ARTERIOLAR DYSFUNCTION IN PLACENTAS OF HIV-EXPOSED SMALL FOR GESTATIONAL AGE NEONATES

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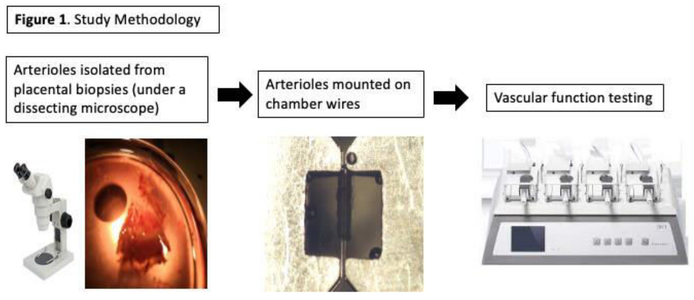
BACKGROUND

- Birthing individuals with HIV are more likely to deliver small-for-gestational-age (SGA) neonates.[1-6] Fetal growth restriction results from limited delivery of nutrients and O_2 during development. **We hypothesized that placental microvascular dysfunction may contribute to SGA among birthing individuals with HIV.**

METHODS

- We conducted a case-control study of fetoplacental arteriolar function from placentas of neonates with/without HIV exposure and with/without SGA birthweight between 36-41 weeks gestation.
- Immediately post-delivery, we collected 5x3x2cm placental biopsies and placed biopsies in cold, physiologic salt buffer solution.
- Fetoplacental arterioles were harvested from the intervillous space under the microscope.
- We assessed fetoplacental arteriolar function by myograph; we measured dose-dependent contraction to U-46,619 (a thromboxane-prostanoid receptor agonist), endothelin (ET1), norepinephrine (NE), and phenylephrine (PE), as well as relaxation to acetylcholine (ACh), sodium nitroprusside (SNP), and AdipoRon (ApR, an adiponectin [ApN] agonist).
- ET1-induced reactive oxygen species (ROS) were measured by DHE fluorescence and apR-induced nitric oxide (NO) activity by DAF-FM fluorescence using a RatioMaster™ system.
- Umbilical cord and maternal plasma ApN and malondialdehyde (MDA, a marker of oxidative stress) were measured by ELISA.
- Dose response curves across groups were compared using two-way mixed ANOVA.

Figure 1. Study Methodology



Fetoplacental arteriolar relaxation was impaired and contraction was enhanced in placentas of HIV-exposed and small-for-gestational-age neonates

RESULTS

- We collected 33 placental biopsies; we excluded 3 due to poor quality from excessive time in transit. We analyzed specimens from 9 placentas of HIV-unexposed normal birthweight (NBW) neonates ("controls"), 6 HIV-unexposed SGA neonates, 11 HIV-exposed NBW neonates, and 4 HIV-exposed SGA neonates (**Table 1**).

Table 1: Demographics and Clinical Characteristics

Characteristic Median (IQR)	Total	NBW	HIV+NBW	SGA	HIV+SGA
Maternal age	29 (25, 33)	30 (26, 33)	26 (24, 31)	31 (29, 36)	30 (26, 34)
Race, n (%)					
Black/AA	23 (89%)	3 (50%)	10 (100%)	6 (100%)	4 (100%)
White	3 (10%)	3 (50%)	0	0	0
Gestational age	39 (38, 39)	39 (38, 40)	39 (39, 40)	37 (37, 38)	38 (38, 39)
Placental Dimensions					
Length (cm)	21 (19, 24)	22 (21, 24)	22 (19, 24)	17 (17, 17)	22 (21, 22)
Width (cm)	19 (18, 20)	19 (18, 22)	20 (19, 20)	17 (15, 18)	20 (19, 20)
Thickness (cm)	1.6 (1.4, 2.1)	2.1 (1.4, 2.2)	1.5 (1.4, 1.5)	1.7 (1.5, 1.8)	1.7 (1.5, 2.1)
Prior # of Pregnancies	3 (2, 4)	2 (1, 3)	2 (2, 3)	4.5 (2.5, 5)	3 (3, 4.3)

Figure 1: Reduced ApR-induced NO and enhanced ET-1-induced ROS generation in fetoplacental arterioles from placentas of HIV-exposed and SGA neonates

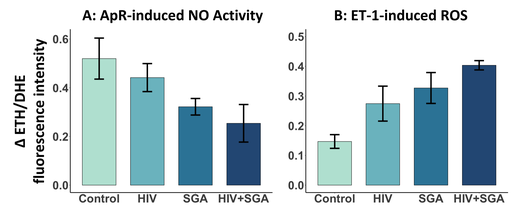
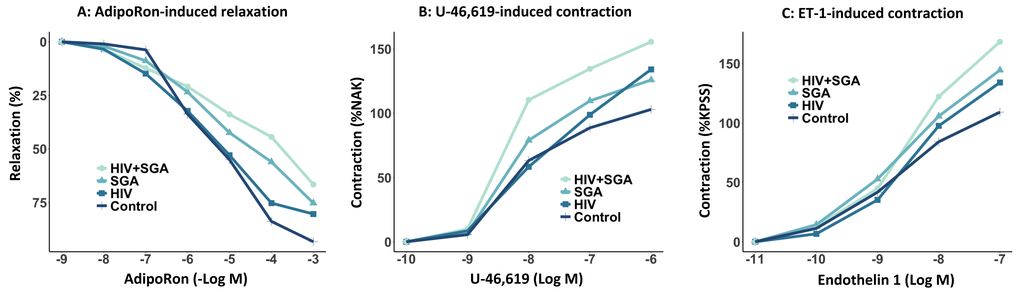


Figure 2: Reduced ApR-induced relaxation and enhanced contraction to U-46,619 and ET-1 in fetoplacental arterioles from placentas of HIV-exposed and SGA neonates



- Both U46,619 (103±4% of KClmax) and ET-1 (109±5%) induced robust contractions, while vessels were unresponsive to NE (7±3%) or PE (5±2%). Contractions to ET-1 and U-46,619 were greater in placentas with HIV-exposure (p=.003; p=.03) or of SGA neonates (p=.01; p<.0001) compared to controls, and greatest in the setting of both HIV-exposure and SGA (p<.0001; p<.0001) (**Figure 2 B&C**).
- U46,619 pre-constricted arterioles relaxed to ApR (93±4%), but only minimally to Ach (7±2%) or SNP (10±2%). Impaired arteriolar relaxation to ApR was associated with HIV-exposure (p=.01), SGA (p=.001), and combined HIV-exposure with SGA (p<.0001) (**Figure 2A)**.
- ApR-induced NO was decreased and ET1-induced ROS was increased with HIV-exposure and SGA (**Figure 1**).
- Birthweight % was correlated directly with ApR-induced relaxation (10^{-4}) (r=.47, p=.02) and ApR-induced NO generation (r=.44, p=.03) and inversely with maternal plasma MDA (r=-.37, p=.05).

DISCUSSION

- Similar to previous work by Baker and colleagues, among others,[7-14] we found minimal relaxation of pre-constricted vessels to ACh or SNP, yet marked **relaxation to ApR.**
- There were **robust contractions to U46,619** and **ET-1**, but minimal response to NE and PE.
- We found fetoplacental arteriolar **impaired ApR-induced relaxation** and **enhanced contraction to ET-1 and U-46,619** among placentas of **HIV-exposed and SGA birthweight** neonates. These were more pronounced in the setting of both HIV-exposure and SGA birthweight.
- Birthweight was correlated with ApR relaxation and inversely correlated with a marker of oxidative stress, MDA.

CONCLUSIONS

- **Fetoplacental arteriolar relaxation was impaired and contraction was enhanced among placentas of HIV-exposed and SGA neonates**.
- These findings contribute to the limited body of research elucidating the pathophysiology of SGA among BIHIV.

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