FETAL FLOW RATE AND OXYGEN TRANSFER IN EX VIVO DUAL PERFUSED HUMAN PLACENTA

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INTRODUCTION

- Optimal placental oxygen transfer is critical for fetal growth
- Placental oxygen transfer and oxygen consumption are determined among other parameters by fetal and maternal flow rates.
- It has been calculated, that in the artificial system of ex vivo placental perfusion the physiological flow rate in 35 g placental tissue would be 12 ml/min.

OBJECTIVE

To estimate fetal oxygen transfer in relation to perfusion flow ratio in dually perfused human placenta

MATERIALS AND METHODS

Three placentas were obtained within one minute after delivery according to the Institutional Review board-approved protocol. Cannulation of the cotyledon and beginning of the perfusion was within 7-10 min after delivery. After initial quality checks and stabilization, the dual perfusion was established with continuous monitoring of the fetal in- and outflow, placental tissue and maternal inflow oxygenation, using sensor array (FirestingO2, Pyro Science, Germany). Fetal-to-maternal leakage was controlled by injection of FITC-conjugated dextran to the fetal circuit. Continuous monitoring of lactate, glucose, pH and temperature was performed. Fetal flow rate was increased from 4.8 ml/min to 12 ml/min in five seven-minute increments. Formula for calculation of oxygen consumption is presented below [1,2,3].

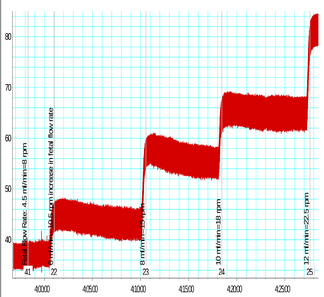


Figure 1. Stepwise increase in fetal flow rate from 4.8 to 12 ml/min.

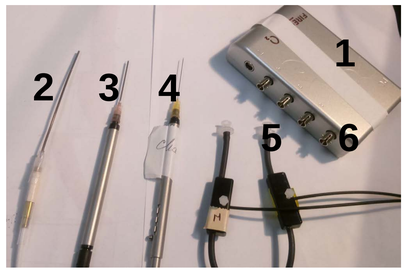


Figure 2. Oxygen and temp sensors with the pre-amp module: **1** Pre-amp module; **2.** reference temp sensor; **3.** fetal venous needle sensor; **4.** needle sensor for measurement of tissue oxygenation; **5 and 6.** flow cells sensors for measurements of maternal arterial and fetal arterial flow oxygenation, respectively.

$$M_{O_2} = \frac{\left(P_{Mat\,A\,O_2} - P_{Mat\,V\,O_2}\right) FR_{Mat} - \left(P_{Fet\,V\,O_2} - P_{Fet\,A\,O_2}\right) FR_{Fet}}{\left(P_B - P_{H_2O}\right) m_{cot}} \beta_{O_2}$$

M_{O_2} = O_2 consumption, P_{O_2} = O_2 partial pressure, Mat = "maternal", Fet = "fetal", A = "arterial", V = "venous", FR = "Flow Rate", β_{O_2} = 0.0244 ml O_2/ml = effective O_2 solubility in perfusate at 37°C, P_B = barometric pressure (mm Hg), P_{H_2O} = water vapor partial pressure = 47 mmHg at 37°C, m_{cot} = weight of a perfused cotyledon (kg)

Statistical data was calculated using a non-parametric two-tailed Mann-Whitney test

RESULTS

Experimental series A. The fetal and maternal flow rates, fetal-to-maternal flow ratio, arterial and venous O_2, and venous-to-arterial O_2 ratio measured at various fetal flow rates of dually perfused placenta (n=3). Data are presented as MEAN±S.E.M. (standard error of mean).

Fetal Flow Rate (ml/min)	Fetal Perfusion Pressure (mmHg)	Maternal Perfusion Pressure (mmHg)	FMVD* (%)	Fetal/ Maternal Flow Ratio	Fetal Inflow (mmHg)	Fetal Venous O_2 (mmHg)	ΔFetal O_2 (mmHg)	ΔMaternal O_2 (mmHg)	Fetal Venous/ Fetal Arterial O_2 Ratio
4.8	40.6±2.5	32.5±8.5		0.3	28.7±6.6	50.7±3.4	22.0±9.9	115.7±12.7	1.8±0.6
6.0	48.7±4.1	32.6±8.4	2.8±1.0	0.4	31.3±8.8	56.0±17.1	24.7±25.9	88.7±10.4	1.8±1.0
8.0	62.8±8.1	33.3±8.0	3.0±1.2	0.5	27.5±5.5	32.0±4.0	4.5±1.5	87.0±3.0	1.2±0.1**
10.0	70.4±11.3	35.0±8.2	3.8±3.1	0.7	29.7±5.2	39.3±13.5	9.7±11.5	89.7±8.0	1.3±0.4
12.0	84.1±15.7	38.4±8.1	2.5±0.6	0.8	27.0±5.0	39.3±3.5	12.3±2.0	88.3±11.8	1.5±0.2

- correlation between fetal and maternal perfusion inflow pressure: R^2=1; p<0.02

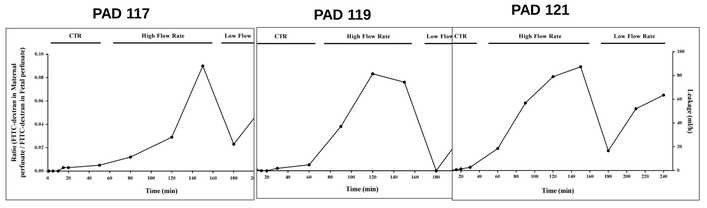
* - FMVD is Flow-Mediated VasoDilation; ** n=2

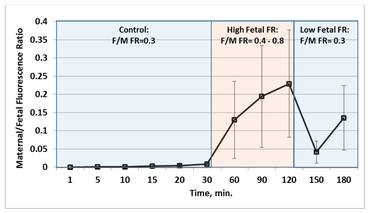
Experimental series B: Oxygen consumption by perfused placentas (n=4) measured at various fetal flow rates of dually perfused placenta (n=3). Data are presented as MEAN±S.E.M. (standard error of mean).

	Specific placental cotyledon Oxygen Consumption; ml O_2/(kg x min)						
	Integrated data*		Stepwise increase in Fetal Flow Rate** (ml/min)				
	4.5	12	4.8	6	8	10	12
PAD115	1.08	0.75	0.87	0.67		0.66	0.82
PAD117		3.31	1.39	1.22	1.36	1.66	1.34
PAD119	1.23	0.27	0.80	0.46	0.48	0.39	0.31
PAD121	0.65	2.28					
AVE±S.E.M.***	0.99±0.2	1.65±0.7	1.02±0.2	0.79±0.2	0.92±0.4	0.90±0.4	0.82±0.3

* O_2 consumption based on the oxygenation data obtained every 30-min. during the experiment
** O_2 consumption obtained at the 4.8 – 6 – 8 – 10 – 12-ml/min stepwise increase in the fetal flow
*** Average O_2 consumption was calculated for the average atmospheric pressure of 763 mmHg.

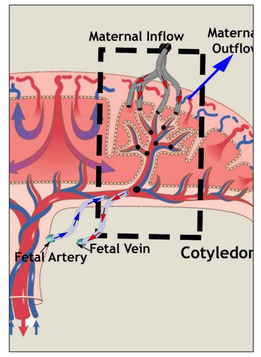
Figure 3. Calculated feto-maternal FITC dextran transport as a function of the increased fetal flow rates and feto-maternal flow ratios in each placenta and mean+SD data.





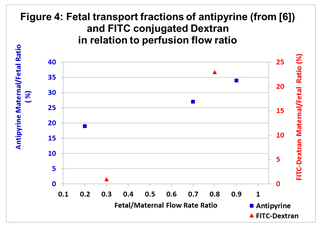
High flow rate: up to 12 ml/min, low flow rate: 4.8 ml/min

DISCUSSION



Placental oxygen consumption depends on flow rate, maternal arterial oxygenation *in vivo. Ex vivo* oxygen delivery in the perfusion system depends on carrying oxygen capacities of buffer or addition of red blood cells /fresh human whole blood/artificial hemoglobin to the perfusate. The low fetal arterial to venous ratio compared to the published data (less than 60 mmHg) might be due to the inadequate overlap between intervillous space oxygenated area and fetal villous tree. The inadequate overlap might be the cause of low oxygen consumption by placenta, compared to published data, e.g. the dual placenta perfusion *ex vivo* with the Earle's buffer at 95% oxygenation, O_2 consumption was less than 5 ml/min/kg [4] compared to *in vivo* oxygen consumption by human normal term placentas oxygen consumption has been reported as 13 ml/min/kg.

In our experiments we increased feto-maternal ratio and fetal flow rates. The increase of the fluid flow rate at flow ratio of 1 resulted in the decrease in the maternal and fetal transport fractions of antipyrine [5]. The comparison of fetal-to-maternal transfer of antipyrine [6] and FITC-conjugated Dextran in our experimental work (Figure 4) showed compatible data at the fetal/maternal flow ratio 0.6-0.9.



Decrease in placental oxygen consumption and increase in feto-maternal transfer of FITC dextran might be due to the fluid shunting between maternal and fetal compartments [6] and therefore inadequate oxygen exchange. The increase flow rates are associated with distension of the peripheral villous tree. The differences in the vascular composition of each cotyledon (SGI poster # T142, Chuecos et al. 2018) might explain differences in the absolute feto-maternal transfer of FITC dextran with the increased fetal flow and flow ratio.

The increased flow ratio is associated with fetal stromal odema (Kaufmann, 1985) – morphological changes, which have been suggested to result in decreased permeability.

CONCLUSIONS

At the ex vivo placental perfusion, the optimal flow rate for oxygen transfer is 4.8 - 6 ml/min.

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