View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by University of Dundee Online Publications

University of Dundee

Arterio-venous differences in cord levels of catecholamines, glucose, lactate and blood gases

Koh, Daisy K M; Hume, Robert; Eisenhofer, Graeme; Watson, Jennifer; Williams, Fiona L R

Published in:
Journal of Perinatal Medicine

DOI:
10.1515/jpm-2015-0323

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

Link to publication in Discovery Research Portal

Citation for published version (APA):
Koh, D. K. M., Hume, R., Eisenhofer, G., Watson, J., & Williams, F. L. R. (2016). Arterio-venous differences in cord levels of catecholamines, glucose, lactate and blood gases. Journal of Perinatal Medicine, 44(6), 695-704. DOI: 10.1515/jpm-2015-0323

General rights
Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Daisy K.M. Koh, Robert Hume, Graeme Eisenhofer, Jennifer Watson and Fiona L.R. Williams*

Arterio-venous differences in cord levels of catecholamines, glucose, lactate and blood gases

DOI 10.1515/jpm-2015-0323
Received September 18, 2015. Accepted November 23, 2015.

Abstract

Background: Norepinephrine (NE) and epinephrine (EPI) levels are higher in cord arterial blood relative to venous blood, consistent with active mechanisms of placental-maternal clearance. There are no contemporary studies of cord arteriovenous blood levels of sulfated and non-sulfated catechols.

Aim: To assess the arteriovenous differences in cord blood levels of dopamine (DA), the sulfated catecholamines and their sulfated and non-sulfated metabolites. To correlate levels of oxygen, H^+/CO_2, and glucose with cord catecholamine levels.

Methods: Fifty-seven term infants, delivered by elective cesarean section, were recruited. Cord arterial and venous blood was sampled; levels of glucose, lactate, blood gases, six catechols and their sulfated conjugates were measured.

Results: With one exception (DOPA sulfate), mean cord arterial levels of sulfated and non-sulfated catechols were significantly higher than venous levels. Arterial lactate and glucose levels were independently associated with NE levels, but only lactate was associated with levels of EPI and DA.

Conclusion: This study establishes that *in vivo* metabolic parameters of hypoxia, respiratory and metabolic acidosis are associated with catecholamine levels, a key relationship for perinatal adaptation and homeostasis, and findings that are consistent with *in vitro* studies of the regulators of catecholamine secretion.

***Corresponding author: Fiona L.R. Williams,** Population Health Sciences, Medical School, Mackenzie Building, University of Dundee, Kirsty Semple Way, Dundee DD2 4BF, Scotland, UK, Tel.: +(44) 1382 383726, E-mail: f.l.r.williams@dundee.ac.uk
Daisy K.M. Koh, Robert Hume and Jennifer Watson: Population Health Sciences, Medical School, Mackenzie Building, University of Dundee, Kirsty Semple Way, Dundee, DD2 4BF, Scotland
Graeme Eisenhofer: Department of Medicine and Institute of Clinical Chemistry and Laboratory Medicine, Technische Universität Dresden, Fetscherstr 74, 01307 Dresden, Germany

Keywords: catecholamines; cesarean section; cord blood; glucose homeostasis.

Introduction

Plasma catecholamine levels rise three-to-tenfold within minutes of delivery [1]. The surge is induced by labor, which is why infants delivered vaginally have considerably higher cord artery and/or cord vein levels of norepinephrine (NE), and/or epinephrine (EPI), than those delivered by elective cesarean section [2–5]. Catecholamines are essential for postnatal adaptation and contribute to the regulation of cardiac output, blood pressure, thermogenesis, surfactant release, lung liquid production and absorption, as well as the regulation of blood glucose levels [6].

NE and EPI levels in cord artery, and to a lesser extent in cord vein, are substantially higher than those in (resting) adults, and maternal levels at delivery [7, 8]. Fetal ovine NE and EPI production and clearance rates are higher than in any other physiological condition [9], with placental transfer largely accounting for the very high intrauterine catecholamine clearance rates [10, 11]. The rapid increase in circulating catecholamine levels at birth is due, in part, to a significant decrease in clearance rates through removal of the placental contribution to whole body clearance [12]. Sulfoconjugation represents an important protective mechanism for inactivating catecholamines, and so offers protection from the adverse effects of excess catecholamine levels [13]. In humans catecholamines circulate mainly (up to 99%) in the sulfoconjugated forms [14, 15].

The known molecular regulators of adrenomedullary catecholamine secretion *in vitro* are oxygen, H^+/CO_2, and glucose, which are proposed as important mediators in perinatal catecholamine regulation [16]. We predicted that levels of these regulators would show the strongest associations, in regression analyses, with dopamine (DA), NE and EPI. That NE and EPI levels are higher in cord artery, than in cord vein, is already documented and consistent with active mechanisms of fetal-placental-maternal clearance [5–7, 17, 18], but there are no contemporary studies of human cord arterial and venous blood levels of sulfated

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

and non-sulfated catechols. We hypothesized that there should also be differences between umbilical cord arterial and venous levels of DA, sulfated NE and EPI, as well as their sulfated and non-sulfated metabolites.

Methods

Participants and procedures

Mothers and infants were recruited in Ninewells Hospital and Medical School, Dundee. All infants were born to women booked for elective cesarean section of a singleton, term infant (37+ gestational weeks). We aimed to recruit a consecutive sample of eligible pregnant women. Exclusion criteria were known Hepatitis B/C and HIV positivity. The study was approved by the Tayside Committee on Medical Research Ethics (Ref: 033/04).

The analytes were measured in umbilical venous and arterial cord blood. All blood samples were taken by DKMK immediately on delivery of the placenta. Approximately 20 mL of blood was taken from the umbilical vein and artery at the point of placental cord insertion (singly-clamped sample) using a 19 gauge butterfly needle (Abbott Ireland, Sligo, Republic of Ireland) and aliquoted within 5 min of delivery into a variety of tubes, according to the analyte to be measured.

Analytes

Plasma glucose and lactate were measured using Roche Glucoquant kits and Cobas Lactate kits on Roche Modular Serum Work Area Analysers (Roche Diagnostics, Mannheim, Germany). Blood gas analyses for pH, PCO_2, PO_2, $cHCO_3$ (bicarbonate), and BE (base excess) used an AVL OMNI Modular System (Roche Diagnostics) in the labor ward, and was serviced by Biochemical Medicine as part of the UK accreditation scheme. Plasma for catechol estimations was prepared in lithium heparin tubes, immediately frozen, and stored at −80°C before air freighting to the laboratory of GE, Dresden, for analysis. Catechols (EPI, NE, DA, dihydroxyphenylalanine (DOPA), dihydroxyphenylglycol (DHPG), and dihydroxyphenylacetic acid (DOPAC)) and their sulfated conjugates (EPI sulfate, NE sulfate, DA sulfate, DOPA sulfate, DHPG sulfate, and DOPAC sulfate) were measured after extraction from plasma using an alumina extraction procedure and then separated and quantified by HPLC with electrochemical detection [19]. The inter-assay coefficient of variation was 5.69% for DHPG, 2.76% for NE, 6.44% for DOPA, 10.27% for EPI, 5.47% for DOPAC, 11.75% for DHPG sulfate, 13.52% for NE sulfate, 13.62% for DOPA sulfate, 6.16% for EPI sulfate and 5.43% for DOPAC sulfate. Intra-assay coefficients of variation were 3.6% (DHPG), 2.9% (NE), 3.1% (DOPA), 3.9% (EPI), 5.1% (DA) and 3.9% (DOPAC); intra-assay variation was not recorded for the sulfate conjugates.

Statistical analyses

Means and standard deviations (SD) and, as appropriate, medians and interquartile ranges, are reported for each analyte. Differences between means were quantified by the paired *t*-test. Correlation matrices were created of blood gas analytes, glucose, lactate and catechols, using Spearman's rho to account for the skewed distributions of some factors for all infants, and also sub-grouped into infants with glucose levels of < and ≥2.6 mmol/L. Univariate general linear regression modeling was used to determine the contribution of arterial levels of PO_2, PCO_2, pH, glucose and lactate on the active (arterial) catecholamines (DA, NE and EPI) contributing to the perinatal surge, using the enter method.

Results

Fifty-seven infants were recruited; mean gestation was 37.6±0.6 weeks; 40% were female. All infants were delivered by elective cesarean section: 14 (25%) because of breech presentation or placenta praevia, 35 (61%) because of previous cesarean section or maternal wish and for eight (14%) the reason was unknown.

In cord arterial blood the mean glucose level was 2.71 mmol/L, which was significantly lower than the level in cord venous blood of 3.07 mmol/L. Although the group as a whole were normoglycaemic, 14 infants had arterial plasma glucose levels ≤2.6 mmol/L, an additional three infants had both arterial and venous plasma glucose levels ≤2.6 mmol/L, and one further infant had venous plasma glucose levels ≤2.6 mmol/L. The mean lactate level was significantly lower in venous plasma (2.14 mmol/L) compared to the arterial sample (2.42 mmol/L). Mean levels of pH and PO_2 were significantly lower in arterial than venous plasma (respectively 7.31 and 2.17 kPa vs. 7.34 and 2.77 kPa); whereas PCO_2 was significantly higher in arterial (6.87 kPa) than venous (6.25 kPa) plasma. Arterial and venous bicarbonate and base excess values slightly, but significantly, varied (Table 1).

In cord arterial plasma, levels of non-sulfated catechols varied appreciably. The highest levels in order of magnitude were those of NE (3494 pg/mL) and DOPA (3315 pg/mL), followed by DOPAC (2603 pg/mL), DHPG (1122 pg mL) and EPI (637 pg/mL), with DA the lowest (35 pg/mL) (Figure 1). The pattern for levels of non-sulfated catechols in cord venous plasma was different, with that of NE showing the greatest reduction. DOPA had the highest circulating level (3073 pg/mL) followed by DOPAC (2370 pg/mL), DHPG (949 pg/mL), NE (647 pg/mL), EPI (58 pg/mL) and DA (19 pg/mL) (Figure 1). The proportion of sulfated-catechols to non-sulfated catechols was variable; in cord arterial plasma the proportion ranged from DA sulfate (>99%) through intermediate figures for NE (40%) and DHPG sulfate (55%) to the lowest percentage DOPA sulfate (18%) (Table 2).

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 1: Arterial and venous levels of glucose, lactate and blood gases in umbilical cord plasma of term infants delivered by elective cesarean section.

	Arterial		Venous		Matched pairs *t*-test	Degree of freedom	P-value
	Mean ***Median***	**Standard deviation** ***Quartile range***	**Mean** ***Median***	**Standard deviation** ***Quartile range***			
Glucose (mmol/L)	2.71	0.42	3.07	0.42	−8.881	45	<0.0001
	2.70	*2.40, 3.00*	*3.00*	*2.80, 3.30*			
Lactate (mmol/L)	2.42	1.15	2.14	0.96	4.845	45	<0.0001
	2.05	*1.80, 2.60*	*2.00*	*1.60, 2.20*			
pH	7.31	0.06	7.34	0.04	−7.797	49	<0.0001
	7.32	*7.27, 7.35*	*7.35*	*7.32, 7.37*			
PO_2 (kPa)	2.17	0.79	2.72	0.78	−3.724	49	0.001
	2.16	*1.59, 2.71*	*2.72*	*2.15, 3.04*			
PCO_2 (kPa)	6.87	1.17	6.19	0.95	5.694	49	<0.0001
	6.68	*6.04, 7.63*	*6.27*	*5.78, 6.66*			
$cHCO_3$ (mmol/L)	25.04	1.81	24.63	1.52	2.209	49	0.03
	25.00	*24.00, 26.60*	*24.95*	*23.58, 25.93*			
BE (mmol/L)	−1.82	1.70	−1.51	1.51	−2.452	50	0.02
	−1.75	*−2.83, −0.55*	*−1.20*	*−2.40, −0.40*			

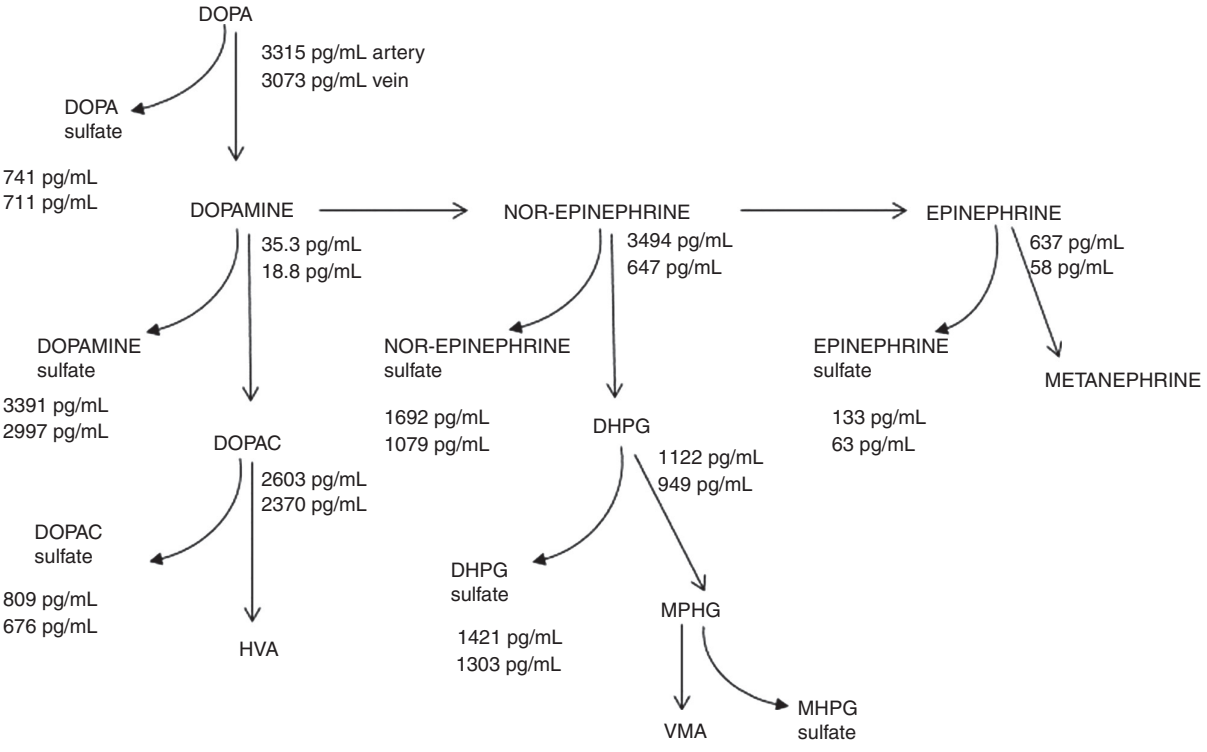

Figure 1: Mean levels of catechols, their precursor, and metabolites in venous and arterial cord blood. (The top row of each pair of data shows arterial levels and the lower row shows venous levels.)

Correlation analyses

The correlation matrices, shown separately for cord and venous blood, included 19 variables; only the strongly associated variables (P<0.0001) are shown (Tables 3 and 4). For the group of infants as a whole, levels of cord arterial plasma glucose were not associated with any of component parts of the blood gas measurements, or levels of catechols. Cord arterial plasma lactate levels were associated positively with NE and NE sulfate (Table 3) and venous

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 2: Arterial and venous levels of plasma catechols and their sulfated conjugates in cord plasma of term infants delivered by elective cesarean section.

	Arterial			Venous			P-value matched pairs Student *t*-test	Arterio-venous differences[a]
	Mean *Median*	Standard deviation *Quartile range*	n	Mean *Median*	Standard deviation *Quartile range*	n		
DOPA (pg/mL)	3315.0	±590.1	56	3073.0	±507.5	56	<0.001	6.7%
	3344.0	*2932.5, 3644.3*		*3079.0*	*2679.8, 3281.5*			
DOPA sulfate (pg/mL)	741.2	±291.3	51	711.3	±229.2	51	0.525	−2.1%
	700.0	*559.0, 842.0*		*685.0*	*585.0, 818.0*			
DOPA sulfate (%)	17.9	±4.4	51	18.6	±4.4	51	0.401	
	17.6	*15.3, 19.3*		*17.7*	*15.9, 21.2*			
DA (pg/mL)	35.3	±42.5	56	18.8	±25.7	56	<0.001	31.4%
	16.5	*10.0, 49.3*		*9.0*	*7.0, 18.0*			
DA sulfate (pg/mL)	3391.1	±1562.6	51	2997.1	±910.2	51	0.003	6.8%
	3128.0	*2274.0, 3703.0*		*2920.0*	*2279.0, 3457.0*			
DA sulfate (%)	98.9	±1.5	51	99.3	±1.2	51	<0.001	
	99.5	*98.7, 99.7*		*99.7*	*99.4, 99.8*			
NE (pg/mL)	3493.5	±3035.6	56	646.6	±731.0	56	<0.001	77.2%
	2234.0	*1166.5, 5219.5*		*379.5*	*186.0, 737.3*			
NE sulfate (pg/mL)	1691.8	±1053.8	51	1079.1	±400.2	51	<0.001	27.4%
	1359.0	*1001.0, 2048.0*		*959.0*	*803.0, 1358.0*			
NE sulfate (%)	40.4	±15.5	51	70.0	±15.3	51	<0.001	
	37.7	*27.8, 48.4*		*73.5*	*61.9, 82.8*			
EPI (pg/mL)	636.7	±685.0	56	58.2	±96.3	56	<0.001	87.2%
	353.0	*205.0, 812.5*		*27.5*	*11.3, 61.3*			
EPI sulfate (pg/mL)	132.8	±112.5	51	62.6	±44.5	51	<0.001	38.7%
	97.0	*55.0, 178.0*		*51.0*	*31.0, 80.0*			
EPI sulfate (%)	23.9	±13.1	51	62.3	±22.1	51	<0.001	
	19.9	*15.7, 29.0*		*64.5*	*45.5, 80.6*			
DOPAC (pg/mL)	2603.3	±765.2	56	2369.6	±717.3	56	<0.001	8.5%
	2513.5	*2098.3, 2932.0*		*2239.0*	*1855.5, 2698.0*			
DOPAC sulfate (pg/mL)	808.5	±563.1	51	676.3	±209.5	51	0.091	8.4%
	698.0	*598.0, 866.0*		*627.0*	*535.0, 745.0*			
DOPAC sulfate (%)	23.3	±8.4	51	22.6	±4.8	51	0.556	
	22.0	*19.1, 25.7*		*23.1*	*18.2, 26.6*			
DHPG (pg/mL)	1122.1	±400.9	56	949.2	±373.7	56	<0.001	15.4%
	1042.0	*891.3, 1279.0*		*881.0*	*737.0, 1051.8*			
DHPG sulfate (pg/mL)	1420.8	±544.8	51	1303.0	±466.1	51	0.002	6.5%
	1367.0	*959.0, 1774.0*		*1281.0*	*885.0, 1645.0*			
DHPG sulfate (%)	55.3	±7.9	51	57.6	±7.8	51	<0.001	
	54.2	*49.7, 60.3*		*57.5*	*52.1, 62.6*			

DA=dopamine, DHPG=dihydroxyphenylglycol, DOPA=dihydroxyphenylalanine, DOPAC=dihydroxyphenylacetic acid, EPI=epinephrine, NE=norepinephrine. Conversion factors to nmol/L multiply: EPI×0.00546, NE×0.00591, DHPG×0.00588, DOPA×0.00507, DA×0.00653, DOPAC×0.00595.

[a]((arterial-venous)/arterial)x100 (calculated for each infant).

lactate levels were correlated positively with NE, DHPG and DOPAC sulfate (Table 4). There were several associations between the component parts of cord artery and venous blood gas measurements and levels of catechols, with pH and $cHCO_3$ showing the strongest correlations (Tables 3 and 4). Unsurprisingly, there were many significant associations between the various measurements of cord arterial plasma and cord venous plasma catechols (Tables 3 and 4).

The correlation matrix for the subgroup of infants whose cord glucose levels were ≥2.6 mmol/L was very similar to those for the group as a whole (Table 5); although there were more significant correlations despite the smaller sample size. The matrix for the smaller subgroup of infants with low glucose levels (<2.6 mmol/L) showed few statistical associations although, and unlike the normoglycaemic group, there were significant negative correlations between glucose and DOPA, DA sulfate and DOPAC sulfate (Table 6).

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 3: Selected correlations between cord artery levels of glucose, lactate, blood gas components and catechols of term infants delivered by elective cesarean section.[a]

Analyte	Cord arterial blood			
	Correlated with	Correlation coefficient (≥0.5)		
		rho	P-value	n
Glucose (mmol/L)		No significant correlations		
Lactate (mmol/L)	NE pg/mL	+0.653	<0.0001	46
	NE sulfate pg/mL	+0.541	<0.0001	43
pH	PCO_2 kPa	−0.899	<0.0001	50
	PO_2 kPa	+0.627	<0.0001	50
	DHPG pg/mL	−0.528	<0.0001	49
PCO_2 (kPa)	PO_2 kPa	−0.604	<0.0001	50
	$cHCO_3$ mmol/L	+0.633	<0.0001	49
$cHCO_3$ (mmol/L)	BE pg/mL	+0.696	<0.0001	49
DA (pg/mL)	NE pg/mL	+0.527	<0.0001	56
NE (pg/mL)	EPI pg/mL	+0.690	<0.0001	56
	DHPG pg/mL	+0.516	<0.0001	56
	NE sulfate pg/mL	+0.650	<0.0001	51
EPI (pg/mL)	DHPG pg/mL	+0.572	<0.0001	56
	EPI sulfate pg/mL	+0.810	<0.0001	51
DHPG (pg/mL)	DOPAC pg/mL	+0.533	<0.0001	56
	DHPG sulfate pg/mL	+0.546	<0.0001	51
	DOPA sulfate pg/mL	+0.520	<0.0001	51
DOPA (pg/mL)	DOPAC pg/mL	+0.525	<0.0001	56
	DOPA sulfate pg/mL	+0.587	<0.0001	51
DA sulfate (pg/mL)	NE sulfate pg/mL	+0.589	<0.0001	51
	DOPA sulfate pg/mL	+0.555	<0.0001	51
NE sulfate (pg/mL)	DOPA sulfate pg/mL	+0.629	<0.0001	51

DA=dopamine, DHPG=dihydroxyphenylglycol, DOPA=dihydroxyphenylalanine, DOPAC=dihydroxyphenylacetic acid, EPI=epinephrine, NE=norepinephrine.

[a]The full correlation matrix is available from the corresponding author; this table shows significant values with Bonferroni correction factor.

Table 4: Selected correlations between cord venous levels of glucose, lactate, blood gas components and catechols of term infants delivered by elective cesarean section.[a]

Analyte	Cord arterial blood			
	Correlated with	Correlation coefficient (≥0.5)		
		rho	P-value	n
Glucose (mmol/L)		No significant correlations		
Lactate (mmol/L)	NE pg/mL	+0.647	<0.0001	45
	DHPG pg/mL	+0.528	<0.0001	45
	DOPAC sulfate pg/mL	+0.521	<0.0001	43
pH	PCO_2 kPa	−0.784	<0.0001	55
PCO_2 (kPa)	$cHCO_3$ mmol/L	+0.669	<0.0001	54
$cHCO_3$ (mmol/L)	BE mmol/L	+0.817	<0.0001	54
NE (pg/mL)	EPI pg/mL	+0.645	<0.0001	56
	DHPG pg/mL	+0.692	<0.0001	56
	NE sulfate pg/mL	+0.518	<0.0001	51
EPI (pg/mL)	DHPG pg/mL	+0.524	<0.0001	56
DHPG (pg/mL)	DOPAC pg/mL	+0.515	<0.0001	56
	DHPG sulfate pg/mL	+0.523	<0.0001	51
DOPA (pg/mL)	DOPAC pg/mL	+0.563	<0.0001	56
DOPA sulfate (pg/mL)	DOPAC sulfate pg/mL	+0.509	<0.0001	51

DA=dopamine, DHPG=dihydroxyphenylglycol, DOPA=dihydroxyphenylalanine, DOPAC=dihydroxyphenylacetic acid, EPI=epinephrine, NE=norepinephrine.

[a]The full correlation matrix is available from the corresponding author; this table shows significant values with Bonferroni correction factor.

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 5: Selected correlations between cord artery levels of glucose, lactate, blood gas components and catechols of term infants with a cord glucose ≥2.6 mmol/L at delivery.[a]

Analyte	Cord arterial blood			
	Correlated with	Correlation coefficient (≥0.5)		
		rho	P-value	N
Glucose (mmol/L)		No significant correlations		
Lactate (mmol/L)	pH	−0.512	0.005	28
	BE pg/mL	−0.630	<0.0001	28
	NE pg/mL	+0.630	<0.0001	29
	DHPG pg/mL	+0.511	0.005	29
	NE sulfate pg/mL	+0.542	0.003	28
	DOPA sulfate pg/mL	+0.550	0.002	28
	DOPAC sulfate pg/mL	+0.524	0.004	28
pH	PCO_2 kPa	−0.910	<0.0001	28
	PO_2 kPa	+0.543	0.003	28
	DOPA sulfate pg/mL	−0.603	0.001	27
PCO_2 (kPa)	$cHCO_3$ mmol/L	+0.565	0.002	28
	DOPAC pg/mL	+0.540	0.003	28
	DOPA sulfate pg/mL	+0.683	<0.0001	27
	DOPAC sulfate pg/mL	+0.522	0.005	27
$cHCO_3$ (mmol/L)	BE pg/mL	+0.644	<0.0001	28
DA (pg/mL)	NE pg/mL	+0.503	0.005	29
NE (pg/mL)	EPI pg/mL	+0.662	<0.0001	29
	DOPAC sulfate pg/mL	+0.544	0.003	28
EPI (pg/mL)	DHPG pg/mL	+0.695	<0.0001	29
	DOPAC pg/mL	+0.504	0.005	29
	EPI sulfate pg/mL	+0.795	<0.0001	28
	DHPG sulfate pg/mL	+0.596	0.001	28
	DOPA sulfate pg/mL	+0.647	<0.0001	28
DHPG (pg/mL)	DOPA pg/mL	+0.629	<0.0001	29
	DOPAC pg/mL	+0.599	0.001	29
	EPI sulfate pg/mL	+0.573	0.001	28
	DHPG sulfate pg/mL	+0.550	0.002	28
	DOPA sulfate pg/mL	+0.688	<0.0001	28
	DOPAC sulfate pg/mL	+0.587	0.001	28
DOPA (pg/mL)	DOPAC pg/mL	+0.695	<0.0001	29
	DOPA sulfate pg/mL	+0.718	<0.0001	28
DOPAC (pg/mL)	DOPA sulfate pg/mL	+0.580	0.001	28
NE sulfate (pg/mL)	DOPA sulfate pg/mL	+0.590	0.001	28
EPI sulfate (pg/mL)	DOPA sulfate pg/ml	+0.576	0.001	28
DHPG sulfate (pg/mL)	DOPA sulfate pg/mL	+0.513	0.005	28
DOPA sulfate (pg/mL)	DOPAC sulfate pg/mL	+0.552	0.002	28

DA=dopamine, DHPG=dihydroxyphenylglycol, DOPA=dihydroxyphenylalanine, DOPAC=dihydroxyphenylacetic acid, EPI=epinephrine, NE=norepinephrine.

[a]The full correlation matrix is available from the corresponding author.

Arteriovenous differences

Mean cord arterial levels of glucose, pH and PO_2 were significantly lower, and of PCO_2 significantly higher than mean cord venous levels. There were no arteriovenous differences in levels of lactate (Table 1).

There were highly significant arteriovenous differences in levels of all plasma catechols and their sulfated conjugates except DOPA sulfate and DOPAC sulfate (Table 2). Mean cord venous catechol levels were all significantly lower than those of cord arterial plasma levels. The smallest differences were for DOPA sulfate (–2%), DOPA (7%), DA sulfate (7%), DOPAC sulfate (8%) and DHPG sulfate (7%); the largest differences were observed for NE (77%) and EPI (87%). Moderate and variable arteriovenous differences were observed for DA

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 6: Selected significant correlations between cord artery levels of glucose, lactate, blood gas components and catechols of term infants with a cord glucose <2.6 mmol/L at delivery.[a]

Analyte	Cord arterial blood			
	Correlated with	Correlation coefficient (≥0.5)		
		rho	P-value	n
Glucose (mmol/L)	DOPA pg/mL	−0.503	0.040	17
	DA sulfate pg/mL	−0.522	0.046	15
	DOPAC sulfate pg/mL	−0.651	0.009	15
Lactate (mmol/L)	NE pg/mL	+0.636	0.006	17
	DA sulfate pg/mL	+0.702	0.004	15
	NE sulfate pg/mL	+0.556	0.028	15
	DOPA sulfate pg/mL	+0.610	0.016	15
pH	PCO_2 kPa	−0.877	<0.0001	14
	PO_2 kPa	+0.710	0.004	14
	DHPG pg/mL	−0.626	0.017	14
PCO_2 (kPa)	PO_2 kPa	−0.754	0.002	14
	$cHCO_3$ mmol/L	+0.802	0.001	14
PO_2 (kPa)	$cHCO_3$ mmol/L	−0.576	0.032	14
$cHCO_3$ (mmol/L)	BE pg/mL	+0.889	<0.0001	14
DA (pg/mL)	NE sulfate pg/mL	+0.543	0.037	14
NE (pg/mL)	EPI pg/mL	+0.623	0.008	14
	DA sulfate pg/mL	+0.525	0.044	14
	NE sulfate pg/mL	+0.868	<0.0001	15
	DOPA sulfate pg/mL	+0.568	0.027	15
EPI (pg/mL)	EPI sulfate pg/mL	+0.757	0.001	15
DHPG (pg/mL)	DOPAC pg/mL	+0.490	0.046	17
	DHPG sulfate pg/mL	+0.654	0.008	15
DOPA (pg/mL)	DOPA sulfate pg/mL	+0.625	0.013	15
DOPAC (pg/mL)	DHPG sulfate pg/mL	+0.582	0.023	15
	DOPAC sulfate pg/mL	+0.518	0.048	15
DA sulfate (pg/mL)	NE sulfate pg/mL	+0.618	0.014	15
	DOPA sulfate pg/mL	+0.586	0.022	15
	DOPAC sulfate pg/mL	+0.697	0.004	15
NE sulfate (pg/mL)	DOPA sulfate pg/mL	+0.661	0.007	15

DA=dopamine, DHPG=dihydroxyphenylglycol, DOPA=dihydroxyphenylalanine, DOPAC=dihydroxyphenylacetic acid, EPI=epinephrine, NE=norepinephrine.

[a]The full correlation matrix is available from the corresponding author.

(31%), NE sulfate (27%), EPI sulfate (39%), and DHPG (15%) (Table 2).

Regression analyses

The regression analyses examined the relationship of the possible metabolic mediators (PO_2, PCO_2, glucose, and lactate) of adrenomedullary catecholamine secretion to the cord artery levels of the active catecholamines (DA, NE, EPI). (Because PCO_2 and pH were highly correlated (−0.899) only PCO_2 was used in the regression modeling.) Only (rising) lactate level was a significant predictor of DA level, accounting for 32.2% of the variation. Falling glucose and rising lactate levels were significant predictors of NE levels, accounting for 35% of the variation. Only rising lactate level was a significant predictor of EPI levels, accounting for 23.3% of the variation (Table 7).

Discussion

Increased catecholamine production or adrenomedullary release has been proposed as the reason for the postnatal surge in levels, responding to combinations of stimuli, such as compression of the fetal head, alternating hypoxia caused by uterine contractions, cooling of the infant, and manual handling at delivery [4, 6, 20, 21]. But there might be a further contributory factor, which is based on active placental metabolism, and/or maternal transfer

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

Table 7: Regression analyses of PO_2, PCO_2, glucose and lactate on the cord arterial catecholamine levels of DA, NE and EPI.

	Unstandardized coefficients		Standardized coefficients	t Statistic	P-value
	B	Standard error	Beta		
Dopamine dependent variable					
Independent variables					
PCO_2 (kPa)	0.094	6.034	0.003	0.016	0.988
PO_2 (kPa)	−10.759	8.008	−0.215	−1.343	0.187
Glucose (mmol/L)	6.693	12.364	0.073	0.541	0.592
Lactate (mmol/L)	17.506	5.407	0.531	3.238	0.003
Adjusted r^2 32.2% residual standard deviation 31.92 residual df 37					
Norepinephrine dependent variable					
Independent variables					
PCO_2 (kPa)	227.119	392.590	0.108	0.579	0.566
PO_2 (kPa)	398.162	521.047	0.120	0.764	0.450
Glucose (mmol/L)	−2029.683	804.468	−0.335	−2.523	0.016
Lactate (mmol/L)	1130.466	351.806	0.516	3.213	0.003
Adjusted r^2 35.0% residual standard deviation 2076.802 residual df 37					
Epinephrine dependent variable					
Independent variables					
PCO_2 (kPa)	13.066	100.296	0.026	0.130	0.897
PO_2 (kPa)	−158.628	133.113	−0.203	−1.192	0.241
Glucose (mmol/L)	−168.807	205.519	−0.119	−0.821	0.417
Lactate (mmol/L)	213.310	89.877	0.415	2.373	0.023
Adjusted r^2 23.3% residual standard deviation 530.565 residual df 37					

of catechols from fetal arterial blood, so creating an A–V difference. At birth, the separation from placental metabolism/maternal transfer allows for an immediate postnatal surge in infant catecholamine levels. This concept is supported by the presence of the relevant catabolic enzymes and transporters in the placenta and associated membranes [e.g. 12]. In addition, catecholamine levels are higher in the fetal umbilical artery relative to the umbilical vein (combined EPI, NE) [22], and singly for EPI, NE [7]. Our results contribute to this evidence for an A–V difference in catecholamine levels. But as far as we are aware, there are no comparable studies of human umbilical blood levels of non-sulfated and sulfated catechols, which we have already shown are very much higher in venous blood of postnatal preterm and term infants [23].

Dopamine is the main inotropic pharmacological agent used to support blood pressure in neonates, and it is likely that it has a similar function physiologically. DA within the brain regulates the proliferation of neuron progenitor cells [24], but the delineation of roles for circulating DA in the fetus have, as yet, been limited to the regulation of pituitary prolactin secretion [25], and to the control of the development of cardiomyocytes, and renal tubular epithelial cells [26, 27].

Sulfation of hormones results in inactivation of biological activity, and is a particularly important mechanism in fetal life. For example, DA is sulfated by a specific sulfotransferase, SULT1A3, which in human postnatal liver is only 10% of the activity found in fetal liver, suggesting a programmed switch in SULT1A3 expression [28], perhaps in response to the significant amounts of brain DA entering the systemic circulation, prior to maturation of the blood-brain barrier [29]. The human fetal adrenal gland secretes dehydroepiandrosterone sulfate, and this hormone is reactivated in the placenta through removal of the sulfate moiety by sulfatase activity [30]. This process of reversible sulfation, which potentially allows hormonal targeting to cells expressing sulfatase activity, has also been described in thyroid hormones in the human fetus [28], but to our knowledge has not been explored for the catecholamines, and in particular DA.

Molecular regulators of carotid body and adrenomedullary catecholamine secretion are oxygen, H^+/CO_2, and glucose, suggesting they are important metabolic mediators in perinatal catecholamine regulation [16, 31]; if this is so, regression analyses should show that these regulators have the strongest associations with DA, NE and EPI. However, bivariate associations between levels of cord artery glucose and catecholamines were very weakly negative in the study group as a whole, and also in the subgroup of normoglycemic infants (glucose

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

levels ≥2.6 mmol/L). However, most cord arterial bloods were normoglycaemic, not surprising, as the fetus benefits from a positive maternal-placental glucose transfer gradient, and the women were normoglycaemic, not in labor, and were delivered by cesarean section. In the small subgroup, with glucose levels <2.6 mmol/L, there were significant associations with rising levels of DOPAC sulfate, and to a lesser extent with DA sulfate, and DOPA, suggesting some activation of catechol metabolism. In our previous studies of infant postnatal glucose homeostasis, it was only when hypoglycaemia was severe and prolonged, (which is not the case in this current subgroup with glucose levels <2.6 mmol/L), that there was an association of low blood glucose levels with increased EPI levels [23].

The non-stressed fetus is relatively hypoxic with a compensated respiratory acidosis, which remains even after placental perfusion. If placental perfusion is reduced, for example by uterine contractions, then the hypoxia and acidosis is compounded. Increases in fetal hypoxia, with decreases in cord arterial PO_2 levels, are associated with increases in a number of catechols. That increasing H^+ and PCO_2 levels in cord arterial blood of non-stressed infants are significantly, and positively associated with many catechols levels, but especially and importantly with NE and EPI, supports the concept that they act as metabolic mediators in perinatal catecholamine regulation.

In addition to oxygen, H^+/CO_2 and glucose, we also included lactate levels in the linear regression modeling of the potential influences on catechol metabolism, because lactate levels are related to the metabolic acidosis arising from the increasingly anaerobic metabolism of glucose as hypoxia develops. That lactate, rather than glucose levels, are such a strong predictor of NE, EPI and DA levels, is a key finding, particularly the highly significant correlation of lactate to NE levels in both artery and vein, and to the immediately related products of NE metabolism (NE sulfate and DHPG). In contrast, in correlation analyses, there is no significant relationship between lactate levels and DA, or its immediate metabolites (DOPAC and DA sulfate), but that to NE and EPI is retained. It is not yet clear whether these associations are indicators of a direct regulatory effect of lactate on catecholamine secretion, such as exists for glucose; or whether it is a surrogate effect of pCO_2/H^+ on the carotid body and adrenomedullary cells [16, 32]. Or indeed, whether it is a surrogate effect of reduced O_2 on adrenomedullary cells, both of which (raised PCO_2/H^+ and reduced PO_2), occur with relative hypoxia, and all of which are known to stimulate catecholamine secretion [16]. A possible independent role for lactate in the catecholamine surge is supported by the regression analyses, which shows that levels of lactate, but not PCO_2 or PO_2 (or glucose consistently) are independently associated with NE, EPI and DA levels in cord artery. A further consideration is that catecholamine infusions in the experimental animal may generate lactate from the hepatic glucose released [33]. Lactate levels are higher in cord arterial blood than in the postnatal infant, although there is a transient increase in lactate levels in the immediate postnatal period, as circulatory perfusion improves into tissues vasoconstricted during delivery. In the early postnatal period, oxygen levels rise rapidly, with reductions in hydrogen ion, PCO_2 and lactate levels, metabolic conditions conducive to reductions in catechol levels, and antagonistic to the circumstances that drive a postnatal catecholamine surge.

Maintenance of oxygen levels, acid-base balance, and energy supply are essential metabolic processes to be regulated by the fetus *in utero*, during labor, and into the postnatal period. Catecholamines have key regulatory roles in this transition, and as the homeostatic setpoints change from the relatively hypoxic, and mildly acidic environment of the fetus to that of relative postnatal hyperoxia and acid-base neutrality, it is perhaps not surprising that the regulatory factors, which influence catechols levels, are also likely to change. The withdrawal of placental catechol metabolism ensures higher postnatal catecholamine levels. But what cannot be answered, as yet, is the postnatal role of oxygen, H^+/CO_2, and glucose in the regulation of catecholamine levels, and as importantly, at what levels, and do they change after birth?

Contributions to the study: Dr. Williams conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted. Professor Hume conceptualized and designed the study, revised the manuscript and approved the final manuscript as submitted. Ms. Watson carried out the initial analyses, designed the data collection forms, critically reviewed the manuscript and approved the final manuscript as submitted. Dr. Koh undertook the recruitment and data collection, critically reviewed the manuscript and approved the final manuscript as submitted. Professor Eisenhofer supervised the analysis of catechols, critically reviewed the manuscript, and approved the final manuscript as submitted.

Funding: Anonymous Trust (Dundee), NHS Tayside Acute Division Grant Scheme, NHS Scotland Programme Support Grant.

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM

References

[1] Sperling MA, Ganguli S, Leslie N, Landt K. Fetal-perinatal catecholamine secretion: role in perinatal glucose homeostasis. Am J Physiol Endocrinol Metab. 1984;247:E69–74.

[2] Falconer AD, Lake DM. Circumstances influencing umbilical-cord plasma catecholamines at delivery. Br J Obstet Gynaecol. 1982;9:44–49.

[3] Padbury JF, Martinez AM. Sympathoadrenal system activity at birth: integration of postnatal adaptation. Semin Perinatol. 1988;12:163–72.

[4] Hirsimäki H, Kero P, Ekblad H, Scheinin M, Saraste M, Erkkola R. Mode of delivery, plasma catecholamines and Doppler-derived cardiac output in healthy term newborn infants. Biol Neonate. 1992;61:285–93.

[5] Agata Y, Hiraishi S, Misawa H, Han JH, Oguchi K, Horiguchi Y, et al. Hemodynamic adaptations at birth and neonates delivered vaginally and by cesarean section. Biol Neonate. 1995;86:404–11.

[6] Nordström L, Marcus C, Persson B, Shimojo N, Westgren M. Lactate in cord blood and its relationship to pH and catecholamines in spontaneous vaginal deliveries. Early Hum Dev. 1996;46:97–104.

[7] Eliot RJ, Lam BSR, Leake RD, Hobel CJ, Fisher DA. Plasma catecholamine concentrations in infants at birth and during the first 48 hours of life. J Pediatr. 1980;96:311–15.

[8] Li W, Weiyan Z, Yanhui Z. The study of maternal and fetal plasma catecholamines levels during pregnancy and delivery. J Perinat Med. 1999;27:195–8.

[9] Padbury JF, Ludlow JK, Humme JA, Agata Y. Metabolic clearance and plasma appearance rates of catecholamines in preterm and term fetal sheep. Pediatr Res. 1986;20:992–5.

[10] Ganapathy V, Ramamoorthy S, Leibach FH. Transport and metabolism of monoamines in the human placenta. Trophoblast Res. 1993;7:35–51.

[11] Bzoskie L, Blount L, Kashiwai K, Tseng Y-T, Hay WW Jr, Padbury JF. Placental norepinephrine clearance: in vivo measurement and physiological role. Am J Physiol. 1995;269: E145–9.

[12] Stein H, Oyama K, Martinez A, Chappell B, Padbury J. Plasma epinephrine appearance and clearance rates in fetal and newborn sheep. Am J Physiol. 1993;265:R756–60.

[13] Boulton AA, Eisenhofer G. Catecholamine metabolism. From molecular understanding to clinical diagnosis and treatment. Overview. Adv Pharmacol. 1998;42:273–92.

[14] Dousa MK, Tyce GM. Free and conjugated plasma catecholamines, DOPA, and 3-*O*-Methyldopa in humans and in various animals species. Proc Soc Exp Biol Med. 1988;188:427–34.

[15] Eisenhofer G, Coughtrie MWH, Goldstein DS. Dopamine sulfate: an enigma resolved: proceedings from the 7th International Conference on Peripheral dopamine. Clin Exp Pharmacol Physiol. 1999;26:S4–26.

[16] Livermore S, Piskuric NA, Buttigieg NAJ, Zhang M, Nurse CA. Low glucose sensitivity and polymodal chemosensing in neonatal rat adrenomedullary chromaffin cells. Am J Physiol Cell Physiol. 2011;301:C1104–15.

[17] Paulick R, Kastendieck E, Wernze H. Catecholamines in arterial and venous umbilical blood: placental extraction, correlation with fetal hypoxia, and transcutaneous partial oxygen tension. J Perinat Med. 1985;13:31–42.

[18] Schwab KO, Breitung B, von Stockhausen HB. Inappropriate secretion of umbilical plasma catecholamines in preterm compared to term neonates. J Perinat Med. 1996;24:373–80.

[19] Eisenhofer G, Goldstein DS, Stull R, Keiser HR, Sunderland T, Murphy DL, et al. Simultaneous liquid-chromatographic determination of 3,4-DHPG, catecholamines, and 3,4-DOPA in plasma, and their responses to inhibition of monoamine oxidase. Clin Chem. 1986;32:2030–3.

[20] Irestedt L, Lagercrantz H, Hjemdahl P, Hägnevik K, Belfrage P. Fetal and maternal plasma catecholamine levels at elective cesarean section under general or epidural anesthesia versus vaginal delivery. Am J Obstet Gynecol. 1982;142:1004–10.

[21] Hägnevik K, Faxelius G, Irestedt L, Lagercrantz H, Lundell B, Persson B. Catecholamine surge and metabolic adaptation in the newborn after vaginal delivery and caesarean section. Acta Paediatr Scand. 1984;73:602–9.

[22] Lagercrantz H, Bistoletti P. Catecholamine release in newborn-infant at birth. Pediatr Res. 1977;11:889–93.

[23] Jackson L, Williams FLR, Burchell A, Coughtrie MWH, Hume R. Plasma catecholamines and the counterregulatory response to hypoglycemia in infants: a critical role for epinephrine and cortisol. J Clin Endocrinol Metab. 2004;89:6251–6.

[24] Borta A, Höglinger GU. Dopamine and adult neurogenesis. J Neurochem. 2007;100:587–95.

[25] Melnikova VI, Orosco M, Rouch C, Calas A, Nicolaidïs S, Proshlyakova E, et al. Prolactin secretion and its dopamine inhibitory control in rat fetuses. Eur J Endocrinol. 1998;139:337–42.

[26] Sarasa M, Climent S. Cardiac differentiation induced by dopamine in undifferentiated cells of early chick embryo. Dev Biol. 1991;148:243–8.

[27] Svennilson J, Aperia A. Dopamine in the developing kidney. Int J Dev Biol. 1999;43:441–3.

[28] Richard K, Hume R, Kaptein E, Stanley E, Visser TJ, Coughtrie MWH. Sulfation of thyroid hormone and dopamine during human development: ontogeny of phenol sulfotransferases and arylsulfatase in liver, lung, and brain. J Clin Endocrinol Metab. 2001;86:2734–42.

[29] Ugrumov MV, Saifetyarova JY, Lavrentieva AV, Sapronova AY. Developing brain as an endocrine organ: Secretion of dopamine. Mol Cell Endocrinol. 2012;348:78–86.

[30] Kuss E. The fetoplacental unit of primates. Exp Clin Endocrinol. 1994;102:135–65.

[31] Alvarez-Buylla R, Alvarez-Buylla ER. Carotid sinus receptors participate in glucose homeostasis. Resp Physiol. 1988;72:347–60.

[32] García-Fernández M, Ortega-Saenz P, Castellano A, Lopez-Barneo J. Mechanisms of low-glucose sensitivity in carotid body glomus cells. Diabetes. 2007;56:2893–900.

[33] Stevenson RW, Steiner KE, Connolly CC, Fuchs H, Alberti KGMM, Williams PE, et al. Dose-related effects of epinephrine on glucose production in conscious dogs. Am J Physiol. 1991;260:E363–70.

The authors stated that there are no conflicts of interest regarding the publication of this article.

Authenticated | f.l.r.williams@dundee.ac.uk author's copy
Download Date | 1/13/16 9:55 AM