gynecologists in the USA and the National Institute of Health and Care Excellence in the UK[15,16].

Secondary outcome measures were acidosis at birth (cord arterial pH ≤ 7.1 or lactate ≥ 6.0 mmol/L or base excess ≤ −12 mmol/L), 5-min Apgar score ≤ 7, suspicious or pathological FHR abnormalities and admission to the NICU. A composite adverse neonatal outcome (defined as acidosis at birth and/or 5-min Apgar score < 7 and/or NICU admission) was also evaluated against fetal cardiac and Doppler parameters. Following enrollment, women who had planned a Cesarean delivery for any reason were excluded from further analysis.

Statistical analysis

Normally distributed data (maternal age, fetal cardiac and Doppler parameters) are reported as mean ± SD. Non-normally distributed data (body mass index, duration of labor, birth weight, gestational age at delivery and birth-weight centile) are reported as median (interquartile range (IQR)). Maternal and infant characteristics were compared using the chi-square or Fisher's exact test for frequencies, and Student's *t*-test or the Wilcoxon rank-sum test (Mann–Whitney *U*-test) for normally distributed or non-normally distributed continuous variables, respectively. To analyze the primary outcome, participants were divided into two groups according to whether or not they required operative delivery owing to IFC (IFC group or no-IFC group). The intraobserver coefficient of variation was calculated according to the root mean square method[17]. Statistical analysis was performed using Stata software version 13.0 (StataCorp, College Station, TX, USA), and significance level was set at $P \leq 0.05$ for all analyses.

RESULTS

In total, 283 women were recruited during the study period, of whom 13 (4.6%) were subsequently excluded from further analysis; these included seven (2.5%) women who underwent elective CS, one (0.4%) who delivered an infant with severe shoulder dystocia, one (0.4%) who developed severe intrapartum urosepsis and four (1.4%) who were excluded owing to missing data or inability to obtain all necessary cardiac measurements. Thus, the final study cohort comprised 270 women (Figure 2). Overall, 51 (18.9%) women had an emergency operative delivery for IFC, with 42 (15.6%) women requiring instrumental delivery and nine (3.3%) having an emergency CS. One hundred and fifty-eight (58.5%) women had umbilical cord blood gas tests performed. Characteristics of the study population are presented in Table 1. Women who required operative birth for IFC were more likely to have babies with lower median birth-weight centiles than were women who did not develop IFC (30th centile (IQR, 17th–50th centile) *vs* 44th centile (IQR, 25th–68th centile); $P = 0.002$).

The coefficient of variation for measurement of the left and right CO was 7.2% (95% CI, 5.8–8.3%) and 7.0% (95% CI, 6.2–8%), respectively. Mean LVCO was lower in fetuses that required emergency operative delivery for IFC than in those that did not (560 ± 44 mL/min *vs* 617 ± 73 mL/min; $P < 0.001$). After correction for EFW, LVCO remained lower in fetuses that required emergency operative delivery for IFC than in the rest of the study cohort (164 ± 19 mL/min/kg *vs* 181 ± 30 mL/min/kg; $P < 0.001$) (Table 2). In contrast, mean RVCO was higher in fetuses that required emergency operative delivery for IFC compared with those that did not (1026 ± 105 mL/min *vs* 978 ± 110 mL/min; $P = 0.003$) and the corrected RVCO was also higher in this group (300 ± 39 mL/min/kg *vs* 290 ± 41 mL/min/kg), although the difference did not reach statistical significance ($P = 0.14$). There were no statistically significant differences in CCO and corrected CCO (mL/min/kg), between fetuses that required emergency operative delivery for IFC and those that did not develop this complication (Table 2).

Mean LVSV was lower in fetuses that required emergency operative delivery for IFC than in those that did not (4.09 ± 0.3 mL *vs* 4.45 ± 0.5 mL; $P < 0.001$).

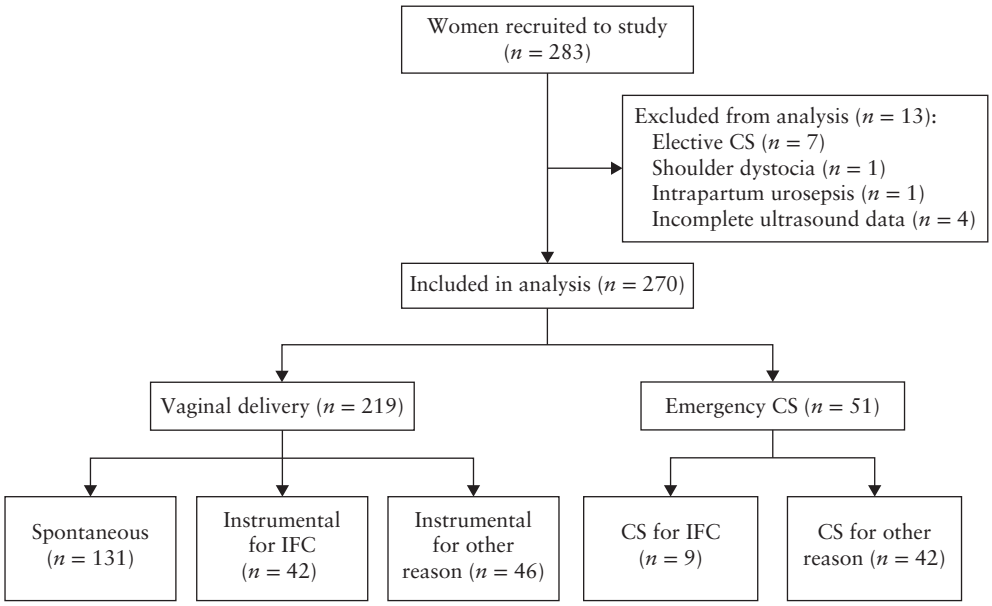

Figure 2 Flowchart showing inclusion of study participants and their mode of delivery, according to whether or not they developed intrapartum fetal compromise (IFC). CS, Cesarean section.

Table 1 Baseline and perinatal characteristics of 270 women with uncomplicated singleton pregnancy, according to whether or not they required operative delivery for intrapartum fetal compromise (IFC)

Characteristic	*All women* (n = *270*)	*No IFC* (n = *219*)	*IFC* (n = *51*)	P
Maternal age (years)	29.5 ± 4.7	30.2 ± 4.9	30.6 ± 3.9	0.40*
Nulliparous	269 (99.6)	218 (99.5)	51 (100.0)	0.96
Ethnicity				0.95†
Caucasian	170 (63.0)	138 (63.0)	32 (62.7)	
East Asian	56 (20.7)	44 (20.1)	12 (23.5)	
Asian	22 (8.1)	18 (8.2)	4 (7.8)	
Other	22 (8.1)	19 (8.7)	3 (5.9)	
BMI (kg/m^2)	22 (20.3–25.0)	21.9 (20.3–25.0)	21.9 (19.5–24.7)	0.90‡
Gestational diabetes	14 (5.2)	14 (6.4)	0 (0.0)	0.07†
Interval from last US to birth (days)	9 (5–12)	9 (5–12)	8 (6–12)	0.88‡
GA at delivery (weeks)	40 (39.3–40.9)	39.9 (39.2–40.7)	40.6 (39.7–41.1)	0.03‡
Duration of labor (min)	433 (281–627)	434 (281–627)	413 (259–640)	0.54‡
BW (g)	3413 ± 397	3438 ± 405.5	3322 ± 352	0.11*
BW centile	42 (25–68)	44 (25–68)	30 (17–50)	0.002‡

Data are reported as *n* (%), mean ± SD or median (interquartile range). *P*-values calculated using: *Student's *t*-test; †Fisher's exact test; ‡Wilcoxon's rank sum test (Mann–Whitney *U*-test). BMI, body mass index; BW, birth weight; GA, gestational age; US, ultrasound assessment.

Table 2 Fetal cardiac and Doppler parameters assessed within 2 weeks prior to delivery in 270 uncomplicated pregnancies, according to whether or not they required operative delivery for intrapartum fetal compromise (IFC)

Parameter	*No IFC* (n = *219*)	*IFC* (n = *51*)	P*
LVCO (mL/min)	617 ± 73	560 ± 44	< 0.001
Corrected LVCO (mL/min/kg)†	181 ± 30	164 ± 19	< 0.001
RVCO (mL/min)	978 ± 110	1026 ± 105	0.003
Corrected RVCO (mL/min/kg)†	290 ± 41	300 ± 39	0.14
LVCO/RVCO ratio‡	0.64 ± 0.11	0.55 ± 0.07	< 0.001
CCO (mL/min)	1592 ± 136	1586 ± 152	0.77
Corrected CCO (mL/min/kg)†	473 ± 61	463 ± 57	0.20
LVSV (mL)	4.45 ± 0.5	4.09 ± 0.3	< 0.001
RVSV (mL)	7.10 ± 1.1	7.46 ± 1.1	< 0.01
MCA-PI	1.52 ± 0.29	1.29 ± 0.22	< 0.001
UA-PI	0.80 ± 0.01	0.82 ± 0.02	0.53
CPR	1.90 ± 0.5	1.62 ± 0.3	< 0.001

Data are given as mean ± SD. **P* calculated using Student's *t*-test. †Corrected LVCO, RVCO and CCO obtained by dividing these measurements by estimated fetal weight. ‡LVCO/RVCO ratio calculated by dividing corrected LVCO by corrected RVCO. CCO, combined cardiac output; CPR, cerebroplacental ratio; LVCO, left ventricular cardiac output; LVSV, left ventricular stroke volume; MCA-PI, middle cerebral artery pulsatility index; RVCO, right ventricular cardiac output; RVSV, right ventricular stroke volume; UA-PI, umbilical artery pulsatility index.

Table 3 Fetal cardiac parameters, assessed within 2 weeks prior to delivery, and intrapartum outcomes of 270 uncomplicated pregnancies, according to delivery mode, indication for delivery and presence of abnormal fetal heart rate

	Any operative delivery for IFC			*Emergency CS for IFC*			*Instrumental vaginal delivery for IFC*			*Abnormal fetal heart rate*		
Outcome	*Yes* (n = *51*)	*No* (n = *219*)	P*	*Yes* (n = *9*)	*No* (n = *261*)	P*	*Yes* (n = *42*)	*No* (n = *228*)	P*	*Yes* (n = *83*)	*No* (n = *187*)	P*
LVCO (mL/min)	560 ± 44	617 ± 73	< 0.001	556 ± 37	617 ± 72	0.01	561 ± 43	617 ± 73	< 0.001	581 ± 75	619 ± 68	< 0.001
Corrected LVCO (mL/min/kg)†	164 ± 19	181 ± 30	< 0.001	157 ± 23	180 ± 30	0.03	164 ± 21	180 ± 30	< 0.001	169 ± 32	185 ± 30	< 0.001
LVSV (mL)	4.09 ± 0.3	4.45 ± 0.5	< 0.001	4.1 ± 0.25	4.40 ± 0.51	0.04	4.08 ± 0.4	4.45 ± 0.5	< 0.001	4.22 ± 0.6	4.45 ± 0.5	< 0.01
RVCO (mL/min)	1026 ± 105	978 ± 110	0.003	977 ± 109	1021 ± 110	0.21	1028 ± 105	978 ± 109	< 0.01	1006 ± 130	975 ± 112	0.04
Corrected RVCO (mL/min/kg)†	300 ± 39	290 ± 41	0.14	290 ± 50	286 ± 41	0.51	290 ± 37	290 ± 41	0.11	301 ± 40	291 ± 44	0.06
RVSV (mL)	7.46 ± 1.1	7.10 ± 1.1	< 0.01	7.68 ± 0.5	7.05 ± 0.8	0.02	7.46 ± 1.0	7.10 ± 1.1	0.01	7.30 ± 1.0	7.02 ± 0.9	0.01
LVCO/RVCO ratio‡	0.55 ± 0.07	0.64 ± 0.11	< 0.001	0.57 ± 0.05	0.63 ± 0.11	0.004	0.56 ± 0.08	0.64 ± 0.11	< 0.001	0.59 ± 0.06	0.64 ± 0.11	< 0.001

Data are given as mean ± SD. *P calculated using Student's t-test. †LVCO, RVCO corrected for estimated fetal weight. ‡LVCO/RVCO ratio calculated by dividing corrected LVCO by corrected RVCO. CS, Cesarean section; IFC, intrapartum fetal compromise; LVCO, left ventricular cardiac output; LVSV, left ventricular stroke volume; RVCO, right ventricular cardiac output; RVSV, right ventricular stroke volume.

Table 4 Fetal cardiac parameters, assessed within 2 weeks prior to delivery, in 270 uncomplicated pregnancies, according to neonatal outcome

	*Abnormal cord gases**			*5-min Apgar ≤ 7*			*Admission to NICU*			*Composite adverse neonatal outcome†*		
Outcome	*Yes* (n = *47*)	*No* (n = *111*)	P‡	*Yes* (n = *4*)	*No* (n = *266*)	P‡	*Yes* (n = *13*)	*No* (n = *257*)	P‡	*Yes* (n = *54*)	*No* (n = *216*)	P‡
LVCO (mL/min)	578 ± 65	593 ± 72	0.02	572 ± 46	607 ± 83	0.35	584 ± 57	608 ± 73	0.23	581 ± 64	612 ± 74	< 0.01
Corrected LVCO (mL/min/kg)§	168 ± 26	174 ± 27	0.10	167 ± 28	176 ± 33	0.42	170 ± 30	177 ± 33	0.31	168 ± 26	180 ± 31	< 0.01
LVSV (mL)	4.18 ± 0.6	4.41 ± 0.6	< 0.01	4.31 ± 0.3	4.38 ± 0.5	0.79	4.32 ± 0.5	4.39 ± 0.6	0.61	4.22 ± 0.5	4.42 ± 0.5	0.01
RVCO (mL/min)	1015 ± 103	990 ± 111	0.11	1007 ± 57	987 ± 122	0.70	1013 ± 160	984 ± 117	0.34	1013 ± 98	979 ± 112	0.04
Corrected RVCO§ (mL/min/kg)	290 ± 42	286 ± 44	0.90	297 ± 26	291 ± 43	0.80	299 ± 60	291 ± 42	0.52	288 ± 41	287 ± 41	0.70
RVSV (mL)	7.34 ± 0.84	7.18 ± 0.81	0.27	7.2 ± 0.4	7.13 ± 0.9	0.80	7.52 ± 1.1	7.09 ± 0.9	0.06	7.33 ± 0.84	7.07 ± 0.81	0.04
LVCO/RVCO ratio¶	0.59 ± 0.08	0.61 ± 0.10	< 0.01	0.57 ± 0.06	0.61 ± 0.1	0.15	0.59 ± 0.10	0.61 ± 0.12	0.30	0.59 ± 0.07	0.63 ± 0.11	< 0.001

Data are given as mean ± SD. *Considered as umbilical artery pH ≤ 7.1, lactate ≥ 6 mmol/L, base excess < 12 mmol/L; data available for 158 pregnancies. †Composite of: abnormal cord gases and/or 5-min Apgar score ≤ 7 and/or admission to NICU. ‡P calculated using Student's t-test. §LVCO, RVCO corrected for estimated fetal weight. ¶LVCO/RVCO ratio calculated by dividing corrected LVCO by corrected RVCO. LVCO, left ventricular cardiac output; LVSV, left ventricular stroke volume; NICU, neonatal intensive care unit; RVCO, right ventricular cardiac output; RVSV, right ventricular stroke volume.

Additionally, subgroup analysis of LVSV by mode of delivery and whether or not the indication for delivery was IFC, showed lower LVSV among fetuses delivered by emergency CS (4.10 ± 0.3 mL *vs* 4.40 ± 0.5 mL; $P = 0.04$) or instrumental delivery (4.08 ± 0.4 mL *vs* 4.45 ± 0.5 mL; $P < 0.001$) for IFC compared with any mode of delivery without IFC. Mean RVSV was higher in fetuses that required emergency operative delivery for IFC than in those that did not (7.46 ± 1.1 mL *vs* 7.10 ± 1.1 mL; $P < 0.01$). Mean RVSV was also higher in fetuses delivered by emergency CS (7.68 ± 0.5 mL *vs* 7.05 ± 0.8 mL; $P = 0.02$) or instrumental delivery (7.46 ± 1.0 mL *vs* 7.10 ± 1.1 mL; $P = 0.01$) for IFC compared with any mode of delivery without IFC (Table 3).

Mean LVCO/RVCO ratio was lower in the cohort of fetuses that required emergency operative delivery for IFC than in those without IFC (0.55 ± 0.07 *vs* 0.64 ± 0.11; $P < 0.001$). Mean LVCO/RVCO ratio was lower in fetuses requiring emergency CS (0.57 ± 0.05 *vs* 0.63 ± 0.11; $P = 0.004$) or instrumental delivery (0.56 ± 0.08 *vs* 0.63 ± 0.11; $P < 0.001$) for IFC compared with fetuses that were not delivered for IFC (Table 3).

Overall, the mean CPR was lower in the cohort of fetuses that required emergency operative delivery for IFC than in those without IFC (1.62 ± 0.3 *vs* 1.90 ± 0.5; $P < 0.001$) (Table 2).

Furthermore, the mean LVCO, LVSV and LVCO/RVCO ratio were all significantly lower in fetuses that had abnormal FHR patterns in labor (Table 3). The cohort of babies with an adverse composite outcome also had significantly lower LVCO, LVSV and LVCO/RVCO ratio compared with those without (Table 4). LVCO and CPR were positively correlated (regression coefficient = 95.6 (95% CI, 76.9–114.2); $P < 0.001$ and $r = 0.55$) (Figure 3).

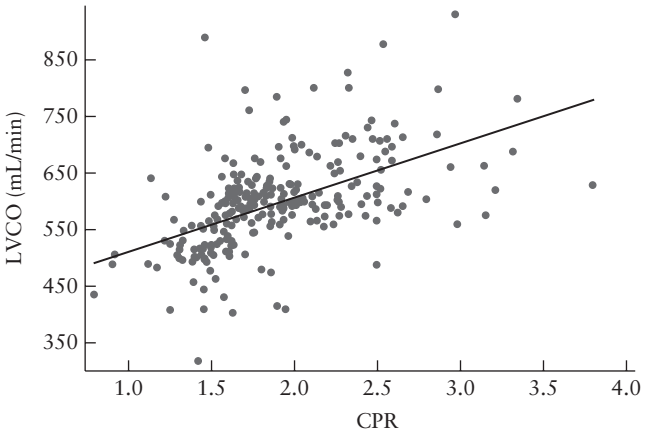

Figure 3 Correlation between left ventricular cardiac output (LVCO) and cerebroplacental ratio (CPR) measured within 2 weeks prior to delivery in 270 uncomplicated pregnancies ($r = 0.55$, $P < 0.001$).

DISCUSSION

The results of this prospective study demonstrate that several parameters of fetal cardiac function assessed within 2 weeks of birth were markedly different in fetuses that developed IFC compared with those that did not. Specifically, we found that LVCO, LVCO/RVCO ratio and LVSV were lower and RVCO and RVSV were higher in fetuses that developed IFC and required emergency operative delivery of any kind. To our knowledge, this is the first time such a finding has been reported in a cohort of neonates with birth weight above the 10th centile, which would not be considered 'small'. In accord with previous research[2,5,18], we also observed that fetuses that developed IFC had lower mean CPR compared with those that did not. A biologically significant positive association between fetal CPR and LVCO was also demonstrated.

Although fetal growth restriction is a known risk factor for several adverse perinatal outcomes, the fetuses in our study cohort would not be considered growth-restricted according to current criteria, considering that they had umbilical artery resistance indices within the normal range (i.e. < 95th centile for gestation) and EFW > 10th centile for gestation. Nevertheless, there is emerging evidence that a low CPR may reflect failure of a fetus to reach its genetic growth potential at term, despite having a normal birth weight[7,19]. Given this, and our finding of a correlation between the CPR and adverse intrapartum and neonatal outcomes, it is probable that this cohort of babies had some degree of suboptimal growth rendering them vulnerable to the stress of labor and consequently to developing IFC. Indeed, there are data to suggest that cardiac function in growth-restricted fetuses is impaired and that this dysfunction persists into the neonatal, infant and childhood periods[12,13,20–24].

Our findings may be explained by the degree or severity of suboptimal fetal growth. Pérez-Cruz *et al.*[20] demonstrated that right heart myocardial performance index measured by conventional Doppler ultrasound was not significantly different in small-for-gestational-age fetuses without growth restriction compared with controls, whereas in overtly growth-restricted fetuses there was poorer right ventricular function. The fetuses in our study may thus represent a cohort of babies with a milder degree of suboptimal growth. However, while there is evidence of cardiovascular dysfunction in growth-restricted fetuses, not all investigators have demonstrated this consistently, with some studies showing that cardiac output is maintained in both growth-restricted and control cohorts, with no significant differences between the two[12,23].

The evaluation of fetal cardiac function is a non-invasive assessment that provides valuable information on fetal hemodynamics and cardiovascular adaptation to an adverse intrauterine environment. Although the analysis of fetal cardiac function in pregnancies complicated by placental dysfunction (e.g. fetal growth restriction) is currently a research tool, our preliminary data suggest that it may also have a role in the prediction of intrapartum outcomes. However, fetal echocardiography requires advanced ultrasound expertise and experience, and this is a limitation to wider application of this technique outside tertiary centers and research studies.

This study has several strengths. It is the first study to assess or evaluate fetal cardiac output in low-risk pregnancies with appropriately grown fetuses at term, and its association with IFC. All data were obtained prospectively and clinicians and midwives were blinded to the ultrasound findings. However, we also acknowledge the limited size of our study cohort.

Fetal CPR is recognized as a marker for cerebral redistribution. Our finding of a correlation with left heart function suggests that the relationship between cardiac function and intrauterine hypoxia may be more complex than previously realized, at least in this subgroup of fetuses. This finding is important because it extends our understanding of the hemodynamic complexity and potential vulnerability of some fetuses to the stress of labor. Identification of fetuses with impaired prelabor cardiac function may prompt more intensive intrapartum FHR monitoring and early recourse to operative delivery should any concerns arise. However, further research is required in this field.

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REFERENCES

1. Prior T, Mullins E, Bennett P, Kumar S. Prediction of fetal compromise in labor. *Obstet Gynecol* 2014; **123**: 1263–1271.
2. Prior T, Mullins E, Bennett P, Kumar S. Prediction of intrapartum fetal compromise using the cerebroumbilical ratio: a prospective observational study. *Am J Obstet Gynecol* 2013; **208**: 124.e1–6.
3. Morales-Roselló J, Khalil A, Alberola-Rubio J, Hervas-Marín D, Morlando M, Bhide A, Papageorghiou A, Perales-Marín A, Thilaganathan B. Neonatal Acid–Base Status in Term Fetuses: Mathematical Models Investigating Cerebroplacental Ratio and Birth Weight. *Fetal Diagn Ther* 2015; **38**: 55–60.
4. Morales-Roselló J, Khalil A, Morlando M, Bhide A, Papageorghiou A, Thilaganathan B. Poor neonatal acid–base status in term fetuses with low cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2015; **45**: 156–161.

5. Khalil AA, Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2015; **213**: 54.e1–10.
6. Khalil A, Morales-Rosello J, Townsend R, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss. *Ultrasound Obstet Gynecol* 2016; **47**: 74–80.
7. Prior T, Paramasivam G, Bennett P, Kumar S. Are fetuses that fail to achieve their growth potential at increased risk of intrapartum compromise? *Ultrasound Obstet Gynecol* 2015; **46**: 460–464.
8. Janbu T, Nesheim BI. Uterine artery blood velocities during contractions in pregnancy and labour related to intrauterine pressure. *Br J Obstet Gynaecol* 1987; **94**: 1150–1155.
9. Fu J, Olofsson P. Intracerebral regional distribution of blood flow in response to uterine contractions in growth-restricted human fetuses. *Early Hum Dev* 2007; **83**: 607–612.
10. Rizzo G, Arduini D, Romanini C. Doppler echocardiographic assessment of fetal cardiac function. *Ultrasound Obstet Gynecol* 1992; **2**: 434–445.
11. Comas M, Crispi F, Cruz-Martinez R, Figueras F, Gratacos E. Tissue Doppler echocardiographic markers of cardiac dysfunction in small-for-gestational age fetuses. *Am J Obstet Gynecol* 2011; **205**: 57.e1–6.
12. Crispi F, Hernandez-Andrade E, Pelsers MM, Plasencia W, Benavides-Serralde JA, Eixarch E, Le Noble F, Ahmed A, Glatz JF, Nicolaides KH, Gratacos E. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. *Am J Obstet Gynecol* 2008; **199**: 254.e1–8.
13. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Gómez O, Sitges M, Bijnens B, Gratacós E. A fetal cardiovascular score to predict infant hypertension and arterial remodeling in intrauterine growth restriction. *Am J Obstet Gynecol* 2014; **210**: 552.e1–22.
14. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. *Intrapartum fetal surveillance*. Clinical guideline. https://www.ranzcog.edu.au/intrapartum-fetal-surveillance-clinical-guidelines.html [9 June 2016].
15. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. *Obstet Gynecol* 2009; **114**: 192–202.
16. National Institute of Health and Care Excellence. Intrapartum care: Interpretation of cardiotocograph traces (NICE guideline CG190), 2014. http://www.nice.org.uk/guidance/cg190/resources/cg190-intrapartum-care-interpretation-of-cardiotocograph-traces-table2 [Accessed September 2016].
17. Bland JM. How should I calculate a within-subject coefficient of variation? http://www-users.york.ac.uk/~mb55/meas/cv.htm. [Accessed 11 March 2017].
18. Sabdia S, Greer R, Prior T, Kumar S. Predicting intrapartum fetal compromise using the fetal cerebro-umbilical ratio. *Placenta* 2015; **36**: 594–598.
19. Morales-Roselló J, Khalil A, Morlando M, Papageorghiou A, Bhide A, Thilaganathan B. Changes in fetal Doppler indices as a marker of failure to reach growth potential at term. *Ultrasound Obstet Gynecol* 2014; **43**: 303–310.
20. Pérez-Cruz M, Cruz-Lemini M, Fernández M, Parra J, Bartrons J, Gómez-Roig M, Crispi F, Gratacós E. Fetal cardiac function in late-onset intrauterine growth restriction *vs* small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. *Ultrasound Obstet Gynecol* 2015; **46**: 465–471.
21. Bahtiyar MO, Copel JA. Cardiac changes in the intrauterine growth-restricted fetus. *Semin Perinatol* 2008; **32**: 190–193.
22. Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R, Welsh A, Mancilla-Ramirez J. Evaluation of conventional Doppler fetal cardiac function parameters: E/A ratios, outflow tracts, and myocardial performance Index. *Fetal Diagn Ther* 2012; **32**: 22–29.
23. Kiserud T, Ebbing C, Kessler J, Rasmussen S. Fetal cardiac output, distribution to the placenta and impact of placental compromise. *Ultrasound Obstet Gynecol* 2006; **28**: 126–136.
24. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, Ahmed A, Gratacós E. Fetal growth restriction results in remodeled and less efficient hearts in children. *Circulation* 2010; **121**: 2427–2436.

