

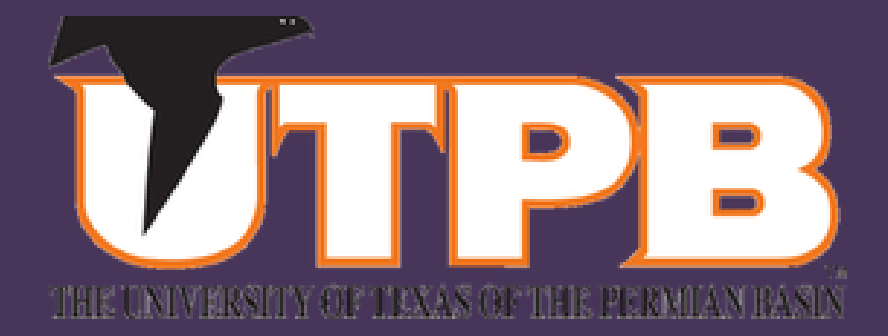


THE PATTERN OF THE FLOW MEDIATED VASODILATATION DEPENDS ON INCREMENTS OF FLOW INCREASE IN AN EX VIVO HUMAN PLACENTA DUAL-PERFUSION SYSTEM

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INTRODUCTION

- Umbilical blood flow is an important determinant of the placental oxygen transfer. In an *ex vivo* models of placental perfusion the inflow rate (corresponding to fetal arterial flow rate (FA)) differs between laboratory settings. At the *ex vivo* perfusion of "35 g of term normal placental tissue, one might expect this mass to have experienced an average of 12 ml min⁻¹ of *in vivo* blood flow after 32 weeks" (J Physiol. 2015 Jul 15; 593(Pt 14): 3077–3092).
- Flow-mediated vasodilatation (FMVD) allows placental vascular adaptation to increase in fetal blood flow. FMVD is impaired in fetal growth restriction. Pathophysiology of this phenomenon involves an increased synthesis of nitric oxide as a result of oxidative stress or functional and structural pathology of vascular remodeling.

OBJECTIVES

- To evaluate fetal venous-arterial oxygen tension ratio at different fetal inflow rates.
- To evaluate FMVD as a function of the numbers of incremental increases in the fetal inflow rate.

MATERIALS AND METHODS

In this study we evaluated the dual perfused human placenta *ex vivo* in closed and open systems. Seventeen placentas from uncomplicated pregnancies have been evaluated. Placenta and buffer oxygenation, maternal and fetal perfusion pressure, pH, glucose, lactate, and temp were monitored.

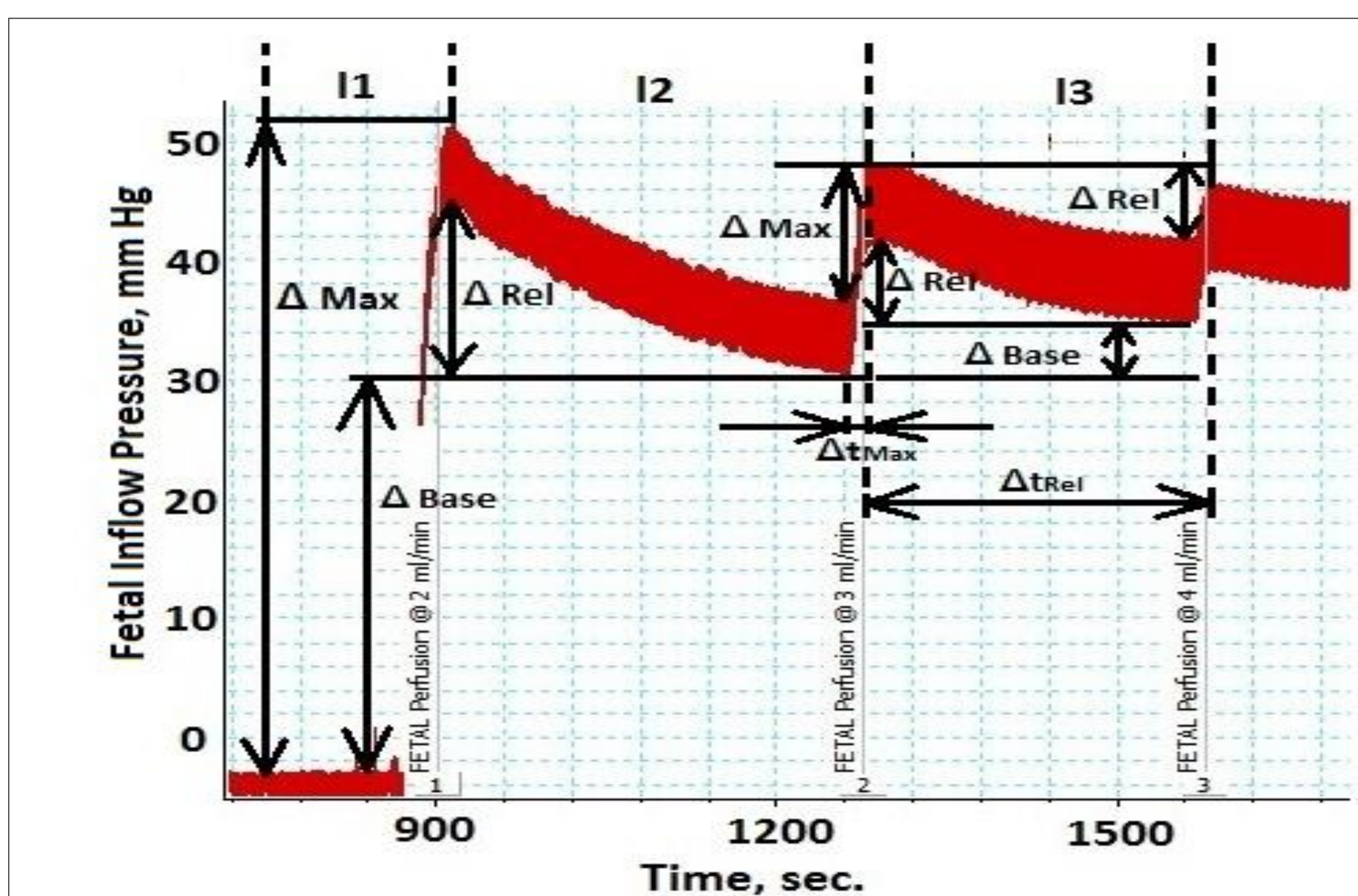


Figure 1. Measured parameters.

Δ Max (%): "pump "systolic" hydrostatic pressure increase upon elevation of flow rate
Δ Rel (%): pump "systolic" hydrostatic pressure drop representing the flow-mediated vasodilation response (FMVD)
Δ Base (%): pump "diastolic" steady state baseline hydrostatic pressure difference between two flow rates

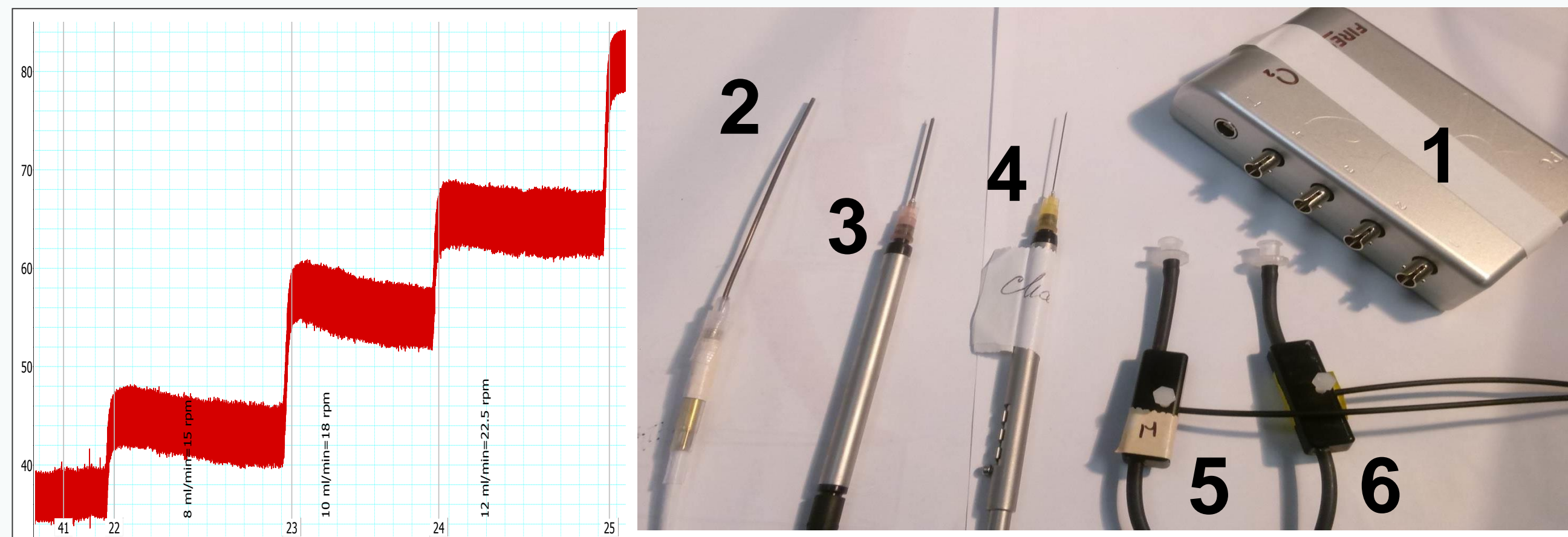


Figure 2. Stepwise increase in fetal flow rate from 4.5 to 12 ml/min.

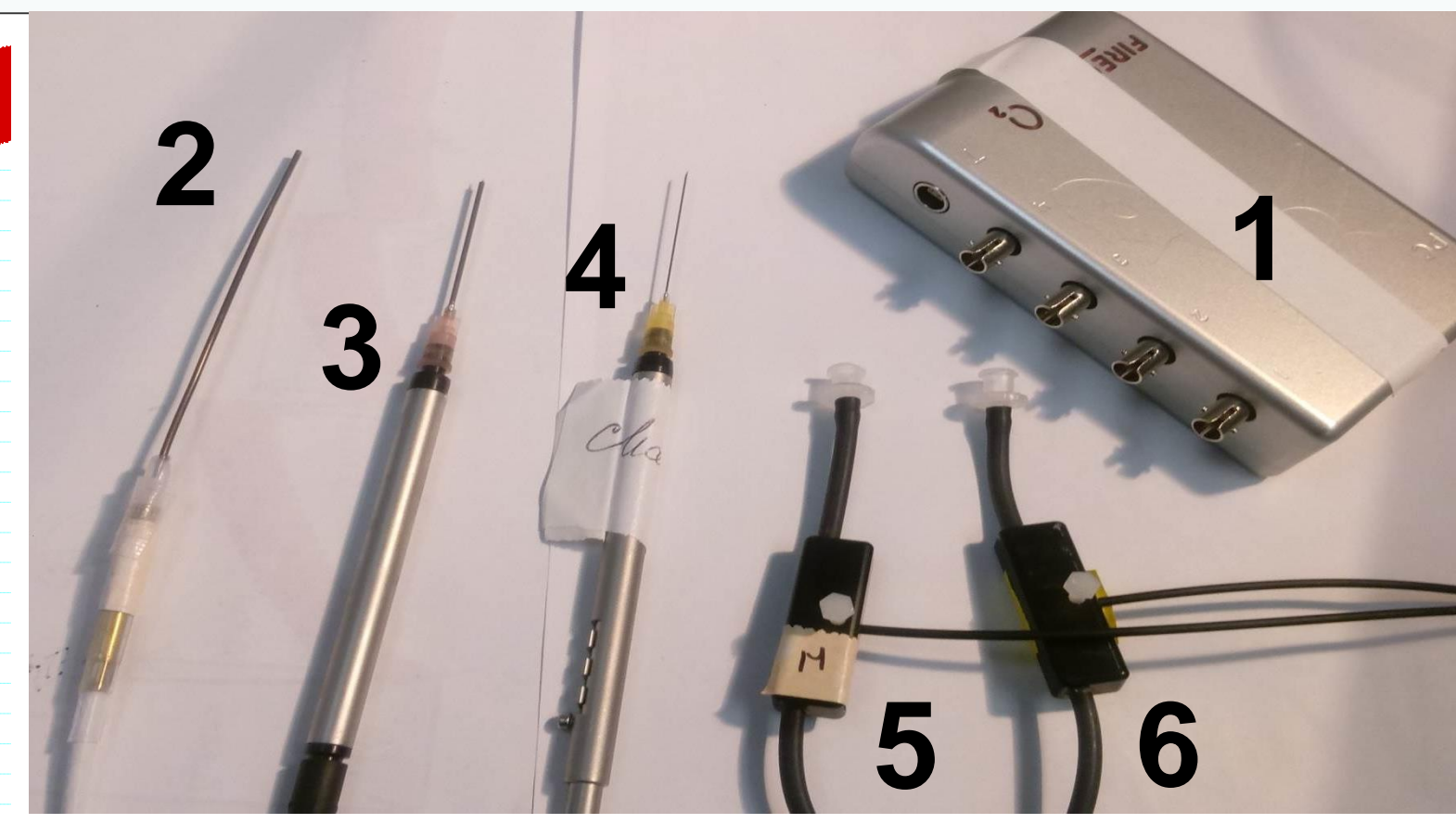


Figure 3. Oxygen and temp sensors with the pre-amp module: 1 Pre-amp module; 2. reference temp sensor; 3. fetal venous needle sensor; 4. needle sensor for measurement of tissue oxygenation; 5 and 6. flow cells sensors for measurements of maternal arterial and fetal arterial flow oxygenation, respectively.

In eleven placentas the fetal inflow rate (FIR) was increased in 2-ml/min incremental steps (I1-I4: from 4.5 ml/min to 12 ml/min), maternal flow rate was set for 15 ml/min.

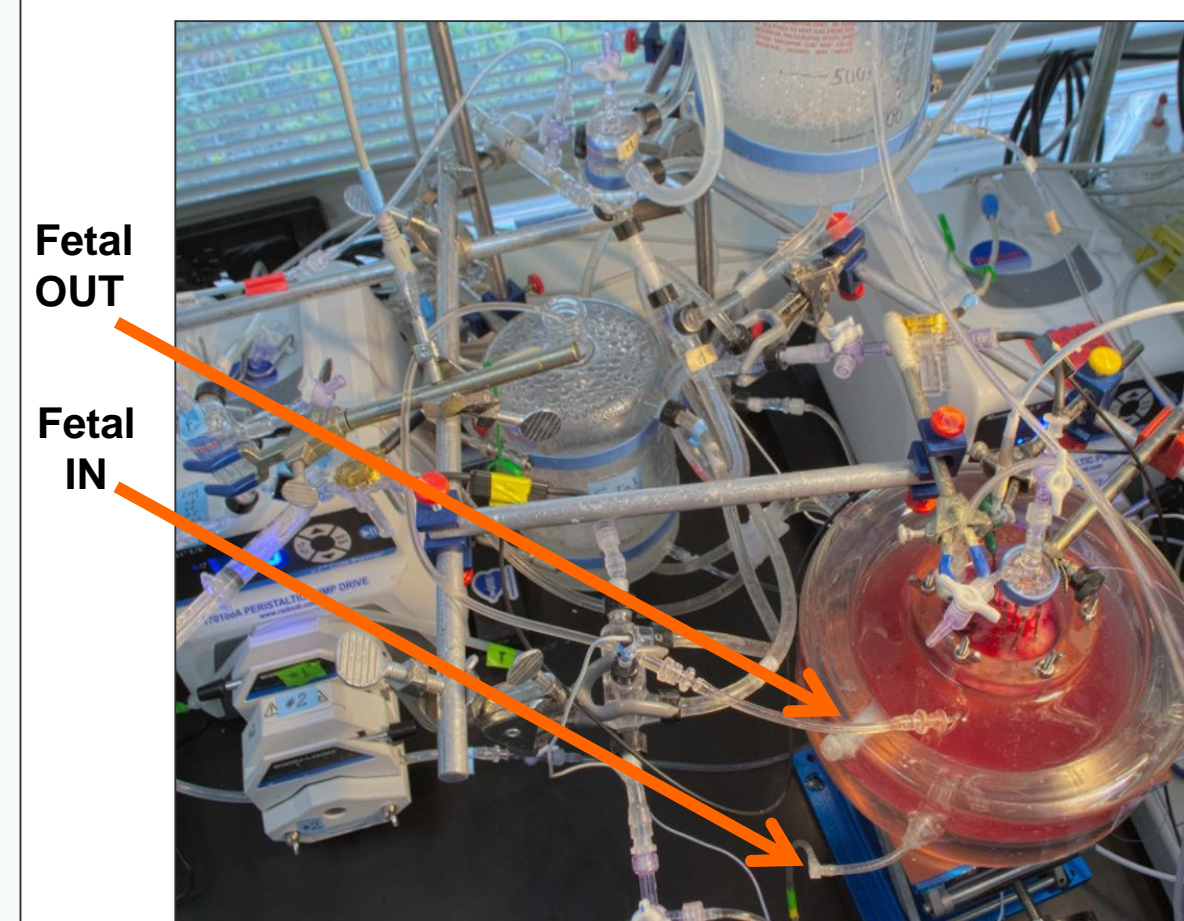


Figure 4. Overview of the perfusion system with the placental cotyledon

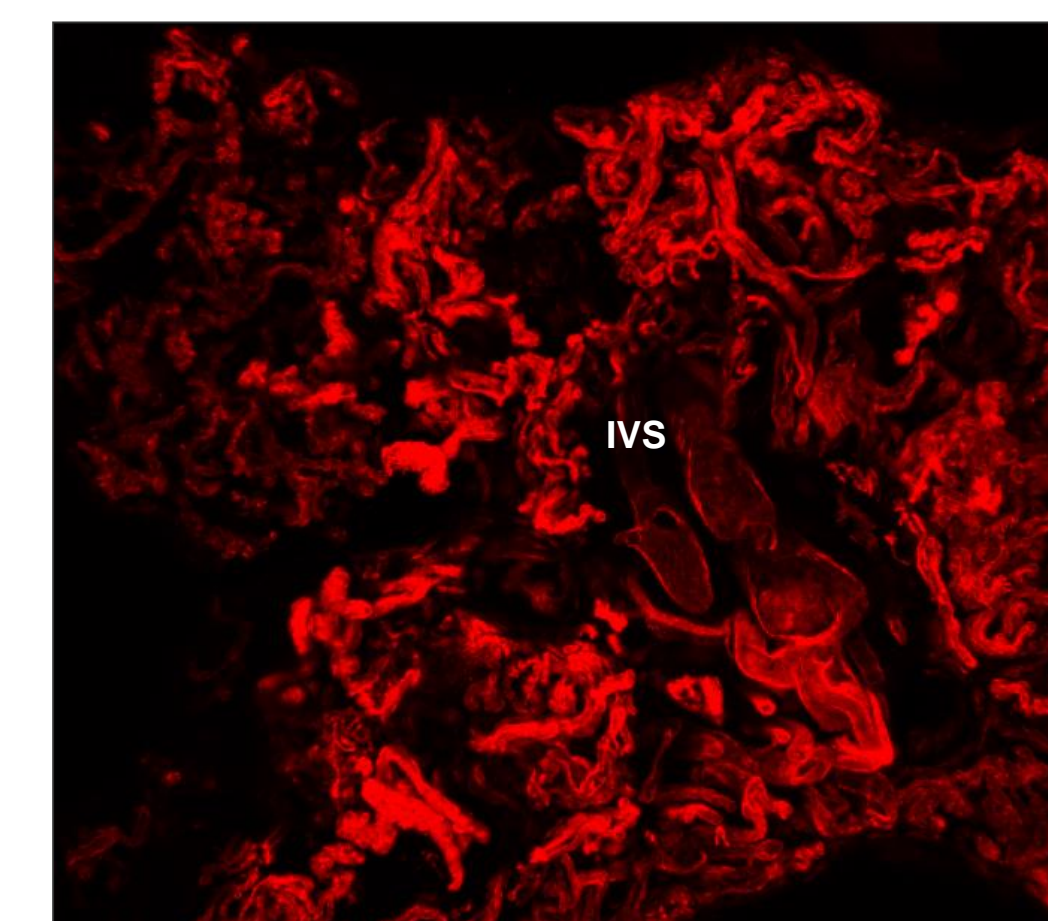


Figure 5. Blood vessels of the perfused placental cotyledon post *ex vivo* perfusion

Notice: IVS – Intervillous space, Fetal OXY IN – fetal inflow (arterial connection).

Table 1. Patients' characteristics

| ID | Maternal Characteristics | | | | | | | | | | Fetal Characteristics | | | Placenta Characteristics | | | |
|--------|--------------------------|--------|------|------------------------|-----|----------|-------------------|---------------------------------|----------------------|-------------|-----------------------|------------|--------|--------------------------|------------|---------------|----------------------|
| | Grav-ity | Parity | BMI | Gestation al Age (wks) | Age | Race | Prenatal vitamins | Prenatal medication | Antibiotics in Labor | Anaesthesia | Mode of Delivery | Weight (g) | gender | Apgar | Weight (g) | Diameter (cm) | Cotyledon Weight (g) |
| PAD059 | 2 | 1 | 28.3 | 41 | 20 | Hispanic | Yes | None | No | Epidural | Vaginal | 3940 | F | 8/9 | 537 | 20 x 18 | 54.91 |
| PAD061 | 2 | 1 | 31.8 | 40 | 32 | Caucas. | Yes | None | No | Epidural | Vaginal | 3470 | M | 8/9 | 423 | 20 x 16.5 | 43.26 |
| PAD062 | 3 | 1 | 32.8 | 37 | 20 | Hispanic | Yes | Novolin R, Humulin N | No | Epidural | Repeat c-section | 3810 | M | 8/9 | 705 | 20 x 22.5 | 43.96 |
| PAD071 | 2 | 1 | 25.5 | 41 | 27 | Hispanic | No | None | No | Epidural | Vaginal | 3030 | F | 8/9 | 484.5 | 19 x 18 | 44.3 |
| PAD076 | 1 | 0 | 34.1 | 40 | 20 | Unk. | Yes | None | Yes | Epidural | Vaginal | 3470 | M | 9/10 | 655 | 22 x 21 | 67.64 |
| PAD086 | 1 | 0 | 22.3 | 39 | 18 | Caucas. | No | None | Yes | General | C-section | 2534.9 | M | 9/9 | 400 | 19 x 14 | 40.09 |
| PAD095 | 3 | 1 | 22.7 | 39.1 | 34 | Caucas. | Yes | Zoloft | Yes | Epidural | Repeat c-section | 3740 | M | 7/8 | 760 | 21 x 19 | 20.95 |
| PAD096 | 5 | 3 | 31.9 | 39 | 29 | Hispanic | Yes | Zoloft, Colare, Senna, Macrobid | Yes | Epidural | Repeat c-section | 3260 | F | 9/9 | 725 | 22 x 17 | 53.76 |
| PAD097 | 3 | 2 | 30.8 | 39 | 37 | Caucas. | Yes | Glyburide, fenofibrate | Yes | Epidural | Repeat c-section | 3460 | F | 7/8 | 555 | 18 x 16.5 | 64.15 |
| PAD099 | 3 | 2 | 30.1 | 39.4 | 32 | Caucas. | Yes | None | Yes | Epidural | Repeat c-section | 3487 | M | 8/9 | 535 | 19 x 20 | 50.24 |

RESULTS

Table 2. Fetal and Maternal oxygen tensions at the beginning and at the end of 2-ml/min incremental increase in fetal flow rate (n=11)

| Fetal inflow Rate (ml/min) | Fetal oxygen tension | Maternal Oxygen tension |
|----------------------------|----------------------|-------------------------|
| | OXY IN (mmHg) | OXY IN (mmHg) |
| 4.5 | 36.3±6.1 | 301.6±33.6 |
| 12 | 37.4±6.8 | 307.0±30.5 |
| p value | 0.9 | >0.9 |
| Significance | ns | ns |

Table 3. Fetal venous-arterial oxygen pressure ratio (FV/FA) at fetal flow rates of 4.5 and 12 ml/min.

| ID | FV/FA | FV/FA |
|---------------|------------|-----------|
| | 4.5 ml/min | 12 ml/min |
| PAD086 | 0.56 | 1.16 |
| PAD095 | 0.27 | 1.76 |
| PAD096 | 1.09 | 1.2 |
| PAD097 | 0.47 | 0.74 |
| PAD099 | 0.74 | 1.18 |
| Average | 0.626 | 1.208 |
| paired t-test | 0.037 | |

Table 4. Feto-placental vascular response to the 2-ml/min increase of the fetal perfusion flow (Data MEAN±SEM) (n=11).

| Fetal Flow Rate ml/min | TIME | | Fetal Pressure | | |
|------------------------|-----------|------------|----------------|----------------|----------|
| | Max sec | Rel sec | Δ Max % | Δ Rel (FMVD) % | Δ Base % |
| 4.5 – 6 | 42.3±6.7 | 351.8±13.5 | 20.1±2.0 | 1.1±2.8 | 15.9±2.1 |
| 6 – 8 | 55.9±13.1 | 319.1±13.0 | 28.7±1.9 | 3.2±1.4 | 23.9±1.9 |
| 8 – 10 | 47.7±9.7 | 335.5±18.5 | 18.3±1.7 | 1.3±0.8 | 15.9±1.7 |
| 10 – 12 | 46.4±9.4 | 312.0±12.0 | 20.2±1.4 | 2.0±0.8 | 16.4±2.1 |

CONCLUSIONS

In the *ex vivo* dually perfused human placenta, the flow-mediated relaxation, but not the max contraction, was dependent on a number of incremental increases in blood flow rate. The increase in the fetal flow rate was associated with increased fetal venous-arterial oxygen pressure ratio. Our results indirectly support the findings of the study published in J Physiol. 2015 Jul 15; 593(Pt 14): 3077–3092, thus demonstrating that factors, other than villous tree formation, might be responsible for the resistance of the umbilical artery. Figure 6 represents images of capillary tree of three perfused placentas. The flow rate of 12 ml/min might be optimal for oxygen transfer in our system.

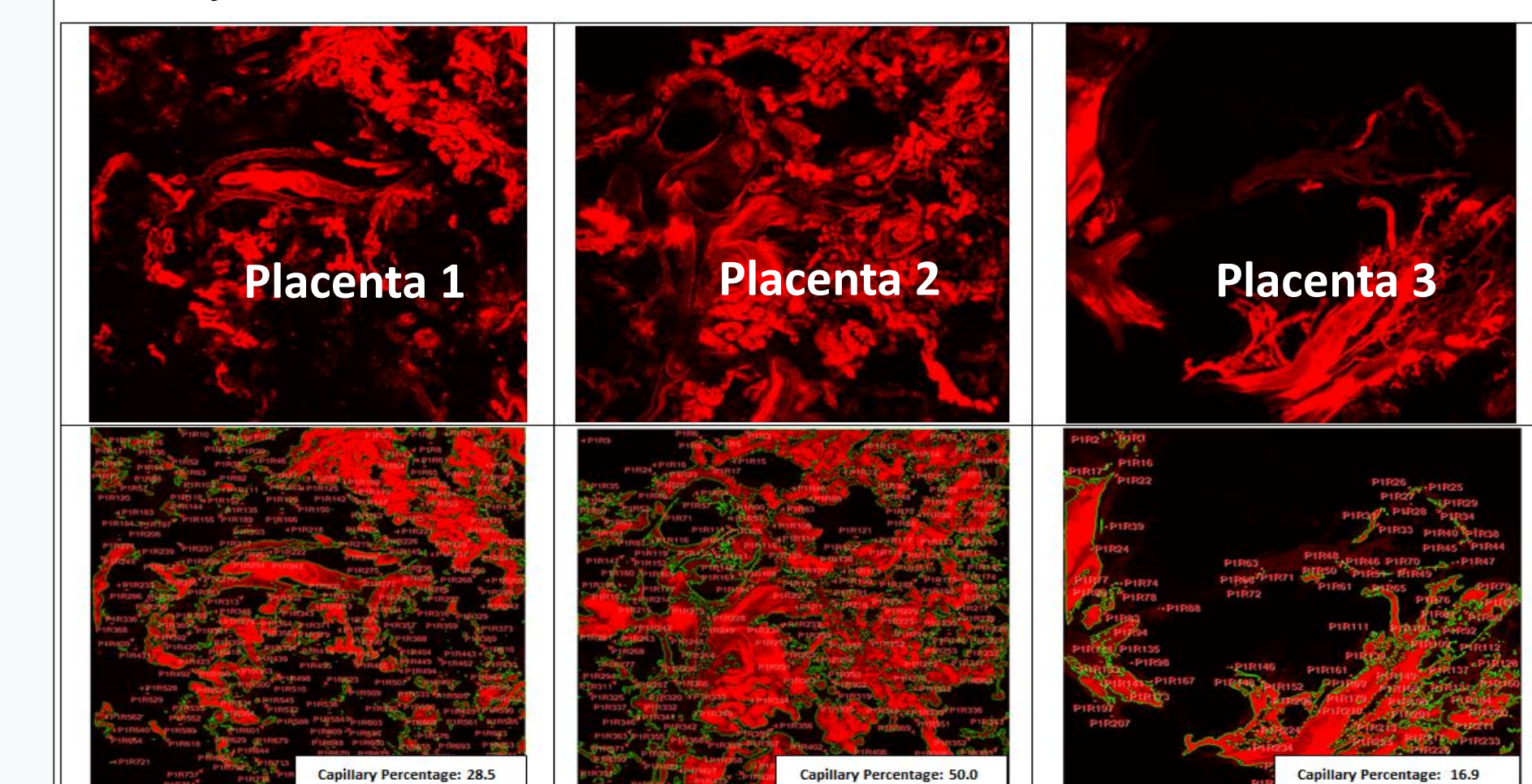


Figure 6. Villous tree capillaries of three different *ex vivo* perfused human placenta cotyledons. Notice: differences in IVS composition.

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